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Population mixing and the risk of childhood leukaemia in Switzerland: A census-based cohort study

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Abstract

Background: Childhood leukaemia (CL) may have an infectious cause and population mixing may therefore increase the risk of CL. We aimed to determine whether CL was associated with population mixing in Switzerland.

Methods: We followed children aged <16 years in the Swiss National Cohort 1990-2008 and linked CL cases from the Swiss Childhood Cancer Registry to the cohort. We calculated adjusted hazard ratios (HRs) for all CL, CL at age <5 years and acute lymphoblastic leukaemia (ALL) for three measures of population mixing (population growth, in-migration and diversity of origin), stratified by degree of urbanisation. Measures of population mixing were calculated for all municipalities for the 5-year period preceding the 1990 and 2000 censuses.

Results: Analyses were based on 2,128,012 children of whom 536 developed CL. HRs comparing highest with lowest quintile of population growth were 1.11 (95%Confidence Interval (CI): 0.65-1.89) in rural and 0.59 (95%CI: 0.43-0.81) in urban municipalities (interaction: p=0.271). Results were similar for ALL and for CL at age <5 years. For level of in-migration there was evidence of a negative association with ALL. HRs comparing highest with lowest quintile were 0.60 (95%CI: 0.41-0.87) in urban and 0.61 (95%CI: 0.30-1.21) in rural settings. There was little evidence of an association with diversity of origin.

Conclusion: This nationwide cohort study of the association between CL and population growth, in-migration and diversity of origin provides little support for the population mixing hypothesis.

Keywords: Population Mixing, Leukaemia, Children, Cohort Study, Switzerland

Introduction

The causes of childhood leukaemia (CL) are largely unknown. Only a minority of cases can be explained by established causes such as ionizing radiation or genetic syndromes [1, 2]. Population mixing was proposed by Kinlen in 1988 as an explanation for excesses of childhood leukaemia observed near the nuclear reprocessing plants at Dounreay and Sellafield [3]. Attempts to explain these excesses by ionizing radiation originating from the plants had failed [4]. Kinlen suggested that, because these areas were geographically isolated, the influx of workers might have led to local epidemics of a yet to be identified, presumably common and subclinical infection causing leukaemia in some of the children.

Since then, a number of studies have investigated leukaemia incidence or mortality in children following historic events of extreme population mixing, such as war time evacuation or large construction sites [5-9]. Other studies used census data to identify areas of increased population mixing. Common measures of population mixing include population growth [10-13], level of in-migration [14-16], or diversity of origin of migrants [17, 18].

A recent systematic review and meta-analysis of studies in which population mixing was measured as population growth showed a positive association between childhood leukaemia incidence and population mixing in rural but not urban areas [19]. No study has compared measures of population growth with other measures of population mixing in the same setting. Furthermore, most previous studies could not adjust analyses for potential confounders like ionizing radiation, socio-economic status, or traffic related air pollution. Apart from one case-control study [17], all previous studies were ecological.

Using a nationwide cohort design, we investigated whether the incidence of childhood leukaemia was elevated in Swiss municipalities experiencing high levels of population mixing. Based on the existing evidence [19], we hypothesized that a positive association would be found in rural but not in urban areas. We used population growth, in-migration, and diversity of origin of migrants as measures of population mixing and adjusted for several potential confounders.

Methods

Population

We included all children aged <16 years registered in the national censuses 1990 or 2000. Participation in these censuses was compulsory and coverage for 2000 was estimated to be 98.6%[20]. Data on these children were obtained from the Swiss National Cohort (SNC) [21], a longitudinal research platform that links records from the national censuses 1990 and 2000 with migration and mortality records. This allowed calculating individual follow-up time (time from census to emigration or death) between 1990 and 2008 for all individuals registered in the censuses.

Incident leukaemia cases were identified through probabilistic record linkage of the SNC with the Swiss Childhood Cancer Registry (SCCR), based on sex, nationality, date of birth, date of birth of parents, residential geo-codes at census and municipality of residence at census and at birth. All leukaemia cases diagnosed in Switzerland at age <16 years between the first census (4th December1990) and 31st December 2008 that were born before and diagnosed after a census (1990 or 2000) were eligible. The SCCR [22, 23] is a population-based registry including all children and adolescents diagnosed with a tumour classified according to the International Classification of Childhood Cancer, third edition [24] (ICCC-3). Completeness of the SCCR was above 91% throughout the study period, with coverage increasing to 96% in 2008 [25]. Addresses were geocoded using the database of geo-referenced buildings maintained by Swiss Post (GeoPost) or manually using the geoportal of the Swiss Federal Office of Topography (www.geo.admin.ch).

