*Disease mapping* has a long history in epidemiology, and may be defined as the estimation and presentation of summary measures of health outcomes.

The aims of disease mapping include

- simple description,
- hypothesis generation,
- allocation of health care resources, assessment of inequalities, and
- estimation of background variability in underlying risk in order to place epidemiological studies in context.

We begin by noting a number of non-statistical issues, for more background see Chapters 12 and 13 of EWBB:

- In broad-scale studies (in particular international endeavors), data comparability is a major issue. Precise disease definition (via ICD codes) is also extremely important.
- Mortality data tend to be more reliable than incidence data, but the latter are of greater epidemiological interest in general.
- There is a trade-off when a geographical scale is chosen: larger geographical areas providing more stable rates and less problems of migration, but relative risk summaries may be distorted due to the large aggregation of individuals.
- If the relative risk shows marked variation within a particular area this information will be lost – if a particular subregion has a high relative risk then this will be diluted under aggregation; finding such subregions is not possible unless there are data available at a lower level of aggregation.

- The size of the areas chosen also determines the sort of questions that can be posed – larger areas are likely to offer greater contrasts in relative risks and exposures. Localized effects can only be detected with data at a smaller level of aggregation.
- Presentation:
  - Choropleth (areas shaded) are the most popular kind of maps, but isopleth (contours) and cartograms (size of areas proportional to denominator), have also been used.
  - Choice of color is important – multiple colors can be confusing, shading with a single color can work well.
  - Cut-points should be chosen to be epidemiologically meaningful and convey as much information as possible.

We first consider mapping for area-level data. Background reading: EWBB: Chapter 7.

Unfortunately there are well-documented difficulties with the mapping of raw estimates since, for small areas and rare diseases in particular, these estimates will be dominated by sampling variability.
For the model

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

the MLE is

$$\widehat{\theta}_i = \text{SMR}_i = \frac{Y_i}{E_i}$$

with variance

$$\text{var}(\widehat{\theta}_i) = \frac{\theta_i}{E_i}$$

so that areas with small $E_i$ have high associated variance.

## Example: Surveillance

We imagine separate monthly surveillance for each of three areas over a 10-year period.
We simulate data from the model

$$Y_i|\theta \sim_{ind} \text{Poisson}(E\theta),$$

$i = 1, ..., 120$, where the relative risk $\theta = 1$ in each case.
Recall that the MLE of the SMR in each time period is $\widehat{\theta}_i = Y_i/E$ with variance proportional to $1/E$ so that areas with small expected numbers have high variability.
The expected numbers differ in the three plots in Figure 1, and the resultant instability in the SMR is apparent.

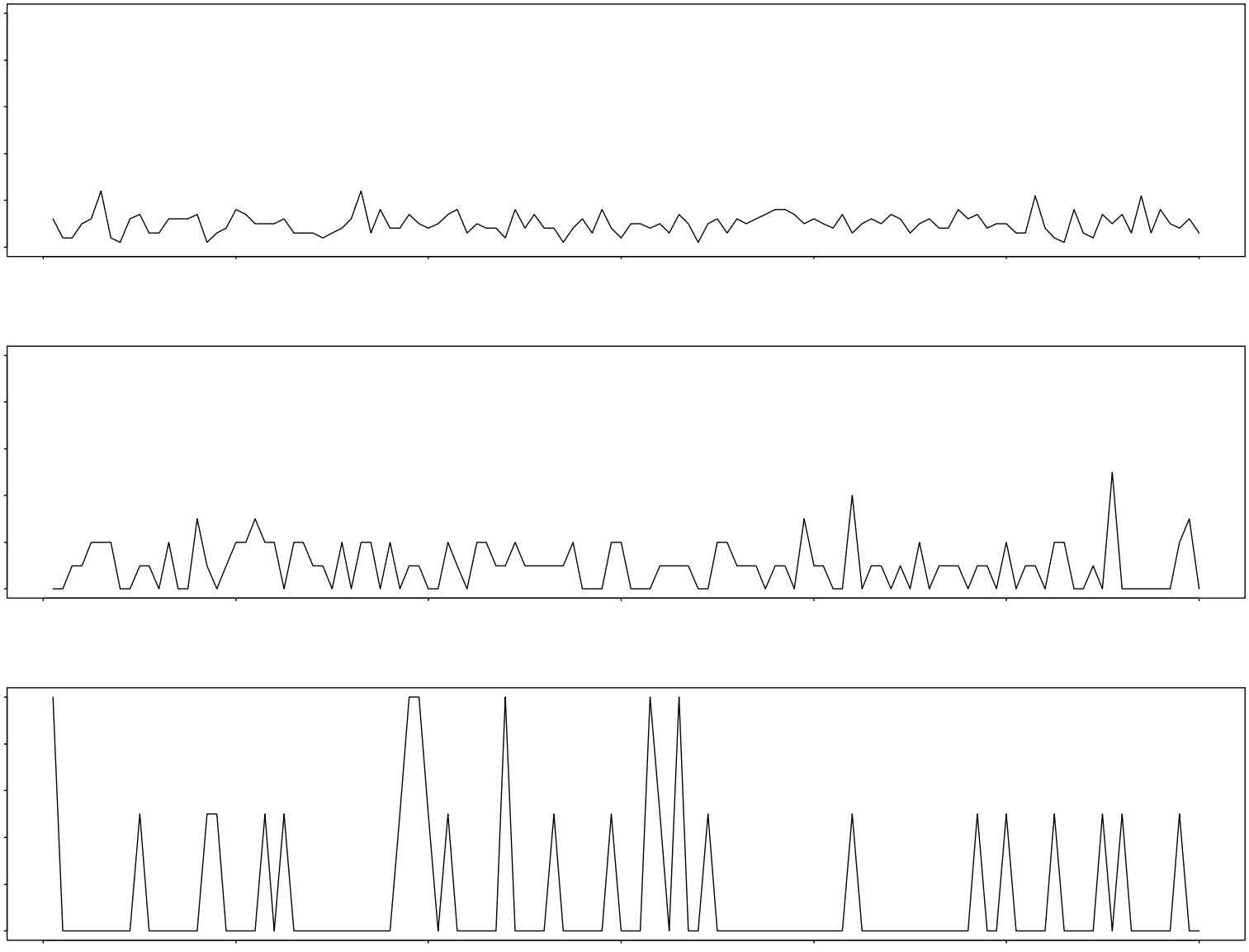


Figure: Simulations from the Poisson distribution under different expected numbers.

## Example: Scottish Lip Cancer

Figure 2 shows the SMRs for the Scottish lip cancer data, and indicates a large spread with an increasing trend in the south-north direction.

The variance of the estimate is $\text{var}(\text{SMR}_i) = \text{SMR}_i/E_i$, which will be large if $E_i$ is small.

For the Scottish data the expected numbers are highly variable, with range 1.1–88.7. This variability suggests that there is a good chance that the extreme SMRs are based on small expected numbers (many of the large, sparsely-populated rural areas in the north have high SMRs).

Figure 3 (left panel) shows the SMRs versus the estimated standard errors and clearly illustrates that the high SMRs have high associated standard error.

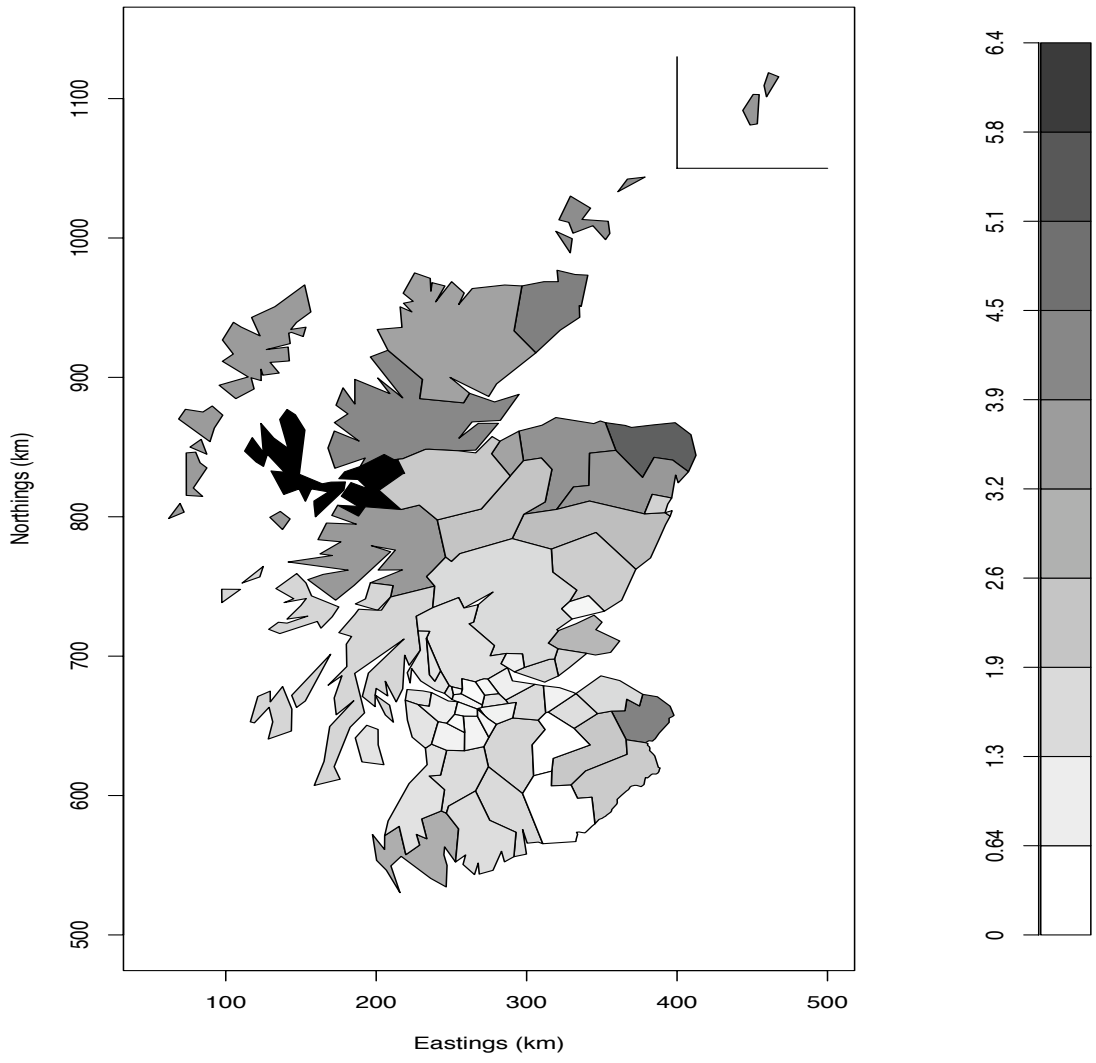



Figure: SMRs in 56 counties of Scotland.

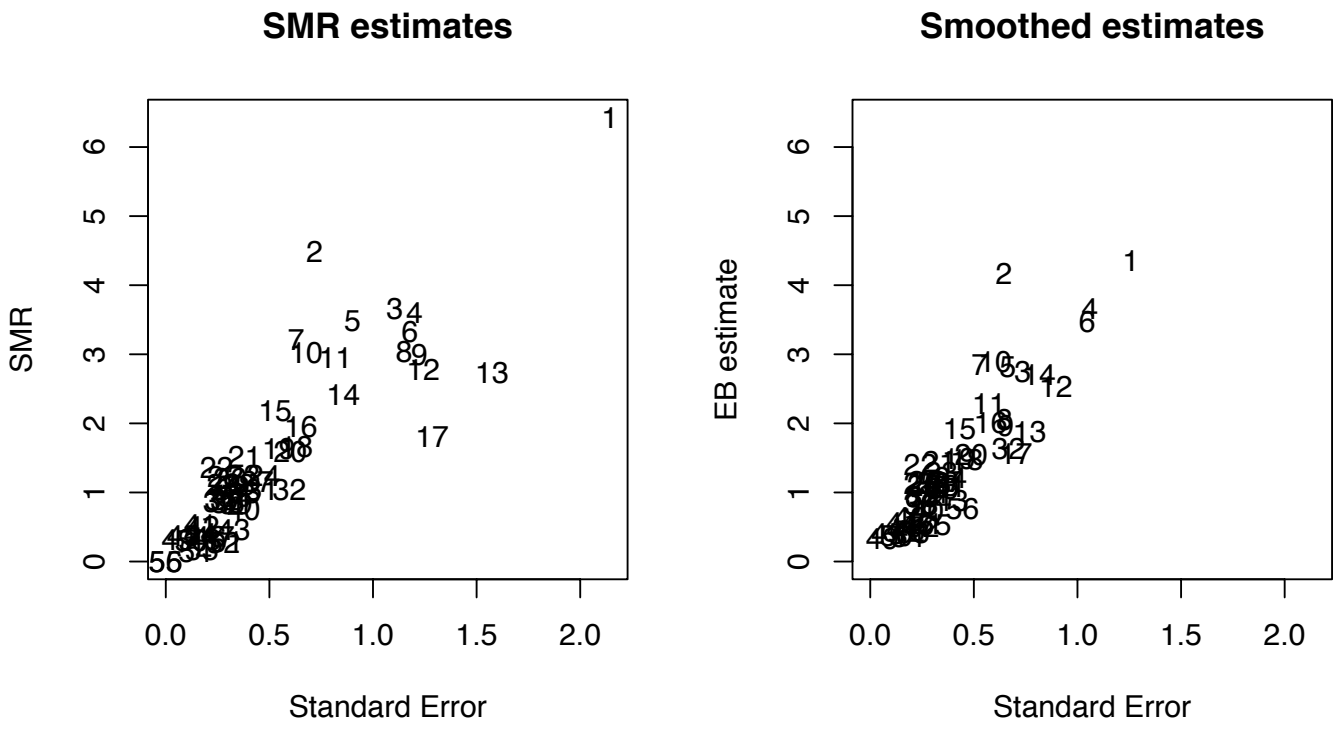



Figure: Estimates versus standard errors for 56 counties of Scotland.

Maps showing p-values of exceedence of 1 are even less informative than maps of SMRs since although they account for sample size they do not show the extent of the risk. Hence areas with large populations may provide statistically significant SMRs, even for small exceedences of 1.

## Smoothing Models

The above considerations led to methods being developed to *smooth* the SMRs using hierarchical/random effects models that use the data from the totality of areas to provide more reliable estimates in each of the constituent areas.

We first describe models that do not use spatial information before turning to models that exploit both spatial and non-spatial informtation.

