Statistical modelling of health-environment relationships: *handling ecological bias*

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Introduction

Recent trends in environmental epidemiology:

- ↑ use of Bayesian hierarchical models to smooth risk estimates
- ↑ availability of high-resolution geo-referenced health and exposure data
- ↑ use of ecological regression models at small-area scale

Standard ecological regression model:

$$Y_i \sim \text{Poisson}(E_i \, \theta_i)$$

$$\log \theta_i = \alpha + \beta \, X_i$$

- $\exp(\beta)$ = RR associated with exposure X

Interpretation of β

- β measures the ecological or group-level association between exposure and disease risk
- Not necessarily equal to the individual-level association → ecological bias
- Can arise for various reasons, including:
  - non-linear exposure-response relationship, combined with within-area variability of exposure
  - within- and between-area confounding
  - area-level effect modification
  - spatial dependence in the residuals

Spatially dependent residuals

- Observed risk factor(s) X are unlikely to explain all of the between-area variation in risk
- Residual variation (in excess of Poisson) can be captured using hierarchical model

$$Y_i \sim \text{Poisson}(E_i \theta_i)$$

$$\log \theta_i = s_i + \beta X_i$$

$$s_i \sim \text{spatial prior}$$

- s_i acts as proxy for unidentified area risk factors
  - captures residual variation in risk not explained by X
  - necessary for correct estimation of precision of exposure effects, β (see Wakefield 2003)

Area-level effect modification

- Effect modification occurs when dose-response relationship depends on level of a third variable
- Common examples of (individual) effect modifiers:
  - age, time, genetic predisposition
- In ecological regression, may suspect geographical heterogeneity in effects of various risk factors:
  - subgroups of people particularly susceptible
  - interaction with location due to contextual effects, effectiveness of health system, socio-economic / cultural / ethnic factors, …..

Spatially varying coefficient models

- Instead of letting spatial structure only influence residual effects in ecological regression model
  - $\rightarrow$ introduce spatial structure on covariate effects, β
  - $\rightarrow$ spatially varying coefficient models
- Widely used in econometrics and geography (Assunçao, 2003)
- Links with generalised additive models (gam) where regression coefficients vary as smooth function of other variables (effect modifiers)

Statistical model:

$$Y_i \sim \text{Poisson}(E_i\, \theta_i)$$

$$\log \theta_i = s_i + \beta_i X_i$$

$$s_i \sim \text{spatial prior}$$

$$\beta_i \sim \textbf{spatial prior}$$

- $\exp(\beta_i)$ = RR associated with exposure X in area i
  - assumed to vary across areas
  - location is acting as proxy for effect modifier

Questions

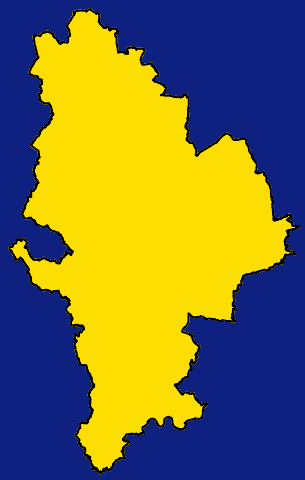
- How well do models capture different patterns of covariate effects when they are present?
- Can the spatial structure of the coefficients be distinguished from that of the spatial residuals?
- Do these models "invent" spatial structure in the coefficients, even when it is not there?
- How much is lost by over-fitting: constant vs varying coefficient model?

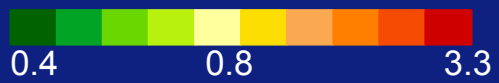
Simulation study

Model	Regression coefficient	Residual
1	Constant	Spatial
2	Random	Spatial
3	Spatial (Patchy)	Spatial
4	Spatial (Smooth)	Spatial

