Spatial analysis of cluster randomised trials

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Context and background: CRTS

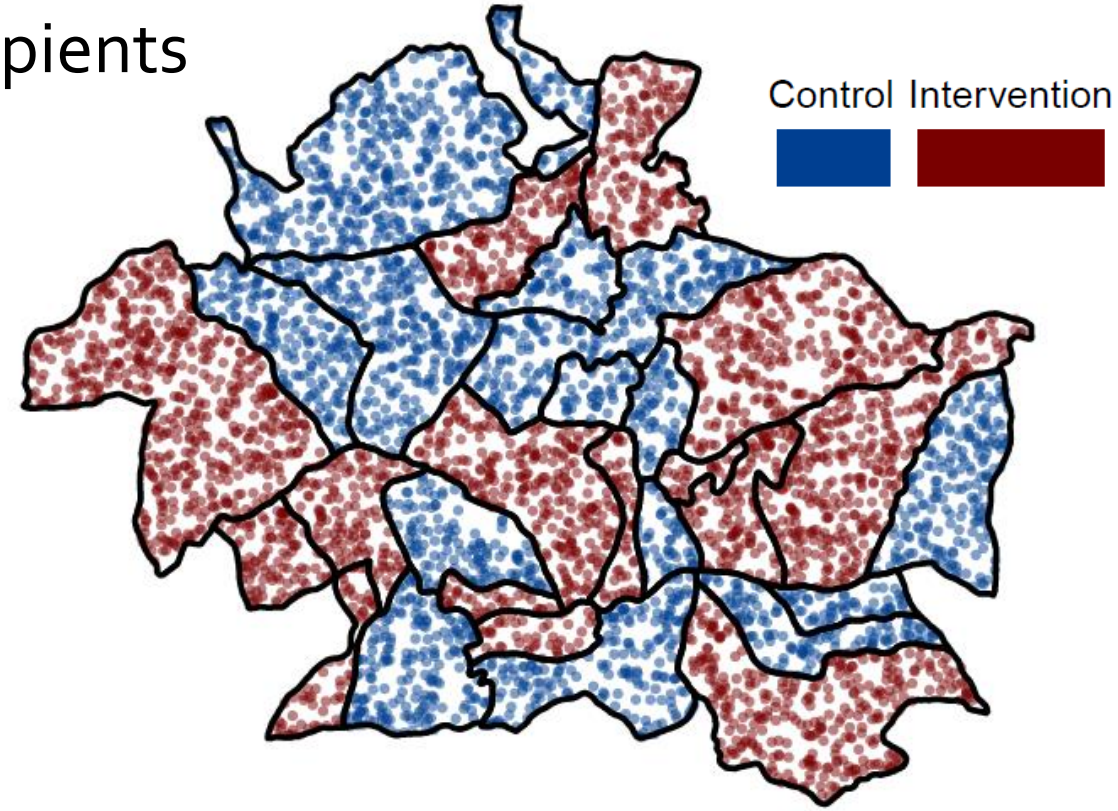
- Background: What is spatial?
- Review: What have people done before?
- Simulation: Does it matter?
- Method: How can I tell if spillover is present?

Context and background: CRTS

- Clusters are often defined geographically and analysed assuming independence
  - When clusters are close together, this may not be true
- We could deal with this at the design stage
  - May not be feasible or practical
  - We might want to measure spillover
- Spatial analyses may enable
  - Controlling for proximity of clusters
  - Measuring spatial spillover effects

Context and background: CRTS

- Clusters – geographical areas
- Infectious diseases
- Intervention may affect non-recipients



Context and background: Spillover

Spillovers are the effects of interventions on people in physical or social proximity to intervention recipients but who do not themselves receive the intervention.

International Journal of Epidemiology, 2018, 332–347
doi: 10.1093/ije/dyx201
Advance Access Publication Date: 2 November 2017
Education Corner

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Spillover effects in epidemiology: parameters, study designs and methodological considerations

Jade Benjamin-Chung,[1]* Benjamin F Arnold,[1,2] David Berger,[3] Stephen P Luby,[4] Edward Miguel,[3] John M Colford Jr[1] and Alan E Hubbard[2]

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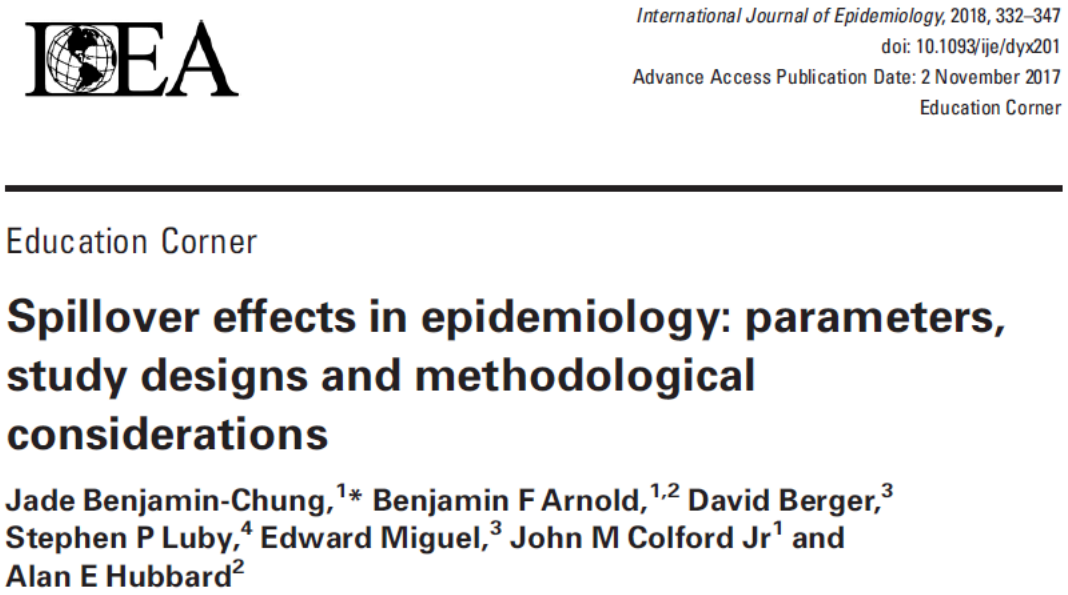

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1. Distance-based
2. Conditional on exposure to other participants' outcomes
3. Conditional on intervention density
4. Treatment coverage mean/ effect
5. Within-cluster
6. Social network

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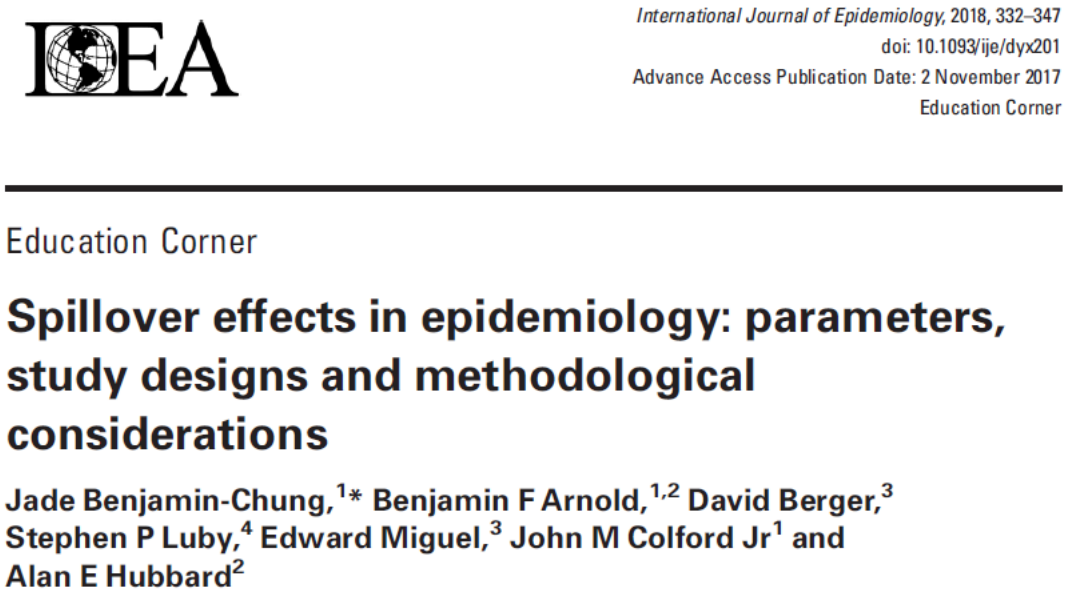

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Context and background: Spatial data

Observations to which labels have been added to show where the observations were collected (Cressie and Wikle 2011)

Discrete – Vector (Points, Lines, Polygons)

Continuous – Raster (a matrix really)

Context and background: Spatial CRTs

Cluster level: Point, Line, or Polygon

Observation level: Point, Line, or Polygon

Same or different location

Context and background: Spatial CRTs

Cluster level: Point, Line, or Polygon

Observation level: Point, Line, or Polygon

Same or different location

Spatial Type			Example		
Cluster	Observation	Location	Trial	Observation	Cluster
Point	Point	Same	Household	House	House
Point	Point	Different	School	House	School
Polygon	Point	Same	Geographical	House	Surrounding area
Polygon	Point	Different	Primary Care	House	Primary care area