Outcomes

Outcomes were any leukaemia (ICCC-3 diagnostic group 1) and acute lymphoblastic leukaemia (ALL, ICCC-3 diagnostic group 1a) in children below 16 years of age; and any leukaemia in children below 5 years of age.

Municipalities

Population mixing was measured at the level of municipalities, the smallest administrative area in Switzerland. We used a classification from the Federal Statistical Office [26] to distinguish urban and rural municipalities. The classification has four categories, urban (main urban centres), semi-urban (urban agglomeration around centres) and isolated towns (towns without surrounding agglomeration) and rural. For the analyses, municipalities of the first three categories were

designated as urban. We merged neighbouring municipalities that underwent territorial changes (e.g. merges or exchanges of territory) to ensure consistent area boundaries between censuses.

Measures of Population Mixing

We used population growth, level of in-migration, and diversity of origin of migrants as measures of population mixing. All measures were calculated for each municipality and each census year (1990, 2000) based on population movements in the 5-year period preceding each census.

Population growth (PG) was calculated as the increase in population during the 5 year period as a proportion of the population 5 years before the census. Calculations were based on the annual population statistics at the municipality level compiled by the Swiss Federal Statistical Office. *Level of in-migration* (IM) was calculated as the proportion of the population at census that lived in a different municipality or abroad 5 years preceding the census based on information from the census questionnaire. *Diversity of origin* was measured using Shannon's Index (*H*)[27]:

$$H_i = -\sum_{j=1}^{M}\{p_{ij} \ln p_{ij}\},$$

where *M* represents the total number of areas of origin and p_{ij} the proportion of population of municipality *i* at time of census reporting to have lived in area of origin *j* 5 years preceding census. Areas of origin were assessed at the district level, an administrative area typically consisting of about 15 municipalities. In-migrants from abroad were designated a single area of origin.

Potential confounding

We considered factors that are potentially associated with location of residence and the risk of childhood leukaemia as potential confounders (supplementary Fig. S1). These included environmental exposures: traffic related air pollution (distance from place of residence to nearest highway in meters: <100, 100-<250, 250-<500, ≥500), exposure to ionizing background radiation (total external dose rates from cosmic and terrestrial sources at place of residence in nSv/h: <100, 100-<150, 150-<200, ≥200 [28]), exposure to electromagnetic fields (field strength from broadcast transmitters at place of residence [29] in V/m: <0.05, 0.05-<0.2, ≥0.2, distance to nearest high voltage powerline in meters: <100, 100-<250, 250-<500, ≥500); as well as household level variables: level of education of head of household (compulsory, upper secondary, tertiary), rent of accommodation in Swiss francs (quintiles) and crowding (number of persons per room in quintiles); an area-based measure of socio-economic status (SES): the Swiss neighbourhood index of socioeconomic position (Swiss-SEP) [Swiss-SEP, 30](quintiles).

Statistical Analysis

We used Cox proportional hazards regression to compare incidence of childhood leukaemia across quintiles of population mixing using the lowest quintile as reference category. Age was used as underlying time scale and follow-up time began at date of the first census the child was recorded in (4th December 1990 or 5th December 2000) and ended at the date of diagnosis, death, emigration, 16th birthday, or administrative censoring (31st December 2008), whichever occurred first. Exposure to population mixing was assessed at time of first census, and was updated at second census for children recorded in both censuses. Children linked to a non-eligible SCCR patient record (e.g. diagnosed with a cancer other than leukaemia or diagnosed before entering follow-up) from the SCCR were no longer considered at risk after diagnosis.

We fitted separate models for each exposure measure (population growth, level of in-migration, diversity of origin) with and without adjustment for listed potential confounders and fitted models stratified by urban and rural municipalities. We used likelihood ratio (LR) to test for the presence of an association between outcomes and exposure measures and for interaction between exposure measures and level of urbanisation. In further analyses, we estimated a linear dose response by including exposure measures as continuous variables. We fitted all models using STATA version 12.1.

Bias modelling and sensitivity analyses

The measure *H* is known to be a negatively biased estimator of Shannon's entropy in small samples, i.e. in small municipalities. In all models using diversity of origin as measure of population mixing, we therefore controlled for population size of the respective municipality. A number of alternative estimators have been proposed to account for this bias [31-33]. In a Monte Carlo experiment based on our data we compared the extent of bias and variance of different estimators. As sensitivity analyses, we repeated our main analyses excluding the municipalities with <100 in-migrants.

