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Perinatal and reproductive factors: a report on haematological malignancies from the UKCCS

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Abstract

The United Kingdom Childhood Cancer Study was designed to examine the potential aetiological role of a range of perinatal and reproductive factors. Our use of clinical records permitted a more exact characterisation of reproductive events than is possible in investigations that rely on self-reporting; and the increased specificity with which antecedent events were measured produced more precise risk estimates, albeit ones based on progressively smaller numbers.

Information on the conduct of this component of the study and results for 1485 children with haematological malignancies and 4864 controls are presented. The 'find' rate for obstetric records was high at 86% for cases, with 81% having information on both matched controls. Associations were seen for severe hyperemesis (Odds Ratio = 3.6, 95%Confidence Interval = 1.3–10.1, for all leukaemias), polyhydramnios (OR = 4.0, 95%CI = 1.5–10.3, for acute myeloid leukaemia (AML)), anaemia (haemoglobin <10 g, OR = 2.6, 95%CI = 1.7–4.1, for AML), and pre-eclampsia (OR = 1.7, 95%CI = 1.1–2.7, for non-Hodgkin's lymphoma). Babies who developed leukaemia were heavier at birth (>4000 g, OR = 1.2, 95%CI = 1.0–1.4), as were their older siblings (>4000 g, OR = 1.4, 95%1.0–1.9). Mothers' whose children developed common B-cell precursor acute lymphoblastic leukaemia (ALL) were more likely to have had a previous molar pregnancy (OR = 5.2, 95%CI = 1.9–14.7). Gender-specific analysis revealed that findings often differed markedly for boys and girls; and, in common with other reports, strong associations with Down's syndrome were seen for both ALL and AML.

Keywords: Childhood; Cancer; Leukaemia; Lymphoma; Parity; Haematological; Case-control; Risk-factors; Perinatal

1. Introduction

Events acting before birth and early in life are recognised determinants of health not only throughout an individual's own lifetime, but also the lifetime of any descendent they may have [1–3]. With respect to haematological malignancies, a number of congenital characteristics including male gender for both lymphomas and leukaemias, and Down's syndrome for acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemias (AML) have been recognised risk factors for around 70 years [4–9]. In addition, for both haematological and non-haematological cancers, increased risks have been reported for a wide-range of factors associated with fetal growth, endogenous and exogenous hormonal exposures in pregnancy, and parental characteristics such as age at conception, fecundity, and history of fetal loss [9–12].

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The first epidemiological evidence that *in utero* exposure to a physical agent could increase subsequent cancer risk was provided over 50 years ago by Stewart and colleagues who reported an association between abdominal X-ray during pregnancy and subsequent development of leukaemia and other cancers in childhood [13]. Some 13 years later, interest in the potential carcinogenic effects of exposures during pregnancy was re-kindled when a striking association between adenocarcinoma of the vagina in young women and their mothers' use of diethylstilboestrol during pregnancy was reported [14]. This non-steroidal oestrogen was prescribed to prevent recurrent or threatened miscarriage, although it was subsequently shown to increase risk of fetal and neonatal death [10,15].

There is now compelling molecular evidence that leucaemogenic gene re-arrangements can originate *in utero* [16–20]. Whilst the triggering exposures/events causing these mutations have yet to be identified; several exogenous and endogenous agents are suspected, including various chemicals and biological agents. Ionizing radiation remains, however, the only confirmed *in utero* cause of childhood leukaemia [21,22].

The United Kingdom Childhood Cancer Study (UKCCS) was designed to examine the potential aetiological role of a range of perinatal and reproductive factors [23]. This report provides important background information on the conduct of this component and the 7500 infant–mother pairs included. In addition, the main findings for haematological malignancies, based on an analysis of obstetric and neonatal records, are described. Findings for vitamin K [24,25] and hepatic tumours are given elsewhere [12].

2. Data and methods

The UKCCS is a national population-based case-control study, details about its conduct and ethical approvals are described elsewhere [23]. Briefly, children aged 0–14 years diagnosed between 1992 and 1996 in Great Britain were eligible. For each case, two controls matched for sex, month and year of birth, and region of residence at diagnosis were randomly recruited from primary care population registers. At interview, parents were asked for consent to access their own and their child's medical records. With the natural mother's consent, her obstetric notes and, where available, the child's neonatal records, were subsequently abstracted onto a previously validated form specifically designed to be applicable across hospitals and time periods [26].

For the purposes of study management, 10 UKCCS regions were created; the conduct of the study within each region being the responsibility of a single epidemiological centre. The analyses presented here are confined to eight of the 10 UKCCS regions: obstetric data were not collected in South Wales, and findings for Scotland have been previously published [27]. In addition, a third of the Southwest region (study centre Southampton) was excluded because of incomplete coverage. Having made these exclusions, enumeration district 'deprivation' indices were re-calculated using the same methods as described for the UK as a whole [23].

Odds ratios (OR), 95% Confidence Intervals (CI) and two-sided *P*-values were estimated using unconditional logistic regression, with adjustment for region of residence at diagnosis, sex, and age at diagnosis (single years) [28]. In order to increase precision [24,29], all available controls were used as the comparison group for each diagnostic group. Analyses were conducted using the statistical software package STATA [30].

