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MULTI-LEVEL MODELLING OF GEOGRAPHICALLY AGGREGATED HEALTH DATA: A CASE STUDY ON MALIGNANT MELANOMA MORTALITY AND UV EXPOSURE IN THE EUROPEAN COMMUNITY

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SUMMARY

A multi-level modelling approach is used to examine the variance in mortality rates from malignant melanoma at different geographical scales within nine European nations with reference to exposure to ultraviolet light (UVB). For males and females, the greatest variations in the relationship between UVB exposure and mortality are seen between nations, rather than regions and sub-regions within nations. This suggests that factors and characteristics acting at a national scale, such as genetic and behavioural differences, are of importance. Multi-level modelling is used to show how a previous suggestion of a quadratic association between UVB exposure and malignant melanoma across Europe is unlikely to be true. The general usefulness of multi-level modelling in the analysis of disease data which is structured in a hierarchy is discussed, with particular reference to geographical analyses of small area data. © 1998 John Wiley & Sons, Ltd.

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1. INTRODUCTION

Multi-level modelling has been developed as a technique for analysing data arranged in a variety of hierarchies.[1] For example, individuals may live in electoral wards which are nested within larger administrative boundaries such as counties or regions. Each individual may have several response variables which add an additional level to the hierarchy, such as multiple indicators of health status.[2] Hence, the emphasis in multi-level modelling is on the individual, but data on individual cases may be expensive and time consuming to collect, or difficult to obtain due to issues of confidentiality. This paper shows how analysis of publically available and easily obtained aggregate data may be analysed using multi-level modelling to provide a greater insight

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than is possible from a conventional 'single-level' approach. Inevitably, such an analysis may be subject to the 'ecological fallacy', which in geographical terms means that results based on mean responses for areas may not reflect the behaviour of a disease or other indicator of health in individuals.[3] Whilst it is individuals we are really interested in, the ready availability of area-based data means that this can be used to provide an insight for development of more detailed studies of individuals.

One of the important issues in geographical analysis is the scale at which the analysis is performed, as different processes may operate at different levels of geographical aggregation.[4–6] Waller and Turnbull[7] discuss this issue with reference to cases of childhood leukaemia occurring in upstate New York. However, in the data set analysed in this paper, we have the lowest level of areal aggregation obtainable as the smallest unit of analysis rather than the individual case. Even so, the example used in this paper will demonstrate that including higher levels of geographical aggregation simultaneously in a model of smaller units is essential to draw useful conclusions from the data analysed. A useful discussion of the general issues involved in modelling area-based data is given in Bailey and Gatrell.[4]

There is strong evidence that exposure to ultraviolet radiation from sunlight is an important factor in the aetiology of malignant melanoma.[8] Incidence is highest in countries at low latitudes such as Australia and South Africa which have received fair-skinned migrants from northern Europe.[9] A striking latitudinal gradient in malignant melanoma mortality has been observed in North America[10] and geographical variation in incidence within the U.S.A. have been shown to be related to local levels of UVB radiation.[11] However, the geographical pattern of the disease within Europe shows some marked discrepancies from a simple latitudinal trend. Armstrong[9] notes that melanoma incidence is lower in Mediterranean countries than in Scandinavia. This contributes to an apparent quadratic relationship between melanoma and latitude with a minimum in incidence at about 52 degrees north, and increasing rates at higher latitudes. Such evidence has led some commentators to doubt the role of sunlight exposure in the aetiology of melanoma.[12] A potential problem with Armstrong's analysis of the geographical pattern of melanoma within Europe is that it involves the collation of information on melanoma incidence from cancer registries within several different countries. It is therefore possible that the apparently discrepant association between melanoma and latitude could be affected by differences between countries in the completeness of cancer registration, genetically determined differences in susceptibility to the effects of sunlight exposure and national differences in patterns of behaviour affecting exposure to sunlight. Analysis of melanoma in relatively small areas may be hampered by lack of variability in UVB doses reaching the surface of the earth, but a multi-level modelling approach may be used to simultaneously model the relationship between UVB dose and melanoma both within and between countries. The variance in melanoma rates between areas can then be modelled as functions of explanatory variables, including UVB dose, at different levels of a geographical hierarchy. This paper focuses on mortality data from the EC-9 nations to study the differential relationships between epidemiologically important doses of UV arriving at the surface and malignant melanoma in different countries. The following section discusses the structure of the data and the use of a multi-level model to account for regional variation in mortality within countries. Results are then presented for male and female mortality rates, and discussion focuses on both the methodological and substantive issues raised by the analysis. The methodology used can be potentially applied to a wide range of epidemiological and public health problems. An Appendix is therefore provided at the end of the paper giving more details on estimation of multi-level non-linear models and extraction of residuals.

2. DATA AND METHODS

Data on malignant melanoma mortality for all ages for males and females was taken from the *Atlas of Cancer Mortality in the European Economic Community*.[13] Malignant melanoma mortalities were defined as being deaths recorded and certified by a medical practitioner and coded as ICD-8 172. These data were collected between 1971 and 1980, although for the United Kingdom, Ireland, Germany, Italy and The Netherlands, data were only available from 1975–1976 onwards, and are aggregated over the period of data collection. As incidence was generally rising during this period, it is important to include nation as a variable (or level) in the analysis to account for this potential source of variation in mortality rates. The geographical resolution of the data was determined by the smallest units for which usable population data was obtainable, this being at levels II or III as identified by EEC statistical services. For example, these units relate to counties in England and Wales, départements in France and Regierungsbezirk in (West) Germany. This means that the data fall naturally into a geographical hierarchy defined by political boundaries, with EEC II or III level areas nested within level I regions, which are in turn nested within countries. The numbers of areas included within the geographical hierarchy for each country are shown in Table I. For convenience, the geographical hierarchy will be referred to as counties within regions within nations. This data structure implies that a multi-level analysis may be appropriate,[14] and counties, regions and nations will be taken to represent levels 1, 2 and 3 of a multi-level model hierarchy, respectively. These three geographical scales are those for which data were available, although other aggregations of the data above the lowest level are possible. It is important to include all three levels in the model as there be important associations between melanoma and ultraviolet light which operate at a regional scale, and/or at a national scale, and omitting one or more of the available levels could lead to biased result at other levels.

