Occupation and cancer: the application of a novel graphical approach to routinely collected registration data

**INTRODUCTION**

For over 150 years, routinely collected mortality data from England and Wales have been used to investigate possible associations between occupation and health. More recently, occupational information provided at cancer registration has also been used. This is especially relevant for cancers with a relatively good survival, such as lip cancer, where mortality data may be less informative. In the past, cancer registration data had the additional advantage of using self-reported occupational information and not relying solely on information supplied by the next of kin (eg occupation recorded on death certificates). Recently, however, several cancer registries have ceased collecting occupational data.

Analyses of routinely collected mortality and morbidity data are subject to a number of specific methodological problems. For example, the simultaneous examination of a large number of outcomes and exposures can produce an unmanageable number of results and multiple comparisons – the analysis of 212 occupational groups and 40 cancer sites generates 8,480 measures of association. How should such a large number of findings be summarised? And how should anomalous associations requiring further investigation be identified?
To deal with these issues, a novel approach involving a graphical display of empirical Bayesian risk estimates has been developed.\textsuperscript{10,11} This method takes some of the limitations of routinely collected data into consideration and, rather than testing hypotheses, it highlights issues for further investigation.

We have applied this method to cancer registration data from England and Wales for 1971–1990. This involves the analysis of 1.3 million cancer registrations in men and women classified into 40 cancer sites and 212 occupational groups. These data and the graphical tools are available on the LRF website (http://www.lrf.leeds.ac.uk/eB_plots),\textsuperscript{12} see Box 1 for further details. The aim of this article is to illustrate the analytical and graphical approach employed by focussing on plots for four cancer sites selected because they resulted in contrasting patterns. The selected cancer sites are nose and nasal sinuses; pleura, thymus and mediastinum; lip; stomach. The plots for all cancer sites and occupational groups (for men and women separately) are available on the LRF website.\textsuperscript{12}

<table>
<thead>
<tr>
<th>Box one</th>
</tr>
</thead>
<tbody>
<tr>
<td>- A stand-alone program has been developed to allow routinely collected data to be displayed graphically using the empirical Bayesian method described.</td>
</tr>
<tr>
<td>- The dataset is included with the software for interrogation by the user.</td>
</tr>
<tr>
<td>- Functions include: full control over plot properties, copy/paste and print facilities, ordering the plots in different manners, etc.</td>
</tr>
<tr>
<td>- The software is free to download from the LRF website at the University of Leeds (<a href="http://www.lrf.leeds.ac.uk/eB_plots">http://www.lrf.leeds.ac.uk/eB_plots</a>).</td>
</tr>
<tr>
<td>- The website has further details about the data and statistical methods. An online help system is also available for the software.</td>
</tr>
</tbody>
</table>

**DATA**

The Office for National Statistics provided individual anonymised data for all cancers registered in England and Wales among adults aged 20–74 years for 1971–1990.\textsuperscript{13} These comprise over 3 million cancers, just over half of which were registered in women (Table 1). Among men, 41 per cent of registrations were excluded, either because occupation was missing (21 per cent) or because they were not gainfully employed (19 per cent). In contrast, among women, 76 per cent of registrations were excluded – mainly because occupation was missing (52 per cent). Further details relating to these exclusions are provided elsewhere.\textsuperscript{12} After making the necessary exclusions, approximately 1.3 million cancer registrations were available for analysis – 895,773 in men and 381,006 in women. Analyses of subsets of these data using traditional methods have been reported elsewhere.\textsuperscript{14} Limitations of the data are discussed later.

