Module IV: Applications of Multi-level Models to Spatial Epidemiology

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Outline

- Multi-level models for spatially correlated data
  – Socio-economic and dietary factors of pellagra deaths in southern US
- Multi-level models for geographic correlation studies
  – The Scottish Lip Cancer Data
- Multi-level models for air pollution mortality risks estimates
  – The National Mortality Morbidity Air Pollution Study

Data characteristics

- Data for disease mapping consists of disease counts and exposure levels in small adjacent geographical area
- The analysis of disease rates or counts for small areas often involves a trade-off between statistical stability of the estimates and geographic precision

An example of multi-level data in spatial epidemiology

- We consider approximately 800 counties clustered within 9 states in southern US
- For each county, data consists of observed and expected number of pellagra deaths
- For each county, we also have several county-specific socio-economic characteristics and dietary factors
  - % acres in cotton
  - % farms under 20 acres
  - dairy cows per capita
  - Access to mental hospital
  - % afro-american
  - % single women

Definition of Standardized Mortality Ratio

- Y_i is the observed number of deaths in area i
- E_i is the expected number of deaths in area i
- The "raw" Standardized Mortality Ratio is so defined:

$$SMR_i = (Y_i/E_i) \times 1000$$

Definition of the expected number of deaths

- The expected number of deaths in area i can be calculated as follows:

$$E_i = \sum_j p_j n_{ij}$$

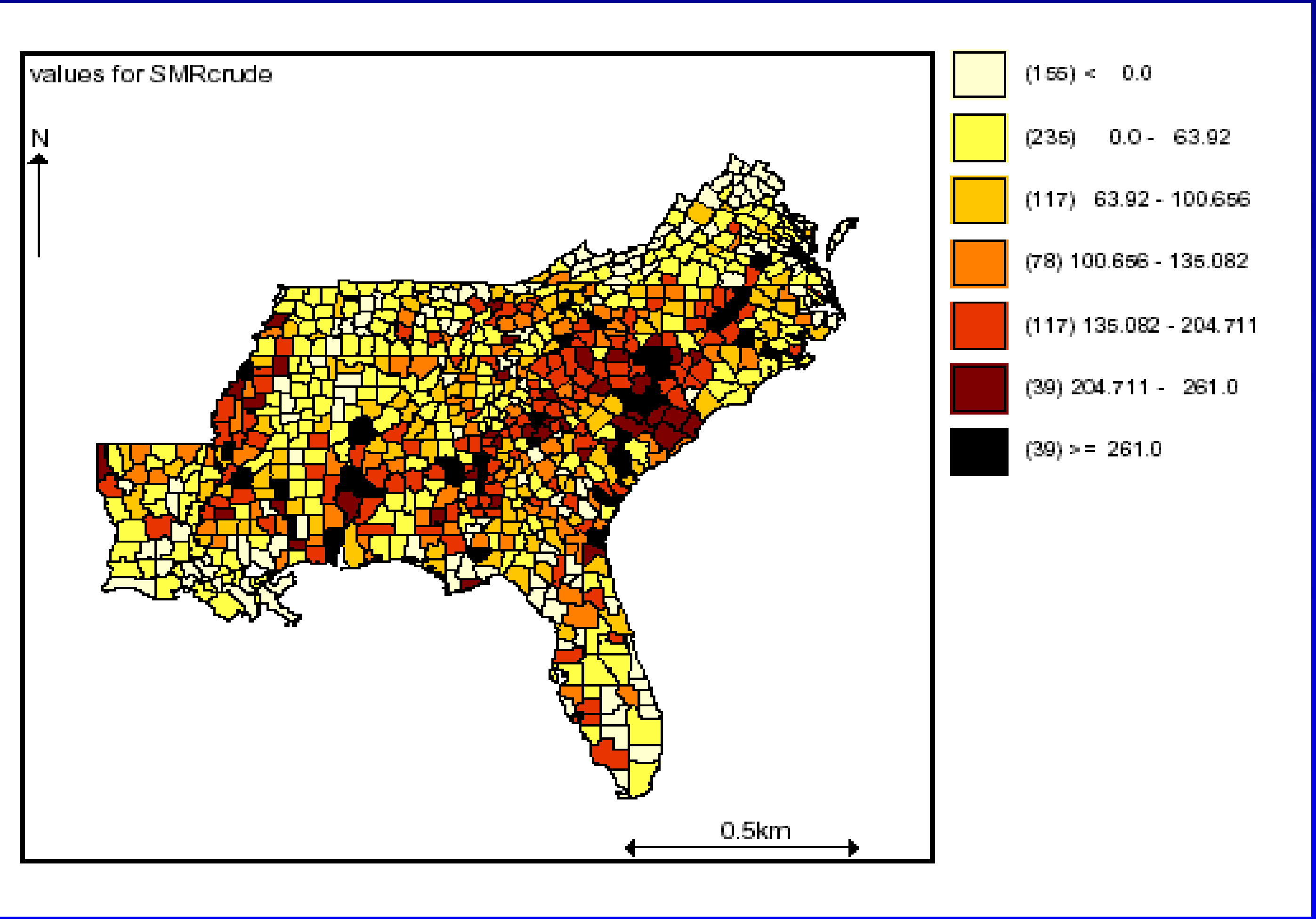
where

- j is the population stratum generally defined by age$\times$gender$\times$race
- p_j is observed frequency of death in the reference population
- n_{ij} is the number of people at risk in area i in stratum j

Definition of Pellagra

- Disease caused by a deficient diet or failure of the body to absorb B complex vitamins or an amino acid.
- Common in certain parts of the world (in people consuming large quantities of corn), the disease is characterized by scaly skin sores, diarrhea, mucosal changes, and mental symptoms (especially a schizophrenia-likedementia). It may develop after gastrointestinal diseases or alcoholism.

Crude Standardized Mortality Ratio (Observed/Expected) of Pellagra Deaths in Southern USA in 1930 (*Courtesy of Dr Harry Marks)*



Scientific Questions

- Which social, economical, behavioral, or dietary factors best explain spatial distribution of pellagra in southern US?
- Which of the above factors is more important for explaining the history of pellagra incidence in the US?
- To which extent, state-laws have affected pellagra?

Statistical Challenges

- For small areas SMR are very instable and maps of SMR can be misleading
  - Spatial smoothing
- SMR are spatially correlated
  - Spatially correlated random effects
- Covariates available at different level of spatial aggregation (county, State)
  - Multi-level regression structure

Spatial Smoothing

- Spatial smoothing can reduce the random noise in maps of observable data (or disease rates)
- Trade-off between geographic resolution and the variability of the mapped estimates
- Spatial smoothing as method for reducing random noise and highlight meaningful geographic patterns in the underlying risk

Shrinkage Estimation

- Shrinkage methods can be used to take into account instable SMR for the small areas
- Idea is that:
  - *smoothed estimate for each area "borrow strength" (precision) from data in other areas, by an amount depending on the precision of the raw estimate of each area*

Shrinkage Estimation

- Estimated rate in area *A* is adjusted by combining knowledge about:
  - Observed rate in that area;
  - Average rate in surrounding areas
- The two rates are combined by taking a form of weighted average, with weights depending on the population size in area *A*

Shrinkage Estimation

- When population in area *A* is large
  - Statistical error associated with observed rate is small
  - High credibility (weight) is given to observed estimate
  - Smoothed rate is close to observed rate
- When population in area *A* is small
  - Statistical error associated with observed rate is large
  - Little credibility (low weight) is given to observed estimate
  - Smoothed rate is “shrunk” towards rate mean in surrounding areas

A Multi-level Model for Spatial Smoothing of SMR

$$\begin{aligned} Y_i \mid \mu_i &\sim \text{Poisson}(\mu_i) \\ \log \mu_i &= \log E_i + b_i \\ b_i \mid b_{j \neq i} &\sim N\left(\frac{\sum_{j \neq i} w_{ij} b_j}{\sum_{j \neq i} w_{ij}}, \sigma^2 \frac{1}{\sum_{j \neq} w_{ij}}\right) \end{aligned}$$

where:

- b_i are area-specific random effects with a spatially correlated random effect distribution
- w_{ij} are weights defining which regions j are neighbors to region i (by convention $w_{ii} = 0$, for all i)
- σ^2 is the variance controlling how similar the b_i is to its neighbors