Table II lists the response and explanatory variables used in the study. The main explanatory variable of interest is biologically effective UVB dose reaching the surface of the earth, and hence potentially determining UVB dose experienced by the population resident in each county. Direct measurements of UV at the earth's surface are too sparse to provide reliable estimates at this geographical scale, and so an index previously employed in epidemiological studies has been calculated for each county[10,15] so that:

$$\mathrm{UVBI} = 100[1 - \Gamma \exp(\theta) C][1 + \exp((L - L_0)/L_f)]^{-1}$$

where Γ is a constant estimated from previous data, taken as 0·056, and $\exp(\theta)$ relates to cloud thickness, taken as being unity as no information is available on this measure for the data considered here.[15] C is mean annual cloud cover (measured by convention in tenths), and is calculated from the inverse of percentage hours of bright sunshine at the meteorological station geographically closest to each county, accounting for factors such as coastal, inland or mountain location. L is the latitude, in degrees, of the geocentroid of each county, and L_0 and L_f are taken as being 30° and 15°, respectively, from best fit values calculated by Mo and Green.[15] A summary of the calculated epidemiological index for each nation is shown in Table III.

Further explanatory variables are shown in Table II, with RGDP representing income in terms of gross domestic product per capita, and RDENS the mean population density as a crude indicator of the degree of urbanization. These represent socio-economic indicators which have previously been shown to have a relationship with risk of malignant melanoma.[16] Intermittent and acute exposure to UVB, often during outdoor recreation, has been shown to be associated with malignant melanoma[17–19] and behaviour leading to this type of exposure may be positively

Table I. The geographical hierarchy of the IARC mortality data

Nation	Regions	Counties
1. Belgium	3	11
2. West Germany	11	30
3. Denmark	3	14
4. France	21	94
5. United Kingdom	11	70
6. Italy	20	95
7. Ireland	4	26
8. Luxembourg	1	3
9. Netherlands	4	11

Table II. Variables used in the analysis

Variable	Description
O	Observed numbers of melanoma deaths for all ages
E	Expected values of melanoma deaths for all ages, calculated from the crude rates, that is, the total number of cases divided by the person-years at risk
UVBI	Epidemiological index of UVB dose at earth's surface (see text)
RDENS	Density of inhabitants per km^2 by region
RGDP	GDP per inhabitant by region

Table III. UVB index: descriptive statistics for each nation

Nation	*N*	Mean	Standard deviation	Min	Max
Belgium	11	12·70	0·29	12·17	13·10
West Germany	30	12·79	1·35	10·45	15·15
Denmark	14	9·96	0·38	9·47	10·49
France	94	17·18	2·59	12·92	23·24
United Kingdom	70	10·91	1·50	6·69	13·46
Italy	95	21·45	3·51	16·83	28·95
Ireland	26	10·54	0·60	9·64	11·70
Luxembourg	3	13·26	0·05	13·22	13·31
Netherlands	11	11·40	0·47	10·62	11·94

associated with high incomes and degree of urbanization. The two variables are measured at the regional scale, as it was not possible, in the majority of cases, to obtain county level data for Eurostat indicators.[20] Hence, this is another reason for modelling the available data within a geographical hierarchy.

The multi-level model fitted to the data was based on generalized least squares estimation,[1] where we can write a model containing fixed and random parameters as follows:[21]

$$Y = X\beta + Z\theta \tag{1}$$

where X is a design matrix associated with a vector of fixed parameters β, and Z is a design matrix (not necessarily the same as X) associated with a vector of random parameters θ, with a vector of responses Y. The components of Z may represent variables random at any level in the model, in this case $Z^{(1)}$ for level 1 counties, $Z^{(2)}$ for level 2 regions and $Z^{(3)}$ for level 3 nations. A description of how indicator variables can be used to define a variance components model by partitioning variance between levels is given in Goldstein.[1] Estimation of parameters is made by iteratively fitting regression models for the fixed and random parts, so that, for the fixed part:

$$\hat{\beta} = (X^{\mathrm{T}} V^{-1} X)^{-1} X^{\mathrm{T}} V^{-1} Y. \tag{2}$$

Having estimated the fixed parameters, $\hat{\beta}$, we can extract a vector of raw residuals $Y' = Y - X\hat{\beta}$, which can be used to estimate the random parameters in the model. We calculate the cross-product matrix of raw residuals, $E(Y^*) = Y' Y'^{\mathrm{T}} = V$ and then stack this as a vector, $Y^{**} = \mathrm{vec}(Y^*)$ to be used as the response variable in a regression equation to estimate the random parameters, so:

$$\hat{\theta} = (Z^{\mathrm{T}} V^{*-1} Z)^{-1} Z^{\mathrm{T}} V^{*-1} Y^{**} \tag{3}$$

where V^* is the Kronecker product of V, namely $V^* = V \otimes V$. Assuming multivariate normality, we alternate between estimation of fixed and random parameter vectors until convergence is reached. However, in this instance we have a Poisson distributed response vector of observed cases, and hence we need to include an offset of expected numbers of cases in the model[22] so that:

$$O \sim \mathrm{Poisson}(\mu)$$

$$\ln(\mu) = \ln(E) + X\beta + Z\theta \tag{4}$$

where E represents the expected numbers of cases for each level 1 unit. We use the Poisson distribution to model the level 1 variance, with a logarithmic link function, and assume random parameters at higher levels (in this case region and nation) as being multivariate normal. An efficient estimation procedure for this non-linear model is penalized, or predictive quasi-likelihood,[21,23] where estimation of random parameters, and associated residuals, is made using a Taylor series expansion around the current values of the fixed and random parts of the model. Details of this procedure, using an updating function which incorporates the current estimated residuals, are given in the Appendix, as well as being discussed in Goldstein,[1] Goldstein and Rasbash[24] and an epidemiological example given in Langford.[25] The models were fitted using the MLn software developed by the Multilevel Models Project, Institute of Education, London, and details of how to fit multi-level log-linear models within this software are given in Rasbash and Woodhouse.[26]

