Is there evidence of clustering in Down syndrome?

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**Background**
Associations between environmental hazards and the occurrence of congenital anomalies may be detectable by seeking evidence of non-random occurrence of cases (clusters). There have been a number of anecdotal reports of occurrences of clusters of Down syndrome (DS).

**Methods**
Data from a national register of cytogenetic diagnoses of Down syndrome births and legal terminations occurring between 1989 and 1995 were used to examine the possibility of clustering. Space-time clustering at Regional Health Authority (RHA) level was examined by comparing the expected monthly number of DS pregnancies given the maternal age distribution, with the observed numbers. Knox's method was used to determine if any clustering of RHA of unexpectedly high prevalence had occurred. Seasonality was also investigated by comparing monthly expected and observed numbers of DS pregnancies. Time clustering was examined by using the scan statistic to determine whether a statistically significant excess of pregnancies in any 3-month period occurred in any individual or adjacent groups of District Health Authority (DHA).

**Results**
The numbers of DS pregnancies were no higher than expected ($P < 0.05$) in the same RHA over consecutive months. There was no evidence of any seasonality of DS pregnancies ($P > 0.3$). Only two individual DHA and three pairs of adjacent DHA had significantly high scan statistics ($P < 0.03$), but as over 400 statistical tests had been completed 12 clusters would be expected to have occurred due to chance alone.

**Conclusion**
There was no evidence of any space-time clustering in DS at DHA level.

**Keywords**
Down syndrome, clusters

**Accepted** 2 October 1997

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An important method of detecting associations between environmental hazards and the occurrence of congenital anomalies is to seek evidence of non-random occurrence as revealed by clusters of cases. The best known clusters over time are of fetal defects which follow the introduction of a new teratogen, such as that which followed the use in pregnancy of thalidomide, leading to a sudden excess of a previously extremely rare malformation.

Even in the case of chromosomal anomalies where the timing of the causal insult has to be pre- or peri-conceptional, there have been a number of anecdotal reports of occurrences clustering over space and/or time. Previous studies have attempted to identify clusters, but due to their small size and lack of ability to adjust for the increase of risk with maternal age, clustering has never been confirmed statistically. The existence of a register of cytogenetically diagnosed Down syndrome (DS) births and legal terminations for the whole of England and Wales, which comprises about 8000 cases occurring between 1989 and 1995, has provided a new opportunity to examine the possibility of space-time clustering at regional, and time clusters at district level.

This report comprises two different approaches to identify any clusters of cytogenetically diagnosed DS at Regional Health Authority (RHA) and District Health Authority (DHA) level in England and Wales, after allowing for the effects of prenatal detection and termination, and maternal age distribution.

**Methods**

The National Down Syndrome Cytogenetic Register (NDSCR) collects reports from all regional cytogenetic laboratories in England and Wales of pre- or postnatally referred cases found to have a karyotype associated with phenotypic DS. The methods
The observed data derived from the register is based on cytogenetically and therefore not ascertained, are inflating the rates of Down syndrome births which would have been aborted spontaneously. The equation used is:

\[
\text{risk} = 0.0005871 + \exp(-16.288 + 0.2916 \cdot \text{maternal age in years})
\]

Calculation of observed numbers of Down syndrome births

The observed data derived from the register is based on cytogenetic diagnoses, and includes terminations of pregnancy as well as still and live births. Since the advent of prenatal screening affected pregnancies which would have been aborted spontaneously and therefore not ascertained, are inflating the rates previously based on live births. As the level of prenatal screening has increased since 1989 and varies between the different RHA in England and Wales, the observed number of DS live births cannot be directly compared temporally or geographically.

In order to adjust for this inflation an estimate has been made of the likely number of live births which would have occurred in the absence of prenatal diagnosis and termination. This uses data on likely fetal losses in affected pregnancies diagnosed early or late in pregnancy, and subtracts them from the observed number of terminations.

Over the years 1989–1995 the NDSCR included 3419 affected pregnancies diagnosed prenatally. 2721 (80%) were terminated, and 3% either miscarried or were stillborn after amniocentesis. In 13% no information on outcome was available. An earlier study estimated the overall risk of early fetal loss of affected pregnancies as about 48% prior to 13 weeks' gestation and 23% over 13 weeks' gestation. Using these rates the additional number of live births that would have occurred if all the prenatally diagnosed pregnancies which were terminated had been left to continue to term was calculated. The same rates were also applied to all the unknown outcomes. These numbers were added to the number of live births between 1989 and 1995 on the NDSCR to give an estimate of the 'natural' observed numbers of live births with DS which would have occurred in the absence of screening.

