Investigation of potential indicators of co-morbidity on outcomes for children with leukaemia using linked Hospital Episode Statistics data

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Summary

Co-morbid conditions, if sufficiently prevalent and serious, may be an explanation for some of the observed variations in cancer survival, because these conditions may affect both the treatment a child is given and the child's subsequent response.

The aim of the research was to identify and evaluate the influence of co-morbid factors on outcomes for children with leukaemia in England. Specifically, data in the National Registry of Childhood Tumours (NRCT) and Hospital Episode Statistics (HES) were used to identify potential co-morbid factors. Then the influence of possible co-morbid conditions on clinical trial recruitment, survival and hospital admissions of children with leukaemia was evaluated.

A series of high-quality data linkages have been made between the NRCT and HES, birth registrations, Children's Cancer and Leukaemia Group (CCLG) Principal Treatment Centre (PTC) forms and MRC Clinical Trials data. During the entire study, only 13 children (<1%) were registered only via a death certificate, which is testimony to the high quality of data held within the NRCT. For 2000-07, the linkage to HES, birth and death certificates, and CCLG PTC forms was excellent with more than 94% linkage between data sources.

Low birth weight was identified as a potential co-morbid factor from NRCT data, and congenital malformations were identified as potential co-morbid factors in both NRCT and HES data. Other significant co-morbid conditions were difficult to identify with any degree of specificity from HES data. Primary care and population-based data are required for detailed analysis on other co-morbid conditions. Unfortunately, we have been advised by trials co-ordinators that quality of life data for children recruited to the UKALL 2003 trial are not currently suitable for analysis. So, we could not assess the influence of co-morbid conditions on quality of life.

Children with lymphoid leukaemia and a low birth weight tended to have slightly poorer five-year survival than other children, but the difference was not significant. Children with Down syndrome had significantly higher mortality than children without a malformation, and their outcome has not improved since the 1990s, which merits further investigation. Children with other malformations had a similar outcome to children with no malformations. Neither low birth weight nor congenital malformations, including Down syndrome, acted as co-morbid factors for children with AML.

Recruitment to clinical trials increased over the study period for children of all ages and approached 90% for some groups. For children with lymphoid leukaemia, no striking variations in recruitment by birth weight or congenital malformations were observed. A slightly smaller proportion of South Asian and other ethnic minority children were recruited to lymphoid leukaemia trials than white children. For children with AML, few children with significant congenital malformations, and in the past fewer low-birth-weight children, were recruited to a trial. No variations in recruitment by ethnicity or socio-economic status were apparent. An exploration of HES data indicate that some children with DS have a severe form of lymphoid leukaemia and die quickly. Children with DS who survive more than a year require and appear to receive more supportive care.

Overall, Down syndrome appears to be a strong co-morbid factor for children with lymphoid leukaemia. It may affect recruitment to both ALL and AML clinical trials, survival and time spent in hospital. Two papers have been prepared for publication based on this project.

Background

Cancer, including leukaemia, remains an important cause of death among children, despite striking improvements in survival and cure resulting from the use of intensive, risk-directed therapy as evaluated in numerous leukaemia clinical trials funded by the Medical Research Council (MRC)[1,2]. Infants and those not recruited to clinical trials are known to have lower survival than other children[3]. Co-morbid conditions in some children with leukaemia may contribute to these findings.

The nature, extent and impact of co-morbidity on childhood leukaemia survival and quality of life are uncertain. Congenital malformations and extremes of birth weight are likely to be the most prevalent and easily identifiable co-morbid factors in children, which influence mortality by complex, ill-defined pathways[4,5]. Separately, these factors also influence the particular risk of cancers occurring in a child[6,7,8]. Congenital malformations are associated with the incidence of leukaemia and other childhood cancers in the UK, and the percentage of children reported with a congenital anomaly who were also diagnosed with cancer has remained remarkably stable at about 4% since 1971[9].

Survival from leukaemia varies for children with Down syndrome in the UK[10], but the effect of other congenital malformations on leukaemia survival is unknown. In Michigan, USA and Ontario, Canada, congenital abnormalities have been found to be associated with increased mortality in children aged up to 9 years. The risk of death was highest in children with congenital malformations who also had endocrine, central nervous system, heart and perinatal conditions[11].

Birth weight has a strong association with mortality during childhood in England and Wales[12,13]. In their second year of life, low-birth-weight babies (<2,500g) born in 1993 had a mortality rate four times that of those whose birth weight was more than 3,000g, and those born during 1993-95 still had at least a twofold mortality risk at ages 5-7 years[13]. A similar association was found in Norway and the USA where the risk of death up to 10 years amongst low-birth-weight babies was higher than those with a normal birth weight[14,15]. The increased risk of death in childhood was attributed to infectious diseases, congenital abnormalities, central nervous system diseases and heart disease. In Taiwan, low birth weight was associated with higher mortality up to five years of age from congenital anomalies, conditions arising in the perinatal period and respiratory diseases[16].

A few studies have investigated associations with childhood cancer mortality. No consistent relationship was seen between birth weight and childhood cancer deaths in Great Britain during 1965-1970[17]. A case-control study in Washington State, USA, found that those with a birth weight of more than 4,000g had an increased risk of dying of cancer[15]. A population-based cohort study in Norway found that low birth weight was associated with a reduced risk of dying of cancer[14].

This study seeks to identify and describe the association between potential co-morbid factors and childhood leukaemia outcomes, while accounting for other known prognostic factors.

Materials

A combination of National Registry of Childhood Tumours (NRCT), Hospital Episode Statistics (HES), birth and death certificates, Children's Cancer and Leukaemia Group (CCLG, formerly the UK Children's Cancer Study Group) Principal Treatment Centre (PTC) information, and Medical Research Council (MRC) clinical trials data have been linked for this study of children (<15 years) who were diagnosed with leukaemia in Great Britain during 1980-2007.

The funded project outline aimed to include those diagnosed during 1980-2006, which has been improved by the inclusion of children diagnosed during 2007. Also, children who were registered in Wales and Scotland have been included in the study since some of them are treated in English hospitals.

The NRCT based at the Childhood Cancer Research Group (CCRG) is a population-based registry of malignant neoplasms and benign brain tumours diagnosed at ages 0-14 years since 1962. CCRG has received information on an estimated 97% of all cases of childhood cancer since 1971. Since 1977, the CCLG have notified CCRG of all children registered and treated by its members, and notifications are now received for 93% of all the children included in the NRCT[1]. CCRG also receive death certificates that have any mention of cancer for individuals aged less than 20 years. Details of all children who survive for at least three years after diagnosis are sent to the NHS Central Registers (NHSCR) in Southport and Edinburgh. These individuals are 'flagged' and the NRCT is then notified if and when NHSCR receives a death certificate relating to these individuals. Less than 2% of cases have been lost to follow-up since 1981.