A further point concerns the assumption of Poisson variation of the cases of malignant melanoma. We can estimate a dispersion parameter at level 1, so that

$$\mathrm{var}(O) = \sigma_1^2 \mu. \tag{5}$$

If $\sigma_1^2 = 1$, then variation is assumed to be Poisson, if $\sigma_1^2 > 1$ then there is extra-Poisson variation present, and if $\sigma_1^2 < 1$ the model is underdispersed as can happen when many of the counts are zero.[25,27] However, there are theoretical reasons to assume that extra-Poisson variation may be present. The counties included in the study have very heterogeneous populations, and hence the expected values for counties may be very different from each other. This situation may be described by stating that the counts of melanoma mortality in each county are being modelled as

Poisson conditional on the distribution of rates between counties. These rates may be assumed to follow a gamma distribution, and hence the mixture of these two distributions can be expressed as a negative binomial distribution of counts. Full details, discussion and examples of this method of modelling mortality rates in discrete areas of heterogeneous population size may be found in Langford,[25,28,29] Tsutakawa,[30] Clayton and Kaldor[31] and Manton *et al.*[32] Hence, it is theoretically more appropriate to consider the level 1 random effects as following a negative binomial distribution, so that the variance of O is a quadratic function of μ:

$$\text{var}(O) = \sigma_1^2\mu + \sigma_2^2\mu^2 \tag{6}$$

where σ_1^2 and σ_2^2 can be estimated from the data. In practice, this simply requires the estimation of these two parameters at level 1 of the model, whereas only one would be required for the Poisson distribution. Additionally, the level 1 variation may be dependent on covariates included in the model.

The model presented has several important properties. First, it allows for variance to be estimated simultaneously as different levels of a hierarchy, so that the proportions of variance occurring at different levels may be directly compared, for example, between regions and nations. Secondly, variance at all levels may be a function of covariates included in the model, allowing for a complex analysis of variance. Thirdly, as all the data is being used to support the parameter estimates, the residuals at higher levels are empirical Bayes estimates, that is, they are shrunken towards the overall mean. The desirability of this effect in any particular model is a matter of debate,[33] but a general rule is the categorical variables included in the model as a *level* will produce shrunken, or conditional estimates of contrasts whilst including a categorical variable as a *variable*, for example, as a set of dummy vectors, will produce unconditional estimates. An example of this is provided in the results.

3. RESULTS

Table IV presents the results for three separate analyses of malignant melanoma mortality for males. Model A is a variance components model with UVBI included in the fixed part of the model, so that, for the ith county in the jth region in the kth nation:

$$\ln(O_{ijk}) = \ln(E_{ijk}) + \beta_0 + \beta_1 \text{UVBI}_{ijk} + s_k + u_{jk} + e_{ijk}$$

$$s_k \sim \text{N}(0, \sigma_s^2),\ u_{jk} \sim \text{N}(0, \sigma_u^2).$$

Hence β_0 is the intercept term, β_1 is the mean (fixed) effect of UVBI, and s_k, u_{jk} and e_{ijk} are random terms associated with the intercept at levels 3, 2 and 1, respectively. σ_{e1}^2 in Table IV is the dispersion parameter associated with the Poisson variance term (labelled as σ_1^2 in equation (5) above). In model A, estimating approximate 95 per cent confidence intervals by twice the standard error (that is, 0·0937) of σ_{e1}^2 shows that the value 1 (representing Poisson variation) is included well within the lower bound. No improvement of fit was found in this case by fitting a negative binomial model. The estimates of variance at levels 2 and 3 are of interest, showing that 76·7 per cent of the variance of malignant mortality rates not explained by Poisson variation at county level is between nations, that is, there is roughly three times as much variation *between* nations as between regions *within* nations. The last line in Table IV shows minus twice the log-likelihood ratio, or residual deviance for model A. As the asymptotic expectation of the residual deviance is approximately the degrees of freedom present in the model,[19,20] there is a large amount of unexplained variance still present in the model. The parameter estimate for the

Table IV. Variance components model for males with UVBI included in the fixed part of the model

	Model A		Model B		Model C	
	Estimate	(SE)	Estimate	(SE)	Estimate	(SE)
Fixed part						
β_0	0·0103	(0·134)	0·189	(0·143)	0·135	(0·137)
β_1 (UVBI)	− 0·0360	(0·0107)	0·00435	(0·0329)	0·010	(0·0274)
β_2 (RDENS)					0·0000730	(0·0000325)
β_3 (RGDP)					0·00385	(0·000114)
Random part						
Level 3: nations						
σ_s^2	0·140	(0·0733)	0·105	(0·0746)	0·106	(0·0712)
σ_{st}			0·00540	(0·00123)	0·00247	(0·00957)
σ_t^2			0·00486	(0·00368)	0·00312	(0·00246)
Level 2: regions						
σ_u^2	0·0424	(0·00956)	0·0147	(0·00498)	0·0114	(0·00444)
σ_{uv}			− 0·00336	(0·000938)	− 0·00140	(0·000628)
σ_v^2			0·000745	(0·000252)	0·000235	(0·000180)
Level 1: counties						
σ_{e1}^2	1.11	(0·0937)	0·907	(0·0769)	0·896	(0·0932)
σ_f^2					0·0000810	(0·000110)
Residual deviance =	2214·23,	d.f. = 349	2205·59,	d.f. = 345	2174·53	d.f. = 343

UVB index in the fixed part of model A is initially surprising, with a significantly negative association ($p < 0{\cdot}01$) between malignant melanoma mortality and UVBI. However, this is only a fixed part estimate, and does not account for differences in the relationships between mortality and UVBI between regions and nations.

Model B in Table IV shows the effects of allowing this relationship to vary randomly between regions and nations, so that

$$\ln(O_{ijk}) = \ln(E_{ijk}) + \beta_0 + \beta_1 \mathrm{UVBI}_{ijk} + s_k + t_k \mathrm{UVBI}_{ijk} + u_{jk} + v_{jk} \mathrm{UVBI}_{ijjk} + e_{ijk}$$

$$s_k \sim \mathrm{N}(0, \sigma_s^2),\ t_k \sim \mathrm{N}(0, \sigma_t^2),\ u_{jk} \sim N(0, \sigma_u^2),\ v_{jk} \sim N(0, \sigma_v^2).$$

Interestingly, the overall fit of the model does not improve significantly by including the extra parameters in the random part of the model ($p > 0{\cdot}05$), as the fixed parameter for UVBI has decreased to almost zero. The parameters σ_t^2 and σ_v^2 represent the variance of the relationships between mortality and UVBI at national and regional levels respectively, that is, the variance of the slopes in the two parameter fixed regression model. Similarly, the parameters σ_{st} and σ_{uv} represent the covariances between the intercepts and the slopes.

