Day care in infancy and risk of childhood acute lymphoblastic leukaemia

Citation for published version:

Digital Object Identifier (DOI):
10.1136/bmj.38428.521042.8F

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
BMJ

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study

C Gilham, J Peto, J Simpson, E Roman, T O B Eden, M F Greaves, F E Alexander, for the UKCCS Investigators

Abstract

Objective To test the hypothesis that reduced exposure to common infections in the first year of life increases the risk of developing acute lymphoblastic leukaemia.

Design and setting The United Kingdom childhood cancer study (UKCCS) is a large population based case-control study of childhood cancer across 10 regions of the UK.

Participants 6305 children (aged 2-14 years) without cancer; 3140 children with cancer (diagnosed 1991-6), of whom 1286 had acute lymphoblastic leukaemia (ALL).

Main outcome measure Day care and social activity during the first year of life were used as proxies for potential exposure to infection in infancy.

Results Increasing levels of social activity were associated with consistent reductions in risk of ALL; a dose-response trend was seen. When children whose mothers reported no regular activity outside the family were used as the reference group, odds ratios for increasing levels of activity were 0.73 (95% confidence interval 0.62 to 0.87) for any social activity, 0.62 (0.51 to 0.75) for regular day care outside the home, and 0.48 (0.37 to 0.62) for formal day care (attendance at facility with at least four children at least twice a week) (P value for trend <0.001). Although not as striking, results for non-ALL malignancies showed a similar pattern (P value for trend <0.001). When children with non-ALL malignancies were taken as the reference group, a significant protective effect for ALL was seen only for formal day care (odds ratio = 0.69, 0.51 to 0.93; P = 0.02). Similar results were obtained for B cell precursor common ALL and other subgroups, as well as for cases diagnosed above and below age 5 years.

Conclusion These results support the hypothesis that reduced exposure to infection in the first few months of life increases the risk of developing acute lymphoblastic leukaemia.

Introduction

The idea that infections are involved in the aetiology of childhood leukaemia dates back to the 1940s. Two key papers appeared in 1988. Greaves proposed that a deficit of exposure to infectious agents in infancy and subsequent “delayed” infectious challenge were causal factors in the development of B cell precursor common acute lymphoblastic leukaemia, which is responsible for the childhood peak of acute lymphoblastic leukaemia (ALL) at age 2-5 years. Kinlen proposed that population influx into isolated communities (population mixing) could generate excesses of childhood leukaemia by causing mini-epidemics of one or more infections to which leukaemia may be a rare response. The UK childhood cancer study (UKCCS), a large population based case-control study, was designed to test several hypotheses, one of which was that leukaemias and lymphomas may be caused by abnormal responses to common infectious agents. Here, we focus on Greaves’s hypothesis that immunological isolation in infancy increases the risk of B cell precursor common ALL (cALL). No single protective agent or transmission pathway has been identified, so proxy variables for exposure to infection must be used. The literature on infectious illnesses occurring in day care settings suggests that social interactions with other children outside the home may be important. Several studies of childhood leukaemia have used such proxies.

Precise molecular subclassification of cALL is potentially important for these analyses. The two largest subgroups are those with hyperdiploidy (hyperdiploid ALL) and with fusion of the TEL and AML1 genes (TEL-AML1 ALL). Most (possibly all) children with these lesions have affected clones present at the time of birth, so initiation usually occurs in utero. However, the modest level of concordance in identical twins with one affected by cALL (approximately 10%), together with the much greater frequency of these lesions in cord blood than the lifetime risk of the cALL subtype, indicates that at least one postnatal event also occurs in the development of cALL. Greaves’s original hypothesis relates to the promotional factors that affect the frequency of this second event.

The UKCCS included all childhood cancers. In this paper we compare social activity of cases and controls during the first year of life for ALL and subgroups of ALL. We also compare ALL with non-ALL malignancies. We excluded children aged under 2 years at the time of diagnosis (cases) or pseudodiagnosis (controls) in order to avoid both dilution of results through overlap for younger children of the two time windows in which associations in opposite directions are predicted and the potential for early symptoms of leukaemia to influence attendance at day care.