3. Results

Numbers of mothers interviewed and numbers for whom obstetric records were abstracted are given by region in Table 1. The study centre city, moving from North to South is given in the left hand column. The obstetric records of 2692 (85.9%) interviewed case mothers and 4864 (78.0%) interviewed control mothers were traced and abstracted. For each case mother, obstetric records of at least one individually age- and sex-matched control mother was obtained. Haematological malignancy (leukaemia and lymphoma) is the focus of the present report, and no further information on the 1207 children diagnosed with other cancers is presented here.

The characteristics of the 1485 children diagnosed with haematological malignancies and the 4864 controls are shown in Table 2. In line with other reports, the age and gender distributions vary with malignancy type; nearly 60% of children with ALL were diagnosed before their 5th birthday, compared with only 21% for those with lymphomas. There are more boys than girls in each malignancy group, the largest sex difference being for lymphomas where just over 71% were male. As expected, trisomy 21 was far more common among children who subsequently developed leukaemia (35/1254 = 2.8%), the proportion varying with leukaemia type (7.8% of those with AML and 2% of those with ALL). The multiple birth frequency, at around 2–3%, is broadly similar across all diagnostic groups.

The control deprivation distribution ranges from 21.9% in the top quintile, through to 20.5% in the middle quintile and 18.5% in the lowest quintile (Table 2). This systematic fall – which reflects the fact that those from more deprived areas were less likely to participate than those from more affluent areas – is a common observation in epidemiological studies requiring participation [23,31]. In contrast, within the case groups, there is no evidence of any such systematic trend. Adjustment for deprivation did not affect the findings presented in

Table 1
Numbers of interviewed subjects and those whose obstetric/neonatal notes were abstracted distributed by UKCCS study region

	Cases		Controls		Controls per case	
	Interviewed	Notes abstracted (% of interviewed)	Interviewed	Notes abstracted (% of interviewed)	Two (% of cases)	One (% of cases)
Total	3133	2692 (85.9%)	6236	4864 (78.0%)	2172 (80.7%)	520 (19.3%)
Study centre						
Leeds	451	376 (83.4%)	901	697 (77.4%)	321 (85.4%)	55 (14.6%)
Manchester	499	437 (87.6%)	996	803 (80.6%)	366 (83.8%)	71 (16.3%)
Nottingham	346	302 (87.3%)	691	551 (79.7%)	249 (82.5%)	53 (17.6%)
Birmingham	316	295 (93.4%)	619	537 (86.8%)	242 (82.0%)	53 (18.0%)
Cambridge	352	316 (89.8%)	703	571 (81.2%)	255 (80.7%)	61 (19.3%)
Oxford	341	307 (90.0%)	682	572 (83.9%)	265 (86.3%)	42 (13.7%)
London	538	420 (78.1%)	1068	715 (67.0%)	295 (70.2%)	125 (29.8%)
Southampton[a]	290[a]	239 (82.4%)	576[a]	418 (72.6%)	179 (74.9%)	60 (25.1%)

UKCCS, United Kingdom Childhood Cancer Study.
[a] Excludes subjects resident in Avon, Dorset, Somerset and the Isle of Wight.

Table 2
Characteristics of subjects diagnosed with a haematological malignancy

	Controls	Leukaemia			Lymphoma		
	N (%)	Total *N* (%)	ALL *N* (%)	AML *N* (%)	Total *N* (%)	Non-Hodgkin's *N* (%)	Hodgkin's *N* (%)
Total	4864 (100)	1254 (100)	1055 (100)	179 (100)	231 (100)	163 (100)	63 (100)
Age at diagnosis (years)							
0	475 (9.8)	75 (6.0)	43 (4.1)	29 (16.2)	0	0	0
1–4	2234 (45.9)	665 (53.0)	588 (55.7)	70 (39.1)	48 (20.8)	40 (24.5)	7 (11.1)
5–9	1325 (27.2)	340 (27.1)	293 (27.8)	42 (23.5)	80 (34.6)	55 (33.7)	23 (36.5)
10–14	830 (17.1)	174 (13.9)	131 (12.4)	38 (21.2)	103 (44.6)	68 (41.7)	33 (52.4)
Median	4.4	4.3	4.3	4.2	9.4	8.9	10.3
Gender							
Male	2692 (55.4)	692 (55.2)	588 (55.7)	92 (51.4)	165 (71.4)	114 (69.9)	46 (73.0)
Female	2172 (44.7)	562 (44.8)	467 (44.3)	87 (48.6)	66 (28.6)	49 (30.1)	17 (27.0)
Trisomy 21[a]	3 (<1)	35 (2.8)	21 (2.0)	14 (7.8)	0	0	0
Multiple birth[a]	108 (2.2%)	25 (2.0)	22 (2.1)	3 (1.7)	6 (2.6)	4 (2.5)	2 (3.2)
Deprivation (quintiles)							
Least 1	1064 (21.9)	258 (20.6)	218 (20.7)	35 (19.6)	39 (16.9)	28 (17.2)	11 (17.5)
2	987 (20.3)	251 (20.0)	217 (20.6)	31 (17.3)	45 (19.5)	35 (21.5)	8 (12.7)
3	998 (20.5)	235 (18.7)	205 (19.4)	27 (15.1)	56 (24.2)	38 (23.3)	17 (27.0)
4	917 (18.9)	248 (19.8)	209 (19.8)	36 (20.1)	41 (17.8)	27 (16.6)	14 (22.2)
Most 5	898 (18.5)	262 (20.9)	206 (19.5)	50 (27.9)	50 (21.7)	35 (21.5)	13 (20.6)

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia.
[a] Two cases, one with ALL and one with AML, had Trisomy 21 and were part of a multiple pregnancy.

this report, and the unadjusted ratios are presented throughout.

