

Acknowledgements

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

This study was supported by Swiss Cancer Research (# 3049-08-2012, # 3515-08-2014), the Swiss Federal Office of Public Health (# 08.001616, #10.002946, # 12.008357) and the Swiss Cancer League (#02224-03-2008). B.D. Spycher was supported by a Swiss National Science Foundation fellowship (PZ00P3_147987).

The work of the Swiss Childhood Cancer Registry is supported by the Swiss Paediatric Oncology Group (www.spog.ch), Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und -direktoren (www.gdk-cds.ch), Swiss Cancer Research (www.krebsforschung.ch), Kinderkrebshilfe Schweiz (www.kinderkrebshilfe.ch), the Federal Office of Health (FOH) and the National Institute of Cancer Epidemiology and Registration (www.nicer.ch).

The members of the Swiss Pediatric Oncology Group Scientific Committee:

R. A. Ammann (Bern), R. Angst (Aarau), M. Ansari (Geneva), M. Beck Popovic (Lausanne), E. Bergstraesser (Zurich), P. Brazzola (Bellinzona), J. Greiner (St. Gallen), M. Grotzer (Zurich), H. Hengartner (St. Gallen), T. Kuehne (Basel), K. Leibundgut (Bern), F. Niggli (Zurich), J. Rischewski (Lucerne), N. von der Weid (Basel)

The members of the Swiss National Cohort Study Group:

M. Egger (Chairman of the Executive Board), A. Spoerri (University of Bern), M. Zwahlen (University of Bern), M. Puhan (Chairman of the Scientific Board), M. Bopp (University of Zurich), D. Fäh (University of Zurich), N. Künzli (University of Basel), F. Paccaud (University of Lausanne), M. Oris (University of Geneva), M. Schwyn (Swiss Federal Statistical Office, Neuchâtel).

1 **Abstract**

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

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

16 Results: Our study included 1,500 incident cases and 2,561 municipalities. The incident rate
17 ratio (IRR) comparing the highest to the lowest quintile of 5-year population growth was 1.18
18 (95%-CI: 0.96, 1.46) including all municipalities and 1.33 (95%-CI: 0.93, 1.92) in rural
19 municipalities only (p-value interaction 0.36). In municipalities with take-off growth, the IRR
20 comparing the take-off period (>6% annual population growth) with the initial period of low or
21 negative growth (<2%) was 2.07 (95%-CI 0.95, 4.51) overall and 2.99 (1.11, 8.05) in rural areas
22 (p interaction 0.52).

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

26
27 Keywords: population mixing, leukaemia, infections, childhood cancer, take-off growth

28
29
30

Introduction

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

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

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

34

1 **Methods**

2 **Population**

3 We identified incident cases of leukaemia in children from the Swiss Childhood Cancer Registry
 4 (SCCR). All cases diagnosed in the period 1985-2010 who were aged 0-15 years and resident in
 5 Switzerland at the time of diagnosis were included. The SCCR [16, 17] is a population-based
 6 registry including all children and adolescents diagnosed with a tumour classified according to
 7 the International Classification of Childhood Cancer, third edition [18] (ICCC-3). Completeness of
 8 the SCCR was above 91% throughout the study period; since the mid-1990s coverage has been
 9 around 95% [19].

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

15 **Outcomes**

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

18 **Measures of population mixing**

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

24 We measured population mixing using two separate approaches as follows:

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

$$28 \quad 5\text{-year relative change in year } t = \frac{Pop_{t+2} - Pop_{t-3}}{Pop_{80}},$$

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

30 Approach B (take-off growth): This approach aimed to identify calendar periods with distinct
 31 levels of average growth. We standardised annual population counts for each municipality for
 32 the years 1981-2010 by dividing by the population in 1980. We fitted segmented linear

1 regression models with two variable breakpoints using the standardized population growth as
2 dependent variable and calendar year as independent variable. The models were fitted using the
3 package ‘segmented’ in the R environment for statistical computing version 3.1.3 [23, 24]. This
4 method simultaneously estimates breakpoints and regression slopes of a continuous piece-wise
5 linear regression line.

