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Temporal association between childhood leukaemia and population growth in Swiss municipalities

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Abstract

Background: The population mixing hypothesis proposes that childhood leukaemia (CL) might be a rare complication to a yet unidentified subclinical infection. Large population influxes into previously isolated rural areas may foster localised epidemics of the postulated infection causing a subsequent increase of CL. While marked population growth after a period of stability was central to the formulation of the hypothesis and to the early studies on population mixing, there is a lack of objective criteria to define such growth patterns. We aimed to determine whether periods of marked population growth coincided with increases in the risk of CL in Swiss municipalities.

Methods: We identified incident cases of CL aged 0-15 years for the period 1985-2010 from the Swiss Childhood Cancer Registry. Annual data on population counts in Swiss municipalities were obtained for 1980-2010. As exposures, we defined (i) cumulative population growth during a 5-year moving time window centred on each year (1985-2010) and (ii) periods of 'take-off growth' identified by segmented linear regression. We compared CL incidence across exposure categories using Poisson regression and tested for effect modification by degree of urbanisation.

Results: Our study included 1,500 incident cases and 2,561 municipalities. The incident rate ratio (IRR) comparing the highest to the lowest quintile of 5-year population growth was 1.18 (95%-CI: 0.96, 1.46) including all municipalities and 1.33 (95%-CI: 0.93, 1.92) in rural municipalities only (p-value interaction 0.36). In municipalities with take-off growth, the IRR comparing the take-off period (>6% annual population growth) with the initial period of low or negative growth (<2%) was 2.07 (95%-CI 0.95, 4.51) overall and 2.99 (1.11, 8.05) in rural areas (p interaction 0.52).

Conclusions: Our study provides further support for the population mixing hypothesis and underlines the need to distinguish take-off growth from other growth patterns in future research.

Keywords: population mixing, leukaemia, infections, childhood cancer, take-off growth

Introduction

The aetiology of childhood leukaemia (CL) is still poorly understood. The population mixing hypothesis proposes that CL might be a rare complication to a yet unidentified subclinical infection [1, 2]. Population influxes after a period of stable population - for instance immigration of the workforce needed for a new large-scale construction site into a previously isolated rural area - may foster localised epidemics of the postulated infection causing a subsequent increase in the incidence of CL. The population mixing hypothesis was originally proposed as an explanation for the higher incidence rates observed close to the nuclear reprocessing plants at Dounreay and Sellafield which could not be linked to ionizing radiation emanating from these installations [3].

Subsequently associations were reported for other historical events that involved extreme population mixing such as wartime movements [4, 5], large industrial sites [6, 7] or the creation of new towns [8]. All of these studies found an increased risk for childhood leukaemia during the period of population mixing. Results from other studies using census data to measure population mixing were less consistent [9-14]. These studies measured population growth or in-migration between census time points or over a defined period prior to the census to identify areas with higher population mixing. The advantage of these more objective measures is that they are widely applicable and can be compared across countries. Their main drawback is that they fail to take into account longer time-periods, leaving it unclear whether population increases followed periods of stable population or had already commenced a long time before the measured time window. Thus, they poorly capture the type of population mixing that is central to the hypothesis. Apart from investigating specific historical events, there is a lack of objective measures of population mixing that capture marked population growth following periods of stability based on commonly available population data. Only few studies have investigated the temporal association between such increases and the risk of CL, i.e. whether risks are higher during the growth period compared to the stable period [15, 8, 4].

In this study, we aimed to determine whether periods of marked population growth coincide with increases in the risk of CL and acute lymphoblastic leukaemia (ALL) in Swiss municipalities from 1985-2010. We developed two objective measures of growth, which can be used to contrast periods of high and low growth within municipalities. First, we identified periods of population growth based on average population change during a moving 5-year window. Second, we identified periods of marked population growth following periods of low growth (take-off growth) using segmented linear regression.

Methods

Population

We identified incident cases of leukaemia in children from the Swiss Childhood Cancer Registry (SCCR). All cases diagnosed in the period 1985-2010 who were aged 0-15 years and resident in Switzerland at the time of diagnosis were included. The SCCR [16, 17] 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 [18] (ICCC-3). Completeness of the SCCR was above 91% throughout the study period; since the mid-1990s coverage has been around 95% [19].

Population counts were available for census years (1980, 1990, 2000, 2010) by municipality, age and sex from the Swiss National Cohort Study [20, 21]. Total population in municipalities (permanent residents only) for all years between these censuses were obtained from the Swiss Federal Statistical Office. These figures are based on the decennial census counts sequentially updated with annual population changes due to births, deaths and migration.

Outcomes

Outcomes were any leukaemia (ICCC-3 diagnostic group I) and acute lymphoblastic leukaemia (ALL; ICCC-3 diagnostic group Ia) diagnosed in children below 16 years of age.

Measures of population mixing

We measured population mixing at the level of municipalities, the smallest administrative area in Switzerland. We merged all neighbouring municipalities that underwent territorial changes to ensure consistent area boundaries throughout the study-period (1980-2010). We used a classification scheme from the Federal Statistical Office to distinguish rural municipalities from urban and semi-urban areas [22].