Raw and Smoothed Standardized Mortality Rates

- Y_i are observed disease counts in area i
- E_i are expected disease counts in area i
- The raw and smoothed standardized mortality ratio (SMR_i and $\widehat{SMR}_i$) are so defined:

$$SMR_i = \frac{Y_i}{E_i}$$

$$\widehat{SMR}_i = \frac{\hat{\mu}_i}{E_i}$$

- **In areas with abundant data:**

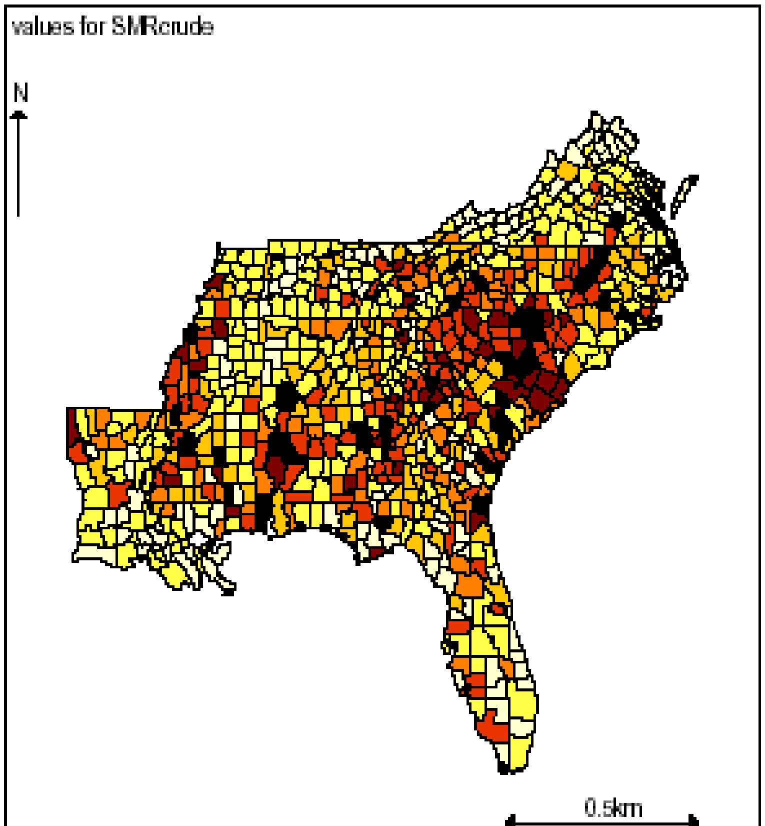
$$\widehat{SMR}_i \approx SMR_i$$

- **In areas with sparse data:**

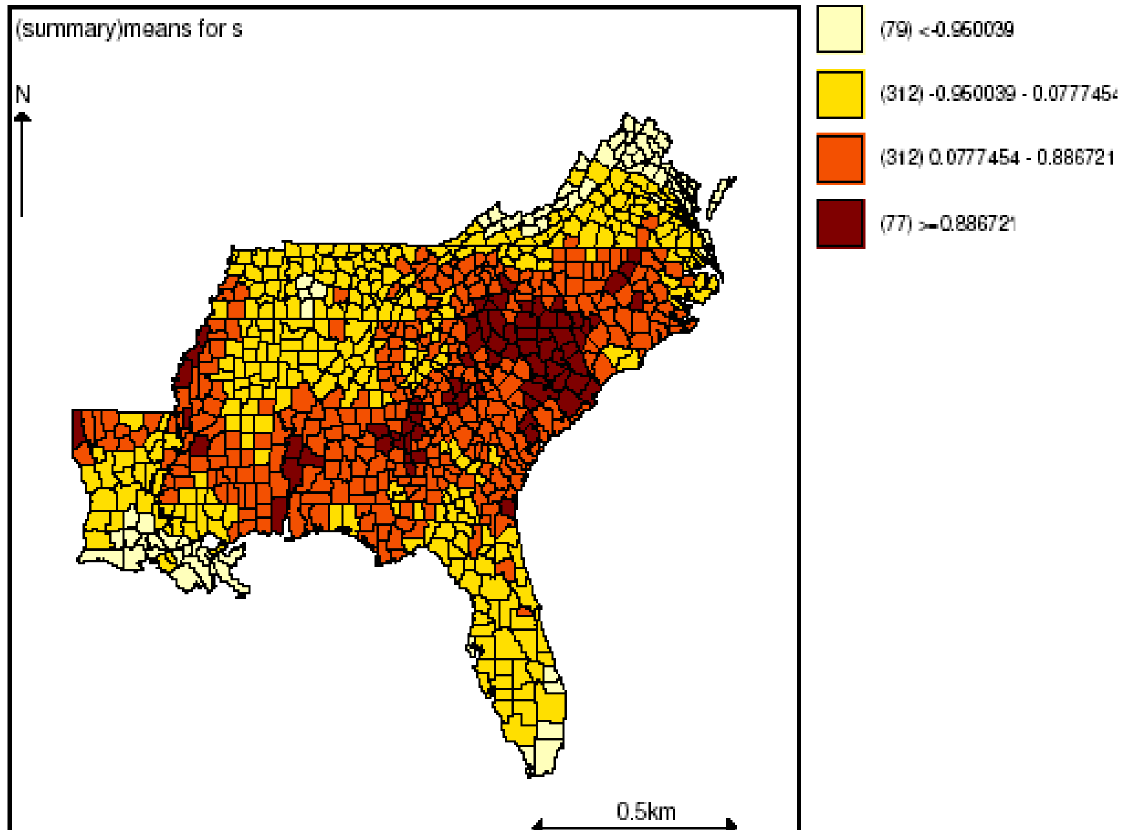
$\widehat{SMR}_i \approx$ weighted average of the SMR in the adjacent counties

SMR of pellagra deaths for 800 southern US counties in 1930

Crude SMR



Smoothed SMR



Multi-level Models for Geographical Correlation Studies

- Geographical correlation studies seek to describe the relationship between the geographical variation in disease and the variation in exposure

A Multilevel model for disease counts

- Y_{is} are observed disease counts in county i within state s
- E_{is} are expected disease counts in county i within state s
- Stage I: County-level, within state model

$$
\begin{aligned}
Y_{is} \mid \mu_{is} &\sim \text{Poisson}(\mu_{is}) \\
\log \mu_{is} &= \log E_{is} + \beta_{1s}(\text{cot}_{is} - \overline{\text{cot}}) + \beta_{2s}(\text{milk}_{is} - \overline{\text{milk}}) + b_i \\
b_i &\sim \text{spatially correlated random effects}
\end{aligned}
$$

- Stage II: Between-states model

$$
\begin{aligned}
\beta_{1s} &= \gamma_{11} + \gamma_{12}\text{state-taxes}_s + N(0, \sigma_1^2) \\
\beta_{2s} &= \gamma_{21} + \gamma_{22}\text{state-taxes}_s + N(0, \sigma_2^2)
\end{aligned}
$$

where:

- β_{1s} and β_{2s} are county-specific log-relative rates
- γ_{11} is the overall log-relative rate of pellagra mortality for the counties with average

Example: Scottish Lip Cancer Data (*Clayton and Kaldor 1987 Biometrics*)

- Observed and expected cases of lip cancer in 56 local government district in Scotland over the period 1975-1980
- Percentage of the population employed in agriculture, fishing, and forestry as a measure of exposure to sunlight, a potential risk factor for lip cancer

A Multilevel model for Lip Cancer Study

- Y_i are observed lip cancer cases in district i
- E_i are expected lip cancer cases in district i

$$Y_i \mid \mu_i \sim \text{Poisson}(\mu_i)$$

$$\log \mu_i = \log E_i + \beta_0 + \beta_1(\text{agr}_i - \overline{\text{agr}}) + b_i$$

We consider two models for the random effects:

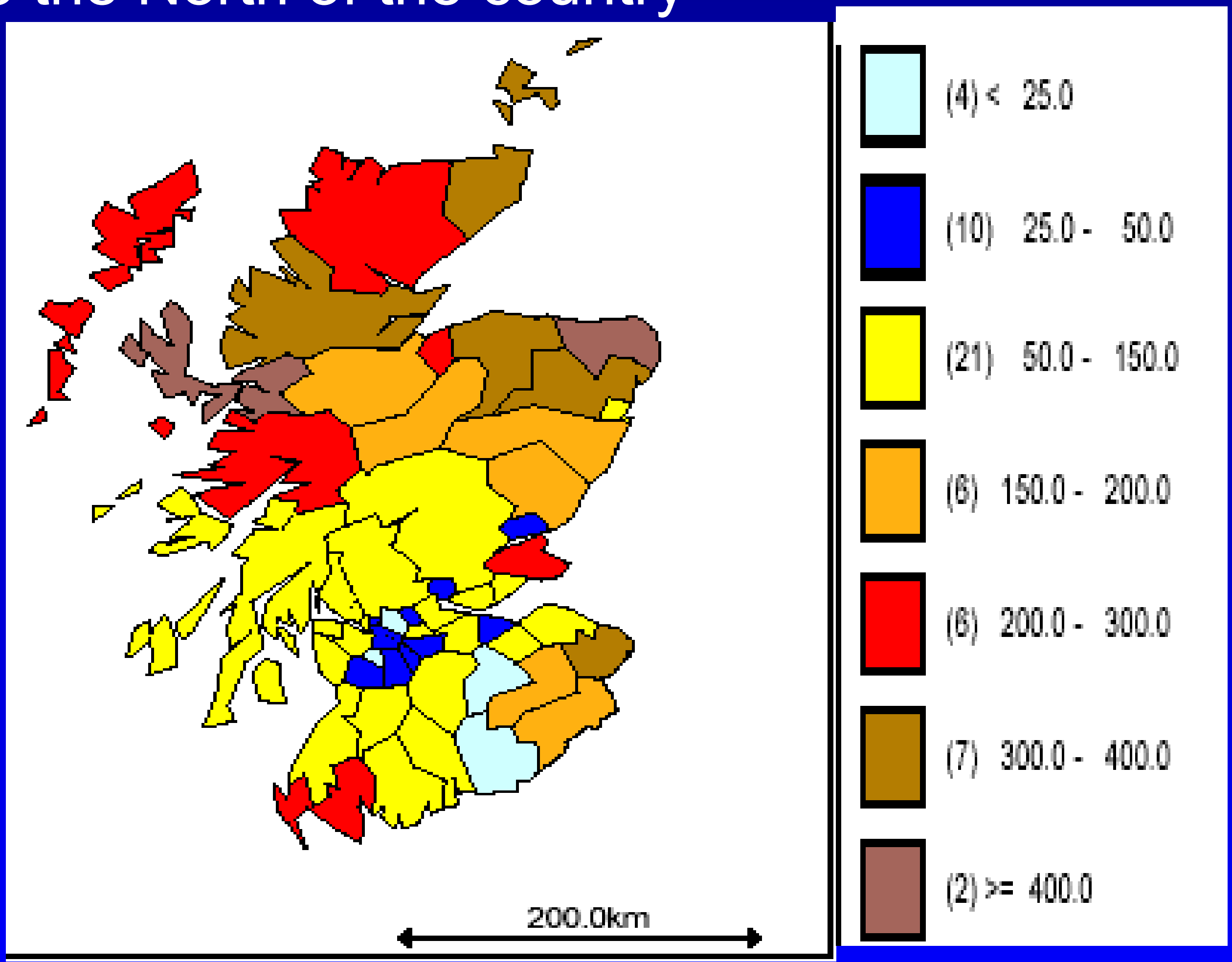
- **A: Global Smoothing**

$$b_i \sim N(0, \sigma^2)$$

- **B: Local Smoothing**

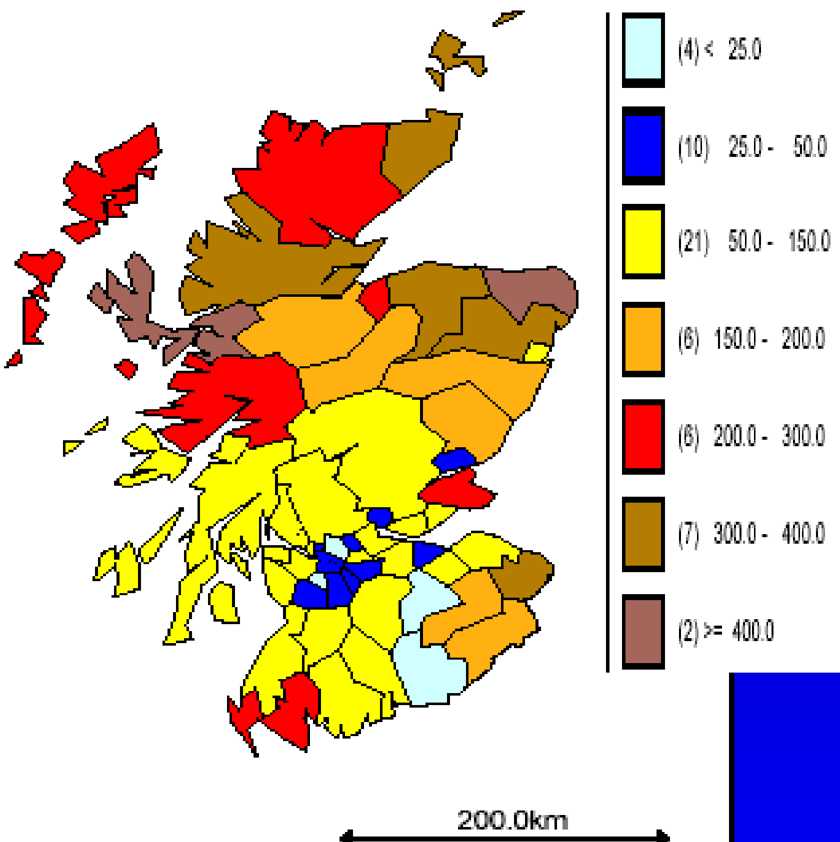
$$b_i \mid b_{j\neq i} \sim N\left(\frac{\sum_{j\neq i} w_{ij} b_j}{\sum_{j\neq i} w_{ij}}, \sigma^2 \frac{1}{\sum_{j\neq} w_{ij}}\right)$$

Crude standardized Mortality rates for each district, Note that there is a tendency for areas to cluster, with a noticeable grouping of areas with SMR> 200 to the North of the country

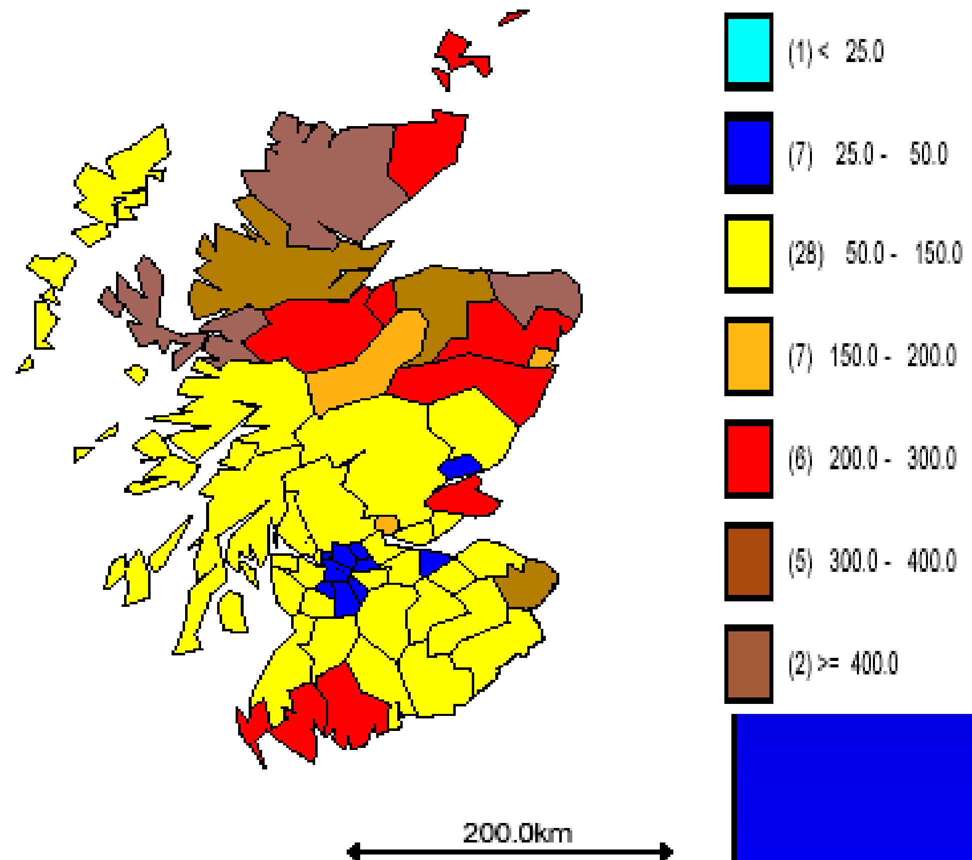


Model B: Local Smoothing

Crude SMR



Smoothed SMR



Parameter estimates

	A	B
intercept	0.099 (SE = 0.098)	0.091 (SE = 0.051)
slope	0.069 (SE = 0.014)	0.045 (SE = 0.012)
variance	0.602 (SE = 0.087)	0.667 (SE = 0.119)