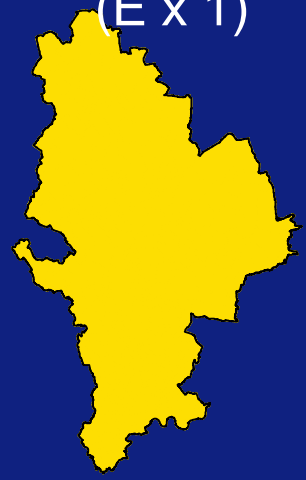
- Geographical scenario: 525 wards in NW London
- Expected counts: based on real population and incidence of rare cancer (median $E_i = 2.8$)
- 50 datasets simulated for each model using E_i x1 and E_i x5
- Analysed using (i) spatially varying coefficient model and (ii) constant coefficient model

True RR
(constant)

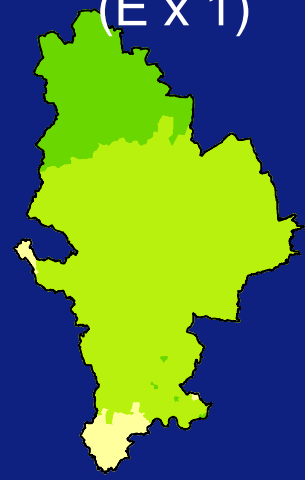


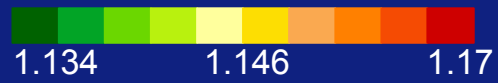


Average
estimated RR
(E x 1)



Average
estimated RR
(E x 1)



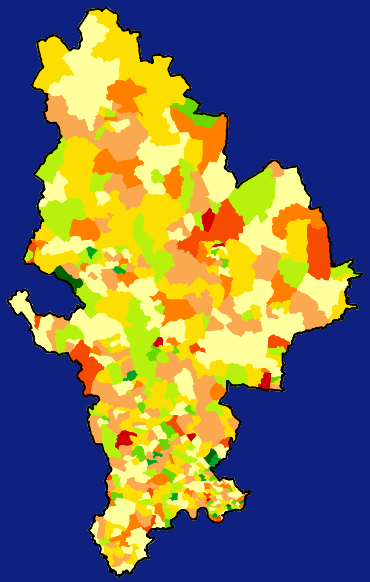


Regression coefficients

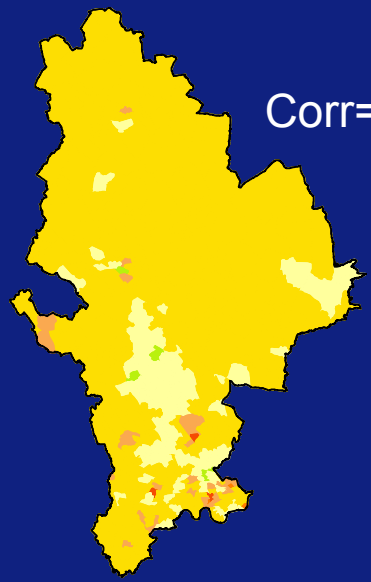
(E x 5)

(E x 5)

True RR
(Random)

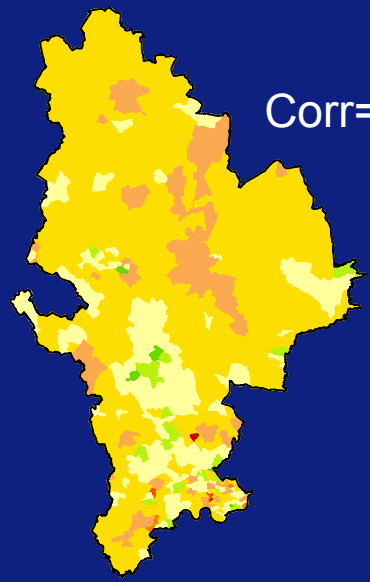


Average
estimated RR
(E x 1)



Corr=0.54

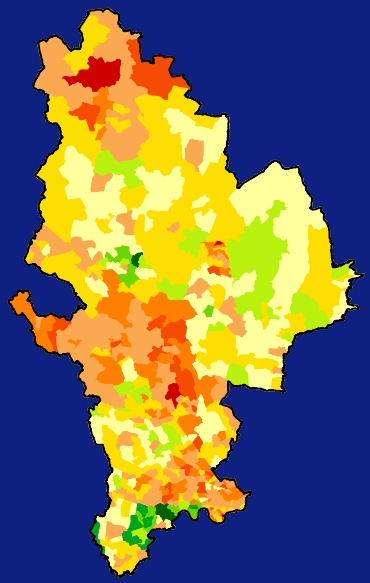
Average
estimated RR
(E x 5)