At the time of the index birth, mothers of case children tended to be slightly, although non-significantly, younger than mothers of control children (Table 3). Approximately 44% of controls were firstborns, but there is no evidence of any systematic case-control differences with respect to the index child's sibship position (Table 3). The total number of previous pregnancies is also similar across groups, although there is some suggestion that mothers whose children developed AML may have had more prior pregnancies. This is largely due to the marginal but non-significant ($P = 0.086$) excess of terminations, as can be seen from Table 4 where information is given on previous pregnancy outcomes of women who had at least one pregnancy before the index child was born.

Results are presented in two ways in Table 4: women are the unit of analysis in the top-half and pregnancies in the bottom-half. In all groups, over 80% of women had at least one prior livebirth (982 case mothers and 3220 control mothers); and over 25% had at least one prior

Table 3
Numbers of haematological malignancies, Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) distributed by maternal age, numbers previous livebirths, and numbers of previous pregnancies

	Controls *N* (%)	Leukaemia						Lymphoma					
		Total		ALL		AML		Total		Non-Hodgkin's		Hodgkin's	
		N (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)
Total	4864 (100)	1254 (100)		1055 (100)		179 (100)		231 (100)		163 (100)		63 (100)	
Age (yrs)													
<25	1442 (29.7)	394 (31.4)	1.1 (1.0–1.3)	323 (30.6)	1.1 (0.9–1.2)	62 (34.6)	1.3 (0.9–1.8)	92 (39.8)	1.3 (1.0–1.7)	60 (36.8)	1.1 (0.8–1.6)	28 (44.4)	1.5 (0.9–2.6)
25–35	2971 (61.1)	753 (60.1)	1.0	643 (61.0)	1.0	100 (55.9)	1.0	127 (55.0)	1.0	94 (57.7)	1.0	32 (50.8)	1.0
>35	451 (9.3)	107 (8.5)	0.9 (0.7–1.2)	89 (8.4)	0.9 (0.7–1.2)	17 (9.5)	1.1 (0.7–1.9)	12 (5.2)	0.7(0.4–1.2)	9 (5.5)	0.7 (0.3–1.3)	3 (4.8)	0.7 (0.2–2.4)
Means ± SD	28.0 ± 5.2	27.7 ± 5.3		27.7 ± 5.2		27.5 ± 5.6		27.0 ± 4.7		27.3 ± 4.8		26.4 ± 4.7	
Previous live births													
0	2130 (43.8)	551 (43.9)	1.0	471 (44.6)	1.0	71 (39.7)	1.0	108 (46.8)	1.0	75 (46.0)	1.0	31 (49.2)	1.0
1	1669 (34.3)	415 (33.1)	1.0 (0.8–1.1)	349 (33.1)	1.0 (0.8–1.1)	62 (34.6)	1.1 (0.8–1.5)	76 (32.9)	0.9 (0.7–1.3)	53 (32.5)	0.9 (0.7–1.3)	20 (31.8)	0.8 (0.5–1.5)
2	725 (14.9)	197 (15.7)	1.1 (0.9–1.3)	166 (15.7)	1.1 (0.9–1.3)	27 (15.1)	1.1 (0.7–1.7)	32 (13.9)	0.9 (0.6–1.3)	23 (14.1)	0.9 (0.6–1.5)	9 (14.3)	0.9 (0.4–1.8)
⩾3	340 (7.0)	91 (7.3)	1.0 (0.8–1.3)	69 (6.5)	0.9 (0.7–1.2)	19 (10.6)	1.6 (1.0–2.8)	15 (6.5)	0.9 (0.5–1.6)	12 (7.4)	1.0 (0.5–1.9)	3 (4.8)	0.7 (0.2–2.2)
Mean ± SD	0.9 ± 1.0	0.9 ± 1.1		0.9 ± 1.1		1.0 ± 1.2		0.8 ± 1.0		0.9 ± 1.0		0.8 ± 0.9	
Previous pregnancies													
0	1629 (33.5)	407 (32.5)	1.0	356 (33.7)	1.0	45 (25.1)	1.0	91 (39.4)	1.0	62 (38.0)	1.0	28 (44.4)	1.0
1	1568 (32.2)	405 (32.3)	1.0 (0.9–1.2)	336 (31.9)	1.0 (0.8–1.2)	65 (36.3)	1.5 (1.0–2.2)	67 (29.0)	0.8 (0.6–1.1)	51 (31.3)	0.9 (0.6–1.3)	16 (25.4)	0.6 (0.3–1.2)
2	891 (18.3)	229 (18.3)	1.0 (0.9–1.2)	186 (17.6)	1.0 (0.8–1.2)	38 (21.2)	1.5 (1.0–2.4)	40 (17.3)	0.9 (0.6–1.3)	24 (14.7)	0.8 (0.5–1.2)	12 (19.1)	0.8 (0.4–1.6)
⩾3	776 (16.0)	213 (17.0)	1.1 (0.9–1.3)	177 (16.8)	1.0 (0.8–1.3)	31 (17.3)	1.4 (0.9–2.3)	33 (14.3)	0.8 (0.5–1.2)	26 (16.0)	0.9 (0.6–1.5)	7 (11.1)	0.6 (0.3–1.4)
Mean ± SD	1.3 ± 1.4	1.4 ± 1.5		1.3 ± 1.4		1.5 ± 1.5		1.2 ± 1.3		1.2 ± 1.3		1.0 ± 1.2	

[a] Adjusted for sex of child, age at diagnosis, and UKCCS study region.

