THEORY AND METHODS

A framework for modelling differences in regional mortality over time

L M Lix, O Ekuma, M Brownell, L L Roos

Study objective: To present a conceptual framework for testing differences in mortality for small geographical areas over time using the generalised linear model with generalised estimating equations. This framework can be used to test whether the magnitude of regional inequalities in health status has changed over time.

Design: A Poisson regression model for correlated data is used to investigate the relation of population health status to demographic, geographical, and temporal explanatory variables. Differences between regions at one or more points in time are tested with linear contrasts.

Setting and participants: A case example shows the application of the framework. All cause mortality and cause specific mortality were compared for three rural regions of Manitoba, Canada between 1985 and 1999. The data were obtained from Vital Statistics records and the provincial health registry.

Main results: Tests of linear contrasts on the regression coefficients for time and region show an increase in the magnitude of the difference in the risk of all cause mortality and heart disease mortality between northern and southern regions of the province for the 1985–1989 and 1995–1999 time periods. No significant differences are identified for cancer, injury, or respiratory disease mortality.

Conclusions: The proposed framework enables testing of a variety of hypotheses about differences between regions and time periods and can be applied to other measures of population health status.

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esearchers and public health officials have long been interested in identifying inequalities in health status for small geographical areas. Persistent differences between areas, particularly those that appear to be increasing in magnitude over time, may be the basis for resource allocation decisions and public health surveillance activities at both the local and national levels. They may also be the impetus for further research on the determinants of health, including studies of small area variations in health services utilisation, socioeconomic characteristics, and environmental exposures.

Descriptive plots of age standardised death rates over time for two or more areas provide only the crudest indication of whether health inequalities exist. In small populations, a single death in a given area and/or year may have a large impact on the observed rates. This inherent variability in rates for small geographical areas may obscure trends in the data. As well, descriptive analyses of the data are of limited value for assessing whether the magnitude of the difference between regions is changing over time, that is, whether there is an interaction between geography and time.

Regression techniques have been used to examine differences in mortality for small areas. However, researchers may be unfamiliar with techniques for correlated data that can be used to model longitudinal data and with the formulation of hypotheses on the interaction regression coefficients that are used to test for differences between small areas. Longitudinal data can be modelled as a function of demographic, geographical, and temporal explanatory variables using a statistical procedure that accounts for the correlation between successive time points. Hypotheses on the time x region regression coefficients are then used to test for differences between regions over time.

This paper presents a framework for applying regression techniques to correlated data to test for regional differences in mortality. It is developed within the context of the generalised linear model (GLM), which has been applied to longitudinal data for a variety of health indicators. The GLM framework subsumes a broad class of statistical models, including the Poisson model, which is often used to describe the distribution of rare population events such as death. Within this framework, we show how to test hypotheses of differences between regions and time periods. A case example builds on 15 years of mortality data for the rural regional health authorities (RHAs) of Manitoba, Canada.

MODEL BASED FRAMEWORK

We begin by defining the model for the simplest case, where counts of the number of deaths in a region are obtained at a single point in time. Let \( Y_i, n_i \), and \( r_i = Y_i/n_i \) respectively represent the number of deaths, total population size, and observed mortality rate for the \( i \)th stratum \((i = 1, \ldots, n)\). The strata are created by defining discrete categories for the values of each model covariate (that is, age group, region) and then classifying the population into cells by forming all possible combinations of these covariate categories.

It is assumed that the \( Y_i \)s are independently distributed as Poisson variates. The expected number of deaths in each stratum, \( E(Y_i) = \mu_i \), is modelled as

\[
\mu_i = n_i \lambda(X, \beta),
\]

where \( X \) is the vector of predictor variables that describes each stratum, \( \beta \) is a \( p \)-vector of population regression parameters, and \( \lambda(X, \beta) \) is the underlying rate function which is estimated by \( r_i \). This multiplicative model can be expressed as a generalised linear model (GLM), which relates

Abbreviations: GEE, generalised estimating equation; GLM, generalised linear model; RHA, regional health authority; PMR, premature mortality rate.
the expected value of the outcome value to the predictor variables via a link function. For the Poisson distribution the log link function is used, 

$$\ln \mu_i = \ln(n_i) + (X_i\beta).$$ (2)

When the data are classified into strata on the basis of age group and region in a two way contingency table, the GLM model can be expressed as 

$$\ln \mu_i = \ln n_{ij} + \mu_0 + a_j + \delta_k,$$ (3)

where $\mu_0$ is the model intercept, $a_j$ is the ‘effect’ of the $j$th age group ($j = 1, \ldots, J$) and $\delta_k$ is the effect of the $k$th region ($k = 1, \ldots, K$).