Hospital Episode Statistics (HES) data have been linked to NRCT data for children with leukaemia treated in hospitals from 1 April 1997 to 31 March 2008 by NHS number, sex, date of birth and postcode. Each time a patient sees a doctor in a hospital, whether as an inpatient or a day case, a record or 'episode' is created and added to the HES database. Each NHS Trust is responsible for sending data on admitted patients to the NHS Wide Clearing Service (NHSWC), which is required for the HES database. NHSWC sends record count and data quality reports to each NHS Trust, so that Trusts can monitor the quality and completeness of their data. The quality of HES data is also assessed annually in Data Quality Indicator reports, which summarise levels of missing or invalid data for 16 variables, including date of admission, date of discharge and details of operations performed. For 2004-05, less than 5% of records had invalid or missing data for these variables, except ethnicity and maternity variables, which are less complete[18]. Outpatient data are only available from 2003 and are not included here because of quality issues, although we had originally hoped to do so. Radiotherapy data has not been collected in HES. Any child who was admitted to hospital with a potential co-morbid factor has had their condition grouped by time period (admitted for the condition 12 months or longer before a diagnosis of leukaemia) and by type of condition classified to ICD-10.

The NRCT holds data on birth weight, as available from birth records in England and Wales, for about 25,000 children born and diagnosed with a malignancy or benign brain tumour from 1980 onwards, which represents the vast majority of children with cancer. Birth weight was categorised as low (<2,500g), normal (2,500-4,000g) or high (>4,000g).

Data on congenital malformations was obtained from CCLG PTC forms and HES. Each type of malformation has been assigned to an index of low, medium, high severity and a separate category for those with Down syndrome, based on EUROCAT guidelines and survival estimates[19,20,21] with assistance from Mr Peter Tennant (a doctoral student investigating congenital malformations at the University of Newcastle) and Dr Patricia Boyd (a clinical geneticist within the National Perinatal Epidemiology Unit at the University of Oxford).

The NRCT includes notifications for all children entered into a leukaemia clinical trial since the 1970s from the Clinical Trial Service Unit (CTSU) in Oxford. High-quality clinical trials data with additional clinical information for children entered into successive leukaemia trials during the study period has been linked to childhood leukaemia registrations. The trials include UKALL VIII, UKALLX, UKALL XI, UKALL97, UKALL99, UKALL2003, AML8, AML10 and AML12.

The third edition of the International Classification of Childhood Cancer[22] was used to classify type of cancer. Ethnicity as recorded on HES was validated between records submitted to HES from different NHS Trusts and between records from CCLG centres. Ethnicity as recorded on CCLG records was used when no other data was available. Deprivation was assigned using the income domain of the Index of Multiple Deprivation 2004 linked to the super output area of a patient's postcode at diagnosis[23].

Overall, a substantial amount of time has been spent linking records from a variety of different sources for each individual child with leukaemia. We have also validated data on congenital malformations and ethnicity from different sources. We are confident that this data linkage is of high quality and is unique. Unfortunately, we have been advised by trials co-ordinators that quality of life data for children recruited to the UKALL 2003 trial are not currently suitable for analysis.

Methods

Relative survival was estimated by birth weight (<2,500g, 2,500-4,000g, >4,000g), severity of congenital anomaly (low, medium, high and Down syndrome), age at diagnosis (0, 1-4, 5-9, 10-14 years), sex, type of leukaemia, ethnicity, socio-economic status, white blood cell count at diagnosis, immunophenotype, treatment at a paediatric oncology PTC and clinical trial participation at the univariate level.

Survival time for each child was calculated as the number of days between diagnosis and the earliest of the dates of emigration, loss to follow-up, death, the end-of-study date (30 April 2011). As is conventional for survival analyses in patient groups that have been passively followed up, patients were assumed to be alive unless death details had been recorded. Patients who were known to have emigrated or who were lost to follow-up were censored without re-entry on the last date they were known to be alive and resident in Great Britain.

Relative survival is the ratio of the survival observed in a group of cancer patients and the survival that would have been expected if they had only been subject to the background mortality observed in the general population. It was estimated using the full likelihood approach for individual records[24], using the *strel* STATA algorithm[25]. Expected survival was estimated by applying the background mortality rates in the general population by age, sex and time period to the patient population. Variance-weighted least squares regression was

used to evaluate trends in survival and to assess differences between children with and without co-morbid conditions. Multivariate analysis[26] was used to model the impact of demographic and co-morbid factors on relative survival. The data were analysed using STATA version 11.1[27].

Results

A total of 12,481 childhood leukaemia patients (<15 years at diagnosis) who were registered in Great Britain during 1980-2007 have been included in the study. Of these patients, 6,190 have been linked to 301,848 HES episodes that were created during 1 April 1997 to 31 March 2008 and linked by NHS number, sex, date of birth and post-code. 612 children were registered in Wales with a leukaemia, of whom 25% had a record within HES linked to their cancer registration.

Details of the linkage of NRCT data with HES, birth certificates, CCLG PTC forms and MRC ALL and AML clinical trials data are given in Table 1. The high quality of data within the NRCT is indicated by the fact that only 13 (0.1%) of children with leukaemia were registered only via a death certificate.

Over the entire study period it was possible to link 50% of children with a registration within the NRCT to a HES episode, which is high given that HES data quality for linkage purposes only became good from 1997 and many of these children were diagnosed up to seventeen years earlier. The linkage between childhood cancer registrations and HES for children diagnosed after 1995 was excellent at over 80% and increased to 88% for children diagnosed during 2000-07.

The proportion of cancer registrations that were linked to birth certificates remained consistently high at about 94% throughout 1980-2007. Birth weight only began to be available in relation to birth registration from about 1980 onwards in England and Wales. Thus, although we have birth records for the majority of children with leukaemia, for many of these birth weight is unavailable.

Overall, 90% of children in the study were registered at CCLG PTCs, which increased from 77% of children diagnosed during 1980-84 to 96% of children diagnosed during 2000-07.

Of all deaths that we have been notified as having occurred in childhood leukaemia patients who were diagnosed during 1980-2007, 99% have been linked to a death certificate.

Table 1: Numbers of children diagnosed with leukaemia during 1980-2007 in Great Britain within the National Registry of Childhood Tumours whose records have been linked to other data

	1980-84		1985-89		1990-94		1995-1999		2000-2007		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	1,952	100	2,053	100	2,293	100	2,393	100	3,790	100	12,481	100
Registered only via a death certificate												
Yes	4	0.20	0	0	1	0	2	0	6	0.16	13	0.10
No	1,948	100	2,053	100	2,292	100	2,391	100	3,784	100	12,468	100
Linked to Hospital Episode Statistics data (for children treated in English hospitals)												
Yes	139	7	207	10	602	26	1,923	80	3,321	88	6,289	50
No	1,813	93	1,846	90	1,691	74	470	20	469	12	6,192	50
Linked to birth certificates												
Yes	1,846	95	1,933	94	2,149	94	2,232	93	3,588	95	11,748	94
No	106	5	120	6	144	6	161	7	202	5	733	6
Linked to Children's Cancer and Leukaemia Group Principal Treatment Centre forms												
Yes	1,498	77	1,747	85	2,071	90	2,253	94	3,621	96	11,190	90
No	454	23	306	15	222	10	140	6	169	4	1,291	10
Linked to MRC Leukaemia clinical trials data												
Yes	851	44	1,464	71	1,666	73	1,736	73	2,125	56	7,842	63
No	1,101	56	589	29	627	27	657	27	1665	44	4,639	37
Linked to death certificates of deaths before 30 April 2011												
Yes	982	99	831	99	735	99	647	99	626	98	3821	99
No	7	1	11	1	6	1	9	1	14	2	47	1
Total dead	989	100	842	100	741	100	656	100	640	100	3,868	100

A low proportion of children (63%) were linked to MRC UKALL VIII, UKALL X, UKALLXI, UKXI (92), UKALL97, UKALL99, UKALL2003, AML8, AML10 and AML12 data. The proportion of children recruited to a trial increased from 44% during 1980-84 to 73% during 1995-99. The observed decrease in recruitment to 55% during 2000-07 is expected since the UKALL99 trial closed in November 2002 and UKALL2003 opened in October 2003. We only have data on patients recruited to the AML12 trial during 1995-97, although recruitment ended in May 2002, because of data access issues. These clinical trial datasets include many of the major clinical trials that were recruiting during the study period, but do not include all the clinical trials and CCLG studies that were operating, such as the AML15 clinical trial, which began recruitment in April 2004.