6 The three periods ($i = 1,2,3$) of each segmented regression were classified according to whether
7 their respective slopes s_i (these correspond to mean annual growth relative to the 1980
8 population) were below a lower threshold a ($s_i < a$) (low growth period), above an upper
9 threshold b ($s_i > b$) (high growth period) or between these two ($a \leq s_i \leq b$). We defined periods
10 of “take-off growth” as periods of high population growth ($s_i > b$) following a period of low
11 growth ($s_j < a$ for $j < i$) (Fig. S1). We used four pre-specified combinations of threshold values with
12 $a = 1\%$ or 2% and $b = 4\%$ or 6% , respectively. The four combinations of threshold values are
13 nested in each other with the combination $a = 2\%$ $b = 4\%$ containing all the other combinations.
14 More details on the definition of take-off growth are provided in the online supplementary
15 material.

16 **Statistical analyses**

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

27 We investigated associations between CL incidence and population mixing using Poisson
28 regression models adjusting for sex, age group (0-4, 5-10, 10-15), year category (5-year blocks)
29 and language region (German, French, Italian). Since the existence of a general cantonal cancer
30 registry might have affected the completeness of registration in a canton [25] we also adjusted
31 for this using a time-varying dichotomous variable indicating the presence or absence of such a
32 registry. We also ran Poisson regression models including a random effects term on the
33 intercept to allow for varying average incidence rates across municipalities. These random
34 effects account for any purely spatial differences such that model estimates only contrast
35 temporal differences within municipalities, i.e. periods of high vs. low population growth. We

1 also investigated effect modification by degree of urbanisation (urban/rural). Incidence rate
2 ratios (IRR) and their 95% confidence intervals (CI) were calculated from these models.

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

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

11 **Results**

12 We identified 1,500 incident cases of CL diagnosed 1985-2010 under the age of 16 years and
13 resident in Switzerland at time of diagnosis. Of these 1,191 (80%) were diagnosed with ALL and
14 862 (58%) were male (supplementary Table S2). Overall, our analyses included 39.7 million
15 person-years at risk over the period 1985-2010 across 2,561 municipal entities (after
16 accounting for boundary changes; hereinafter referred to simply as 'municipalities'). Of these
17 municipalities, 1,651 (64%) were rural and 396 (15.5%) could be classified as municipalities
18 with take-off growth based on threshold value combinations of mean annual population growth
19 of below $a = 1\%$ or 2% (low growth period) and above $b = 4\%$ or 6% (high growth period)
20 (Table 1). Median population size was 794 in 1980 increasing to 1,151 in 2010, and average
21 annual population growth over this period had a median of 1% (Table 1).

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

31 Segmented linear regressions used to define municipalities with take-off growth (approach B)
32 generally showed a good fit to annual growth curves (Some randomly selected examples are
33 shown in Fig. 1); however, in some cases three breakpoints might have been more appropriate.
34 Among municipalities with take-off growth, the high growth period was most marked if it was

1 preceded and followed by a low growth period (Fig. 2). Municipalities with take-off growth were
2 distributed across the whole country (Fig. 3).

3 Table 3 shows the results of analyses comparing high and low growth periods. Here periods of
4 high mean annual growth relative to 1980 population ($s > b$) or medium growth ($a \leq s \leq b$) are
5 compared to periods of low growth ($s < a$) for different thresholds (a, b) without taking into
6 account the sequence of these periods, i.e. disregarding take-off growth. Including all
7 municipalities, IRRs tended to be higher for periods of high annual growth compared to periods
8 of low growth, but there was little evidence for an association ($p > 0.4$). When we included only
9 rural municipalities, IRRs for periods of high growth were about 1.45. While lower bounds of
10 95%-CIs exceeded unity for the annual growth threshold of $b = 4\%$, p-values did not show strong
11 evidence of an association ($p > 0.1$) (Table 3). There was little evidence of effect modification by
12 degree of urbanisation (p LR test: 0.15).

