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Spatial Clustering of Childhood Leukaemia in Switzerland: A nationwide study

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Background

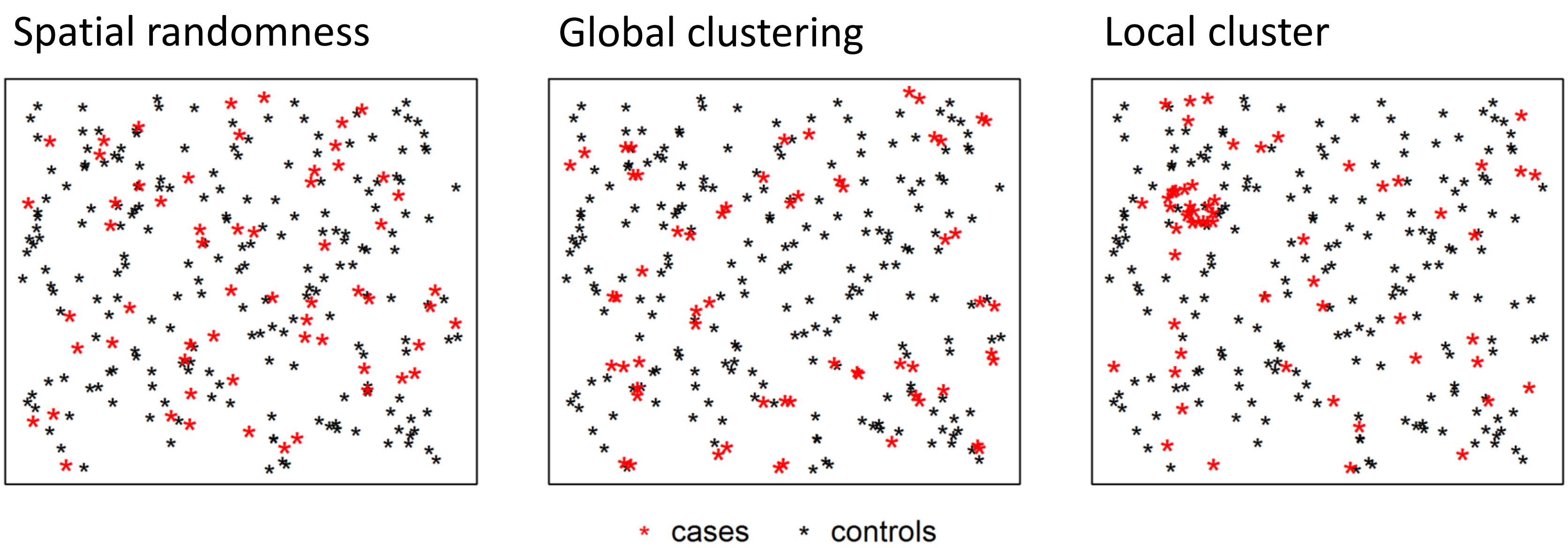
- The aetiology of childhood leukaemia is largely unknown
- Established risk factors
    - Genetic syndromes (e.g. Down syndrome)
    - Ionising radiation in high doses
- Putative (environmental) risk factors
    - Air pollution
    - Pesticide exposure
    - Ionising radiation in low doses
    - …

Such exposures might suggest spatial variation of the childhood leukaemia incidence.

Background: Global clustering vs Cluster detection

Two type of tests are used:

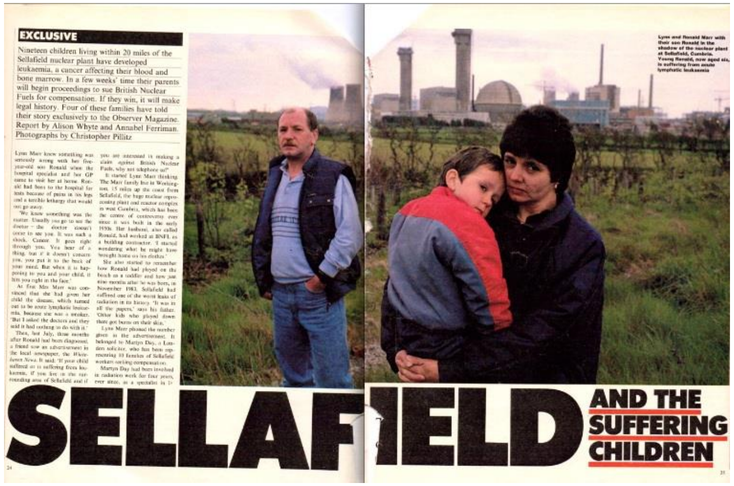
- Global clustering test: An overall tendency of cases to occur close to each other (many clusters possibly small and on the same spatial extent)
- Cluster detection test: A single local area of high risk



Background: Previous studies

Post hoc research on clusters:

- Seascale, Cumbria
- Krümmel, Germany
- Fallon, Nevada



Research on clusters without prior indication of clustering:

- Mixed results
- Low geographical resolution
- Methodological limitations

Area	Leukaemia (significant results)
United Kingdom	13 (8)
United States	10 (3)
Europe	9 (3)
other	4 (3)
total	**36 (17)**

Aims

- To investigate if childhood leukaemia cases tend to occur closer than expected (**global clustering**)
- To examine if there are any local clusters of childhood leukaemia in Switzerland (**cluster detection**)

Methods

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Population

- Children aged 0-15 years at diagnosis
- Registered in the Swiss Childhood Cancer Registry (SCCR)
- Diagnosed in Switzerland

Outcome

- Leukaemia (ALL, AML)
- Different age groups (0-4, 0-15)

Control selection

- Case-control ratio 1:10
- Randomly sampled geocodes from the Swiss censuses (1990, 2000, 2010 and onwards)
- Matching variables: time at diagnosis or birth, sex and age at diagnosis

Spatial resolution

- Precise geocodes of residence for both cases and controls

Methods: Statistical analysis

Test for global clustering:

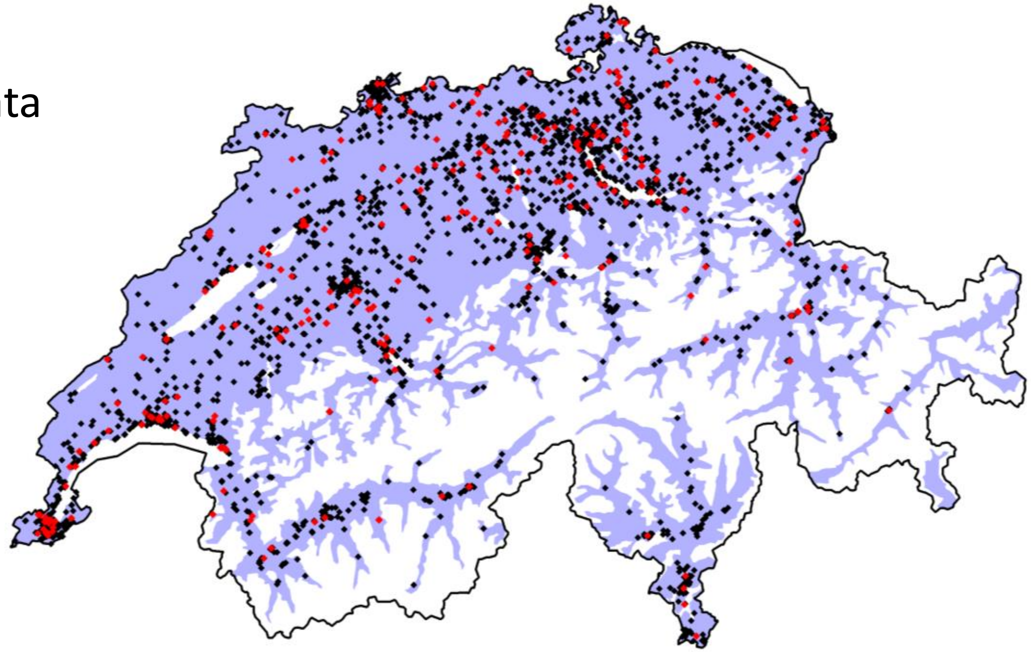
- Difference in k-functions
- Cuzick-Edwards' test
- Tango's index for point data

Cluster detection test:

- Kulldorff's circular scan

Null hypothesis: Monte Carlo samples based on random relabelling.

Multiple testing adjustment for different input values and for tests and diagnostic groups



Results; Table of p-values

		Birth			
Diagnostic group	Age	Difference of k-functions (distance in m)	Cuzick-Edwards' test (no. of NN)	Tango's Index (parameter θ)	Kulldorff's scan statistic (Radius in m)
Leukaemia	0-15	0.218 (600)	0.404 (6)	0.239 (1414)	0.308 (800)
	0-4	0.754 (600)	0.500 (6)	0.720 (1414)	0.063 (500)
	5-15	0.482 (1000)	0.800 (1)	0.586 (636)	0.970 (400)
ALL	0-15	0.112 (600)	0.059 (6)	0.106 (849)	0.756 (4300)
	0-4	0.329 (100)	0.461 (6)	0.669 (1414)	**0.048 (500)**
AML	0-15	0.452 (1000)	0.143 (76)	0.628 (2121)	0.305 (21000)
					***Adjusted* p-value = 0.544**
		Diagnosis			
Leukaemia	0-15	0.108 (250)	0.112 (1)	0.132 (636)	0.128 (500)
	0-4	0.415 (4000)	0.333 (11)	0.375 (7071)	0.073 (500)
	5-15	**0.049 (100)**	**0.042 (1)**	**0.052 (354)**	0.233 (3000)
ALL	0-15	0.422 (5000)	0.332 (1)	0.383 (7071)	0.095 (500)
	0-4	0.490 (5000)	0.455 (6)	0.424 (7071)	0.056 (500)
AML	0-15	0.614 (5000)	0.582 (52)	0.700 (7071)	0.885 (2500)
					***Adjusted* p-value = 0.516**