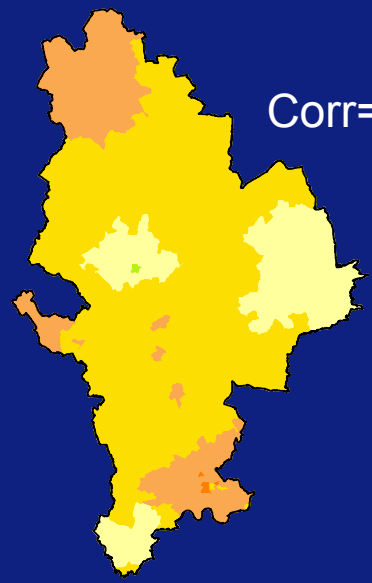
Corr=0.69

0.4 0.8 3.3

True RR
(Patchy A)

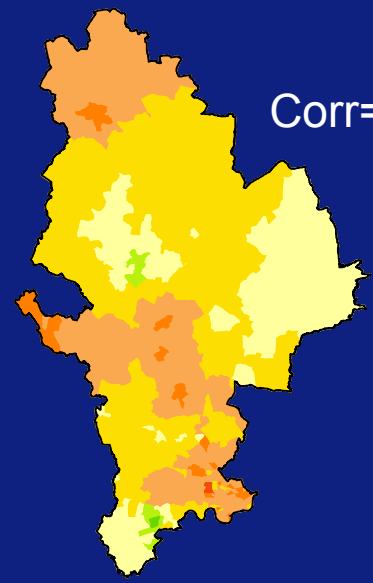


Average
estimated RR
(E x 1)