The demographic and prognostic characteristics of the children who were diagnosed with leukaemia during 1980-2007 in England and Wales are presented in Table 2. The annual number of children registered with leukaemia increased gradually from 378 in 1980 to 429 in 2007, reflecting the increase in population at risk and incidence that has been described elsewhere[28].

Lymphoid leukaemia was the most common type of leukaemia occurring in children (78%). Acute myeloid leukaemia (AML) was the second most commonly occurring leukaemia (15%), and all other types of leukaemia accounted for 7% of all cases. More patients were boys (56%) than girls (44%), and many children (48%) were aged 1-4 years at diagnosis.

Ethnicity was recorded and validated by CCLG PTCs and HES providers for 86% of all childhood leukaemia patients, which increased from 60% for those registered during 1980-84 to 95% during 2000-07. Overall, 76% of all children with leukaemia were white, 6% South Asian, 4% any 'Other' ethnicity and 14% were of unknown ethnicity. Over 98% of children who were white, South Asian and another ethnicity were treated in CCLG specialist paediatric centres, but ethnicity was only recorded for 4% of the children who were not treated at CCLG centres. Children in each ethnic group were similar with respect to age and white blood cell count at diagnosis and type of leukaemia, but a higher proportion of children from ethnic minorities (52% of South Asians and 41% of 'Other' minorities) were classified as deprived compared with white children (19%).

Similar proportions of children were classified to each quintile of the income domain of the Index of Multiple Deprivation. The majority of childhood leukaemia patients had a low white blood cell count (WBC) at diagnosis (53% with less than 20 x 10^9 cells per litre), which is an indicator of less advanced disease. No difference in WBC was observed by sex, but more infants (<1 year at diagnosis) had a high WBC at diagnosis than children of other ages (47% compared with less than 20% of other children had a WBC of 100 or more x 10^9 cell per litre).

The proportion of children with leukaemia who were treated at CCLG PTCs increased from 77% during 1980-84 to 96% during 2000-07. The age distribution, WBC and socio-economic status of CCLG patients was similar to those not treated in their centres, except that fewer patients treated at CCLG centres had an unknown WBC. The proportion of children treated at CCLG centres who were recruited to clinical trials and studies increased from 84% during 1980-84 to 99% during 2000-07.

Table 2: Characteristics of children diagnosed with leukaemia during 1980-2007 in Great Britain

	1980-84		1985-89		1990-94		1995-1999		2000-2007		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Type of leukaemia												
All types	1,952	100	2,053	100	2,293	100	2,393	100	3,790	100	12,481	100
Lymphoid leukaemia	1,574	81	1,590	77	1,811	79	1,857	78	2,961	78	9,793	78
Acute myeloid leukaemia	286	15	326	16	341	15	351	15	574	15	1,878	15
Other	92	5	137	7	141	6	185	8	255	7	810	6
Sex												
Boys	1,089	56	1,123	55	1,313	57	1,317	55	2,111	56	6,953	56
Girls	863	44	930	45	980	43	1,076	45	1,679	44	5,528	44
Age at diagnosis												
<1 year	102	5	125	6	135	6	156	7	245	6	763	6
1-4 years	897	46	1,021	50	1,133	49	1,146	48	1,738	46	5,935	48
5-9 years	515	26	528	26	609	27	645	27	1,015	27	3,312	27
10-14 years	438	22	379	18	416	18	446	19	792	21	2,471	20
Ethnicity												
White	1,082	55	1,554	76	1,813	79	1,973	82	3,085	81	9,507	76
Asian	56	3	111	5	117	5	146	6	276	7	706	6
Other	33	2	58	3	85	4	126	5	247	7	549	4
Unknown	781	40	330	16	278	12	148	6	182	5	1,719	14
Socio-economic status (quintile of deprivation)												
Affluent	448	23	437	21	489	21	463	19	749	20	2,586	21
2	391	20	446	22	478	21	475	20	736	19	2,526	20
3	365	19	352	17	427	19	432	18	714	19	2,290	18
4	358	18	394	19	403	18	466	19	689	18	2,310	19
Deprived	359	18	412	20	493	22	557	23	901	24	2,722	22
Unknown	31	2	12	1	3	<1	0	0	1	0	47	<1
White blood cell count (x 10^9 cells/litre) at diagnosis												
0-19	1,108	57	1,103	54	1,231	54	1,230	51	1,923	51	6,595	53
20-49	263	13	330	16	351	15	379	16	582	15	1,905	15
50-99	169	9	190	9	230	10	233	10	366	10	1,188	10
100-199	134	7	158	8	159	7	188	8	263	7	902	7
>=200	151	8	156	8	170	7	198	8	287	8	962	8
No record	127	7	116	6	152	7	165	7	369	10	929	7
Immunophenotype												
B precursor	1,084	56	1,301	63	1,468	64	1,516	63	2,348	62	7,717	62
T-cell	198	10	171	8	210	9	215	9	271	9	1,065	9
No record	670	34	581	28	615	27	662	28	1,171	204	3,699	30
Treated at a Children's Cancer and Leukaemia Group Principal Treatment Centres												
Yes	1,498	77	1,747	85	2,071	90	2,253	94	3,621	96	11,190	90
No	454	23	306	15	222	10	140	6	169	6	1,291	10
Clinical trial participation												
Yes	1,041	53	1,455	71	1,709	75	1,936	81	2,458	65	8,599	69
No	911	47	598	29	584	25	457	19	1,332	35	3,882	31
Birth weight												
<2500 g	16	<1	62	3	88	4	104	4	224	6	494	4
2500-4000 g	275	14	923	47	1,357	59	1,573	66	2,534	67	6,662	53
>4000g	21	1	119	6	187	8	251	10	427	11	1,005	8
No record	1,640	84	949	49	661	29	465	19	605	16	4,320	35
Severity of congenital malformation												
Down syndrome	68	3	52	3	73	2	89	4	128	3	410	3
Other: low severity	27	1	20	1	35	1	38	2	112	3	232	2
Other: medium severity	40	2	29	1	28	<1	68	3	117	3	282	2
Other: high severity	10	<1	12	<1	11	<1	35	1	81	2	149	1
No malformation	1,807	93	1,940	94	2,146	94	2,163	90	3,352	88	11,408	91

Recruitment to a MRC clinical trial or a CCLG study increased from 53% in 1980-84 to 81% during 1995-99, but decreased to 65% during 2000-07 because of the period of time between the closure and opening of both UKALL and AML trials. Overall, 78% of all children with lymphoid leukaemia were recruited to a clinical trial or study, as were 48% of children with AML.