Estimating Relative Risks

Relative Risk is defined as

$$RR(\mathrm{agr}_i) \;=\; \exp\left(\beta_0 + \beta_1(\mathrm{agr}_i - \overline{\mathrm{agr}})\right)$$

We approximated the posterior distributions of:

- RR of lip cancer in the areas with the highest proportion for workers in agriculture ($\mathrm{agr}_i = 24\%$):

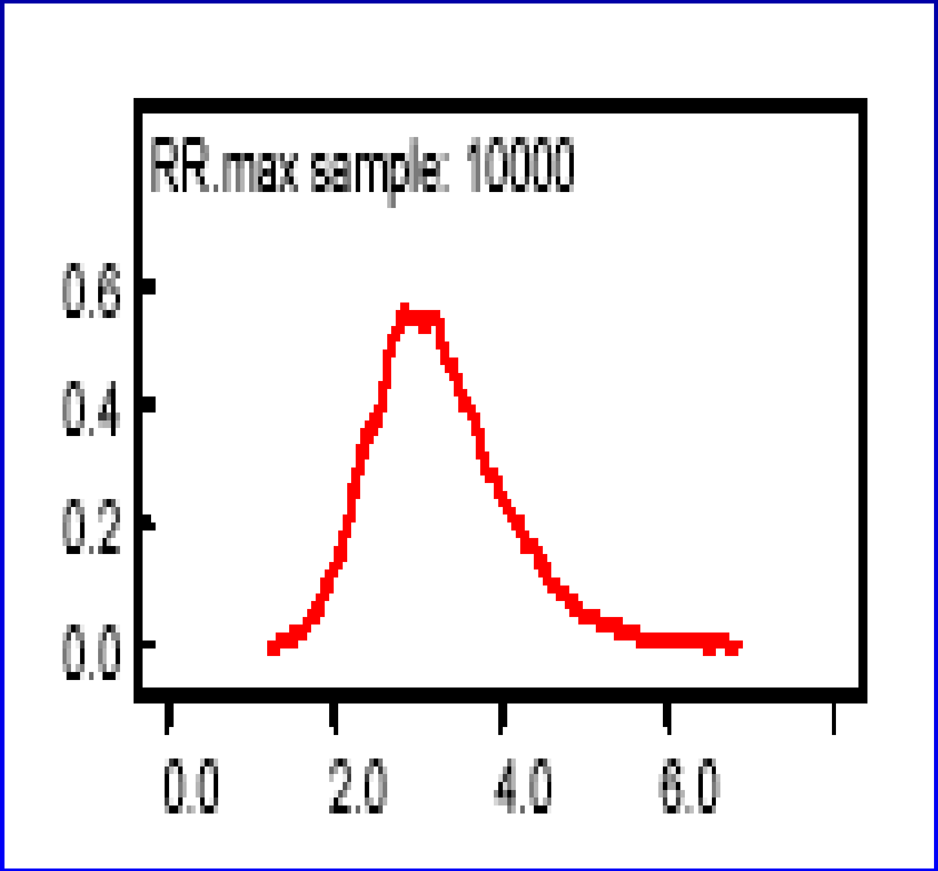
$$RR(\mathrm{agr}_i = 24) \;= \exp\left(\beta_0 + \beta_1(24 - \overline{\mathrm{agr}})\right)$$

- RR of lip cancer in the areas with the average proportion for workers in agriculture ($\mathrm{agr}_i = \overline{\mathrm{agr}_i}$)

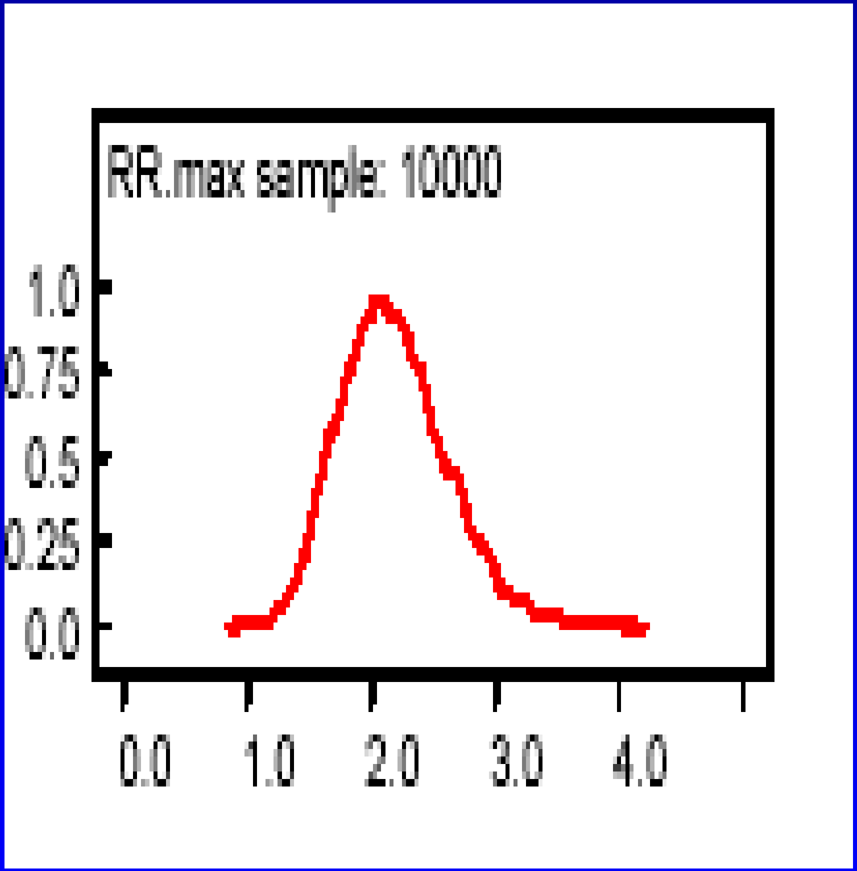
$$RR(\mathrm{agr}_i = \overline{\mathrm{agr}_i}) \;=\; \exp\left(\beta_0\right)$$

Posterior distribution of Relative Risks for maximum exposure

A: Global smoothing
(posterior mean = 3.25%)



