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Population-mixing at the place of residence at the time of birth and incidence of childhood leukaemia in France

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ABSTRACT

The association between the risk of childhood leukaemia before age 7 years and population-mixing at the place of residence at birth was investigated by retrospectively considering all the children born in mainland French *communes* between 1st January 1990 and 31st December 1998. An increased risk of acute lymphoblastic leukaemia was found with higher levels of migration for children residing at birth in isolated *communes* with a population density $\geqslant$50 people per km^2 (SIRR = 2.59, 95% CI: 1.48–4.49). No association was observed with lower population densities. For children residing in non-isolated *communes* at birth, the results were similar but less marked. The risk tended to increase only for population densities $\geqslant$5000 people per km^2 (SIRR = 1.57, 95% CI: 0.99–2.52). The findings are consistent with epidemic models and support the hypothesis of an infectious aetiology relating to population-mixing. Population density may be seen as an indicator of the opportunity of contacts between inhabitants and should therefore be taken into account when investigating an infectious hypothesis. This is the first systematic study of population-mixing at the place of residence at the time of birth to be conducted on a national scale.

1. Introduction

Kinlen suggested that childhood leukaemia could be a rare response to a common viral infection.[1] According to this hypothesis, population-mixing in an isolated area may lead to increases in childhood leukaemia. The spread of infection in a given population is regulated by the proportion of infected, carrier, susceptible and immune subjects and by the rate of contacts between susceptible and infected or carrier subjects.[2,3] Susceptible subjects are those who have not previously been exposed to the virus. In an isolated area, the proportion of subjects susceptible to the unidentified viral agent may be high enough to result in epidemics when infected and susceptible subjects arrive with a large migrant population and imbalance group immunity.

In earlier studies, various criteria were used to define the isolated status of an area. Authors have used "rural status" often based on national institute definitions,[4–13] population density[12,14] and distance from a large population centre.[1,6,7,15] A variety of variables have also been used to express population-mixing. Population increase has been frequently used.[1,9,10,12,16,17] Migration influxes, both global[18] and specific, have also been studied. The specific characteristics of incomers include incomer migration distance,[11,18] incomer diversity of origins using Shannon's diversity index,[14,18–20] military servicemen's professional relocations,[4,8,18] construction workers' professional relocations,[6,7,13] incomer age,[14,18,19] migration movements at country level,[21] and wartime government evacuees.[5] Commuting[18] and commuting increase[22] between home and work has also been investigated. While

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commuting is not migration it nonetheless engenders contacts between individuals.

Most of those authors reported significant higher rates of childhood leukaemia with increased population-mixing, mainly in isolated areas,[1,4–8,10,12,13,15,21,22] but also in urban areas[11] or in areas for where urban/rural status was not specified.[16,18,19,22] Only two papers reported no significant association in rural areas[9,11] although increased risks were observed by Dickinson and colleagues.[11] However, Law and colleagues[14] recently revisited 17 published studies on acute lymphoblastic leukaemia (ALL) and population-mixing with a critical view on subgroups analysis and concluded that these studies did not support consistently Kinlen's hypothesis.

The aim of the present study was to investigate the association between the risk of childhood leukaemia before age 7 years and population-mixing at the place of residence at the time of birth in mainland France. This is the first systematic study of population-mixing at the place of residence at the time of birth to be conducted on a national scale.

2. Patients and methods

The study addressed all the *communes* of mainland France, excluding overseas *départements*. The *commune* is the smallest administrative unit. In 1999, there were 36,565 *communes*. The average area was 15 km^2 and the average population 1600 people (87% of the *communes* had a population of less than 2000). The *communes* make up 95 *départements* of average area 5700 km^2, and 22 *régions*, the largest administrative unit, of approximate average area 25,000 km^2.

The demographic and geographic data on the *communes* were obtained from the last two censuses, which took place in 1990 and 1999 (French National Institute of Statistics and Economic Studies [INSEE]).