Focusing on nations at level 3, the majority of the variance between nations is due to differences in the intercepts, σ_s^2 at the point at which the intercepts are evaluated. In the analysis, each explanatory variable, in this case UVBI, is centred around its mean. This is because estimating the variance of the intercepts at UVBI = 0 is a useless measurement as no county

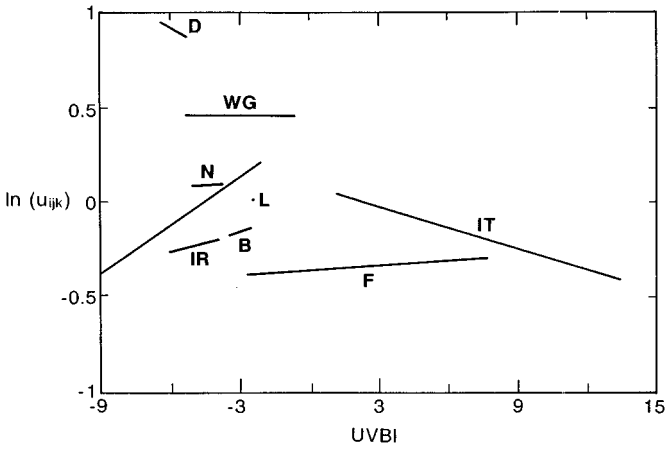

Figure 1. Random intercepts and slopes for UVBI by nation for males

experiences a zero UV dose. Hence, the variance of the intercepts is measured at the mean of UVBI, a value of 15·6. Since some nations do not have counties with this value of UVBI, it is still somewhat artificial, but useful. The standard error around the estimate of σ_s^2 is large, but we have only nine nations to estimate the parameter at level 3. The positive value of σ_{st} demonstrates a positive correlation ($R = 0{\cdot}239$) between the intercepts and the slopes, suggesting that nations with higher rates of malignant melanoma have a stronger positive association with UVBI. No variance in UVBI at level 1 between counties was estimated.

Model C in Table IV includes other explanatory variables in the fixed part of the model. Including various combinations of these variables in the random part of the model produced zero estimates of variance, and hence no improvement in fit. The model presented is therefore:

$$\ln(O_{ijk}) = \ln(E_{ijk}) + \beta_0 + \beta_1 \mathrm{UVBI}_{ijk} + \beta_2 \mathrm{RDENS}_{ijk} + \beta_3 \mathrm{RGDP}_{ijk} + s_k + t_k UVBI_{ijk} + u_{jk} + v_{jk} UVBI_{ijk} + e_{ijk} + f_{ijk} \mathrm{UVBI}_{ijk}$$

$$s_k \sim \mathrm{N}(0, \sigma_s^2),\ t_k \sim \mathrm{N}(0, \sigma_t^2),\ u_{jk} \sim \mathrm{N}(0, \sigma_u^2),\ v_{jk} \sim \mathrm{N}(0, \sigma_v^2),\ f_{ijk} \sim \mathrm{N}(0, \sigma_f^2).$$

A small random effect for UVBI is now estimated between counties at level 1. Note that this has been estimated separately from the error term associated with the Poisson distribution, assuming Normality (see Appendix). The interpretation of this parameter is rather complex, but may be expressed as there being extra-Poisson variance in the model which is dependent on UVBI, that is, the variance at level 1 is not strictly Poisson but increases by the quantity $\sigma_f^2(\mathrm{UVBI})^2$ for a unit increase in the transformed dependent variable. The effect is similar to heteroscedasticity in single level models with Normally distributed errors. A discussion of this interpretation is given in Goldstein.[1] Although the standard error around the random parameters at level 3 are relatively large, we must remember that we are looking for *structure* in the model, and hence residuals were then calculated for each nation varying randomly at level 3, for the intercepts and slopes for UVBI (see Appendix). These residuals represent the deviation of each nation from the fixed parameter estimates for the intercept and UVBI, and from these predicted values were calculated and plotted in Figure 1, showing large variation between different EC nations. However, the predicted values plotted in Figure 1 are shrunken estimates, conditional on the data hierarchy

Table V. Shrunken and fixed parameter estimates for UVBI by nation for males

Nation	Shrunken estimate	Standard error	Fixed estimate	Standard error
Belgium	0·0244	0·0626	0·0945	0·2637
West Germany	− 0·0113	0·0441	− 0·0128	0·0279
Denmark	− 0·0706	0·0715	− 0·0004	0·1517
France	− 0·0010	0·0394	0·0178	0·0158
United Kingdom	0·0770	0·0486	0·1230	0·0355
Italy	− 0·0481	0·0398	− 0·0742	0·0170
Ireland	0·0243	0·0583	0·0229	0·2669
Luxembourg	0·0048	0·0618	6·3401	7·3710
Netherlands	0·0005	0·0557	0·0572	0·1943

(that is, larger nations with many regions and counties are given more weight). This may not be a useful process here, as it assumes the slopes and intercepts are drawn from the same hyper-population of slopes and intercepts for all nations. For comparison, as the relationship between malignant melanoma mortality and UVBI is of primary concern here, the shrunken and fixed estimates for slope of UVBI are given in Table V. The separate fixed estimates were generated by fitting a separate dummy variable for the intercepts and slopes for UVBI at level 2 for each nation rather than including nation as a level. This is in contrast to the multi-level model where a single fixed effect is calculated for all nations, and then random departures for each nation are estimated around this mean. The standard errors for the shrunken estimates were calculated from the variance of the fixed part estimate added to the comparative variance of each residual. The comparative variances were adjusted using a delta method approximation[34] to account for sampling bias due to there only being nine nations at level 3. An interesting feature of the shrunken residuals should be noted, with respect to UVBI. For nations with larger numbers of regions (West Germany, France, United Kingdom and Italy), the standard errors of the shrunken parameter estimates tend to be larger than for the fixed estimates. However, for nations with smaller numbers of regions (Belgium, Denmark, Ireland, Luxembourg and The Netherlands), the standard errors of the estimates decrease. However, the parameter estimates are always shrunken towards the mean, and more so for nations with smaller numbers of regions (counties). This is important, because taking shrunken estimates increases the degree of uniformity seen in the distribution of parameter estimates for UVBI, but the degree of uncertainty in these estimates may be increased.