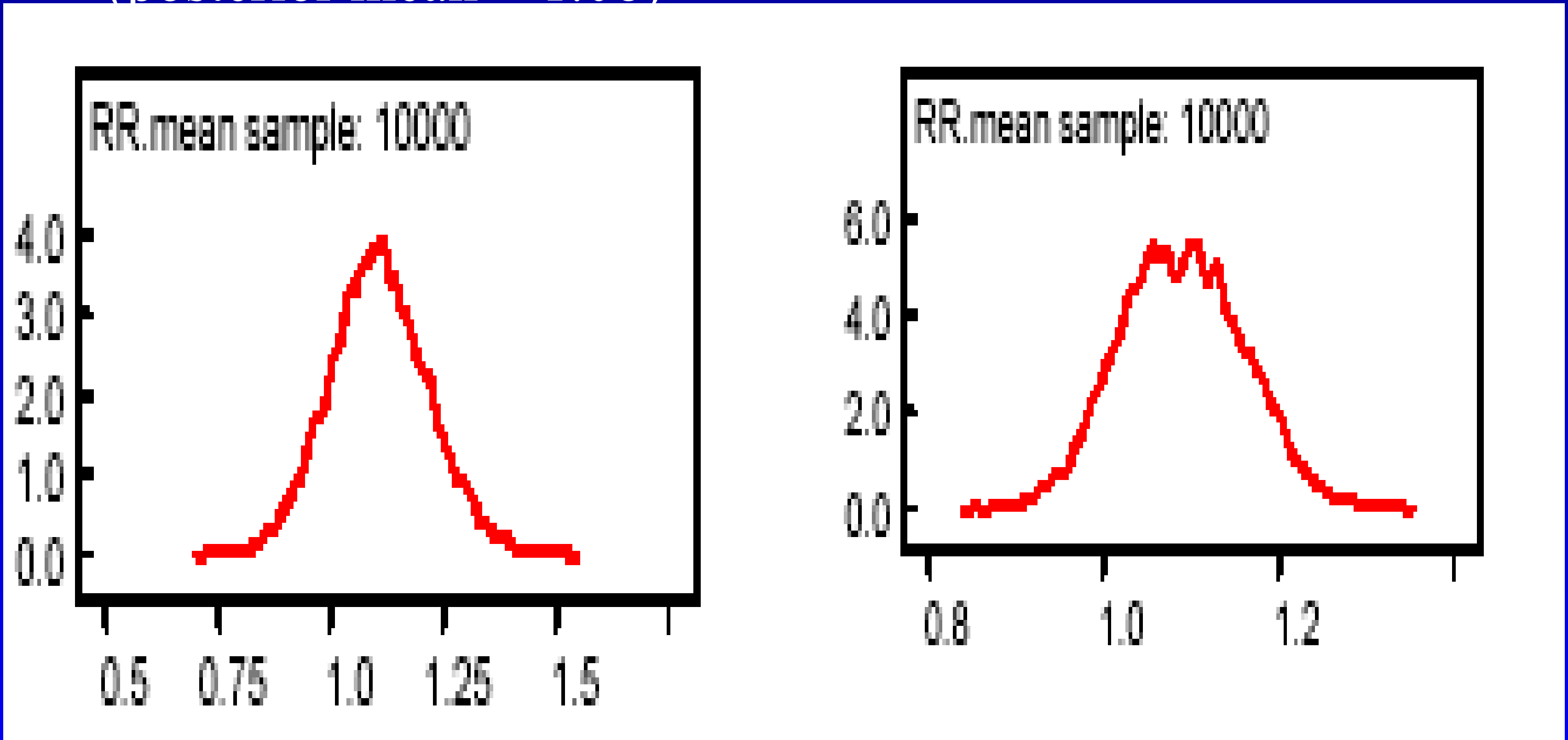
B: Local smoothing
(posterior mean = 2.18%)



Posterior distribution of Relative Risks for average exposure

A: Global smoothing
(posterior mean = 1.08)

B: Local smoothing
(posterior mean=1.09)



Results

- Under a model for global smoothing, the posterior mean of the relative risk for lip cancer in areas with the highest percentage of outdoor workers in 3.25%
- Under model for local smoothing, the posterior mean is lower and equal to 2.18%

Discussion

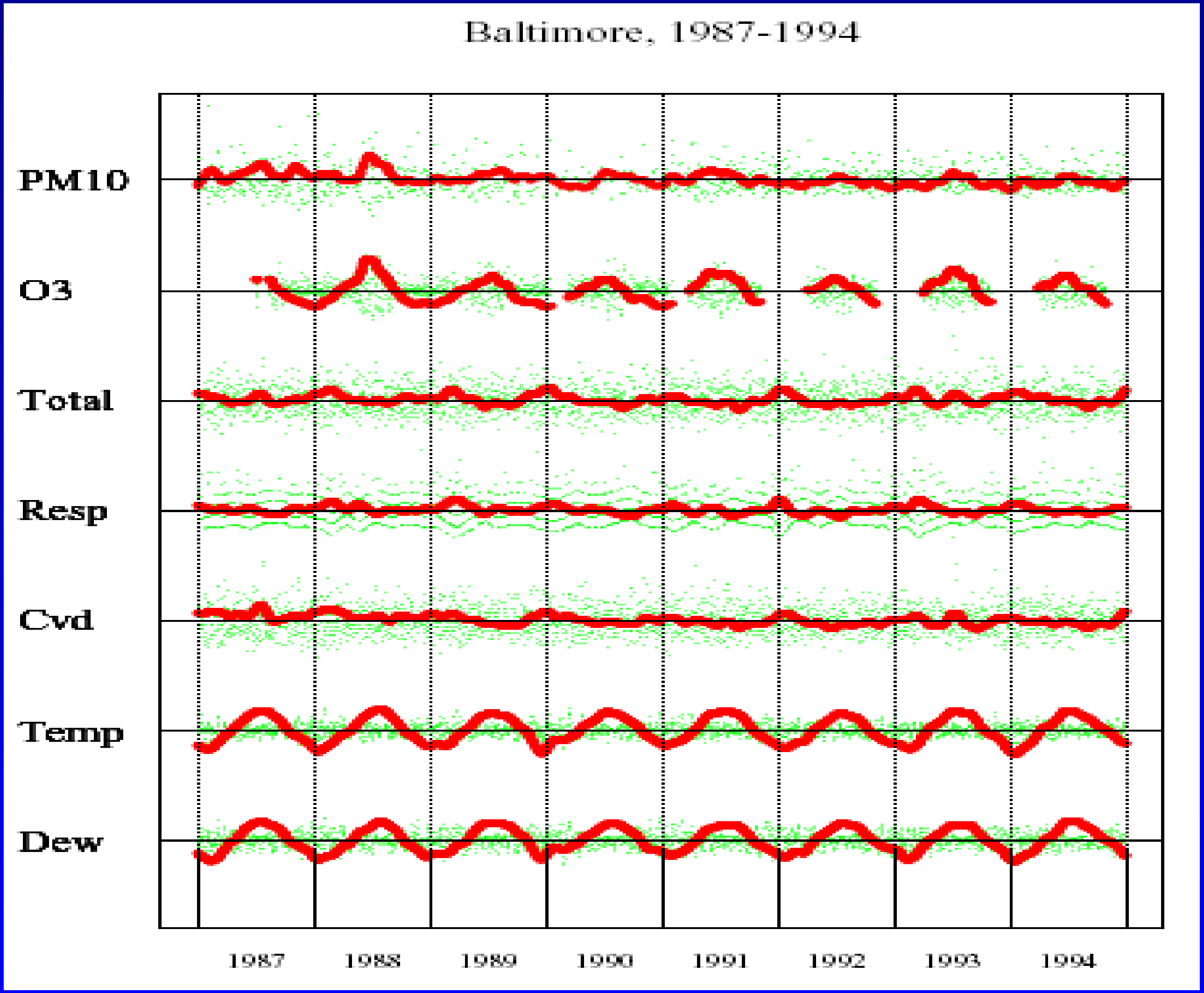
- In multi-level models is important to explore the sensitivity of the results to the assumptions inherent with the distribution of the random effects
- Specially for spatially correlated data the assumption of global smoothing, where the area-specific random effects are shrunk toward and overall mean might not be appropriate
- In the lip cancer study, the sensitivity of the results to global and local smoothing, suggest presence of spatially correlated latent factors