Context and background: Spatial effects

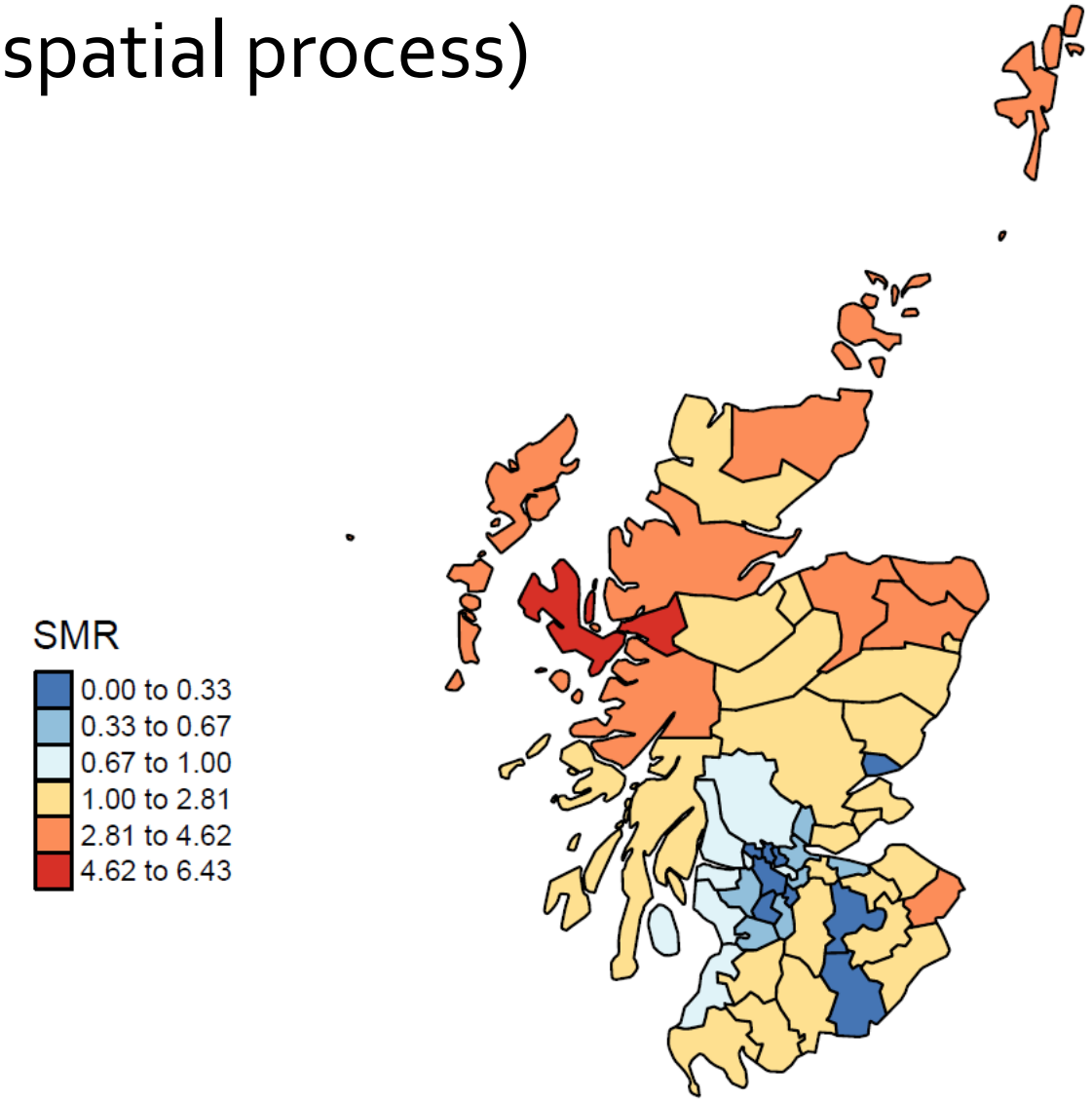
- "everything is related to everything else, but near things are more related than distant things." (Tobler 1970)
- Spatial correlation

Context and background: Spatial statistics

- Areal (Discrete spatial process)
- Geostatistical (Continuous spatial process)
- Point patterns

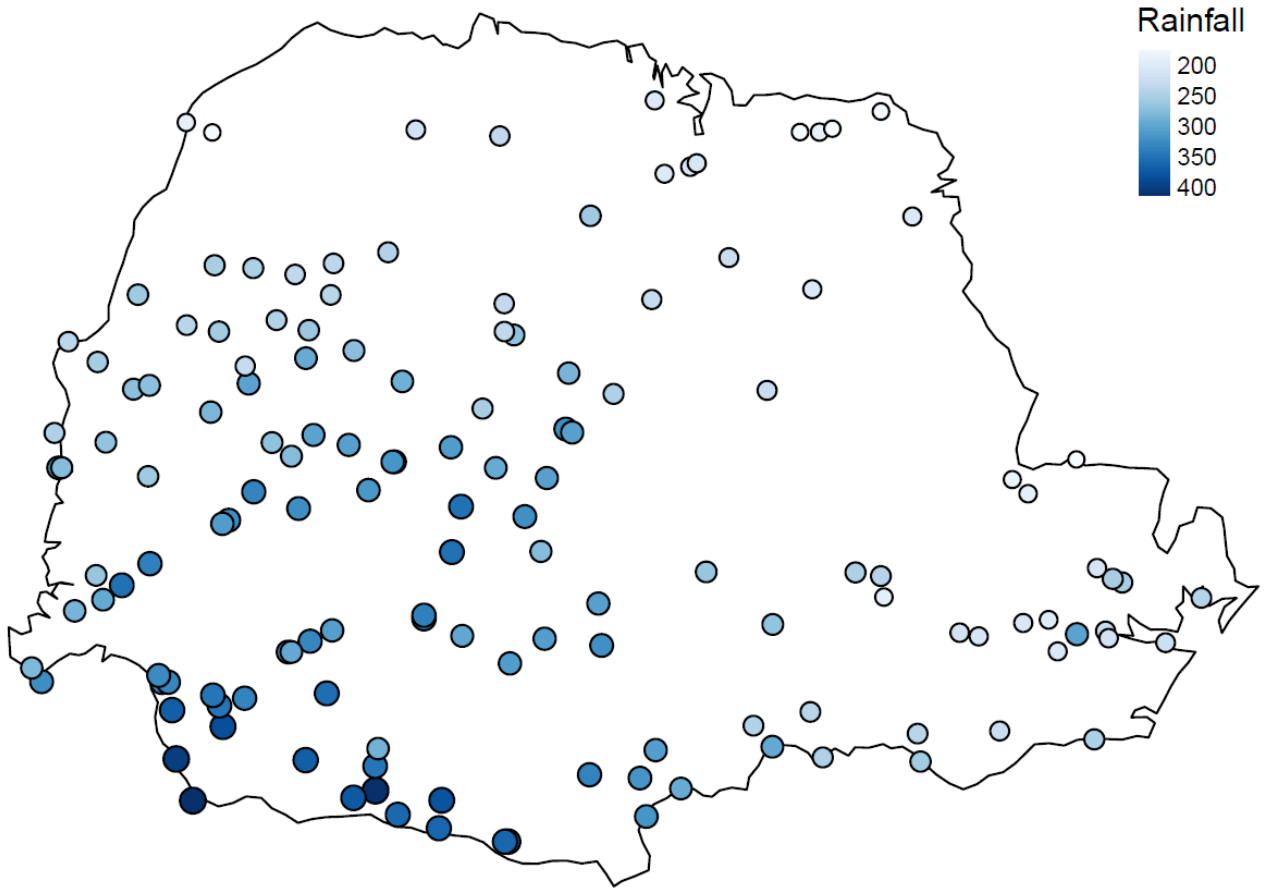
Context and background: Spatial statistics

Areal (Discrete spatial process)



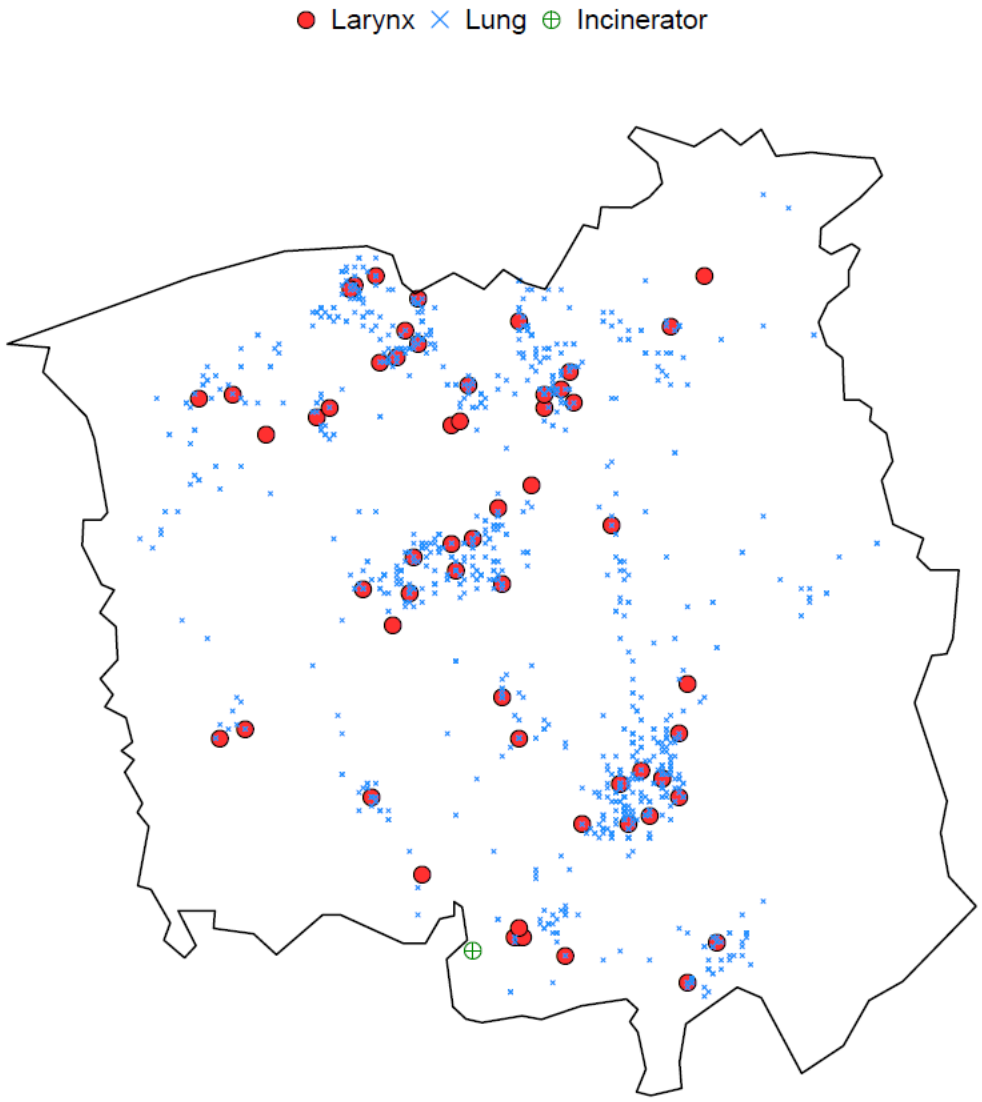
Context and background: Spatial statistics

Geostatistical (Continuous spatial process)