An equivalent set of models for females is shown in Table VI. In this case, a negative binomial was found to provide the best fit to the data, and so two parameters are estimated at level 1, namely σ^2_{e1} and σ^2_{e2}. In model D, the linear term σ^2_{e1} is not significantly different from 1 ($p > 0{\cdot}05$), whilst σ^2_{e2} is significantly different from zero at $p < 0{\cdot}01$. Including UVBI in the fixed part again shows a significant negative relationship with malignant melanoma mortality, which becomes non-significant when UVBI is included in the random part of model E. Model F shows the final model, with other explanatory variables included in the fixed part of the model, as before. In this case, no random effects for UVBI were estimated at level 1, although the quadratic term for the variance associated with the intercept was still significant ($p < 0{\cdot}05$). Figure 2 depicts the predicted relationships between malignant melanoma mortality and UVBI for each nation, and Table VII shows the shrunken parameter estimators for UVBI from model F alongside fixed estimates from dummy variable as for males.

Table VI. Variance components model for females with UVBI included in the fixed part of the model

	Model D		Model E		Model F	
	Estimate	(SE)	Estimate	(SE)	Estimate	(SE)
Fixed part						
β_0	− 0·0739	(0·0922)	0·110	(0·155)	0·0898	(0·147)
β_1 (UVBI)	− 0·0542	(0·0102)	− 0·0101	(0·0364)	− 0·00760	(0·0320)
β_2 (RDENS)					0·0000790	(0·0000343)
β_3 (RGDP)					0·00127	(0·00109)
Random part						
Level 3: nations						
σ_s^2	0·0589	(0·0335)	0·114	(0·0829)	0·109	(0·0776)
σ_{st}			0·0170	(0·0168)	0·0127	(0·0137)
σ_t^2			0·00583	(0·00578)	0·00424	(0·00335)
Level 2: regions						
σ_u^2	0·031	(0·00872)	0·00481	(0·00384)	0·00539	(0·00400)
σ_{uv}			− 0·00210	(0·000702)	0·00136	(0·000599)
σ_v^2			0·000538	(0·000218)	0·000289	(0·000181)
Level 1: counties						
σ_{e1}^2	1·08	(0·170)	0·884	(0·147)	0·956	(0·148)
σ_{e2}^2	0·0221	(0·00746)	0·0169	(0·00564)	0·0143	(0·00541)
Residual deviance =	2295·85,	d.f. = 348	2291·54	d.f. = 344	2278·43,	d.f. = 342

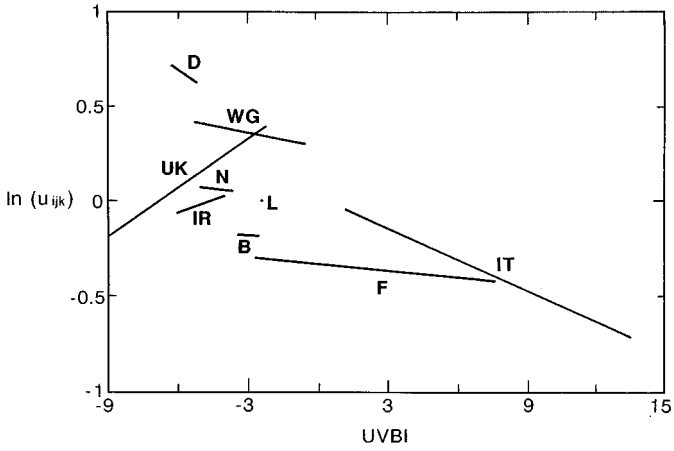

Figure 2. Random intercepts and slopes for UVBI by nation for females

4. DISCUSSION

Models A and D suggest that there is slightly more variation in malignant melanoma at regional and national levels for males than females (a variance parameter estimate of 0·14 between nations for males compared to 0·06 for females, although the difference is not significant at the 0·05 level),

Table VII. Shrunken and fixed parameter estimates for UVBI by nation for females

Nation	Shrunken estimate	Standard error	Fixed estimate	Standard error
Belgium	0·0068	0·0773	− 0·1113	0·2929
West Germany	− 0·0158	0·0509	− 0·0278	0·0274
Denmark	− 0·0659	0·0816	− 0·1000	0·1939
France	− 0·0046	0·0455	0·0049	0·0151
United Kingdom	0·0921	0·0553	0·1232	0·0344
Italy	− 0·0480	0·0460	− 0·0967	0·0177
Ireland	0·0494	0·0694	0·5759	0·2504
Luxembourg	− 0·0034	0·0723	9·2490	8·5750
Netherlands	− 0·0046	0·0688	− 0·0695	0·2097

apparently supporting previous results.[35] However, the more complex models C and F show a different picture, with slightly more variance being estimated for females between nations. The negative binomial model for females may suggest that there is relatively more variation on a local scale (at county level) for females. However, as can be seen from Figures 1 and 2, there are similar relationships between malignant melanoma mortality and UVBI for males and females at the national level, suggesting that there are important factors acting at this level which have a roughly equal impact on males and females. Models A and D also demonstrate the dangers of using aggregated data, taken from different sources, without specifying an appropriate hierarchy, as UVBI shows a significant negative association with mortality, of roughly similar magnitude for males and females.

4.1. The relationship between mortality and UVB exposure

Models B and E, which include UVBI in the random part of the model, show that this overall relationship is spurious in both cases, and due to the aggregated effects of differential relationships between UVBI and mortality within the hierarchy. The reason for the near zero relationship between malignant melanoma mortality and UVBI in the fixed part of models B and E can be seen in Figures 1 and 2, as the United Kingdom, Belgium, Ireland and The Netherlands have a positive relationship with UVBI with relatively low values of UVBI, whereas Italy has the highest values of UVBI but a negative relationship between mortality and UVBI. If the hierarchical nature of the data has been unknown, or unused, and a simple single-level model of counties fitted to the data, then a quadratic relationship between mortality and UVBI could have been erroneously fitted to the data (and did produce a significant reduction in deviance). In this case where data are analysed in very distinctive geopolitical units it may seem obvious to use a hierarchical model, but this may not be the case in other situations, that is, model misspecification may be due to an incorrect data hierarchy as well as being due to non-linearities, outliers, overdispersion and so on at the basic level of analysis (in this case counties).