We measured population mixing using two separate approaches as follows:

Approach A (5-year growth): This approach measures relative population growth over a moving time window of 5 years. For each municipality and year (1985-2008) we calculated population growth during a 5-year period centred on that year as percentage of the 1980 population:

$$5 - year\ relative\ change\ in\ year\ t = \frac{Pop_{t+2} - Pop_{t-3}}{Pop_{80}},$$

where Pop_t is the total population at the end of year t.

Approach B (take-off growth): This approach aimed to identify calendar periods with distinct levels of average growth. We standardised annual population counts for each municipality for the years 1981-2010 by dividing by the population in 1980. We fitted segmented linear regression models with two variable breakpoints using the standardized population growth as dependent variable and calendar year as independent variable. The models were fitted using the package 'segmented' in the R environment for statistical computing version 3.1.3 [23, 24]. This method simultaneously estimates breakpoints and regression slopes of a continuous piece-wise linear regression line.

The three periods (i = 1,2,3) of each segmented regression were classified according to whether their respective slopes s_i (these correspond to mean annual growth relative to the 1980 population) were below a lower threshold a ($s_i < a$) (low growth period), above an upper threshold b ($s_i > b$) (high growth period) or between these two ($a <= s_i <= b$). We defined periods of "take-off growth" as periods of high population growth ($s_i > b$) following a period of low growth ($s_j < a$ for $j<i$) (Fig. S1). We used four pre-specified combinations of threshold values with a = 1% or 2% and b = 4% or 6%, respectively. The four combinations of threshold values are nested in each other with the combination a = 2% b = 4% containing all the other combinations. More details on the definition of take-off growth are provided in the online supplementary material.

Statistical analyses

We calculated person-years at risk for all Swiss residents aged 0-15 years at diagnosis by sex, age group (0-4, 5-9, 10-15), calendar year (1980-2010) and municipality. In order to do this we calculated the fraction of the total population in each municipality belonging to each sex and age group in census years (1980, 1990, 2000, 2010). Corresponding fractions for the years between censuses were obtained through linear interpolation. For a given municipality, we then calculated person years as the product of these fractions and the total population of that municipality. Incident cases of cancer were identified from the SCCR and assigned to municipalities and calendar years according to their place of residence at diagnosis. This resulted in a multilevel dataset with multiple records (calendar years) per municipality containing numbers of person-years and cases.

We investigated associations between CL incidence and population mixing using Poisson regression models adjusting for sex, age group (0-4, 5-10, 10-15), year category (5-year blocks) and language region (German, French, Italian). Since the existence of a general cantonal cancer registry might have affected the completeness of registration in a canton [25] we also adjusted for this using a time-varying dichotomous variable indicating the presence or absence of such a registry. We also ran Poisson regression models including a random effects term on the intercept to allow for varying average incidence rates across municipalities. These random effects account for any purely spatial differences such that model estimates only contrast temporal differences within municipalities, i.e. periods of high vs. low population growth. We also investigated effect modification by degree of urbanisation (urban/rural). Incidence rate ratios (IRR) and their 95% confidence intervals (CI) were calculated from these models.

For approach A (5-year growth) the exposure of interest, 5-year relative change, was divided into quintiles with the lowest quintile (lowest growth) set as reference category. We also fitted models with the outcome variable shifted by a 1 to 4-year lag after exposure. This allows for possible latent periods between population growth and the onset of overt CL.

For approach B (take-off growth) we calculated incidence rate ratios for periods of intermediate growth ($a <= s <= b$) and high growth ($s > b$) compared to periods of low growth ($s < a$). This was done for all four possible combinations of a = 1% or 2% and b = 4% or 6%. Models were fitted separately including all municipalities and including only municipalities with take-off growth.

Results

We identified 1,500 incident cases of CL diagnosed 1985-2010 under the age of 16 years and resident in Switzerland at time of diagnosis. Of these 1,191 (80%) were diagnosed with ALL and 862 (58%) were male (supplementary Table S2). Overall, our analyses included 39.7 million person-years at risk over the period 1985-2010 across 2,561 municipal entities (after accounting for boundary changes; hereinafter referred to simply as 'municipalities'). Of these municipalities, 1,651(64%) were rural and 396 (15.5%) could be classified as municipalities with take-off growth based on threshold value combinations of mean annual population growth of below a = 1% or 2% (low growth period) and above b = 4% or 6% (high growth period) (Table 1). Median population size was 794 in 1980 increasing to 1,151 in 2010, and average annual population growth over this period had a median of 1% (Table 1).

Table 2 shows the results of analyses of the association between CL and 5-year growth (approach A). Analysing all municipalities combined, the IRR comparing the highest with the lowest quintile was 1.18 (95% CI: 0.96-1.46, p likelihood ratio (LR) test for no differences between quintiles: 0.50) and 1.33 (95% CI: 0.35-1.92, p LR test: 0.30) for rural municipalities only. There was no evidence of effect modification by degree of urbanisation (p LR test: 0.36). Similarly, there was little evidence of an association between leukaemia incidence and 5-year growth or for effect modification by degree of urbanisation when we accounted for different latent periods between population growth and CL (Supplementary Tables S3-S6). Results for ALL were also similar (Supplementary Table S7).