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

21 In separate analyses of cases of ALL, the pattern of associations was more pronounced with
22 evidence of association both in urban and rural municipalities for growth periods exceeding 6%
23 annually (Table 5). In rural areas, IRRs for ALL comparing the take-off growth period to the low
24 growth period exceeded 4 ($a = 1\%$, $b = 6\%$: IRR: 5.61, 95%CI: 1.26-21.10, p LR: 0.043; $a = 2\%$, b
25 $= 6\%$: IRR: 4.89, 95%CI: 1.74-13.71, p LR: 0.006). Results from models including random
26 intercepts for municipalities were highly similar (data not shown).

27

28

Discussion

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35

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

1 after that period. This approach cannot capture the starting point of population increases, i.e.
2 take-off population growth. Similarly, a number of other studies have used population increases
3 or in-migration of short time periods (irrespective of prior growth) to measure population
4 mixing [10, 13, 12, 9]. Other measures of population mixing that have been studied in relation to
5 the risk of childhood leukaemia include diversity of place of origin of in-migrants [27, 14], social
6 contacts at parents' workplace [28-30], or population density [31-33]. The results of these
7 studies are heterogeneous.

8 **Strengths and weaknesses**

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

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

32 **Interpretation of results**

33 Under the population mixing hypothesis, CL risk is predicted to rise in rural areas that
34 experience a sudden population influx. Our findings of a higher risk in municipalities with take-
35 off growth are thus in good agreement with this hypothesis, while little evidence of increased

1 risk was found for more general measures of population growth. Estimated risk increases were
2 stronger in rural than in urban municipalities – though these differences were not supported by
3 interaction tests – and particularly strong for ALL. Assuming that these observed risk increases
4 were caused by a putative infection, as implicated by the hypothesis, then our findings
5 demonstrate the necessity of measuring take-off growth rather than growth in general as many
6 previous studies have done.

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

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

31 **Conclusions**

32 Our study provides further support for the population mixing hypothesis. We defined an
33 objective measure of population mixing *a priori* by analysing the temporal patterns of
34 population growth in municipalities and isolating municipalities with high population growth
35 following a period of low growth (take-off growth). As predicted by the hypothesis, leukaemia

1 risks in these municipalities tended to be higher during the period of high growth compared to
2 the period of low growth, especially in rural areas. We propose that future studies on population
3 mixing and childhood leukaemia should observe population change over long periods and
4 distinguish take-off growth from ordinary growth periods.