## Poisson-Gamma Model Without Covariates

We begin by describing a simple Poisson-Gamma two-stage model that offers analytic tractability and ease of estimation.
We assume there are no covariates and assume the first stage likelihood is given by

$$Y_i|\theta_i, \beta \sim_{ind} \text{Poisson}\left(\mu E_i \theta_i\right), \tag{1}$$

where $\mu$ is the overall relative risk, and reflects differences between the reference rates and the rates in the study region.
At the second stage the random effects $\theta_i$ are assigned a distribution. We initially assume that across the map the deviations of the relative risks from the mean, $\mu$, are modelled by

$$\theta_i|\alpha \sim_{iid} \text{Ga}(\alpha, \alpha), \tag{2}$$

a gamma distribution with mean $1$, and variance $1/\alpha$.

The advantage of this Poisson-gamma formulation is that the marginal distribution of $Y_i|\mu, \alpha$ (obtained by integrating out the random effects $\theta_i$), is negative binomial.
Marginally, the mean and variance are given, respectively, by

$$\begin{aligned} E[Y_i|\mu,\alpha] &= E_i\mu \\ \text{var}(Y_i|\mu,\alpha) &= \text{E}[Y_i|\mu,\alpha](1+\text{E}[Y_i|\mu,\alpha]/\alpha), \end{aligned} \tag{3}$$

so that the variance increases as a quadratic function of the mean, and the scale parameter $\alpha$ can accommodate different levels of "overdispersion".
This form is substantively more reasonable than the naive Poisson model; it is important to consider excess-Poisson variability resulting from unmeasured confounders, data anomalies in numerator and denominator, and model misspecification.

## Empirical Bayes Estimation without Covariates

If $\mu$ and $\alpha$ were known then the posterior distribution of $\theta_i$ would be gamma.

Suppose we have estimates $\widehat{\mu}$, $\widehat{\alpha}$. Then the distribution is given by

$$\theta_i|\text{by}, \widehat{\mu}, \widehat{\alpha} \sim \text{Ga}(\widehat{\alpha} + y_i, \widehat{\alpha} + E_i\widehat{\mu}).$$

The relative risk (relative to the reference rates used in the expected numbers) is given by $\text{RR}_i = \mu\theta_i$, and has mean

$$\begin{aligned} \widehat{RR_i} &= \widehat{\mu} \times \text{E}[\theta_i|\text{by}, \widehat{\mu}, \widehat{\alpha}] = \widehat{\mu}\left(\frac{\widehat{\alpha} + Y_i}{\widehat{\alpha} + \widehat{\mu}E_i}\right) \\ &= \text{E}[\text{RR}_i] \times (1 - w_i) + \text{SMR}_i \times w_i, \end{aligned} \tag{4}$$

a weighted combination of the prior estimate $\text{E}[\text{RR}_i] = \mu$, and the SMR in area $i$.

The *weight*

$$w_i = \frac{E_i \widehat{\mu}}{\widehat{\alpha} + E_i \widehat{\mu}}. \tag{5}$$

on the observed SMR increases as $E_i$ increases so that for areas with large populations the estimate is dominated by the data.
If $\alpha$ is large then the random effects have a tight spread, and there is more shrinkage since SMRs that are far from unity are inconsistent with the total collection of estimates – the weight is small in this case.
This behavior illustrates both the potential benefits and hazards of smoothing; the estimates will be less variable than the SMRs, but an outlying estimate that is not based on a large expected number, will be shrunk, and we may miss an important excess.

## Poisson-Gamma Model with Covariates

With area-level covariates we have the model

$$Y_i|\theta_i, \beta \sim_{\mathbf{ind}} \text{Poisson}\left(\mu_{\mathbf{i}}\mathbf{E_i}\theta_{\mathbf{i}}\right),$$

At the second stage the random effects $\theta_i$ are assigned a distribution. We assume that across the map the deviations of the relative risks from the mean, $\mu_i$, are modelled by

$$\theta_i|\alpha \sim_{iid} \text{Ga}(\alpha, \alpha),$$

a gamma distribution with mean 1, and variance $1/\alpha$.

## Empirical Bayes Estimation with Covariates

Suppose we have estimates $\widehat{\beta}$, $\widehat{\alpha}$. Then the distribution is given by

$$\theta_i | \text{by}, \widehat{\beta}, \widehat{\alpha} \sim \text{Ga}(\widehat{\alpha} + y_i, \widehat{\alpha} + E_i \widehat{\mu}_i),$$

which has mean

$$\widehat{RR}_i = \text{E}[\text{RR}_i] \times (1 - w_i) + \text{SMR}_i \times w_i, \tag{6}$$

a weighted combination of the prior estimate $\text{E}[\text{RR}_i] = \mu_i$, and the SMR in area $i$.

The *weight* is given by

$$w_i = \frac{E_i \widehat{\mu}_i}{\widehat{\alpha} + E_i \widehat{\mu}_i}. \tag{7}$$

In the right hand panel of Figure 3 we plot empirical Bayes estimates versus standard errors using a log-linear model in AFF.

One possibility for obtaining estimates $\widehat{\beta}, \widehat{\alpha}$ is to use maximum likelihood estimation over the marginal likelihood $\prod_{i=1}^{n} \Pr(Y_i | \beta, \alpha)$ (each term is a negative binomial).

## Example: Scottish Lip Cancer

Figure 5 shows relative risk estimates from a variety of models, with the SMRs on the left (referenced as position 0).
At position 1 the empirical Bayes estimates obtained without the use of the covariate AFF are displayed.
The weights on the SMR, (5), range between 0.45 and 0.99, with median 0.83. For these data the residual variability is large.
The standard deviation of the random effects is $1/\sqrt{\alpha}$, and is estimated as $0.73$, with 90% interval for residual relative risks (0.16,2.4).

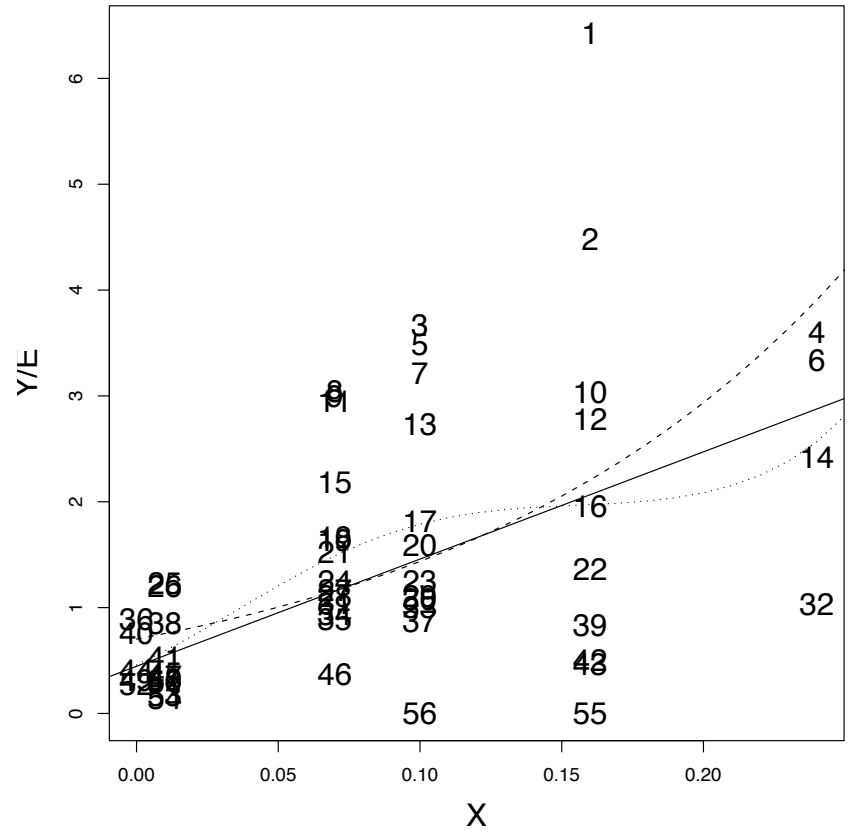



Figure: Plot of $Y/E$ versus proportion in AFF, $x$. Solid line corresponds to a linear in $x$ model; dashed line to a log link, linear in $x$ model; and dotted line to log link, cubic in $x$ model.

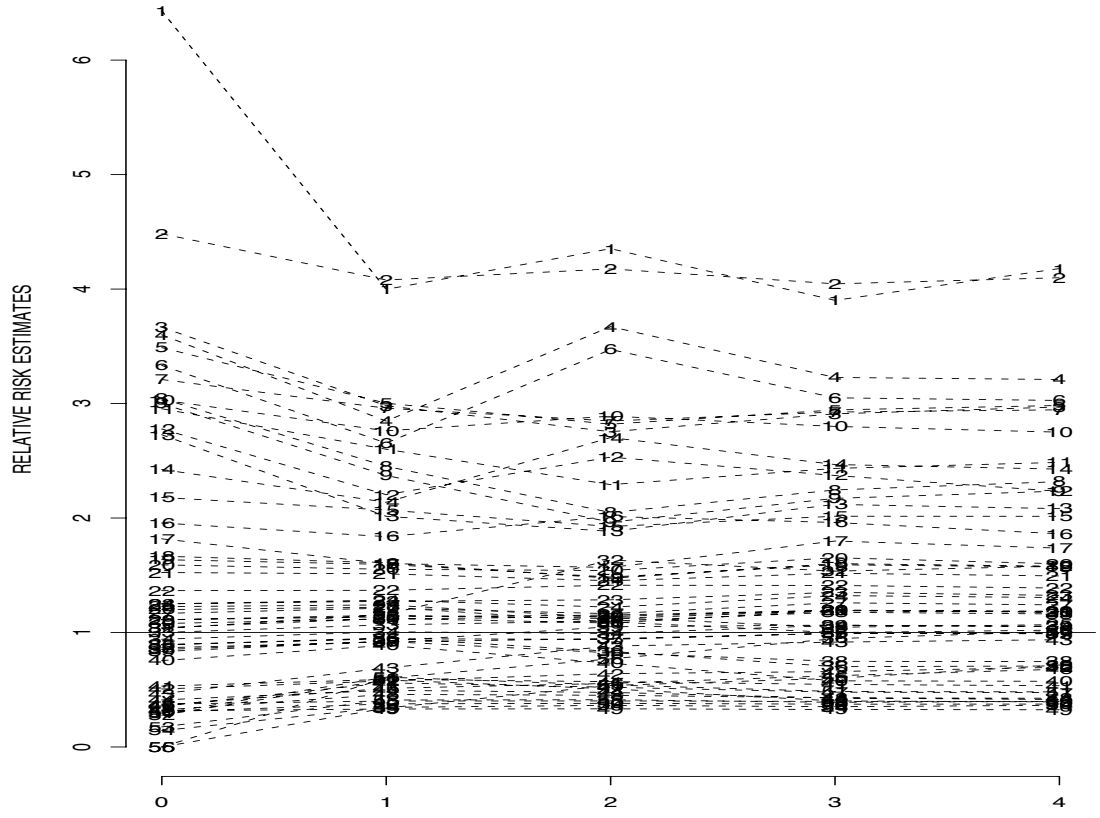



Figure:

Figure details: Relative risk estimates for Scottish lip cancer data:

- 0 denote the SMRs;
- 1 the empirical Bayes estimates without the use of AFF;
- 2 the empirical Bayes estimates with log link and a linear model in AFF;
- 3 the empirical Bayes estimates with a log-linear cubic model in AFF;
- 4 the fully Bayes estimates with a log-linear cubic model in AFF.

Plotting symbol is county number.

In position 2 gives EB estimates using a log-linear model in AFF,

$$\log \mu_i = \beta_0 + \beta_1 x_i.$$

The standard errors of the estimates are shown in the right hand panel of Figure 3. Four of the counties (4, 6, 14 and 32) have proportion in AFF equal to 0.24 (the highest value) and we see that the estimates for these counties are all moved upwards relative to the no covariate model (position 1) when the covariate is added to the model.

The latter is worrying, and we see the reason in Figure 4; the log-linear model (dashed line) does not fit the data well for large values of AFF.

This suggests that we use a more flexible model; after some exploratory work we choose the cubic form

$$\log \mu_i = \beta_0 + \beta_1 (x_i - \overline{x}) + \beta_2 (x_i - \overline{x})^2 + \beta_3 (x_i - \overline{x})^3 \qquad (8)$$

Figure 4 shows that this cubic model provides a better fit to the data (dotted line), and in particular flattens off for larger values of $x$. With linear and cubic models the sd of the random effects are $0.58$ and 0.53.

We might expect the standard deviation to be reduced in size when we add an important covariate but this does not have to happen. In position 3 of Figure 15 the cubic estimates are plotted and we see that for counties 4 and 6 in particular the estimates are more reasonable.

In this study there are only six distinct AFF values and so one could treat AFF as a factor and smooth using only those counties with identical covariate values.

This example illustrates how smoothing is carried out via the covariates, and the importance of deciding how much local smoothing is appropriate. A similar issue is relevant to the extent and nature of spatial smoothing.

## Review

- The aim is the provide stable relative risk estimates for area-level data.
- We have assumed that the relative risks arise from a common gamma distribution, which allows smoothing towards a common value.
- An empirical Bayes approach estimates the parameters of the negative binomial model ($\beta$ and $\alpha$) and then combines the gamma distribution with the data to obtain the empirical Bayes posterior distribution for the relative risks.

## Drawing Maps in R

Stages for mapping:

1. Require a set of polygons for each of the constituent areas in the study region, each polygon defined by a set of $x - y$ coordinates.
2. Need to be able to draw a map using these polygons.
3. Data to be mapped needs to be spatially-referenced with a common set of labels/order as the polygons.
4. Need to be able to fill in the polygons of the map using the data.

Usually the number of polygons will be greater than the number of areas, because some areas will be made up of disjoint sub-areas (for example, islands).

# The maps Library

```
> library(maps)
> map.text("county", "ohio")
> testdat <- runif(88) # need to read in the OhioMap function
> OhioMap(testdat,ncol=8,type="e",figmain="Ohio",lower=0,upper=2)
> OhioMap(testdat,ncol=8,type="e",figmain="Ohio random numbers",lower=0,upper=2)
> temp <- map("county","ohio")
> temp$names
 [1] "ohio,adams"      "ohio,allen"      "ohio,ashland"    "ohio,ashtabula"
 [5] "ohio,athens"     "ohio,auglaize"   "ohio,belmont"    "ohio,brown"
 [9] "ohio,butler"     "ohio,carroll"    "ohio,champaign"  "ohio,clark"
...
[77] "ohio,summit"     "ohio,trumbull"   "ohio,tuscarawas" "ohio,union"
[81] "ohio,van wert"   "ohio,vinton"     "ohio,warren"     "ohio,washington"
[85] "ohio,wayne"      "ohio,williams"   "ohio,wood"       "ohio,wyandot"
```


Figure: Map of Ohio counties, with names.