Segmented linear regressions used to define municipalities with take-off growth (approach B) generally showed a good fit to annual growth curves (Some randomly selected examples are shown in Fig. 1); however, in some cases three breakpoints might have been more appropriate. Among municipalities with take-off growth, the high growth period was most marked if it was preceded and followed by a low growth period (Fig. 2). Municipalities with take-off growth were distributed across the whole country (Fig. 3).

Table 3 shows the results of analyses comparing high and low growth periods. Here periods of high mean annual growth relative to 1980 population ($s > b$) or medium growth ($a \leq s \leq b$) are compared to periods of low growth ($s < a$) for different thresholds (a, b) without taking into account the sequence of these periods, i.e. disregarding take-off growth. Including all municipalities, IRRs tended to be higher for periods of high annual growth compared to periods of low growth, but there was little evidence for an association ($p > 0.4$). When we included only rural municipalities, IRRs for periods of high growth were about 1.45. While lower bounds of 95%-CIs exceeded unity for the annual growth threshold of $b = 4\%$, p-values did not show strong evidence of an association ($p > 0.1$) (Table 3). There was little evidence of effect modification by degree of urbanisation (p LR test: 0.15).

Restricting the analyses only to municipalities with take-off growth, effect estimates were consistently higher, particularly in rural areas for periods with annual growth exceeding 6% (Table 4 and Fig. 4); IRRs were 2.37 (95%-CI: 0.63, 8.85) when comparing to low growth of <1%, and 2.99 (95%-CI: 1.11, 8.05) comparing to low growth of <2%. However, the number of cases observed during periods of high growth was low; LR tests provide only weak evidence of association ($p > 0.1$). There was no evidence for differences between rural and urban municipalities except for the least restrictive combination of cut-offs ($a = 2\%$, $b = 4\%$; p interaction: 0.06).

In separate analyses of cases of ALL, the pattern of associations was more pronounced with evidence of association both in urban and rural municipalities for growth periods exceeding 6% annually (Table 5). In rural areas, IRRs for ALL comparing the take-off growth period to the low growth period exceeded 4 ($a = 1\%$, $b = 6\%$: IRR: 5.61, 95%CI: 1.26-21.10, p LR: 0.043; $a = 2\%$, $b = 6\%$: IRR: 4.89, 95%CI: 1.74-13.71, p LR: 0.006). Results from models including random intercepts for municipalities were highly similar (data not shown).

Discussion

Summary of results

In this study, we investigated whether the risk of developing CL was increased during periods of higher population growth compared to periods of low growth in Swiss municipalities using two different measures of population growth. Taking 5-year moving average growth as growth measure, we found little evidence for an association with risks of CL although risks tended to be higher during periods of higher growth. Using segmented linear regression to identify periods with average annual growth above specific thresholds, we found some evidence of an increased risk of CL in rural municipalities during periods with annual growth above 4%. When we restricted the analyses to municipalities with take-off growth (defined as periods of high growth following low growth as identified by segmented linear regression), we found evidence of an increased risk of ALL during periods of high growth exceeding 6% both in urban and rural areas. There was little or only weak evidence for effect modification by degree of urbanisation in all models.

Comparison to other studies

Previous studies that tried to isolate events of extreme population mixing to analyse the association with CL incidence mostly focused on specific historical events. Our study is best compared with studies that have investigated a temporal association, i.e. that have calculated rates during the event of interest as well as rates before or after the event. One such study found an excess of leukaemia mortality in rural new towns during the main growth period compared to national rates but not thereafter [8]. Another study found that leukaemia mortality was increased for children exposed to wartime population mixing in Orkney and Shetland, where many servicemen were stationed, compared to children from the post war period, when servicemen had left [4]. A third study found an excess risk of leukaemia incidence during the construction period of large construction sites and the year after compared to national rates, but not during the 5-year periods before construction and after completion [15]. In contrast to these historical studies, we identified municipalities and periods with rapid growth based purely on routine population statistics without any indication of historical events that may have caused particularly rapid migration movements. The increases we identified do not appear to be abnormally high and are less dramatic than the historical events previously investigated by these studies.

In our own previous study [26], we had used a nationwide cohort study approach and did not find an increased incidence of CL in municipalities with high population mixing. However, as commonly done in other studies, we had measured population growth only during a fixed (5-year) period preceding census points irrespective of the pattern of population change before or after that period. This approach cannot capture the starting point of population increases, i.e. take-off population growth. Similarly, a number of other studies have used population increases or in-migration of short time periods (irrespective of prior growth) to measure population mixing [10, 13, 12, 9]. Other measures of population mixing that have been studied in relation to the risk of childhood leukaemia include diversity of place of origin of in-migrants [27, 14], social contacts at parents' workplace [28-30], or population density [31-33]. The results of these studies are heterogeneous.