A small number of children with leukaemia had a low birth weight (<2,500g: 494) or a high birth weight (>4,000g: 1,005) in the study, but the proportion increased gradually with time. A substantial proportion of children had no record of birth weight (35%), but this proportion had decreased from 84% during 1980-84 to 16% during 2000-07. The high numbers of children with no recorded birth weight are expected since birth weight was only available for children who were born from 1980 onwards in England and Wales, and many children diagnosed during the 1980s and 1990s were born before then.

A small proportion of children with leukaemia also had a congenital malformation (8%), of which Down syndrome was the most common occurring in 3% of patients. Other malformations (Down syndrome remaining separate) have been classified to low (2%), medium (2%) and high (1%) severity. This pattern was seen for children with lymphoid leukaemia, but 8% of children with AML had Down syndrome, confirming this well-known association.

Identification of possible co-morbid conditions

Numbers of children with leukaemia and potential co-morbid conditions that were recorded within the NRCT are given in Table 3. The most frequent set of co-morbid conditions that were recorded were congenital anomalies (694 children), which includes Down syndrome. The second most prevalent condition was chronic obstructive pulmonary disease (COPD) (220 children), and each of the remaining conditions affected less than 100 children with leukaemia. The only condition with sufficient numbers to detect robust differences was the congenital anomalies. Recording of conditions other than congenital anomalies and genetic conditions is also believed to be less complete.

Table 3: Numbers of children with leukaemia who also have a co-morbid condition as recorded within the National Registry of Childhood Tumours during 1980-2007, Great Britain

Disease	**Number**	**%**
Congenital anomalies	694	6
Chronic Obstructive Pulmonary Disease	220	2
Skin and tissue conditions	87	1
Blood diseases	78	1
CNS diseases	54	<1%

The exploration of potential co-morbid conditions recorded in HES is based on the assumptions that co-morbid conditions antedate the onset of leukaemia, and either may predispose to the leukaemia or make treatment more difficult. In some cases a co-morbid condition may result in a decision not to treat, which is now rare. The exploration of potential co-morbid conditions is complicated by not having population rates for these conditions, and often a lack of specificity of the conditions amongst the HES diagnostic codes. The caveat with this approach is that any potential co-morbid condition is likely to be severe given that it

is noted at the time of admission to hospital. Patients with less severe conditions would be missed, and, therefore, the data are incomplete.

Diagnosis codes grouped to ICD-10 classification within HES data were considered by Dr Jane Passmore at intervals of 1 month up to a year prior to diagnosis and by year up to 10 years prior to a diagnosis of leukaemia (Tables 4 and 5). Only categories involving more than 150 children were considered in detail. Infections mostly occurred in the year prior to diagnosis and were mostly attributable to 'other bacterial and viral diseases'. In the two to 10 years prior to diagnosis, children admitted to hospital for infections were rare. If additional information were available, it would be of interest to see what proportion of children with leukaemia also have the HIV, Epstein-Barr and hepatitis viruses, and their impact on outcome.

The categories 'Neoplasms', 'Blood/Blood organs', 'Circulatory system', 'Symptoms and signs' and 'Influential factors', which mostly occur within a month of leukaemia diagnosis, are likely to relate to the leukaemia. A small number of diagnoses may relate to anaemia and clotting disorders, which are usually temporary and associated with leukaemia. Only 110 cases had a diagnosis of 'Endocrine/Metabolic disorders', which includes diabetes and thyroid disorders, but these conditions are mostly treated in primary rather than secondary care. Similarly, there were few cases of nervous system disease, which includes epilepsy. To further evaluate the influence of diabetes and epilepsy, population rates of these conditions would be required and more complete data on children with these conditions using data from primary care.

Respiratory diseases were the most common category of potential co-morbid conditions, mostly accounted for by 'Acute respiratory infections', 'Chronic lower respiratory diseases' and 'Influenza and pneumonia'. It would be of interest to further investigate the occurrence and influence of asthma and cystic fibrosis on leukaemia outcome using primary care data.

Admissions for digestive system disorders were fairly frequent, and mostly accounted for by 'Other diseases of intestines' and 'Non-infective enteritis and colitis'. Similarly, musculoskeletal diagnoses were fairly frequent and mostly accounted for non-specific joint and soft-tissue conditions in the year prior to diagnosis. Perinatal conditions related to length of gestation, foetal growth disorders and respiratory and cardiac disorders occurring in the perinatal period. Most admissions amongst the 'Injuries and poisoning' category, were for injuries to the head and limbs. Congenital malformations, as recorded in HES, were evaluated further and validated using data from the NRCT.

In summary, HES data do not provide the required detail on diagnoses for high quality evaluation, although interesting lines of investigation have arisen. Also, possible co-morbid conditions, such as asthma, diabetes and epilepsy, are incompletely recorded within HES. For a thorough, robust and valid assessment of childhood co-morbid conditions a linkage involving the NRCT, HES and primary care data is required.

For further analyses, we evaluated extremes of birth weight and congenital malformations on clinical trial recruitment and survival. Within the linked dataset, 1,072 (9%) children were recorded as having a congenital malformation (including Down syndrome), 628 within HES and 694 within the NRCT. Only 250 children were recorded as having a congenital malformation from both data sources.

Table 4: Hospital Episode Statistics diagnoses up to a year prior to a leukaemia diagnosis for children during 1 April 1998-31 December 2007, Great Britain

Months	Infectious/Parasitic		Neoplasms		Blood/Blood Organs		Endocrine/Metabolic		Behaviour Problems		Nervous System		Eye/Adnexa		Ear/Mastoid Process	
Prior *	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes
1	223	433	2260	3912	724	1167	99	183	27	44	54	93	42	62	28	41
2	20	22	13	26	35	74	3	3	2	3	4	6	5	6	3	3
3	11	16	6	13	15	30	2	2			1	1	1	1	6	6
4	10	13	3	6	5	8	3	5			1	2	2	2		
5	4	4	3	6	2	9	3	3	2	2	4	6			6	10
6	7	7	3	7	2	3	2	2			4	4	1	1	6	8
7	5	5	3	4	2	3					5	7	1	1	1	2
8	4	6	1	2	4	6	3	5	1	1	2	2	1	1	5	5
9	3	3	2	2	2	2	1	2			1	2	2	2	2	5
10	1	1	1	1	1	8	1	1			3	3	1	1		
11	5	5	2	4	1	1	2	2	1	3	1	1			1	1
12	6	6	1	1	1	2	1	2	1	6	2	3	1	1	3	3
Total	284	521	2263	3984	747	1313	110	210	31	59	62	130	54	78	54	84

Months	Circulatory System		Respiratory System		Digestive System		Skin/Subcutaneous		Musculoskeletal		Genitourinary		Perinatal Conditions		Congenital Anomalies	
Prior	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes
1	92	157	228	367	181	316	64	75	235	365	56	106	4	8	87	181
2	5	9	24	34	12	17	6	7	48	72	7	10	2	2	7	7
3			16	20	9	12	4	4	15	22	3	3	1	3	7	9
4			5	6	5	5	4	6	11	14	2	3	4	16	6	8
5			9	12	4	4	3	10	8	9	2	2	2	2	5	5
6	2	2	9	9	4	5			6	6	2	2	3	3	7	7
7			9	11	3	3	3	3	3	3	1	1	6	11	10	11
8			6	9	3	7	3	4	4	7	1	1	3	7	8	11
9			10	10	2	2			1	1					4	5
10			9	10	4	5			2	2			1	1	4	5
11			11	13	1	1	1	1	1	1					10	16
12			6	6	3	3			2	4	1	1			8	22
Total	97	168	307	507	223	380	86	110	285	506	73	129	24	53	113	287