The National Morbidity Mortality Air Pollution Study

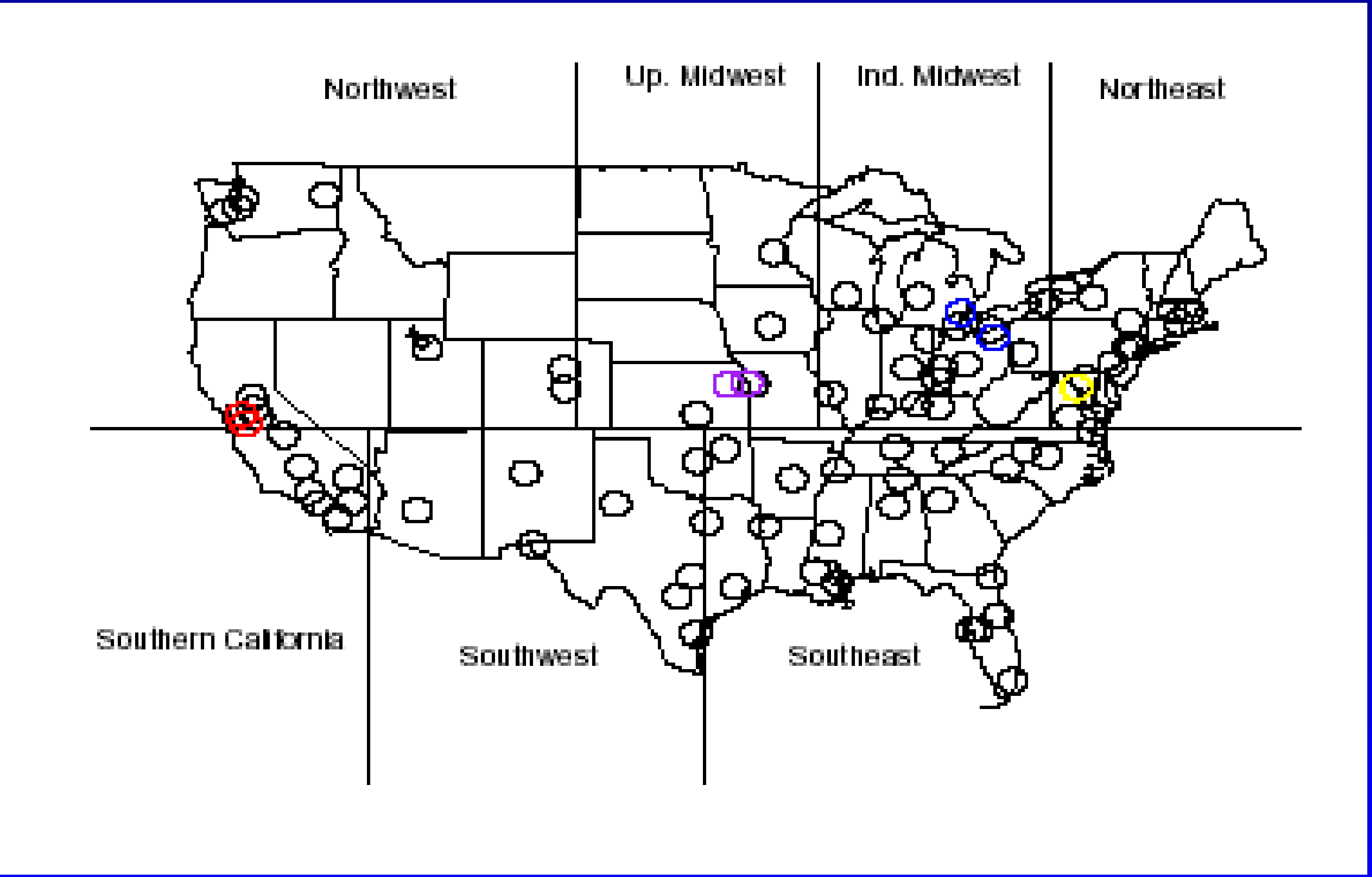
NMMAPS is a multi-site time series study assessing short-term effects of air pollution on mortality/morbidity comprising:

1. a national data base of air pollution and mortality;
2. statistical methods for estimating associations between air pollution and mortality for the 90 largest US cities, and on average for the entire nation.

Daily time series of air pollution, mortality and weather in Baltimore 1987-1994



90 Largest Locations in the USA



A Multilevel Model for NMMAPS

- Let $\hat{\beta}_{cr}$ and v_{cr} the relative rate estimate and its statistical variance of the percentage increase in mortality associated with a $10\mu/m^3$ increase in particulate matter in city c in region r.
- These estimates are obtained by fitting time series models with each city (Dominici et al 2000, Royal Statistical Society).
- The NMMAPS multilevel model is so defined:
- Stage I: county-level, within region

$$\begin{aligned} \hat{\beta}_{cr} &= \beta_{cr} + N(0, v_{cr}) \\ \beta_{cr} &= \alpha_{0r} + \alpha_{1r}\text{income}_{cr} + \alpha_{2r}\text{traffic}_{cr} + N(0, \sigma^2) \end{aligned}$$

- Stage II: region-level

$$\begin{aligned} \alpha_{0r} &= \gamma_{00} + \gamma_{01}\text{reg.charc}_r + N(0, \tau_1^2) \\ \alpha_{1r} &= \gamma_{10} + \gamma_{11}\text{reg.charc}_r + N(0, \tau_2^2) \end{aligned}$$

Multilevel Model for NMMAPS: Analysis of Variance

- We re-write the multilevel model for NMMAPS without covariates:

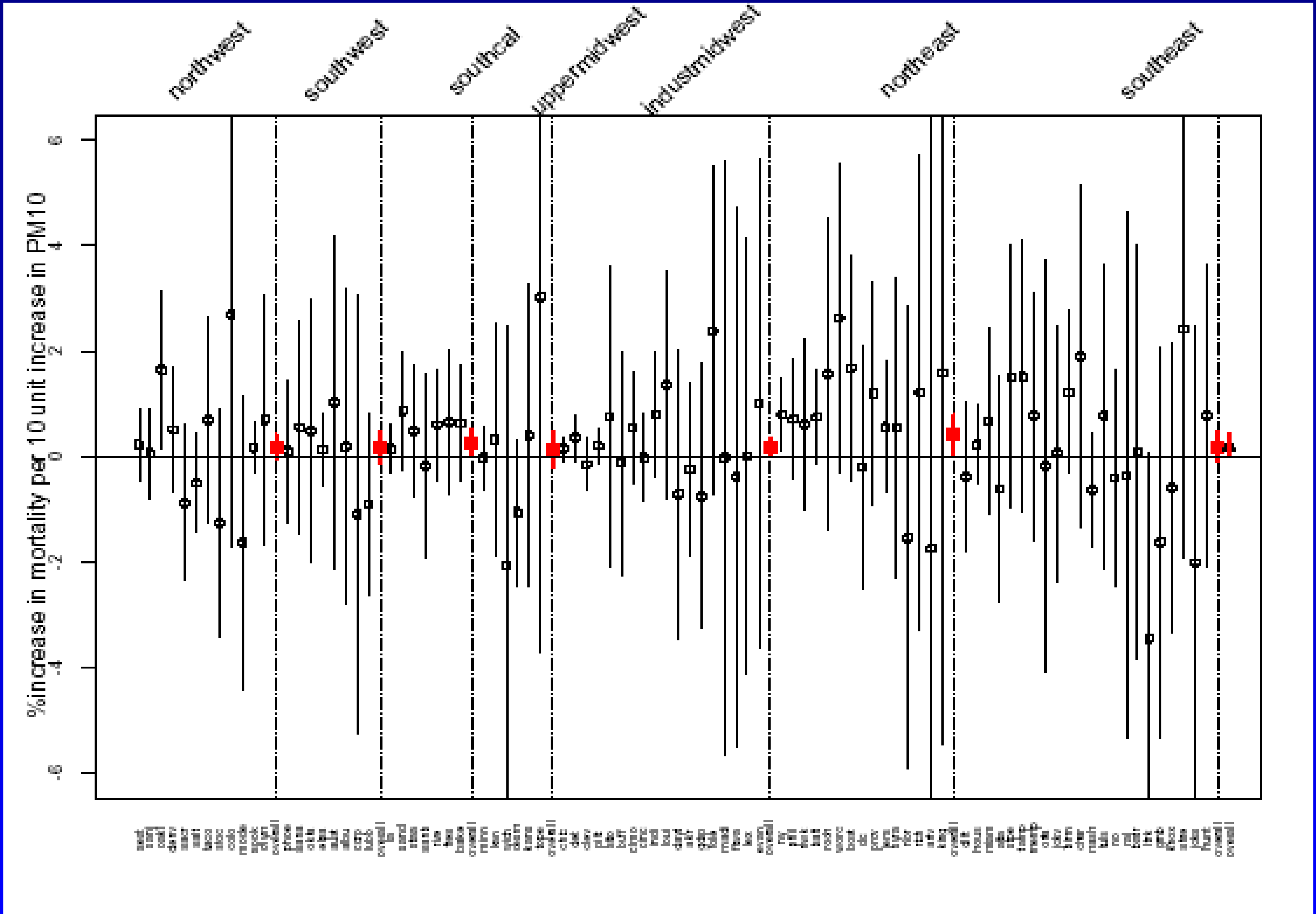
$$\begin{aligned}\hat{\beta}_{cr} &= \beta_{cr} + N(0, v_{cr})\\ \beta_{cr} &= \alpha_r + N(0, \sigma^2)\\ \alpha_r &= \gamma + N(0, \tau^2)\end{aligned}$$

- β_{cr} is the true city-specific pollution effect
- α_r is the regional-average air pollution effect
- γ is the national average air pollution effect
- σ^2 heterogeneity of air pollution effects within region
- τ^2 heterogeneity of air pollution effects across regions