Table 4
Previous pregnancy outcomes, Odds Ratios (OR)[a] and 95% Confidence Intervals (CI): mothers' of children with a haematological malignancy compared with mother's of controls

	Controls *N* (%)	Leukaemia						Lymphoma					
		Total		ALL		AML		Total		Non-Hodgkin's		Hodgkin's	
		N (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)
(A) Denominator = women													
Women	3220 (100)	842 (100)		694 (100)		134 (100)		140 (100)		101 (100)		35 (100)	
⩾1 Live birth	2707 (84.1)	696 (82.7)	0.9 (0.7–1.1)	577 (83.1)	1.0 (0.8–1.2)	108 (80.6)	0.8 (0.5–1.2)	122 (87.1)	1.2 (0.7–2.1)	88 (87.1)	1.2 (0.7–2.3)	31 (88.6)	1.3 (0.5–3.9)
⩾1 Miscarriage	893 (27.7)	245 (29.1)	1.1 (0.9–1.2)	204 (29.4)	1.1 (0.9–1.3)	36 (26.9)	1.0 (0.7–1.5)	36 (25.7)	0.9 (0.6–1.3)	26 (25.7)	0.9 (0.6–1.4)	9 (25.7)	1.0 (0.5–2.1)
⩾1 Still birth	58 (1.8)	15 (1.8)	1.0 (0.6–1.8)	12 (1.7)	1.0 (0.5–1.9)	2 (1.5)	0.8 (0.2–3.3)	5 (3.6)	1.9 (0.7–5.1)	5 (5.0)	2.8 (1.0–7.4)	0	–
⩾1 Termination	582 (18.1)	178 (21.1)	1.2 (1.0–1.4)	143 (20.6)	1.2 (0.9–1.4)	32 (23.9)	1.4 (1.0–2.2)	27 (19.3)	1.2 (0.8–1.9)	16 (15.8)	0.9 (0.5–1.6)	7 (20.0)	1.3 (0.6–3.1)
⩾1 Ectopic	35 (1.1)	7 (0.8)	0.8 (0.4–1.8)	5 (0.7)	0.7 (0.3–1.7)	2 (1.5)	1.5 (0.4–6.4)	1 (0.7)	0.7 (0.1–5.5)	1 (1.0)	1.0 (0.1–7.6)	0	–
⩾1 Molar[2]	9 (0.3)	7 (0.8)	3.0 (1.1–8.2)	7 (1.0)	3.8 (1.4–10.4)	0	–	0	–	0	-	0	–
(B) denominator = pregnancies													
Pregnancies	6172 (100)	1675 (100)		1372 (100)		268 (100)		265 (100)		195 (100)		62 (100)	
Live births	4242 (68.7)	1131 (67.5)	1.0 (0.9–1.1)	923 (67.3)	1.0 (0.8–1.1)	185 (69.0)	1.0 (0.8–1.3)	186 (70.2)	1.0 (0.8–1.4)	137 (70.3)	1.1 (0.8–1.4)	46 (74.2)	1.2 (0.7–2.2)
Miscarriage	1148 (18.6)	315 (18.8)	1.0 (0.9–1.2)	266 (19.4)	1.0 (0.9–1.2)	43 (16.0)	0.9 (0.6–1.2)	44 (16.6)	0.8 (0.6–1.2)	34 (17.4)	0.9 (0.6–1.3)	9 (14.5)	0.8 (0.4–1.6)
Still birth	67 (1.1)	16 (1.0)	0.9 (0.5–1.6)	13 (1.0)	0.9 (0.5–1.7)	2 (0.8)	0.7 (0.2–2.8)	5 (1.9)	1.7 (0.7–4.4)	5 (2.6)	2.3 (0.9–6.1)	0	–
Termination	669 (10.8)	199 (11.9)	1.1 (0.9–1.3)	158 (11.5)	1.1 (0.9–1.3)	36 (13.4)	1.3 (0.9–1.9)	29 (10.9)	1.2 (0.8–1.7)	18 (9.2)	1.0 (0.6–1.6)	7 (11.3)	1.2 (0.6–1.8)
Ectopic	36 (0.6)	7 (0.4)	0.7 (0.3–1.7)	5 (0.4)	0.6 (0.3–1.7)	2 (0.8)	1.3 (0.3–5.5)	1 (0.4)	0.7 (0.1–5.4)	1 (0.5)	1.0 (0.1–7.2)	0	–
Molar[b]	10 (0.2)	7 (0.4)	2.6 (1.0–6.9)	7 (0.5)	3.3 (1.2–8.7)	0	–	0	–	0		0	–

[a] Adjusted for sex of child, age at diagnosis, and UKCCS study region.
[b] Hydatidiform mole.

miscarriage. Expressed as a proportion of total pregnancies, the corresponding rates of around 70% for live-births and 18% for miscarriages are broadly in line with other large surveys. The threefold excess of hydatidiform mole (HM) among mothers of children with ALL is the only statistically significant finding in both sets of analyses: the risk estimates being 3.8 (95%CI = 1.4–10.4; $P = 0.010$) based on women and 3.3 (95%CI = 1.2–8.7; $P = 0.018$) based on pregnancies. All 7 ALLs were of the common precursor-B cell ALL phenotype (OR = 5.22, 95%CI = 1.9–14.7; $P = 0.002$). At least one of the 7 molar pregnancies in the case series was a partial hydatitidiform mole (PHM), but no information about type of HM (complete or partial) was recorded for the controls or the remaining 6 cases. In the case series, the 7 molar pregnancies were separated from the index ALL child by a single intervening pregnancy (6 of the 7 being live births/sibs and one a miscarriage), but no similar pattern was evident in the control series.

