Cancers and immune related diseases associated with Down’s syndrome: a record linkage study

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Objective: To determine the risk of cancers and selected immune related diseases in people with Down’s syndrome, relative to risk in other people.

Design: Cohort analysis of a linked dataset of abstracts of hospital and death records; results expressed as the ratios of rates of disease in people with and without Down’s syndrome.


Subjects: Cohort of 1453 people with Down’s syndrome and cohort of 460 000 people with other conditions for comparison.

Main outcomes: As expected, the rate ratio for leukaemia was substantially elevated in people with Down’s syndrome: it was 19-fold higher (95% confidence intervals 10.4 to 31.5) than the rate in the comparison cohort. For other cancers combined, excluding leukaemia, the rate ratio was not significantly elevated (1.2; 0.6 to 2.2). The risk of testicular cancer was increased (12.0; 2.5 to 35.6), although this was based on only three cases in the cohort of subjects with Down’s syndrome. Significantly elevated risks were found for coeliac disease (4.7; 1.3 to 12.2), acquired hypothyroidism (9.4; 3.4, 20.5), other thyroid disorders, and type 1 diabetes mellitus (2.8; 1.0 to 6.1). A decreased risk was found for asthma (0.4; 0.2 to 0.6).

Conclusions: Our data add to the body of information on the risks of co-morbidity in people with Down’s syndrome. The finding on asthma needs to be confirmed or refuted by other studies.
**Statistical methods**

We calculated rates of each cancer or immune related disease based on person-years at risk. We took date of entry into each cohort as date of first admission for Down's syndrome or reference condition, and date of exit for each individual disease as the date of subsequent admission for the disease (if any occurred), death, or 31 March 1999, whichever was the earliest. In comparing the Down's cohort with the reference cohort, we first calculated rates, standardised by age (in 5 year age groups for those aged 5 years and over, and in 1 year age groups for those aged less than 5 years), sex, calendar year of first recorded admission, and district of residence, taking the combined Down's and reference cohorts as the standard population. We then calculated the ratio of the standardised rate of occurrence in the Down's cohort relative to that in the reference cohort. The confidence interval for the rate ratio and χ² statistics for its significance were calculated as described elsewhere.11

In comparing the Down's and reference cohorts, the precision of the rate ratio depends on the number of people with each subsequent disease within each cohort. The size of the Down's cohort is fixed by the number in the database with the condition. In the reference cohort, we included all the people in the database with the comparison conditions in each age group. We did this to maximise the numbers in each stratum in the reference cohort in order to maximise the precision of the rate ratios.

**RESULTS**

There were 1453 individuals in the Down's syndrome cohort and over 460 000 in the comparison cohort. Table 1 shows the age distribution of Down's syndrome patients and the reference cohort, at the time of first recorded admission. The median age at first admission for Down's syndrome was 3 years, mean age 13 years, and the average length of follow up was 10.4 years. Fifty two per cent of the Down's syndrome patients were under 5 years of age, and 67% under 20 years, at the time of first recorded admission.

As expected, leukaemia was much more common in people with Down's syndrome than in the comparison cohort: the ratio in the former was 18.9 times higher than that in the latter (95% confidence intervals (95% CI): 10.4 to 31.5; table 2). A high rate ratio was found for both lymphoid and myeloid leukaemia. Of the 15 people with leukaemia, 11 were admitted aged less than 10 years. The rate ratio for leukaemia in people under 10 years of age with Down's syndrome, compared with people in the reference cohort with leukaemia aged less than 10 years was 31.0 (14.4 to 61.0). These figures exclude people with a first admission record for leukaemia and either Down's syndrome or reference condition (see Methods): there were five such people with leukaemia and Down's syndrome at the first admission. When the cases with simultaneous diagnoses were added to the analysis, the observed number of people with Down's and leukaemia was 20, the expected number was 9.9, and rate ratio for leukaemia in the Down's cohort syndrome cohort compared with the reference cohort was 22.3 (95% CI 13.5 to 35.0).

