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Population mixing, childhood leukaemia, CNS tumours and other childhood cancers in Yorkshire

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Abstract

We tested the hypothesis that variation in population mixing attributable to the diversity of migrants moving to an area is associated with the incidence of childhood leukaemia and other childhood cancers. An ecological analysis was performed on 954 children (<15 years) diagnosed with a malignancy between 1986 and 1996 in 532 electoral wards in Yorkshire, UK. Incidence rate ratios (IRR) were calculated for all childhood leukaemias ($n=325$), acute lymphoblastic leukaemia (ALL) ($n=248$), central nervous system (CNS) tumours ($n=236$) and other solid tumours (n = 393) Incidence of all childhood leukaemias was significantly lower in areas of high (top decile) population mixing (IRR 0.72, 95% Confidence Interval (CI) 0.54–0.97) and higher in areas of low (bottom decile) population mixing (IRR 1.56, 95% CI 0.73–3.34), but similar patterns of incidence were not observed for central nervous system or other solid tumours. Population mixing may be a proxy for the range of infections circulating in a community and these results are consistent with the hypothesis that greater exposure to infections reduces the risk of developing childhood leukaemia by conferring efficient modulation of the immune system.

Keywords: Childhood leukaemia; Cancer; Population mixing; Infection

1. Introduction

Infections have long been thought to play a role in the development of childhood malignant diseases originating in cells of the immune system including the leukaemias and lymphomas [1]. The majority of childhood leukaemias originate in lymphoid cell lines and present acutely, occurring most commonly in the 1–4 year age group [2]. The subgroup of acute lymphoblastic leukaemia (ALL) has been most strongly linked with an infectious aetiology [3], but convincing epidemiological and biological evidence does not exist for an association between other paediatric cancers (excluding leukaemia and lymphomas) and any form of microbial pathogen [1].

The association between microbial pathogens and the development of chronic paediatric conditions such as diabetes [4], asthma and atopy [5] and leukaemia [6] may be explained by developmental programming of the immune system in response to early exposure to common or endemic infection associated with the mother, siblings or other early social contacts. For childhood leukaemia, it has been suggested that ALL is frequently initiated by a chromosome translocation event *in utero*, but for clinical leukaemia to develop, it is necessary for some form of postnatal promotional event to occur [6,7]. This promotional event may be an abnormal immune response to a common infection later in life occurring in those who have not been exposed to common or endemic infections in early life.

Areas with high levels of population mixing are likely to represent communities where the prevalence and range of infections is high due to the mixing of infectives and susceptibles [8]. Communities with low population density and low migration rates are less likely to maintain a wide range of endemic infections and hence immunity [8,9]: a classic example is the observation that children in rural areas are infected with measles later

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than those in urban areas [10]. Kinlen has proposed that childhood leukaemia is a result of an uncommon response to a relevant infection in susceptible individuals [11] without reference to an early translocation event. Excess leukaemia incidence can be detected in areas where population mixing has occurred to an exceptional extent [11]. In this case, it is suggested that susceptibility is conferred upon individuals by living at a low population density or belonging to a professional worker class who have high standards of hygiene and relative social isolation. High levels of inward and outward migration to an area involving these populations could result in a sufficiently high population density to cause outbreaks of the relevant infections affecting both incomers and the indigenous population.

Stiller and Boyle [12] investigated the relationship between socio-economic status, population mixing and ALL using information derived from the 1981 UK Census. They found a raised incidence for ALL in 0–4 and 5–9 year olds in those county districts with higher proportions of child immigrants and those districts receiving incomers of any age with a greater diversity of origins. In this study, we have used a similar measure to that used by Stiller and Boyle and have applied it at a finer geographical scale (the electoral ward) to examine the association between childhood leukaemia and other childhood cancers and population mixing attributable to the diversity of incomers of any age and children under 16 years.

2. Patients and methods

2.1. Subjects

Children aged under 15 years diagnosed with a malignant disease between 1986 and 1996 were selected from the population based Yorkshire Specialist Register of Cancer in Children and Young People [13]. Using the International Classification of Childhood Cancer [14] four main diagnostic groups were defined—all leukaemias, ALL, central nervous system (CNS) tumours and other solid cancers. Lymphomas were not included as a distinct group in the analysis due to the low numbers.