Methods

Participants

This case-control study was conducted in 10 regions across the United Kingdom between 1991 and 1996. The UKCCS study design, data collection and consenting procedures, ethical approvals, and participation rates are described in detail elsewhere. Briefly, children diagnosed as having a confirmed malignancy were ascertained through paediatric oncology units, and two controls matched to each case for sex, month and year of birth, and region of residence at diagnosis were randomly selected from population registers. Age at diagnosis of the case was designated as the age at “pseudodiagnosis” of the matched control. A structured questionnaire was used to interview participants.
Continuous variable. Across the combined hierarchical variable by treating it as a con-


trolled trials. We used a dichotomous variable of any social activity (table 2) and extended this to

to the reduced odds ratio for formal day care (odds ratio = 0.69, 95% confidence interval 0.51 to 0.93).


to cases aged 2-5 years gave similar results, although statistical significance was reduced.


discussed. The proportion of children who had an older sibling living in the home at the time of birth was similar for ALL (56%), cALL (54%), non-ALL malignancies (57%), and controls (57%), and we observed no significant trends with numbers of older siblings in any diagnostic group (table 3). As any relation between social activity and ALL might be expected to be more marked among children born into households without other children, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.


development, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.
### Table 2: Levels of social activity in the first year of life for acute lymphoblastic leukaemia (ALL), ALL subgroups, and non-ALL malignancies

<table>
<thead>
<tr>
<th>Activity level</th>
<th>Controls (No (%))</th>
<th>Odds ratio* (95% CI)</th>
<th>Odds ratio* (95% CI)</th>
<th>Odds ratio* (95% CI)</th>
<th>Odds ratio* (95% CI)</th>
<th>Odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>ALL</td>
<td>cALL</td>
<td>TEL-AML1</td>
<td>Hyperdiploid ALL</td>
<td>Non-ALL malignancies</td>
</tr>
<tr>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Aged over 2 years</td>
<td>6338</td>
<td>1272</td>
<td>791</td>
<td>138</td>
<td>417</td>
<td>1825</td>
</tr>
<tr>
<td>Any social activity</td>
<td>5343 (85.7)</td>
<td>1020 (80.2)</td>
<td>640 (80.9)</td>
<td>110 (79.7)</td>
<td>335 (80.3)</td>
<td>1496 (82.0)</td>
</tr>
<tr>
<td></td>
<td>0.66</td>
<td>0.56 to 0.77</td>
<td>0.55 to 0.82</td>
<td>0.38 to 0.90</td>
<td>0.50 to 0.83</td>
<td>0.68 to 0.90</td>
</tr>
<tr>
<td>No social activity</td>
<td>895 (14.4)</td>
<td>252 (19.8)</td>
<td>151 (19.1)</td>
<td>28 (20.3)</td>
<td>82 (19.7)</td>
<td>329 (18.0)</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.56 to 1.00</td>
<td>0.61 to 0.91</td>
<td>0.76</td>
<td>0.83 &amp; 0.91</td>
<td>1.00</td>
</tr>
<tr>
<td>Social activity, but no day care</td>
<td>2940 (45.5)</td>
<td>587 (46.1)</td>
<td>358 (45.3)</td>
<td>60 (43.5)</td>
<td>199 (47.7)</td>
<td>580 (48.2)</td>
</tr>
<tr>
<td></td>
<td>0.73</td>
<td>0.62 to 0.87</td>
<td>0.60 to 0.91</td>
<td>0.87</td>
<td>0.71 to 0.96</td>
<td>0.74 to 1.11</td>
</tr>
<tr>
<td>Informal day care only</td>
<td>1768 (28.3)</td>
<td>325 (25.6)</td>
<td>218 (27.5)</td>
<td>38 (25.6)</td>
<td>105 (25.2)</td>
<td>435 (23.8)</td>
</tr>
<tr>
<td></td>
<td>0.62</td>
<td>0.51 to 0.75</td>
<td>0.53 to 0.84</td>
<td>0.60</td>
<td>0.42 to 0.78</td>
<td>0.61 to 0.85</td>
</tr>
<tr>
<td>Formal day care</td>
<td>735 (11.8)</td>
<td>108 (8.5)</td>
<td>64 (8.1)</td>
<td>12 (8.7)</td>
<td>31 (7.4)</td>
<td>181 (9.9)</td>
</tr>
<tr>
<td></td>
<td>0.48</td>
<td>0.37 to 0.62</td>
<td>0.32 to 0.80</td>
<td>0.47</td>
<td>0.24 to 0.94</td>
<td>0.59 to 0.90</td>
</tr>
</tbody>
</table>