Coding schemes for both cancer and occupation changed during the time period covered by these data. Cancers were coded according to either the 8th or 9th revision of the International Classification of Diseases (ICD)\textsuperscript{14,15} and occupations were coded using the 1970 or 1980 version of the Classification of Occupations.\textsuperscript{16,17} For the purposes of these analyses, ICD cancer codes were assigned to one of 40 groups defined according to cancer site. Occupations were bridge-coded to one of 212 occupational groups (based on the 1970 Classification of Occupations\textsuperscript{18}) using a coding scheme specifically developed for this purpose.\textsuperscript{19} Details of the original codes making up these classifications, together with the bridge-coding schemes, are provided elsewhere.\textsuperscript{20}

**STATISTICAL METHODS**

The approach, full details of which are provided elsewhere,\textsuperscript{19–22} involves a refinement of that based on proportional registration ratios (PRRs). Briefly, the data may be considered as a large two-way contingency table where each cell contains the number of cancers for a particular occupational group and cancer site. The approach involves calculating observed to expected ratios (OER) on the (natural) log scale for each occupational group-cancer site combination – the expected number of cancers being based on the distribution of cancers in the margins of the table (using the same method that is used for the traditional PRR).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Total number of cancer registrations in men and women aged 20–74 years, and reasons for exclusion</th>
<th>England and Wales</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Number</td>
<td>Percentage</td>
<td>Number</td>
</tr>
<tr>
<td>Cancer registrations</td>
<td>1,511,858</td>
<td>100.0</td>
</tr>
<tr>
<td>Exclusions</td>
<td>616,085</td>
<td>40.8</td>
</tr>
<tr>
<td>- Missing information</td>
<td>316,612</td>
<td>20.9</td>
</tr>
<tr>
<td>- Region</td>
<td>309,381</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>7,231</td>
<td>0.5</td>
</tr>
<tr>
<td>- Inconsistent diagnosis*</td>
<td>7,231</td>
<td>0.5</td>
</tr>
<tr>
<td>- Diagnostic category</td>
<td>377</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>- Not gainfully employed</td>
<td>289,855</td>
<td>19.2</td>
</tr>
<tr>
<td>- Regional reasons**</td>
<td>9,240</td>
<td>0.6</td>
</tr>
<tr>
<td>Registrations available for analysis</td>
<td>895,773</td>
<td>59.2</td>
</tr>
</tbody>
</table>

* Sex and site code combination invalid (e.g., cervix in males). 
† Conditions not coded as malignant or benign neoplasms. 
** Inconsistent occupational coding which was cancer registry specific.
An empirical Bayesian shrinkage procedure is then performed by either cancer site or occupational group. The general purpose of this procedure is to adjust the (log) OERs so that those based on small numbers of observations carry less weight. The method takes account of two levels of statistical variation: within and between cells. Random variation of the observed number of cancers within a cell is assumed to follow a Poisson distribution with a theoretical mean determined by the ‘true’ rate for that cell. The variation between cells, within a particular occupational group or cancer site (row or column of the table), then relates to the frequency distribution of the underlying ‘true’ rates. Each occupational group, or cancer site, is assumed to have an underlying distribution of ‘true’ (natural logarithm (log)) OERs with a mean of zero (OER = 1) and standard deviation of $\sigma$ (the measure of between-cell variation). If the (log) OERs are bunched closely around the mean of zero then (will be small, and if they are scattered over considerable distances (so some (log) OERs are far from zero) then $\sigma$ will be large.

The estimated standard deviation, $\sigma$, can be seen as a measure of the strength of association between occupation and cancer and is called the index of sensitivity. For example, applying the empirical Bayesian procedure by occupational group, if the distribution of cancers across the different cancer sites within a particular occupational group differs only by chance from the distribution of cancers by site over all occupational groups together (i.e. it is consistent with the Poisson distribution), then the index of sensitivity will be zero (or estimated as negative, which, for our purposes, is classified as zero). In that case there is no evidence of an association between that particular occupational group and cancer. Empirical Bayesian shrinkage of the OERs is then not appropriate and no plot is produced. If, however, the distribution of cancers across the different cancer sites within a particular occupational group differs only by chance from the distribution of cancers by site over all occupational groups combined by more than would be expected from random (Poisson) error, then the index of sensitivity will be greater than zero, suggesting that there may be an association between the occupational group under examination and cancer. This may be in the form of a general departure from the distribution of cancers by site in the margin of the table, or there may be a small number of outlying values corresponding to abnormally high or low values of the (log) OER that may be of interest to study further. The greater the index of sensitivity the stronger the ‘evidence’ for an overall association between the occupational group and interest and cancer.