To extend this model to longitudinal data, let $Y_i = [Y_{i1}, \ldots, Y_{iT}]^T$ represent the vector of counts of the number of deaths for the $i$th stratum for $t$ points in time, where $A^T$ is the transpose of $A$. Furthermore, let $\mu_i = [\mu_{i1}, \mu_{i2}, \ldots, \mu_{iK}]^T$ denote $E(Y_i)$. It is assumed that the elements of $Y_i$ are correlated, where $V_i$ represents the covariance matrix. The model is

$$\ln \mu_i = \ln(n_{ij}) + (X_i\beta),$$ (4)

where $X_i$ is the p vector of covariates for $Y_i$. Generalised estimating equations (GEEs) were developed so that the GLM could be applied to correlated data.14 GEEs are a series of equations, which are solved iteratively to estimate $\beta$ when the structure of $V_i$ is specified. GEEs account for the correlation between successive time points, ensuring that the standard errors of the regression coefficients are correctly estimated and tests of these coefficients are unbiased and efficient. A variety of structures that can model the relation between successive time points are described by Carriere et al.6

Using the notation of equation 3, a model for longitudinal mortality data is 

$$\ln \mu_i = \ln(n_{ij}) + \mu_0 + a_j + \delta_k + \gamma_m + \eta_{km},$$ (5)

where $\gamma_m$ is the effect associated with the $m$th time period ($m = 1, \ldots, T$) and $\eta_{km}$ is the effect of the $k$th region and $m$th time period. The region $x$ time interaction term is the basis for testing hypotheses about changes in regional differences over time. Additional two way and three way interaction terms may be included in the model. The addition of interaction terms will be guided by the hypotheses of interest, theoretical considerations, and their contribution to model fit. Only rarely will the researcher be interested in testing the omnibus hypothesis for an interaction. Rather, contrasts, which are linear combinations of the regression coefficients, will be of greatest interest. To test for a difference between two regions, $k$ and $k'$, in a single year while holding age constant*, the null hypothesis is $H_0: \psi_{kk'} = 0$, where

$$\psi_{kk'} = (\mu_0 + \delta_k + \gamma_m + \eta_{km}) - (\mu_0 + \delta_{k'} + \gamma_m + \eta_{k'm}) = \delta_k + \eta_{km} - \delta_{k'} - \eta_{k'm}.$$ (6)

which can be estimated by

$$\hat{\psi}_{kk'} = \hat{\delta}_k + \hat{\eta}_{km} - \hat{\delta}_{k'} - \hat{\eta}_{k'm}. $$

A Wald statistic

$$Z_{kk'} = \frac{\hat{\psi}_{kk'}}{\sqrt{\text{Var}(\hat{\psi}_{kk'})}},$$ (7)

can be used to test the null hypothesis. The statistic $Z^2_{kk'}$ is referred to the critical value, $\chi^2_{(1-\alpha)}$, the $(1-\alpha)$ centile of the $\chi^2$ distribution with one degree of freedom. Exp$(\hat{\psi}_{kk'})$ represents the ratio of the average mortality risk for region $k'$ to the average for region $k$ in the $m$th time period, holding age constant. A positive value for Exp$(\hat{\psi}_{kk'})$ indicates that the relative risk of mortality for region $k'$ is higher than that of region $k$ at this single point in time.