2.1. Birth cohort

All the children born in the *communes* of mainland France between 1st January 1990 and 31st December 1998 were considered retrospectively and anonymously. Leukaemia incidence before the age of 7 years or to the end of 1998 for children born in 1992 or after was estimated. The 0–6 year age group corresponds to the highest incidence rates for acute lymphoblastic leukaemia (ALL).

Person-years at risk, the sum of the number of years of follow-up for each child, were estimated for each French *commune* of residence at birth, taking into account the live birth counts and number of deaths before age one year for each *commune* from 1990 to 1998, assuming that children who died before age one year died in the *commune* where they were born. Deaths occurring after age one year were not considered.

The leukaemia cases were obtained from the French National Registry of Childhood Leukaemia and Lymphomas (NRCL).[23] The Registry has an average of 2.5 sources per case and 99.2% exhaustiveness for leukaemia.[23] The cases were assigned to their *communes* of residence at the time of birth. Administrative authorisation was required in order to obtain the parents' *commune* of residence at the time of the child's birth from the place of birth registered in the NRCL. The data could not be obtained for 38 cases out of 1576 (2.4%): 4 children were homeless, the place of residence at birth could not be obtained from the administrative authorities for 7 cases, and 27 children were unknown to the administrative authorities, probably because of mistakes in noting the place of birth. Eleven of the 27 (41%) unknown children had attended the same hospital in the "Provence-Alpes-Côtes-d'Azur" *région*, while 6.7% of the cases were diagnosed in that hospital.

2.2. Demographic characteristics

2.2.1. Isolated status

The 1990 census data were used to characterise the initial status of each *commune*. The French urban zoning system (ZAU) provides for 7 categories of *commune* on the basis of the *commune's* dependence and influence in terms of employment (Table 1).[24–26] ZAU categories 1, 2 and 3 are predominantly urban area while categories 4, 5, 6 and 7 are predominantly rural area. Urban (ZAU 1) and rural (ZAU 5) 'poles' are attractive *communes* in terms of employment in that they attract commuters living in other *communes*. Non-pole *communes* were inhabited by 35% of the total French population and accounted for 90% of the *communes* in 1990. Conversely, 65% of the total population lived in urban and rural 'poles' but those areas only accounted for 10% of the *communes*.

INSEE has also elaborated a classification according to the size of urban units. An urban unit is a *commune* or group of *communes* containing a built-up area in which no dwelling is more than 200 m from its nearest neighbour.[27] This classification was obtained from the 1990 census.

For the analysis, both classifications were used. Isolated *communes* were defined as non-pole *communes* from urban units of population less than 5000 people. They accounted for 89% of *communes* and 31% of French population in 1990.

Two further INSEE variables: accessibility of facilities and services and population density were also employed.

Accessibility of facilities and services is the average distance of the *commune* from 36 predefined basic facilities and services. This characteristic was obtained from the 1998 *Municipal Inventory*.[28]

We used population density as an indicator of the opportunity of contacts between inhabitants. Since density is linked to spread of infections,[2,3] our hypothesis was that in too low-density isolated communes, contacts between individuals would be insufficient for an epidemic to occur during population-mixing. Similarly, in non-isolated *communes*, where the frequency of susceptible subjects is supposed to be smaller, higher level of population density could favour contacts and engender spread of infections in susceptible individuals.

Cut-point of density was defined a priori in order to contrast low- and high-density *communes* in both isolated and non-isolated categories of *communes*. Density lines were 50 inhabitants per km^2 for isolated *communes* and 5000 inhabitants per km^2 for non-isolated communes. These cut-points correspond to the 10th and the 85th percentiles of the cohort person-years. Population density was also obtained from the 1990 census.