Information about the index neonate and pregnancy is presented in Tables 5 and 6. Because of potentially confounding effects, those who were part of a multiple birth and those with Down's syndrome have been excluded from these Tables. However, neither the inclusion nor exclusion of these subjects had any impact on the findings presented.

Table 5 gives findings for drugs administered to the mother during labour and for the condition of the neonate at birth. Over 40% of mothers were given pethidine, the odds ratio for those whose offspring subsequently developed Hodgkin's disease being significantly raised (1.8, 95%CI 1.1–2.9; $P = 0.031$). Approximately 1 in every 15 mothers had a general anaesthetic, the estimated risk associated with non-Hodgkin's lymphoma being 1.8 (95%CI 1.1–3.0; $P = 0.018$). Around 24% of babies had a record of being jaundiced and 4% were prescribed phototherapy, those who went on to develop ALL being marginally more likely to have been jaundiced (OR 1.2, CI 1.1–1.5; $P = 0.028$). With respect to birthweight, those subsequently diagnosed with leukaemia tended to be heavier than those who were not, the excess being most marked for AML for those weighing 4000g or more (OR = 1.6, 95%CI = 1.1–2.5; $P = 0.028$). Importantly, the immediately preceding sib of those diagnosed with leukaemia also tended to be heavier than the preceding sib of controls, (OR = 1.4, 95%CI 1.0–1.9; $P = 0.035$) for those weighing 4000g or more.

The pregnancy experience of case mothers is compared with control mothers in Table 6. At around 3%, the frequency of pelvic radiography was similar for mothers of cases and controls. Overall, more than 95% of radiographic examinations were undertaken in the third trimester (data not shown). Approximately 1 in 20 mothers was diagnosed with hyperemesis, but severe

Table 5
Number of subjects (%), Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) distributed by delivery and characteristics of the baby

	Controls *N* (%)	Leukaemia						Lymphoma					
		Total		ALL		AML		Total		Non-Hodgkin's		Hodgkin's	
		N (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)
Total	4753 (100)	1196 (100)		1013 (100)		163 (100)		225 (100)		159 (100)		61 (100)	
Drugs in labour													
Pethidine	1987 (41.8)	489 (40.9)	1.0 (0.9–1.1)	415 (41.0)	1.0 (0.9–1.1)	66 (40.5)	0.9 (0.7–1.3)	99 (44.0)	1.0 (0.7–1.3)	64 (40.3)	0.9 (0.6–1.2)	34 (55.7)	1.8 (1.1–2.9)
Epidural	885 (18.6)	197 (16.5)	0.9 (0.7–1.0)	169 (16.7)	0.9 (0.7–1.0)	24 (14.7)	0.8 (0.5–1.2)	41 (18.2)	1.2 (0.9–1.8)	32 (20.1)	1.4 (0.9–2.1)	8 (13.1)	0.6 (0.3–1.4)
General anaesthetic	310 (6.5)	74 (6.2)	1.0 (0.7–1.2)	64 (6.3)	1.0 (0.7–1.3)	8 (4.9)	0.8 (0.4–1.5)	21 (9.3)	1.3 (0.8–2.1)	20 (12.6)	1.8 (1.1–3.0)	1 (1.6)	0.2 (0.0–1.6)
Jaundice													
Diagnosed	1125 (23.7)	309 (25.8)	1.2 (1.0–1.4)	270 (26.6)	1.2 (1.1–1.5)	36 (22.1)	1.0 (0.7–1.5)	45 (20.0)	0.8 (0.6–1.1)	28 (17.6)	0.7 (0.4–1.0)	16 (26.2)	1.2 (0.7–2.2)
Phototherapy	189 (4.0)	55 (4.6)	1.2 (0.9–1.6)	48 (4.7)	1.2 (0.9–1.7)	7 (4.3)	1.1 (0.5–2.3)	7 (3.1)	0.8 (0.3–1.6)	5 (3.1)	0.8 (0.3–1.9)	2 (3.3)	0.8 (0.2–3.5)
Birthweight (g)													
Index $\geqslant$4000	497 (10.5)	144 (12.0)	1.2 (1.0–1.4)	115 (11.4)	1.1 (0.9 –1.4)	26 (16.0)	1.6 (1.1–2.5)	22 (9.8)	0.9 (0.6–1.4)	12 (7.6)	0.7 (0.4–1.2)	6 (9.8)	0.9 (0.4–2.1)
Siblings $\geqslant$4000[b]	202 (7.7)	68 (10.4)	1.4 (1.0–1.9)	55 (10.0)	1.3 (1.0–1.8)	12 (12.6)	1.8 (0.9–3.3)	6 (5.2)	0.6 (0.3–1.5)	5 (6.0)	0.7 (0.3–1.9)	0	–

[a] Adjusted for sex of child, age at diagnosis, and UKCCS study region.
[b] Adjusted for sex of sib, age of sib, and UKCCS study region.