When the index of sensitivity is found to be greater than zero, the (log) OERs are then adjusted (‘shrunk’) towards zero (OER=1) according to the number of observed cancer cases in the cell, accounting simultaneously for both the within (Poisson) and between ($\sigma$) cell error. Effectively a weighted average of zero and the unadjusted estimate of the (log) OER is produced. In this way OERs based on small numbers of observations (imprecise estimates) are shrunk more than those based on large numbers (precise estimates).

### Interpreting the plots

Shrunken estimates of the OER that are atypically high or low are identified by plotting them on a natural log scale against the expected order statistics from a standard Normal distribution. If there are no anomalous values, then the distribution of estimates should follow a smooth curve. Attention is focussed on the highest and lowest estimates: their interpretation will to some extent depend on whether some or all of the values are deemed to fall on the smooth curve formed by extrapolation from the central part of the distribution.

The slope of the plot represents the index of sensitivity: the higher the index, the steeper the slope. If none of the shrunken estimates is an outlier, i.e. the frequency distribution of the estimates is reasonably smooth, the conclusion (when the index of sensitivity is greater than zero) would be that there is a general departure of the pattern across occupational groups from that obtained in the population overall (across all cancer sites) but that no specific occupational group is anomalously high or low. Therefore, a high index of sensitivity indicates a strong relationship between that cancer site and occupations (or that occupation and cancer sites) depending on the plot.

The quantitative interpretation of the index of sensitivity can best be seen as follows: roughly two-thirds of the ‘true’ log OERs lie within plus and minus the index, thus if the index is 0.15, roughly two-thirds of the true OERs lie between the exponential of -0.15 (which equals 0.86) and the exponential of +0.15 (which equals 1.16) showing the range of deviations from proportionality involved.

### Results

The estimated index of sensitivity was zero, or less than zero, for 13 occupational groups in men, and 21 cancer sites and 100 occupational groups in women. These occupational groups and cancer sites provide no information regarding overall associations between cancer and occupation. Details are provided elsewhere.12

A total of 239 plots were produced for men: one for each of the 40 cancer sites and for 199 of the 212 occupational groups (Table 2). The number of cancer registrations contributing data to each cancer plot ranged from 1,232 for cancer of the nasopharynx to 284,776 for cancer of the trachea, bronchus and lung, while the number contributing to each occupational plot ranged from 115 for winders and reelers to 54,232 for clerks and cashiers. The median number of cancer registrations was 6,401 for the cancer plots and 1,673 for the occupational plots.

For women, a total of 130 plots were produced for 19 of the 40 cancer sites and 111 of the 211 occupational groups (Table 2). There were only 211 occupational groups among women; no women were coded as workers below ground not elsewhere classified (nec). The cancer plot with the smallest number of registrations was cancer of the gall bladder (1,866), whilst the largest was breast cancer (93,948). Across the occupational plots, the number of cancer registrations ranged from 36 for steel erectors and riggers to 54,849 for clerks and cashiers. The median number of cancer registrations was 10,494 for the cancer plots and 707 for the occupational plots.

For men, the index of sensitivity (where it was greater than zero) ranged from 0.002 for cancer of the pancreas to 0.491 for testicular cancer for the cancer plots. For the occupational plots, the index of sensitivity ranged from 0.003 for hairdressers to 0.605 for rolling, tube mill operators, metal drawers (Table 2).

For women, the index of sensitivity ranged from 0.002 for cancer of the rectum to 0.361 for other benign neoplasms for the cancer plots, and for the occupational plots from 0.002 for printers (so described) to 0.505 for furnace and chemical production process workers (Table 2).

A high index of sensitivity indicates a strong relationship between that cancer site and occupations (or that occupation and cancer sites) depending on the plot.

As an illustration of the novel graphical approach, the following sections present the results for four cancer sites (nose and nasal sinuses; pleura, thymus and mediastinum; lip; stomach) with attention focused on anomalously high values. Data for women are presented for stomach cancer only; for the other three cancer sites the index of sensitivity was...
zero. The results for each cancer site and occupational group are available on the LRF website at the University of Leeds.\textsuperscript{12}

**Cancer of the nose and nasal sinuses**

**Men**

The index of sensitivity for cancer of the nose and nasal sinuses among men is 0.112 indicating a weak association between occupation and the risk of this cancer (Figure 1a). The plot for this cancer site produces three outliers – cabinetmakers; woodworkers nec; sawyers and woodworking machinists. In these three occupational groups, the index of sensitivity is 0.194 for cabinetmakers, 0.049 for woodworkers nec and 0.041 for sawyers and woodworking machinists.