For *communes* which merged or subdivided after the 1990 census, the merged definition of the *communes* was retained,

Table 1 – INSEE ZAU urban zoning categories and numbers (percentage) of communes and ZAU population at the 1990 census

Urban zoning categories (ZAU)	Definition	Communes N (%)	Population (million) N (%)
Predominantly urban area			
ZAU 1 Urban pole	At least 5000 jobs and not belonging to the peri-urban area of another urban pole	2791 (8%)	34.4 (61%)
ZAU 2 Peri-urban area	At least 40% of the working population has a job in a given urban pole or its peri-urban area	7892 (22%)	6.9 (12%)
ZAU 3 Multipolarised dependence on urban poles	Not ZAU 1 or 2 where at least 40% of the working population has a job in several urban poles or their peri-urban areas	2536 (7%)	2.0 (4%)
Predominantly rural area			
ZAU 4 Weak dependence on urban poles	Not rural pole and between 20% and 39% of the working population has a job in urban poles or their peri-urban areas	8876 (24%)	5.1 (9%)
ZAU5 Rural pole	Between 2000 and 5000 jobs. Total number of jobs must be greater than the total number of workers living in the rural pole	594 (2%)	2.1 (4%)
ZAU 6 Dependence on rural pole	Not ZAU 4 or 5 and at least 20% of active residents working in rural poles	2934 (8%)	1.1 (2%)
ZAU 7 Rural isolated	Not belonging to other ZAUs	10912 (30%)	5.1 (9%)

Total number of *communes:* 36,535. Total population: 56.7 million.

and the entity was assigned the values of the most urban of its constituents.

2.2.2. *Population-mixing*

Detailed data on the origins of incomers were extracted from the 1999 population census. The number of incomers to each *commune* was the number of inhabitants in 1999 who had been living in a different *commune* on 1st January 1990. Immigration rates were calculated as the number of incomers between the 1990 and 1999 censuses divided by the 1999 population. Three definitions of immigration were considered: incomers from another *commune*, incomers from another *département* and incomers from another *région*. The four *départements* of Paris and its immediate suburbs were considered a single *département*. Migration rate cut-points were defined a priori for each category of communes.

2.3. *Statistical method*

The expected numbers of cases were calculated by year of age from the national incidence rates.[23] Yearly standardised incidence ratios (SIR) were calculated as the ratio between the observed number of cases (O) in each category of commune and the expected number (E) in that category. The SIR ratio (SIRR) was used as an estimate of the Incidence Rate Ratio, which assumes that age-specific incidence rates in each categories are proportional to age-specific reference incidence rates. For a given level of migration rate, SIRR was calculated as the ratio of the corresponding SIR to the SIR with the lowest incomer rates. The 95% confidence intervals were calculated on the basis of Breslow and Days recommendations for SMR ratios.[29] SIRR were calculated for all leukaemia, ALL, B-cell common ALL, other ALL (T-cell and unspecified ALL), acute myeloblastic leukaemia (AML) and non-ALL non-AML leukaemia, and for ages 0, 1–6 and 0–6 years. SIRR were also calculated after excluding the Provence-Alpes-Côte d'Azur *région* since it had the most missing data.

3. Results

A total of 6 602,974 children were born in France during the study period, and 35,597 deaths before the age of one year were reported. The cohort totalled 28 230,352 person-years. A total of 1576 cases were registered, and consisted in 1273 ALL (81%), 283 AML (18%) and 20 non-specified AL (1%). B-cell common ALL accounted for 88% of ALL. Incidence rates per million and per year for the cohort were 55.8 for all AL, 45.1 for ALL and 10.0 for AML.

The cross-distribution of cohort person-years by isolated status and by urban zoning categories, size of urban unit, accessibility of goods and services and population density are shown Table 2. The two groups of *communes* according to the isolated status appeared well contrasted. Only 0.4% of the person-years of isolated communes were accounted for by *communes* providing the 36 facilities and services, compared to 66.9% for non-isolated *communes*. Similarly, 9.5% of the person-years of isolated communes were accounted for by *communes* with a population density of more than 200 people per km^2, compared to 93.0% for non-isolated *communes*.