5

6

7

1 **Conflict of interest**

2 The authors declare that they have no conflict of interest

3 **Ethical approval**

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

5

References

- 1
- 2
- 3
- 4
- 5 1. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new
- 6 town with nuclear reprocessing sites in Britain. *Lancet.* 1988;2:1323-7.
- 7 2. Kinlen LJ. An examination, with a meta-analysis, of studies of childhood leukaemia in relation
- 8 to population mixing. *Br J Cancer.* 2012;107:1163-8.
- 9 3. Black D. Investigation of the Possible Increased Incidence of Cancer in West Cumbria; Report
- 10 of the Independent Advisory Group. London, HMSO. 1984.
- 11 4. Kinlen LJ, Balkwill A. Infective cause of childhood leukaemia and wartime population mixing
- 12 in Orkney and Shetland, UK. *Lancet.* 2001;357:858.
- 13 5. Kinlen L. Childhood leukaemia and ordnance factories in west Cumbria during the Second
- 14 World War. *Br J Cancer.* 2006;95:102-6.
- 15 6. Kinlen LJ, O'Brien F, Clarke K, Balkwill A, Matthews F. Rural population mixing and childhood
- 16 leukaemia: effects of the North Sea oil industry in Scotland, including the area near Dounreay
- 17 nuclear site. *BMJ.* 1993;306:743-8.
- 18 7. Boutou O, Guizard AV, Slama R, Pottier D, Spira A. Population mixing and leukaemia in young
- 19 people around the La Hague nuclear waste reprocessing plant. *Br J Cancer.* 2002;87:740-5.
- 20 8. Kinlen LJ, Clarke K, Hudson C. Evidence from population mixing in British New Towns 1946-
- 21 85 of an infective basis for childhood leukaemia. *Lancet.* 1990;336:577-82.
- 22 9. Stiller CA, Kroll ME, Boyle PJ, Feng Z. Population mixing, socioeconomic status and incidence of
- 23 childhood acute lymphoblastic leukaemia in England and Wales: analysis by census ward. *Br J*
- 24 *Cancer.* 2008;98:1006-11.
- 25 10. Wartenberg D, Schneider D, Brown S. Childhood leukaemia incidence and the population
- 26 mixing hypothesis in US SEER data. *Br J Cancer.* 2004;90:1771-6.
- 27 11. Clark BR, Ferketich AK, Fisher JL, Ruymann FB, Harris RE, Wilkins JR, 3rd. Evidence of
- 28 population mixing based on the geographical distribution of childhood leukemia in Ohio. *Pediatr*
- 29 *Blood Cancer.* 2007;49:797-802.
- 30 12. Rudant J, Baccaini B, Ripert M, Goubin A, Bellec S, Hemon D, Clavel J. Population-mixing at the
- 31 place of residence at the time of birth and incidence of childhood leukaemia in France. *Eur J*
- 32 *Cancer.* 2006;42:927-33.
- 33 13. Koushik A, King WD, McLaughlin JR. An ecologic study of childhood leukemia and population
- 34 mixing in Ontario, Canada. *Cancer Causes Control.* 2001;12:483-90.
- 35 14. Parslow RC, Law GR, Feltbower R, Kinsey SE, McKinney PA. Population mixing, childhood
- 36 leukaemia, CNS tumours and other childhood cancers in Yorkshire. *Eur J Cancer.* 2002;38:2033-
- 37 40.
- 38 15. Kinlen LJ, Dickson M, Stiller CA. Childhood leukaemia and non-Hodgkin's lymphoma near
- 39 large rural construction sites, with a comparison with Sellafield nuclear site. *BMJ.* 1995;310:763-
- 40 8.
- 41 16. Michel G, von der Weid NX, Zwahlen M, Adam M, Rebholz CE, Kuehni CE, Swiss Childhood
- 42 Cancer R, Swiss Paediatric Oncology Group Scientific C. The Swiss Childhood Cancer Registry:
- 43 rationale, organisation and results for the years 2001-2005. *Swiss Med Wkly.* 2007;137:502-9.
- 44 17. Michel G, von der Weid NX, Zwahlen M, Redmond S, Strippoli MP, Kuehni CE, Swiss Paediatric
- 45 Oncology G. Incidence of childhood cancer in Switzerland: the Swiss Childhood Cancer Registry.
- 46 *Pediatr Blood Cancer.* 2008;50:46-51.
- 47 18. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood
- 48 Cancer, third edition. *Cancer.* 2005;103:1457-67.
- 49 19. Schindler M, Mitter V, Bergstraesser E, Gummy-Pause F, Michel G, Kuehni CE. Death certificate
- 50 notifications in the Swiss Childhood Cancer Registry: assessing completeness and registration
- 51 procedures. *Swiss Med Wkly.* 2015;145:w14225.
- 52 20. Bopp M, Spoerri A, Zwahlen M, Gutzwiller F, Paccaud F, Braun-Fahrlander C, Rougemont A,
- 53 Egger M. Cohort Profile: the Swiss National Cohort--a longitudinal study of 6.8 million people. *Int*
- 54 *J Epidemiol.* 2009;38:379-84.