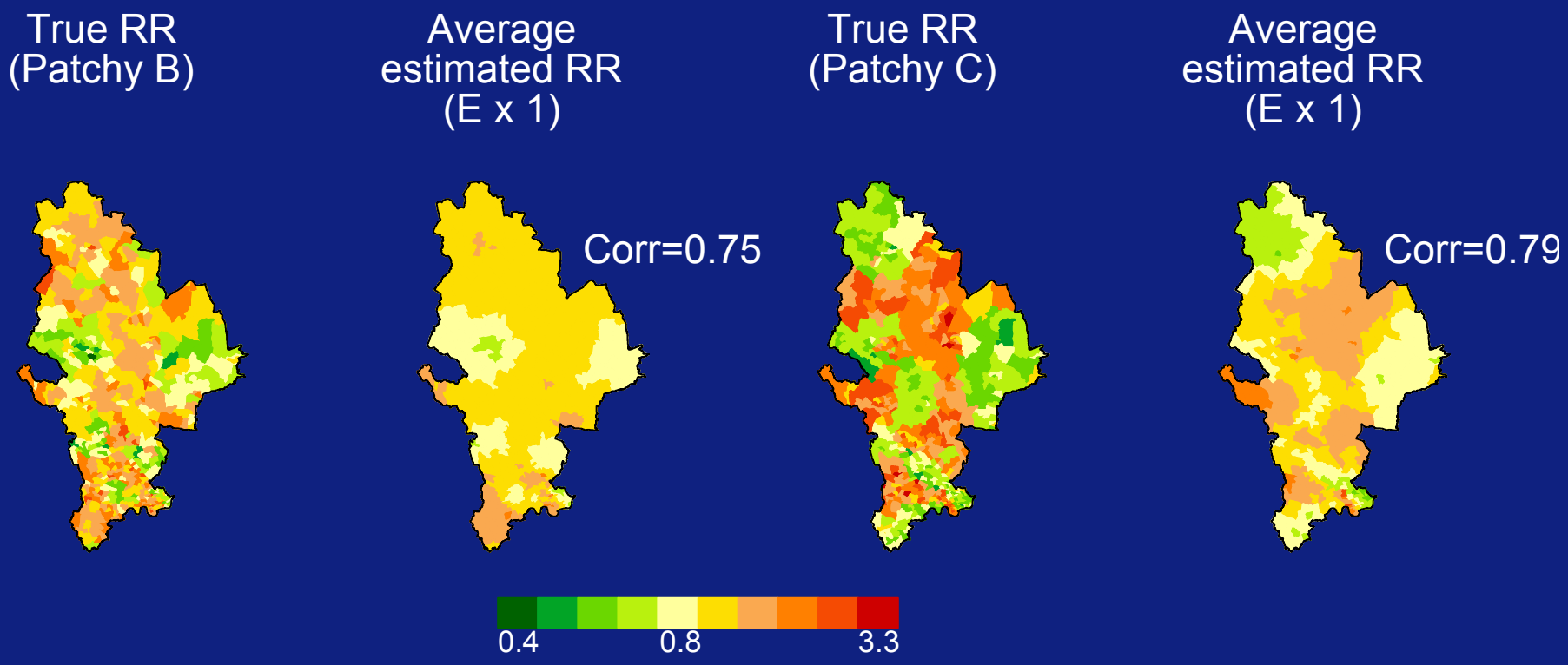


Corr=0.6

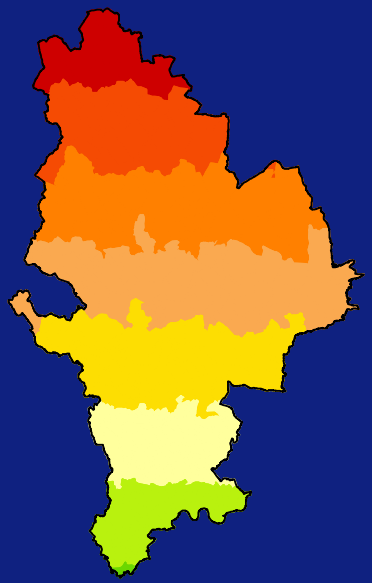
Average
estimated RR
(E x 5)



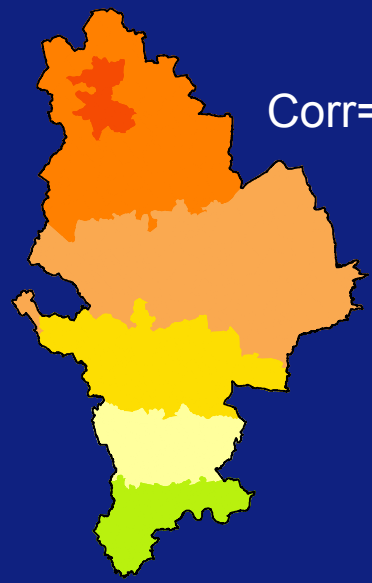
Corr=0.76


True RR
(Patchy B)
Average
estimated RR
(E x 1)
Corr=0.75
True RR
(Patchy C)
Average
estimated RR
(E x 1)
Corr=0.79
0.4
0.8
3.3

True RR
(Smooth)

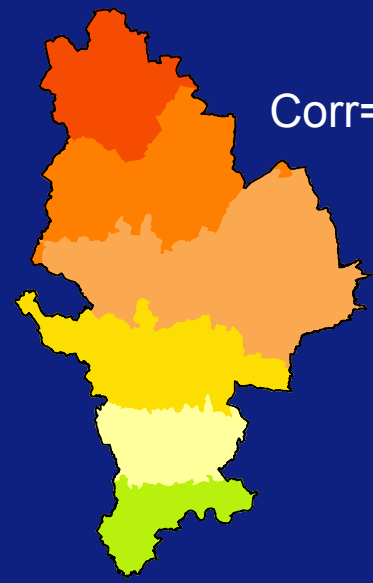


Average
estimated RR
(E x 1)



Corr=0.99

Average
estimated RR
(E x 5)