Strengths and weaknesses

The main strength of our study was that we were able to analyse population mixing over an extensive period allowing us to identify municipalities with periods of high growth following an initial period of low growth (take-off growth). This corresponds more closely to the population mixing events – such as the influx of workers into the village of Seascale, north-west England, during construction and operations of the Sellafield nuclear fuel reprocessing plant - that motivated Kinlen's hypothesis [1]. Our measures of population growth and take-off growth were defined *a priori* and can be reproduced in different settings provided annual population data for extensive periods are available. Our analyses were not restricted to a singular historical event or to periods dictated by census time points. Incident cases were identified from a population-based registry with high coverage during the study period.

A major weakness that our study shares with other studies is that we were only able to test indirect measures of exposure to infections based on population growth. We could not verify whether the identified periods of high growth were indeed associated with higher transmission rates of a particular infection in the respective municipalities. Furthermore, some municipalities were quite large in size or population, or both, which might have diluted very localised effects. The segmented linear regression models with two variable breakpoints might have been too imprecise for some municipalities for which three breakpoints or only one would have provided a better fit. Restricting the analyses to the municipalities with take-off growth greatly reduced statistical power as only few municipalities fitted these strict criteria. In order to avoid too restrictive a selection, we had to allow for some heterogeneity in municipalities with take-off growth, e.g. to include municipalities which returned to stable growth after the period of high growth or to allow for a wider variation in the duration of the periods of stable or take-off growth.

Interpretation of results

Under the population mixing hypothesis, CL risk is predicted to rise in rural areas that experience a sudden population influx. Our findings of a higher risk in municipalities with take-off growth are thus in good agreement with this hypothesis, while little evidence of increased risk was found for more general measures of population growth. Estimated risk increases were stronger in rural than in urban municipalities – though these differences were not supported by interaction tests – and particularly strong for ALL. Assuming that these observed risk increases were caused by a putative infection, as implicated by the hypothesis, then our findings demonstrate the necessity of measuring take-off growth rather than growth in general as many previous studies have done.

Finding the appropriate measures of population mixing will not be sufficient to confirm the population mixing hypothesis, however, as it would also have to be shown that an association with an increased leukaemia risk is mediated through a circulating infection. A number of studies have suggested that infectious exposure in early life is associated with a reduced risk of CL. This association is particularly evident for day-care attendance [34, 35] and has been widely seen as supporting Greaves delayed infection hypothesis [36]. This hypothesis states that a lack of exposure to common early infections could predispose the immune system to an aberrant response to later (delayed) infections resulting in leukaemia. These observations do not necessarily conflict with the findings of our study, however. In fact, Kinlen's population mixing hypothesis describes specific events in which mini-epidemics of infections might result in a higher incidence of leukaemia development among children who are more susceptible due to the fact that they were previously less or not exposed to these infections. The observed association between take-off growth and leukaemia risk in our data set, which was more pronounced in rural than in urban municipalities, thus bears out the hallmarks of the Kinlen hypothesis without conflicting with Greaves' hypothesis.

Care must be taken not to over-interpret our results: even though we found increased risk during periods of high growth, the evidence for an association was weak except for ALL in association with take-off growth with annual growth >6% compared to 1980 levels. The lack of consistent evidence may be due to the low number of cases in municipalities that met the strict criteria for take-off growth. It remains to be seen whether the association between CL and take-off growth is reproduced in other populations. Furthermore, it would be important to validate that periods of take-off growth do in fact coincide with increased incidence of known infections. This would provide further support that an infection still to be identified, is driving the associations observed in our and other studies.

Conclusions

Our study provides further support for the population mixing hypothesis. We defined an objective measure of population mixing *a priori* by analysing the temporal patterns of population growth in municipalities and isolating municipalities with high population growth following a period of low growth (take-off growth). As predicted by the hypothesis, leukaemia risks in these municipalities tended to be higher during the period of high growth compared to the period of low growth, especially in rural areas. We propose that future studies on population mixing and childhood leukaemia should observe population change over long periods and distinguish take-off growth from ordinary growth periods.

Conflict of interest

The authors declare that they have no conflict of interest

Ethical approval

Ethics approval was granted through the ethics committee of the canton of Bern to the SCCR.

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Tables

Table 1: Characteristics of municipalities

			Population count 1980			Population count 2010			Mean annual growth 1985-2010 [%]		
	N	%	median	minimum	maximum	median	minimum	maximum	median	minimum	maximum
All municipalities	2561	100	794	24	370103	1151	15	371633	0.98	-3.55	5.32
Municipalities with take-off growth[a]											
a = 1%; b = 4%	188	7.3	403	30	12523	501	29	17412	0.64	-1.46	3.47
a = 1%; b = 6%	85	3.3	363	31	12523	470	29	16077	0.56	-1.46	3.47
a = 2%; b = 4%	396	15.5	536	25	12523	766	29	17412	1.18	-1.46	4.72
a = 2%; b = 6%	177	6.9	447	31	12523	609	29	16077	1.15	-1.46	4.72
Rural municipalities	1651	100	533	24	10161	719	15	12232	0.81	-3.55	4.72
Municipalities with take-off growth[a]											
a = 1%; b = 4%	156	9.4	357	30	5477	442	29	6972	0.51	-1.46	3.47
a = 1%; b = 6%	74	4.5	358	31	5477	439	29	6972	0.41	-1.46	3.47
a = 2%; b = 4%	292	17.7	403	25	5477	554	29	6972	1.01	-1.46	4.72
a = 2%; b = 6%	137	8.3	356	31	5477	482	29	6972	0.94	-1.46	4.72

[a] Defined as a period of low (< a) followed by a period of high (> b) mean annual growth.