All DS pregnancies that occurred in women ≥45 years were excluded to be consistent with the ONS data. This affected only 0.9% of pregnancies. Dates of birth were assigned to prenatally diagnosed cases that were terminated, by assuming that the birth would have occurred in the 38\textsuperscript{th} week of gestation (the median gestational age at birth). The data covered all cases karyotyped from 1989 to 1995, but as we were interested in births from 1990 to 1995, those cases that were diagnosed prenatally in 1995, but whose expected date of birth was in 1996 were excluded from the analysis. Of 7994 cases karyotyped 7036 were included in the analysis.

Identification of high prevalence areas

The ratio of the 'natural' observed numbers of live births with DS compared with the expected numbers was calculated for each RHA for each month. The assumption was made that the numbers of DS live births in a month in an RHA follow a Poisson distribution with a mean equal to the expected number of DS live births for that month in that RHA. Any observed values that differed significantly from the expected values were identified as 'high' occurrences. Two levels of statistical significance were used: 90% and 95%.

Test for clustering of high prevalence areas

Evidence of clustering of these 'high' occurrences was then examined using Knox's method of space-time clustering. This involves classifying simultaneously all possible pairs of 'high' occurrences according to their distances apart in space and time. Two 'high' occurrences are assumed to be near in time if they occurred within one month of each other and near in space if they occurred in the same RHA. The frequencies of combined short-distance and short-time intervals are compared with the number which would be expected by chance.

Clustering due to seasonality

The effect of seasonality was investigated by summing both the 'natural' observed numbers of live births with DS and the expected numbers calculated above across all RHA for each
month. A Poisson distribution was then fitted to the observed national number of births for each month, with a mean equal to the expected number of DS live births nationally for that month.

**Time clustering at District Health Authority level**

For each DHA we estimated monthly numbers of DS in the absence of prenatal diagnosis and termination. The aim was to determine whether, given the total number of births from 1989 to 1995 in that particular DHA, there was a sudden excess of births in any particular 3-month period. No allowance was made for maternal age distribution, but it was assumed that within a DHA this does not vary sharply over time.

**Calculation of the scan statistic in each District Health Authority**

Given the total number of 'natural' observed DS births occurring in a DHA from 1989 to 1995, the expected maximum number of cases occurring in any 3-month period was calculated. This is the scan statistic. In each DHA, the expected value was compared with the observed 3-monthly maximum using Glaz's approximations of the probabilities and moments of the scan statistic. Data from all the DHA were then combined by summing the maximum observed numbers in all DHA and comparing this with the sum of the expected values.

**Calculation of the scan statistic in pair of adjacent District Health Authorities**

This analysis was then repeated for all pairs of adjacent DHA, i.e. the 3-month period in which the maximum 'natural' observed number of DS births that occurred in two adjacent DHA was identified. Given the total number of 'natural' observed DS births occurring in these two DHA from 1989 to 1995, the expected maximum number of cases occurring in any 3-month period was calculated. This was done in case single DHA were too small to detect clusters. As any single DHA will be part of several pairs of adjacent DHA, no statistic was calculated to detect the overall level of clustering.

**Calculation of the scan statistic in sets of adjacent District Health Authorities**

The above analysis was then repeated for all triplets of adjacent DHA. Finally, for each DHA separately, the 3-monthly maximum was calculated for it and all DHA adjacent to it.

**Results**

**Regional Health Authority analysis**

For the 15 regions over the 84 months there were 21 occurrences of significantly higher than expected numbers of babies born with DS at the 95% level of significance and 69 at the 90% level of significance. If there is evidence of clustering, it would be expected that the pairs of these 'high' occurrences would occur close to each other in time (i.e. in consecutive months) or space (i.e. in the same RHA). Therefore all possible pairs of 'high' occurrences were classified according to whether they were close in time or space (Tables 1 and 2). At the 95% level of significance only 16 out of 210 possible pairs (21*20/2) occurred in the same RHA and none were within consecutive months (Table 1). Similarly, at the 90% level of significance only 178 out of 2346 possible pairs occurred in the same RHA and only three were within consecutive months (Table 2). There is no evidence that regions with greater numbers of DS live births than expected are occurring in clusters in time or space.

**Seasonality**

Fitting a Poisson distribution found that there was also no evidence of any seasonality of DS births ($P > 0.5$).