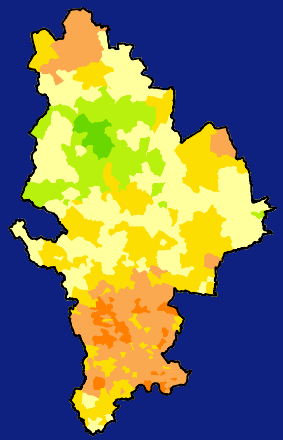


Corr=0.99

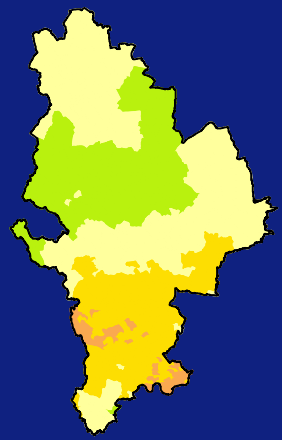
0.4 0.8 3.3

Spatial residuals

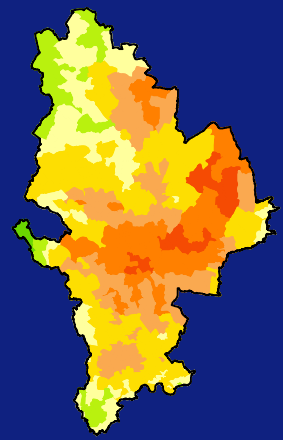
True Residual



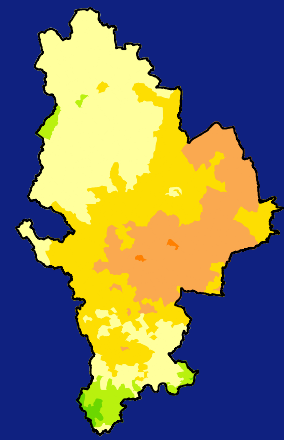
Posterior mean



True Residual



Posterior mean



Model comparison

- Compare constant and varying coefficient models using Deviance Information Criterion (DIC)
  - similar to AIC but for hierarchical models
  - model with smaller DIC is preferred

Model	True coefficient	$DIC_{var} - DIC_{const}$ (10 datasets)
1	Constant	-0.9 to 1.3 across datasets
2	Random	-23 to -55 across datasets
3	Spatial (Patchy)	-19 to -42 across datasets
4	Spatial (Smooth)	-32 to -90 across datasets

Non-linear exposure-response

- Most epidemiological models assume multiplicative relationship between exposure and risk

  $\rightarrow$ Individual and group (area)-level relationships have different functional form, e.g.

x_{ik} is a binary exposure for person k in area i

p_{ik} = risk of person k developing (rare) disease

$\log p_{ik} = \alpha + \beta x_{ik} \Rightarrow p_{ik} = e^{\alpha}$ if unexposed; $p_{ik} = e^{\alpha+\beta}$ if exposed

X_i = proportion of people exposed to x in area i (mean of x_{ik})

θ_i = average risk of disease in area i

$= e^{\alpha} (1-X_i) + e^{\alpha+\beta} X_i = e^{\alpha}(1 + (e^{\beta}-1) X_i)$