Months	Symptoms & Signs		Injury/Poisoning		External Causes		Influential Factors	
Prior	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes
1	963	1985	112	159	176	220	961	1294
2	48	76	9	10	9	9	16	43
3	24	34	2	2	3	3	20	24
4	15	16	8	8	9	11	20	24
5	7	16	4	5	3	3	19	26
6	15	17	4	4	5	5	15	17
7	13	21					18	24
8	6	7	2	2	2	2	7	11
9	9	16	1	1	1	1	6	7
10	4	6	4	5	4	4	13	18
11	8	11	8	9	6	6	10	15
12	7	17	6	7	6	6	8	11
Total	1038	2222	157	212	223	270	1053	1514

*** Month = 30 Day period**
Total = 360 Days Prior to Diagnosis

Total Cases = 4692

Table 5: Hospital Episode Statistics diagnoses by year up to 10 years prior to a leukaemia diagnosis for children during 1 April 1998-31 December 2007, Great Britain

Years Prior	Diag Dates	Diag Age	Total Cases	Infectious/Parasitic		Neoplasm		Blood/Blood Organ		Endocrine/Metabolic		Behaviour Problem		Nervous System		Eye/Adnexa	
				Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes
1	Apr 1998 - Dec 2007	0-14	4692	284	521	2263	3984	747	1313	110	211	31	59	62	130	54	78
2	Apr 1999 - Dec 2007	1-14	4201	38	44	4	4	4	22	4	5	5	7	11	17	7	8
3	Apr 2000 - Dec 2007	2-14	3718	44	51	1	1	7	16	3	5			7	11	8	8
4	Apr 2001 - Dec 2007	3-14	3249	15	18			6	12	2	2			3	12	6	8
5	Apr 2002 - Dec 2007	4-14	2773	11	13	3	3	1	2	2	2			1	2	4	5
6	Apr 2003 - Dec 2007	5-14	2245	7	7	2	2	1	5	1	1			2	2	2	4
7	Apr 2004 - Dec 2007	6-14	1754	3	4	3	3	1	3					1	1	3	4
8	Apr 2005 - Dec 2007	7-14	1291	2	3			2	12							1	2
9	Apr 2006 - Dec 2007	8-14	792	1	1			1	1					1	1		
10	Apr 2007 - Dec 2007	9-14	316														
Total			4692	384	662	2267	3997	754	1386	116	226	34	66	71	176	79	117

Years Prior	Diag Dates	Diag Age	Total Cases	Ear/Mastoid Process		Circulatory System		Respiratory System		Digestive System		Skin/Subcutaneous		Musculoskeletal		Genitourinary	
				Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes
1	Apr 1998 - Dec 2007	0-14	4692	54	84	97	168	308	508	224	382	86	110	285	506	73	129
2	Apr 1999 - Dec 2007	1-14	4201	17	22	4	17	77	113	30	49	4	5	2	3	7	10
3	Apr 2000 - Dec 2007	2-14	3718	19	27	4	8	57	85	24	34	9	11	3	5	14	18
4	Apr 2001 - Dec 2007	3-14	3249	6	8	1	10	36	56	19	19	2	3	1	1	6	6
5	Apr 2002 - Dec 2007	4-14	2773	16	19			28	41	12	14	4	4			5	6
6	Apr 2003 - Dec 2007	5-14	2245	9	10	1	1	20	24	4	6	1	1	1	1	3	4
7	Apr 2004 - Dec 2007	6-14	1754	7	8			11	12	5	6	2	2	1	1	1	1
8	Apr 2005 - Dec 2007	7-14	1291	3	3			5	9	5	10	1	1			2	3
9	Apr 2006 - Dec 2007	8-14	792	2	3			4	5	1	2					2	2
10	Apr 2007 - Dec 2007	9-14	316					1	1	1	1						
Total			4692	111	184	103	204	476	854	297	523	108	137	292	517	108	179

Years Prior	Diag Dates	Diag Age	Total Cases	Perinatal Condition		Congenital Anomaly		Symptom/Sign		Injury/Poisoning		External Cause		Influential Factor	
				Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes	Cases	Episodes
1	Apr 1998 - Dec 2007	0-14	4692	24	53	113	288	1038	2223	157	212	223	270	1053	1514
2	Apr 1999 - Dec 2007	1-14	4201	46	93	45	118	99	154	35	39	33	34	177	240
3	Apr 2000 - Dec 2007	2-14	3718	50	106	43	137	75	121	17	20	17	19	200	249
4	Apr 2001 - Dec 2007	3-14	3249	67	142	46	124	70	92	15	21	16	17	184	218
5	Apr 2002 - Dec 2007	4-14	2773	32	72	18	47	48	67	8	11	8	12	94	106
6	Apr 2003 - Dec 2007	5-14	2245	17	28	7	12	31	35	3	3	4	4	44	48
7	Apr 2004 - Dec 2007	6-14	1754	8	39	8	21	13	15	4	8	3	4	28	40
8	Apr 2005 - Dec 2007	7-14	1291	6	11	4	26	3	9	1	1	1	1	14	20
9	Apr 2006 - Dec 2007	8-14	792			1	2	1	1					4	5
10	Apr 2007 - Dec 2007	9-14	316					1	1					1	1
Total			4692	248	544	194	775	1233	2718	235	315	299	361	1511	2441

Recruitment of childhood leukaemia patients with possible co-morbid conditions to clinical trials

Numbers of children who were recruited to specific MRC clinical trials that have been linked to the NRCT are given in Table 6. Less than half of all infants with lymphoid leukaemia were recruited to a trial during the 1980s, but this increased to 80% for Infant 92 and 69% for Interfant-99. For children aged over 1 year with lymphoid leukaemia, the percentage recruited to a trial was only 57% in UKALL VIII, but increased to over 80% from 1985 and has remained over 85% in the last four trials. For children with AML, recruitment increased from less than 50% during the 1980s to 77% in AML12.

A paper entitled *Recruitment of childhood leukaemia patients to clinical trials in Great Britain during 1980-2007: variation by birth weight, congenital malformation, socioeconomic status and ethnicity* has been submitted to *Archives of Disease in Childhood.* The abstract for the paper is below.

Abstract

Objective
To assess recruitment of children to national clinical trials for acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) in Great Britain during 1980-2007, and describe variation by some factors that might influence trial entry.

Design and setting
Records of leukaemia patients aged 0-14 years at diagnosis were identified in the National Registry of Childhood Tumours, and linked to birth registrations, Children's Cancer and Leukaemia Group records, Hospital Episode Statistics, and Medical Research Council clinical trial registers. Trial entry rates were compared between categories of birth weight, congenital malformation, socioeconomic status and ethnicity.