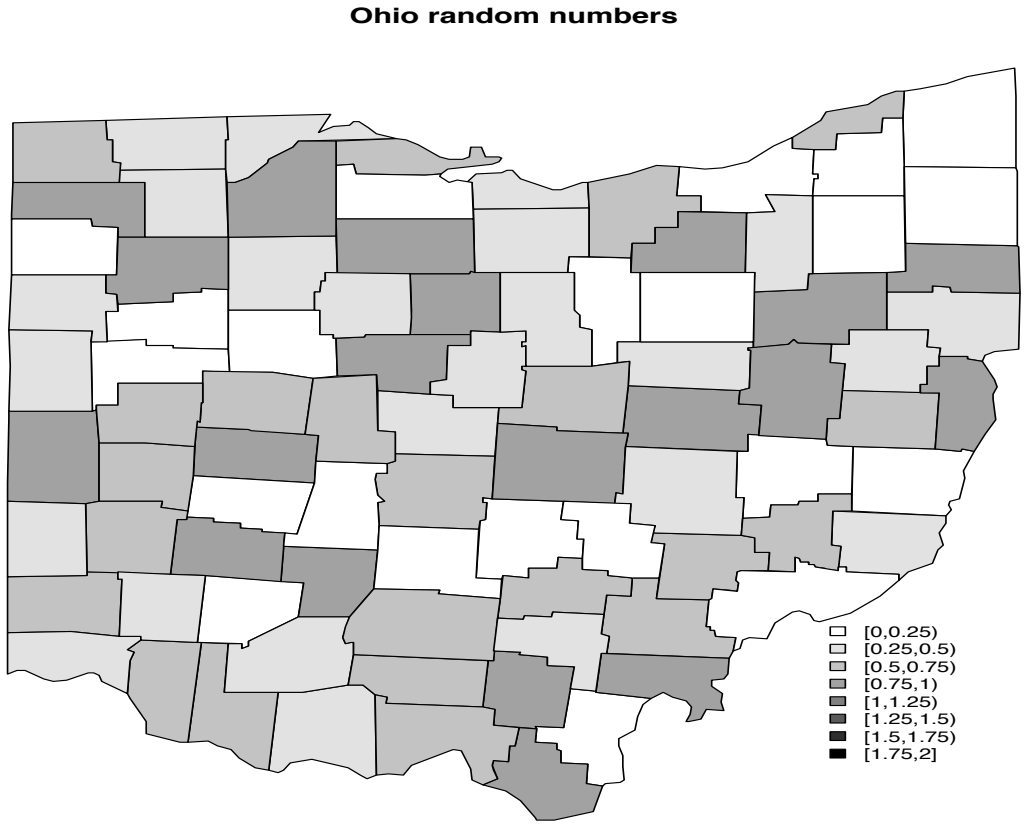



Figure: Map of Ohio random numbers, using the ÔhioMap function.

## Example: Disease Mapping for Scotland

We make use of a mapping function that is on the class website:

```
PrettyPoly <- function(y, poly, nrepeats, ncut=1000,
nlevels=10, lower=NULL, upper=NULL )
```

with arguments:

- `y` the variable to be mapped
- `poly` the $x - y$ coordinates of the polygons, with different polygons separated by `NA`s.
- `nrepeats` a vector of the same length as `y` with each entry containing the number of repeats of the appropriate entry in `y`.
- `ncut` The number of grey-scale levels to convert `y` to.
- `nlevels` The number of grey levels to plot.
- `lower` The value (on the same scale as `y`) that white is assigned to.
- `upper` The value (on the same scale as `y`) that black is assigned to.

The following code produces Figure 8.

```
> library(MASS)
> source("PolyMap.R")
> source("scotdat.txt")
> SMR <- z$Y/z$E
> zp <- read.table("SMRSplusmap.txt")
> x <- zp[,2]/1000
> y <- zp[,3]/1000
> poly <- matrix(c(x,y),ncol=2)
> nrepeats <- c(3,1,1,1,1,3,1,2,2,1,5,1,1,1,1,1,1,1,1,1,1,2,8,1,1,1,1,1,1,1,
              1,1,1,1,1,1,2,1,2,1,1,1,1,1,1,1,1,1,2,2,1,1,1,1,1,1)
> PrettyPoly(SMR,poly,nrepeats=nrepeats)#,lower=0,upper=10)
```

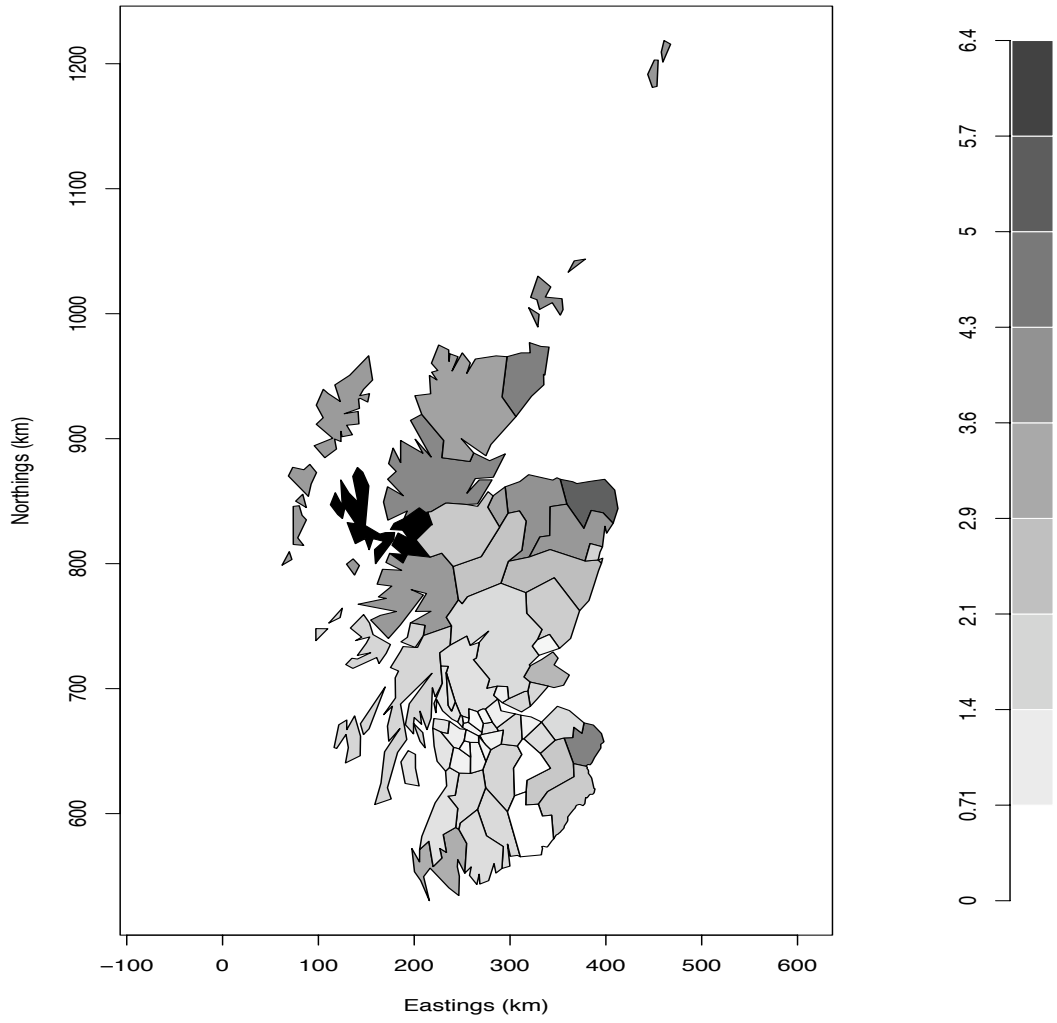



Figure: SMRs for Scottish counties.

The code below produces EB posterior mean estimates, the results are plotted in Figure 9. Notice that the extremes have been smoothed. It makes use of the function

```
eBayes <- function(Y,E,Xmat=NULL)
```

which takes as input, in addition to $Y$ and $E$, an $n \times p$ matrix of ecological covariates where $n$ is the number of areas and $p$ is the number of covariates.

The outputs are:

- `RR` the ecological relative risk posterior mean estimates
- `RRmed` the ecological relative risk posterior median estimates
- `beta` the MLEs of the regression coefficients
- `alpha` the MLE of negative binomial dispersion parameter
- `SMR` the standardized moratility/morbifity ratio, Y/E.

```
> emp <- eBayes(z$Y,z$E,Xmat=cbind(z$X,z$X^2,z$X^3))
> postscript("Scotland_gamma.ps", horizontal=FALSE)
> PrettyPoly(emp$RR, poly, nrepeats=nrepeats,lower=0,upper=max(SMR))
```

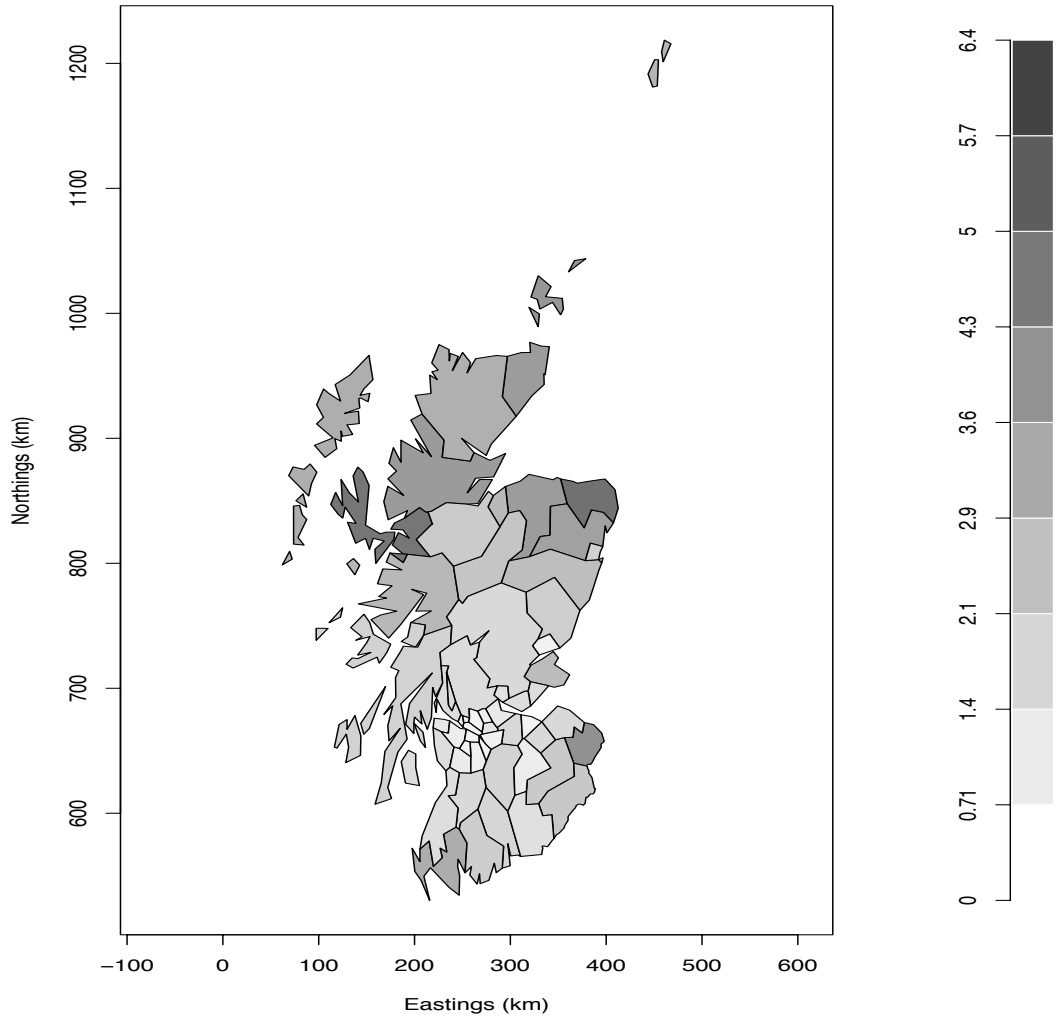



Figure: Empirical Bayes posterior mean estimates for Scottish counties.

As an alternative summary measure we plot the posterior medians in Figure 10. Produced using:

```
> PrettyPoly(emp$RRmed, poly, nrepeats=nrepeats,lower=0,upper=max(SMR))
```

Compared with 9, the estimates are higher, because the median exceeds the mean for a gamma distribution (for examples see Figure 11). So, for example, the areas with SMRs greater than 1 terd to have median estimates closer to the SMRs than the posterior means.
Figure 11 gives the empirical Bayes posterior densities for areas 1, 2, 55 and 56 – the vertical line denotes the SMR. Arguments to the function `EBpostdens` are reasonably self-explanatory.

```
> xvals <- seq(0,15,.01)
> beta <- matrix(c(emp$beta),nrow=4,ncol=1)
> Xrow1 <- matrix(c(1,z$X[1],z$X[1]^2,z$X[1]^3),nrow=1,ncol=4)
> EBpostdens(z$Y[1],z$E[1],emp$alpha,emp$beta,Xrow1,
lower=0,upper=15,main="Area 1")
```

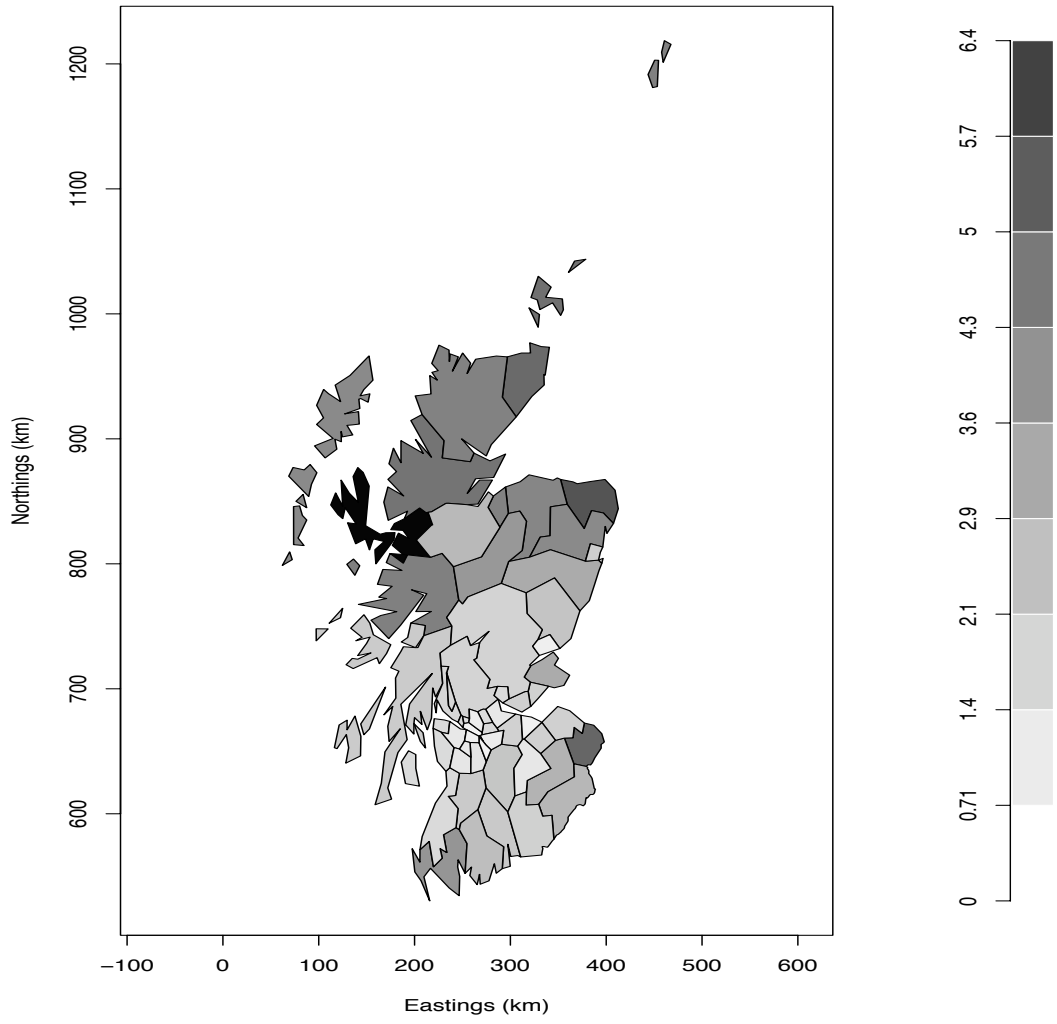



Figure: Empirical Bayes posterior median estimates for Scottish counties.