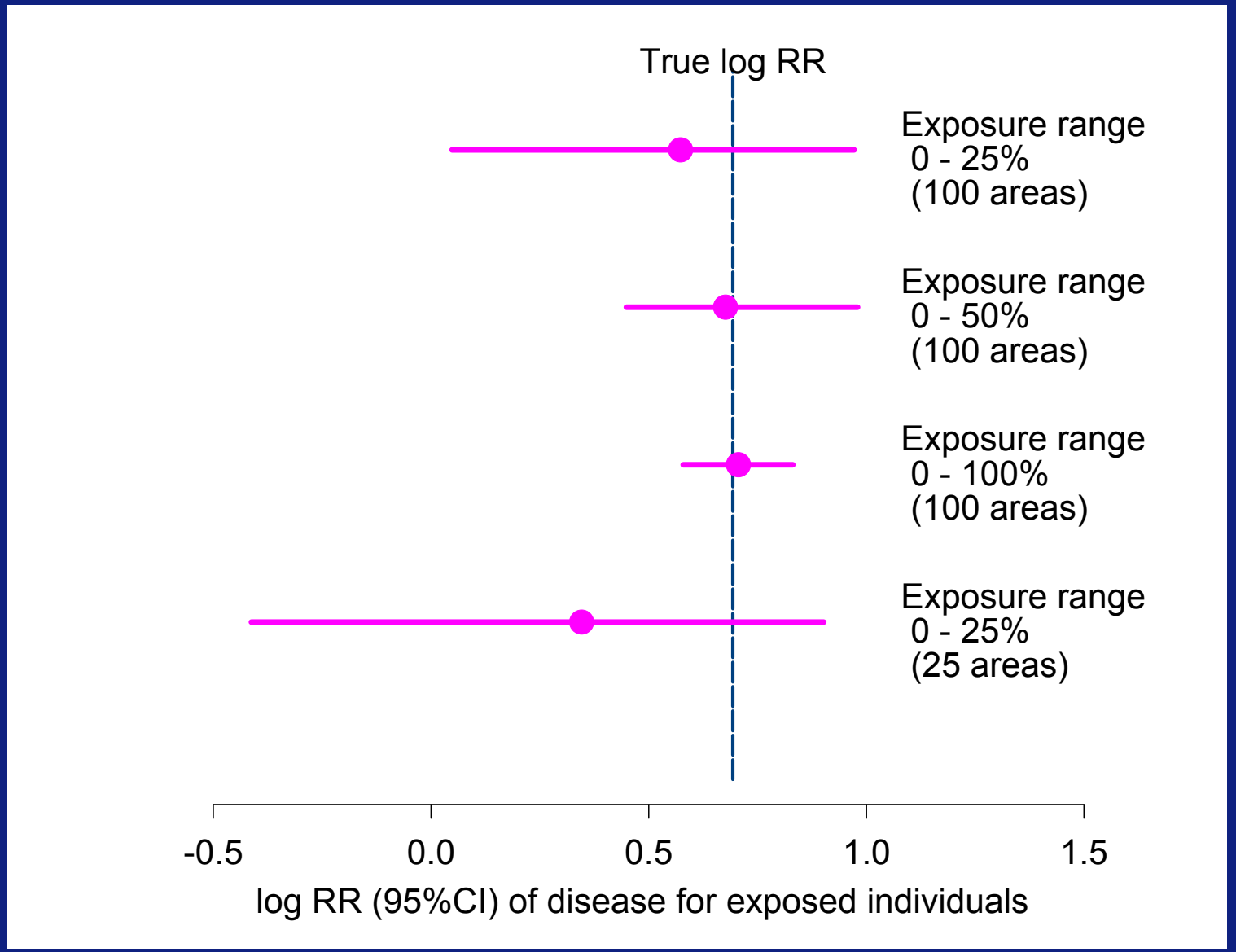
$\Rightarrow \log \theta_i \neq \alpha + \beta X_i$ (unless $X_i = 0$ or 1)

- Similar result holds for continuous exposures
  - For example, if the x_{ik} are approximately Normally distributed with mean X_i and variance V_i in area i, and $\log p_{ik} = \alpha + \beta x_{ik}$ as before, then