- 1 21. Spoerri A, Zwahlen M, Egger M, Bopp M. The Swiss National Cohort: a unique database for
2 national and international researchers. *Int J Public Health.* 2010;55:239-42.
- 3 22. Schuler M, Dessemontet P, Joye D. Die Raumgliederung der Schweiz. Neuchatel, Switzerland
4 Swiss Federal Statistical Office; 2005.
5 doi:[http://www.bfs.admin.ch/bfs/portal/de/index/news/publikationen.html?publicationID=18](http://www.bfs.admin.ch/bfs/portal/de/index/news/publikationen.html?publicationID=1881)
6 [81](http://www.bfs.admin.ch/bfs/portal/de/index/news/publikationen.html?publicationID=1881).
- 7 23. Muggeo VM. Estimating regression models with unknown break-points. *Stat Med.*
8 2003;22:3055-71.
- 9 24. Muggeo VMR. segmented: an R Package to Fit Regression Models with Broken-Line
10 Relationships. *R News.* 2008;8:20-5.
- 11 25. Schindler M, Mitter V, Rueegg C, Bergstrasser E, Gumy-Pause F, Michel G, Kuehni C. Death
12 Certificate Notations in the Swiss Childhood Cancer Registry: Validation of Registration
13 Procedures and Completeness. Abstract presented at ENCR Scientific Meeting and General
14 Assembly, 12-14 Nov, Ispra, Italy. 2014.
- 15 26. Lupatsch JE, Kuehni CE, Niggli F, Ammann RA, Egger M, Spycher BD. Population mixing and
16 the risk of childhood leukaemia in Switzerland: a census-based cohort study. *Eur J Epidemiol.*
17 2015.
- 18 27. Law GR, Parslow RC, Roman E, United Kingdom Childhood Cancer Study I. Childhood cancer
19 and population mixing. *Am J Epidemiol.* 2003;158:328-36.
- 20 28. Chang JS, Metayer C, Fear NT, Reinier K, Yin X, Urayama K, Russo C, Jolly KW, Buffler PA.
21 Parental social contact in the work place and the risk of childhood acute lymphoblastic
22 leukaemia. *British Journal of Cancer.* 2007;97:1315-21.
- 23 29. Fear NT, Roman E, Reeves G, Pannett B. Are the children of fathers whose jobs involve
24 contact with many people at an increased risk of leukaemia? *Occup Environ Med.* 1999;56:438-
25 42.
- 26 30. Kinlen LJ. High-contact paternal occupations, infection and childhood leukaemia: five studies
27 of unusual population-mixing of adults. *British Journal of Cancer.* 1997;76:1539-45.
- 28 31. Li CY, Lin RS, Lin CH. Urbanization and childhood leukaemia in Taiwan. *Int J Epidemiol.*
29 1998;27:587-91.
- 30 32. Hjalmarsson U, Gustafsson G, on behalf of the Swedish Child Leukaemia G. Higher risk for acute
31 childhood lymphoblastic leukaemia in Swedish population centres 1973-94. *British Journal of*
32 *Cancer.* 1999;79:30-3.
- 33 33. Alexander FE, Boyle P, Carli PM, Coebergh JW, Ekblom A, Levi F, McKinney PA, McWhirter W,
34 Michaelis J, Peris-Bonet R, Petridou E, Pompe-Kirn V, Plěško I, Pukkala E, Rahu M, Stiller CA,
35 Storm H, Terracini B, Vatten L, Wray N. Population density and childhood leukaemia: results of
36 the EUROCLUS study. *European Journal of Cancer.* 1999;35:439-44.
- 37 34. Urayama KY, Buffler PA, Gallagher ER, Ayoob JM, Ma X. A meta-analysis of the association
38 between day-care attendance and childhood acute lymphoblastic leukaemia. *Int J Epidemiol.*
39 2010;39:718-32.
- 40 35. Rudant J, Lightfoot T, Urayama KY, Petridou E, Dockerty JD, Magnani C, Milne E, Spector LG,
41 Ashton LJ, Dessypris N, Kang AY, Miller M, Rondelli R, Simpson J, Stiakaki E, Orsi L, Roman E,
42 Metayer C, Infante-Rivard C, Clavel J. Childhood acute lymphoblastic leukemia and indicators of
43 early immune stimulation: a childhood leukemia international consortium study. *Am J*
44 *Epidemiol.* 2015;181:549-62.
- 45 36. Greaves MF. Speculations on the cause of childhood acute lymphoblastic leukemia. *Leukemia.*
46 1988;2:120-5.