The corresponding plots for all three occupational groups show cancer of the nose and nasal sinuses to be an outlier (Figures 1b-d) based on 25, 20 and 23 cancer registrations, respectively.

**Comment**

Increased risks of cancer of the nose and nasal sinuses in men were confined to workers exposed to wood-dust. In contrast with findings of Demers and Boffetta,\textsuperscript{18} these occupational groups show little evidence of an excess risk of nasopharyngeal cancer or multiple myeloma. In the data presented here, cancer of the nasopharynx was the third highest cancer among cabinetmakers based on only 5 cancer registrations.

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**Table 2** Summary statistics for the cancer site and occupational group plots for men and women

<table>
<thead>
<tr>
<th>Cancer sites</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sites</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Number excluded(^\star)</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Number of plots</td>
<td>40</td>
<td>19</td>
</tr>
<tr>
<td>Number of registrations(^\dagger)</td>
<td>1,222–284,776</td>
<td>1,866–93,948</td>
</tr>
<tr>
<td>Range</td>
<td>22,394 (46,610)</td>
<td>18,591 (22,037)</td>
</tr>
<tr>
<td>Mean (SD(^\star))</td>
<td>6,401</td>
<td>10,494</td>
</tr>
<tr>
<td>Median</td>
<td>2,057–22,771</td>
<td>6,390–19,609</td>
</tr>
<tr>
<td>IQR(^\ddagger)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index of sensitivity(^\star)</td>
<td>0.002–0.491</td>
<td>0.002–0.361</td>
</tr>
<tr>
<td>Range</td>
<td>0.119 (0.107)</td>
<td>0.106 (0.091)</td>
</tr>
<tr>
<td>Mean (SD(^\star))</td>
<td>0.095</td>
<td>0.073</td>
</tr>
<tr>
<td>Median</td>
<td>0.041–0.167</td>
<td>0.049–0.155</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupational groups</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of groups</td>
<td>212</td>
<td>211***</td>
</tr>
<tr>
<td>Number excluded(^\star)</td>
<td>13</td>
<td>100</td>
</tr>
<tr>
<td>Number of plots</td>
<td>199</td>
<td>111</td>
</tr>
<tr>
<td>Number of registrations(^\dagger)</td>
<td>115–54,232</td>
<td>36–54,849</td>
</tr>
<tr>
<td>Range</td>
<td>4,449 (8,625)</td>
<td>3,241 (7,949)</td>
</tr>
<tr>
<td>Mean (SD(^\star))</td>
<td>1,673</td>
<td>707</td>
</tr>
<tr>
<td>Median</td>
<td>895–4,483</td>
<td>282–2,133</td>
</tr>
<tr>
<td>IQR(^\ddagger)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index of sensitivity(^\star)</td>
<td>0.003–0.605</td>
<td>0.0002–0.505</td>
</tr>
<tr>
<td>Range</td>
<td>0.138 (0.103)</td>
<td>0.108 (0.087)</td>
</tr>
<tr>
<td>Mean (SD(^\star))</td>
<td>0.119</td>
<td>0.087</td>
</tr>
<tr>
<td>Median</td>
<td>0.057–0.197</td>
<td>0.044–0.149</td>
</tr>
</tbody>
</table>

\(^\star\) Index of sensitivity ≤ 0. 
\(^\dagger\) Summary statistics based on cancer registration data contributing to the plots. 
\(^\ddagger\) SD = standard deviation. 
*** No women were coded as workers below ground not elsewhere classified.
Cancer of the pleura, thymus and mediastinum

Men
The index of sensitivity for cancer of the pleura, thymus and mediastinum is 0.310 (Figure 2a). The plot for this cancer site produces one outlier for metal plate workers, riveters. The next highest points on this cancer plot correspond to (highest to lowest): plumbers, fitters, heating engineers etc; coach, carriage, wagon builders and repairers; electricians, electrical and electronic fitters; carpenters and joiners. Among these occupational groups, the index of sensitivity is 0.197 for electricians, electrical and electronic fitters; carpenters and joiners.