Table 6
Numbers of subjects (%), Odds Ratios (OR)[a] (95% Confidence Intervals) distributed by events during pregnancy

	Controls *N* (%)	Leukaemia						Lymphoma					
		Total		ALL		AML		Total		Non-Hodgkin's		Hodgkin's	
		N (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)	*N* (%)	OR (95%CI)
Total	4753 (100)	1196 (100)		1013 (100)		163 (100)		225 (100)		159 (100)		61 (100)	
Radiography													
Any	182 (3.8)	48 (4.0)	1.1 (0.8–1.5)	36 (3.6)	1.0 (0.7–1.4)	11 (6.8)	1.8 (0.9–3.3)	14 (6.2)	1.2 (0.7–2.1)	12 (7.6)	1.6 (0.8–2.9)	2 (3.3)	0.8 (0.2–3.5)
Pelvic	140 (3.0)	37 (3.1)	1.1 (0.8–1.6)	29 (2.9)	1.0 (0.7–1.6)	8 (4.9)	1.6 (0.8–3.4)	7 (3.1)	0.8 (0.4–1.7)	7 (4.4)	1.2 (0.5–2.6)	0	–
Hyperemesis													
All diagnoses	234 (4.9)	57 (4.8)	1.0 (0.7–1.3)	50 (4.9)	1.0 (0.7–1.4)	7 (4.3)	0.9 (0.4–2.0)	9 (4.0)	0.9 (0.4–1.7)	6 (3.8)	0.8 (0.3–1.8)	3 (4.9)	1.1 (0.3–3.5)
Severe	8 (0.2)	7 (0.6)	3.6 (1.3–10.1)	6 (0.6)	3.8 (1.3–11.2)	1 (0.6)	5.0 (0.6–41.7)	1 (0.4)	5.1 (0.6–45.9)	1 (0.6)	6.8 (0.8–60.2)	0	–
Poly-hydramnios													
All diagnoses	41 (0.9)	18 (1.5)	1.8 (1.0–3.1)	13 (1.3)	1.5 (0.8–2.8)	5 (3.1)	4.0 (1.5–10.3)	4 (1.8)	1.7 (0.6–5.0)	4 (2.5)	2.5 (0.9–7.3)	0	–
Pre-eclampsia													
All diagnoses	464 (9.8)	118 (9.9)	1.0 (0.8–1.2)	102 (10.1)	1.0 (0.8–1.3)	15 (9.2)	1.0 (0.6–1.7)	30 (13.6)	1.4 (0.9–2.1)	26 (16.4)	1.7 (1.1–2.7)	4 (6.6)	0.7 (0.2–1.8)
Severe	25 (0.5)	7 (0.6)	1.1 (0.5–2.6)	7 (0.7)	1.3 (0.5–3.0)	0	–	3 (1.4)	2.8 (0.8–10.1)	3 (1.9)	3.8 (1.1–13.6)	0	–
Anaemia													
Hb <10 g[b]	331 (7.0)	102 (8.5)	1.2 (1.0–1.6)	74 (7.3)	1.0 (0.8–1.3)	25 (15.3)	2.6 (1.7–4.1)	9 (4.0)	0.9 (0.4–1.7)	5 (3.1)	0.6 (0.3–1.6)	4 (6.6)	1.0 (0.3–2.7)

[a] Adjusted for gender of child, age at diagnosis, and UKCCS study region.
[b] Hb, haemoglobin.

hyperemesis necessitating admission was rare (1 in 500 pregnancies). Although the numbers are small, there is some suggestion that mothers whose children subsequently developed leukaemia (ALL and AML) were more likely to have had severe hyperemesis: the odds ratios being for all leukaemias combined being 3.6 (95%CI 1.3–10.1; $P = 0.015$). The incidence of polyhydramnios was also raised in case mothers: the odds ratios being 1.8 (95%CI 1.0–3.1; $P = 0.049$) for all leukaemias combined and 4.0 (95%CI 1.5–10.3; $P = 0.005$) for AML alone.

Nearly 10% of control mothers were diagnosed with pre-eclampsia, but in only 0.5% was the condition classified as severe (ICD = O14.1 – pregnancy-induced hypertension with significant proteinuria). There is some indication that pregnancies of mothers whose children were diagnosed with non-Hodgkin's lymphoma may have been more likely to have been complicated by pre-eclampsia; the risk estimates being 1.7 (95%CI = 1.1–2.7; $P = 0.017$) and 3.8 (95%CI = 1.1–13.6; $P = 0.037$) for all diagnoses and for severe pre-eclampsia, respectively (Table 6). Around 7% of control mothers had at least one haemoglobin level below 10 g (anaemia) and, by comparison, the 15% level observed among those whose children developed AML is significantly raised (OR = 2.6, 95% CI 1.7–4.1; $P < 0.001$).

4. Discussion

This component of the UK childhood cancer study (UKCCS) was specifically designed to investigate associations between obstetric and perinatal factors and the subsequent development of childhood cancer [23]. Information was systematically abstracted from medical records compiled before diagnosis/interview, and none of the findings are subject to reporting/recall bias.

The 'find' rate for obstetric records was high at 86% for cases and 78% for controls: the lower control rate reflecting the fact that a lower priority was placed on tracing the second control when the first had been found. Overall, obstetric notes of both control mothers were abstracted for over 80% of cases. The high quality of the diagnostic data available within the UKCCS allowed detailed examination of immunophenotype and karyotype. Findings for the former, as well as the age-specific results, are presented. However, no unusual patterns were, seen either for the chromosomal translocations *TEL-AML1* ($N = 109$) and t(11q23) ($N = 35$) or for hyperdiploidy ($N = 313$).