Table 2: Association between childhood leukaemia and quintiles of 5-year population growth (1985-2010)

5-year population growth	Quintile	Median (%)	Range (%)	Cases	IR[a]	IRR	95% CI	p LR	p interaction[b]
All municipalities	1	-3.64	(-60.0 to -0.7)	223	4.12	1.00		0.503	
	2	1.40	(-0.7 to 3.3)	413	4.52	1.11	(0.93 , 1.32)		
	3	5.21	(3.3 to 7.4)	341	4.66	1.15	(0.96 , 1.37)		
	4	10.04	(7.4 to 13.6)	231	4.24	1.07	(0.88 , 1.30)		
	5	19.86	(13.6 to 200.0)	179	4.89	1.18	(0.96 , 1.46)		
Rural municipalities	1	-3.98	(-60.0 to -0.7)	71	4.05	1.00		0.301	0.365
	2	1.33	(-0.7 to 3.3)	95	4.14	1.12	(0.81 , 1.55)		
	3	5.17	(3.3 to 7.4)	107	4.92	1.30	(0.94 , 1.79)		
	4	10.00	(7.4 to 13.6)	73	3.85	1.03	(0.72 , 1.46)		
	5	19.40	(13.6 to 200.0)	65	5.00	1.33	(0.93 , 1.92)		

IR incidence rate, IRR incidence rate ratio, CI confidence interval, LR Likelihood ratio test

[a] From Poisson regression models adjusted for sex, age group, calendar year, language region and presence of a general cancer registry in the canton of residence.

[b] Test for interaction between urbanisation and quintiles of 5-year growth

Table 3: Association between childhood leukaemia and time periods of high, medium and low growth (1985-2010)

		All municipalities					only rural municipalities					
Growth thresholds	Period[a]	No. Cases	IR	IRR[b]	95% CI	p LR	No. Cases	IR	IRR[b]	95% CI	p LR	p interaction[c]
a =1%; b = 4%	low growth	862	4.50	1.00		0.722	239	4.39	1.00		0.146	0.149
	medium growth	549	4.37	0.99	0.89 , 1.11		174	4.21	1.03	0.83 , 1.27		
	high growth	89	4.96	1.09	0.87 , 1.38		36	6.30	1.46	1.01 , 2.11		
a = 1%; b = 6%	low growth	862	4.50	1.00		0.471	239	4.39	1.00		0.502	0.631
	medium growth	602	4.38	1.00	0.89 , 1.11		199	4.40	1.07	0.87 , 1.30		
	high growth	36	5.75	1.25	0.88 , 1.78		11	5.97	1.43	0.77 , 2.65		
a = 2%; b = 4%	low growth	1194	4.44	1.00		0.706	345	4.39	1.00		0.150	0.151
	medium growth	217	4.48	1.02	0.87 , 1.19		68	3.98	0.99	0.75 , 1.29		
	high growth	89	4.96	1.10	0.88 , 1.38		36	6.30	1.44	1.01 , 2.05		
a = 2%; b = 6%	low growth	1194	4.44	1.00		0.457	345	4.39	1.00		0.508	0.735
	medium growth	270	4.49	1.02	0.89 , 1.17		93	4.44	1.08	0.85 , 1.36		
	high growth	36	5.75	1.26	0.89 , 1.78		11	5.97	1.41	0.77 , 2.59		

IR incidence rate, IRR incidence rate ratio, CI confidence interval, LR likelihood ratio test

[a] Municipality specific time periods differing in mean annual population change (s) as identified by segmented linear regression: low growth (s < a), medium growth (a ≤ s ≤ b), high growth (s > b)

[b] From Poisson regression models adjusted for sex, age group, calendar year category, language region and the presence of general cancer registry in the canton of residence.

[c] Interaction growth periods and urbanisation

Table 4: Only municipalities with take-off growth: Association between childhood leukaemia and time periods of high and low growth (1985-2010)

		All municipalities					only rural municipalities					
Growth thresholds	Period[a]	No. Cases	IR	IRR[b]	95%CI	p LR	No. Cases	IR	IRR[b]	95%CI	p LR	p interaction[c]
a = 1%; b = 4%	low growth	45	5.47	1.00		0.064	27	5.35	1.00		0.116	0.776
	high growth	14	6.66	1.06	0.55 , 2.02		8	7.53	1.34	0.53 , 3.36		
a = 1%; b = 6%	low growth	15	4.32	1.00		0.350	12	4.83	1.00		0.449	0.842
	high growth	6	14.50	2.27	0.75 , 6.87		4	15.66	2.37	0.63 , 8.85		
a = 2%; b = 4%	low growth	106	4.73	1.00		0.182	52	4.67	1.00		0.194	0.059
	high growth	27	5.24	1.04	0.67 , 1.62		19	7.41	1.61	0.91 , 2.86		
a = 2%; b = 6%	low growth	31	3.52	1.00		0.131	19	3.99	1.00		0.110	0.517
	high growth	10	8.69	2.07	0.95 , 4.51		7	11.31	2.99	1.11 , 8.05		