Models C and F show several interesting relationships. In the fixed parts, there are positive associations between population density and mortality for both males and females which reach significance at the 5 per cent level. This supports previous findings[16,17] that urban populations are at higher risk, possibly due to intermittent high exposure to UVB, whereas the more continuous exposure of rural populations, particularly those employed in outdoor occupations, may protect against the risk of this particular type of skin cancer. Higher GDP, as measured at

a regional level, is also associated with an increased melanoma mortality in males, potentially due to recreational exposure. In the case of both variables the absence of random effects, that is, variations between nations, suggests that these factors have a similar effect across Europe, given the variability in response to UVBI. In the random part of the models, the greatest variation is seen between nations, suggesting that factors operating at this level provide the greatest distinction between populations. The possible causes for these are discussed below. However, the parameter estimates for variance between nations tend to have large standard errors, as we have only nine nations in our sample. Hence, it is unwise to judge the significance of these random effects using a simple t-statistic (parameter estimate divided by standard error) for two reasons. First, it may be wrong to assume that the random effects are approximately normally distributed, and a test of significance would be better based on the change in log-likelihood ratio between models. Secondly, it is important to judge the impact on other parameters in the model by including the random effects, and here it is clear that differences between nations lead to misleading parameter effects for UVBI in models A and D. At level 1, it is interesting to note that the variation in females at level 1 is negative binomial, suggesting a greater heterogeneity in melanoma rates at this level, perhaps due to the lower overall mortality rate, that is, there is a greater possibility of heterogeneity in rates caused by small numbers of cases occurring in areas of differing demoninator populations. In contrast, the level 1 variance for males is lower, but in the final model (C) there is some variance which is associated with UVB exposure. This demonstrates the potential for multi-level modelling in exploring complex variance relationships with covariates at the lowest level of the model, as well as providing insight into variance components. In fact, even with no data hierarchy present, the MLn software used for the analysis can conveniently be used to model variance heterogeneity.

4.2. Different relationships for individual nations

The influence of particular higher level units, such as nations, on random part parameter estimates may be best measured by changes in deviance resulting from deletion, or exclusion from the random part of the model of particular nations.[37] However, here the differences are displayed graphically in Figures 1 and 2 for each nation. Figure 1 shows that the relationship between UVBI and mortality is strongest, in the positive direction, in the United Kingdom, a similar result being found for females in Figure 2. However, the shrunken and fixed estimates are somewhat different, for example, in males (0·123 fixed, 0·077 shrunken) for the United Kingdom. In general, the shrunken estimates are biased towards the overall mean, and the variance of these estimates will be smaller or greater, depending largely on the number of counties within each nation. The usefulness of shrunken estimates can be to estimate a population mean for a sample large enough and homogeneous enough to support the assumption of similarity. However, it is of dubious value here, as such striking differences are seen for different nations. Nevertheless, the shrunken estimates give a conservative measure of effect conditional on the whole data set. Hence, relationships which stand out after shrinkage are more likely to be of genuine interest. Not surprisingly, the fixed estimate for Luxembourg is very unreliable, as there are only three counties included in this nation, and the standard error is very large. The shrunken estimates are potentially more realistic, being pulled into roughly equal the mean relationship, but basically this simply states that more data is required for Luxembourg.

In general, the United Kingdom, Ireland, Belgium and The Netherlands show some positive relationship with UVBI, effects which are broadly similar for males and females. Germany and

Denmark both have higher rates of malignant melanoma mortality, but do not show a positive relationship with mortality. France shows very little overall relationship, whilst Italy, with the highest UVBI has a negative relationship between mortality and UVBI. The reasons for these large differences are unlikely to be due to registration[13] although we can only speculate as to possible explanations for the observed differences between nations. First, there may be differences in behaviour affecting exposure which lead to differences in basic mortality rates between nations, as well as differences in the relationship with UVBI. Northern Europeans may be more at risk of intermittent high exposures due to the occurrence of less hot sunny days at home and more recreational travel to warmer climates. There are also suggestions that damage to the ozone layer may result in an increase in malignant melanoma in northern European countries, although this effect may not be detectable at present.[16,36] The lack of a positive association with UVB index for Denmark and Germany compared to the United Kingdom in particular cannot be explained here, but could be due to differences in knowledge of risk or other factors influencing behaviour. A second set of explanatory factors which could be investigated in more detail are related to differences between nations in genetic type, with high risk, fair skinned populations occurring in northern Europe. Cavalli-Sforza *et al.*[37] discuss genetic differences between European populations. Significant differences in genetic type are seen not only between nations, but within nations. Whilst evidence tends to be patchy at local scales, France shows a distinct boundary between north and south based on measured genetic factors as well as linguistics[38] and Italy has a higher prevalence of low risk dark skinned people in the south,[39] potentially explaining the observed negative relationship between mortality and UVB index. Further research is needed on these regional differences in malignant melanoma and genetic type.

4.3. The usefulness of multi-level modelling

In summary, this study has demonstrated the potential usefulness of multi-level modelling in epidemiological analyses of disease risk measured across a large and heterogeneous population spanning several major geopolitical boundaries. The results have shown systematic differences in the relationship between UVB exposure and malignant melanoma mortality in different nations of the European community, which are of greater magnitude than variations seen between regions within countries. Estimating a relationship with UVB exposure without taking into account the hierarchical nature of the data has been shown to be mistaken, and there is unlikely to be a genuine quadratic relationship between UVB and melanoma mortality in Europe as previously suggested.[9] However, this paper has also attempted to demonstrate the potential for routine use of multi-level models to investigate health data which is contained within a hierarchy. In this case, we dealt with data which were aggregated at the lowest level of analysis, but even if we had used data on individuals, the same arguments as those developed here would apply to higher levels in the hierarchy. For the particular case of spatially distributed data, there are several issues to be addressed, which form the basis of research currently being undertaken by the authors. For example, there is no reason to believe that the geopolitical units within which data are collected are necessarily important to disease aetiology. If data are available in relatively small units, such as enumeration districts, these could be built into more meaningful units (such as neighbourhoods) based on the similarity of their characteristics.[40] Different spatial structures can also be imposed on the data which are not strictly hierarchical, but are cross-classified,[1] for example, Langford and Bentham[27] examined mortality rates in districts which belonged to both a geographical and a socio-economic higher level classification. Adjacency and proximity