4.1. Maternal age, parity and previous reproductive history

A number of investigators have suggested that certain aspects of a woman's reproductive history may predispose towards leukaemia in her offspring. Advanced maternal age, nulliparity, history of fetal death, and low fertility being the most frequently implicated risk factors. This is a complex area, since disentangling relationships between maternal age, prior reproductive history, and birth order is far from straightforward – accordingly, it is not surprising that many reports on this topic are equivocal and contradictory.

Our findings for maternal age, parity and gravidity are essentially negative – no evidence being found for associations with advanced maternal age, numbers of previous pregnancies or numbers of previous births. With respect to advanced maternal age, our results are in broad agreement with the accumulating literature on this topic, since although some researchers have reported increased risks [32] others have not [27,33–39].

Our lack of association for the index child's position in the family is more controversial. This is because in resource-rich countries, birth order is considered by many to be an important proxy for exposure to infection in infancy, and it is widely believed that lack of immune modulation in the first year of life increases the risk that common precursor B-cell ALL will arise as a result of exposure to infection in the peak incidence years (12–72 months) [22]. Nonetheless, as with maternal age, whilst some studies have reported an increased risk for first-borns [13,32,40–42], others have not [26,33–35,38,39,43,44,44–47]. In our study, average numbers of previous live-births, births (live plus still) and pregnancies were identical for mothers of both controls and children diagnosed with ALL at 0.9, 1.0 and 1.3, respectively; and no trends with birth order were found. In addition, separate birth-order and maternal age subgroup analyses were performed for common precursor B-cell ALL (76% of ALL), ALL diagnosed between the ages of 12 and 72 months (65% of ALL) and precursor B-cell ALL diagnosed between the ages of 12 and 72 months (53% of ALL); and as with the total data, no significant associations/trends emerged. Furthermore, using similar methods to those of Dockerty and colleagues [41] we also examined marital parity (live plus still births) as recorded at birth registration, but their positive results could not be duplicated here (data not shown).

With respect to previous pregnancy outcome, the fivefold increased risk of precursor-B cell ALL among offspring of mothers who had a previous molar pregnancy (hydatidiform mole – HM) was the only association of note. None of the mothers of children with AML or NHL had any record of having had such pregnancies. Importantly, this finding is unlikely to be due to a low rate among mothers of controls, since at 1.6/1000 pregnancies (10/6172) the incidence in control pregnancies is slightly higher than has been reported elsewhere [48–50].

The epidemiology of HM, which is associated with abnormal gametogenesis and/or fertilisation, is unclear.

Complete HM (CHM) arises from the fertilisation of an anuclear ovum either by a haploid 23X sperm that subsequently divides, or by two haploid sperm (23X or 23Y); and partial HM (PHM) from the fertilisation of a haploid 23X ovum by two sperm [48,49]. Unfortunately, definitive cytogenetic information was only recorded for one mother – a case with a PHM. Whilst the association reported here requires confirmation and is based on small numbers, it is possible that our findings may provide clues to the aetiology of both conditions.

4.2. Characteristics of the baby

A number of congenital features have been linked with subsequent haematological malignancy in children and young adults. With respect to obvious genetic traits, Down's syndrome (trisomy 21) and male sex have been recognised risk factors for leukaemia for decades [4,6,9,51]. Both associations, alongside other more transitory characteristics such as heavy birthweight [52], were evident in the present study.

The pattern of malignancy associated with Down's has long been an active area of research [4,7,53]. In the present study, 3/4864 (0.06%) controls had Down's, which is close to the UK population's expected value for children with the age and birth year distributions included in this report [7,54]. This contrasts with 2.0% among children with ALL (OR = 32.9, 95%CI = 9.8–110.5) and 7.8% among children with AML (OR = 137.5, 95%CI = 39.1–483.0). In addition, whereas the age profile of children with both Trisomy 21 and ALL was similar to that of other children with ALL, those with Trisomy 21 and AML were, on average, markedly younger at diagnosis than other children with AML (median age at diagnosis = 2.0 years). This is consistent with other reports: more than 40% of AML in children with trisomy 21 are megakaryoblastic (M7), a sub-type usually diagnosed between 1 and 3 years [55,56].

In the population as a whole, male births account for 51–53% of births, yielding a sex ratio of approximately 1.05. During the first few months of life, although the majority of cancers are just as likely to be diagnosed in girls, a characteristic male predominance emerges as age increases. This gender difference is particularly marked for haematological malignancies, the most notable male excess being for lymphomas [8,9,57]. The sex differences in our data (71% of lymphomas and 55% of leukaemias were diagnosed in boys) accords with expectation, but unfortunately risk estimates for gender cannot be generated because controls were matched to cases on sex. Whilst the explanation for these gender differences remains unknown, a number of interesting possibilities including hormonal, immunological and various metabolic processes have been suggested [58,59]. Boys are, on average, heavier than girls at birth and the related suggestion that factors associated with fetal growth, may be associated with subsequent leukaemia development, particularly AML, is not new. Indeed, several investigators have reported that heavy babies are at increased risk of leukaemia – both ALL and AML [39,42,43,52,59,60]. Further, it has been suggested that the association with heavy birthweight is most marked among those diagnosed in infancy [35,59,61]. In our study, when the data were stratified by age and sex, no associations of any type remained for boys, whereas the effects strengthened for girls – the largest risk being seen among girls diagnosed with AML under 2 years of age (OR = 5.4; 95%CI = 1.9–15.04, $P = 0.001$).