Context and background: Spatial statistics

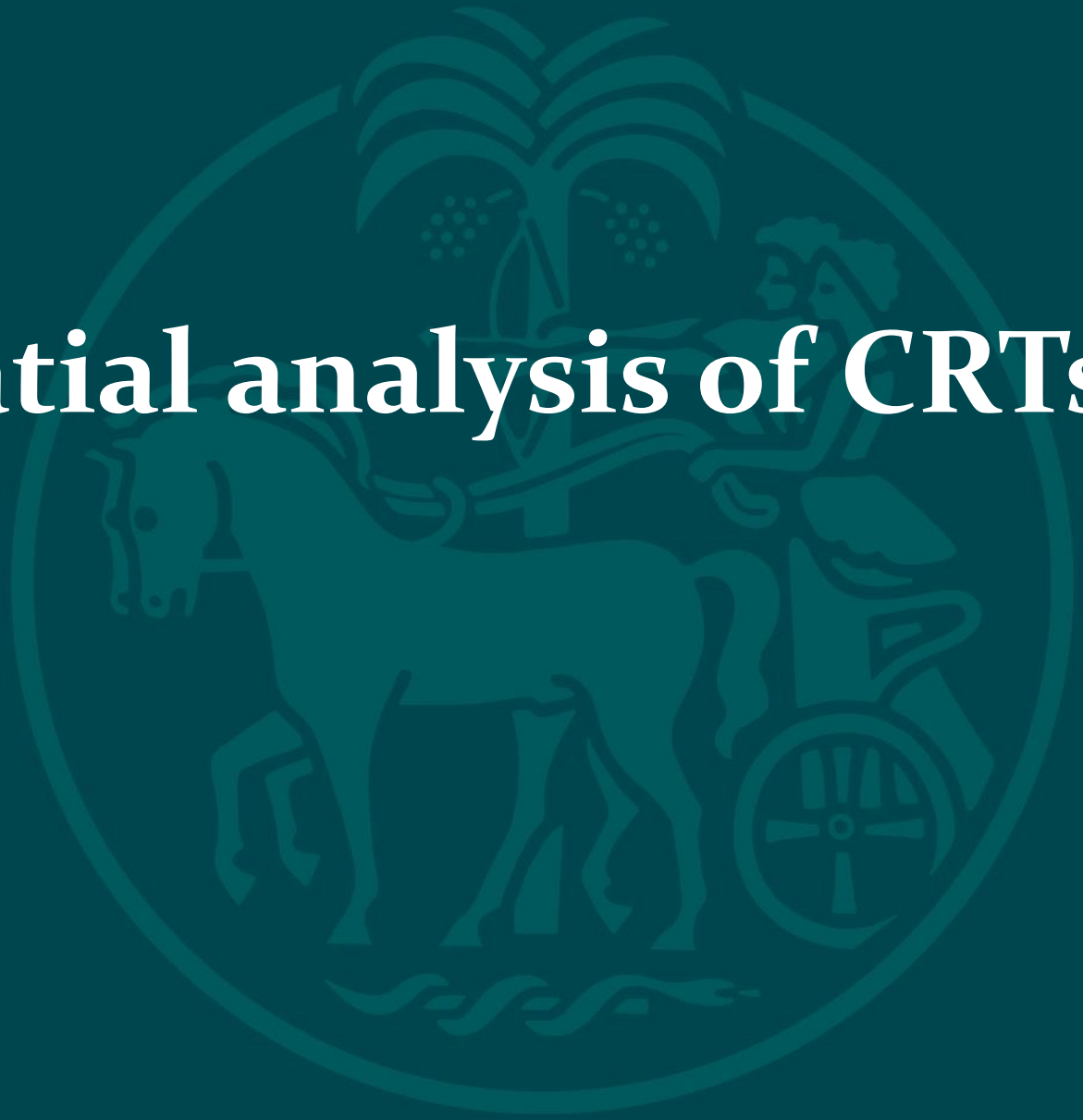
Point patterns



Context and background: Summary

- Trials where clusters are close together
- Infectious diseases
- Spatial data: points, lines polygons
- Spatial stat: areal, geostats, point patterns

Spatial analysis of CRTs



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Systematic review

Jarvis *et al. Emerg Themes Epidemiol (2017) 14:12*
DOI 10.1186/s12982-017-0066-2

Emerging Themes in Epidemiology

REVIEW Open Access

Spatial analysis of cluster randomised trials: a systematic review of analysis methods

Christopher Jarvis[1,2*], Gian Luca Di Tanna[3], Daniel Lewis[1], Neal Alexander[1] and W. John Edmunds[1]

Systematic review: Studies included

- 13 trials (10 papers published 1998 to 2015)
- A single stepped wedge trial - the rest parallel CRT
- 7 trials related to mosquitoes (mostly ITNs)
- 2 Vaccine trials, a deworming trial
- Primary care trial (two simulated and one real dataset)

Systematic review: Summary of methods

- Spatial variables (estimating spatial effects)
  - 8 papers (8 trials)
- Spatial models (adjusting for spatial effects)
  - 2 papers (4 trials – 2 simulated)

Systematic review: Estimating spatial spillover

- Typically a measurement of proximity (distance)
- Put as a covariate in a regression model.
- Need to consider spillover mechanism.