The occupational plot for metal plate workers, riveters shows cancer of the pleura, thymus and mediastinum to be an outlier based on 101 cancer registrations (Figure 2b). Plots for the other four occupational groups also have cancer of the pleura, thymus and mediastinum as an outlier (Figures 2c–f) based on 147, 26, 163 and 200 cancer registrations, respectively.

Comment
These data indicate a strong association between occupation and the risk of cancer of the pleura, thymus and mediastinum in men. The majority of cancers of the pleura are mesotheliomas, which are known to be associated with exposure to asbestos. While the increased risks seen here among men are across a range of different occupational groups, these occupations all have the potential to be exposed to asbestos. The excess previously reported for electrical workers, using traditional methods applied to a subset of these data, is still evident. The occupational groups at increased risk closely correspond to those noted by Coggon et al in the analysis of death certification data from England and Wales.

Lip cancer

Men
The index of sensitivity for lip cancer is 0.343 (Figure 3a). The plot for this cancer site produces one outlier – agricultural workers nec. The next highest occupational groups on the lip cancer plot correspond to (highest to lowest): labourers and unskilled workers, building etc; bricklayers etc, labourers nec; farmers, farm managers, market gardeners; fishermen. Indices of sensitivity for these five occupational groups are 0.176 for agricultural workers nec, 0.178 for labourers and unskilled workers, building etc, 0.407 for bricklayers etc, labourers nec, 0.109 for farmers, farm managers, market gardeners and 0.332 for fishermen.

Examination of the corresponding occupational plots for the five highest points in Figure 3a show that all have lip cancer as outliers (Figures 3b–f) based on 100, 36, 13, 85 and 9 cancer registrations, respectively.

Comment
The high index of sensitivity for lip cancer indicates a strong association between occupation and this cancer in men. The occupational groups at highest risk tend to be those engaged in outdoor work, which is consistent with exposure to ultraviolet radiation.

Unlike agricultural occupations, building labourers and bricklayers have received less attention with regard to lip cancer, but excesses have recently been reported among these types of workers.

Stomach cancer

Women
The index of sensitivity for cancer of the stomach is 0.237 (Figure 4a). Occupational groups corresponding to the five highest points on the stomach cancer plot are (highest to lowest): spinners, doublers and twisters; ceramic decorators and finishers; brewers, wine makers & related workers; weavers; winders and reelers. Among these five occupational groups, the index of sensitivity is 0.198 for spinners, doublers and twisters, 0.073 for ceramic decorators and finishers, 0 for brewers, wine makers & related workers, 0.262 for weavers and 0.095 for winders and reelers.

For spinners, doublers and twisters; and, ceramic decorators and finishers, the corresponding occupational plots show cancer of the stomach to be an outlier based on 73 and 23 cancer registrations, respectively (Figures 4b and c). No occupational plot is available for brewers, wine makers & related workers because the index of sensitivity for this plot is zero. Occupational plots for weavers and winders and reelers both have stomach cancer as the highest point based on 151 and 62 cancer registrations, respectively (Figures 4d and e).

Comment
There is a lack of strong prior evidence associating stomach cancer with occupation (and related exposures).

However, the high index of sensitivity indicates a strong association between occupation and stomach cancer in women. Some of the occupational groups identified here are likely to be exposed to inorganic dust, which has been previously associated with stomach cancer.

Discussion

We report here the results from the analysis of 1.3 million cancer registrations accumulated across England and Wales over a 20-year period. This is illustrated by focusing on anomalously high values for four cancer sites; anomalously low values can be similarly examined. Summarising the results of analyses of routinely collected data such as these pose several problems, one of which is how best to present them. The novel graphical approach used here allows all measures of association to be presented, rather than just those selected in some way – for example, on the basis of their statistical significance. This empirical Bayesian approach offers several advantages over traditional analytical methods.