P for trend: <0.001 <0.001 0.4 <0.001 0.01 0.2

### Table 3: Number of older children in household ("siblings") at time of index birth for acute lymphoblastic leukaemia (ALL), ALL subgroups, and non-ALL malignancies

<table>
<thead>
<tr>
<th>No of siblings</th>
<th>Controls (No (%))</th>
<th>Odds ratio* (95% CI)</th>
<th>Odds ratio* (95% CI)</th>
<th>Odds ratio* (95% CI)</th>
<th>Odds ratio* (95% CI)</th>
<th>Odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Cases aged 2-5 years</td>
<td>615 720</td>
<td>789</td>
<td>118</td>
<td>416</td>
<td>1830</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2680 (43.4)</td>
<td>565 (44.5)</td>
<td>365 (46.3)</td>
<td>62 (44.9)</td>
<td>189 (45.4)</td>
<td>799 (43.7)</td>
</tr>
<tr>
<td>1</td>
<td>2216 (35.8)</td>
<td>443 (34.8)</td>
<td>266 (33.7)</td>
<td>49 (35.5)</td>
<td>149 (35.8)</td>
<td>667 (36.5)</td>
</tr>
<tr>
<td></td>
<td>0.96</td>
<td>0.84 to 1.11</td>
<td>0.74 to 1.05</td>
<td>0.89</td>
<td>0.77 to 1.22</td>
<td>0.91 to 1.16</td>
</tr>
<tr>
<td>2</td>
<td>899 (14.5)</td>
<td>189 (14.3)</td>
<td>115 (14.6)</td>
<td>20 (14.5)</td>
<td>57 (13.7)</td>
<td>291 (15.4)</td>
</tr>
<tr>
<td></td>
<td>0.99</td>
<td>0.82 to 1.21</td>
<td>0.74 to 1.20</td>
<td>0.86</td>
<td>0.68 to 1.30</td>
<td>0.94 to 1.31</td>
</tr>
<tr>
<td>≥3</td>
<td>382 (6.3)</td>
<td>80 (6.3)</td>
<td>43 (5.4)</td>
<td>7 (5.1)</td>
<td>21 (5.0)</td>
<td>83 (4.5)</td>
</tr>
<tr>
<td></td>
<td>0.99</td>
<td>0.74 to 1.30</td>
<td>0.54 to 1.12</td>
<td>0.70</td>
<td>0.46 to 1.25</td>
<td>0.58 to 1.00</td>
</tr>
</tbody>
</table>

P for trend: <0.001 0.4 <0.001 0.4 0.7

### Notes:
- cALL=B cell precursor common ALL; TEL-AML1=ALL with fusion of the TEL and AML1 genes.
- *Odds ratio for cases compared with all controls, adjusted for age at diagnosis/pseudo diagnosis, sex, region, maternal age, mother working at time of birth, and deprivation.
- †Excluding missing values.
- ‡Trend test across categories none through to formal day care.
social activity outside the home, may be affected by the pre-clinical effects of incipient disease.

Some systematic differences between cases and controls existed in this study. Analysis of census data revealed that controls who agreed to take part were living in more affluent areas, and some control parents were interviewed when their children were older than their matched cases. The average interval from diagnosis or pseudodiagnosis to interview was six months for cases and 14 months for controls. Children destined to develop a malignancy may also have more periods of illness in early life, leading to lower attendance at day care. Health status in early life will be the subject of a future paper from the UKCCS, but preliminary analyses (Roman, personal communication) indicate that, compared with controls, more frequent periods of illness are seen in children who develop solid tumours but not in children who develop ALL. If this is an effect rather than a cause of the development of cancer, reverse causation might contribute to the protective effect of day care for non-ALL malignancies but not for ALL.