matrices may also be used to define potential spatial structures in the data,[4,5] with random effects being associated with particular autocorrelation structures linking the occurrence of disease in a set of geographical areas. Work currently in progress[41,42] is exploring the possibility of building conditional and simultaneous autoregressive models into multi-level modelling analyses, which would provide for models of spatial correlation between areas at different geographical scales simultaneously. This is important, because in our present models we have assumed that areas are exchangeable,[43] and hence we shrink estimates for particular areas towards a global mean. For smaller areas, particularly, countries, this may not be so, as malignant melanoma risk in neighbouring counties may be expected to be similar as UVB exposure does not vary greatly at this smaller geographical scale. Hence, it would perhaps be wiser to shrink estimates towards local means, for example, the mean risk in adjacent countries. In addition, other explanatory variables may be built into the spatial correlation structure. However, whilst the development of the methodology is substantially advanced, there are still some computational difficulties to overcome. A further issue relates to differences between nations. It would be unwise to assume that the nine nations analysed here are drawn from the same population (and hence the effects and exchangeable) as there are noticeable differences between nations in the relationship between mortality and UVB exposure. It may be that a different hierarchical structure, perhaps distinguishing northern and southern European populations, would be more effective, and further research is needed here. Langford and Lewis[44] discuss methods for examining hidden structures in multi-level models.

In conclusion, multi-level modelling offers a flexible and general framework for analysing health data which is distributed in a hierarchical structure, geographical or otherwise. Further research is also being focused on developing particular tools for different data structures commonly found in epidemiology and public health medicine.

APPENDIX

In the Poisson model fitted in this paper, we have a non-linear relationship in equation (4) which we need to linearize. Following the methods presented by Goldstein[1] and Goldstein and Rasbash,[24] we can use a Taylor series approximation for the residuals by using the following updating function for the $t + 1$th interaction:

$$f(H_{t+1}) = f(H_t) + X_{ij}(\hat{\beta}_{t+1} - \hat{\beta}_t)f'(H_t) + u_i f'(H_t) + u_j^2 f'''(H_t)/2$$

for a simple two-level model with random effects u_j associated with the intercept at level 2. The model can easily be generalized to include more levels and more complex random structures are presented in the paper. The Taylor expansion shown includes the second-order term $u_j^2 f''(H_t)/2$ which improves estimation of the random parameters beyond a first-order approximation. However, for some of the models presented in this paper, the second-order approximation did not converge, and so a first-order approximation was used. However, a more important issue concerns the function used for H. In this case, penalized (or predictive) quasi-likelihood estimation has been used[1,21] where the estimated residuals are added back onto the fixed part predictor, so that:

$$f(H) = f'(H) = f''(H) = \exp(X_{ij}\hat{\beta}_t + \hat{u}_j)$$

and estimation is made about the current value of $\hat{u}_j$ rather than zero. This procedure, which can be easily implemented in MLn, noticeably improves the estimation of the random parameters and reduces bias compared to the marginal quasi-likelihood approach used in ML3.

Residuals at each level in the model may also be estimated with standard errors.[1] The residuals are posterior, or predicted residuals, so that for the residuals associated with the kth variable random at level m, we estimate:

$$\hat{p}_{mk} = E(p_{mk} | \tilde{Y}, V).$$

We do this by regressing all the residuals on $\tilde{Y}$ so that, for level m:

$$\hat{p}_m = R_m^{\mathrm{T}} V^{-1} \tilde{Y}$$

where R_m is a block diagonal matrix, with each block representing one unit at level m consisting of the product of the explanatory variables for random coefficients at level m and the covariance matrix of the residuals. Note that we have inherently assumed that the residuals have a multivariate normal distribution at higher levels than level 1, and we take their unconditional covariance matrix to be

$$R_m^{\mathrm{T}} V^{-1} (V - X(X^{\mathrm{T}} V^{-1} X)^{-1} X^{\mathrm{T}}) V^{-1} R_m$$

where the second term corrects for sampling variation of the fixed coefficients. For example, we only have nine nations random at level 3 in the model presented here, although this term may be ignored in larger samples. At level 1, we account for the fact that we are modelling Poisson distributed counts, where $\mathrm{var}(O) \cong \mu$, and so we declare an explanatory variable in the random part of the model for each unit at level 1 of $z_{1ijk} = \sqrt{(\mu_{ijk})}$. We can constrain the parameter associated with this variable to be unity if we wish the variance to be exactly Poisson, or estimate the parameter as explained in the text. Including a second level 1 variable of $z_{2ijk} = \mu_{ijk}$ means the negative binomial distribution is being used to estimate the level 1 variance, with $\mathrm{var}(O) = \sigma_1^2 \mu + \sigma_2^2 \mu^2$.

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REFERENCES

1. Goldstein, H. *Multilevel Statistical Models*, Edward Arnold, London, 1995.
2. Cox, B. D., Huppert, F. A. and Whichelow, M. J. (eds). *The Health and Lifestyle Survey, Seven Years On*, Dartmouth, Aldershot, 1993.
3. Jones, K. 'Specifying and estimating multilevel models for geographical research', *Transactions of the IBG*, New Series, **16.2**, 148–159 (1991).
4. Bailey, T. C. and Gatrell, A. C. *Interactive Spatial Data Analysis*, Longman, Harlow, 1995.
5. Elliott, P., Cuzick, J. and English, D. *Geographical and Environmental Epidemiology: Methods for Small Area Studies*, Open University Press, New York, 1992.
6. Elliott, P., Martuzzi, M. and Shadick, G. 'Spatial statistical methods in environmental epidemiology: a critique', *Statistical Methods in Medical Research*, **4**, 137–159 (1995).
7. Waller, L. A. and Turnbull, B. W. 'The effects of scale on tests of disease clustering', *Statistics in Medicine*, **12**, 1869–1884 (1993).