Because the emphasis in this work is on hypothesis-generation and because of the very large number of comparisons involved, attachment of meaningful levels of statistical significance or error rates is not feasible. Interpretation of the plots, and especially of the outliers, must be guided in part by subject-matter knowledge. It is, however, possible to calculate guide-rails showing the amount of variation to be expected under certain very idealized conditions and these provide some help in assessing the importance of apparent outliers. We have chosen not to include these here in order to stress the essentially descriptive nature of the method. The guide-rails are, however, included on the plots to be found on the LRF website.

Application of this approach to the analysis of routinely collected data has the potential to generate new hypotheses for possible further investigation. In this respect, Bayesian shrinkage combined with the graphical approach has the benefit of reducing the number of false-positive associations – outliers that occur by chance. Furthermore,
Figure 2: Pleura, thymus and mediastinum cancer plot for men (a) and occupational plots for metal plate workers, riveters (b), plumbers, fitters, heating engineers etc (c), coach, carriage, wagon builders and repairers (d), electricians, electrical and electronic fitters (e) and carpenters and joiners (f)
Figure 3 Lip cancer plot for men (a) and occupational plots for agricultural workers not elsewhere classified (nec) (b), labourers and unskilled workers, building etc (c), bricklayers etc and labourers nec (d), farmers, farm managers and market gardeners (e) and fishermen (f)
Figure 4: Stomach cancer plot for women (a) and occupational plots for spinners, doublers and twisters (b), ceramic decorators and finishers (c), weavers (d) and winders and reelers (e).
using large datasets from routine national sources helps to minimise the chance of overlooking real associations due to low statistical power.

Whilst providing a valuable resource for identifying occupational groups at increased risk of certain cancers, cancer registration data are subject to limitations. For example, a large percentage of cancer registrations among men (21 per cent), and particularly women (52 per cent), were excluded because occupation was missing. Even when present, occupational information is limited. For example, occupation may be incorrectly coded. Indeed several cancer registries have recently ceased collecting occupational data resulting in ascertainment that may vary geographically and over time. Whilst the pattern of missing data may be largely haphazard, the possibility of bias cannot be ruled out. Moreover occupation recorded may reflect recent job changes resulting from pre-diagnostic symptoms. In addition, there are no reliable denominator data on the numbers of people at risk by occupation in the general population. Individual data on certain confounding factors, such as smoking status, alcohol consumption and reproductive history (for women), were also not available. Such limitations need to be borne in mind when examining these types of data since complex methods of analysis with many assumptions will often not be warranted, and the drawing of firm conclusions not justified.

Occupational health data are rarely reported for women: of the 1.3 million cancer registrations available here, 400,000 were in women, with sufficient data available to produce plots for 19 cancer sites and 111 occupational groups. Despite the inability to look at certain cancer sites and occupational groups in women, it is still possible to examine whether patterns observed among men are also evident in women.

The analytical approach used here may be appropriate for the analysis of other routinely collected sets of data, for example, death certifications. Apart from the analysis of routinely collected data, there are also several other potential applications. For example, this method may be of particular value in genetic epidemiology where, in general, large numbers of groups are examined.

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Telephone number: +44(0) 113 244 3517

REFERENCES
12. The website (http://www.lrf.leeds.ac.uk/eB_plots).

Key findings

- Examining associations between occupation and cancer using a novel approach, combining empirical Bayesian risk estimates with a graphical display, has been applied to cancer registration data from England and Wales (1971–1990).
- This approach is illustrated by presenting the results for four cancer sites: nose and nasal sinuses; pleura, thymus and mediastinum; lip; stomach.
- In men, excess risks of cancer of the nose and nasal sinuses in workers exposed to wood-dust, pleura cancer in asbestos-exposed workers and lip cancer in outdoor workers were observed.
- In women, excess risks of stomach cancer among workers exposed to inorganic dusts were evident.
- This method is sensitive for detecting previously established associations.
- Plots for all cancer sites and occupational groups are available on the LRF website at the University of Leeds (http://www.lrf.leeds.ac.uk/eB_plots).