2.2. Population base

Population totals by sex and 5-year age band and data on unemployment, household overcrowding, housing tenure and car ownership were obtained for the 532 electoral wards in the study area from the 1991 UK Census (The 1991 Census, Crown Copyright, ESRC purchase). The latter four variables were used to calculate the Townsend deprivation score [15]. The population weighted average of the population density (persons per hectare) for each census enumeration district was aggregated to electoral ward to provide a measure of population density which more accurately reflects the density at which the average person lives [16].

2.3. Measures of population mixing

Using the 1991 Census Special Migration Statistics (The 1991 Census, Crown Copyright, ESRC purchase) population migration and population mixing were calculated separately for 'any age' (1 year or older) and 'children' (1–15 years). Migration was the proportion of either the 'any age' or 'childhood' population with a different address 1 year before the census, excluding those moving within wards. A measure of population mixing based on the Shannon index of diversity, H_j [17] was calculated based on the diversity of the origins of these incoming migrants. This used flows of all migrants, i.e. 'any age' and 'children' from all other wards (England and Wales) and postcode sectors (Scotland) into individual wards in the Yorkshire region:

$$H_j = -\sum_{i=1}^{S}\left\{p_i \ln p_i - \frac{S-1}{N_j} + \frac{1-\sum p_i^{-1}}{12N^2} + \frac{\sum\left(p_i^{-1}-p_i^{-2}\right)}{12N^3}\right\}$$

where for each area j, p_i is the proportion of migrant individuals coming from the ith area as a proportion of all migrants moving into the total number of areas S, and N is the total number of migrants. Higher values indicate higher diversity of originating areas and higher levels of population mixing. These measures have been described in detail elsewhere in Ref. [18]. Using digitised electoral ward boundaries, 'childhood' and 'any age' population mixing were mapped as standard deviations from the mean.

2.4. Statistical analysis

Age–sex standardised incidence rates were calculated using population estimates from the 1991 Census (The 1991 Census, Crown Copyright, ESRC purchase). Poisson regression models were fitted to observed counts of cases in each ward using the log of the number of expected cases as the offset derived from age–sex specific incidence rates. Incidence rate ratios (IRR) with 95% confidence intervals (CI) are reported as a measure of association between disease incidence and the following independent variables: Townsend score, population density, migration and population mixing ('childhood' and 'any age'). In an initial univariate analysis, each variable was analysed as a continuous value and in five categories, each category containing approximately equal populations. The IRR for a continuous variable quantifies the change in incidence per unit change in the independent variable. Population mixing was also

categorised into those wards in the Yorkshire study region below the 10th centile, between the 10th and 90th centile and those above the 90th centile for comparability with Stiller and Boyles' study [12]. The proportion of individuals with an address different to that 1 year ago ('children' and 'any age') and population density were highly skewed and were therefore subject to a log transformation which gave a more random spread of deviance residuals when plotted against fitted values.

The two multivariate models used population mixing ('any age' or 'childhood') categorised into those wards below the 10th centile, between the 10th and 90th centile and those above the 90th centile, log population density, log proportion movers ('any age' or 'childhood'), and Townsend score as continuous variables. These co-variates were included as continuous variables to ensure model simplicity and reduce the overall degrees of freedom. Improvement in model fit following addition of the population mixing variable to these base models was assessed by comparing the change in residual deviance to a χ^2 distribution with $n-1$ degrees of freedom. An analysis restricted to ALL in 0–9 year olds was also performed.

2.5. Regression diagnostics

Due to the sparse nature of the data, simulation was used to test the assumption that data were Poisson distributed [19,20]. Standardised deviance residual plots were examined for any sign of abnormal distribution of deviance residuals together with plots of fitted values.

3. Results

The numbers of malignancies by broad diagnostic group are given in Table 1 together with age–sex standardised incidence rates (per million per year). It should be noted that lymphomas are included in the numbers and rates for all malignancies, but not elsewhere. Fig. 1 illustrates the location of the study area and the geographical distribution of 'any age' and 'childhood' population mixing in Yorkshire by electoral ward as standard deviations from the mean. Univariate analysis revealed a significantly reduced IRR for ALL in association with childhood population mixing as a continuous value of 0.75 (95% CI 0.58–0.96) and the fifth quintile (IRR 0.63 (95% CI 0.41–0.96). The association with childhood population mixing was similar, but less marked, for all leukaemias combined.