IR incidence rate, IRR incidence rate ratio, CI confidence interval, LR likelihood ratio test

Note: The medium growth period is not presented here, as it is restricted to individual break point years between the low and high growth periods. By definition, municipalities with take-off growth should only have periods of low and high growth. However, breakpoints occur on a continuous time scale and annual growth during a year with a breakpoint was obtained as a time-weighted average of high and low-growth sometimes resulting in medium growth. Only one case occurred in the medium growth category and the resulting imprecision in the effect estimates for this category explains why LR-tests are non-significant even when lower confidence bounds for the high growth category are close to or exceed 1.

[a] Municipality specific time periods differing in mean annual population change (s) as identified by segmented linear regression: Low growth($s < a$), medium growth ($a \le s \le b$), high growth ($s > b$)

[b] From Poisson regression models adjusted for sex, age group, calendar year category, language region and the presence of general cancer registry in the canton of residence.

[c] Interaction growth periods and urbanisation

Table 5: Only municipalities with take-off growth: Association between childhood ALL and time periods of take-off growth (1985-2010)

		All municipalities					only rural municipalities					
Growth thresholds s	Period[a]	No. Cases	IR	IRR[b]	95%CI	p LR	No. Cases	IR	IRR[b]	95%CI	p LR	p interaction[c]
a = 1%; b = 4%	low growth	36	4.37	1.00		0.135	22	4.36	1.00		0.260	0.980
	high growth	11	5.23	1.08	0.52 , 2.25		5	4.71	1.27	0.42 , 3.86		
a = 1%; b = 6%	low growth	12	3.46	1.00		0.044	9	3.62	1.00		0.043	0.968
	high growth	6	14.50	3.54	1.12 , 11.19		4	15.66	5.16	1.26 , 21.10		
a = 2%; b = 4%	low growth	82	3.66	1.00		0.368	41	3.68	1.00		0.319	0.096
	high growth	22	4.27	1.06	0.64 , 1.74		15	5.85	1.63	0.85 , 3.12		
a = 2%; b = 6%	low growth	24	2.73	1.00		0.022	14	2.94	1.00		0.006	0.320
	high growth	9	7.82	2.48	1.07 , 5.72		7	11.31	4.89	1.74 , 13.71		

IR incidence rate, IRR incidence rate ratio, CI confidence interval, LR likelihood ratio test, ALL acute lymphoblastic leukaemia

Note: The medium growth period is not presented here, as it is restricted to individual break point years between the low and high growth periods. By definition, municipalities with take-off growth should only have periods of low and high growth. However, breakpoints occur on a continuous time scale and annual growth during a year with a breakpoint was obtained as a time-weighted average of high and low-growth sometimes resulting in medium growth. Only one case occurred in the medium growth category and the resulting imprecision in the effect estimates for this category explains why LR-tests are non-significant even when lower confidence bounds for the high growth category are close to or exceed 1.

[a] Municipality specific time periods differing in mean annual population change (s) as identified by segmented linear regression: Low growth($s < a$), medium growth ($a \leq s \leq b$), high growth ($s > b$)

[b] From Poisson regression models adjusted for sex, age group, calendar year category, language region and the presence of general cancer registry in the canton of residence.