Table 2 – Person-years distribution by isolated status and by urban zoning categories, population size of urban unit, accessibility of facilities and services, and population density

Demographic variables	All *communes*	Isolated[a] *communes*	Non-isolated *communes*
	(36,535 *communes*) (%)	26% of cohort person-years (32,494 communes) (%)	74% of cohort person-years (4041 communes) (%)
Urban zoning categories			
1	66	–	89.6
2	11	33.1	3.2
3	3	10.0	0.8
4	8	25.9	1.3
5	3	–	4.7
6	2	6.1	–
7	7	24.9	0.4
	100	100	100
Population of urban unit			
<5000	26	100	0.9
5000–19,999	10	–	13.6
20,000–99,999	14	–	18.4
100,000–199,999	7	–	9.7
⩾200,000	43	–	57.4
	100	100	100
Accessibility of facilities and services (km)			
>4	10	36.0	0.2
1.6–4	16	47.2	5.0
0.1–1.5	25	16.4	27.9
0	49	0.4	66.9
	100	100	100
Population density, People per km²			
<50	11	39.9	0.2
50–199	18	50.6	6.8
200–999	22	9.3	26.9
1000–4999	33	0.2	44.7
⩾5000	16	–	21.4
	100	100	100

a Isolated *communes* were defined as non-pole *communes* from urban units of population less than 5000 people.

Table 3 shows the estimated SIRR for ALL cases aged 1–6 years among children living at birth in isolated *communes*, which accounted for 26% of the person-years, by rate of migration from another *commune*, another *département* and another *région*. ALL risk increased with migration rate in isolated *communes* with population density of at least 50 people per km^2. The trend towards an increase was more marked for migrations defined at the highest level of aggregation (*région*) and corresponding to the longest average migration distance. Below the population density of 50 people per km^2, no association was observed.

A similar but weaker trend was observed for children living at birth in non-isolated *communes* that accounted for 74% of the person-years (Table 4). Those living at birth in *communes* with a population density greater than 5000 people per km^2 were at increased risk of leukaemia when exposed to higher rates of population-mixing, while no relationship was observed for those living at birth in *communes* with a population density of less than 5000 people per km^2.

Table 5 shows results of migration from another *département* for different categories of AL cases: AL age 0–6, AML age 0–6, ALL age 0–6 and 1–6, B-cell common ALL age 1–6 and other ALL age 1–6 years, for both isolated *communes* with a population density of more than 50 people per km^2 and for non-isolated *communes* with a population density of more than 5000 people per km^2. The associations were less marked for all AL and the AML categories. The results for B-cell common ALL were similar to those for all ALL, with no differences in terms of ALL sub-type.

When the data for the "Provence-Alpes-Côte d'Azur" *région*, which accounted for 41% of the unknown places of birth, were excluded, the results were similar.

4. Discussion

The present study was carried out to test the hypothesis that ALL is a rare sequel of a specific infection and that population-mixing may lead to micro-epidemics. For this purpose, the demographic parameters and their categorization were a priori defined with INSEE. A clear positive association between ALL incidence and the migration rate of the place of residence at birth was observed before the age of 7 years when the population density was sufficiently high. Below a population density of 50 people per km^2 for isolated *communes* and 5000 for non-isolated *communes*, no association with the indicators of population-mixing was observed.

Bias due to missing data is unlikely. First, only 2.4% of the data was missing. Secondly, there is no obvious reason why cases without an address at the time of birth would have lived in *communes* with the lowest immigration rates, since the presence or absence of that item mainly depends on whether or not the hospital files include the place of birth. Finally, exclusion of the "Provence-Alpes-Côte d'Azur" *region*, which had the greatest number of missing places of birth, did not alter the results. Person-years were calculated with the assumptions that the children lived in the same *commune* until the age of one year, and that deaths occurring after that age could be discounted. In fact, in the period 1990–1998, deaths between ages 1 and 6 years accounted for 22% of the deaths before age 7 years and 0.1% of all the births included.

Isolated *communes* were defined as non-pole *communes* from urban units of population less than 5000 people. Two complementary criteria were thus combined: a functional one, based on influence and dependence in terms of employment, and a more geographic one, referring to the physical continuity of urban units. As an INSEE report on Europe's towns[30] points out, European countries do not share a clear-cut definition of rural and urban zones. This makes international comparisons difficult.[31] Interpreting previous studies on population-mixing and urban/rural status is complicated by the fact that clear definitions are not always stated.