As well as comparing the birthweights of index children, we also examined the weights of their immediately preceding siblings. Given the well documented correlation between sibling weights [62,63], it is not surprising that older siblings of leukaemic cases tended to be heavier than those of their corresponding controls. This observation, noted in a previous study [26], has obvious implications for the biological mechanism underpinning the birthweight observations.

4.3. Pregnancy and delivery complications

The medical record-based nature of the present study permitted a more precise examination of events within the *in utero* period than is possible in studies based on self-report. Associations were noted for NHL with pre-eclampsia/eclampsia, for ALL with hyperemesis, and for AML with polyhydramnios and anaemia. All conditions were clinically diagnosed, and all diagnoses were supported by documentary evidence. Interestingly, in contrast to some reports [9,63], no decreased risk for those who were part of a multiple pregnancy was observed (OR for leukaemia = 1.0, 95%CI = 0.8–1.4).

Pre-eclampsia, which includes gestational hypertension, was diagnosed in approximately 10% of pregnancies. Severe pre-eclampsia/eclampsia (ICD 10 = O14.1 and O15.0–9) is rare [64], and only 25(0.5%) of control mothers were diagnosed with this condition. Mothers' whose children developed NHL were almost twice as likely to be diagnosed with pre-eclampsia (OR = 1.7, 95%CI = 1.1–2.7; $P = 0.038$), and four-times as likely to be diagnosed with severe pre-eclampsia/eclampsia (OR = 3.8, 95%CI = 1.1–13.6; $P = 0.037$). Importantly, all diagnoses were validated against other sources of information, and were systematically reviewed by one of the authors and a senior academic midwife who was blinded to case-control status. The potential links between maternal pre-eclampsia, low-birthweight and subsequent malignancy is an area that might benefit from further research [12].

Nausea is a common symptom of pregnancy which usually abates as pregnancy progresses. The severity

and duration of symptoms varies widely from one woman to another, and within the same woman from one pregnancy to another. In our data, in line with other reports, less than 1 in a 100 women diagnosed with hyperemesis were ill-enough to be hospitalised [65]. Admissions were, however almost four times higher among mothers of leukaemia cases than among mothers of controls, although the numbers involved are small: 8 controls (0.17%), compared with six ALLs (0.59%), one AML (0.61%) and one NHL (0.63%). With respect to sex, four of the ALLs were male (OR = 9.4, 95%CI = 1.7–53.5, $P = 0.011$) and two were female (OR = 1.8, 95%CI = 0.4–9.3, $P = 0.469$). With respect to immunophenotype: the four males had common B-cell precursor ALL (OR = 3.2, 95%CI = 0.9–11.1, $P = 0.070$), one of the two females had T-cell ALL, and no cell phenotype was recorded for the other.

Polyhydramnios is linked with malformation [66], and for AML associations were seen with both polyhydramnios and maternal anaemia (Hb <10 g). Sex-specific analyses revealed that both associations were stronger in girls: the respective odds ratios for polyhydramnios and anaemia being 7.2 (95%CI 2.2–22.9; $P = 0.001$; based on 4 cases) and 4.1 (95%CI 2.3–7.4; $P < 0.0001$; based on 17 cases) for girls, compared with 1.4 (95%CI 0.2–10.4; based on 1 case) and 1.5 (95%CI 0.7–3.3; based on 8 cases) for boys. Two mothers whose daughters developed AML were diagnosed with both polyhydramnios and anaemia (Hb <10 g), and the daughter of a third who was diagnosed with gestational anaemia was a constitutional 47 XXX (super female). Although sex chromosome abnormalities have been associated with a range of haematological malignancies in adults [67,68], they are not usually reported in children, largely because such anomalies are rarely diagnosed before puberty.

The association with maternal anaemia and leukaemia has been noted before [26,69]. With a median birthweight of 3656 g, the 25 children with AML whose mothers had haemoglobin levels below 10 g were, on average, heavier than any other diagnostic group. In addition, they were diagnosed at an earlier age (median 1.9 years) than other children with AML (median 5.4 years). The complex relationship between maternal haemoglobin, folate status, fetal growth, placentation, and pre-eclampsia is the subject of current research [64,70]. Unfortunately, folate status is not routinely monitored during pregnancy. However, pre-treatment and remission blood samples were collected as part of the UKCCS [23] and findings for folate metabolism [21,71] will form the subject of a future UKCCS publication.

4.4. Summary and conclusions

Marked improvements in survival seen for children diagnosed with haematological malignancies have, in general, not been matched by similar aetiological advances. The relative crudity of exposure assessment in many studies, which sits starkly against sophisticated modern molecular classifications, is one reason why this might be so. Our use of clinical records permitted a more precise characterisation of events and exposures than is possible in investigations that rely on self-reporting. Furthermore, our results are unlikely to be biased since information was collected from records compiled before diagnosis, and the 'find' rate was high at 86% for cases, with 81% of cases having information on both matched controls.

Increasing the specificity with which antecedent events are measured yields more precise risk estimates, albeit ones based on progressively smaller numbers. Careful study of these small, sometimes overlapping, groups may, however, prove more informative than the broad-brush "lumping" approach. Indeed, it is the laboratory-based molecular studies of small specific groups of children (for example, twins with leukaemia) that have provided important mechanistic clues in recent years. A more focused strategy to studying the epidemiology of paediatric cancers may provide more aetiological insight.

Conflict of interest statement

None declared.

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