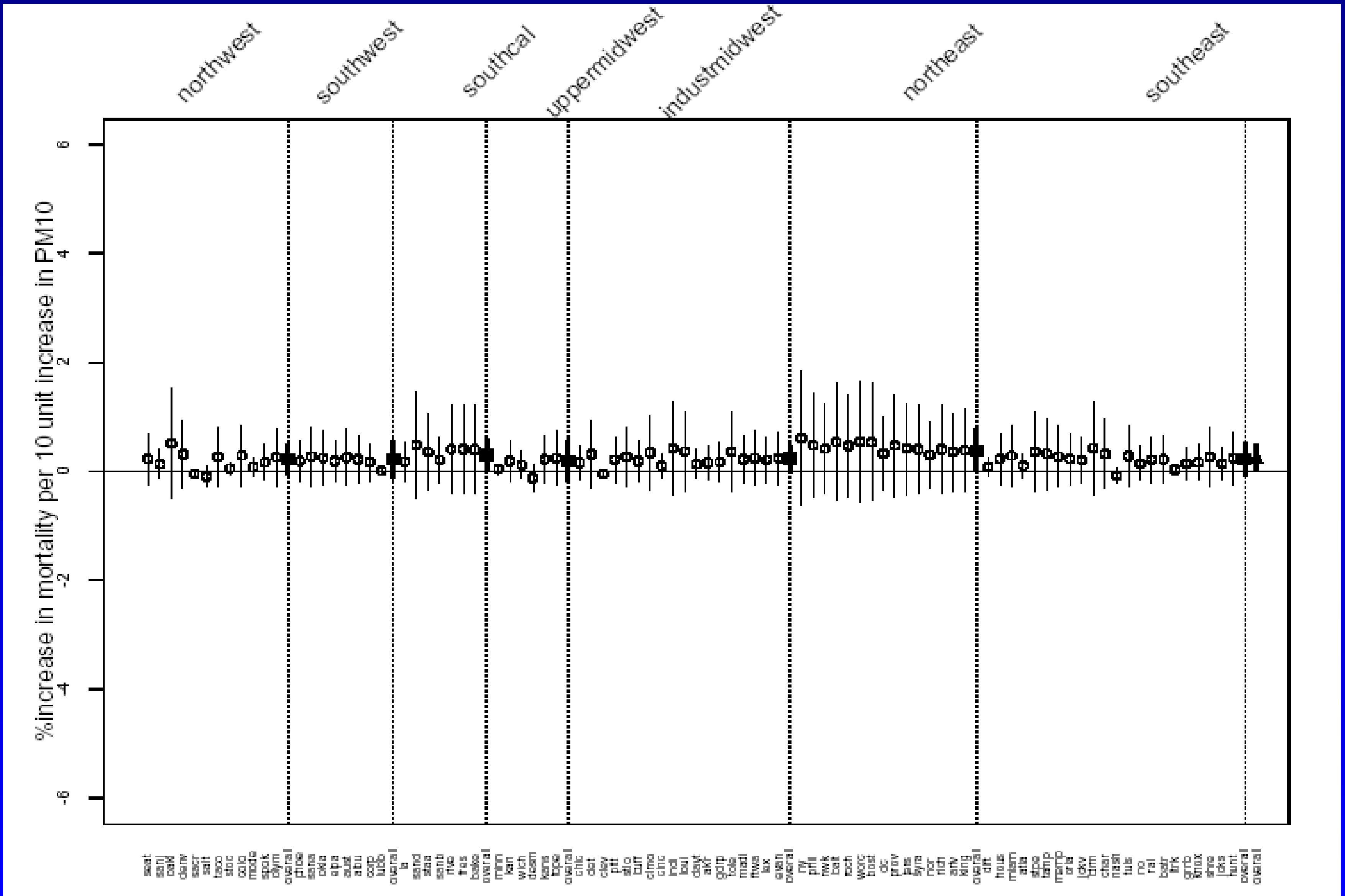
We can write the total difference between the city-specific estimate and the national average estimate as follows:

$$\underbrace{(\hat{\beta}_{cr} - \gamma)}_{\text{total diff}} = \underbrace{(\hat{\beta}_{cr} - \beta_{cr})}_{\text{within city}} + \underbrace{(\beta_{cr} - \alpha_r)}_{\text{within region}} + \underbrace{(\alpha_r - \gamma)}_{\text{between regions}}$$