47

48

49

Tables

Table 1: Characteristics of municipalities

	N	%	Population count 1980			Population count 2010			Mean annual growth 1985-2010 [%]		
			media n	minimu m	maximu m	media n	minimu m	maximu m	media n	minimu m	maximu m
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)

Growth thresholds	Period ^a	All municipalities					only rural municipalities					
		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 ($a \leq s \leq b$), 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

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

Growth thresholds	Period ^a	All municipalities					only rural municipalities					
		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 ($a \leq s \leq b$), 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

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

Growth thresholds s	Period ^a	All municipalities					only rural municipalities					
		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

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.

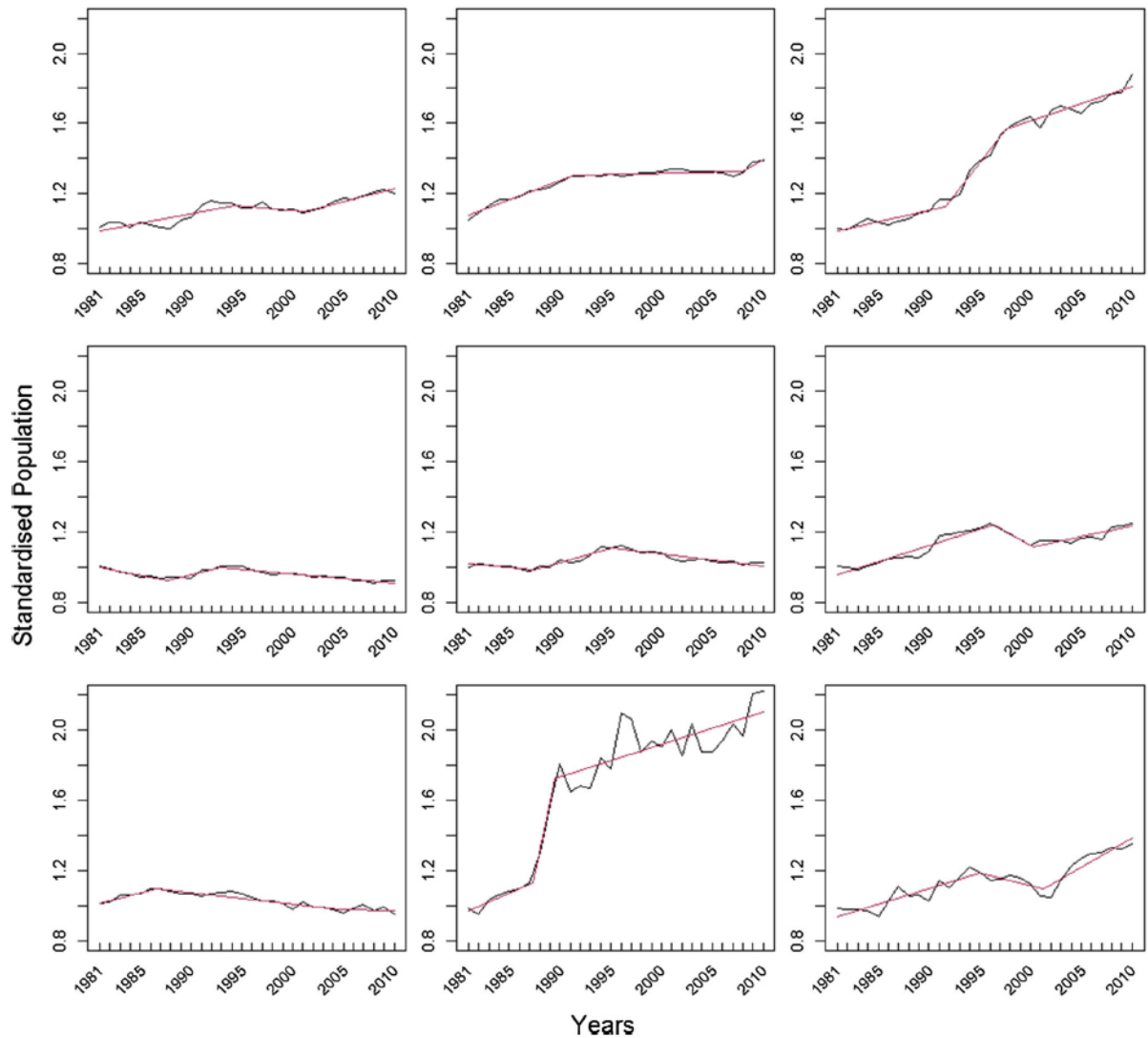


Fig. 2: Patterns of segmented linear regression for randomly selected municipalities with different types of take-off growth.

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.