Results

Population

Of the 642 eligible incident cases, 539 (84%) could be linked to an SNC record, 3 were diagnosed after recorded emigration, leaving 536 cases for the time to event analysis (*Fig. 1*). The proportion of cases with ALL was somewhat higher among those included than among those not included into the analyses (supplementary *table S1*). The SNC included a total of 2,129,261 children aged <16 years at time of census. Of these, 1,249 children were diagnosed with a cancer before entry into the cohort, leaving 2,128,012 children included in time to event analysis (*Fig. 1*). Median follow-up time was 8.1 years, children had a median age of 6.6 years at entry into the cohort and 8.1 years at diagnosis. *Table 1* shows characteristics of included childhood leukaemia cases, number of children and person-years at risk.

Municipalities

Our analyses included 2,584 municipalities of which 920 (36%) were urban and 1,664 (64 %) were rural (*Table 2*). In 1990 median population size of these municipalities was 874 (range 22 to 345,795), median population density was 121 inhabitants per km^2 of productive land area (excluding water bodies and areas with no vegetation or only unproductive vegetation), and median population growth between 1985-90 was 6.4% (range -28% to 124%). Measures of population mixing tended to be higher in urban areas than in rural areas. They were similar for the periods 1985-90 and 1995-2000, except for population growth which tended to be higher in 1985-90 (Table 2). *Fig. 2* shows choropleth maps of Switzerland mapping the three measures of population mixing (population growth, level of in-migration, diversity of origin) and the level of urbanisation for all municipalities.

Association between childhood leukaemia and measures of population mixing

Table 3 shows the results from Cox regressions for population growth. For any leukaemia diagnosed before 16 years of age, when including all municipalities, we found evidence for a negative association between leukaemia incidence and population growth (*p* value from LR test: unadjusted model 0.094, fully adjusted model 0.008). The HR comparing the highest to the lowest quintile of population growth (which only contained municipalities with negative growth) was 0.78 (95% Confidence Interval (CI): 0.60-1.00) and 0.68 (0.52-0.88) in the crude and adjusted model respectively. The negative association was slightly stronger in urban municipalities - particularly when adjusting for confounding (*p* LR: 0.002, HR comparing the highest to the lowest quintile 0.59,

95%CI 0.43-0.81). We found no evidence of an association in rural municipalities and HR were close to 1 for all quintiles. However, the interaction test could not confirm a difference between urban and rural municipalities regarding the association between leukaemia risk and population growth (*p* LR: 0.271). Findings were broadly similar for ALL and for leukaemia in children aged <5 years. HRs for leukaemia diagnosed before 5 years of age tended to be greater than 1 for children in rural municipalities with high population, but confidence intervals were wide and LR tests showed no evidence of an association (*p* LR: 0.649) or of an interaction between rural and urban municipalities (*p* LR: 0.577).

There was evidence of a negative dose response relationship for population growth in the adjusted model for leukaemia diagnosed <16 years of age (HR per 100% increase 0.25, 95% CI 0.07-0.97, *p* LR: 0.045; online supplement *table S2*).

Table 4 shows the results from Cox regressions for level of in-migration. For leukaemia and ALL in children aged <16 years there was weak evidence of a reduced risk with higher levels of in-migration, particularly in urban areas and in fully adjusted models (*p* LR leukaemia: 0.098, *p* LR: ALL 0.062). However there was no evidence that this association differed between urban and rural municipalities (*p* LR: 0.790).

Table 5 shows the results from Cox regressions for diversity of origin. There was little evidence for any association between diversity of origin and childhood leukaemia except for leukaemia in children under 5 years (*p* LR: 0.047). However confidence intervals included 1 in all analyses and there was no evidence of interaction by urbanisation.

Bias modelling and sensitivity analyses

Considerable bias and variance of the Shannon Index were observed for municipalities with less than 100 in-coming migrants but none of the alternative measures performed better than *H* (*supplementary text S1 and fig. S1*). Estimates for diversity of origin did not change substantially in sensitivity analysis excluding communities with <100 in-migrants (*supplementary table S3*).

Discussion

This census-based cohort study in Switzerland found that population mixing, when measured as population growth, was negatively associated with childhood leukaemia in urban municipalities: a higher risk of childhood leukaemia was found in the lowest quintile of population growth which only contains municipalities with negative growth. In rural areas, point estimates were suggestive of a positive association between leukaemia risk and population growth as we had hypothesised, particularly for leukaemia occurring before the age of 5. However, statistical evidence for this association was weak and interaction tests did not confirm a difference between rural and urban areas. When using level of in-migration as a measure, there was again evidence of a negative association with leukaemia risk, and no indication of a difference between urban and rural municipalities. Little evidence of an association was found between childhood leukaemia risks and the diversity of origin of incoming migrants. Associations were strengthened when adjusted for a range of potential confounders including socio-economic factors, ionizing background radiation and proximity to highways and power lines.