[c] Interaction growth periods and urbanisation

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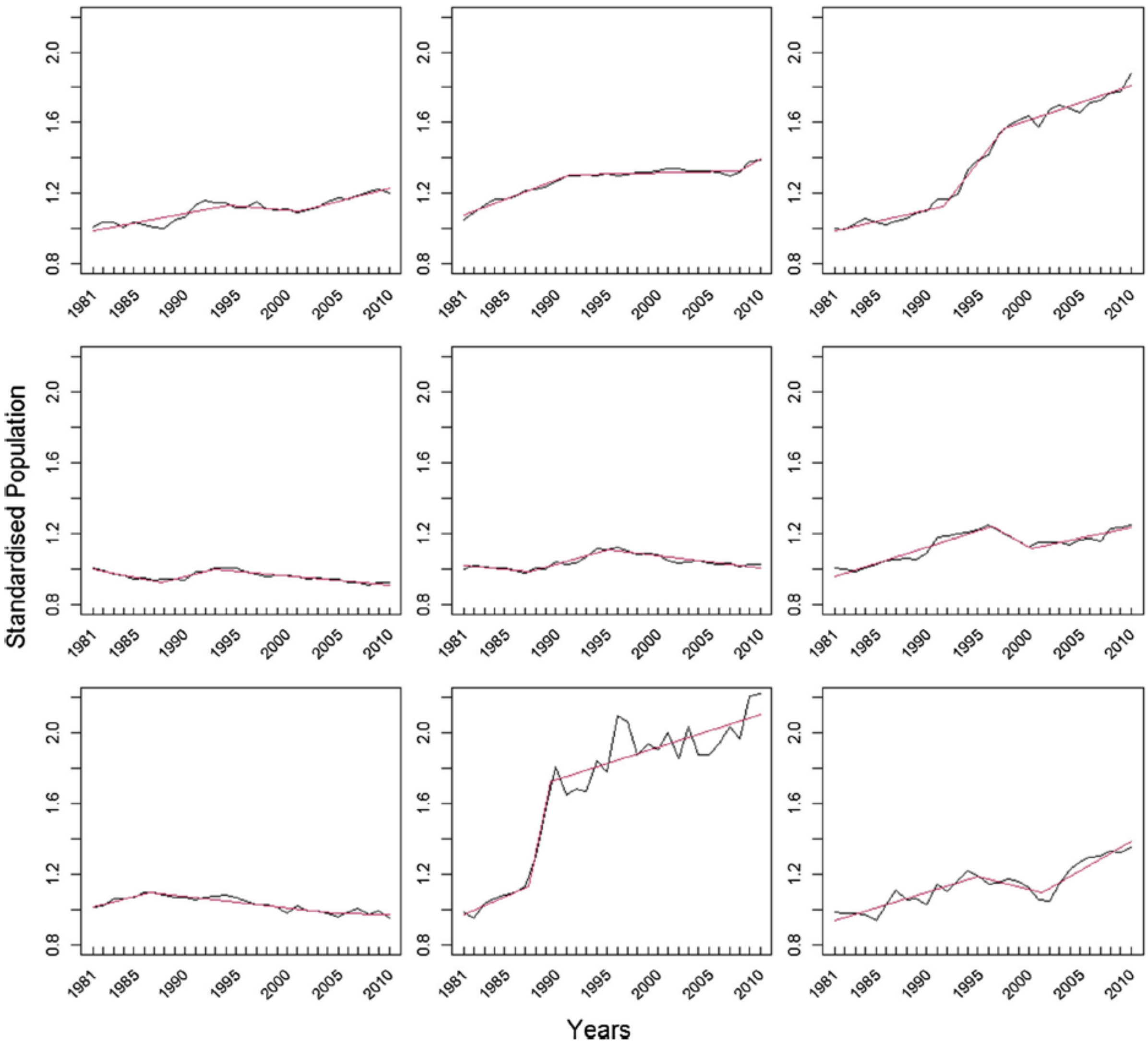
Figures Texts

Fig. 1: Examples of segmented linear regression with two knots (variable breakpoints) for 9 randomly selected municipalities.

Standardised population size relative to the 1980 population shown in black and fitted segmented regression shown in red.



Published in final forma as: *Eur J Epidemiol.* 2016 Aug;31(8):763-74. doi: 10.1007/s10654-016-0162-6

Fig. 2: Patterns of segmented linear regression for randomly selected municipalities with different types of take-off growth.

Type I: 1st period low growth (average annual growth <a), 2nd and 3rd period high growth (average annual growth >b); Type II: 1st and 2nd period low growth, 3rd period high growth; Type III: 1st and 3rd period low growth, 2nd period high growth. Curves show fitted standardised population size relative to the 1980 population.