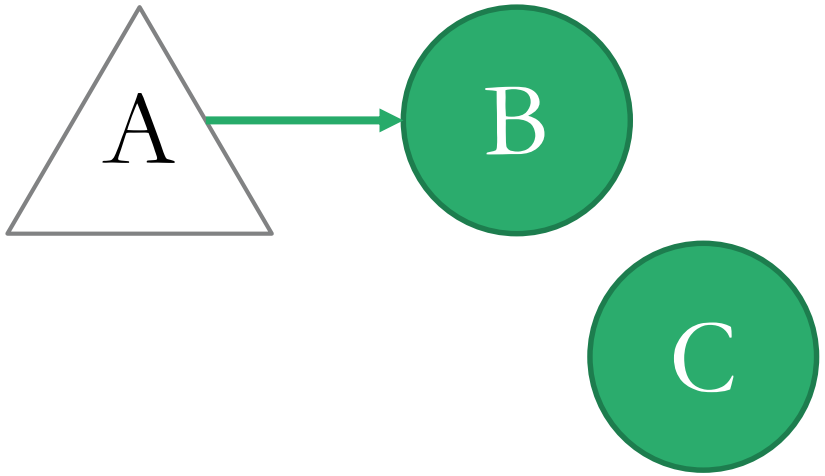
$$y = \gamma d + \epsilon$$

Systematic review: Proximity variable 1

Control

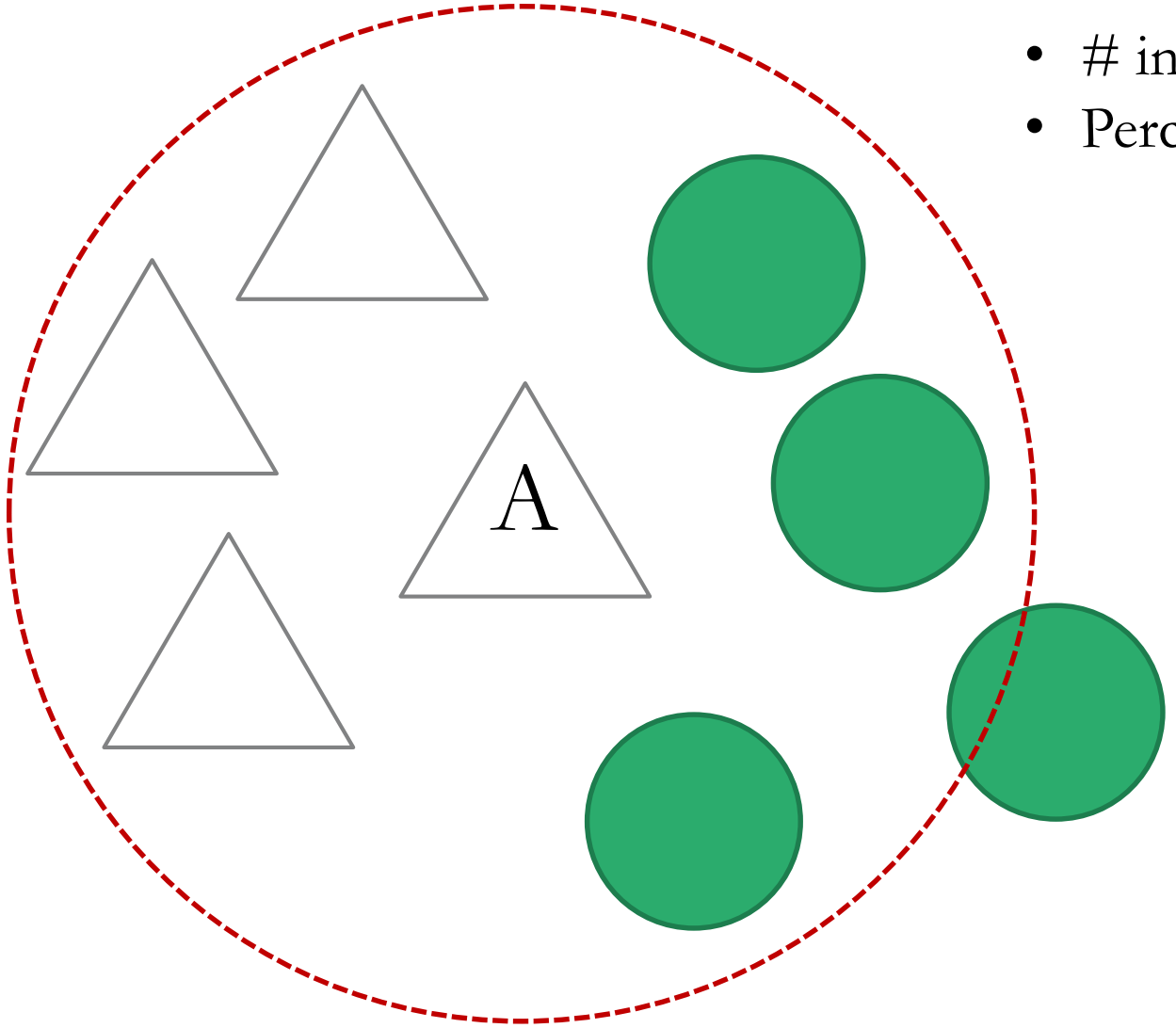
Intervention

Observation A's closest intervention observation is B



Trials: 1-5

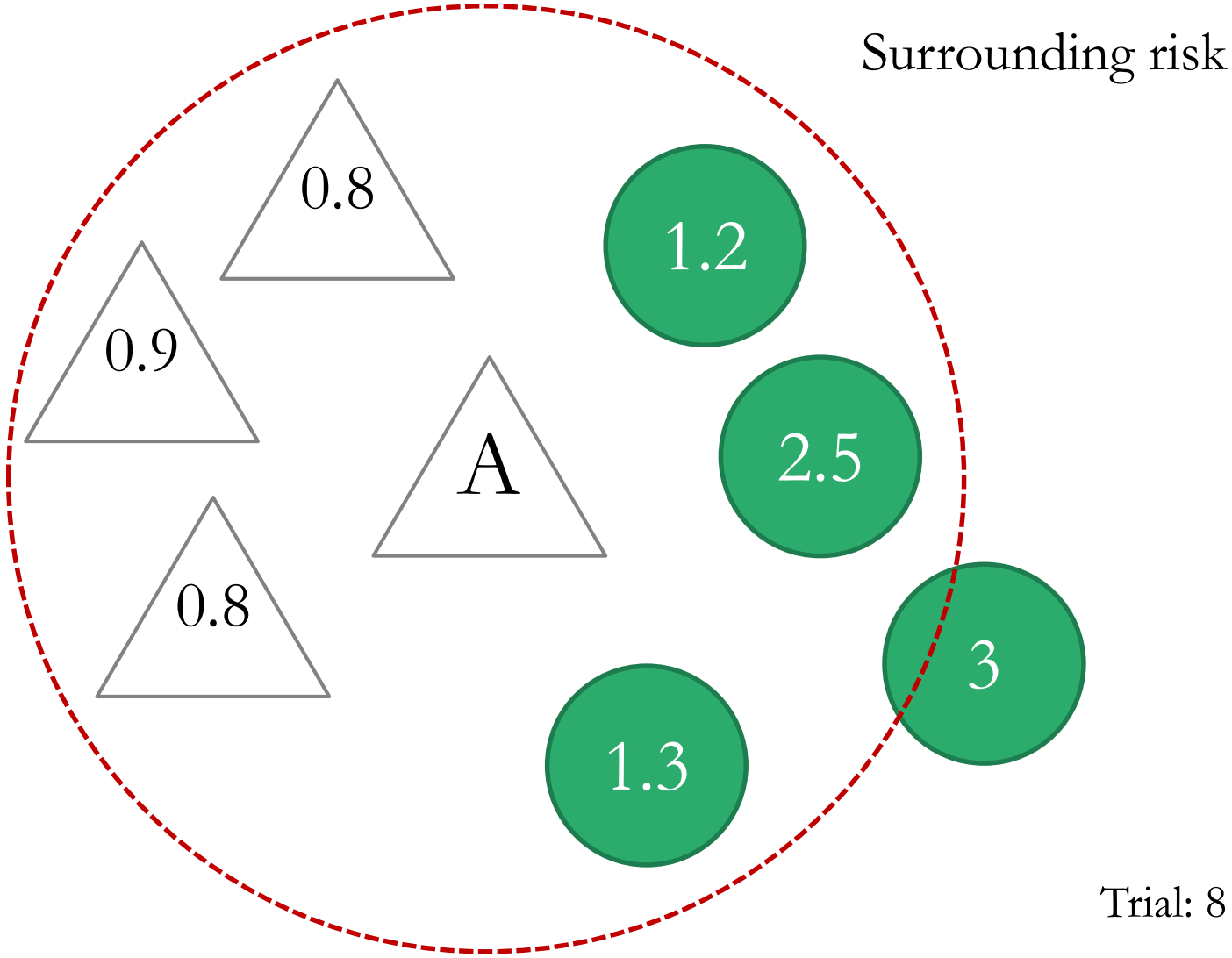
Systematic review: Proximity variable 2



- # intervention participants
- Percentage treated

Trials: 5-8

Proximity variable 3



Trial: 8

Systematic review: Adjusting for spatial correlation

$$y = \beta X + U + \epsilon$$

- Using spatial random effects
- Covariance structure incorporates connectivity

Systematic review: Spatial model

$$y = \beta X + U + \epsilon$$

Systematic review: Spatial model

$$y = \beta X + U + \epsilon$$

$$U \sim MVN(0, \sigma_u^2 \Sigma)$$

$$\Sigma = (I - \rho W)^{-1}$$

Systematic review: Spatial model

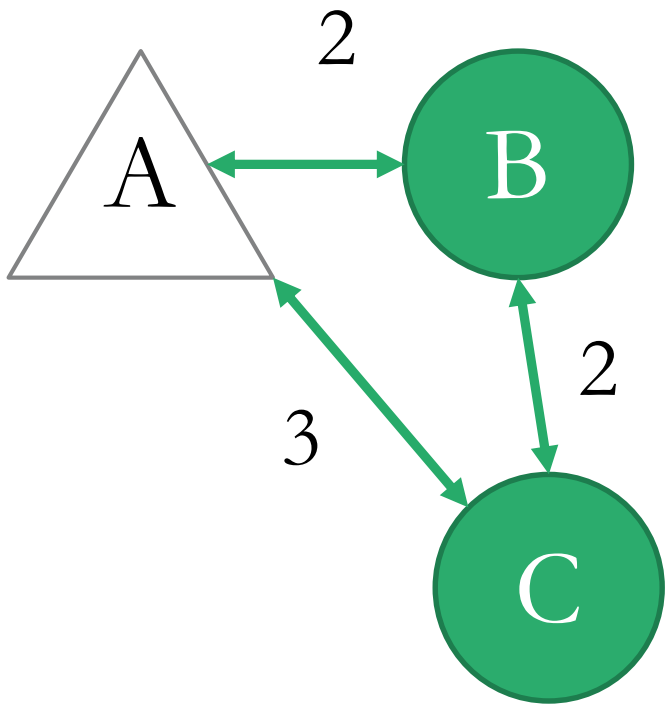
$$y = \beta X + U + \epsilon$$

$$U \sim MVN(0, \sigma_u^2 \Sigma)$$

$$\Sigma = (I - \rho W)^{-1}$$

Systematic review: Spatial weights matrix

Spatial Structure



W

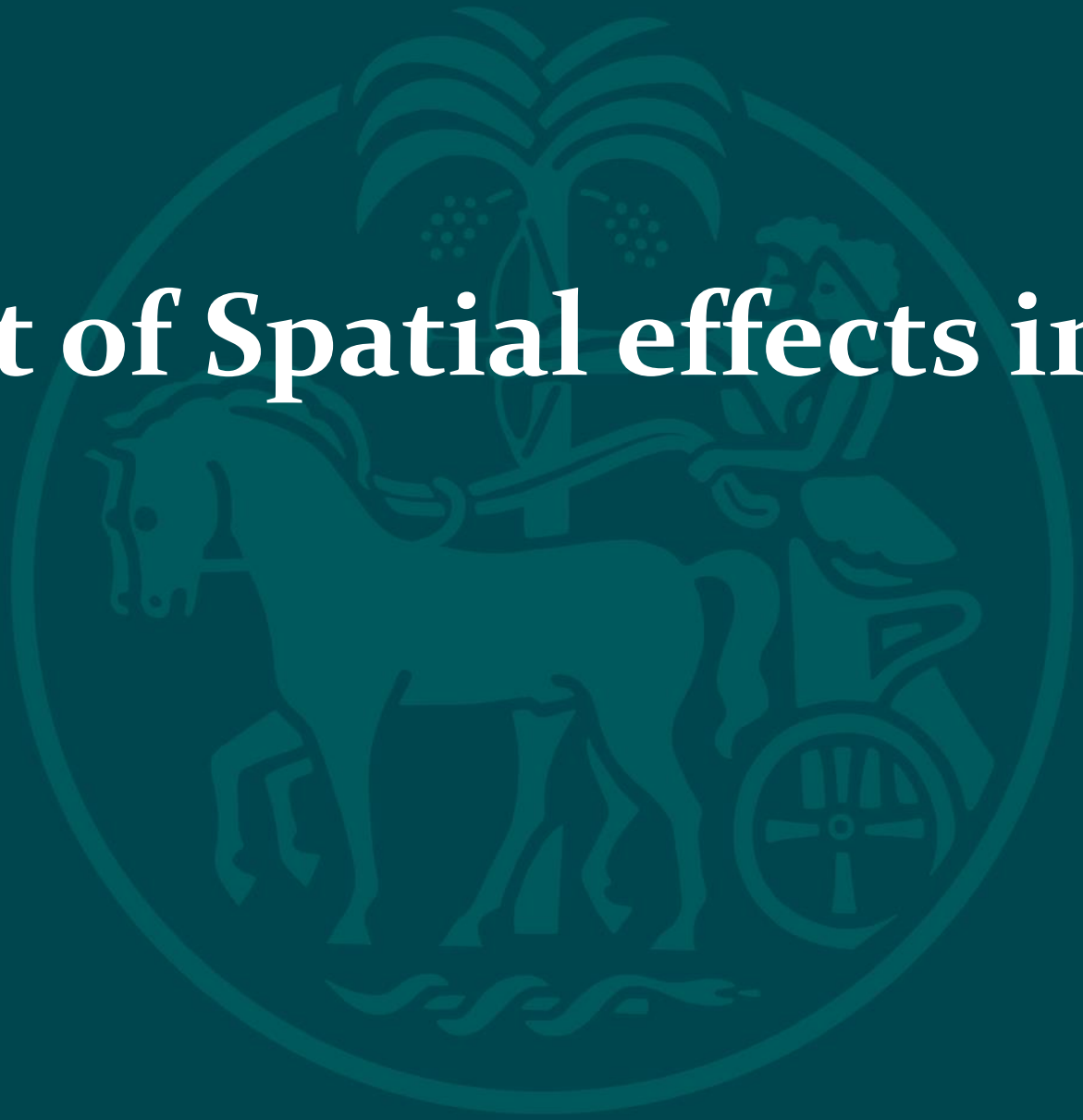
	A	B	C
A	0	2	3
B	2	0	2
C	3	2	0

Trial: 9, 10

Systematic review: Summary

- Few examples in literature
- Two approaches
  - Spatial variables
  - Spatial models
- Mostly a secondary analysis

Impact of Spatial effects in CRTs



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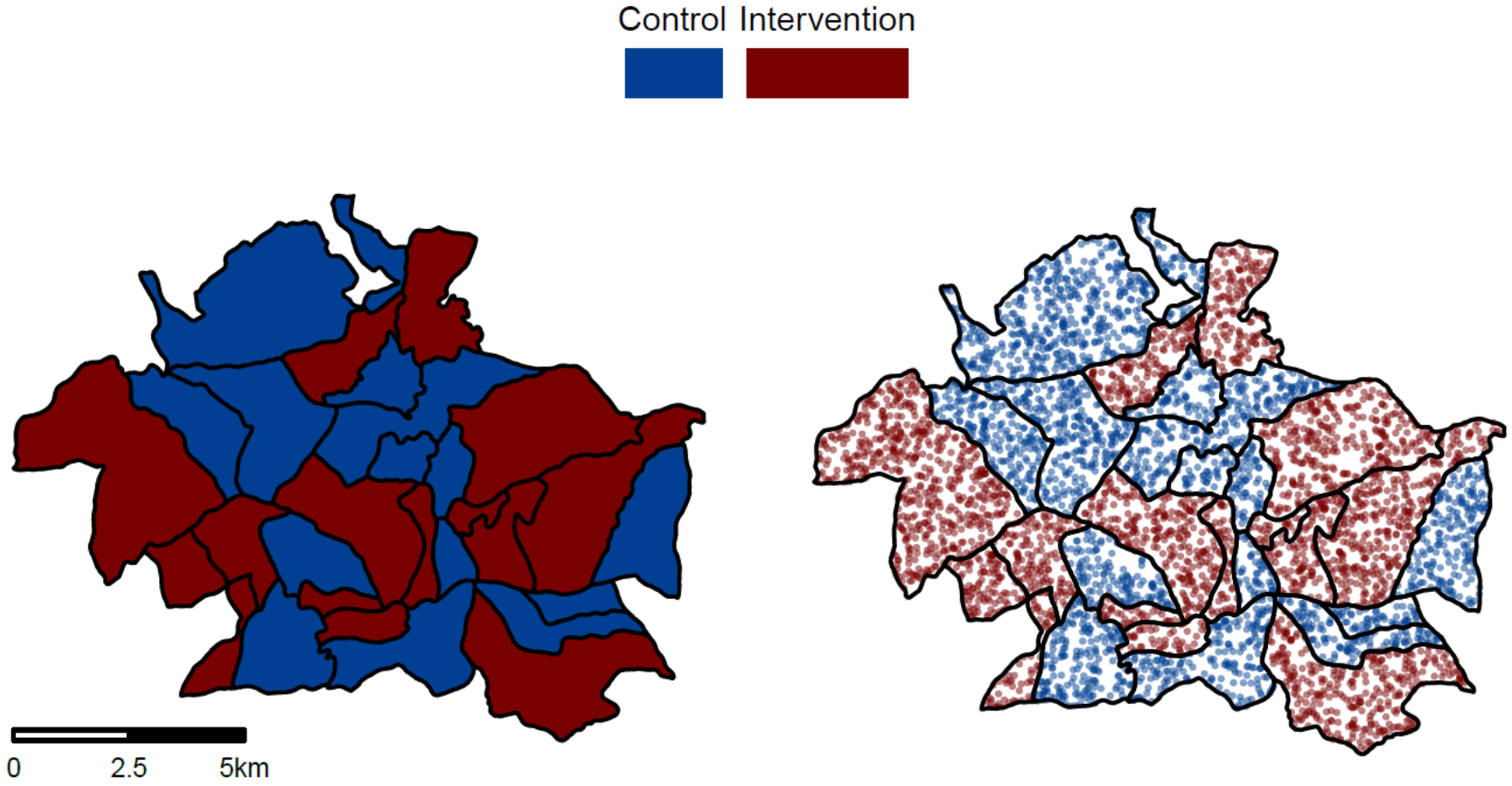
Simulation: Simulating spatial effects

- Simulated a CRT with 30 clusters, 5,000 points, ICC of 0.05 and continuous outcome
- Standard iid random effects model adjusting for cluster and two spatial models.