Population density was considered a marker of the probability of contact between individuals. Contact frequency is a pivotal parameter for modelling the propagation of

Table 3 – Isolateda communes: observed numbers of cases (O) and ratios of SIR (SIRR) for risk of ALL (age 1–6 years) by measure of population-mixing for children residing in isolated communes at the time of birth

% incomers in *commune*	Population density <50/km^2 O = 139			Population density ⩾50/km^2 O = 184		
	O	SIRR	95% CI	O	SIRR	95% CI
From another commune						
<30%	47	1.00	–	43	1.00	–
30%–39%	66	1.15	[0.78–1.71]	97	1.31	[0.90–1.92]
40%–49%	23	1.20	[0.70–2.02]	37	1.41	[0.89–2.25]
⩾50%	3	0.93	[0.18–2.89]	7	2.04	[0.77–4.57]
From another département						
<10%	46	1.00	–	49	1.00	–
10%–19%	71	0.93	[0.63–1.38]	94	1.37	[0.96–1.98]
20%–29%	18	0.79	[0.43–1.40]	31	1.80	[1.11–2.89]
⩾30%	4	0.71	[0.19–1.95]	10	2.36	[1.07–4.71]
From another région						
<6%	25	1.00	–	33	1.00	–
6%–11%	67	1.25	[0.78–2.06]	85	1.43	[0.95–2.21]
12%; 17%	30	1.06	[0.60–1.88]	41	1.70	[1.05–2.78]
⩾18%	17	1.22	[0.62–2.35]	25	2.59	[1.48–4.49]

a Isolated *communes* were defined as non-pole *communes* from urban units of population less than 5000 people.

Table 4 – Non-isolated communes: observed numbers of cases (O) and ratios of SIR (SIRR) for risk of ALL (age 1–6 years) by measure of population-mixing for children living in non-isolated communes at the time of birth

% incomers in *commune*	Population density <5000/km^2 O = 665			Population density ⩾5000/km^2 O = 173		
	O	SIRR	95% CI	O	SIRR	95% CI
From another commune						
<30%	237	1.00	–	61	1.00	–
30%–39%	314	0.90	[0.76–1.07]	66	0.93	[0.65–1.34]
40%–49%	108	0.98	[0.77–1.23]	46	1.20	[0.80–1.79]
⩾50%	6	0.66	[0.24–1.47]	0	–	–
From another département						
<15%	300	1.00	–	26	1.00	–
15%–19%	179	0.98	[0.81–1.18]	33	1.43	[0.98–2.01]
20%–24%	103	0.89	[0.70–1.12]	90	1.76	[1.41–2.16]
⩾25%	83	0.96	[0.74–1.23]	24	1.78	[0.98–3.22]
From another région						
<10%	273	1.00	–	31	1.00	–
10%; 14%	257	1.02	[0.86–1.21]	49	1.35	[0.84–2.18]
15%; 17%	60	0.71	[0.53–0.95]	39	1.86	[1.13–3.09]
⩾18%	75	0.84	[0.65–1.09]	54	1.57	[0.99–2.52]

epidemics.[2,3] In isolated communes, where the frequency of susceptible subjects may be high, a certain population density was assumed to be necessary to induce sufficient contacts between infected and susceptible people to lead to small epidemics. In contrast, in non-isolated *communes*, the frequency of susceptible subjects may be small, and a very high population density may be necessary for virus transmission. Kinlen and colleagues, in a study of rural new towns in the UK, which experienced a marked increase in population in the 1950s, observed a greater leukaemia excess in the rural new towns with the highest population density[15] and suggested that this finding could be explained by the increase in contacts between individuals.