The risk ratio for all cancers combined, including leukaemia, was 2.7 (1.8 to 3.9). The risk ratio for cancers excluding leukaemia was 1.2 (0.6 to 2.2). Our results showed a significant increase in testicular cancer in people with Down’s syndrome (table 2), albeit based on only three cases. No other cancer showed evidence of an increased risk associated with Down’s syndrome, though numbers were small. The cancers that we analysed, but have not tabulated in this paper as there was only one case or none in the Down's cohort, were those of bladder, bone, brain, breast, cervix, kidney, liver, lung, nasopharynx, oesophagus, ovary, pancreas, prostate, rectum, salivary gland, skin, stomach, thyroid, upper respiratory tract, and uterus, and Hodgkin’s lymphoma, multiple myeloma, and malignant melanoma.

People with Down’s syndrome were significantly more likely than those in the reference cohort to have coeliac disease, acquired hypothyroidism, thyroiditis, thyrotoxicosis, chronic active hepatitis, and diabetes mellitus (table 3). Type 1 and type 2 diabetes mellitus are not distinguished as such in the dataset. In studying diabetes we therefore used an age cut off of less than 30 years, assuming that all (or almost all) such patients had type 1 diabetes. Diabetes mellitus under the age of 30 years was significantly more common in the Down’s than in the reference cohort (rate ratio 2.8; 1.0 to 6.1). These figures excluded five people with a first admission record for both Down’s syndrome and diabetes mellitus under age 30. When the simultaneous cases were included in the analysis, the rate ratio for diabetes under the age of 30 was 3.3 (95% CI 1.8 to 5.4). Acquired hypothyroidism was significantly more common in people with Down’s syndrome than the reference cohort (rate ratio: 9.4; 3.4 to 20.5). These figures exclude people with a first admission record for both Down’s syndrome and hypothyroidism: there were 15 such people. When the simultaneous cases were included in the analysis, the rate ratio for hypothyroidism in the Down’s syndrome cohort was 29.5 times higher than in the comparison cohort (95% CI 17.6 to 46.6). Asthma was significantly less common in people with Down’s syndrome than in the reference cohort (rate ratio 0.4; 0.2 to 0.6).

The immune related diseases that we studied, but that had one case or none in the Down’s cohort, were Addison’s disease, allergic dermatitis, ankylosing spondylitis, autoimmune haemolytic anaemia, dermato-myositis, Goodpasture’s syndrome, idiopathic thrombocytopenia purpura, multiple sclerosis, myasthenia gravis, pemphigus, pernicious anaemia, polyarteritis nodosa, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, Sjogren’s syndrome, and systemic lupus erythematosus.

**DISCUSSION**

A strength of using the linked dataset is that some of the reporting and selection biases that may occur in interview based studies, based on clinical series at specialist centres, cannot occur in a population based, record based dataset.
Studies of associations between diseases are probably also subject to publication bias. In this context, this is the bias that may occur if clinicians (and journal editors) regard a finding of significant association between two diseases more worthy of publication than a finding of no significant association between the same two diseases. This is particularly likely if there is no apparent reason to expect an association between the two diseases. Envisage one case series of disease X in which disease Y is observed, perhaps unexpectedly, to occur more commonly than in the general population; and another case series in which it does not occur more commonly. Typically, the first is more likely to be reported than the second: the finding in the second series would probably be considered unremarkable. A strength of our study is that we were able to study a range of cancers and immune related diseases within the same population of people with Down’s syndrome. We report findings, both those that are positive and those that are not, from a single population across a range of conditions. Our results add strength to most of the findings summarised in Roizen and Patterson’s literature review: they and we report associations of relative risk of occurrence, comparing disease in those with Down’s syndrome and the reference cohort, should be reliable with the following assumptions. We make the assumption that the extent of under-enumeration, as a result of using hospital data only, is similar in the Down’s syndrome and reference cohort. We standardised the comparison between the Down’s and reference cohorts for district and year of admission. We did this to try to make the two cohorts as comparable as possible in respect of clinical thresholds for admission (for example, for asthma or diabetes) which may vary by place and time. There is little or no information on other potential confounding factors or on clinical or cytogenetic characteristics of the patients. Finally, despite the size of the cohort, and the time span covered by it, the numbers of people with many of the diseases studied are still fairly small. This is particularly so for cancers that occur in the middle aged and elderly rather than the young.