Several studies have used routine data to investigate associations between childhood leukaemia and measures of population mixing. Studies looking at *population growth* mostly found a positive association between growth and incidence of childhood leukaemia for rural areas [3]. A Canadian study reported a positive association between population growth and leukaemia in rural areas of Ontario, particularly for ALL in <5 year olds, and a negative association in urban areas [11]. A study from the United States of America also found an increased risk of ALL in rural areas with high population growth [10]. Other studies reported an association between leukaemia and population growth without distinguishing between rural and urban areas [34, 35, 12, 36]. A negative association between population growth and leukaemia was reported in a study of French municipalities [13]. Studies looking at *level of incoming migrants* as measure for population mixing found contradictory results. Some studies did not find an association between in-migration levels and leukaemia [14, 37], while other studies found positive associations [16, 15, 38, 39]. Studies looking at *diversity of origin* also found mixed results: some found increased incidence rates with higher diversity [14, 39] and others negative associations between ALL and diversity [17, 18].

Limitations and strengths

This study shares several limitations with previous studies. Most importantly, there is no agreed definition or operationalization of population mixing. Though a number of measures have been used in the past, it remains unclear whether these actually identify areas at increased risk of localised

epidemics of infections that may be causing leukaemia [40]. The size of the municipalities in Switzerland varies greatly and data from larger municipalities may not have had the resolution to capture population mixing occurring at a smaller scale. The time frame of the exposure (5 years) is arbitrary and was given by the questionnaire design of the Swiss census. Our study did not account for population changes occurring before or after this period. Incomplete coverage of the SCCR and linkage errors are likely to have caused some misclassification of exposures and outcomes. Children were aged 0-15 years when they entered the cohort. It is possible that the older among these children were more likely to be immune to a putative leukemogenic infection and this may have diluted potential effects of population mixing in our study. However, this problem is less likely to have affected the analysis of the 0-4 year age group.

A main strength of our study is that it was based on individual-level data and included virtually the whole population. It is therefore essentially free of selection and response bias. The individual-level, time to event data ensured that exposures preceded the outcome and accounted for loss to follow-up by migration or death. Our study considered a variety of exposure measures, each capturing a different aspect of population mixing. For instance, for a municipality with a high population turnover, but where in-migration is roughly in balance with out-migration, population growth will be small while level of in-migration will be high. We measured population mixing over a 5-year period prior to two censuses. Compared to other studies that used shorter time frames reflecting short-term fluctuations [18, 14, 17] our measures are more likely to capture population trends over several years. We were able to adjust for a number of potentially important confounders. Few previous studies have considered potential confounding.

Interpretation of findings

Our findings of a decreased risk of leukaemia in urban municipalities experiencing population growth cannot be explained by Kinlen's hypothesis, which predicts a positive association in rural areas and the lack of an association in urban areas. It is possible that areas with large population growth differ from regions with low or negative growth regarding one or more risk factors for leukaemia not fully accounted for in our analyses. One such factor might be air pollution which was included in our analyses only through proximity to highways. All major city centres of Switzerland are in the lowest two quintiles of population growth while high population growth areas are mainly in the surrounding urban agglomeration. Air pollution levels also tends to be higher in city centres.

Another factor might be exposure to common childhood infections which is likely to be high in urban areas with high population growth. Greaves [41] suggested that early exposure to childhood

infections may be protective against leukaemia, whereas delayed exposure could result in abnormal immune responses and, in rare cases, to leukaemia. If children in urban areas with negative population growth were exposed to common infections at a later age than children in growing urban areas, Greaves' hypothesis is a possible explanation for the higher risk observed in the former compared to the latter.

Our findings in rural areas also provide little support for the population mixing hypothesis. Consistent with the hypothesis, leukaemia risks in children under 5 and risk for ALL under 16 tended to be higher in municipalities with high population growth. However tests of interaction did not suggest that the association between leukaemia and population growth differed between urban and rural areas. Assuming the population mixing hypothesis is true, our study might have lacked the statistical power to detect an association in rural areas (sufficient power for urban areas is demonstrated by the detection of a negative association). Alternatively, the hypothesised leukaemia causing infection may not have commonly occurred in localised epidemics in Switzerland or such epidemics were poorly captured by our measures of population mixing. Throughout the period of investigation the population of Switzerland was steadily growing (mainly through immigration) but there were no rapid population shifts comparable to those reported in other studies, for example war time evacuations. Also, residential mobility was not markedly lower in rural areas compared to urban areas of Switzerland and the remote alpine regions in Switzerland have for a long time been frequented by large numbers of tourists. Herd immunity to common infections might therefore be high even in rural areas. Our measures of population mixing would thus fail to reflect any increased risk of epidemics.