8. Magnus, K. 'Epidemiology of malignant melanoma of the skin', *in* Veronesi, U., Cascinelli, N. and Santinami, M. (eds), *Cutaneous Melanoma*: *Status of Knowledge and Future Perspective*, Academic Press, London, 1987.
9. Armstrong, B. K. 'Melanoma of the skin', *British Medical Bulletin*, **40**, 346–350 (1984).
10. Elwood, J. M., Lee, J. A., Walter, S. D., Mo, T. and Green, A. E. S. 'Relationship of melanoma and other skin cancer mortality to latitude and ultraviolet radiation in the United States and Canada', *International Journal of Epidemiology*, **3**, 325–332 (1974).
11. Scotto, J. and Fears, T. R. 'The association of solar ultraviolet and skin melanoma incidence among Caucasians in the United States', *Cancer Investigations*, **5**, 275–283 (1987).
12. Rampen, F. H. J. and Fleuren, E. 'Melanoma of the skin is not caused by ultraviolet radiation but by a chemical xenobiotic', *Medical Hypotheses*, **22**, 341–346 (1987).
13. Smans, M., Muir, C. S. and Boyle, P. *Atlas of Cancer Mortality in the European Economic Community*, IARC Scientific Publications, France, 1992.
14. Goldstein, H. *Multilevel Models in Educational and Social Research*, Charles Griffen, London, 1987.
15. Mo, T. and Green, A. E. S. 'A climatology of solar erythema dose', *Photochemistry and Photobiology*, **20**, 483–496 (1974).
16. Aase, A. and Bentham, G. 'The geography of malignant melanoma in the Nordic countries: the implications of stratospheric ozone depletion', *Geographiska Annaler*, **76**, 129–139 (1994).
17. Osterlind, A. 'Epidemiology on malignant melanoma in Europe', *Acta Oncologica*, **31.8**, 903–908 (1992).
18. Osterlind, A., Tucker, M. A., Stone, B. J. and Jensen, O. M. 'The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure', *International Journal of Cancer*, **42**, 319–324 (1988).
19. Elwood, J. M., Gallagher, R. P., Hill, G. B. and Pearson, J. C. G. 'Cutaneous melanoma in relation to intermittent and constant exposure: the Western Canada Melanoma Study', *International Journal of Cancer*, **35**, 427–433 (1985).
20. European Communities. *Regions - Statistical Yearbook*, HMSO, European Communities, 1989.
21. Breslow, N. E. and Clayton, D. G. 'Approximate inference in generalized linear mixed models', *Journal of the American Statistical Association*, **88**, 9–25 (1993).
22. McCullagh, P. and Nelder, J. A. *Generalized Linear Models*, 2nd edn, Chapman and Hall, London, 1989.
23. Wolfinger, R. 'Laplace's approximation for nonlinear mixed models', *Biometrika*, **80**, 791–795 (1993).
24. Goldstein, H. and Rasbash, J. *Improved Approximations for Multilevel Models with Binary Responses*. Multilevel Models Project Working Paper, Institute of Education, University of London, 1995.
25. Langford, I. H. 'A log-linear multilevel model of childhood leukaemia mortality', *Journal of Health and Place*, **1.2**, 113–120 (1995).
26. Rasbash, J. and Woodhouse, G. *MLn Command Reference*, Institute of Education, University of London, 1995.
27. Langford, I. H. and Bentham, G. 'Regional variations in mortality rates in England and Wales: an analysis using multilevel modelling', *Social Science and Medicine*, **42.6,** 897–908 (1996).
28. Langford, I. H. 'A cross-classified multilevel model of district mortality rates', *Multilevel Modelling Newsletter*, **6.2**, 9–11 (1994).
29. Langford, I. H. 'Using empirical Bayes estimates in the geographical analysis of disease risk', *Area*, **26.2**, 142–149 (1994).
30. Tsutakawa, R. K. 'Mixed model for analyzing geographic variability in mortality rates', *Journal of the American Statistical Association*, **83**, 37–42 (1988).
31. Clayton, D. and Kaldor, J. 'Empirical Bayes estimates of age-standardized relative risks for use in disease mapping', *Biometrics*, **43**, 671–681 (1987).
32. Manton, K. G., Stallard, E., Woodbury, M. A., Riggan, W. B., Creason, J. P. and Mason, T. J., 'Statistically adjusted estimates of geographic mortality profiles', *Journal of National Cancer Institute*, **78.5**, 805–815 (1987).
33. Bryk, A. S. and Raudenbush, S. W. *Hierarchical Linear Models*: *Applications and Data Analysis Methods*, Sage Publications, London, 1992.
34. Goldstein, H. *Delta method adjustments to covariance matrix estimators for random parameters and residuals*, Multilevel Models Project Working Paper, Institute of Education, University of London, 1994.

35. Jensen, O. M., Esteve, J., Moller, H. and Rebard, H. 'Cancer in the European Community and its member states', *European Journal of Cancer*, **26**, 1167–1256 (1990).
36. Schaart, F. M., Garbe, C. and Orfanos, C. E. 'Disappearance of the ozone layer and skin cancer: attempt at risk assessment', *Hautarzt*, **44**, 63–68 (1993).
37. Cavalli-Sforza, L. L., Menozzi, P. and Piazza, A. *The History and Geography of Human Genes*, Princeton University Press, Princeton, 1994.
38. Bonnaud, P. *Terres et Langages*, *Peuple et regions*, Clemont-Ferrand, France, 1981.
39. Piazza, A., Cappello, N., Olivetti, E. and Rendine, S. 'A genetic history of Italy', *Annals of Human Genetics*, **52**, 203–213 (1988).
40. Haining, R., Wise, S. and Blake, M. 'Constructing regions for small area analysis: material deprivation and colorectal cancer', *Journal of Public Health Medicine*, **16**, 429–438 (1994).
41. Langford, I. H. and Jones, A. P. (1996) *Comparing Area Mortality Rates using a Random Effects Model and Bootstrapping*, ESDA with LISA Conference, University of Leicester, United Kingdom, July, 1996.
42. Langford, I. H., Leyland, A. H., Rasbash, J. and Goldstein, H. 'Multilevel modelling of the goegraphical distributions of rare diseases', Symposium on the Expansion Method, University of Odense, Denmark, October, 1996.
43. Clayton, D. and Bernardinelli, L. 'Bayesian methods for mapping disease risk', *in* Eilliott, P., Cuzick, J. and English, D. (eds), *Geographical and Environmental Epidemiology*: *Methods for Small Area Studies*, Open University Press, 1992, pp. 105–220.
44. Langford, I. H. and Lewis, T. 'Outliers in multilevel data', *Journal of the Royal Statistical Society*, *Series A*, in press.