To test for a difference between two regions, $k$ and $k'$, and two years, $m$ and $m'$, the null hypothesis is $H_0: \psi_{kk'mm'} = 0$, and the contrast is given by

$$\psi_{kk'mm'} = \begin{bmatrix} \mu_0 + \delta_k + \gamma_m + \eta_{km} \\ \mu_0 + \delta_k + \gamma_m + \eta_{km} \\ \mu_0 + \delta_{k'} + \gamma_m + \eta_{k'm} \\ \mu_0 + \delta_{k'} + \gamma_m + \eta_{k'm} \end{bmatrix} - \begin{bmatrix} \mu_0 + \delta_k + \gamma_m + \eta_{km} \\ \mu_0 + \delta_k + \gamma_m + \eta_{km} \\ \mu_0 + \delta_{k'} + \gamma_m + \eta_{k'm} \\ \mu_0 + \delta_{k'} + \gamma_m + \eta_{k'm} \end{bmatrix} = \begin{bmatrix} \eta_{km} - \eta_{k'm} \end{bmatrix},$$ (8)

which can be estimated by

$$\hat{\psi}_{kk'mm'} = \hat{\eta}_{km} - \hat{\eta}_{k'm}.$$
Table 1  Number of deaths and total population by age group for Manitoba rural regions, 1985–1999

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<th>North 45–74</th>
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between the northern region (that is, the RHAs with the highest PMR) and the southern region (that is, the RHAs with the lowest PMR) increased between two time periods: 1985–1989 and 1995–1999.

Study data were obtained from Vital Statistics records and the Manitoba Health Services Insurance Plan (MHSIP) Registry. The former was used to compile in-province deaths for all Manitoba residents on an annual basis for the period from 1 January 1985 to 31 December 1999. All cause mortality was examined in addition to specific causes identified using the 9th version of the International Classification of Diseases. These included cancer (ICD-9 140–208), heart disease (ICD-9 390–459), injury (ICD-9 E800–E999), and respiratory disease (ICD-9 460–519). The MHSIP Registry was used to obtain population counts for regions. Ethics approval for data access was obtained from the Health Research Ethics Board of the University of Manitoba; the Manitoba Health Information Privacy Committee was kept informed of the research.

The data were classified into strata on the basis of age group, sex, and region. For all cause mortality, five year age groups were chosen to describe the effect of age on mortality: 0–4, 5–9, … 80–84, 85 and older. For cause specific mortality, because of the small numbers of deaths in some of the five year age strata, the data were instead assigned to four age groups: under 45 years, 45–64, 65–74, and 75 years and older. The 11 rural RHAs of Manitoba were classified into three health status regions based on the work of Roos et al. North or highest PMR (Nor-Man, Burntwood, Churchill), Central or average PMR (Marquette, Parkland, North Eastman, Interlake), and South or lowest PMR (Central, South Eastman, South Westman, Brandon). This classification is based on standardised PMR rates at the start of the study period; each region of the province is comprised of a set of geographically contiguous RHAs.

To model the covariance across time an exchangeable structure was adopted; it assumes equivalent correlations between successive study years. This structure seemed the most appropriate given descriptive analyses of the data that showed a relatively constant degree of correlation across successive study years, and previous research. An unstructured covariance matrix could not be fitted to the data because of the large number of parameter estimates required, and a first order autoregressive structure did not produce appreciable differences in the standard errors of the regression coefficients. Close agreement between the true covariance structure and VI is desirable from the point of view of efficiency of estimation but is not necessary for consistency of estimation.

The final model contained the main effects of age group, sex, region, year, and the region x year interaction. All predictor variables were categorial. Additional two way interactions were considered in preliminary models, but were not retained because they did not improve the fit of the model and were not statistically significant predictors of mortality. Our goal was to fit the most parsimonious model given the research objectives. The GENMOD procedure of SAS was used to perform all analyses.

Table 1 summarises the number of deaths for each year and each of the three regions of the province for the 15 year study period for three age groups: 0 to 44 years, 45 to 74 years, and 75 years and older. The population, and hence the number of deaths, is substantially lower in the northern region of the province than in the southern region. Random variation in the age and sex standardised rates, particularly for the north, makes it difficult to determine whether the difference between these two regions of the province is increasing or decreasing over time (see fig 1).

The results for the Poisson regression analyses are presented in figure 2 and in table 2. Figure 2 graphically displays the difference in the relative risk of all cause mortality between the North and South regions for each year of the study period. These results were obtained by applying the contrast of equation 6 to the data for each of the 15 study years. They suggest a difference between the two regions that may be increasing in magnitude over time.