Results

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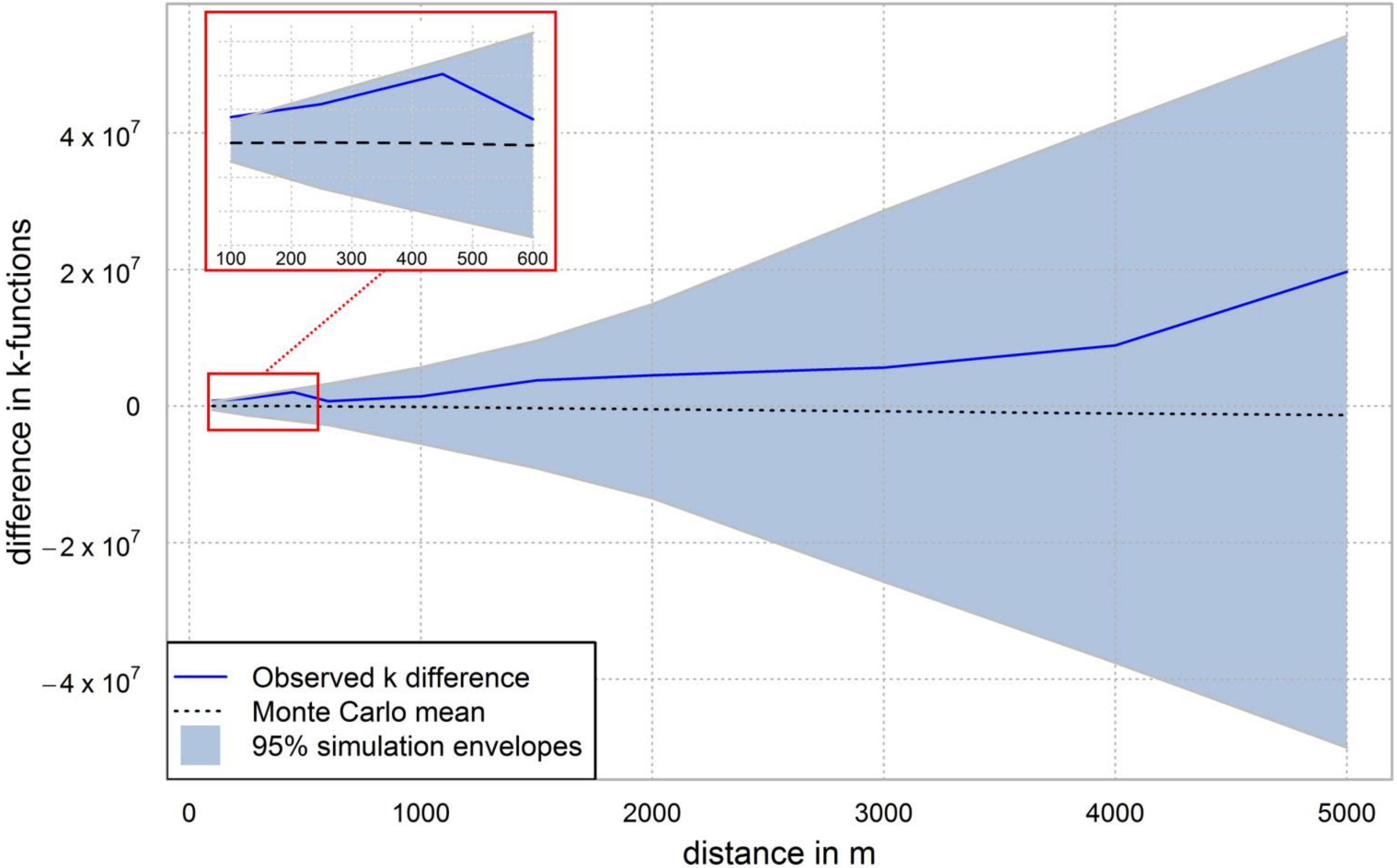
Difference in k-functions for leukaemia cases 5-15 years old at diagnosis



Results

Kulldorff’s scan highlighted a possible cluster:

- Small spatial extent (500m)
- Small rural area (9,000 residents)
- 5 ALL cases; all 0-4 years old; 4 males 1 female
- Expected number of cases 0.39

Discussion

Summary

- No overall evidence of spatial clustering or clusters

Interpretation

- Chance is the most likely explanation for clustering or clusters of leukaemia in Switzerland
- If there was clustering, this would be at very small spatial scale

Strength and limitations

Strengths:

- Precise geocodes for both cases and controls
- Different tests sensitive to different clustering scenarios
- Carefully corrected for multiple tests

Limitations:

- Not adjusted for residential history or time away from homes
- A small proportion of cases is missing
- Geocodes of controls only at time of census

Take home messages:

- Multiple testing needs to be corrected in such studies
- Seemingly extra-ordinary clusters might be due to chance

Thank you for your attention!

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