Interpretation of our findings depends crucially on whether the protective effect of social activity for non-ALL malignancies is real or due to bias, as the protective effect for ALL is both smaller and less significant when non-ALL malignancies are used as the reference group. Despite this uncertainty, we believe that the difference between ALL and non-ALL malignancies may well be real. A prior hypothesis was that the risk of leukaemia would be increased by a lack of social activity, and the effect of day care is particularly marked during the first three periods of illness are seen in children who develop solid tumours but not in children who develop ALL. If this is an effect rather than a cause of the development of cancer, reverse causation might contribute to the protective effect of day care for non-ALL malignancies but not for ALL.

Comparison with other studies
Other case-control studies of childhood leukaemia have looked at social activity and day care. Diversity exists for both ages at diagnosis and ages of day care attendance, as well as the definition of day care used. The only study that quantified exposure to other children reported a significant protective effect. Most other studies suggest a reduction in risk of around 30%-40% for day care attendance or social activity, though lack of statistical power often leads to imprecise risk estimates.

The difficulty of establishing small effects reliably is illustrated by the lack of consensus among studies investigating an association between childhood ALL and birth order or mother’s parity. Although reduced risks in children with several older siblings have been seen in some studies, most studies, like ours, have found no such effects. As well as sibling position, other studies have considered different proxies for exposure to the spectrum of infectious agents. The only European study with comparable numbers of ALL cases to our series inferred social contact from parents’ employment status and found no association. Several investigators have reported reduced risks of ALL or call in children with many infections, or with specific infections in infancy, such as frequent otitis media or roseola, but others have not found such associations.

In support of an infectious aetiology for childhood ALL, several ecological studies have reported that marked influxes of population into isolated areas are followed by transiently increased rates of childhood leukaemia. Furthermore, evidence of inherited susceptibility to ALL associated with HLA and alleles of other immune system genes is consistent with the suggestion that infection may be associated with ALL. The UKCCS has recently reported statistically significant associations between call and specific HLA-DPB1 variants. This is further supported by evidence that immunisation of infants may protect against ALL.

Possible mechanisms
The hypotheses proposed by Greaves and Kinlen differ with respect to their speculation as to the underlying mechanisms and the roles of specific infections, viral or otherwise, as well as the postulated timing of key events. Kinlen has proposed that the mini-epidemics that generate excesses of childhood leukaemia are due to one or a small number of specific though unknown leukaemia causing agents, probably viruses. For Greaves, however, the consequences of immunological isolation in the first year of life were predicted to be, firstly, inadequate priming of the naive immune system and, secondly, continuing susceptibility to infections responsible for a later challenge, which, in the absence of adequate priming may precipitate a highly dysregulated immune response. This, in turn, was predicted to promote the development of call indirectly by proliferative stress to the bone marrow, which facilitated further mutations. The effect of the later infectious challenge is thus immunological.

Table 4 Effect of age at first day care during the first year of life for acute lymphoblastic leukaemia (ALL) and non-ALL malignancies

<table>
<thead>
<tr>
<th>Age first attended (months)</th>
<th>Controls (n=6285)</th>
<th>ALL (n=1274)</th>
<th>Non-ALL (n=1830)</th>
<th>Odds ratio* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1210 (66.1)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-ALL ALl</td>
<td>5534 (86.3)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>All v non-ALL</td>
<td>1170 (91.5)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Controls</td>
<td>1652 (90.1)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-ALL ALl</td>
<td>1850 (69.5)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>All v non-ALL</td>
<td>1210 (66.1)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Odds ratio* (95%CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>1997 (17.5)</td>
<td>0.71</td>
<td>0.88</td>
<td>0.62 to 1.03</td>
</tr>
<tr>
<td></td>
<td>185 (14.5)</td>
<td>0.82</td>
<td>1.02</td>
<td>0.68 to 1.52</td>
</tr>
<tr>
<td></td>
<td>135 (17.5)</td>
<td>0.82</td>
<td>1.08</td>
<td>0.68 to 1.64</td>
</tr>
<tr>
<td>3-5</td>
<td>548 (8.8)</td>
<td>0.71</td>
<td>0.83</td>
<td>0.60 to 1.02</td>
</tr>
<tr>
<td></td>
<td>130 (7.7)</td>
<td>0.91</td>
<td>1.02</td>
<td>0.68 to 1.52</td>
</tr>
<tr>
<td></td>
<td>204 (3.3)</td>
<td>0.71</td>
<td>0.83</td>
<td>0.60 to 1.02</td>
</tr>
<tr>
<td>6-11</td>
<td>875 (14.0)</td>
<td>0.76</td>
<td>0.76</td>
<td>0.50 to 1.06</td>
</tr>
<tr>
<td></td>
<td>156 (12.2)</td>
<td>1.00</td>
<td>1.00</td>
<td>0.62 to 1.06</td>
</tr>
<tr>
<td></td>
<td>201 (11.0)</td>
<td>0.76</td>
<td>0.76</td>
<td>0.50 to 1.06</td>
</tr>
</tbody>
</table>