Cancer

The level of risk of leukaemia found by us is very similar to the 20-fold increase quoted in standard texts. It is noteworthy that the data in an administrative NHS statistics database can indeed be used to quantify such a risk reliably. Other studies of linked datasets have also identified the high risk of asthma, rheumatoid arthritis, and diabetes.

### Table 2 Occurrence of cancer in people with Down’s syndrome

<table>
<thead>
<tr>
<th>Cancer (ICD code)*</th>
<th>Number in reference cohort with each cancer</th>
<th>Observed number in Down’s cohort</th>
<th>Expected number in Down’s cohort</th>
<th>Adjusted rate ratio‡</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers (140–208)</td>
<td>9833</td>
<td>26</td>
<td>9.7</td>
<td>2.7</td>
<td>1.8 to 3.9</td>
</tr>
<tr>
<td>Leukaemia (204–208)</td>
<td>348</td>
<td>15</td>
<td>0.8</td>
<td>18.9</td>
<td>10.4 to 31.5</td>
</tr>
<tr>
<td>Lymphoid leukaemia (204)</td>
<td>181</td>
<td>11</td>
<td>0.5</td>
<td>22.2</td>
<td>10.9 to 40.6</td>
</tr>
<tr>
<td>Myeloid leukaemia (205)</td>
<td>173</td>
<td>5</td>
<td>0.3</td>
<td>17.2</td>
<td>5.5 to 40.9</td>
</tr>
<tr>
<td>Lymphoma (200–202)</td>
<td>520</td>
<td>2</td>
<td>0.8</td>
<td>2.7</td>
<td>0.3 to 9.6</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (200, 202)</td>
<td>407</td>
<td>2</td>
<td>0.5</td>
<td>3.8</td>
<td>0.5 to 13.6</td>
</tr>
<tr>
<td>Colon (153)</td>
<td>884</td>
<td>2</td>
<td>0.7</td>
<td>3.1</td>
<td>0.4 to 11.1</td>
</tr>
<tr>
<td>Testis (186)</td>
<td>151</td>
<td>3</td>
<td>0.3</td>
<td>12.0</td>
<td>2.5 to 35.6</td>
</tr>
</tbody>
</table>

*ICD 9 codes for each cancer (equivalent codes were used for cases coded in ICD Revisions 7, 8, and 10).
‡Adjusted for sex, age in 5 year bands (and in 1 year bands in those aged under 5 years), district of residence, and time period in single calendar years.

The table gives the number of people with cancer in the reference cohort, the observed and expected number of people with cancer in the Down’s syndrome cohort, the ratio of rates in the Down’s syndrome cohort to that in the reference cohort, and 95% CI for the rate ratio.