To conclude, this nationwide cohort study suggests that population increases in urban areas are associated with a decreased risk of childhood leukaemia. Overall, the study therefore provides little support for the population mixing hypothesis proposed by Kinlen.

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Compliance with Ethical Standards

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Conflict of interest

The authors declare that they have no conflict of interest

Ethical approval

Approval of the study was granted through the general cancer registry permission of the Swiss Childhood Cancer Registry by the ethics committee of the canton of Bern.

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Tables

Table 1: Characteristics of childhood leukaemia cases, number of children at risk and person-years of follow-up

	Age group	
	0-4 years	0-16 years
No. of leukaemia cases (ICCC*)	147 (100.0%)	536 (100.0%)
(1a) Acute lymphoblastic leukaemia	130 (88.4%)	420 (78.4%)
(1b) Acute myeloid leukaemia	13 (8.8%)	82 (15.3%)
(1c) Chronic myeloproliferative diseases	0 (0.0%)	9 (1.7%)
(1d) Myelodysplastic syndrome	2 (1.3%)	16 (3.0%)
(1e) Unspecified and other specified leukaemia	2 (1.3%)	6 (1.1%)
No. of leukaemia cases in a rural region	33 (22.4%)	151 (28.1%)
Gender		
Male	86 (58.5%)	319 (59.5%)
Female	61 (41.5%)	217 (40.5%)
Median age at diagnosis in years (IQR**)	3.3 (2.4-4.04)	8.1 (4.7-12.2)
No. of children at risk	794'473	2'128'012
Person-years at risk	1'959'394	16'412'861

**ICCC, International Classification of Childhood Cancer, **IQR= Interquartile range*

Table 2: Characteristics of municipalities in Switzerland

		Municipalities					
		all		urban		rural	
N		2,584		920	(35.60%)	1,664	(66.40%)
		median	range	median	range	median	range
Population size	1990	874	22 to 345,795	2087	56 to 345,795	560	22 to 9,908
Population density[a]	1990	121	2 to 11,136	374	18 to 11,136	77	18 to 1,399
Population growth[b]	1985-1990	6%	-28 to 124%	75%	-11% to 101%	6%	-28% to 124%
Level of in-migration[c]	1985-1990	24%	0% to 67%	27%	9% to 59%	22%	0% to 67%
Diversity of origin[d]	1985-1990	2.24	0.00 to 3.73	2.32	0.66 to 3.39	2.20	0.00 to 3.73
Population size	2000	974	12 to 333,259	2340	65 to 333,259	607	12 to 10,403
Population density[a]	2000	136	2 to 11,586	443	21 to 11,586	85	2 to 1765
Population growth[b]	1995-2000	26%	-50% to 78%	46%	-39% to 44%	10%	-50% to 78%
Level of in-migration[c]	1995-2000	23%	0% to 75%	26%	5% to 46%	21%	0% to 75%
Diversity of origin[d]	1995-2000	2.17	0.00 to 3.61	2.20	0.37 to 3.52	2.15	0.00 to 3.61

[a] Number of inhabitants per square km of productive land area within municipalities;[b] Percent population increase relative to populations in 1985 and 1995, respectively; [c] Percent in-migrated population relative to populations in 1990 and 2000, respectively; [d] Shannon-Index of in-migrated population

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Tabelle 3. Time to event analysis for population growth