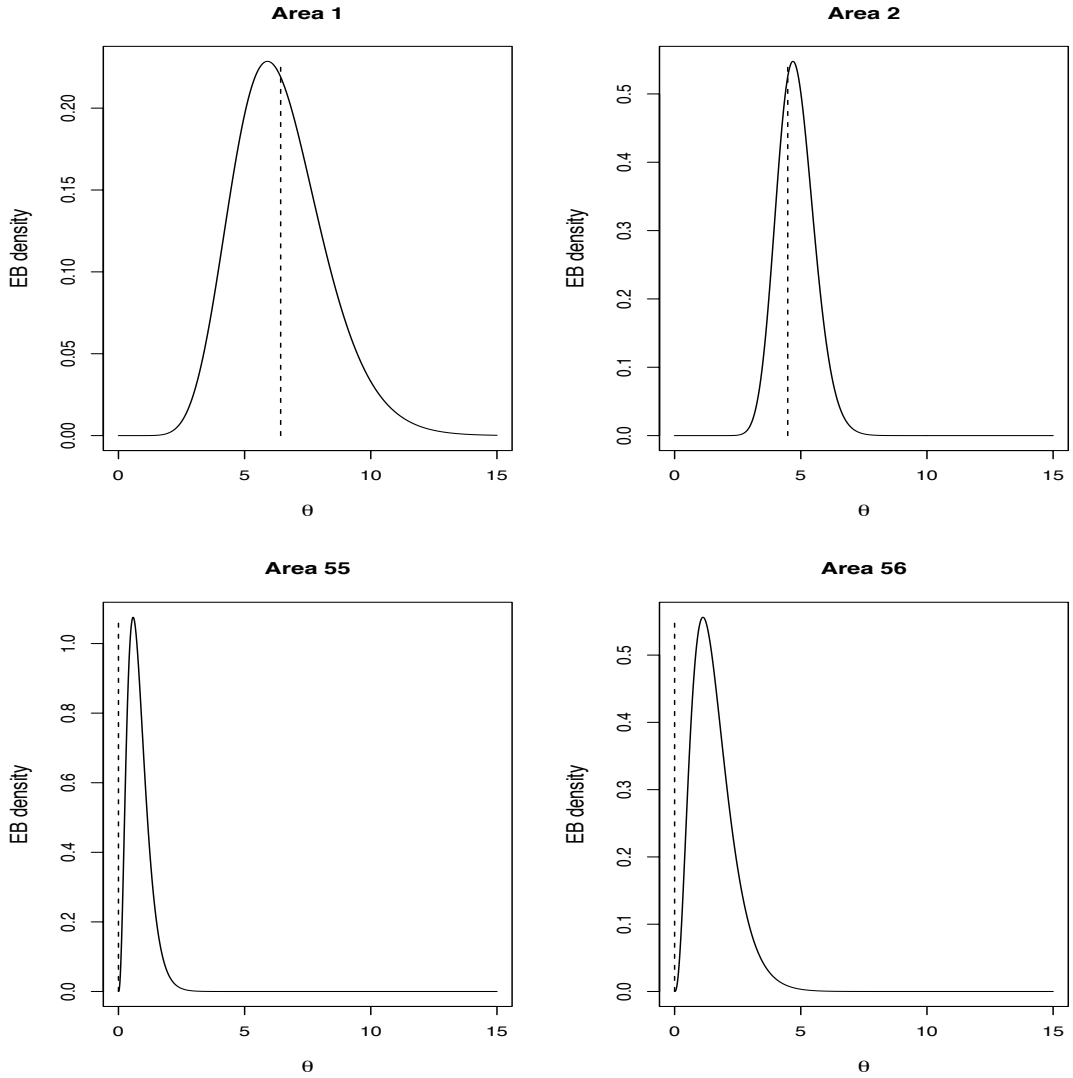



Figure: Empirical Bayes densities for 4 counties.

Figure 12 gives the posterior probability that the relative risk exceeds the value 3 in each area, given the gamma global smoothing model.
Arguments to the function `EBpostthresh` are reasonably self-explanatory.

```
> Xrow <- matrix(cbind(1,z$X,z$X^2,z$X^3),nrow=56,ncol=4)
> thresh3 <- EBpostthresh(z$Y,z$E,emp$alpha,emp$beta,Xrow,rrthresh=3)
> PrettyPoly(thresh3,poly,nrepeats,nlevels=11,lower=0,upper=1)
```

We see that the probabilities cover the full range of (0,1). Plots such as these are a very useful accompaniment to the raw SMRs and the smoothed estimates, since they reflect the uncertainty in the estimates.
Code for posterior probability threshold function:

```
EBpostthresh <- function(Y,E,alpha,beta,Xrow=NULL,rrthresh){
if (is.null(Xrow)) Xrow <- matrix(rep(1,length(Y)),
nrow=length(Y),ncol=1)
mu <- as.numeric(exp(Xrow %*% beta))
thresh <- 1-pgamma(rrthresh,alpha+Y,(alpha+E*mu)/mu)
return(thresh=thresh)
}
```

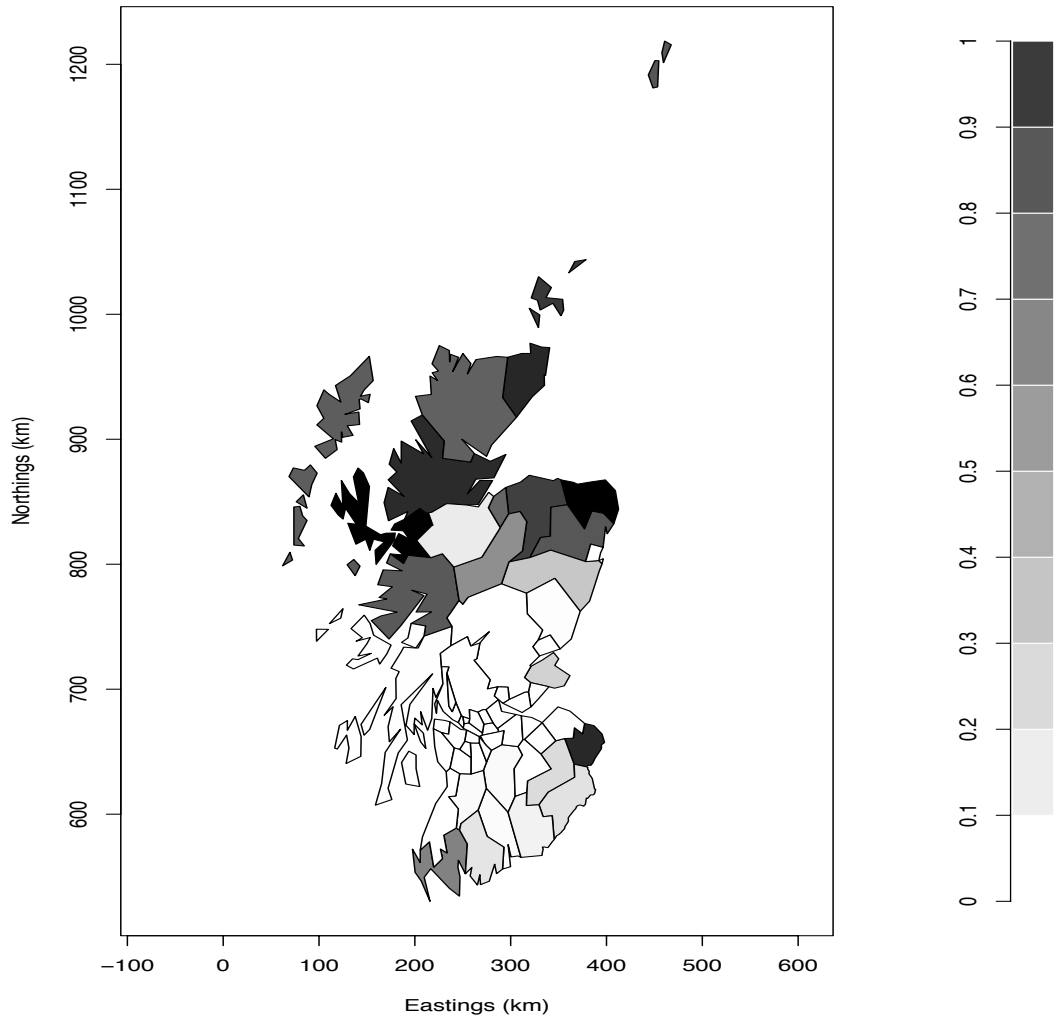



Figure: Empirical Bayes posterior probabilities that relative risk exceeds 3 in each county.

## Poisson-Gamma Model

We now carry out a fully Bayesian analysis of the model for which empirical Bayes was used previously:

$$\begin{aligned} Y_i|\theta_i, \beta_0 &\sim \text{Poisson}(E_i \mathrm{e}^{\beta_0}\theta_i) \\ \theta_i &\sim \text{Ga}(\alpha, \alpha) \end{aligned}$$

We require priors for $\beta_0$ and $\alpha$. For example:

$$\begin{aligned} \beta_0 &\sim \text{N}(m, v) \\ \alpha &\sim \text{Ga}(a, b) \end{aligned}$$

with $m, v, a, b$ picked to reflect beliefs about $\beta_0$ and $\alpha$.

## Empirical Bayes for Scotland

We recap on the previous analyses – this involved maximum likelihood estimation for $\beta_0$ and $\alpha$ in a negative binomial model and produced:

```
> emp0 <- eBayes(z$Y,z$E)
> emp0$beta
  0.3521065
> emp0$alpha
[1] 1.87949
> emp0$RR
 [1] 3.9973624 4.0791107 2.9802133 2.8467916 3.0025773 2.6545872 2.9590825
 [8] 2.4517687 2.3721492 2.7619805 2.6005515 2.2037872 2.0149301 2.1376464
...
[43] 0.6900960 0.4948910 0.4013614 0.5124617 0.5604849 0.4593902 0.3319144
[50] 0.3766186 0.6098460 0.5850639 0.4100864 0.3460232 0.3403845 0.6020789
> emp0$RRmed
 [1] 3.8755781 4.0458981 2.9034476 2.7600608 2.9434956 2.5655788 2.9237792
 [8] 2.3603697 2.2725880 2.7200177 2.5425312 2.0979757 1.8790820 2.0659710
...
[43] 0.6317935 0.4741200 0.3949723 0.4779112 0.5131326 0.4284178 0.3282190
[50] 0.3608116 0.5408883 0.5189084 0.3637163 0.3068970 0.2822885 0.4993176
```

## Bayesian Analysis and WinBUGS

Inference for models with a spatial component is often not reliable using likelihood, and so Bayesian methods are commonly used.
Unfortunately, most Bayesian models are not conducive to analytical analysis, and so are not available in standard software packages.
`WinBUGS` is a package that allows very general Bayesian modeling; the `GeoBUGS` module contains a number of useful spatial models, and mapping facilities.
Dependent samples that are approximate draws from the posterior distribution are produced and summarized within `WinBUGS`.
The algorithm that produces these samples require (a Markov chain) a starting point for initialization. To lose dependence on this starting point, initial iterations of the algorithm are discarded (and not used for inference) – this is known as the *burn in*.

## WinBUGS analysis of the Poisson-Gamma model

In the example that follows we specify a flat prior for $\beta_0$, and a Ga(1,1) prior for $\alpha$.

The iterative algorithm is run for 10,000 iterations, with the first 4,000 discarded as "burn-in".

We summarize the posteriors for the relative risks:

$$\text{RR}_i = \exp(\beta_0)\theta_i$$

and for $\beta_0$ and $\alpha$. The posterior mean for $\beta_0$ is 0.36, compared to 0.35 under empirical Bayes, and the posterior mean for $\alpha$ is 1.79, compared to 1.88 under empirical Bayes.