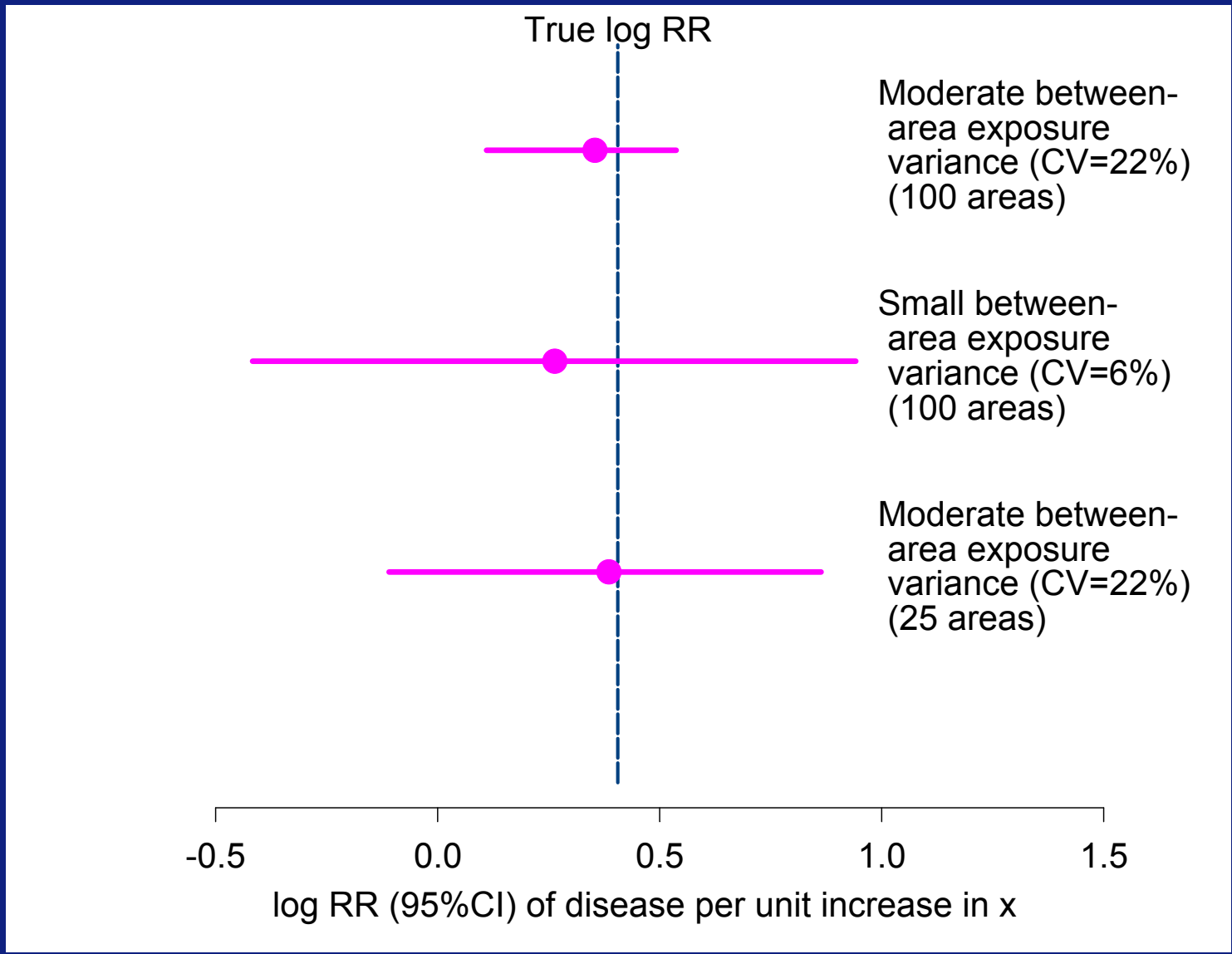
    $\log \theta_i = \alpha + \beta X_i + \beta^2 V_i / 2 \neq \alpha + \beta X_i$ (unless $V_i = 0$)

- If exposure varies within areas, and multiplicative risk model holds at individual level
  - appropriate integrated (aggregated) functional form should be used for the ecological regression model
- Even if correct model used, ecological data often contain little information about some of the risks

Simulation study to investigate bias of β coefficient in ecological regression model with binary exposure