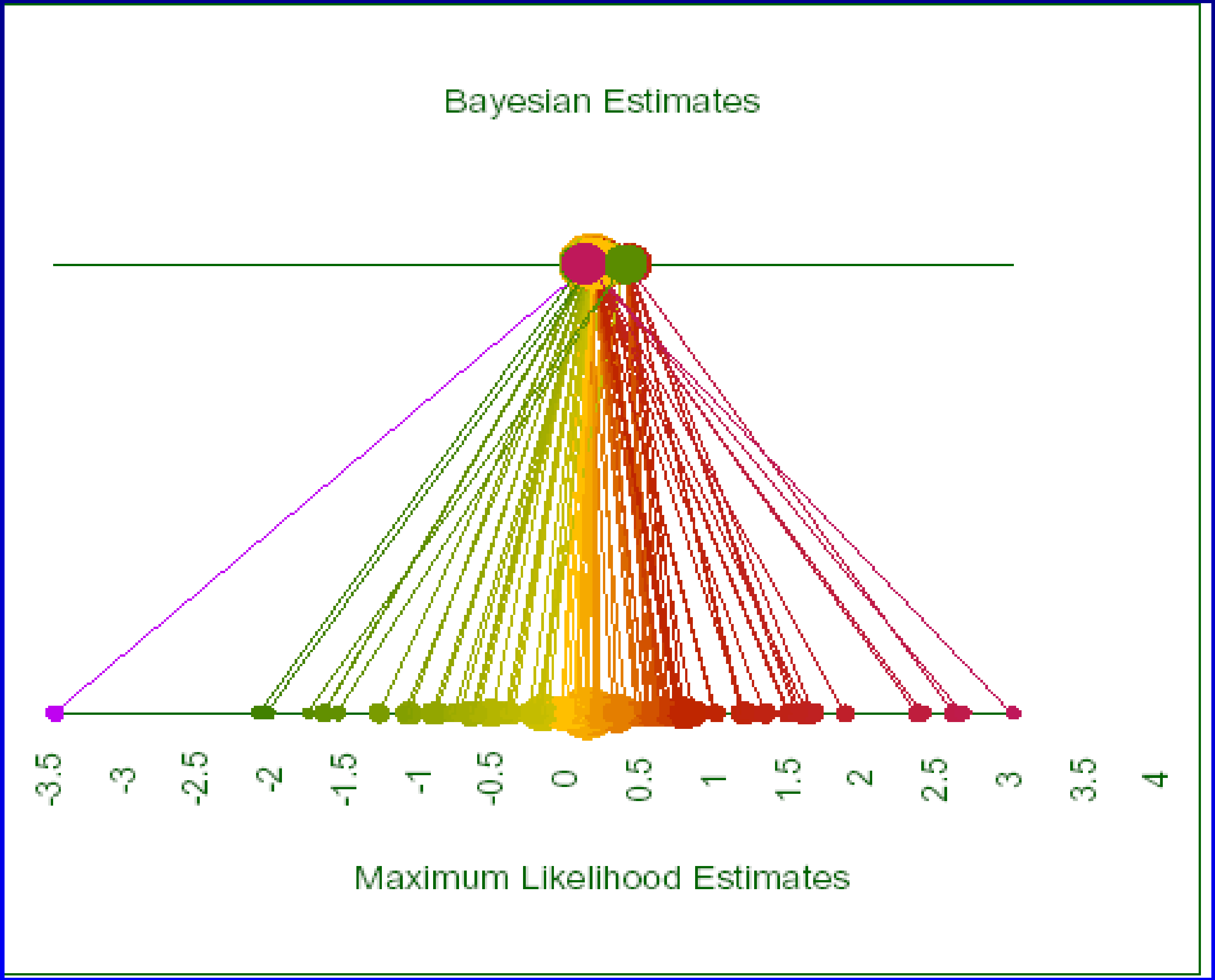
City-specific MLE



City-specific Bayesian Estimates

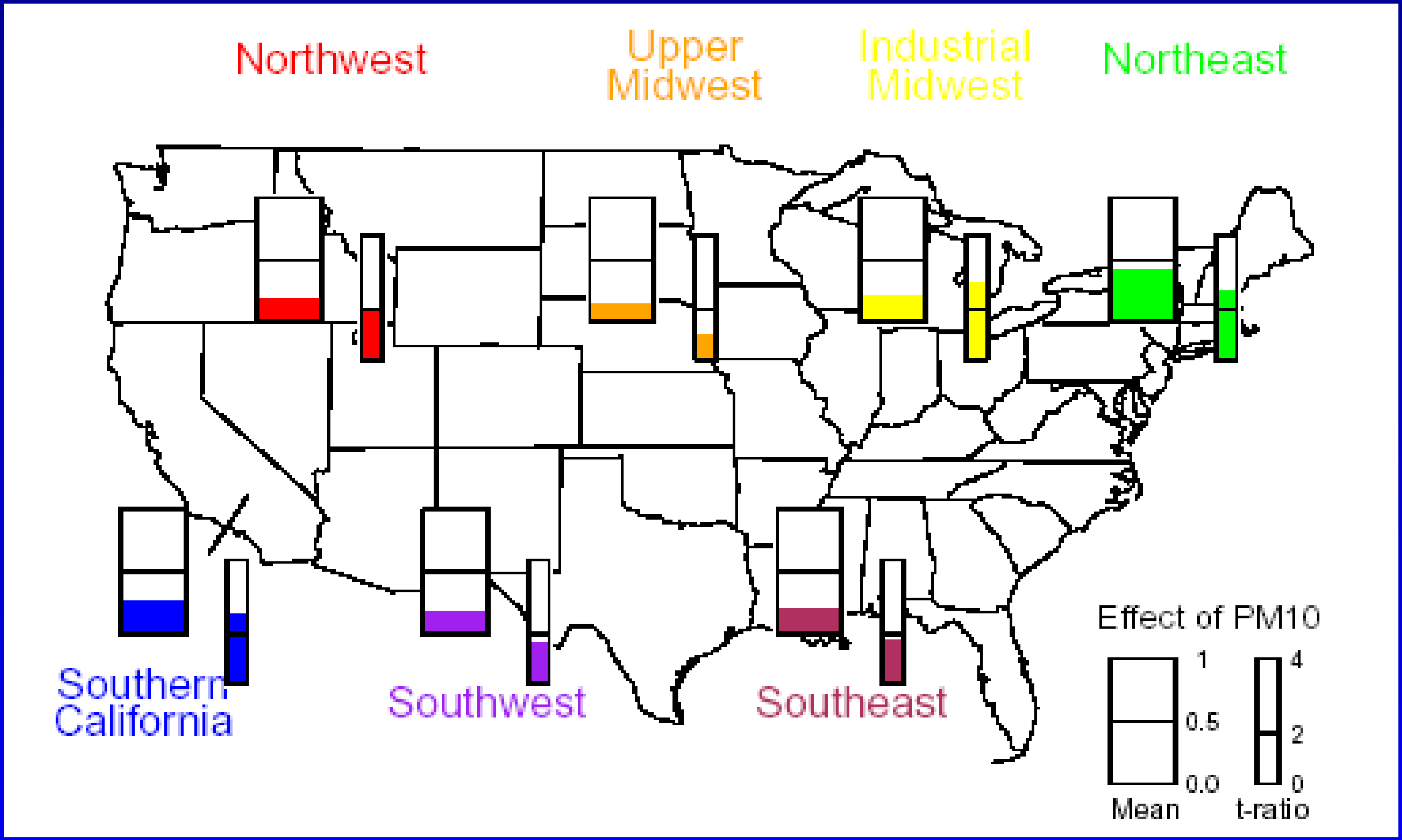


Shrinkage



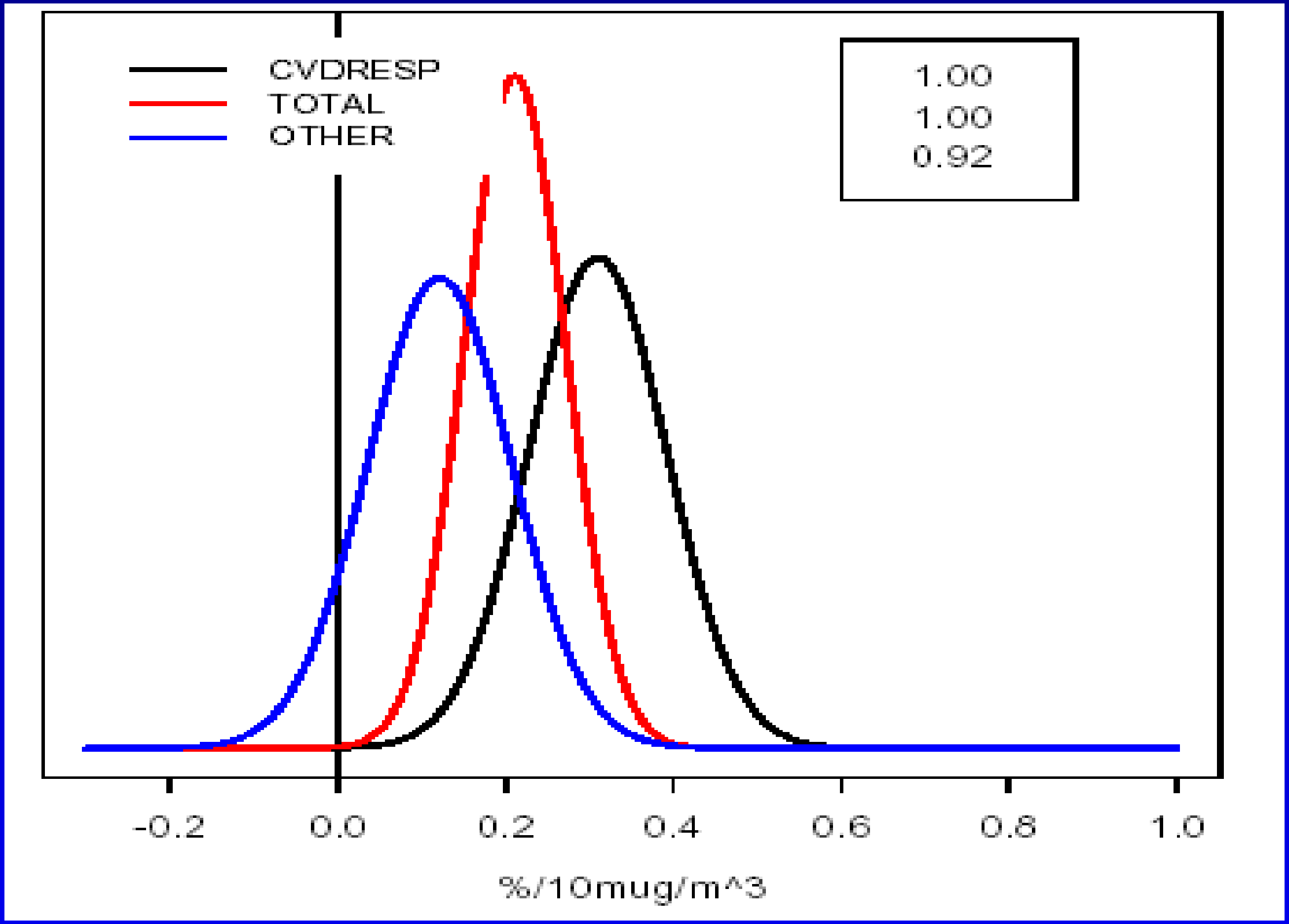
Bayesian Estimates
-3.5
-3
-2.5
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
4
Maximum Likelihood Estimates

Regional map of air pollution effects



Partition of the United States used in the 1996 Review of the NAAQS

National-average estimates for CVDRESP, Total and Other causes mortality



Samet, Dominici, Zeger et al. NEJM 2000

Pooling

City-specific relative rates are pooled across cities to:

1. estimate a *national-average* air pollution effect on mortality;
2. explore geographical patterns of variation of air pollution effects across the country

Pooling

- Implement the old idea of *borrowing strength across studies*
- Estimate heterogeneity and its uncertainty
- Estimate a national-average effect which takes into account heterogeneity

Discussion

- Multilevel models are a natural approach to analyze data collected at different level of spatial aggregation
- Provide an easy framework to model sources of variability (within county, across counties, within regions etc..)
- Allow to incorporate covariates at the different levels to explain heterogeneity within clusters
- Allow flexibility in specifying the distribution of the random effects, which for example, can take into account spatially correlated latent variables

Key Words

- Spatial Smoothing
- Disease Mapping
- Geographical Correlation Study
- Hierarchical Poisson Regression Model
- Spatially correlated random effects
- Posterior distributions of relative risks