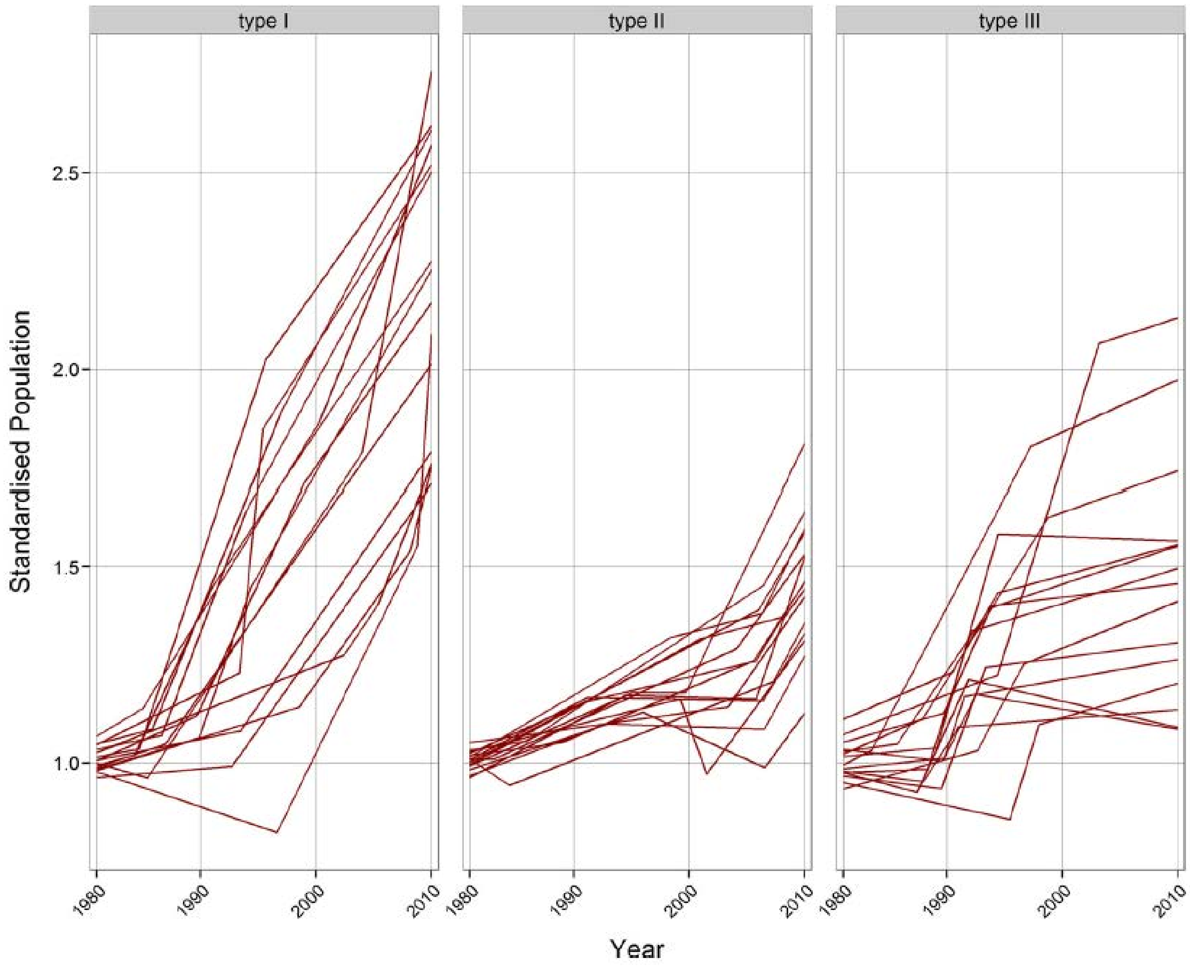


Fig. 3: Municipalities with take-off growth defined as period of high growth following an initial period of low growth based on segmented linear regression

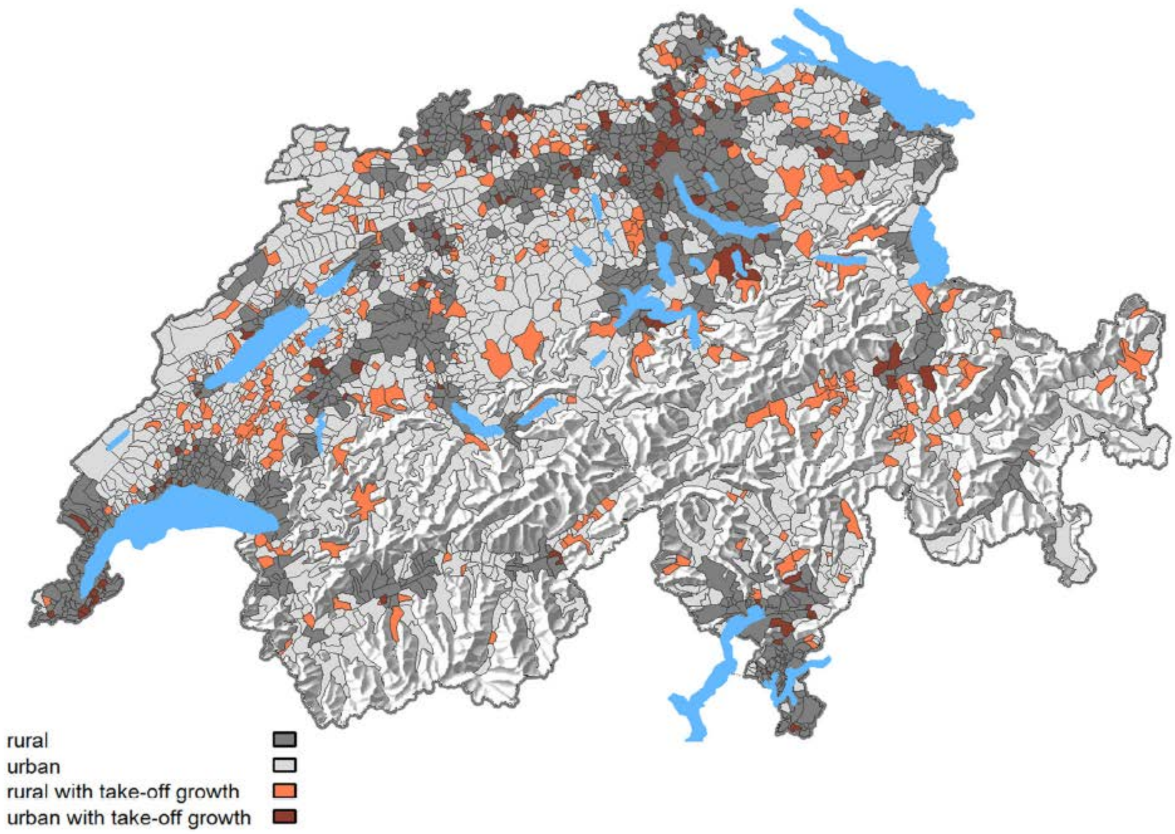


Fig. 4: Comparison of childhood leukaemia risk in high versus low growth periods in municipalities with take-off growth.

Take-off-growth is defined as an initial period of high growth (regression slope s > b) following a period of low growth (s < a). The periods and their slopes were defined for each municipality individually using segmented linear regression.