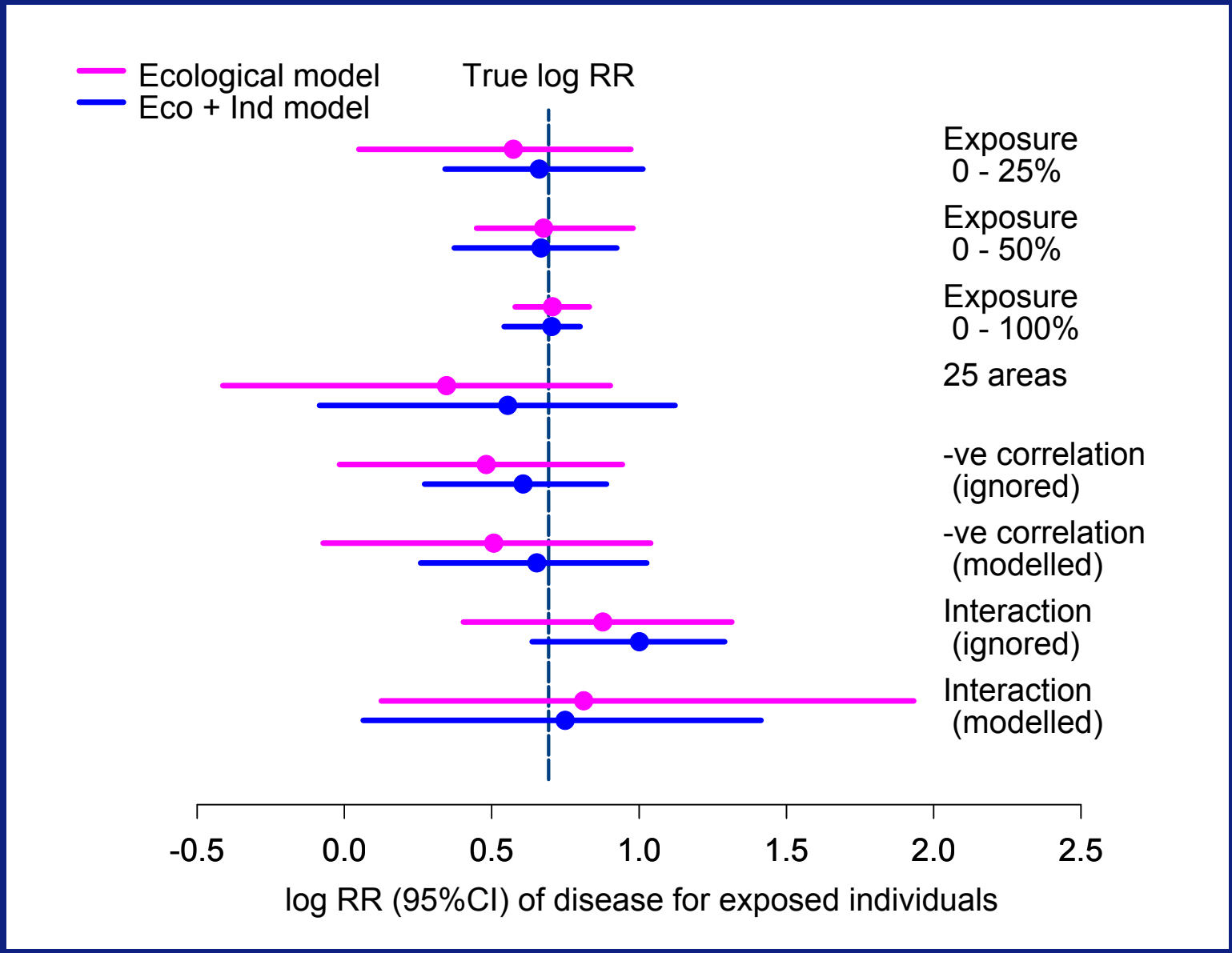


Simulation study to investigate bias of β coefficient in ecological regression model with continuous exposure



- Substantial improvements can be achieved by including individual-level data on a small sub-sample of people in each area
- Simultaneously estimate individual-level and ecological regressions (easily implemented in Bayesian paradigm)

Effect of including sample of 10 individuals per area on estimates of binary exposure effect



Conclusions

- Bayesian hierarchical models allow “borrowing of information” about disease risk across areas
- This property allows estimation of varying coefficient models
  - Models have reasonable power to detect true spatial variation in covariate effects, even with sparse data
  - Over-fitting does not appear to be a problem when no effect modification is present
  - able to separate spatial pattern of effect modification from that of the residuals

Conclusions continued

- When exposures vary within areas, care needed to fit appropriate aggregated risk model
  - Need large exposure contrasts between areas
  - Inclusion of even small sub-samples of individual level data can reduce bias and improve precision
  - More work needed on optimal study design
- Combining varying coefficient models and individual sub-samples should further improve our ability to handle ecological bias

Thank you