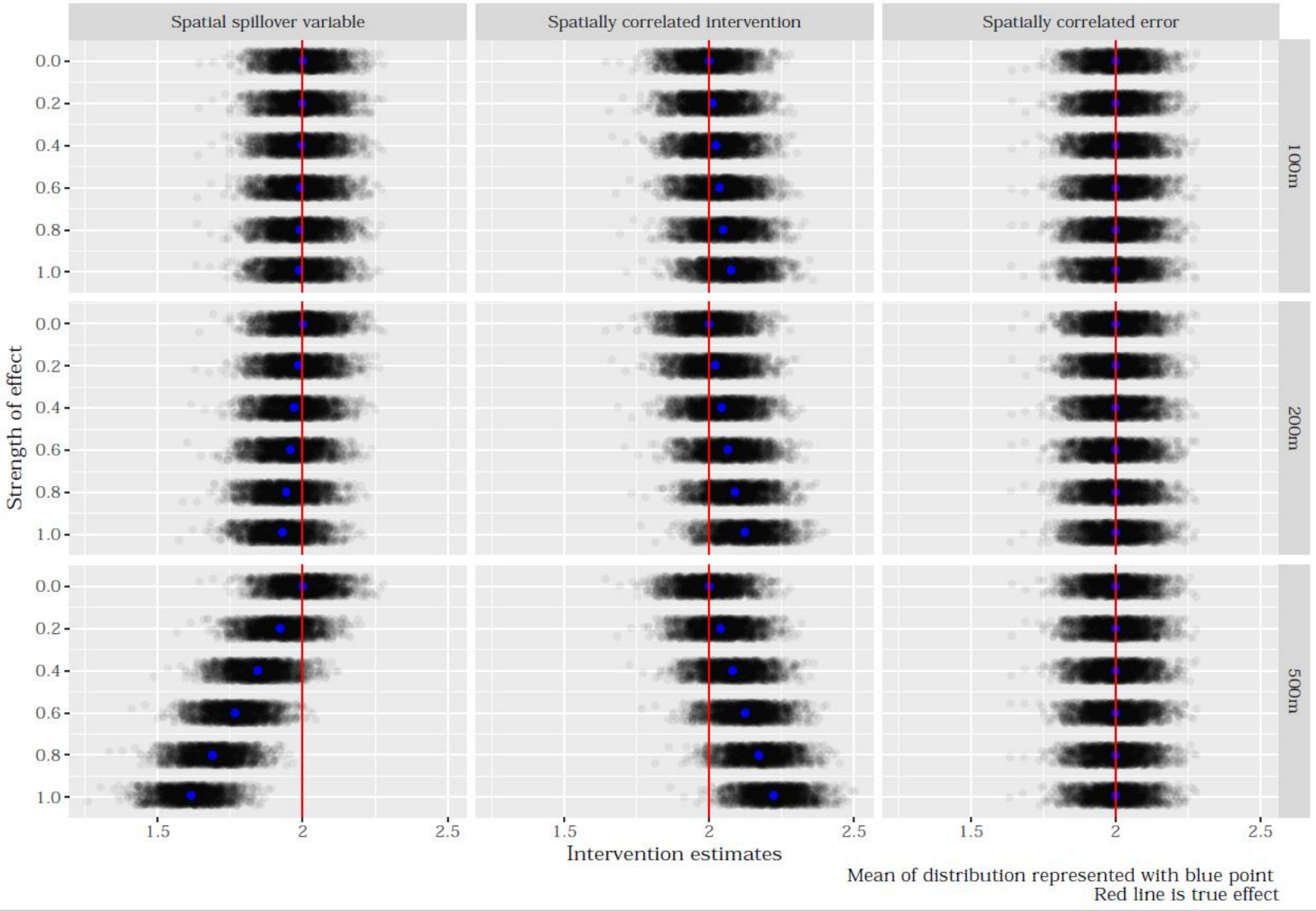
Simulation: Study values held constant

- Intervention effect ($\beta = 2$)
- ICC ($\sigma_b = 0.05, \sigma_w = 0.95$)
- Number of clusters (30)
- Sample size (5000)
- Locations (simulated under spatial randomness)
- 2000 simulations for iid
- 200 for spatial models

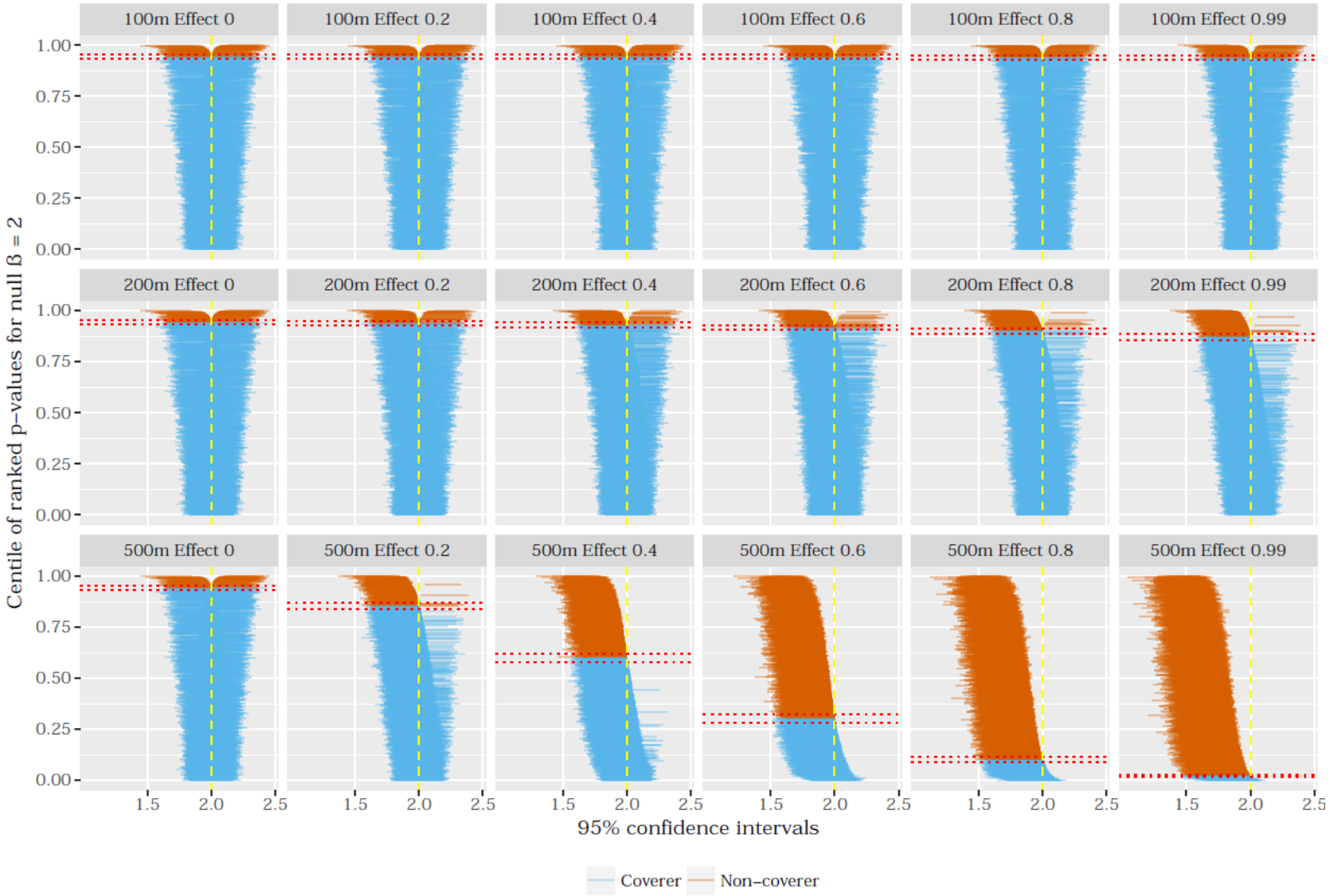
Simulation: Study values varied

- Spatial spillover variable
  - Intervention causes a benefit individuals nearby
- Spatial correlated intervention
  - Intervention effect is smoothed among nearby individuals
- Spatially correlated error
  - A separate factor which affects the outcome which is spatially distributed.
- Range of effect (100, 200, and 500 m)
- Size of effect (0, 0.2, 0.4, 0.6, 0.8, 0.99)
  - Spatial variable (Proportion of intervention effect)
  - Spatial correlation (strength of correlation)