The main result of interest in the other diagnostic groups was a significant reduction in IRR for CNS tumours in association with increased deprivation (IRR 0.95, 95% CI 0.92–0.98). There was also a reduction in IRR for increasing deprivation for ALL (IRR 0.97, 95% CI 0.94–1.01) as a continuous variable and a more marked reduction in the highest 5th of socio-economic status (IRR 0.67, 95% CI 0.44–1.01). Other univariate data are not presented for brevity. Table 2 summarises the results of the multivariate Poisson regression modelling by diagnostic group and for 'any age' and 'childhood' population mixing, with significant reductions in IRR for ALL and all leukaemias associated with the top decile of population mixing. It should be noted that the decreased IRRs for ALL and all leukaemias associated with the decile with the highest 'any age' population mixing reflect those of the childhood population mixing, but there is no corresponding increased IRR in the lowest decile. The reduction in IRR with increasing deprivation is retained in the multivariate model for CNS tumours. While there is an increased incidence in the lowest decile of childhood population mixing for CNS tumours, this is not significant and there is no corresponding reduction in incidence in the highest decile. Incidence is higher in the top and bottom deciles of 'any age' population mixing for CNS tumours and reduced incidence is observed for other solid tumours for both population mixing variables.

Significant improvements in model fit were seen for ALLs and all leukaemias following the addition of the 'childhood' population mixing variable to the base model (χ^2 6.95, two degrees of freedom (d.f.), $P=0.03$

Table 1
Numbers of children diagnosed with a malignancy in Yorkshire between 1986 and 1996 by broad (ICCC)[a] diagnostic group and age group together with age–sex standardised incidence rates

	ICCC group	Age band (years)			Total	Incidence rate (per 10^6 year^{-1})
		0–4	5–9	10–14		
All malignancies	I-XII	500	281	283	1064	135.7
Leukaemias	I	179	83	63	325	41.5
ALL	Ia	139	67	42	248	31.6
CNS tumours	III	78	89	69	236	30.1
Other solid tumours	IV-XII	214	75	104	393	50.1

[a] ICCC, international classification of childhood cancer [14]; ALL, acute lymphoblastic leukaemia; CNS central nervous system.