Outcome	Population growth	All municipalities		Rural municipalities		Urban municipalities		Test for interaction[a]	
	(quintiles)	Crude	Adjusted[b]	Crude	Adjusted[b]	Crude	Adjusted[b]	Crude	Adjusted[b]
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		
All leukaemia, <16 y	1	1	1	1	1	1	1	0.603	0.271
	2	0.82 (0.64 - 1.06)	0.78 (0.60 - 1.01)	1.09 (0.63 - 1.90)	1.13 (0.65 - 1.96)	0.77 (0.58 - 1.04)	0.73 (0.54 - 0.98)		
	3	0.71 (0.54 - 0.92)	0.64 (0.49 - 0.84)	0.98 (0.56 - 1.71)	0.94 (0.53 - 1.67)	0.66 (0.48 - 0.89)	0.59 (0.43 - 0.80)		
	4	0.76 (0.58 - 0.98)	0.68 (0.52 - 0.89)	1.07 (0.62 - 1.84)	1.07 (0.62 - 1.87)	0.70 (0.51 - 0.94)	0.60 (0.44 - 0.82)		
	5	0.78 (0.60 - 1.00)	0.68 (0.52 - 0.88)	1.11 (0.66 - 1.87)	1.11 (0.65 - 1.89)	0.71 (0.52 - 0.96)	0.59 (0.43 - 0.81)		
Acute lymphoblastic leukaemia, <16 y	1	1	1	1		1	1	0.486	0.262
	2	0.90 (0.67 - 1.20)	0.86 (0.64 - 1.15)	1.34 (0.70 - 2.53)	1.40 (0.74 - 2.67)	0.82 (0.59 - 1.14)	0.78 (0.56 - 1.09)		
	3	0.76 (0.56 - 1.03)	0.70 (0.51 - 0.95)	1.27 (0.67 - 2.42)	1.25 (0.65 - 2.39)	0.67 (0.47 - 0.95)	0.60 (0.42 - 0.86)		
	4	0.83 (0.62 - 1.12)	0.75 (0.56 - 1.02)	1.22 (0.64 - 2.31)	1.25 (0.65 - 2.41)	0.77 (0.55 - 1.08)	0.67 (0.48 - 0.96)		
	5	0.78 (0.58 - 1.05)	0.68 (0.50 - 0.92)	1.17 (0.63 - 2.19)	1.22 (0.64 - 2.30)	0.71 (0.50 - 1.01)	0.58 (0.40 - 0.85)		
All leukaemia, <5 y	1	1	1	1	1	1	1	0.582	0.577
	2	0.82 (0.49 - 1.36)	0.78 (0.46 - 1.30)	1.46 (0.35 - 6.09)	1.54 (0.37 - 6.46)	0.77 (0.44 - 1.34)	0.72 (0.41 - 1.27)		
	3	0.93 (0.57 - 1.53)	0.88 (0.53 - 1.46)	1.85 (0.48 - 7.14)	2.05 (0.53 - 7.97)	0.86 (0.50 - 1.50)	0.77 (0.44 - 1.36)		
	4	0.96 (0.58 - 1.57)	0.90 (0.54 - 1.49)	2.50 (0.69 - 9.08)	2.98 (0.81 - 10.95)	0.80 (0.46 - 1.41)	0.69 (0.39 - 1.24)		
	5	0.93 (0.56 - 1.52)	0.86 (0.51 - 1.43)	1.79 (0.47 - 6.73)	2.16 (0.56 - 8.29)	0.89 (0.51 - 1.56)	0.74 (0.41 - 1.32)		

CI confidence interval; HR hazard ratio

[a] *Likelihood ratio test interaction between population growth and urbanity*

[b] *adjusted for level of education of head of household, flat rent, crowding, the Swiss neighbourhood index of socioeconomic position, distance to highways, ionizing background radiation (dose rates from terrestrial gamma and cosmic radiation), electromagnetic fields from broadcast transmitters, distance to high voltage power lines*

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Tabelle 4. Time to event analysis for level of in-migration

Outcome	Level of in-migration (quintiles)	All municipalities		Rural municipalities		Urban municipalities		Test for interaction[a]	
		Crude HR (95% CI)	Adjusted[b] HR (95% CI)	Crude HR (95% CI)	Adjusted[b] HR (95% CI)	Crude HR (95% CI)	Adjusted[b] HR (95% CI)	Crude	Adjusted[b]
All leukaemia, <16 y	1	1	1	1	1	1	1	0.863	0.790
	2	0.96 (0.74 - 1.24)	0.95 (0.73 - 1.23)	1.11 (0.74 - 1.68)	1.18 (0.76 - 1.81)	0.83 (0.59 - 1.15)	0.80 (0.57 - 1.11)		
	3	0.77 (0.59 - 1.01)	0.76 (0.57 - 1.00)	0.76 (0.44 - 1.31)	0.80 (0.45 - 1.40)	0.69 (0.49 - 0.96)	0.66 (0.47 - 0.93)		
	4	0.93 (0.72 - 1.20)	0.86 (0.66 - 1.13)	0.93 (0.57 - 1.51)	0.97 (0.58 - 1.63)	0.83 (0.60 - 1.15)	0.74 (0.53 - 1.03)		
	5	0.79 (0.60 - 1.03)	0.73 (0.55 - 0.96)	0.75 (0.44 - 1.29)	0.69 (0.38 - 1.24)	0.71 (0.51 - 0.99)	0.65 (0.46 - 0.92)		
Acute lymphoblastic leukaemia, <16 y	1	1	1	1	1	1	1	0.873	0.739
	2	0.83 (0.62 - 1.11)	0.81 (0.60 - 1.09)	0.93 (0.57 - 1.50)	1.01 (0.61 - 1.68)	0.72 (0.49 - 1.04)	0.69 (0.47 - 1.00)		
	3	0.72 (0.53 - 0.98)	0.71 (0.52 - 0.97)	0.82 (0.46 - 1.46)	0.90 (0.49 - 1.66)	0.62 (0.43 - 0.90)	0.59 (0.40 - 0.86)		
	4	0.91 (0.68 - 1.20)	0.83 (0.62 - 1.13)	0.94 (0.55 - 1.60)	1.03 (0.58 - 1.83)	0.80 (0.56 - 1.14)	0.70 (0.48 - 1.01)		
	5	0.73 (0.54 - 0.98)	0.66 (0.48 - 0.91)	0.64 (0.34 - 1.21)	0.61 (0.30 - 1.21)	0.66 (0.46 - 0.95)	0.60 (0.41 - 0.87)		
All leukaemia, <5 y	1	1	1	1	1	1	1	0.681	0.571
	2	1.51 (0.90 - 2.53)	1.50 (0.88 - 2.54)	0.81 (0.31 - 2.13)	0.92 (0.34 - 2.48)	1.84 (0.92 - 3.67)	1.79 (0.89 - 3.58)		
	3	1.17 (0.68 - 2.01)	1.14 (0.65 - 1.99)	0.79 (0.26 - 2.41)	0.93 (0.29 - 2.95)	1.28 (0.63 - 2.61)	1.21 (0.59 - 2.49)		
	4	1.33 (0.78 - 2.25)	1.24 (0.72 - 2.15)	0.87 (0.31 - 2.44)	1.05 (0.35 - 3.12)	1.48 (0.73 - 2.98)	1.33 (0.65 - 2.71)		
	5	1.05 (0.60 - 1.82)	0.98 (0.55 - 1.74)	0.94 (0.34 - 2.64)	1.15 (0.38 - 3.45)	1.08 (0.52 - 2.25)	0.97 (0.46 - 2.04)		