Similarly the posterior means and posterior medians agree very closely.

```
model
{
  for (i in 1 : N) {
      Y[i]  ~ dpois(mu[i])
      mu[i] <- E[i]*exp(beta0)*theta[i]
      RR[i] <- exp(beta0)*theta[i]
      theta[i] ~ dgamma(alpha,alpha)
  }
# Priors
  alpha ~ dgamma(1,1)
  beta0 ~ dflat()
# Functions of interest:
  sigma.theta <- sqrt(1/alpha)   # standard deviation of non-spatial
  base <- exp(beta0)
}
```

```
DATA
list(N = 56,
  Y = c( 9, 39, 11, 9, 15, 8, 26, 7, 6, 20, 13, 5, 3, 8, 17, 9, 2, 7,
  9, 7, 16, 31, 11, 7, 19, 15, 7, 10, 16, 11, 5, 3, 7, 8, 11, 9, 11,
  8, 6, 4, 10, 8, 2, 6, 19, 3, 2, 3, 28, 6, 1, 1, 1, 1, 0, 0), E = c(
  1.4, 8.7, 3.0, 2.5, 4.3, 2.4, 8.1, 2.3, 2.0, 6.6, 4.4, 1.8, 1.1,
  3.3, 7.8, 4.6, 1.1, 4.2, 5.5, 4.4, 10.5,22.7, 8.8, 5.6,15.5,12.5,
  6.0, 9.0,14.4,10.2, 4.8, 2.9, 7.0, 8.5,12.3,10.1,12.7, 9.4, 7.2,
  5.3, 18.8,15.8, 4.3,14.6,50.7, 8.2, 5.6, 9.3,88.7,19.6, 3.4, 3.6,
  5.7, 7.0, 4.2, 1.8))

INTIAL ESTIMATES
list(alpha = 1, beta0 = 0,
  theta=c(1,1,1,1,1,1,1,1,1,1,1,1,1,
  1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,
  1,1,1,1,1,1,1,1,1,1,1,1,1))
```

| node | mean | sd | MC error | 2.5% | median | 97.5% | start | sample |
|---|---|---|---|---|---|---|---|---|
| RR[1] | 4.07 | 1.297 | 0.01877 | 1.959 | 3.92 | 7.001 | 4000 | 6001 |
| RR[2] | 4.105 | 0.6469 | 0.00864 | 2.938 | 4.068 | 5.48 | 4000 | 6001 |
| RR[3] | 3.006 | 0.858 | 0.01159 | 1.607 | 2.915 | 4.937 | 4000 | 6001 |
| RR[4] | 2.875 | 0.8995 | 0.01019 | 1.391 | 2.773 | 4.886 | 4000 | 6001 |
| RR[5] | 3.016 | 0.7406 | 0.01114 | 1.754 | 2.955 | 4.668 | 4000 | 6001 |
| RR[6] | 2.68 | 0.8865 | 0.01325 | 1.227 | 2.568 | 4.696 | 4000 | 6001 |
| RR[7] | 2.975 | 0.5666 | 0.00830 | 1.994 | 2.929 | 4.236 | 4000 | 6001 |
| RR[8] | 2.476 | 0.8492 | 0.01224 | 1.082 | 2.379 | 4.412 | 4000 | 6001 |
| .... | | | | | | | | |
| RR[49] | 0.3321 | 0.06051 | 7.88E-4 | 0.2261 | 0.3286 | 0.4612 | 4000 | 6001 |
| RR[50] | 0.3685 | 0.1334 | 0.00162 | 0.1603 | 0.3522 | 0.6725 | 4000 | 6001 |
| RR[51] | 0.6 | 0.3539 | 0.00424 | 0.1112 | 0.5327 | 1.45 | 4000 | 6001 |
| RR[52] | 0.5702 | 0.3425 | 0.00519 | 0.1034 | 0.5017 | 1.4 | 4000 | 6001 |
| RR[53] | 0.4021 | 0.2446 | 0.00316 | 0.07137 | 0.3546 | 0.9934 | 4000 | 6001 |
| RR[54] | 0.3327 | 0.2042 | 0.00227 | 0.05706 | 0.2924 | 0.8143 | 4000 | 6001 |
| RR[55] | 0.3259 | 0.2533 | 0.00345 | 0.02491 | 0.2646 | 0.9605 | 4000 | 6001 |
| RR[56] | 0.5814 | 0.4538 | 0.00636 | 0.04737 | 0.4723 | 1.745 | 4000 | 6001 |
| alpha | 1.79 | 0.3985 | 0.00792 | 1.129 | 1.753 | 2.682 | 4001 | 6000 |
| beta0 | 0.3567 | 0.1188 | 0.00591 | 0.1315 | 0.353 | 0.5966 | 4000 | 6001 |

## Summary of Smoothing Models for Disease Mapping

- The aim is to reduce the instability inherent in SMRs based on small expected numbers.
- This is achieved by fitting a random effects model which assumes that area-level deviations from the regression model arise from a probability distribution (e.g. gamma or lognormal).
- Care should be exercised in the regression model that is used, to make sure appropriate smoothing is being carried out (recall the inadequate log-linear model in the Scottish data).
- Comparing SMRs with smoothed estimates is important – if there are big changes, are they appropriate? i.e. Were the expected numbers small? Did the regression model fit this area well?
- Fitting can be carried out using empirical Bayes or full Bayes.

- *Empirical Bayes* – MLE used for regression parameters and variance parameters of random effects distribution ($\alpha$ in the gamma model).
  - Advantage: ease of fitting.
  - Disadvantages: cannot do spatial smoothing, not quite right statistically.
- *Full Bayes* – requires a prior distribution on regression parameters and variance parameters of random effects distribution.
  - Advantages: all uncertainties correctly accounted for, extends to spatial models.
  - Disadvantages: computation must be carried out with Markov chain Monte Carlo, which requires some experience.
- Posterior distributions for each area relative risk can be summarized in a number of ways, e.g. posterior mean, posterior median, posterior quantiles, posterior probability of exceedence of a threshold.

## Poisson-Lognormal Model

The Poisson-gamma model offers analytic tractability, but does not easily allow the incorporation of spatial random effects.
A Poisson-lognormal non-spatial random effect model is given by:

$$Y_i|\beta, V_i \sim_{ind} \text{Poisson}(E_i\mu_i e^{V_i}) \quad V_i \sim_{iid} N(0, \sigma_v^2) \tag{9}$$

where $V_i$ are area-specific random effects that capture the residual or unexplained (log) relative risk of disease in area $i$, $i = 1, ..., n$.
Whereas in the Poisson-Gamma model we have $\theta \sim \text{Ga}(\alpha, \alpha)$, here we have $\theta = e^{V_i} \sim \text{LogNormal}(0, \sigma^2)$.
Model (9) does not give a marginal distribution of known form, but does naturally lead to the addition of spatial random effects.
The marginal variance is of the same quadratic form as (3).
Empirical Bayes is not so convenient for this model, and so we resort to a fully Bayesian approach for which we need to specify prior distributions.

## Prior Choice for Non-Spatial Model

We need to specify priors for:

- The regression coefficients $\beta$.
- The variance of the random effets $\sigma_v^2$.

For a rare disease, a log-linear link is a natural choice:

$$\log \mu(\mathbf{x_i}, \beta) = \beta_\mathbf{0} + \sum_{\mathbf{j=1}}^{\mathbf{J}} \beta_\mathbf{j} \mathbf{x_{ij}},$$

where $x_{ij}$ is the value of the $j$-th covariate in area $i$.
For regression parameters $\beta = (\beta_\mathbf{0}, \beta_\mathbf{1}, ..., \beta_\mathbf{J})$, an improper prior

$$p(\beta) \propto \mathbf{1}$$

may often be used, but in very circumstances such a choice may lead to an improper posterior.
If there are a large numbers of covariates, or high dependence amongst the elements of $\mathbf{x}$, then more informative priors will be beneficial.

## Lognormal Priors

It is convenient to specify lognormal priors for positive parameters $\exp(\beta_j)$, since one may specify two quantiles of the distribution, and directly solve for the two parameters of the lognormal. Denote by LN$(\mu, \sigma)$ the lognormal distribution for a generic parameter $\theta$ with $\mathrm{E}[\log\theta] = \mu$ and $\mathrm{var}(\log\theta) = \sigma^2$, and let $\theta_1$ and $\theta_2$ be the $q_1$ and $q_2$ quantiles of this prior. Then it is straightforward to show that

$$\mu = \log(\theta_1)\left(\frac{z_{q_2}}{z_{q_2} - z_{q_1}}\right) - \log(\theta_2)\left(\frac{z_{q_1}}{z_{q_2} - z_{q_1}}\right),\ \sigma = \frac{\log(\theta_1) - \log(\theta_2)}{z_{q_1} - z_{q_2}}.$$

As an example, suppose that for the ecological relative risk $e^{\beta_1}$ we believe there is a 50% chance that the relative risk is less than 1 and a 95% chance that it is less than 5; with $q_1 = 0.5, \theta_1 = 1.0$ and $q_2 = 0.95, \theta_2 = 5.0$, we obtain lognormal parameters $\mu = 0$ and $\sigma = \log 5/1.645 = 0.98$.

## Prior for $\sigma_v^2$

*Bottom line:* the priors $\sigma_v^{-2} \sim \text{Ga}(1, 0.0260)$ or $\sigma_v^{-2} \sim \text{Ga}(0.5, 0.0005)$ will often be suitable in a mapping context, though sensitivity of the results to the specification should be carried out, particularly if the number of areas is not large.

## Prior for $\sigma_v^2$ †

It is not straightforward to specify a prior for $\sigma_v$, which represents the standard deviation of the log residual relative risks, a difficult parameter to interpret.

We specify a gamma prior $\text{Ga}(a, b)$ for the precision $\tau_v = 1/\sigma_v^2$.

The choice of a gamma distribution is convenient since it produces a marginal distribution for the residual relative risks in closed form.

Specifically the two-stage model

$$V_i|\sigma_v \sim_{iid} N(0,\sigma_v^2), \quad \tau_v = \sigma_v^{-2} \quad \sim \quad \text{Ga}(a,b)$$

produces a marginal distribution for $V_i$ which is $t_d(0,\lambda^2)$, a Student's t distribution with $d = 2a$ degrees of freedom, location zero, and scale $b/a$; this is equivalent to the residual relative risks following a log t distribution.

We specify the range $\exp(\pm R)$ within which the residual relative risks lie with probability $q$, and use the relationship $\pm t^d_{q/2}\sqrt{b/a} = \pm R$, where $t^d_q$ is the $q$-th quantile of a Student t random variable with $d$ degrees of freedom, to give $a = d/2$, $b = R^2 d/2(t^d_{q/2})^2$.

For example, if we assume *a priori* that the residual relative risks follow a log Student t distribution with 2 degrees of freedom, with 95% of these risks falling in the interval (0.5,2.0), we obtain the prior, $\tau_v \sim \text{Ga}(1, 0.0260)$, an exponential distribution.

In terms of $\sigma_v$ this results in (2.5%, 97.5%) quantiles of (0.084,1.01) with posterior median 0.19.

## Non-Spatial Analysis of the Scottish Lip Cancer Data

We now report a fully Bayesian version of the normal model, (9), with log-linear cubic model.

The covariates are centered here in order to reduce dependence in the parameter estimates, which reduces the computational burden; this model was fitted using so-called Markov chain Monte Carlo via the `WinBUGS` software.

Flat priors were placed on $\beta_0, \beta_1, \beta_2, \beta_3$ and the previously-discussed gamma prior, $\text{Ga}(1, 0.0260)$, was assumed for $\sigma_v^{-2}$.

## WinBUGS code

Below we give code for fitting the cubic log-linear Poisson-lognormal model.

We define the random variables $\exp(\pm 1.96 \times \sigma_v)$ as the endpoints of a 95% interval for the residual relative risks.

In Figure 5 we see that the estimates under the empirical Bayes gamma and fully Bayesian normal model, at positions 3 and 4 respectively, each with cubic mean model, are very similar, illustrating that the most important aspect is not the inferential method or the choice of gamma or lognormal random effects, but the judicious choice of the covariate model.

```
model {
  for (i in 1 : N) {
      Y[i]  ~ dpois(mu[i])
      X1c[i] <- X[i]-mean(X[1:N])
      X2c[i] <- X1c[i]*X1c[i]
      X3c[i] <- X1c[i]*X1c[i]*X1c[i]
      log(mu[i]) <- log(E[i]) + beta0 +
                    beta1*X1c[i] + beta2*X2c[i] + beta3*X3c[i] + V[i]
      RR[i] <- exp(beta0 + beta1*X1c[i] + beta2*X2c[i]+ beta3*X3c[i] + V[i])
      V[i] ~ dnorm(0,tau.V)
  }
# The gamma prior corresponds to df=2, q=0.95, R=log 2.
  tau.V ~ dgamma(1,0.0260)
  beta0 ~ dflat()
  beta1 ~ dflat()
  beta2 ~ dflat()
  beta3 ~ dflat()
# Functions of interest:
  sigma.V <- sqrt(1/tau.V)       # standard deviation of non-spatial
  RRRlo <- exp(-1.96*sigma.V)
  RRRhi <- exp(1.96*sigma.V) }
```

- In general we might expect residual relative risks in areas that are "close" to be more similar than in areas that are not "close".
- We would like to exploit this information in order to provide more reliable relative risk estimates in each area.
- This is analogous to the use of a covariate $x$, in that areas with similar $x$ values are likely to have similar relative risks.
- Unfortunately the modelling of spatial dependence is much more difficult since spatial location is acting as a surrogate for unobserved covariates.
- We need to choose an appropriate spatial model, but do not directly observe the covariates whose effect we are trying to mimic.

We first consider the model

$$Y_i|\beta,\gamma,\mathbf{U_i},\mathbf{V_i} \sim_{\mathbf{ind}} \text{Poisson}(\mathbf{E_i}\mu_\mathbf{i}\mathrm{e}^{\mathbf{U_i}+\mathbf{V_i}})$$

with

$$\log \mu_i = g(\mathbf{S}_i,\gamma) + \mathbf{f}(\mathbf{x_i},\beta), \tag{10}$$

where

- $\mathbf{S}_i = (S_{i1}, S_{i2})$ denotes spatial location, the centroid of area $i$,
- $f(\mathbf{x_i},\beta)$ is a regression model,
- $g(\mathbf{S}_i,\gamma)$ is an expression that we may include to capture large-scale spatial trend – the form

$$f(\mathbf{S}_i) = \gamma_1 S_{i1} + \gamma_2 S_{i2},$$

  is a simple way of accommodating long-term spatial trend.
- The random effects $V_i \sim_{iid} N(0,\sigma_v^2)$ represent non-spatial overdispersion,
- $U_i$ are random effects with spatial structure. We describe two forms.

## A Joint Model

- Assume that $\mathbf{U} = (U_1, ..., U_n)$ arise from a zero mean multivariate normal distribution with variances $\text{var}(U_i) = \sigma_u^2$ and correlations $\text{corr}(U_i, U_j) = \exp(-\phi d_{ij}) = \rho^{d_{ij}}$ where $d_{ij}$ is the distance between the centroids of areas $i$ and $j$, and $\rho > 0$ is a parameter that determines the extent of the correlation.
- This model is *isotropic* since it assumes that the correlation is the same in all spatial directions. We refer to this as the *joint* model, since we have specified the joint distribution for $\mathbf{U}$.
- More generally the correlations can be modeled as $\text{corr}(U_i, U_j) = \exp(-(\phi d_{ij})^\kappa)$.