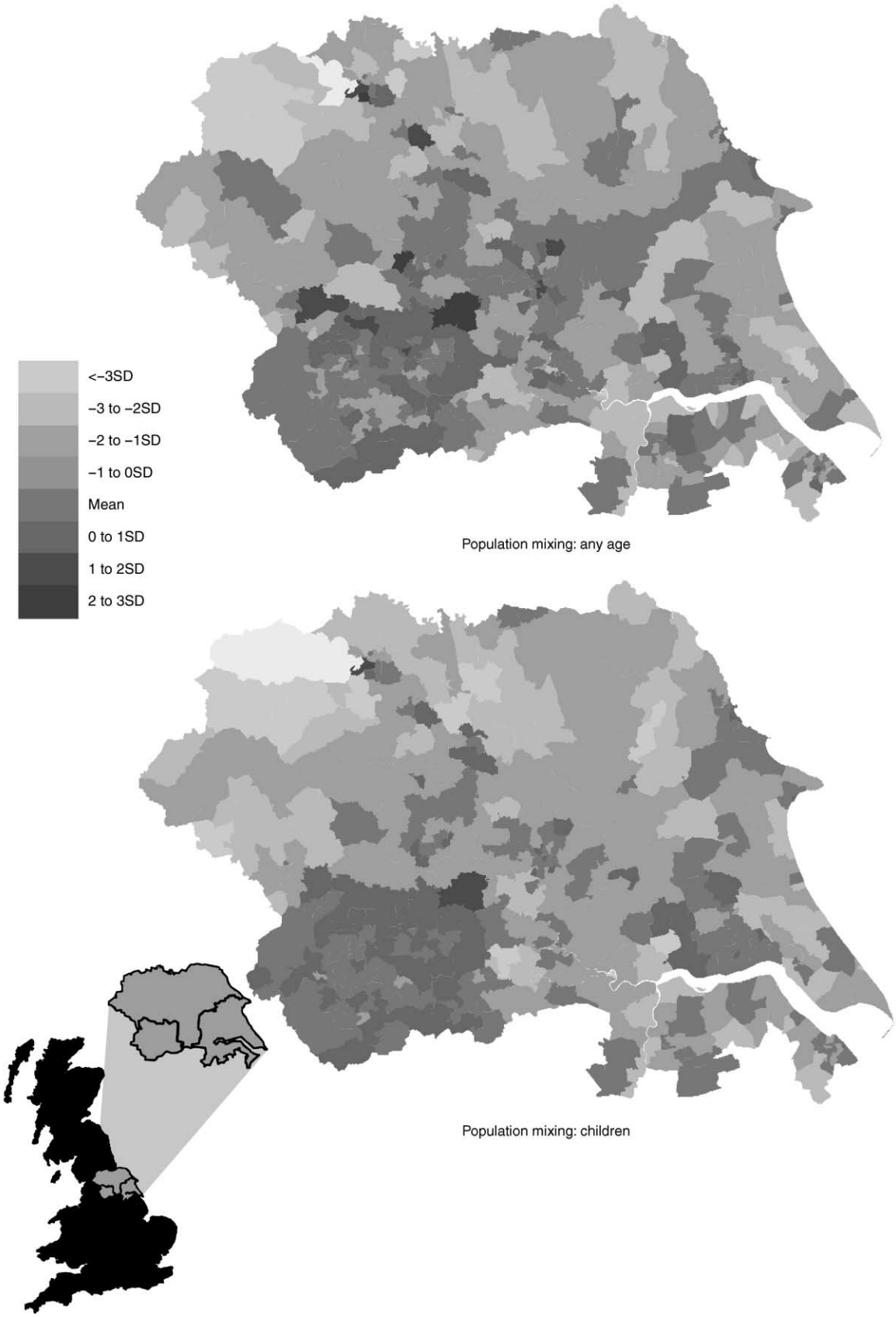

Fig. 1. Population mixing in Yorkshire by 1991 census ward for children and all ages expressed as standard deviations from the mean Shannon index score.

Table 2
Incidence rate ratios (IRR) and 95% confidence intervals (CI) for childhood cancer associated with 'childhood' and 'any age' population mixing, adjusting for socio-economic status, childhood population density and proportion of migrants using Poisson regression modelling

Model/variables	Variable type/category	ALL		All Leukaemias		CNS		Other solid tumours	
		IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
'Childhood' population mixing									
'Childhood' population mixing	<10th decile	1.55	0.68–3.51	1.56	0.73–3.34	1.69	0.71–4.02	0.69	0.24–1.62
	10th–90th decile	1.00	–	1	–	1	–	1	–
	>90th decile	0.67	0.47–0.94	0.72	0.54–0.97	1.00	0.73–1.36	0.96	0.75–1.13
Townsend score	Continuous	0.96	0.92–1.00	0.96	0.93–1.00	0.94	0.90–0.98	0.99	0.96–1.02
Log_n 'childhood' migrants	Continuous	0.89	0.60–1.33	1.00	0.70–1.42	1.20	0.80–1.81	0.95	0.69–1.31
Log_n population density	Continuous	1.06	0.92–1.22	1.09	0.96–1.24	1.10	0.95–1.27	1.01	0.90–1.13
Model fit χ^2 (d.f.), P[a]			6.95(2) $P=0.03$		6.49(2) $P=0.04$		1.29(2) $P=0.53$		1.12(2) $P=0.57$
'Any age' population mixing									
'Any age' population	<10th decile	0.86	0.41–1.78	0.79	0.50–1.56	1.72	0.93–3.17	0.81	0.44–1.50
Mixing	10th–90th decile	1	–	1	–	1	–	1	–
	>90th decile	0.68	0.47–0.99	0.71	0.51–0.99	1.35	0.98–1.85	0.91	0.69–1.19
Townsend score	Continuous	0.97	0.93–1.01	0.97	0.94–1.01	0.94	0.90–0.98	0.99	0.96–1.02
Log_n 'any age' migrants	Continuous	0.84	0.57–1.34	0.98	0.65–1.46	1.17	0.75–1.85	0.89	0.62–1.29
Log_n population density	Continuous	1.01	0.89–1.15	1.04	0.92–1.17	1.07	0.93–1.23	1.02	0.91–1.14
Model fit χ^2 (d.f.) P[a]			4.30(2) $P=0.12$		4.89(2) $P=0.09$		5.64(2) $P=0.06$		0.9(2) $P=0.63$

d.f. degrees of freedom; ALL, acute lymphoblastic leukaemia; CNS, central nervous system.
[a] Improvement in model fit following addition of population mixing variable.

and χ^2 6.49, 2 d.f., $P=0.04$, respectively). Addition of the 'any age' population mixing variable to the base model did not significantly improve model fit for these disease groups and no significant improvements in model fit were observed for the addition of 'childhood' or 'any age' population mixing for CNS and other solid tumours. The analysis of ALL restricted to children aged 0–9 years produced very similar results with a slightly more marked effect in the high population mixing decile (IRR 0.60, 95% CI 0.41–0.89) and better model fit (χ^2 8.20, 2 d.f., $P=0.017$).