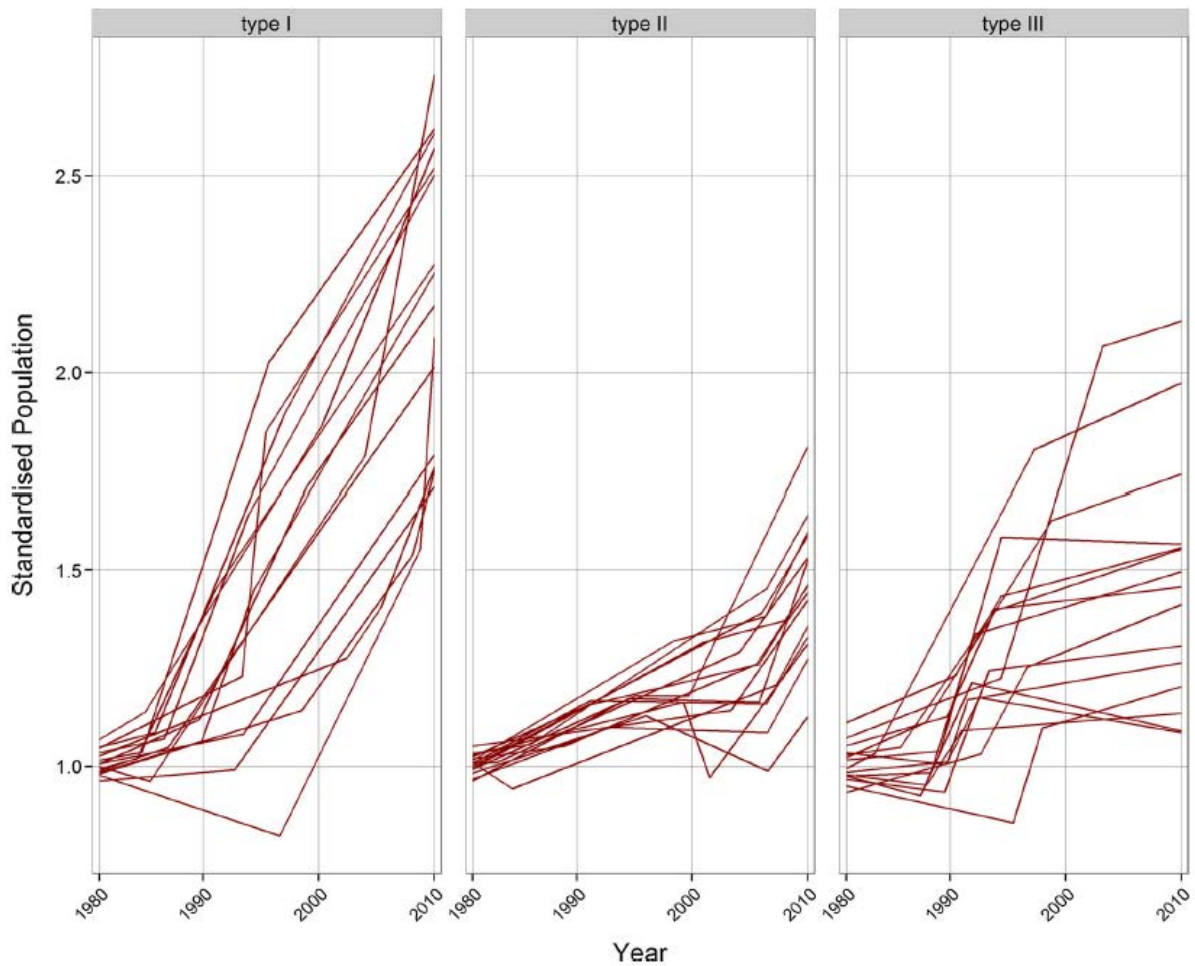


Fig. 3: Municipalities with take-off growth defined as period of high growth following an initial period of low growth based on segmented linear regression