# WinBUGS *representation*

The above model with

$$\text{cov}(U_i, U_j) = \tau_u^{-1} \exp(-(\phi d)^\kappa)$$

and $\phi > 0$, $0 < \kappa < 2$ can be specified via the function:

`U[1:N]` $\sim$ `spatial.exp(mu[],x[],y[],tau,phi,kappa)`

where:

- `mu[]`: A vector giving the mean for each area.
- `x[]` and `y[]`: Vectors of length $n$ (the number of areas) giving the x and y coordinates of the centroid of each area.
- `phi` $= \phi$.
- `kappa` $= \kappa$.
- This model can be very slow for even moderate sized datasets (because a matrix inversion is required at each iteration).

## A Conditional Model

- An alternative approach is to specify the distribution of each $U_i$ as if we knew the values of the spatial random effects $U_j$ in "neighboring areas"
- We need to specify a rule for determining the "neighbours" of each area.
- Spatial models that start with the $n$ area-specific residual spatial random effects all suffer from a level of arbitrariness in their specification – in an epidemiological context the areas are not regular in shape (as opposed to images for example, which are on a regular grid).
- To define *neighbors*, a number of authors have taken the neighborhood scheme to be such that areas $i$ and $j$ are taken to be neighbors if they share a *common boundary*. This is reasonable if all regions are of similar size and arranged in a regular pattern (as is the case for pixels in image analysis where these models originated), but is not particularly attractive otherwise.

- Various other neighborhood/weighting schemes are possible.
- We could take the neighborhood structure to depend on the distance between area centroids and determine the extent of the spatial correlation (i.e. the distance within which regions are considered neighbors).
- In typical applications it is difficult to assess whether the spatial model chosen is appropriate, which argues for a simple form, and to assess the sensitivity of conclusions to different choices.
- In Figure 13 we show a close-up of a portion of the Birmingham study. One of the wards in the center of the Birmingham region is such that it 'just' shares a common boundary with a number of close-by wards. In terms of the common-boundary prior, it could be considered to have between four and ten neighbors.

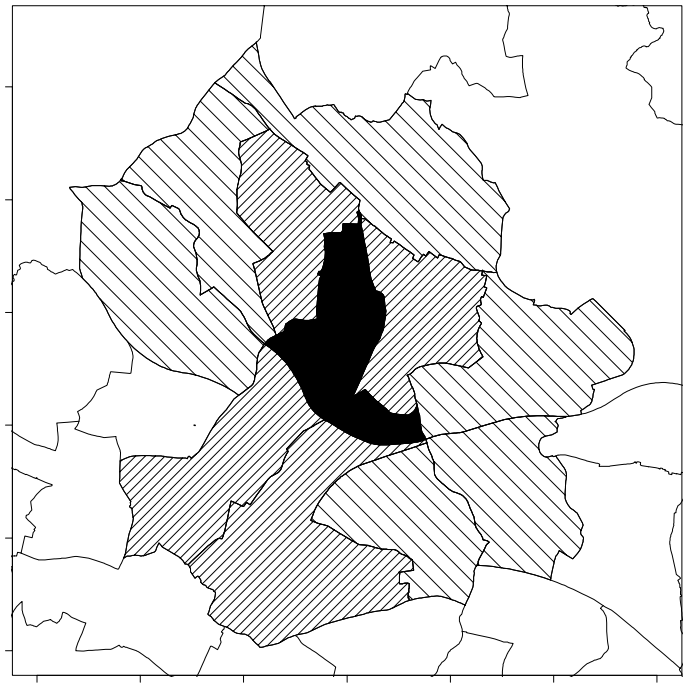


Figure: Close-up of a region of the Birmingham study.

## The ICAR model†

- A common model is to assign the spatial random effects an intrinsic conditional autorgressive (ICAR) prior.
- Under this specification it is assumed that

$$U_i | U_j, j \in \partial_i \sim N\left(\overline{U}_i, \frac{\omega_u^2}{m_i}\right),$$

  where $\partial i$ is the set of neighbors of area $i$, $m_i$ is the number of neighbours, and $\overline{U}_i$ is the mean of the spatial random effects of these neighbors.
- The parameter $\omega_u^2$ is a conditional variance and its magnitude determines the amount of spatial variation.
- The variance parameters $\sigma_v^2$ and $\omega_u^2$ are on different scales, $\sigma_v$ is on the log odds scale while $\omega_u$ is on the log odds scale, *conditional* on $U_j, j \in \partial i$; hence they are not comparable (in contrast to the joint model in which $\sigma_u$ is on the same scale as $\sigma_v$).

- Notice that if $\omega_u^2$ is "small" then although the residual is strongly dependent on the neighboring value the overall contribution to the residual relative risk is small.
- This is a little counterintuitive but stems from spatial models having two aspects, strength of dependence and total amount of spatial dependence, and in the ICAR model there is only a single parameter which controls both aspects.
- In the joint model the strength is determined by $\rho$ and the total amount by $\sigma_u^2$. A non-spatial random effect should always be included along with the ICAR random effect since this model cannot take a limiting form that allows non-spatial variability; in the joint model with $U_i$ only, this is achieved as $\rho \to 0$. If the majority of the variability is non-spatial, inference for this model might incorrectly suggest that spatial dependence was present.

# WinBUGS *representation*

The ICAR model can be specified via the function:

$$\texttt{U[1:N]} \sim \texttt{car.normal(adj[],weights[],num[],tau)}$$

where:

- `adj[]`: A vector listing the ID numbers of the adjacent areas for each area (this can be generated using the Adjacency Tool from the Map menu in GeoBUGS).
- `weights[]`: A vector the same length as `adj[]` giving unnormalized weights associated with each pair of areas.
- `num[]`: A vector of length N (the total number of areas) giving the number of neighbors $n_i$ for each area.
- The `car.normal` distribution is parameterized to include a sum-to-zero constraint on the random effects. A separate intercept term must be used in the model and this must be assigned an improper uniform prior using the `dflat()` distribution (see full code below).

*Bottom line:* For the joint model we can specify $\sigma_u^{-2}$ as having the same prior as $\sigma_v^{-2}$. For $\phi$ the choice of prior depends on the scale of the study region (examples below).
For the ICAR model, the choice depends on the neighborhood structure assumed, but sometimes one may be able to specify the same prior for $\omega_u^{-2}$ as for $\sigma_v^{-2}$.

Previously, priors have been specified for each of the variance components separately, but it is more natural to represent beliefs about the total variability.
Proper priors are required for the parameters of the spatial model.
For the joint model in which a multivariate normal distribution is assigned to $\mathbf{U}$, we have $V_i \sim_{iid} N(0, \sigma_v^2)$ and, independently, $U_i \sim_{iid} N(0, \sigma_u^2)$ so that the residual relative risk $e^{V_i+U_i}$ is lognormal with parameters 0 and $\sigma_v^2 + \sigma_u^2$.
We write the total precision as $\tau_T = (\sigma_v^2 + \sigma_u^2)^{-1}$, and specify $\tau_T \sim \text{Ga}(a, b)$ so that marginally we have a log Student's t distribution for the total residual relative risks.

We let $p = \sigma_u^2/(\sigma_u^2 + \sigma_v^2)$ represent the proportion of the total residual variation that is attributable to the spatial component, and assign a beta prior, Be$(c, d)$, to $p$, and transform from $(\sigma_T^2, p)$ to $(\sigma_v^2, \sigma_u^2)$ via

$$\begin{aligned} \sigma_v^2 &= (1-p)\tau_T^{-1} = (1-p)(\sigma_v^2 + \sigma_u^2) \\ \sigma_u^2 &= p\tau_T^{-1} = p(\sigma_v^2 + \sigma_u^2). \end{aligned}$$

This prior allows us to control the amount of total residual variability, and induces positive dependence in the joint prior for $(\sigma_v^2, \sigma_u^2)$.
Rather than consider the parameter $\rho$, we specify a lognormal prior for the distance at which the correlations fall to a half,

$$d_{1/2} = \log 2 / \log \rho$$

in the manner summarised in equations (10). For example, if we believe there is a 5% chance that the correlation falls to a half in less than 5km, and a 95% chance that it falls to a half in less than 100km we obtain $d_{1/2} \sim$ LN$(3.107, 0.9106)$.

Given its conditional interpretation it is not straightforward to specify a prior for the ICAR parameter $\omega_u^2$. Specifying an ICAR model for the spatial effects does not define a proper $n$-dimensional joint distribution, rather

$$\begin{aligned} p(\mathbf{U}|\omega_u^2) &\propto (\omega_u^2)^{-(n-1)/2} \exp\left[-\frac{1}{2}\mathbf{U}^\top \mathbf{Q}\mathbf{U}\right] \\ &= (\omega_u^2)^{-(n-1)/2} \exp\left[-\frac{1}{2\omega_u^2}\sum_{i<j}(U_i - U_j)^2\right], \quad (11) \end{aligned}$$

where $\mathbf{Q}$ is the $n \times n$ matrix with, for $i \neq j$, $Q_{ij} = -1/\omega_u^2$, if areas $i$ and $j$ are neighbours and $Q_{ij} = 0$ otherwise, and $Q_{ii} = m_i/\omega_u^2$. The form (11) does not provide a well defined joint distribution, and the marginal distributions for $U_i$ do not exist.

For prior specification we follow an approximate strategy and consider the $n-1$, random variables $\mathbf{Z} = (Z_1, ..., Z_{n-1})$ where $Z_i = U_i - U_n$, $i = 1, ..., n-1$.
Hence $\mathbf{Z} = \mathbf{AU}$, where $\mathbf{A} = [\mathbf{I}|-\mathbf{1}]$, $-1$ is the $(n-1) \times (n-1)$ identity matrix, and $-\mathbf{1}$ is an $(n-1) \times 1$ vector of -1's.
The joint distribution of $\mathbf{Z}$ exists, and is an $(n-1)$-dimensional normal distribution with mean zero and precision matrix $\overline{\mathbf{A}}^{\mathsf{T}}\mathbf{Q}\overline{\mathbf{A}}$ with
$\overline{\mathbf{A}} = [\mathbf{I}|\mathbf{0}]^{\mathsf{T}}$ a generalized inverse of $\mathbf{A}$, where $\mathbf{0}$ is the $(n-1) \times 1$ vector of 0's.
The marginal variance for $Z_i$ is var$(Z_i) = a_i\omega_u^2$, where the constants
$a_i$ are determined by the neighbourhood structure, and are given by the diagonal elements of $(\overline{\mathbf{A}}^{\mathsf{T}}\mathbf{Q}\overline{\mathbf{A}})^{-1}$.

We let $\overline{\sigma}_z^2 = \overline{a}\omega_u^2$ represent the average marginal variance, and specify a prior for $\overline{\sigma}_z^2$, which induces a prior for $\omega_u^2$.
Once the calibration between $\omega_u^2$ and $\overline{\sigma}_z^2$ has been carried out we specify priors for $\tau_T = (1/\sigma_v^2 + 1/\overline{\sigma}_z^2)$ and $p$, as described for the joint model, and then take $\sigma_v^2 = (1-p)\tau_T^{-1}$ and $\omega_u^2 = p\tau_T^{-1}/\overline{a}$.
This procedure is approximate in a number of ways; we have considered $\mathbf{Z}$ rather than $\mathbf{U}$, and $U_i$ is not marginally normally distributed.
Since the joint distribution for $\mathbf{U}$ is not well-defined, we do not have a parameter to describe the marginal variance (which would be useful to compare with $\sigma_v^2$ to see the spatial contribution), but we can examine the empirical variance via $\frac{1}{n-1}\sum_{i=1}^n U_i^2$.

We assign improper flat priors to each element of $\beta$, and for the joint spatial model assume initially that

$$\begin{aligned} \tau_T &\sim \text{Ga}(1, 0.0260) \\ p &\sim \text{Be}(1, 1) \\ d_{1/2} &\sim \text{LN}(3.107, 0.9106) \end{aligned}$$

Figure 14 shows smoothed marginal densities based on samples from these priors for the joint model, including induced quantities of interest such as $\rho^{10}$, the correlation at a distance of 10km, and the residual relative risk $\exp(U_i + V_i)$.
The induced dependence between $\sigma_v$ and $\sigma_u$ is apparent.

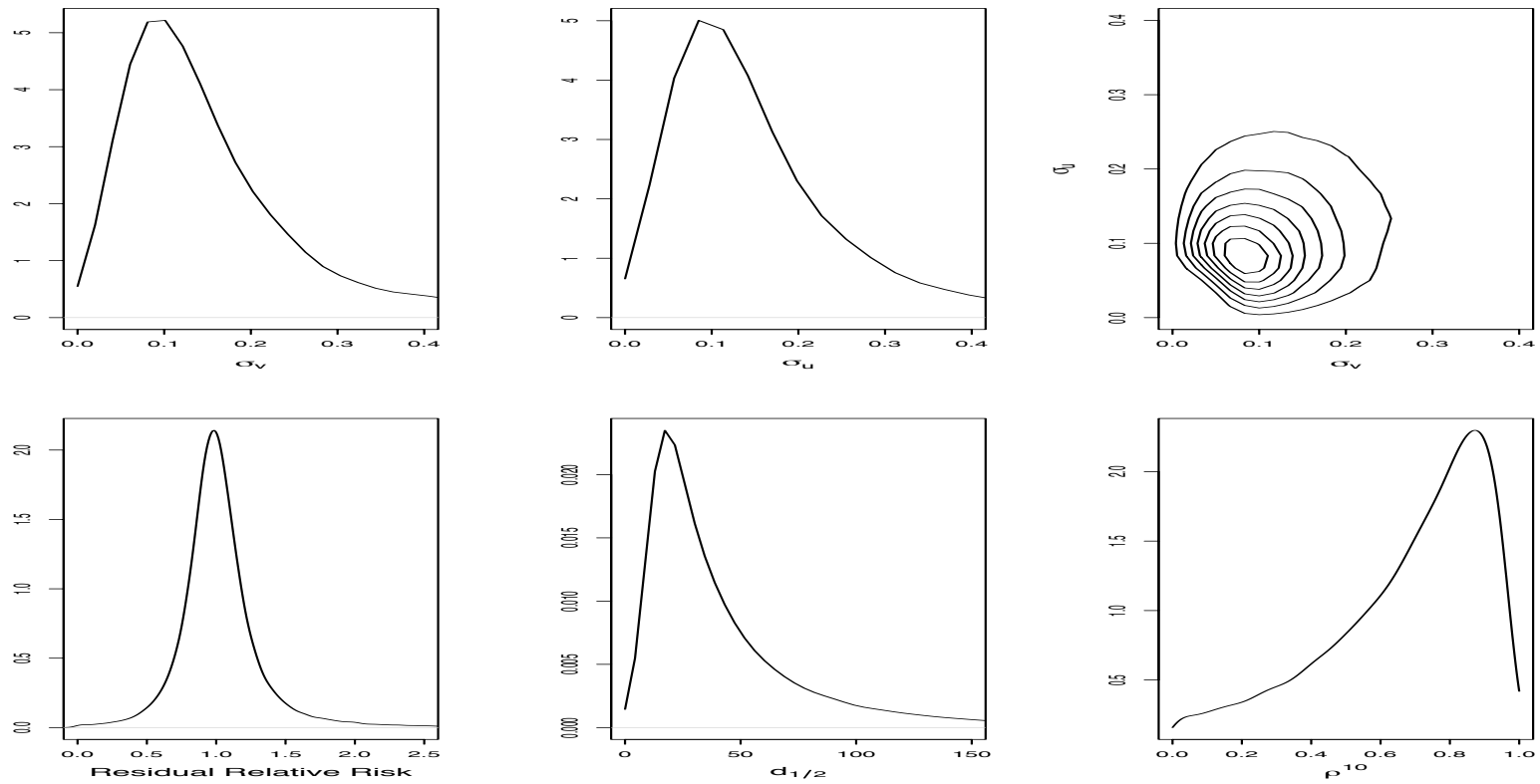



Figure: Priors for the joint spatial model. First row: univariate and joint marginals for $\sigma_v$ and $\sigma_u$. Second row: the residual relative risk $\exp(V_i + U_i)$ margin, the distance at which correlations fall to a half, $d_{1/2}$, and the correlation between areas whose centroids are 10km apart, $\rho^{10}$.