4. Discussion

4.1. Childhood leukaemia and ALL

In Yorkshire, the incidence of all childhood leukaemia, and ALL in particular, was significantly lower in electoral wards where mixing of the childhood population based on their diversity of origins from other electoral wards within the UK was highest. There is also a non-significant, but increased, IRR in the lowest decile of childhood population mixing for both groups. Adjusting for other demographic factors that have been associated with childhood leukaemia such as social deprivation [12,21,22] and population density [23,24] did not remove the observed association with population mixing although the borderline significant reduction in IRR for increasing deprivation was in line with earlier studies [21]. Explanations of infectious aetiology for leukaemia in childhood put forward by Greaves [6] relate specifically to common ALL and although high population mixing was protective overall for leukaemia, the effect was more marked in this subgroup. There is no plausible explanation linking our results to an event that initiates ALL *in utero*. However, the negative association between leukaemia incidence and living in areas of high population mixing would be consistent with the hypothesis that early life exposure to microbial pathogens is necessary to modulate the immune system thus priming against an abnormal response (i.e. leukaemia) to a late infection [6,7].

Our results contrast with those of Stiller and Boyle [12] whose data indicate that there is *increased* incidence of childhood leukaemia in areas of high and diverse population mixing. They suggest that this effect is seen at a young age (0–9 years) as a result of early infection with a corresponding decrease in incidence in the 10–14 year olds. We were able to analyse the effect of population mixing in the 0–9 year age range at ward level and noted an increase in effect of high population mixing and better model fit, but could not compare these results with the 10–14 year olds due to low numbers. One explanation for the differences between these results is likely to be the geographical unit of analysis. Stiller and Boyle [12] analysed incidence for the England and Wales in county districts whereas this study has used the considerably smaller electoral ward: in Yorkshire, populations in the 532 census wards range between 500 and 25 000 individuals, whereas populations range from 2000–1 000 000 in the county districts of England and

Wales. If population mixing acts as a proxy measure for exposure to community infections, it is difficult to interpret what the single value calculated for a large heterogeneous district may represent in terms of contacts between individuals. By using the smaller electoral ward as the geographical unit of analysis, this study has added a level of refinement to the population mixing measure and is therefore more likely to represent prevailing local conditions with respect to circulating infections. Despite this, there will inevitably be small scale variation which will not be accounted for within the wards themselves. Our results, which show a negative association between childhood leukaemia and high population mixing are difficult to compare with those of Kinlen [11] who found increased incidence of childhood leukaemia in areas that had unusually high levels of population mixing in extreme situations [11]. These included rapid population changes resulting from influxes into relatively isolated areas of a variety of populations such as construction workers, service personnel and incomers to new towns. All these studies examined specific geographical areas over certain time periods and offered explanations for observed increases in childhood leukaemia rates. Thus, Kinlen has studied 'clusters' of leukaemia in areas that undergo extreme population mixing on a retrospective basis. Our study and that of Stiller and Boyle [12] have examined these effects prospectively across the whole population of a region and did not look either at specific areas or specific influxes of population. A recent study in Canada used population change in census areas over a five-year period as a measure of population mixing [25]. It identified increased incidence in leukaemia, particularly in 0–4 year olds with ALL in rural areas with high levels of population mixing, but no similar increase in incidence in urban areas. Yorkshire is an ideal area to conduct such a study with its combination of highly urbanised areas such as Leeds and Bradford, rural arable farming in the vale of York and the sparsely populated rural areas of the Pennines and north Yorkshire moors. Population weighted population density may act as a proxy for urban rural status and is incorporated in our statistical modelling *a priori* as it is clearly associated with the dynamics of infection in a population [9].