CI confidence interval; HR hazard ratio

[a] *Likelihood ratio test interaction between population growth and urbanity*

[b] *adjusted for level of education of head of household, flat rent, crowding, the Swiss neighbourhood index of socioeconomic position, distance to highways, ionizing background radiation (dose rates from terrestrial gamma and cosmic radiation), electromagnetic fields from broadcast transmitters, distance to high voltage power lines*

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Tabelle 5. Time to event analysis for diversity of origin

Outcome	Diversity of origin (quintiles)	All municipalities		Rural municipalities		Urban municipalities		Test for interaction[a]	
		Crude	Adjusted[b]	Crude	Adjusted[b]	Crude	Adjusted[b]	Crude	Adjusted[b]
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		
All leukaemia, <16 y	1	1	1	1	1	1	1	0.988	0.994
	2	0.94 (0.71 - 1.25)	0.93 (0.70 - 1.24)	0.98 (0.59 - 1.60)	1.01 (0.61 - 1.68)	0.97 (0.69 - 1.37)	0.90 (0.64 - 1.28)		
	3	1.00 (0.76 - 1.32)	0.95 (0.72 - 1.26)	1.02 (0.61 - 1.72)	0.99 (0.58 - 1.70)	1.05 (0.75 - 1.46)	0.93 (0.66 - 1.31)		
	4	1.14 (0.87 - 1.50)	1.13 (0.85 - 1.49)	1.35 (0.80 - 2.25)	1.41 (0.83 - 2.40)	1.15 (0.83 - 1.60)	1.05 (0.75 - 1.46)		
	5	1.18 (0.88 - 1.59)	1.14 (0.85 - 1.55)	1.30 (0.71 - 2.39)	1.35 (0.72 - 2.52)	1.20 (0.85 - 1.69)	1.07 (0.76 - 1.53)		
Acute lymphoblastic leukaemia, <16 y	1	1	1	1	1	1	1	0.901	0.922
	2	1.00 (0.73 - 1.39)	1.00 (0.72 - 1.40)	1.10 (0.63 - 1.93)	1.18 (0.67 - 2.10)	0.99 (0.66 - 1.49)	0.91 (0.61 - 1.38)		
	3	1.06 (0.77 - 1.46)	1.01 (0.73 - 1.40)	1.03 (0.57 - 1.88)	1.03 (0.55 - 1.93)	1.12 (0.76 - 1.64)	0.99 (0.67 - 1.46)		
	4	1.31 (0.96 - 1.77)	1.30 (0.95 - 1.78)	1.30 (0.71 - 2.36)	1.43 (0.77 - 2.66)	1.39 (0.96 - 2.02)	1.25 (0.86 - 1.82)		
	5	1.25 (0.89 - 1.76)	1.22 (0.86 - 1.73)	1.54 (0.78 - 3.01)	1.67 (0.84 - 3.34)	1.23 (0.82 - 1.83)	1.09 (0.73 - 1.63)		
All leukaemia, <5 y	1	1	1	1	1	1	1	0.545	0.547
	2	1.09 (0.64 - 1.86)	1.06 (0.62 - 1.82)	1.94 (0.65 - 5.80)	2.06 (0.68 - 6.25)	0.88 (0.47 - 1.65)	0.79 (0.42 - 1.50)		
	3	0.81 (0.46 - 1.44)	0.77 (0.43 - 1.38)	1.53 (0.47 - 5.05)	1.63 (0.48 - 5.47)	0.66 (0.34 - 1.30)	0.59 (0.30 - 1.16)		
	4	1.43 (0.86 - 2.37)	1.33 (0.79 - 2.24)	1.73 (0.52 - 5.82)	1.89 (0.55 - 6.45)	1.44 (0.82 - 2.53)	1.23 (0.69 - 2.20)		
	5	1.14 (0.65 - 2.02)	1.05 (0.59 - 1.88)	1.27 (0.28 - 5.74)	1.39 (0.30 - 6.50)	1.20 (0.64 - 2.25)	1.04 (0.55 - 1.96)		