Results
9,147 ALL and 1,466 AML patients were eligible for national clinical trials during 1980-2007. Overall recruitment rates were 81% and 60% respectively. For ALL, rates varied significantly with congenital malformation (Down syndrome 61%, other malformations 80%, none 82%; P<0.001) and ethnicity (South Asian 78%, other minority groups 80%, white 85%; P<0.001). For AML, rates varied with birth weight (<2500g 48%, 2500-4000g 69%, >4000g 67%; P=0.005) and congenital malformation (Down syndrome 28%, other malformations 56%, none 63%; P<0.001).

Conclusion
Although recruitment rates to clinical trials for childhood leukaemia are high, future trials should monitor possible variation by birth weight, ethnicity and presence of congenital malformations.

Table 6: Recruitment of children to the acute lymphoblastic leukaemia and acute myeloid leukaemia clinical trials during 1980-2007 in Great Britain

	Period of entry	Number	Percentage in trial (%)
Lymphoid leukaemia			
ALL age at diagnosis <1 year			
UKALL VIII	09/1980-12/1984	18	29
UKALL X	01/1985-12/1988	25	46
UKALL XI	10/1990-02/1997	1	
Infant 92	01/1992-07/1999	83	80
ALL97	03/1997-10/1999	1	
Interfant-99	08/1999-12/2005	63	69
ALL2003	10/2003-12/2007	1	
Not in a trial	01/1980-12/2007	118	
Total		**310**	
ALL age at diagnosis 1-14 years			
UKALL VI	01/1980-03/1980	17	
UKALL VII	01/1980-03/1980	15	
UKALL VIII	09/1980-12/1984	722	57
UKALL IX	10/1980-03/1984	17	
UKALL X	01/1985-09/1990	1,442	80
UKALL XI	10/1990-02/1997	1,912	87
UKALL 97	03/1997-10/1999	893	90
UKALL 97/99[#]	11/1999-11/2002	857	90
UKALL 2003	10/2003-12/2007	1,319	88
ESPHALL	05/2004-12/2007	23	
Not in a trial	01/1980-12/2007	1,620	
Total		**8,837**	
Acute myeloid leukaemia			
UKAML	01/1980-04/1980	4	
AML 8	05/1980-05/1983	71	46*
Joint AML	01/1983-03/1987	108	44
AML 9	01/1984-04/1988	11	
AML 10	05/1988-03/1995	306	64
AML 12	04/1995-05/2002	385	77
Not in a trial	01/1980-05/2002	581	
Total		**1,466**	

[#]The UKALL 97/99 trial was closed for randomisation in June 2002, and thereafter patients were only registered. The Clinical Trials Service Unit excluded patients who were registered after June 2002 from their analyses.

*The AML 8 and Joint AML trials overlapped, and thus the patients who were not recruited to AML 8 were diagnosed during 05/1980-01/1983. The recruits and the non-recruits to the Joint AML trial were diagnosed during the same time period: 01/1983-03/1987.

Survival of childhood lymphoid leukaemia patients with possible co-morbid conditions

A paper entitled *The influence of birth weight and congenital malformations on childhood lymphoid leukaemia survival in Great Britain, 1980- 2007* is being prepared for submission to *Paediatric Blood and Cancer* journal. The abstract for the paper is below.

Abstract

Purpose
The influence of birth weight and congenital malformations on five-year survival, as possible predictors of co-morbidity, in children who were diagnosed with lymphoid leukaemia is unknown.

Materials and Methods
Records for children who were diagnosed with lymphoid leukaemia aged 0-14 years while resident in Great Britain during 1980-2007 were identified in the National Registry of Childhood Tumours. The registrations were linked to birth records, Children's Cancer and Leukaemia Group records, Hospital Episode Statistics (HES) data and Medical Research Council UKALL clinical trials records.

Relative survival was estimated by birth weight, presence of Down syndrome or another congenital malformation, clinical trial entry and other demographic and prognostic factors. Multivariable analysis was used to model the influence of these factors on survival.

Results
Children with a low birth weight tended to have slightly poorer five-year survival than other children, but the difference was not significant. Children with Down syndrome had significantly higher mortality than children without a malformation, and their outcome has not improved since 1990. Children with other malformations had a similar outcome to children with no malformations. Children aged less than one year and aged 10-14 years at diagnosis and those with a high white blood cell count at diagnosis had significantly poorer survival than other children.

Conclusion
Birth weight and congenital malformations, not including Down syndrome, are not strong, independent prognostic factors for childhood lymphoid leukaemia survival. Down syndrome is associated with significantly higher mortality, and the lack of improvement in outcome since 1990 requires further investigation.

Survival of childhood AML patients with possible co-morbid conditions

A total of 1,878 children were diagnosed with AML in Great Britain during 1980-2007, and 51% had died by the end of the study. Birth certificates were available for 93% of children, and of those who died, 99% of all death certificates have been collected. Birth weight was available from the birth certificates of 1,164 children who were born from 1980 onwards in England and Wales. Birth weight was not available for 697 (37%) patients either because they were born prior to 1980 or born outside England and Wales.

Altogether, 268 children (15%) had some form of congenital malformation with similar proportions (2-3%) being classified as low, medium or high severity, and 8% had Down syndrome. CCLG PTC forms for 90% of children in the study have been obtained and linked. Notifications of 62% of all children with AML having been recruited to clinical trials have been received for the period 1980-2002. We do not have access to data from the

AML 15 trial, which precludes the evaluation of the influence of clinical trial participation beyond 2002. Of all patients, 45% have at least one linked HES episode, which is high given that HES data linkage possibly are only high since 1997. The high quality of the data within the NRCT is indicated by only 5 children (<0.01%) with AML being registered via only a death certificate.

There was a slight excess of boys (M:F 1.1:1). Most children (86%) were aged 1-14 years at diagnosis (Table 7). Ten percent of children with AML are from ethnic minorities and similar proportions were classified to each quintile of deprivation. The majority of childhood leukaemia patients had a low white blood cell count (WBC) at diagnosis (44% with less than 20 x 10^9 cells per litre), which is an indicator of less advanced disease. The proportion of children treated at a CCLG PTC increased from 74% in the early 1980s to 95% during 2000-07. Recruitment to the MRC trials increased from 45% during the early 1980s to 75% during the late 1990s. A small proportion (5%) of children weighed less than 2,500g at birth. For survival analyses, 27 children (0.3%) were excluded because they were only registered via a death certificate, their vital status was unknown after diagnosis or they died on the same day they were born.

Due to small numbers it was not possible to evaluate time trends in five-year relative survival, so estimates for the entire study by each demographic and prognostic factor have been presented (Table 8). Survival was slightly lower for infants and children aged 10-14 years. Five-year survival increased from 20% during 1980-84 to 66% during 2000-07. Survival decreased by increasing white blood cell count at diagnosis. Children with M4 and M6 FAB classification of disease had slightly poorer survival than other children. The small proportion of children who were not treated at a CCLG PTC had significantly poorer survival. Some of the children who were not treated at a CCLG PTC (23%) died within a week of diagnosis, indicating that they may have received no treatment or only palliative care. No striking patterns in survival were apparent for children with AML by sex, ethnicity, socio-economic status, birth weight or severity of congenital malformation.

Age at diagnosis, period of diagnosis, WBC count at diagnosis and FAB classification were the most important prognostic factors for children with AML, each of which confounded the relationship between some other factors and survival. Age at diagnosis (P=0.02) and white blood cell count at diagnosis (p=0.10) individually had an interaction with time since diagnosis. Greater excess mortality was seen in the first year after diagnosis, which subsequently decreased.