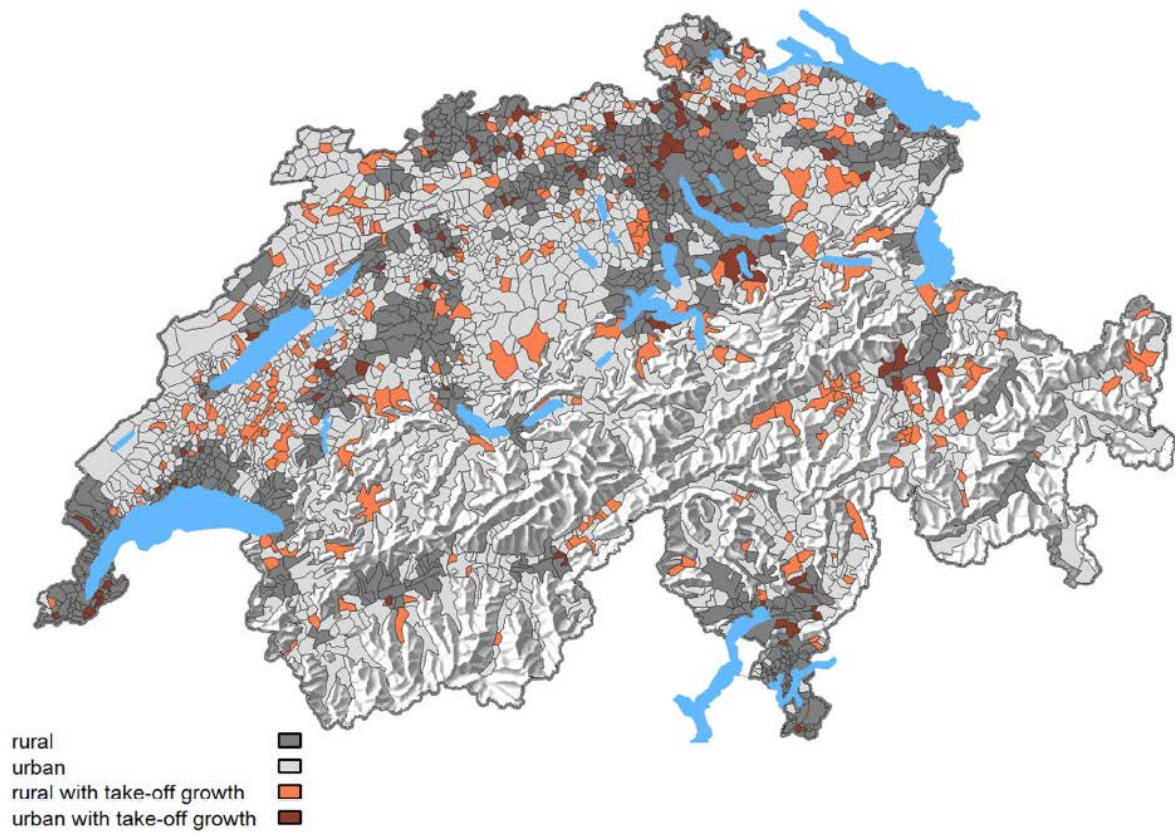


Fig. 4: Comparison of childhood leukaemia risk in high versus low growth periods in municipalities with take-off growth.

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.