CI confidence interval; HR hazard ratio

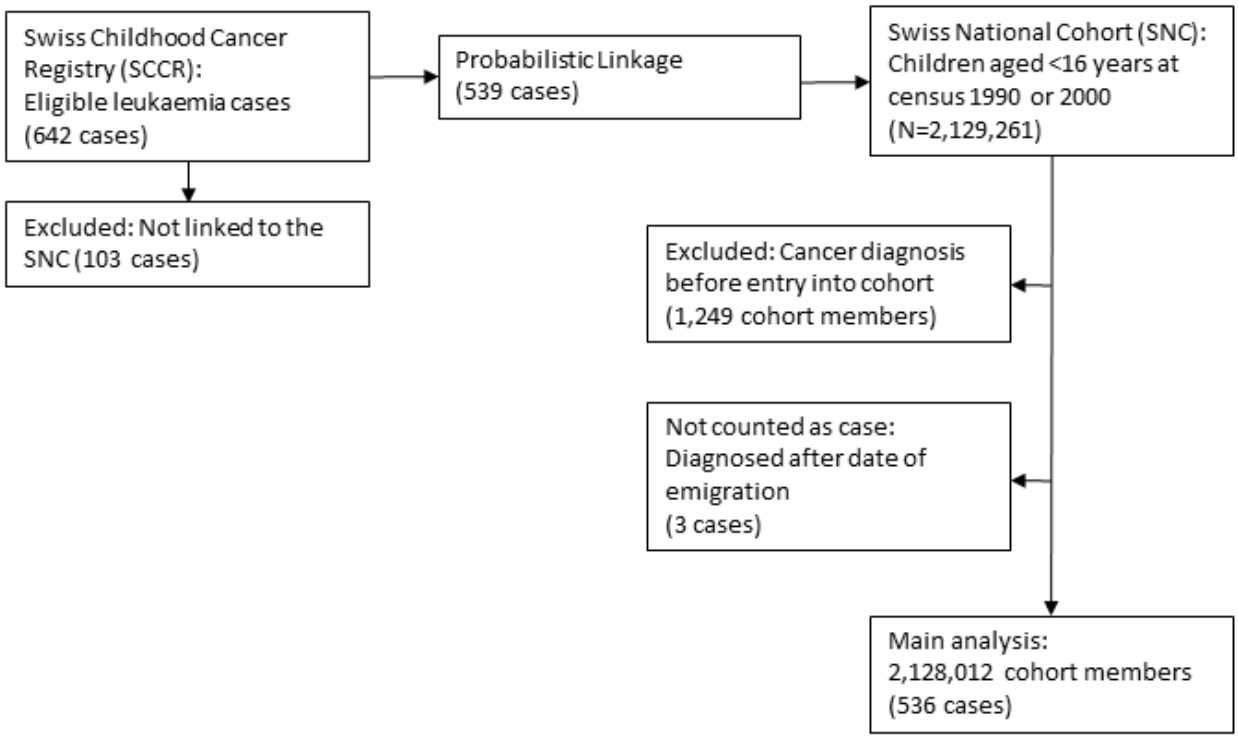
[a] *Likelihood ratio test interaction between population growth and urbanity*

[b] *adjusted for level of education of head of household, flat rent, crowding, the Swiss neighbourhood index of socioeconomic position, distance to highways, ionizing background radiation (dose rates from terrestrial gamma and cosmic radiation), electromagnetic fields from broadcast transmitters, distance to high voltage power lines*

Figures Titles

Fig. 1. Flow chart of leukaemia cases and cohort members

Fig. 2. Population growth, level of in-migration, diversity of origin and level of urbanisation for all Swiss municipalities as of date of census 2000.



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