We tested the null hypothesis of no difference in the relative risk between the two regions in the first and last five years of the study period, that is, $H_0: \psi_{SN(1985–89)(1995–99)} = 0$, where
The results in table 2 indicate a statistically significant result was obtained for all cause mortality and for heart disease mortality, but that no differences were detected for cancer, injury, and respiratory disease mortality. These results suggest that regional differences in heart disease mortality have contributed to the increased disparity in overall mortality between the northern and southern regions of the province over time.

**DISCUSSION**

The purpose of this research was to present a model based framework for correlated data that can be used to test for differences in mortality between geographical areas over time. This framework provides one analytical tool for examining small area inequalities in health status.

The GLM with GEEs was used to describe the relation between counts of the number of deaths in population strata and the explanatory variables of age, region, and time. By including age as an explanatory variable in the model, the researcher accounts for differences in the demographic structure of small areas that may affect the number of deaths.

Random variation in the number of deaths for small areas means that mortality rates may fluctuate substantially from one year to the next. This may mask the identification of trends in the data or differences in mortality between regions. The adoption of significance tests within the GLM framework permits the researcher to test whether differences between regions are in fact attributable to these chance fluctuations. As this paper has shown, the interaction between geography and time must be probed to determine whether the magnitude of the differences between regions is increasing or decreasing.

While the application of a Poisson model to mortality data is well reported in the literature, there is less information on using GEEs to incorporate information on the correlation structure of the data. The correct standard error for the contrast test statistic is obtained when information on the association between successive points in time is modelled.

There are a number of hypotheses that can be examined within the context of this framework. The mortality rate for one region could be compared with the average rate for two or more different regions. Hypotheses of differences between individual study years, average differences between two or more years, or of linear trends across time periods may be tested when time is treated as a categorical variable in the model. When time is specified as a continuous variable, the regression coefficient represents the average change per unit of time. Differences between regions may be tested, but not differences between time periods. Time may also be treated as a continuous variable, but in a piecewise fashion. A

$$\hat{\psi}_{SN(1985-89),(1995-99)} = \left( \hat{\psi}_{N,1985} + \hat{\psi}_{N,1986} + \cdots + \hat{\psi}_{N,1999} \right) \left( \hat{\psi}_{N,1985} + \hat{\psi}_{N,1986} + \cdots + \hat{\psi}_{N,1999} \right)$$

(9)

The results in table 2 indicate a statistically significant result was obtained for all cause mortality and for heart disease mortality, but that no differences were detected for cancer, injury, and respiratory disease mortality. These results suggest that regional differences in heart disease mortality have contributed to the increased disparity in overall mortality between the northern and southern regions of the province over time.

**Table 2** Contrast estimate results for the difference in all cause and cause specific mortality risk for North and South Manitoba rural regions, 1985/89–1995/99

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</tr>
<tr>
<td>Heart disease</td>
<td>0.11</td>
<td>1.22</td>
<td>0.07</td>
<td>8.54</td>
<td>0.06 to 0.33*</td>
</tr>
<tr>
<td>Injury</td>
<td>-0.17</td>
<td>0.91</td>
<td>0.14</td>
<td>0.43</td>
<td>-0.37 to 0.19</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0.03</td>
<td>1.13</td>
<td>0.10</td>
<td>2.22</td>
<td>-0.07 to 0.31</td>
</tr>
</tbody>
</table>

*Indicates a result that is significant at $\alpha=0.05$
categorical variable is used to distinguish successive time periods (that is, before and after periods). Hypotheses of differences between periods in the average change per unit of time are tested. Such an approach has been adopted in both clinical and epidemiological research to examine critical phases of change.\textsuperscript{4, 5} The choice among these approaches will depend on the objectives of the research.

Finally, such a framework based on the GLM can be applied to other measures of population health status, including incidence or prevalence of chronic health conditions such as diabetes or respiratory illness.\textsuperscript{6, 7} To extend the framework, the researcher must be able to identify the distribution of the data, the link function that relates the expected value of the dependent variable to the independent variables using a linear model, and the correlation structure of the longitudinal data. As well, the researcher must be able to articulate one or more hypotheses regarding differences between regions and time periods.

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