Simulation: Bias for IID model



Simulation: Coverage for spatial spillover variable

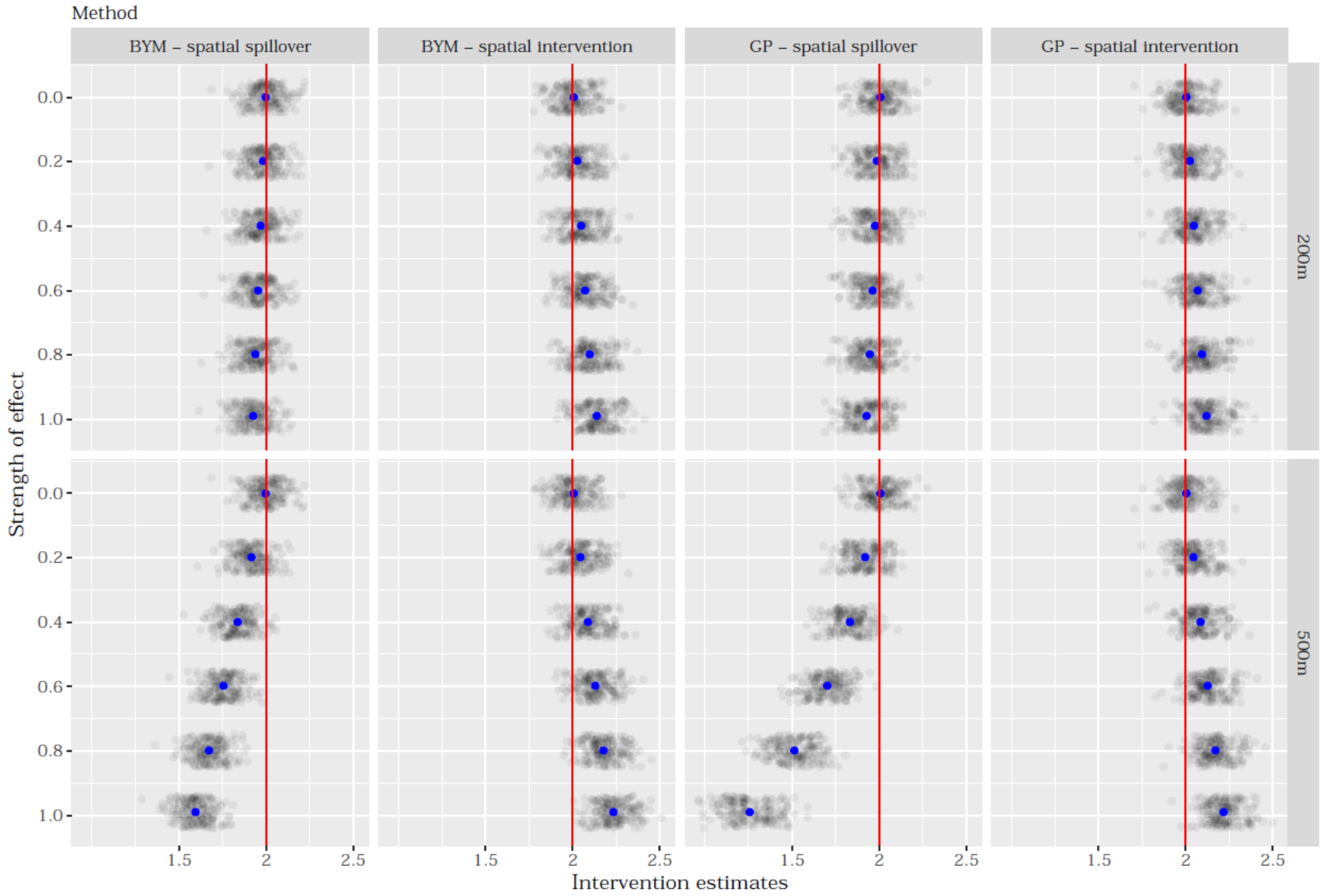


Simulation: Spatial models

- Tested spatial models to see if they can adjust for the spatial effects

- Spatial models were fitted using Integrated nested Laplace approximation (INLA)
  - Besag, Yorke, and Mollie (BYM) model (Cluster level spatial effect)
  - Geostatistical or Gaussian process model (Observation level spatial effect)

Simulation: Bias spatial models



Mean of distribution represented with blue point
Red line is true effect

Simulation: Summary

- Spatial intervention effects did impact the estimate of the intervention
  - Need to be concerned when the intervention has an effect on individuals who do not receive the intervention
  - Though it needs to be quite strong or over a large distance compared to study regions to affect results
- Spatially correlated errors did not impact estimate of the intervention
  - Less concern about other factors affecting the outcome which are spatially correlated.
- Useful to have a way to assess if spillover is present.

Cluster reallocation: Exploring spatial spillover

Method: Motivation

- Create a method to explore for spillover in the intervention
- Require minimal spatial knowledge
- Exploratory rather than confirmatory
- Use methods similar to those used for CRTs
- Allow for different CRT methods

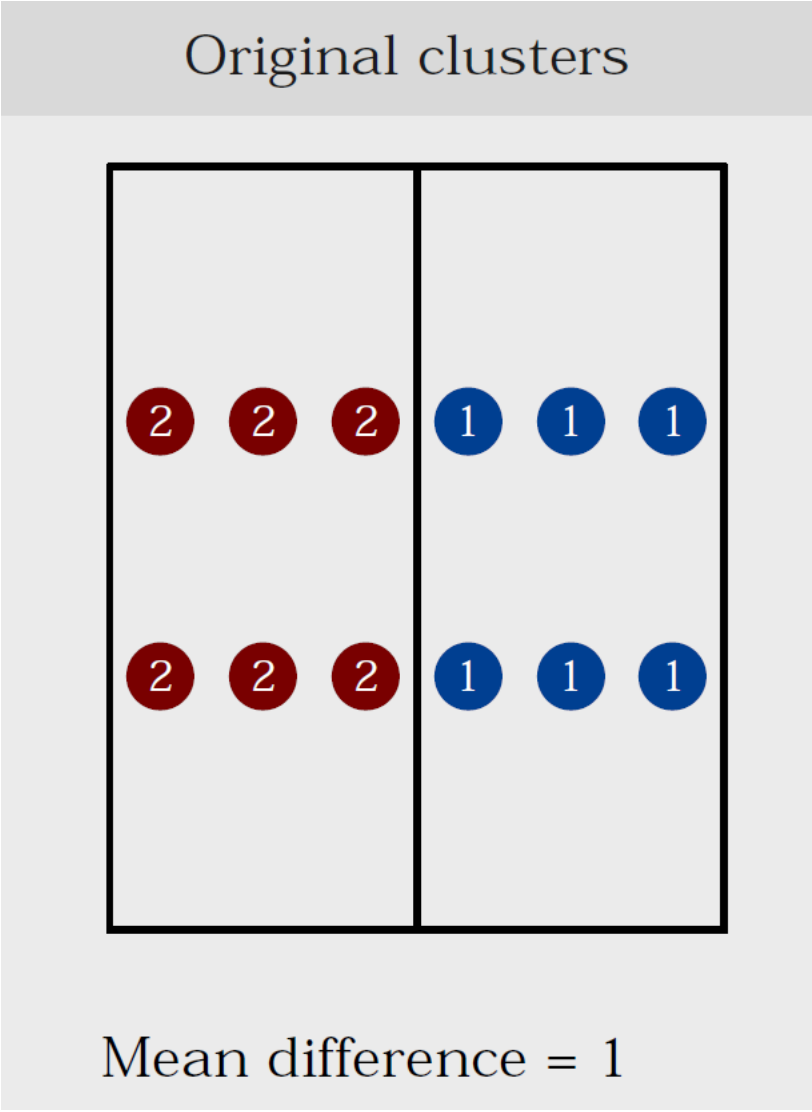
Method: Approach

- Imagine a positive spatial spillover effect is present.
- Individuals near to intervention effect receive a beneficial effect.
- Underestimate of the intervention as some control individuals are more similar to intervention participants as they benefit from an indirect intervention effect.
- We could reallocate individuals from the control cluster into the intervention cluster and recalculate the intervention effect.
- This would result in a stronger intervention effect as we moved individuals more who benefit from the intervention into the intervention arm.

Method: Problem

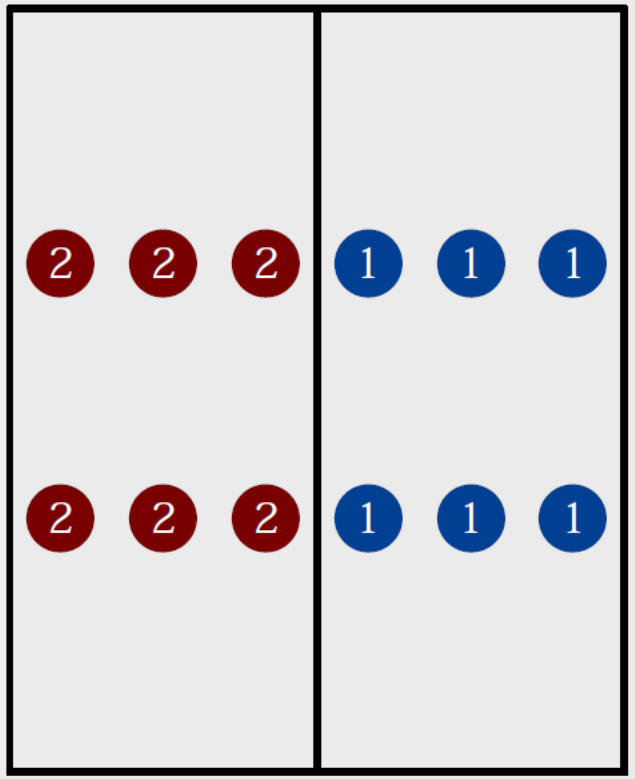
- We do not know who receives an indirect effect (Use distance as a proxy).