Neither birth weight nor congenital malformations acted as co-morbid factors for children with AML during 1980-2007 in Great Britain.

Table 7: Characteristics of children diagnosed with acute myeloid leukaemia during 1980-2007, Great Britain

	1980-84		1985-89		1990-94		1995-1999		2000-2007		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Acute myeloid leukaemia	286	15	326	17	341	18	351	19	574	31	1,878	100
Sex												
Boys	146	51	161	49	195	57	192	55	302	53	996	53
Girls	140	49	165	51	146	43	159	45	272	47	882	47
Age at diagnosis												
<1 year	35	12	36	11	46	13	53	15	95	17	265	14
1-4 years	89	31	122	37	115	34	117	33	175	30	618	33
5-9 years	63	22	69	21	77	23	87	25	131	23	427	23
10-14 years	99	35	99	30	103	30	94	27	173	30	568	30
Ethnicity												
White	171	60	252	77	274	80	293	83	465	81	1,455	77
Asian	6	2	19	6	11	3	14	4	41	7	91	5
Other	3	1	12	4	18	5	30	9	34	6	97	5
Unknown	106	37	43	13	38	11	14	4	34	6	235	13
Socio-economic status (quintile of deprivation)												
Affluent	62	22	71	22	50	15	66	19	112	20	361	19
2	57	20	72	22	72	21	64	18	117	20	382	20
3	55	19	58	18	64	19	59	17	93	16	329	18
4	60	21	58	18	65	19	68	19	119	21	370	20
Deprived	45	16	64	20	90	26	94	27	132	23	425	23
Unknown	7	2	3	1	0	0	0	0	1	0	11	1
White blood cell count (x 10^9 cells/litre) at diagnosis												
0-19	144	50	160	49	148	43	155	44	220	38	827	44
20-49	42	15	53	16	59	17	62	18	80	14	296	16
50-99	26	9	35	11	33	10	36	10	58	10	188	10
100-199	47	16	54	17	60	18	62	18	111	19	334	18
>=200	27	9	24	7	41	12	36	10	105	18	233	12
No record												
French-American-British classification												
M0	0	0	1	0	3	1	9	3	7	1	20	1
M1	12	4	22	7	37	11	23	7	29	5	123	7
M2	49	17	56	17	47	14	43	12	47	8	242	13
M3	14	5	24	7	36	11	25	7	41	7	140	7
M4	47	16	73	22	41	12	50	14	79	14	290	15
M5	33	12	46	14	59	17	55	16	91	16	284	15
M6	18	6	10	3	4	1	8	2	14	2	54	3
M7	14	5	26	8	45	13	34	10	53	9	172	9
Unknown	93	33	66	20	62	18	100	28	204	36	525	28
Treated at a Children's Cancer and Leukaemia Group Principal Treatment Centres												
Yes	212	74	288	88	310	91	339	97	547	95	1,696	90
No	74	26	38	12	31	9	12	3	27	5	182	10
Clinical trial participation*												
Yes	128	45	143	44	228	67	262	75				
No	158	55	183	56	113	33	89	25				
Birth weight												
<2500 g	7	2	15	5	10	3	13	4	43	7	88	5
2500-4000 g	44	15	118	36	194	57	234	67	356	62	946	50
>4000g	4	1	19	6	23	7	37	11	64	11	147	8
No record	231	81	174	53	114	33	67	19	111	19	697	37
Severity of congenital malformation												
Down syndrome	28	10	20	6	29	9	28	8	47	8	152	8
Other: low severity	5	2	4	1	5	1	6	2	16	3	36	2
Other: medium severity	3	1	9	3	8	2	10	3	17	3	47	3
Other: high severity	1	0	3	1	2	1	5	1	22	4	33	2
No malformation	249	87	290	89	297	87	302	86	472	82	1,610	86

*Please note that we are unaware of which children were recruited to the AML 15 trial and, therefore, data on trial recruitment during 2000-07 have not been presented.

Table 8: Five-year survival by demographic and prognostic factors for children diagnosed with acute myeloid leukaemia during 1980-2007 in Great Britain

	1980-2007			
	N	**RS**	95% CI	
Sex				
Boys	983	**51.3**	48.1	54.4
Girls	868	**51.2**	47.8	54.4
Age at diagnosis				
<1 year	246	**46.7**	40.3	52.8
1-4 years	615	**53.1**	49.1	57.0
5-9 years	425	**55.1**	50.3	59.8
10-14 years	565	**48.1**	43.9	52.2
Period of diagnosis				
1980-84	280	**20.1**	15.6	25.0
1985-89	325	**42.2**	36.8	47.6
1990-94	334	**51.5**	46.0	56.7
1995-99	347	**60.4**	55.0	65.3
2000-07	565	**66.1**	62.0	69.9
Ethnicity				
White	1,447	**54.9**	52.3	57.5
South Asian	91	**53.8**	43.0	63.4
Other	97	**55.8**	45.2	65.1
No record	216	**23.1**	17.7	28.8
Socio-economic status (quintile of the Index of Multiple Deprivation)				
Affluent	357	**54.4**	49.0	59.4
2	375	**52.6**	47.4	57.5
3	326	**51.9**	46.4	57.2
4	363	**46.6**	41.4	51.7
Deprived	421	**51.0**	46.1	55.7
White blood cell count (x 10^9 cells/litre)				
0-19	827	**55.9**	52.4	59.2
20-49	296	**56.4**	50.5	61.8
50-99	186	**47.6**	40.3	54.6
>=100	327	**36.6**	31.3	41.8
No record	215	**50.4**	43.5	56.9
French-American-British classification				
M0	20	**sn**	sn	sn
M1	123	**48.3**	39.2	56.8
M2	242	**60.8**	54.3	66.6
M3	140	**66.1**	57.6	73.3
M4	290	**41.2**	35.4	46.8
M5	284	**52.3**	46.3	58.0
M6	54	**42.4**	29.1	55.1
M7	172	**52.2**	44.4	59.4
Unknown	525	**48.6**	44.3	52.9
Treated at a Children's Cancer and Leukaemia Group centre				
Yes	1,688	**54.2**	51.8	56.6
No	163	**20.1**	14.4	26.5
Birth weight				
<2500 g	83	**53.6**	42.2	63.7
2500-4000 g	935	**59.2**	56.0	62.3
>4000g	146	**57.2**	48.7	64.8
No record	687	**38.8**	35.1	42.4
Severity of congenital malformation				
Down syndrome	146	**55.2**	46.7	62.8
Other: low severity	36	**55.3**	37.7	69.8
Other: medium severity	46	**47.9**	32.9	61.3
Other: high severity	33	**53.7**	35.2	69.1
No malformation	1,590	**50.8**	48.3	53.3

*sn - small numbers of patients or deaths. It was not possible to estimate 5-year survival

Table 9: Excess hazard ratios (HRs) and 95% confidence intervals (CI) for various prognostic factors for children born and diagnosed with acute myeloid leukaemia during 1980-2007 in Great Britain (a) univariate (b) multivariable analysis[1]