For the ICAR model the same priors were assumed and we set $\omega_u^2 = p\tau_T^{-1}/\overline{a}$ where $\overline{a} = 1.164$ for the Scottish geography with a common boundary neighbourhood scheme.
This neighbourhood scheme is not particularly appealing for the Scottish geography because of the irregularity of the areas.
We initially assumed that the three islands, which have no common boundary neighbours, only had a non-spatial random effect.

# WinBUGS code for the joint model

```
model {
  for (i in 1 : N) {
      Y[i]  ~ dpois(mu[i])
      X1c[i] <- X[i]-mean(X[1:N])
      X2c[i] <- X1c[i]*X1c[i]
      X3c[i] <- X1c[i]*X1c[i]*X1c[i]
      log(mu[i]) <- log(E[i]) + beta0 + beta1*X1c[i] + beta2*X2c[i] +
                    beta3*X3c[i] + V[i] + U[i]
      RR[i] <- exp(beta0 + beta1*X1c[i] + beta2*X2c[i]+
               beta3*X3c[i] + V[i] + U[i])
      V[i] ~ dnorm(0,tau.V)
      mean[i] <- 0
  }
  U[1:N] ~ spatial.exp(mean[], xm[], ym[], tau.U, phi, 1)
  tau.T ~ dgamma(1,0.0260)
  p ~ dbeta(1,1) # p is the proportion of the variance that is spatial
  sigma.U <- sqrt(p/tau.T)
  sigma.V <- sqrt((1-p)/tau.T)
  tau.V <- 1/(sigma.V*sigma.V)
  tau.U <- 1/(sigma.U*sigma.U)
  dhalf ~ dlnorm(3.107,0.9106)
  phi <- 0.6931/dhalf
  beta0 ~ dflat()
  beta1 ~ dflat()
  beta2 ~ dflat()
  beta3 ~ dflat()
}
```

```
DATA
list(N = 56, Y = c( 9, 39, 11, 9, 15, 8, 26, 7, 6, 20, 13, 5, 3,
8, 17, 9, 2, 7, 9, 7, 16, 31, 11, 7, 19, 15, 7, 10, 16, 11, 5, 3, 7,
8, 11, 9, 11, 8, 6, 4, 10, 8, 2, 6, 19, 3, 2, 3, 28, 6, 1, 1, 1, 1, 0,
0), E = c( 1.4, 8.7, 3.0, 2.5, 4.3, 2.4, 8.1, 2.3, 2.0, 6.6, 4.4, 1.8,
1.1, 3.3, 7.8, 4.6, 1.1, 4.2, 5.5, 4.4, 10.5,22.7, 8.8, 5.6,15.5,12.5,
6.0, 9.0,14.4,10.2, 4.8, 2.9, 7.0, 8.5,12.3,10.1,12.7, 9.4, 7.2, 5.3,
18.8,15.8, 4.3,14.6,50.7, 8.2, 5.6, 9.3,88.7,19.6, 3.4, 3.6, 5.7, 7.0,
4.2, 1.8), X = c(0.16,0.16,0.10,0.24,0.10,0.24,0.10, 0.07, 0.07,0.16,
0.07,0.16,0.10,0.24, 0.07,0.16,0.10, 0.07, 0.07,0.10, 0.07,0.16,0.10,
0.07, 0.01, 0.01, 0.07, 0.07,0.10,0.10, 0.07,0.24,0.10, 0.07, 0.07,
0,0.10, 0.01,0.16, 0, 0.01,0.16,0.16, 0, 0.01, 0.07, 0.01, 0.01, 0,
0.01, 0.01, 0, 0.01, 0.01,0.16,0.10), xm = c( 162.1894, 385.7761,
293.9555, 377.9338, 220.6786, 340.1739, 324.9915, 442.2445, 194.5176,
367.6924, 112.8916, 247.7566, 289.5922, 227.9563, 342.3574, 351.3505,
280.4916, 341.6081, 249.6855, 359.5902, 348.7138, 388.7655, 180.4228,
295.4908, 333.1159, 312.0605, 290.1701, 359.4153, 291.3727, 303.4219,
257.4402, 264.9711, 336.4464, 258.0319, 227.1801, 234.5294, 218.3428,
279.1010, 235.0805, 254.1736, 250.8301, 287.1202, 292.3773, 288.0333,
320.5682, 257.8758, 276.9737, 281.9644, 267.8444, 342.226, 274.8713,
257.8069, 265.5934, 267.8921, 321.4991, 322.1780), ym =c(834.7496,
852.3782, 946.0722, 650501, 870.9356, 1015.154, 842.0317, 1168904,
781.3746, 828.219, 903.1592, 924.9536, 842.3052, 561.1628, 713.0808,
792.1617, 801.0356, 628.6406, 825.8545, 610.6554, 760.2982, 812.7655,
699.6693, 635.7658, 701.8189, 691.102, 586.6673, 669.4746, 746.2605,
670.1395, 605.9585, 568.3428, 658.671, 716.452, 598.2521, 668.0481,
641.4785, 670.285, 697.044, 677.589, 657.4675, 680.7535, 699.3761,
665.2905, 671.6064, 631.046, 640.8285, 654.6629, 666.7073, 736.4561,
678.8585, 683.7104, 646.5754, 682.2943, 640.1429, 589.9408))
```

INITIAL ESTIMATES

```
list(tau.T = 1, p=0.5,beta0 = 0, beta1 = 0, beta2 = 0, beta3 =0, dhalf =1,
V=c(0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0),
U=c(0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0))
```

# The WinBUGS code for the ICAR model

```
model {
  for (i in 1 : N) {
      Y[i]  ~ dpois(mu[i])
      X1c[i] <- X[i]-mean(X[1:N])
      X2c[i] <- X1c[i]*X1c[i]
      X3c[i] <- X1c[i]*X1c[i]*X1c[i]
      log(mu[i]) <- log(E[i]) + beta0 + beta1*X1c[i]  +
                    beta2*X2c[i] + beta3*X3c[i] + V[i] + U[i]
      RR[i] <- exp(beta0 + beta1*X1c[i] +
                   beta2*X2c[i] + beta3*X3c[i] + V[i] + U[i])
      V[i] ~ dnorm(0,tau.V)
  }
# ICAR prior distribution for spatial random effects:
  U[1:N] ~ car.normal(adj[], weights[], num[], tauomega.U)
  for(k in 1:sumNumNeigh) {
      weights[k] <- 1
  }
  tau.T ~ dgamma(1,0.0260)
  p ~ dbeta(1,1)
  sigma.Z <- sqrt(p/tau.T)
  omega.U <- sigma.Z/sqrt(1.164)
  sigma.V <- sqrt((1-p)/tau.T)
  tau.V <- 1/(sigma.V*sigma.V)
  tauomega.U <- 1/(omega.U*omega.U)
  beta0 ~ dflat()
  beta1 ~ dflat()
  beta2 ~ dflat()
  beta3 ~ dflat()
  sd.U <- sd(U[1:N])
  vratio <- sd.U*sd.U/(sd.U*sd.U+sigma.V*sigma.V)
}
```

DATA

```
list(N = 56, Y = c( 9, 39, 11, 9, 15, 8, 26, 7, 6, 20, 13, 5, 3, 8,
17, 9, 2, 7, 9, 7, 16, 31, 11, 7, 19, 15, 7, 10, 16, 11, 5, 3, 7, 8,
11, 9, 11, 8, 6, 4, 10, 8, 2, 6, 19, 3, 2, 3, 28, 6, 1, 1, 1, 1, 0,
0), E = c( 1.4, 8.7, 3.0, 2.5, 4.3, 2.4, 8.1, 2.3, 2.0, 6.6, 4.4, 1.8,
1.1, 3.3, 7.8, 4.6, 1.1, 4.2, 5.5, 4.4, 10.5,22.7, 8.8, 5.6,15.5,12.5,
6.0, 9.0,14.4,10.2, 4.8, 2.9, 7.0, 8.5,12.3,10.1,12.7, 9.4, 7.2, 5.3,
18.8,15.8, 4.3,14.6,50.7, 8.2, 5.6, 9.3,88.7,19.6, 3.4, 3.6, 5.7, 7.0,
4.2, 1.8), X = c(0.16,0.16,0.10,0.24,0.10,0.24,0.10, 0.07, 0.07,0.16,
0.07,0.16,0.10,0.24, 0.07,0.16,0.10, 0.07, 0.07,0.10, 0.07,0.16,0.10,
0.07, 0.01, 0.01, 0.07, 0.07,0.10,0.10, 0.07,0.24,0.10, 0.07, 0.07,
0,0.10, 0.01,0.16, 0, 0.01,0.16,0.16, 0, 0.01, 0.07, 0.01, 0.01, 0,
0.01, 0.01, 0, 0.01, 0.01,0.16,0.10),
num = c(3, 2, 2, 3, 4, 2, 5, 1, 5, 4, 1, 2, 3, 3, 2, 6, 6, 6, 5, 3,
3, 2, 4, 8, 3, 3, 4, 4, 11, 6, 7, 3, 4, 9, 4, 2, 4, 6, 3, 4,
5, 5, 4, 5, 4, 6, 6, 4, 9, 2, 4, 4, 4, 5, 6, 5),
adj = c(
19, 9, 5,
10, 7,
12, 6,
28, 20, 18,
19, 12, 11, 1,
3,8,
17, 16, 13, 10, 2,
6,
29, 23, 19, 17, 1,
22, 16, 7, 2,
5,
5, 3,
19, 17, 7,
35, 32, 31,
29, 25,
...
```

```
53, 49, 48, 46, 31, 24,
49, 47, 44, 24,
54, 53, 52, 48, 47, 44, 41, 40, 38,
29, 21,
54, 42, 38, 34,
54, 49, 40, 34,
49, 47, 46, 41,
52, 51, 49, 38, 34,
56, 45, 33, 30, 24, 18,
55, 27, 24, 20, 18
),
sumNumNeigh = 240))

INITIAL ESTIMATES

list(tau.T = 1, p=0.5, beta0 = 0, beta1 = 0, beta2 = 0, beta3 = 0,
V=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0),
U=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0))
```

Figure 16 shows the centroids for each area, allowing us to confirm the number and labels of the neighbors of each area.

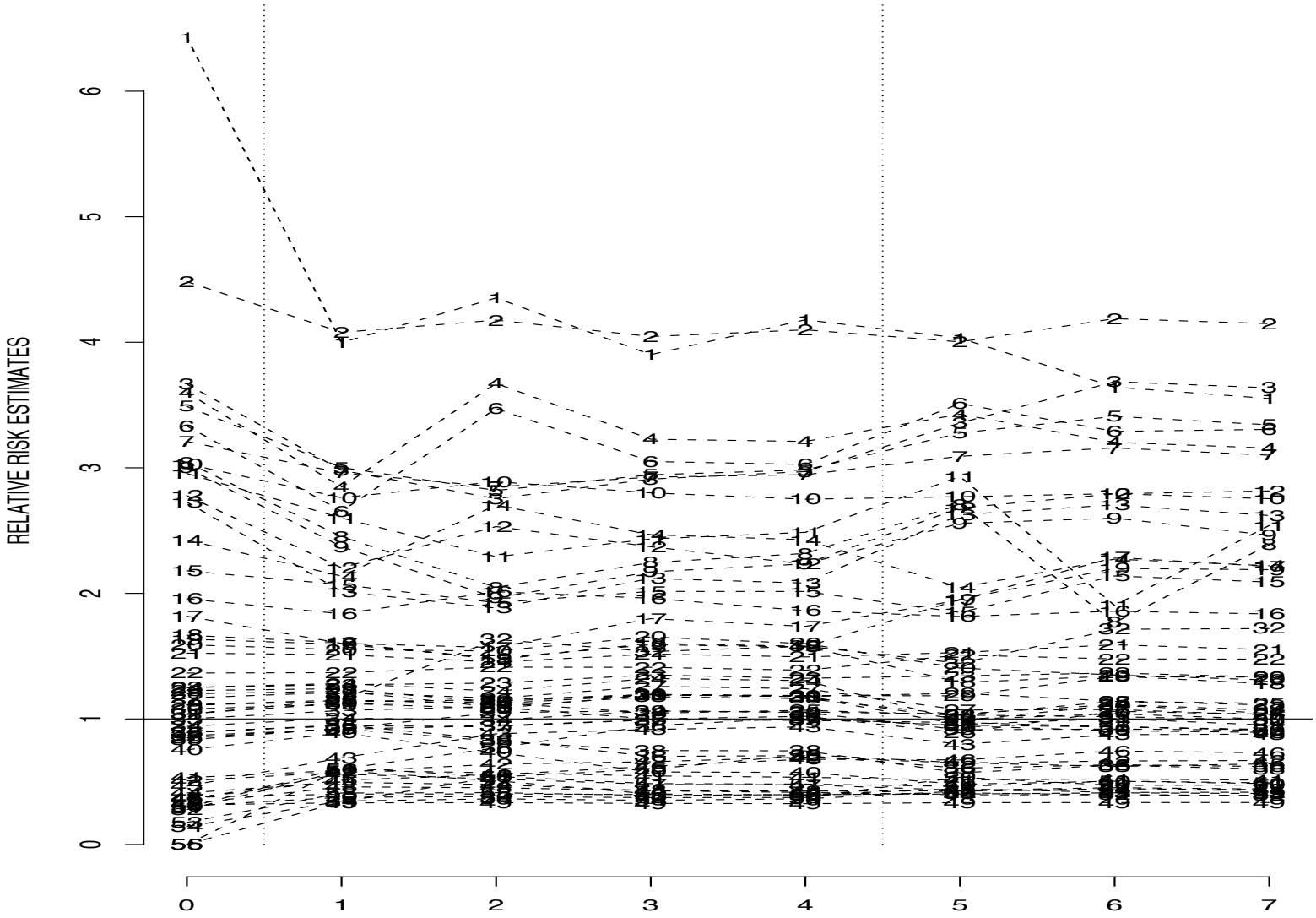



Figure:

Figure details: Relative risk estimates for Scottish lip cancer data:

0. denote the SMRs;
1. the empirical Bayes estimates without the use of AFF;
2. the empirical Bayes estimates with log link and a linear model in AFF;
3. the empirical Bayes estimates with a log-linear cubic model in AFF;
4. the fully Bayes non-spatial estimates with a log-linear cubic model in AFF;
5. estimates under the joint model;
6. estimates under the initial ICAR model;
7. estimates under the refined ICAR model. Estimates 5–7 are based upon a log-linear cubic covariate model.