4.2. CNS and other solid tumours

The incidence of CNS and other solid tumours do not follow the same pattern as ALL and all leukaemias. These findings apply to a heterogeneous group of tumours, but analysis of sub-types is not possible due to small numbers. They provide little evidence that population mixing is involved in the aetiology of these tumours.

In our study, population mixing appears to explain some of the variability in incidence of childhood leukaemia and especially ALL at a relatively small geographical level. We restricted our analysis to an 11-year period about the 1991 Census as Census data only provides information at a fixed point in time and in the case of the Special Migration Statistics our calculation of population mixing relied on the address of individuals 1 year prior to the census date. We have not taken into account any large-scale population movements occurring between 1986 and 1996, but no data were available to include such changes in the modelling. Categorisation of the population mixing variables was used to investigate the possibility of a threshold effect in those areas subject to very high or low levels of population mixing and for comparability with Stiller and Boyles' study [12]. Categorisation also removes the assumption of linearity in the relationship between log incidence and population density and population mixing.

It is clear that in Yorkshire, interward migration often occurs within the same district, especially in urban areas. In Leeds, a predominately urban area in Yorkshire, intradistrict migration runs at approximately 70%, but in Hambleton, a predominately rural area, only 36% of migrants came from the same district. As a result, the distance travelled may be relatively small in urban areas and it may be suggested such migration will have little effect on exposure to infection. Quantifying the effect of moving to a different ward on exposure to infection is difficult, however: we are looking specifically at the effect of population mixing among children for whom a move of even a relatively short distance may result in changes of school or childcare arrangements, factors that may influence infectious contacts. We had considered using a measure of Euclidean distance to weight the contribution to 'mixing' of a particular origin, but there was little information on how such a weight should be constructed. Similarly, the construction of an adjacency matrix to identify coterminous wards becomes less meaningful in rural areas in which population centres may be very close or separated by a significant distance. Rather than creating an over-elaborate model that potentially increases error due to misclassification we decided to use a relatively simple measure comparable to that used by Stiller and Boyle [12]. The Shannon index of diversity measures the diversity of origins of incoming migrants, but does not take into account the overall numbers moving into an electoral ward from each originating ward. To control for this factor, the number of migrants calculated as a proportion of the ward population was included in the modelling, but this did not improve model fit, most probably due to a significant positive correlation between these two variables. Migration flows were calculated for each ward/postal sector in Great Britain from every other ward/postal sector, but not for incomers from outside these areas as there were anecdotal

suggestions that these data were not reliable in view of the sensitivity of immigrant status. With better validated data, it would be appropriate to include these flows.

Separate measures of 'any age' and 'childhood' population mixing were used to differentiate between the likely exposure or contact of children with other children in a community and their contact with adults. Although children might be expected to move with adults the reverse is not the case: out of 1036 wards in England and Wales categorised as being in the bottom decile in terms of population mixing for 1–15 year olds, for 425 of those wards 'any age' population mixing lies between the 10th and 90th percentiles. We did not use other potential measures of population mixing such as commuting patterns or mode of commuter transport as they were considered to only be applicable to adult–child exposures and there were no comparable variables that related to child–child exposures. In addition, the effect of parental occupational mixing with other individuals is equivocal: Kinlen found increased risk with increasing parental occupational mixing [26] while Fear and colleagues did not [27]. Our study and that of Stiller and Boyle [12] are set in the context of a gradual increase in the incidence of childhood leukaemia in the UK [2], with some suggestion that this has been driven by precursor B-cell ALL [28], although not in the Yorkshire region [29]. Our analysis was carried out later and covers a period of 11 years in contrast to the 7 years of Stiller and Boyles' study. It is not possible to assess changes in migration at the ward level between 1981 and 1991, as the 1981 Special Migration Statistics used by Stiller and Boyle are only available by district, and a variable, although reasonably large proportion of population mixing occurs within districts. As a result, it is not possible to assess the effect of the two studies being conducted at different times.

Our study lends support to the contention that variation in incidence of childhood leukaemia may be attributable to early infectious exposure for which population mixing may act as one of many proxy measures. However, it is unable to distinguish between risk associated with possible exposure (or lack of exposure) either to a single agent or to a broad spectrum of infections, which may be symptomatic or asymptomatic. Further investigations of population mixing around the time of birth may clarify the time at which exposure to infections, or lack of infectious contacts, may modify risk.

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