*Odds ratio for cases compared with all controls or with non-ALL malignancies where stated, adjusted for age at diagnosis or pseudodiagnosis, sex, region, maternal age, mother working at time of birth, and deprivation.
†Excluding missing values.
what is already known on this topic

Childhood leukemia is a biologically diverse disease and is likely to arise by several aetiological pathways

---

The common, B cell precursor, form of acute lymphoblastic leukemia accounts for the incidence peak between 2 and 5 years of age, and immunological isolation may be a causal factor.

---

Children attending day care have an increased risk of contracting a variety of common infections.

What this study adds

Children attending day care centres on a regular basis in the first few months of life are less likely to develop acute lymphoblastic leukemia than are children who do not.

Conclusion

Our results provide further support that social activity with other infants and children during the first few months of life protects against subsequent risk of ALL. The effect is less pronounced among cases diagnosed at age 2-5 years than at older ages and is not confined to cALL. The most plausible interpretation is that this protection comes from exposure to common infections.

Similar associations have been reported for type 1 diabetes and allergies in children.

Whether early exposure to one or more specific infections, or to a spectrum of non-specific agents, protects against each of these disparate diseases remains to be clarified. Nevertheless, we conclude that some degree of early exposure to infection seems to be important for child health.

We thank the members of the UK Childhood Cancer Study Group for their support. We also thank local hospital staff, general practitioners, general practice staff, and UKCCS interviewers and technicians. We especially thank the families of the children included in the study. The UK childhood cancer study is sponsored and administered by the Leukaemia Research Fund. This study was conducted by 12 teams of investigators (10 clinical and epidemiological and two biological) based in university departments, research institutes, and the NHS in Scotland. The work was coordinated by a management committee. It was supported by the UK Children's Cancer Study Group of paediatric oncologists and by the National Radiological Protection Board.

Contributors: FEA, TOBE, MGF, JP, ER, and JS were involved in the design and conduct of the study throughout. FEA, CG, JP, and JS were responsible for management and analysis of the data. All authors contributed to writing the manuscript. ER is the guarantor.

Funding: Financial support has been provided by the Cancer Research Campaign and Imperial Cancer Research Fund (now Cancer Research UK), the Leukaemia Research Fund, and the Medical Research Council through grants to their units; by the Leukaemia Research Fund, the Department of Health, the Electricity Supply Board, the National Grid Company, and Westlakes Research (Trading) through grants for the general expenses of the study; and by the Kay Kendall Leukaemia Fund for the associated laboratories studies. The investigation in Scotland is funded by the Scottish Office, Scottish Power, Scottish Hydro-Electric, and Scottish Nuclear.

Competing interests: None declared.

Ethical approval: See previous publications (references 6 and 23).


Received 15 March 2005

doi 10.1136/bmj.38482.521042.8F
Papers

Health Sciences, University of York, York YO10 5DD
J Simpson research fellow
E Roman professor of epidemiology
Academic Unit of Paediatric Oncology, Christie Hospital and Central Manchester
and Manchester Children's University Hospitals NHS Trusts, Manchester M20 4BX
T O B Eden professor of paediatric oncology

Section of Haematology Oncology, Institute of Cancer Research, London SW3 6JB
M F Greaves professor of cell biology
Public Health Sciences, University of Edinburgh, Edinburgh EH8 9AG
F E Alexander professor of statistics
Correspondence to: T O B Eden tim.eden@manchester.ac.uk