The finding that the strongest association was between leukaemia and migrations defined at the higher levels of aggregation (*département* and *région*) and thus corresponding to the longest average migration distances, also argues in favour of an infectious aetiology. It was assumed that, on average, the subjects would have had more contact with incomers from other *communes* than with those from other *départements* or other *régions*. Incomers from closer places may have been more likely to share current infections with the local host population. Distant populations may exhibit greater contrasts with respect to the hypothetical viral agent than proximity populations.

The results reported herein may be the product of chance. However, the strength of the relationship and its increase with the degree of population-mixing suggest the contrary. Moreover, there is no obvious confounding factor, since no presently known or suspected risk factor for ALL is expected

Table 5 – Observed numbers of cases (O) and ratios of SIR (SIRR) for risk of AL (age 0–6 years), AML age 0–6, ALL ages 0–6 and 1–6, B-cell common ALL age 1–6 and other ALL age 1–6 years, by percentage of incomers coming from another département for isolated communes and non-isolated communes with a population density above predefined limits

Isolated[a] *communes with population density* ⩾ 50/km²																				
% incomers from another *département*	AL 0–6 O = 241			AML 0–6 O = 38			ALL 0–6 O = 199			ALL 1–6 O = 184			B-cell common ALL 1–6 O = 167			other ALL 1–6 O = 17				
	O	SIRR	95% CI	O	SIRR	95% CI	O	SIRR	95% CI	O	SIRR	95% CI	O	SIRR	95% CI	O	SIRR	95% CI		
<10%	71	1.00	–	14	1.00	–	54	1.00	–	49	1.00	–	43	1.00	–	6	1.00	–		
10%–19%	118	1.19	[0.88–1.62]	15	0.76	[0.34–1.70]	102	1.35	[0.96–1.92]	94	1.37	[0.96–1.98]	86	1.43	[0.98–2.12]	8	0.96	[0.29–3.35]		
20%–29%	39	1.56	[1.03–2.34]	7	1.41	[0.48–3.74]	32	1.69	[1.05–2.66]	31	1.80	[1.11–2.89]	30	1.99	[1.20–3.24]	1	0.48	[0.01–3.93]		
⩾ 30%	13	2.10	[1.07–3.82]	2	1.61	[0.18–6.99]	11	2.35	[1.11–4.54]	10	2.36	[1.07–4.71]	8	2.15	[0.87–4.62]	2	3.89	[0.38–21.76]		
Non-isolated communes with population density ⩾ 5000/km²																				
% incomers from another *département*	AL 0–6 O = 228			AML 0–6 O = 39			ALL 0–6 O = 188			ALL 1–6 O = 173			B-cell common ALL 1–6 O = 154			other ALL 1–6 O = 19				
	O	SIRR	95% CI	O	SIRR	95% CI	O	SIRR	95% CI	O	SIRR	95% CI	O	SIRR	95% CI	O	SIRR	95% CI		
<15%	42	1.00	–	12	1.00	–	29	1.00	–	26	1.00	–	26	1.00	–	0	–	–		
15%–19%	44	1.18	[0.75–1.84]	8	0.75	[0.26–1.99]	36	1.40	[0.83–2.36]	33	1.43	[0.83–2.49]	30	1.30	[0.74–2.29]	3	–	–		
20%–24%	111	1.34	[0.93–1.96]	15	0.63	[0.28–1.48]	96	1.68	[1.10–2.64]	90	1.76	[1.13–2.84]	75	1.47	[0.93–2.39]	15	–	–		
⩾ 25%	31	1.42	[0.86–2.31]	4	0.64	[0.15–2.11]	27	1.79	[1.02–3.14]	24	1.78	[0.98–3.22]	23	1.70	[0.93–3.11]	1	–	–		

a Isolated *communes* were defined as non-pole *communes* from urban units of population less than 5000 people.

to vary with migration rates only in isolated *communes* with a population density of more than 50 people per km^2 and in non-isolated *communes* with more than 5000 people per km^2, and not in other *communes*. In particular, the present study, which focuses on the place of residence at the time of birth, was not appropriate to investigate Greaves hypothesis of a protective role of early common infections[32] supported by our previous case-control studies in the French childhood population.[33,34] Given the large variation in children habits within the defined categories of communes, density could not be considered a surrogate of early contacts between children. Therefore, it is unlikely that early common infections and population-mixing could confound each other in the present data.