**District Health Authority analysis**

**Individual District Health Authorities**

Overall the sum of the expected 3-monthly maximum for each DHA was greater than the sum of the observed 3-monthly maximum (766 versus 707). If there had been any clusters over any 3-month period the reverse would have been true. Only two DHA out of 180 appeared to have a significantly high scan statistic. In East Yorkshire there were 19 'natural' observed births during 5 years and six births were observed in one 3-month period compared with an expected maximum of two ($P < 0.0052$). In South Manchester there were 47 births during 5 years and eight births were observed in one 3-month period compared with an expected maximum of five ($P < 0.03$).

**Pairs of adjacent District Health Authorities**

Due to the non-independence of all pairs of adjacent DHA the overall sum of the expected scan statistics for each DHA was not calculated. Only three pairs of DHA appeared to have a significantly high scan statistic. They were: (1) Hull and East Yorkshire DHA: out of 46 births during 6 years, eight births were observed in one 3-month period compared with an expected maximum of six ($P < 0.03$). (2) South Parkside and Hampstead DHA: out of 105 births during 6 years, 13 births were observed in one 3-month period compared with an expected maximum of 10 ($P < 0.02$). (3) Halton and Warrington DHA: where out of 25 births during 6 years, seven births were observed in one 3-month period compared with an expected maximum of three ($P < 0.003$).

**Triplets of adjacent District Health Authorities**

Only one DHA triplet appeared to have a significantly high scan statistic. This was in City and Hackney. Tower Hamlets and Enfield where out of 248 births during 6 years, 22 births were observed in one 3-month period compared with an expected maximum of 18 ($P < 0.03$).

**Adjacent District Health Authorities**

No 3-monthly maximums for any index DHA with all its adjacent DHA were statistically significant.

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**Table 1** Pairs of 'high' occurrences at the 95% level of significance

<table>
<thead>
<tr>
<th>In same RHA</th>
<th>Within consecutive months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
</tr>
</tbody>
</table>

Knox's test for clustering: $P = 0.78$.

**Table 2** Pairs of 'high' occurrences at the 90% level of significance

<table>
<thead>
<tr>
<th>In same RHA</th>
<th>Within consecutive months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>No</td>
<td>2087</td>
</tr>
</tbody>
</table>

Knox's test for clustering: $P = 0.92$. 

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Discussion
This study has found no evidence of any space-time clustering or any seasonality effects. There have been very few studies examining the occurrence of clustering of DS births and such studies have used statistical techniques that lack power. The study by Rothman and Fabia found no evidence of clustering in DS births in Massachusetts, but did note a slight seasonal peak in the summer. A much earlier review of studies examining the clustering of DS reached the conclusion that there was no evidence for clustering over space and time and also that there were no seasonal variations. Recent studies using more powerful clustering techniques have concentrated on investigating the association between ionizing radiation and the prevalence of DS, but have reached differing conclusions.

The scan statistic used in this study has been shown to be reasonably sensitive at detecting clusters, but the lack of precise geographical location of the occurrence of births is a limitation to the study. The postcode for the mother's home is now being recorded in the NDSCR and so it will be possible to perform more precise analysis in the future.

Conclusion
There is no evidence that clustering occurs in DS. Five potential clusters have occurred at the 3% level of significance, but considering that over 400 individual statistical tests have been completed about 12 clusters would be expected to have occurred due to chance alone.

Acknowledgements
The National Down Syndrome Register was first funded by the Medical Research Council and then by North Thames and South Thames Research and Development. The data collection was made possible by the collaboration of cytogeneticists, their colleagues, and referring clinicians. We thank Sarah Darby for her advice with the initiation of the work and Roy Ide for his data processing. The collaborating cytogeneticists were: Cambridge: Dr T Andrews; North Thames (East) Region: London: Mr LJ Butler (Director); Teesside: Dr C Clarke; Cardiff: Dr MR Creasy; Queen Charlotte's, London: Mr EDG Davies; Birmingham: Mrs EV Davison; South East Thames Region, London: Dr Z Docherty; Leicester: Dr DP Duckett; Chichester: Dr R Ede; Manchester: Dr S J Fennell; Oxford: Mrs M Fitchett; Manchester: Dr KL Gaunt; St Mary's Hospital, London: Mr Clifford Gray; University College, London: Dr R Hastings; Liverpool: Mr PJ Howard; Salisbury: Professor P Jacobs; Birmingham: Mr P Leedham; Bristol: Dr A McDermott; London: Mr R Meredith; Nottingham: Dr CA Parkin; Norwich: Mr J Pearson; Sheffield: Mr A Polter; Harrow: Miss KS Rodgers; Cumbria: Dr EJ Tawn; St George's Hospital, London: Dr JW Taylor; Leeds: Mr J Williams; Newcastle upon Tyne: Dr J Wolstenholme.

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