	Table a univariate analysis				Table b multivariate analysis				
Prognostic factor	**No.[2]**	**RR**	**95% CI**		**RR**	**95% CI**		**LR (df)[3]**	**P value**
Age at diagnosis								9.25 (3)	0.0262
1-4 years	300	1.00			1.00				
<1 year	137	1.28	0.94	1.74	1.22	0.89	1.67		
5-9 years	184	0.75	0.55	1.01	0.97	0.70	1.37		
10-14 years	140	0.90	0.65	1.24	1.53	1.07	2.21		
Period of diagnosis								45.49 (4)	<0.001
1980-84	33	1.00			1.00				
1985-89	110	0.63	0.39	1.02	0.62	0.38	1.01		
1990-94	167	0.44	0.28	0.70	0.44	0.27	0.73		
1995-99	194	0.35	0.22	0.56	0.34	0.21	0.55		
2000-07	257	0.24	0.15	0.38	0.21	0.13	0.35		
White blood cell count (10^9/litre)								26.83 (3)	<0.001
<20	359	1.00			1.00				
20-49	148	1.12	0.81	1.56	1.12	0.81	1.57		
50-99	95	1.70	1.21	2.38	1.58	1.12	2.22		
100-199	159	2.00	1.50	2.66	2.20	1.63	2.98		
French-American-British classification								22.73 (7)	0.0019
M0	18	1.26	0.56	2.84	1.00				
M1	72	1.36	0.83	2.23	1.32	0.80	2.18		
M2	118	1.00			1.52	0.67	3.45		
M3	76	0.85	0.49	1.49	0.99	0.56	1.73		
M4	151	2.02	1.36	3.02	1.96	1.30	2.94		
M5	186	1.42	0.95	2.13	1.26	0.82	1.93		
M6	25	1.70	0.86	3.37	1.78	0.89	3.54		
M7	115	1.74	1.13	2.67	2.19	1.38	3.48		
Sex									
Boys	397	1.00							
Girls	364	1.13	0.90	1.42					
Ethnicity									
White	661	1.00							
South Asian	53	1.13	0.73	1.76					
Other	47	1.21	0.77	1.89					
Presence of a congenital malformation									
No malformation	652	1.00							
Other: low severity	13	0.74	0.27	2.01					
Other: medium severity	21	0.93	0.46	1.88					
Other: high severity	14	1.00	0.44	2.27					
Down syndrome	61	0.94	0.60	1.45					
Birth weight									
2500g - 3,999g	616	1.00							
<2,500g	46	0.90	0.54	1.50					
>4,000g	99	1.13	0.82	1.58					
Socio-economic status									
Affluent	131	1.00							
2	161	1.10	0.75	1.61					
3	133	1.18	0.79	1.76					
4	156	1.22	0.83	1.79					
Deprived	180	1.24	0.85	1.79					

1 - Rate ratios mutually adjusted for all other variables.
2 - Number of children
3 - Likelihood ratio test with degrees of freedom.

Hospital admissions for children with lymphoid leukaemia and Down syndrome

Children who are diagnosed with lymphoid leukaemia and who also have Down syndrome (DS) were less likely to be recruited to a clinical trial and tend to have poorer survival at five years during 1980-2007 in Great Britain.

Patterns of hospital admissions for children with and without DS who were treated in an NHS hospital in England and who were diagnosed during 1 April 1998 – 31 December 2007 have been described using HES data (Table 10). Amongst children who lived less than a year, survival was shorter by 50% amongst children with DS compared with other children, and correspondingly hospital episodes and time spend in hospital was also shorter for these children. For children who lived more than one year, survival for children with DS was shorter, but numbers of hospital episodes were similar to other children though more time was spent in hospital. This implies that some children with DS have a severe form of lymphoid leukaemia and die quickly. Children with DS who survive more than a year require and appear to receive more supportive care. The difference in average survival for children with DS compared with other children is less marked than for children who live less than a year.

Table 10: Children diagnosed with lymphoid leukaemia, by Down syndrome (DS) status, who were diagnosed during 1 April 1998 - 31 December 2007 in England

	Children who lived less than a year		**Children who lived more than a year**	
	Children with DS	Other children	Children with DS	Other children
Number of children	19	124	50	2,937
Average survival in days	80	163	2,411	2,783
Average number of hospital episodes	13	22	65	66
Average bed days spent in hospital	45	76	123	84

Hospital admissions for children aged 1-14 years with lymphoid leukaemia who survived at least three years

Hospital admissions for children with lymphoid leukaemia who lived at least three years during the recruitment period for UKALL 97 and 99 (March 1997- November 2002) have also been described using available HES data (Table 11). Because the full programme of treatment for ALL diagnosed during this period lasted for approximately 2-3 years, these data roughly correspond to total time spent in hospital for children who completed treatment during the era of a recent trial. (Not all children were entered in the trial, but the great majority of non-participants would have received similar treatment.) Overall, children had an average of 69 hospital episodes and spent 94 days in hospital. Survival, HES episodes and time spent in hospital were all less for children with DS compared with other children.

Table 11: Children diagnosed with lymphoid leukaemia at age 1-14, by Down syndrome (DS) status, who were diagnosed during 1 April 1997 - 30 November 2002 in England

	Children who lived at least three years		
	Children with DS	Other children	Total
Number of children	43	1,759	1,802
Average survival in days	2,272	3,565	5,837
Average number of hospital episodes	53	69	123
Average bed days spent in hospital	84	94	178

Conclusions

Extremes of birth weight and congenital malformations were identified as possible co-morbid conditions for children with leukaemia. Other conditions such as infections, asthma, diabetes and epilepsy may also have influence, but the linkage of cancer registry, HES and primary care data are required to make a thorough evaluation. Most childhood leukaemia patients are recruited to clinical trials, although some variations in recruitment by ethnicity, low-birth weight and Down syndrome have been described. Birth weight was not a significant prognostic factor for survival. Children diagnosed with lymphoid leukaemia who also had Down syndrome had significantly higher mortality than other children, and their prognosis has not improved since the 1990s. Differences in admission to hospital also occur for children with Down syndrome, some of whom probably have a severe form of the disease and who die within a year. Differences in survival and hospital admissions by Down syndrome status were less marked for children who survived at least one year.

Conference presentations given by Dr Anjali Shah

National Cancer Intelligence Network/UK Association of Cancer Registries conference, London (June 2011)
The impact of predictors of co-morbidity and treatment intensity on survival from childhood leukaemia in England and Wales, 1980-2006 (poster)
Place of death and hospital care for children who died of cancer in England, 1999-2006 (poster)
Trends in survival and the proportion cured of adult acute myeloid leukaemia in England, 1971-2006: a population-based study (poster)
Pattern of hospital admissions in children and young adults with an intracranial tumour (poster)

International Society for Paediatric Oncology (SIOP), Auckland (Oct 2011)
The impact of predictors of co-morbidity and treatment intensity on survival from childhood leukaemia in England and Wales, 1980-2006 (poster)
Place of death and hospital care for children who died of cancer in England, 1999-2006 (poster)
Trends in survival and the proportion cured of adult acute myeloid leukaemia in England, 1971-2006: a population-based study (poster)

CHILDREN with CANCER UK International Scientific conference, London (April 2012)
The influence of potential co-morbid factors on survival from childhood lymphoid leukaemia in Great Britain, 1980-2007 (poster)

National Cancer Intelligence Network/UK Association of Cancer Registries conference, London (June 2012)
The influence of potential co-morbid factors on survival from childhood lymphoid leukaemia in Great Britain, 1980-2007 (oral)

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