Method: No spillover



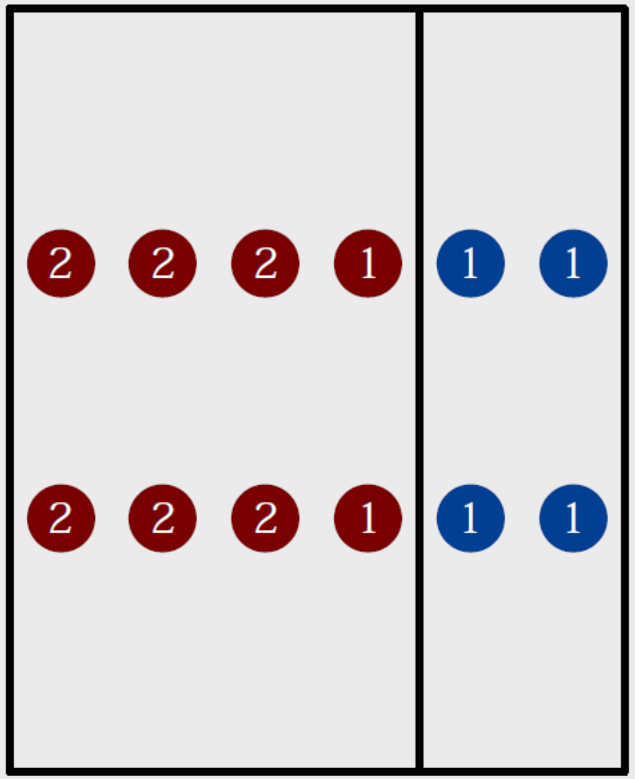
Method: No spillover

Original clusters



Mean difference = 1

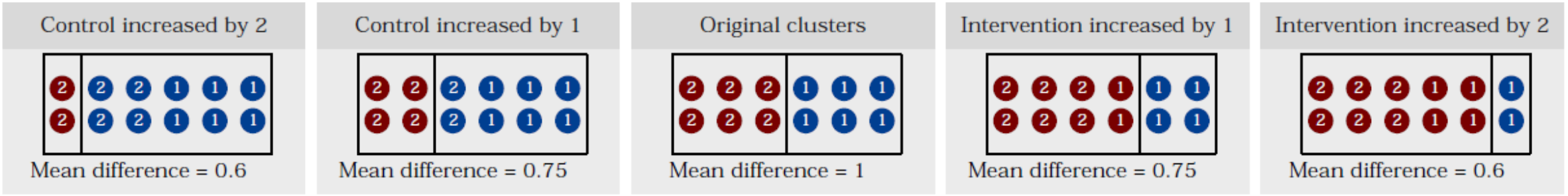
Intervention increased by 1



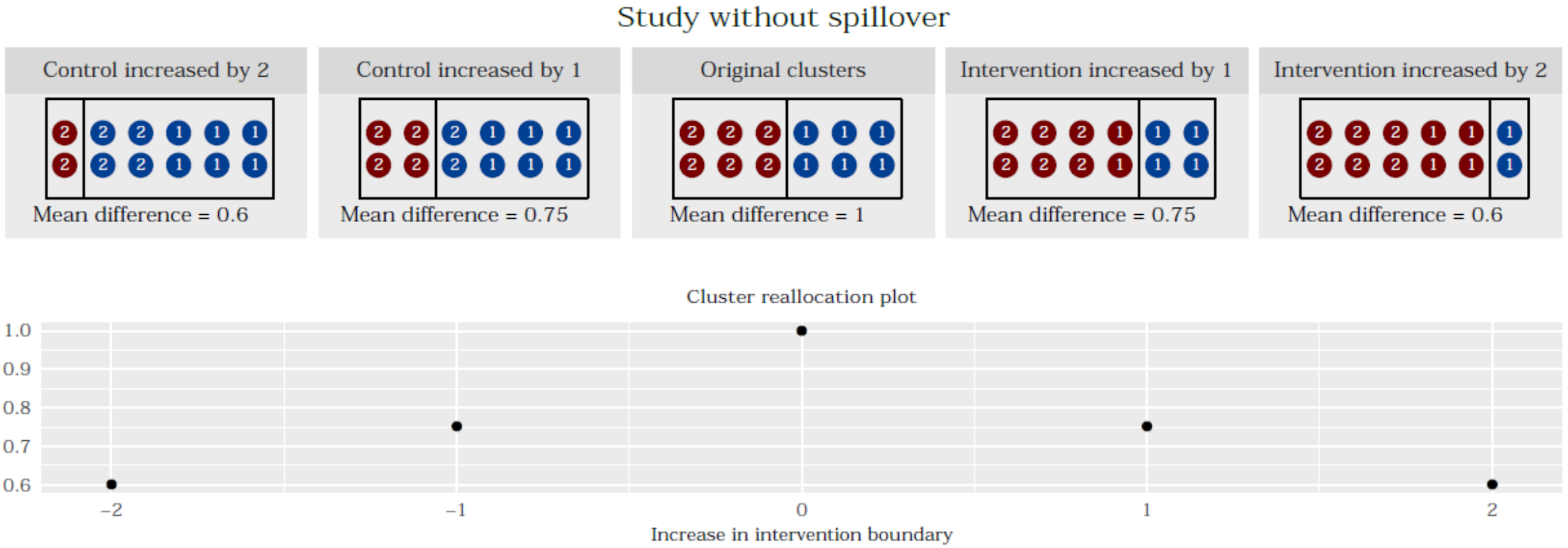
Mean difference = 0.75

Method: No spillover

Study without spillover

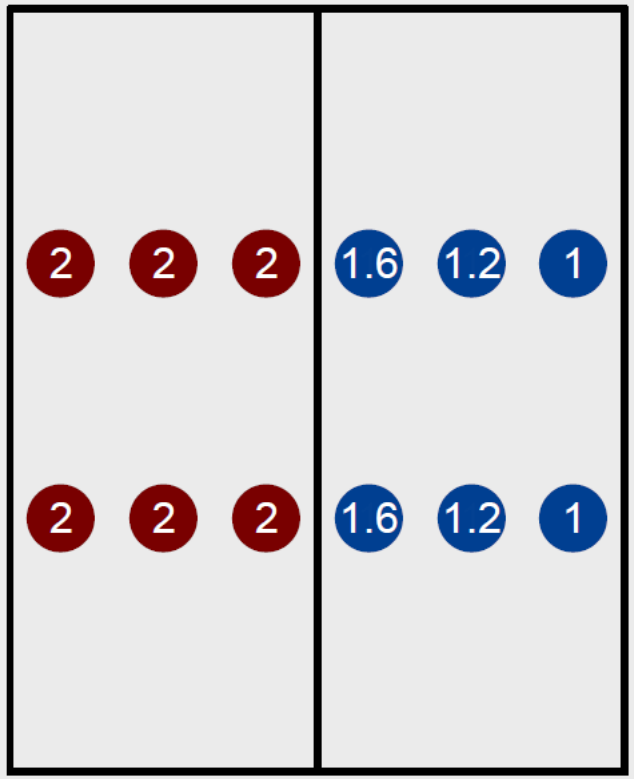


Method: No spillover



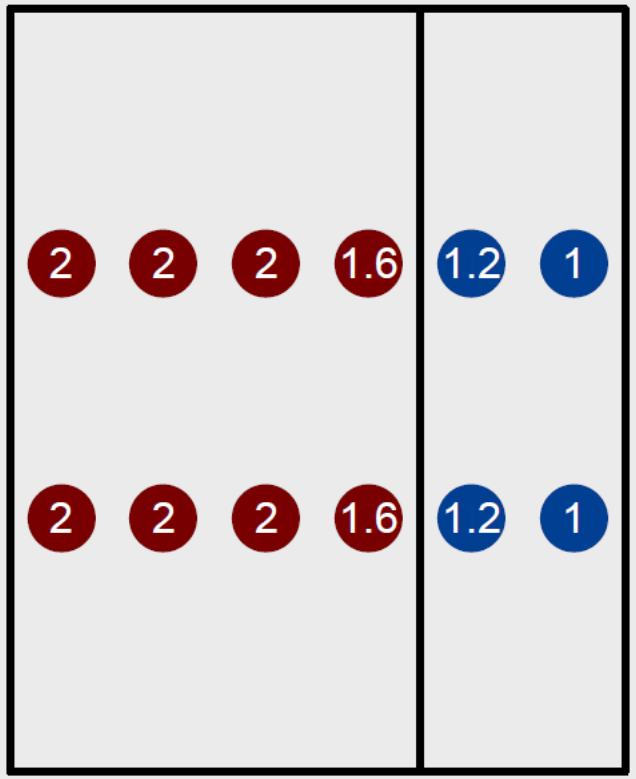
Method: Spillover

Original clusters



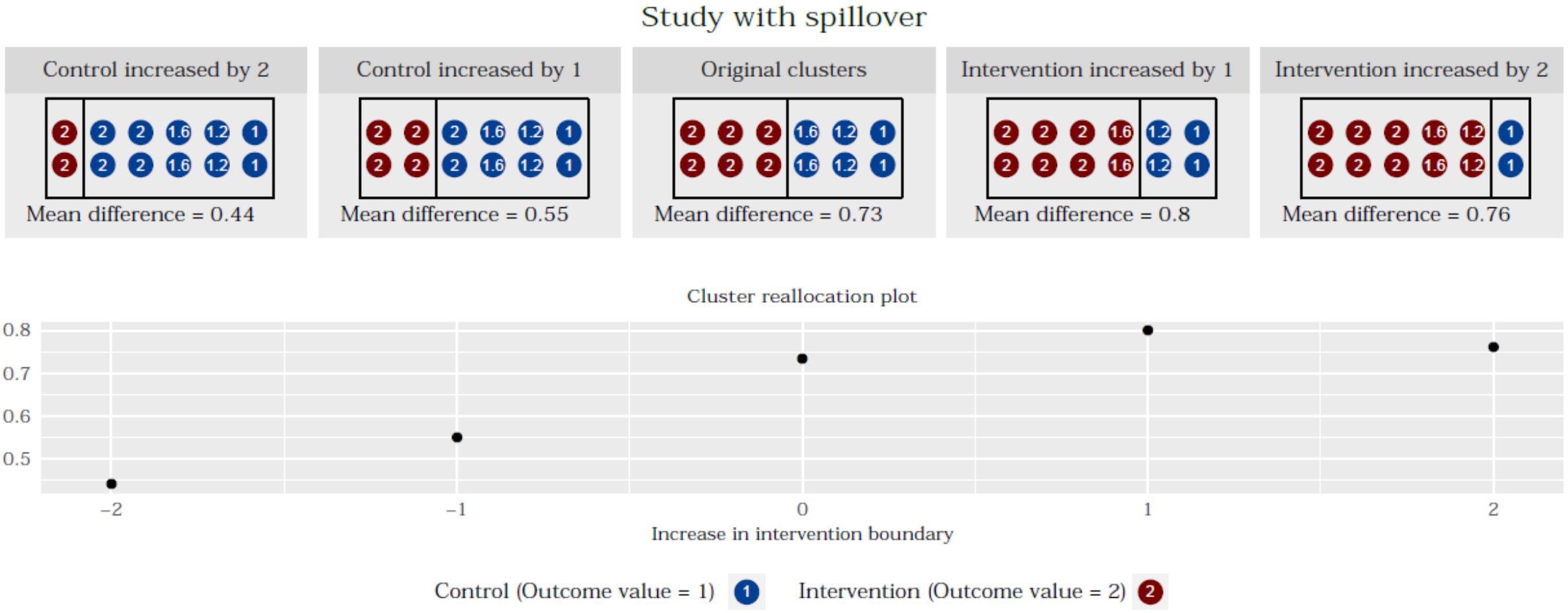
Mean difference = 0.73

Intervention increased by 1

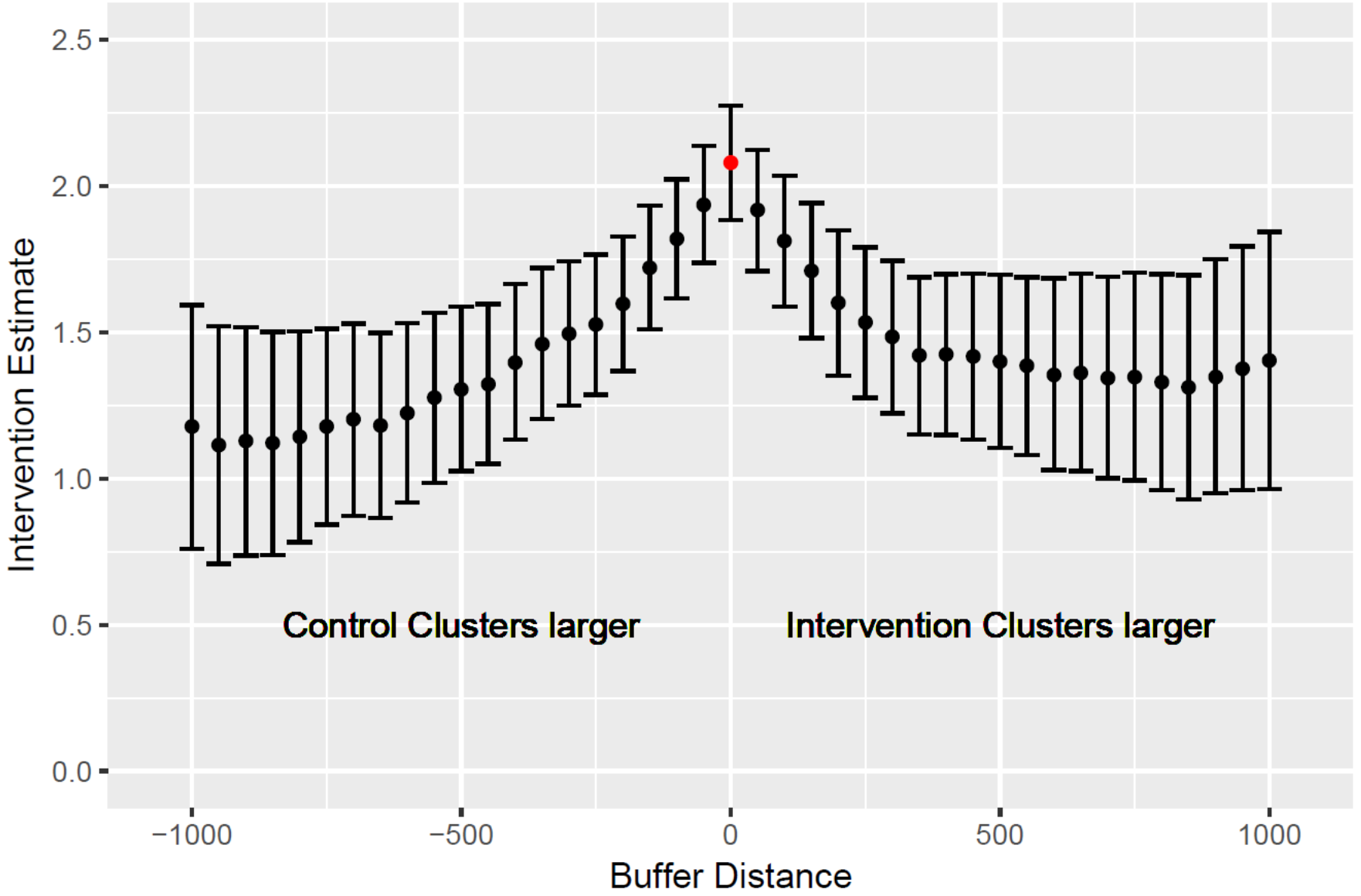


Mean difference = 0.8

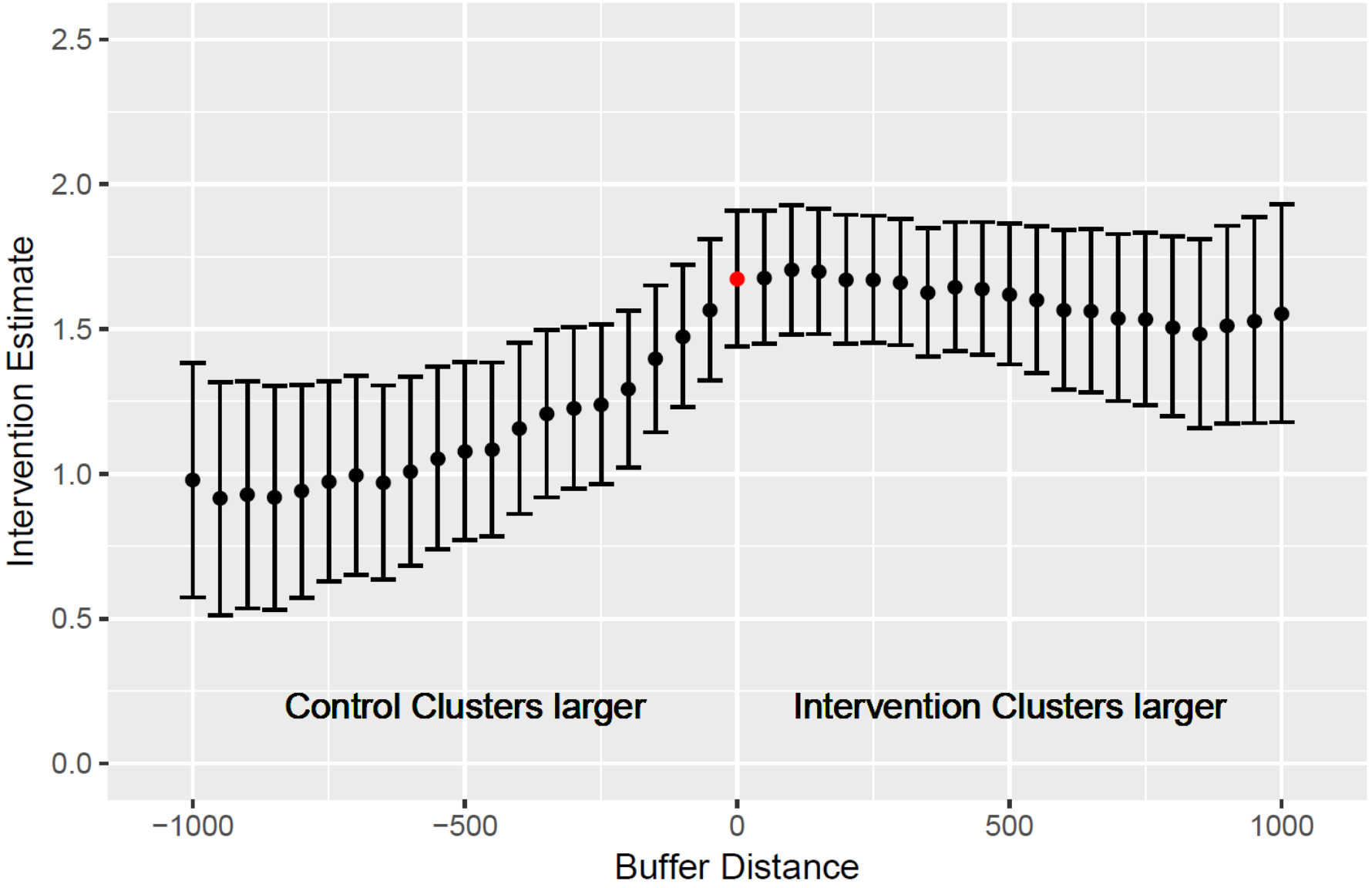
Method: Spillover



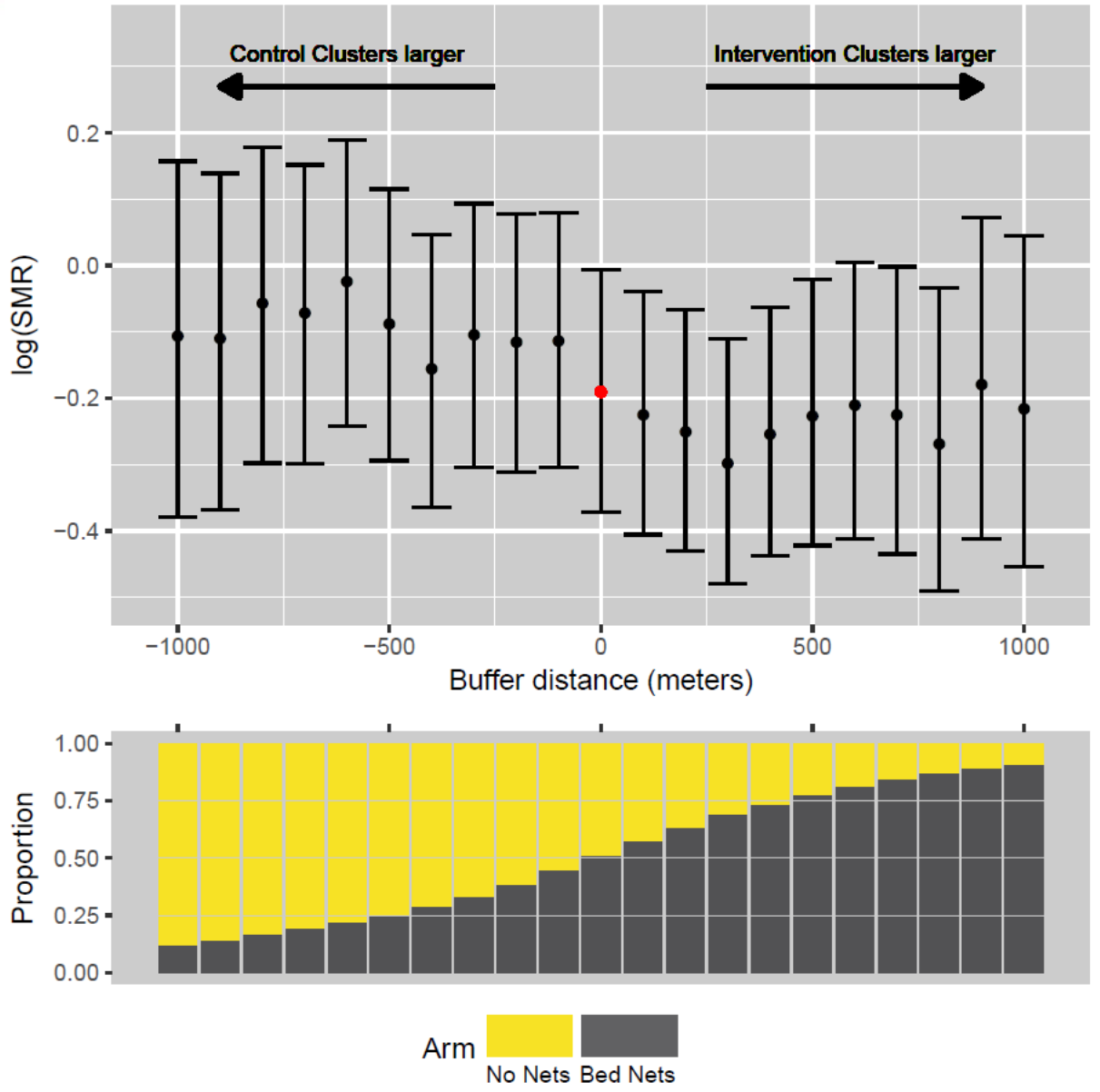
Method: CR plot – no spillover



Method: CR plot – no spillover



Method: CR plot – Imbalance in arms



Method: Summary

- Cluster reallocation allows the user to explore spatial spillover
- Does not require advanced knowledge of spatial stats
- Model agnostic GEE, two-stage, random effect
- Could be extended to other types of networks such as social
- Package in R being developed.

Summary

- CRT can be conceptualised spatially using only a few spatial types
- Spatial analyses in CRTs are rare but can be useful for additional analyses
- Potential to bias results but likely spatial effects need to be strong
- Spatial models tested so far are not much help
- Cluster reallocation allows for assessing whether spatial spillover is present.

Acknowledgements

- Gian Luca di Tanna, Jo Lines, Karim Anaya-Izquierdo

- Thomas Smith, Lea Multerer, and Fred Binka

- Yvonne Maldonado, Jonathan Altamirano, and Clea Sarnquist

Support

- This work was funded by the Medical Research Council London Hub for Trials Methodology Research, grant number MR/L004933/1-Q42

Spillover terms

- Contamination

Individuals in one arm receive or are exposed to the intervention in the other arm

- Interference

Intervention given to an individual affects not only that person, but also other participants.

- Externalities

Effect on an individual who did not choose to receive that effect.