Plotting symbol is county number.

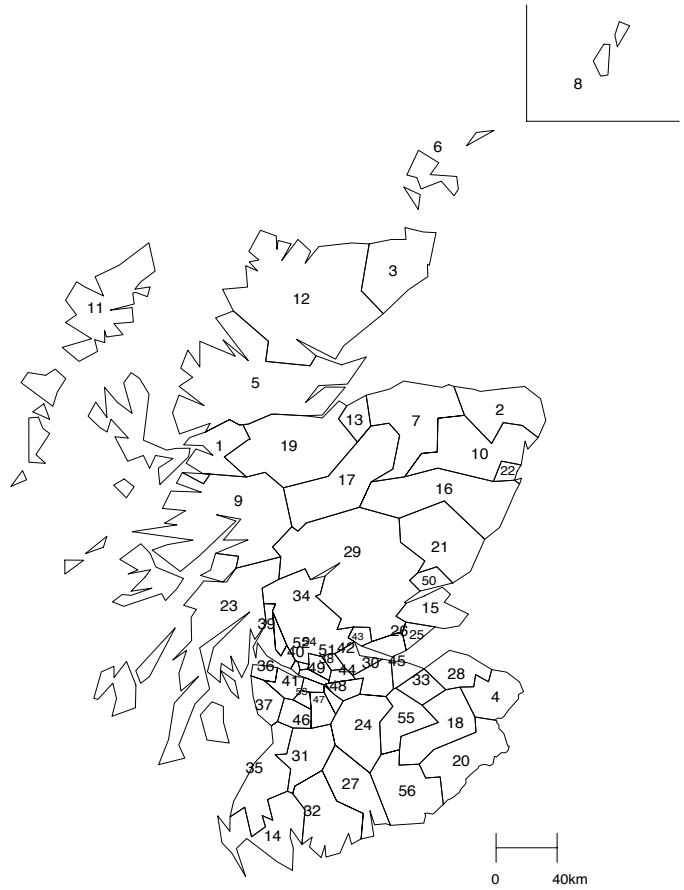


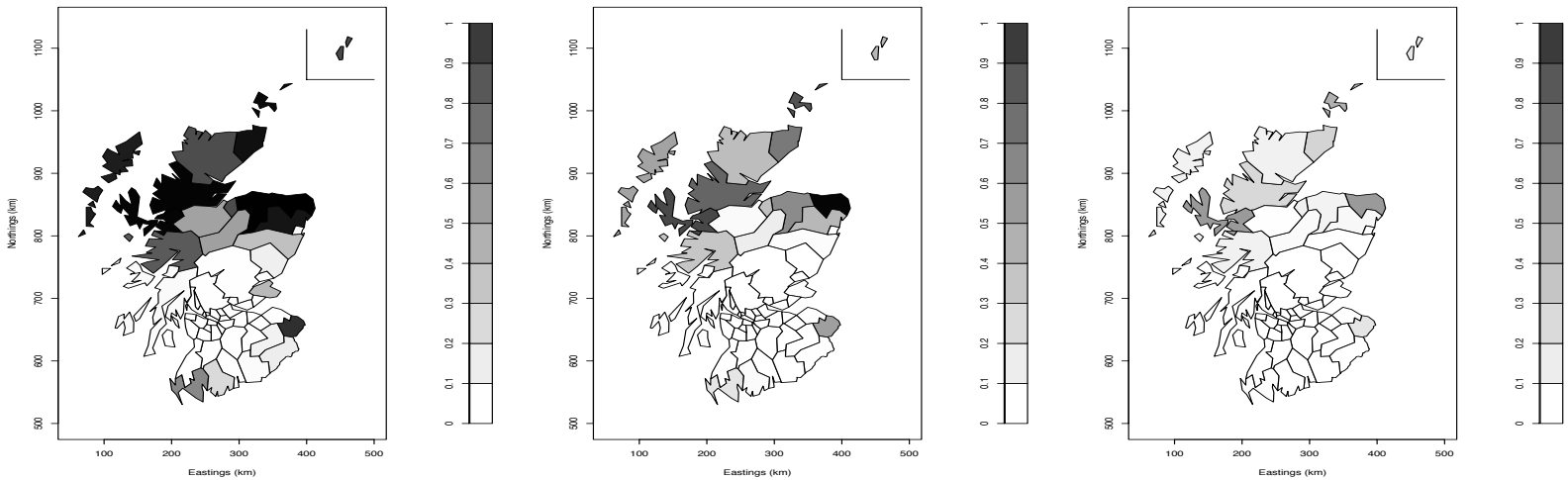

Figure: Labels for 56 counties of Scotland.

## Results

- Positions 5–7 of Figure 15 show estimates from spatial models, each with a cubic model in AFF.
- In the non-spatial model we have shrinkage to the overall regression prediction but in the spatial model we have local and global smoothing so that estimates can move away from the regression model prediction.
- A striking aspect in Figure 15 is the differences in the estimates for areas 8 and 11 under the joint spatial model (position 5) and the ICAR model (position 6).
- For the three islands without neighbours under our ICAR formulation, there are only non-spatial contributions to the relative risk.
- Table 1 reports posterior summaries for the parameters of the random effects distributions, and shows that the majority of the total variability is spatial for these data.

- We see large shrinkage for the three islands since we are assuming a *common* non-spatial model across islands and non-islands, resulting in too much shrinkage for the islands.
- There are a number of possibilities for refining this model. One is to assume $V \sim_{iid} N(0, \tau_T^{-1})$ for the islands so that we have the same total variability as non-islands, but with all of this variability assumed to be non-spatial. Given our parameterization of the prior it is straightforward to fit this model for the three islands.
- The resultant estimates are shown in position 7, and differ little from those in position 6, which is reassuring.
- Further possibilities include defining neighbours for the islands as the nearest points of the mainland (or the nearest island), or assuming a distinct non-spatial distribution for the islands (with only three islands this option is not feasible here).

- Figure 18(b) shows relative risk estimates under the joint model; the smoothness compared to the SMRs in Figure 18(a) is apparent.
- Under a Bayesian sampling-based approach it is straightforward to carry out inference for functions of interest.
- As an illustration, Figure 17(a)–(c) shows the posterior probabilities that the relative risk in each area exceeds the values 2, 3 and 4.
- We see a number of areas with high probabilities, suggesting that, in a serious investigation, these be examined more closely to discover the characteristics of the individuals, or health hazards that are present, in these areas.
- Such plots are also useful for reflecting the uncertainties inherent in smoothed maps.




(a) Threshold = 2 (b) Threshold = 3 (c) Threshold = 4

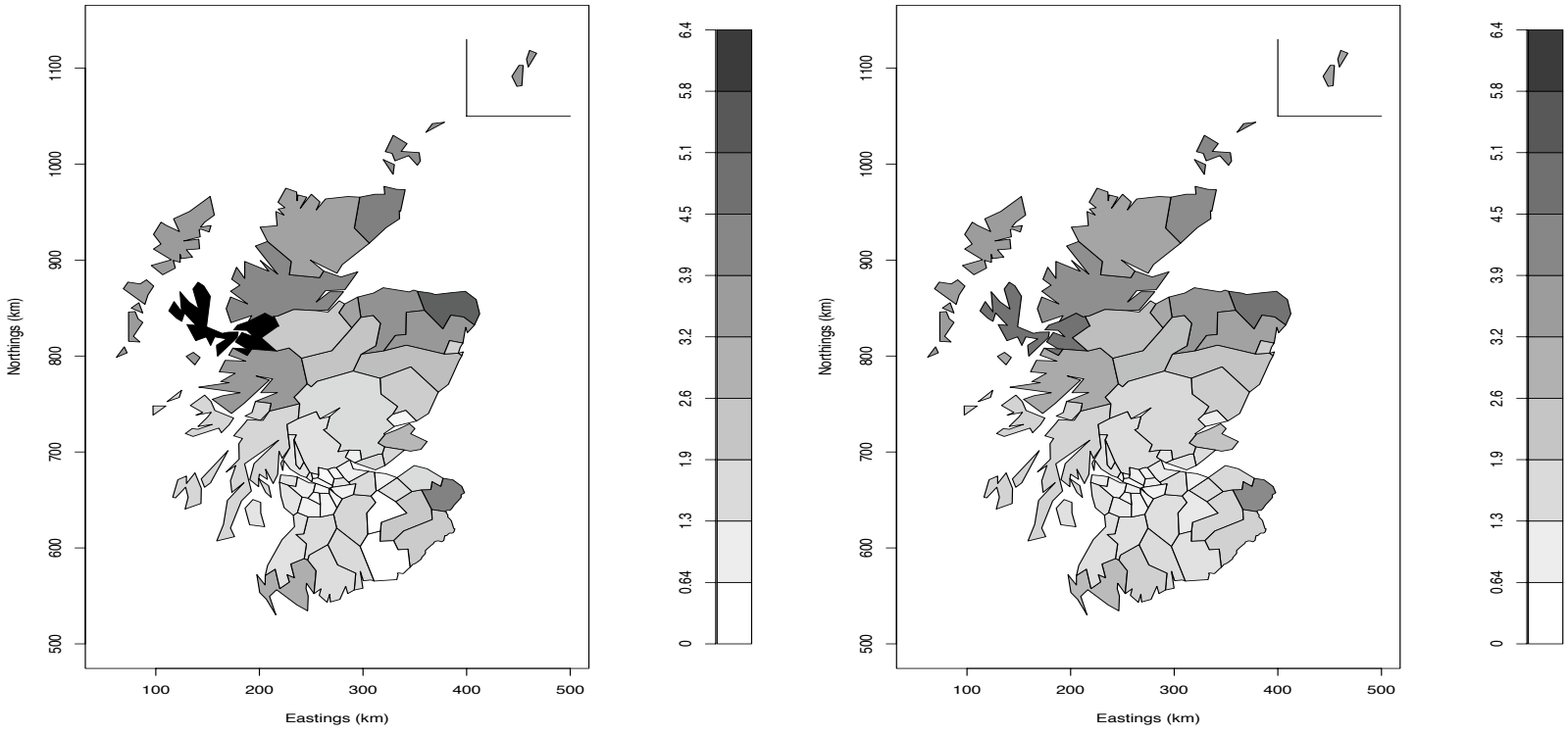
Figure: Posterior probabilities of exceedance of different thresholds under the joint model.

Table: Sensitivity of spatial model parameters to prior choice, $\tau_T = (\sigma_u^2 + \sigma_v^2)^{-1}$ and $p$ is the proportion of the total variability that is spatial.

| Spatial Model | Prior Specification | | Posterior median | | | |
|---|---|---|---|---|---|---|
| | | | $\sigma_v$ | $\sigma_u$ | $p$ | $d_{1/2}$ (km) |
| Joint | $\tau_T \sim \text{Ga}(1, 0.0260)$ | $d_{1/2} \sim \text{LN}(3.107, 0.9106)$ | 0.23 | 0.48 | 0.82 | 78.8 |
| Joint | $\tau_T \sim \text{Ga}(1, 0.1399)$ | $d_{1/2} \sim \text{LN}(3.107, 0.9106)$ | 0.24 | 0.49 | 0.82 | 79.6 |
| Joint | $\tau_T \sim \text{Ga}(1, 0.0260)$ | $d_{1/2} \sim \text{LN}(2.303, 0.4214)$ | 0.23 | 0.48 | 0.79 | 85.9 |
| ICAR | $\tau_T \sim \text{Ga}(1, 0.0260)$ | – | 0.23 | 0.53 | 0.85 | – |
| ICAR | $\tau_T \sim \text{Ga}(1, 0.1399)$ | – | 0.22 | 0.54 | 0.86 | – |

- In Table 1 we examine the sensitivity of estimates of the non-spatial and spatial contributions of residual relative risk, to the prior choices for $\sigma_v$, $\sigma_u$, $\omega_u^2$ and $d_{1/2}$.
- The prior $\tau_T \sim \text{Ga}(1, 0.1399)$ gives relative risks that follow a log student t distribution with 2 degrees of freedom, and fall within the range (0.2,5) with probability 0.95. The choice $d_{1/2} \sim \text{LN}(2.303, 0.4214)$ assumes that there is a 5% chance that the correlations die to 0.5 in less that 5km, and a 95% chance that they die to 0.5 in less than 20km.

- We see that the majority of the residual variability is explained by the spatial component; under the various models, 79%–86% of the total variability is spatial in nature.
- Overall there is little sensitivity of these parameters to the priors though, as we saw, the joint and ICAR models can give quite different estimates in particular areas. Interval estimates for $d_{1/2}$ are very wide, reflecting the lack of information on the strength of the residual spatial variability.
- For example, for the prior choices in row 1 of Table 1, a 95% interval for $d_{1/2}$ is 32km to 243km.




(a) SMR estimates

(b) Smoothed estimates

Figure: Raw and smoothed estimates in 56 counties of Scotland.

## Conclusions

- The preferred model here would be that which includes a cubic model in AFF and a spatial component, since the association with AFF is strong and there is significant residual spatial dependence.
- A full analysis would examine the sensitivity of the relative risk estimates to the prior specifications. There is a large amount of residual variability for these data, which suggests unobserved risk factors, and is not surprising since we have no information on lifestyle variables such as smoking, alcohol and diet.
- Although it is important to consider models that include residual spatial dependence for small-area studies, empirical Bayes models are very useful for exploratory purposes, particularly for choosing an appropriate mean model.