### Table 3 Occurrence of autoimmune diseases in people with Down’s syndrome

<table>
<thead>
<tr>
<th>Immune related disease (ICD code)*</th>
<th>Number in reference cohort with each immune related disease</th>
<th>Observed number in Down’s cohort</th>
<th>Expected number in Down’s cohort</th>
<th>Adjusted rate ratio‡</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma (493)</td>
<td>884</td>
<td>20</td>
<td>51.7</td>
<td>0.4</td>
<td>0.2 to 0.6</td>
</tr>
<tr>
<td>Crohn’s disease (555)</td>
<td>662</td>
<td>3</td>
<td>1.2</td>
<td>2.6</td>
<td>0.5 to 7.7</td>
</tr>
<tr>
<td>Ulcerative colitis (556)</td>
<td>652</td>
<td>3</td>
<td>0.9</td>
<td>3.3</td>
<td>0.7 to 9.6</td>
</tr>
<tr>
<td>Coeliac disease (579.0)</td>
<td>181</td>
<td>4</td>
<td>0.9</td>
<td>4.7</td>
<td>1.3 to 12.2</td>
</tr>
<tr>
<td>Diabetes mellitus under age 30 (250)</td>
<td>582</td>
<td>6</td>
<td>2.2</td>
<td>2.8</td>
<td>1.0 to 6.1</td>
</tr>
<tr>
<td>Thyrotoxicosis (242)</td>
<td>387</td>
<td>5</td>
<td>0.7</td>
<td>17.4</td>
<td>2.4 to 17.4</td>
</tr>
<tr>
<td>Acquired hypothyroidism (244)</td>
<td>413</td>
<td>6</td>
<td>0.6</td>
<td>9.4</td>
<td>3.4 to 20.5</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis (245)</td>
<td>40</td>
<td>2</td>
<td>0.04</td>
<td>44.1</td>
<td>5.2 to 170</td>
</tr>
<tr>
<td>Chronic active hepatitis (571.4)</td>
<td>42</td>
<td>2</td>
<td>0.05</td>
<td>47.0</td>
<td>5.5 to 181</td>
</tr>
<tr>
<td>Psoriasis (696.0, 696.1, 696.8, 696.9)</td>
<td>367</td>
<td>3</td>
<td>0.7</td>
<td>4.2</td>
<td>0.9 to 12.2</td>
</tr>
</tbody>
</table>

*ICD 9 and equivalent codes in Revisions 7, 8, and 10.
‡Adjusted for sex, age in 5 year bands (and in 1 year bands in those aged under 5 years), district of residence, and time period in single calendar years.

The table gives the number of people with each immune related disease in the reference cohort, the observed and expected number of people with each disease in the Down’s syndrome cohort, the ratio of rates in the Down’s syndrome cohort to that in the reference cohort, and 95% CI for the rate ratio. ICD, International Classification of Diseases.
risk of leukaemia. These findings support the validity of the study methods in assessing levels of risk for the other diseases studied.

It is sometimes considered that the risk of leukaemia is particularly high for acute myeloid leukaemia, but we found similarly high risks for both myeloid and lymphoid forms. Our data add some evidence to the suggestion that there is an increase in the risk of testicular cancer. The elevated risk of leukaemia can be considered in the broader context of how much the overall risk of cancer is increased: in our data, the overall risk is 2.9 times that of the general population in the age range and follow up periods studied.

Immune related diseases

As mentioned above, we corroborate the elevation of risk of coeliac disease and thyroid disease. The threefold increase in diabetes mellitus under the age of 30 years in people with Down’s syndrome, is similar to that reported by others. Congenital hypothyroidism, as well as acquired hypothyroidism, is more common in Down’s syndrome patients than the general population. We excluded the few people coded with congenital hypothyroidism from the analysis. We accept, however, that there may have been some diagnostic cross classification in our dataset which might have accounted for some of the strength of the observed association between hypothyroidism and Down’s syndrome.

We found a significant deficit of asthma in people with Down’s syndrome. Various explanations are possible and we cannot distinguish between them. It is possible that, although significant, this is in fact a chance finding or that it is attributable to uncontrolled factors in study design. If the deficit is real, one possibility is that people with Down’s syndrome may be less predisposed than others to asthma. Another is that they may come into contact with asthma inducing allergens or pollutants less than other people. A third is that, if the hygiene hypothesis is correct, they may have more infections than others early in life, with boosting of their immune systems and reduced antibody production against self antigens. Finally, people with Down’s syndrome may have the same risk of asthma as other people but a lower rate of hospital admission. However, we think that, if anything, people with Down’s syndrome would be more likely, rather than less likely, than those without to be admitted to hospital for a given level of symptoms. The findings on asthma need to be confirmed or refuted by other studies.

ACKNOWLEDGEMENTS

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REFERENCES