The present study addressed population-mixing at the place of residence at the time of birth, while most studies have investigated place of residence at the time of diagnosis. However, the suspected viral infection is thought to occur in utero or in early infancy.[35] In addition, viral exposure early in life may be more likely to induce leukaemia than later exposure. Therefore, population-mixing at the place of residence at the time of birth rather than of diagnosis is particularly relevant.

Dickinson and colleagues[19] reported a strong association with a RR of 11.7 between the extreme groups of population-mixing in children born in West Cumbria. In that area, 53% of cases were estimated to be attributable to population-mixing. Focussing on a geographical area where an excess of cases has been observed is probably more likely to evidence epidemic features.

In conclusion, the present study addressed variables expressing isolation and population-mixing, which determine susceptible and infected subject frequencies, together with population density as an indicator of the opportunity of contacts between inhabitants. The present results do not actually support Kinlen's hypothesis in which the relationship between ALL incidence and population-mixing had to be observed in the most "rural" areas (isolated communes with less than 50 inhabitants per km^2). However, they are consistent with epidemic models, with higher risks of ALL observed under conditions of density and migration rates favourable to spread of infections. Further studies are needed to investigate the impact of population density on the relationship between leukaemia incidence and population-mixing. It would be of particular interest to see whether upper limits of population density are found for isolated and non-isolated geographic units in other countries.

Conflict of interest statement

None declared.

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REFERENCES

1. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet* 1988;**2**:1323–7.
2. Fox JP, Elveback L, Scott W, Gatewood L, Ackerman E. Herd immunity: basic concept and relevance to public health immunization practices. *Am J Epidemiol* 1971;**94**:179–89.
3. Anderson RM, May RM. Directly transmitted infections diseases: control by vaccination. *Science* 1982;**215**:1053–60.
4. Kinlen LJ, Hudson C. Childhood leukaemia and poliomyelitis in relation to military encampments in England and Wales in the period of national military service, 1950–63. *Br Med J* 1991;**303**:1357–62.
5. Kinlen LJ, John SM. Wartime evacuation and mortality from childhood leukaemia in England and Wales in 1945–9. *Br Med J* 1994;**309**:1197–202.
6. Kinlen LJ, O'Brien F, Clarke K, Balkwill A, Matthews F. Rural population-mixing and childhood leukaemia: effects of the North Sea oil industry in Scotland, including the area near Dounreay nuclear site. *Br Med J* 1993;**306**:743–8.
7. Kinlen LJ, Dickson M, Stiller CA. Childhood leukaemia and non-Hodgkin's lymphoma near large rural construction sites, with a comparison with Sellafield nuclear site. *Br Med J* 1995;**310**:763–8.
8. Kinlen LJ, Balkwill A. Infective cause of childhood leukaemia and wartime population-mixing in Orkney and Shetland, UK. *Lancet* 2001;**357**:858.
9. Dockerty JD, Cox B, Borman B, Sharples K. Population-mixing and the incidence of childhood leukaemias: retrospective comparison in rural areas of New Zealand. *Br Med J* 1996;**312**:1203–4.
10. Koushik A, King WD, McLaughlin JR. An ecologic study of childhood leukemia and population-mixing in Ontario, Canada. *Cancer Causes Control* 2001;**12**:483–90.
11. Dickinson HO, Hammal DM, Bithell JF, Parker L. Population-mixing and childhood leukaemia and non-Hodgkin's lymphoma in census wards in England and Wales, 1966–87. *Br J Cancer* 2002;**86**:1411–3.
12. Wartenberg D, Schneider D, Brown S. Childhood leukaemia incidence and the population-mixing hypothesis in US SEER data. *Br J Cancer* 2004;**90**:1771–6.
13. Boutou O, Guizard AV, Slama R, Pottier D, Spira A. Population-mixing and leukaemia in young people around the La Hague nuclear waste reprocessing plant. *Br J Cancer* 2002;**87**:740–5.
14. Law GR, Parslow RC, Roman E. Childhood cancer and population-mixing. *Am J Epidemiol* 2003;**158**:328–36.
15. Kinlen LJ, Clarke K, Hudson C. Evidence from population-mixing in British New Towns 1946–85 of an infective basis for childhood leukaemia. *Lancet* 1990;**336**:577–82.
16. Langford I. Childhood leukaemia mortality and population change in England and Wales 1969–73. *Soc Sci Med* 1991;**33**:435–40.
17. Laplanche A, de Vathaire F. Leukaemia mortality in French communes (administrative units) with a large and rapid population increase. *Br J Cancer* 1994;**69**:110–3.
18. Stiller CA, Boyle PJ. Effect of population-mixing and socioeconomic status in England and Wales, 1979–85, on lymphoblastic leukaemia in children. *Br Med J* 1996;**313**:1297–300.
19. Dickinson HO, Parker L. Quantifying the effect of population-mixing on childhood leukaemia risk: the seascale cluster. *Br J Cancer* 1999;**81**:144–51.
20. Parslow RC, Law GR, Feltbower R, Kinsey SE, McKinney PA. Population-mixing, childhood leukaemia, CNS tumours and other childhood cancers in Yorkshire. *Eur J Cancer* 2002;**38**:2033–40.
21. Kinlen LJ, Petridou E. Childhood leukemia and rural population movements: Greece, Italy, and other countries. *Cancer Causes Control* 1995;**6**:445–50.
22. Kinlen LJ, Hudson CM, Stiller CA. Contacts between adults as evidence for an infective origin of childhood leukaemia: an explanation for the excess near nuclear establishments in west Berkshire? *Br J Cancer* 1991;**64**:549–54.
23. Clavel J, Goubin A, Auclerc MF, Auvrignon A, Waterkeyn C, Patte C, et al. Incidence of childhood leukaemia and non-Hodgkin's lymphoma in France: National Registry of Childhood Leukaemia and Lymphoma, 1990–99. *Eur J Cancer Prev* 2004;**13**:97–103.
24. Le Jeannic T, Vidalenc J. Pôles urbains et périurbanisation – Le zonage en aires urbaines. *Insee Première*:516.
25. Bessy-Pietri P, Sicamois Y. Le zonage en aires urbaines en 1999–4 millions d'habitants en plus dans les aires urbaines. *Insee Première*:765.
26. http://www.insee.fr//fr//nom_def_met//nomenclatures//zonages_etudes//zonage_def/NZ1.PDF.
27. http://www.insee.fr//fr//nom_def_met//nomenclatures//zonages_etudes//zonage_def/NZ2.PDF.
28. http://www.insee.fr/fr/ico98/ico98.asp.
29. Breslow NE, Day NE. Statistical methods in cancer research, vol. II – The design and analysis of cohort studies. Lyon, IARC Scientific Publication No. 82, 1987.
30. Le Gléau J, Pumain D, Saint-Julien T. Towns of Europe: to each country its definition. *Economie et statistiques* 1996; **294–295**:9–23.
31. Moriconi-Ebrard F. *Geopolis, pour comparer les villes du monde*. Paris, Anthropos, Collection Villes, 1994.
32. Greaves MF. Aetiology of acute leukaemia. *Lancet* 1997;**349**:344–9.
33. Jourdan-Da Silva N, Perel Y, Mechinaud F, Plouvier E, Gandemer P, Lutz P, et al. Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. *Br J Cancer* 2004;**90**:139–45.
34. Perrillat F, Clavel J, Auclerc MF, Baruchel A, Leverger G, Nelken B, et al. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. *Br J Cancer* 2002;**86**:1064–9.
35. Kinlen LJ. Epidemiological evidence for an infective basis in childhood leukaemia. *Br J Cancer* 1995;**71**:1–5.