

Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study

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Summary A case control study of Scottish children aimed to identify risk factors for leukaemia and other cancers operating in the prenatal environment, during delivery and neonatally. Cases (0–14 years) were age- and sex- matched to two population-based controls and details abstracted from the mother's hospital obstetric notes. Analyses of 144 leukaemias (124 acute lymphoblastic leukaemias (ALL)), 45 lymphomas, 75 central nervous system (CNS) tumours and 126 'other solid tumours' were conducted using conditional logistic regression. The presence of a neonatal infection significantly reduced the risk of ALL (odds ratio (OR) 0.49, 95% confidence interval (CI) 0.26–0.95), particularly in 0- to 4-year-olds. Positive swab tests confirmed 47% of ALL cases with any infection and 46% of controls. This is consistent with the hypothesis that early exposure to infections may reduce the risk of childhood ALL. Asphyxia at birth significantly increased the risk of leukaemia, which was accounted for by ALL. For the 'other solid tumours' higher levels of maternal education were inversely associated with risk (OR 0.59, 95% CI 0.37–0.94) but positively associated with antibiotics (OR 2.16 95% CI 1.10–4.25) and respiratory tract infections (OR 14.1, 95% CI 1.76–113.7) in pregnancy. No obvious plausible patterns of risk were detected either within or across disease subgroups.

Keywords: childhood; leukaemia; cancer; epidemiology; risk factors; antenatal

The considerable burden of childhood cancer, in terms of both morbidity and mortality, has generated extensive aetiological research over recent decades. Despite these efforts, apart from ionizing radiation, the causes of childhood leukaemia and other malignancies remain largely unexplained (Doll, 1989). The identification of risk factors has frequently focused on the vulnerable period of intrauterine growth and development, birth and neonatal life. The population-based Scottish case control study of childhood leukaemia and cancer has investigated potential risk factors occurring in the prenatal and perinatal period based on data abstracted from the hospital records of both mothers and neonates. A key aspect was to test prior hypotheses as well as identify associations for separate diagnostic subgroups and search for patterns of risk within and across distinct subsets of childhood malignancy.

SUBJECTS AND METHODS

The cases studied were children (0–14 years) diagnosed with leukaemia or another malignancy during 1991–1994 while living in Scotland. The childhood population of Scotland at the 1991 census was 959 268. Pathological confirmation of diagnosis was required and cross-checked with the Scottish Cancer Registry and the UK National Register of Childhood Cancers (Stiller, 1995) optimized completeness of case ascertainment. Population-based controls matched on age (to within one calendar month), sex and health board area of residence were randomly selected from all eligible children registered for primary care. This sampling frame is considered appropriate representation of the general population in this age group (Roberts et al, 1995). An optimum two controls

per case were selected and a full description of the study methodology is published elsewhere (McKinney et al, 1995). Scotland is a participating centre in the UK Children's Cancer Study (UKCCS).

The study was approved by the Local Research Ethics Committees of the 15 Health Boards in Scotland. Consultant clinicians or general practitioners gave consent to approach and interview mothers who gave their signed permission for information to be abstracted from their medical notes. In Scotland, 76 hospitals and maternity units gave access to medical records relating to births from 1976 to 1994. Records for births occurring in England and Wales (3.4%) were obtained by post.

Information from obstetric, delivery and neonatal records was recorded by two trained abstractors onto a specifically designed and highly structured standard form which has been validated in a previous study (Roman et al, 1997). Consistency and data quality were maximized through a programme of continual monitoring, coding checks and duplicate abstractions by the senior midwife abstractor (EF).

Demographic details of the mother were collected at interview. Each child was assigned a deprivation score (five categories representing quintiles of the Scottish population) according to Carstairs and Morris (1991) from the home address at the time of birth and its validated postcode. This was based on 1981 census data for pre-1986 births and the 1991 census thereafter. Illnesses were coded according to the 10th edition of the International Classification of Diseases (WHO, 1994) and the drug codes were classified using groups within the British National Formulary (British National Formulary, 1992).

The Birch and Marsden classification (Birch and Marsden, 1987) was used to define the following diagnostic subsets of cases – leukaemias, lymphomas, central nervous system (CNS) tumours and other solid tumours (neuroblastomas, retinoblastomas, renal,

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Table 1 Odds ratios (OR), 95% confidence intervals (CI) and numbers of exposed cases (ca) and controls (co) for demographic risk factors by diagnostic subgroup

Mother	Category ^a	Total leukaemias	Acute lymphoblastic leukaemia (subset)	Lymphomas	CNS tumours	Other solid tumours
		OR (95% CI) Ca 144, Co 271	OR (95% CI) Ca 124, Co 236	OR (95% CI) Ca 45, Co 82	OR (95% CI) Ca 75, Co 133	OR (95% CI) Ca 126, Co 230
School leaving age (years)	≤ 16 vs > 16	0.77 (0.45–1.29) 36, 77	0.92 (0.53–1.60) 33, 64	1.40 (0.63–3.14) 17, 25	0.61 (0.30–1.25) 14, 35	0.75 (0.46–1.21) 34, 72
Educational qualifications	None vs some	1.18 (0.73–1.91) 100, 180	1.22 (0.73–2.02) 86, 155	0.52 (0.22–1.26) 27, 59	0.73 (0.39–1.36) 47, 92	0.59 ^b (0.37–0.94) 73, 161
Deprivation index at birth	I – least deprived	1.00 24, 50	1.00 18, 45	1.00 8, 11	1.00 12, 17	1.00 16, 29
	II	0.92 (0.46–1.83) 24, 53	1.31 (0.62–2.76) 23, 43	1.01 (0.28–3.60) 10, 13	0.23 (0.06–0.86) 7, 31	0.89 (0.38–2.10) 23, 40
	III	1.27 (0.64–2.48) 30, 48	1.38 (0.66–2.85) 25, 44	0.79 (0.21–3.00) 9, 17	0.96 (0.35–2.60) 18, 23	1.11 (0.47–2.67) 23, 38
	IV	1.03 (0.53–2.03) 27, 53	1.32 (0.63–2.75) 24, 44	0.54 (0.13–2.25) 5, 14	0.79 (0.26–2.38) 13, 25	0.86 (0.36–2.02) 24, 46
	V – most deprived	1.18 (0.56–2.49) 33, 60	1.35 (0.60–3.03) 28, 54	0.53 (0.14–1.96) 8, 17	0.79 (0.28–2.24) 18, 30	0.77 (0.34–1.73) 30, 63
Ethnic group	White vs non-white	1.00 (0.36–2.80) 6, 11	1.10 (0.38–3.16) 6, 10	– 2, 4	– 1, 1	– 3, 5

^aReference category stated first. ^b $P = 0.027$.

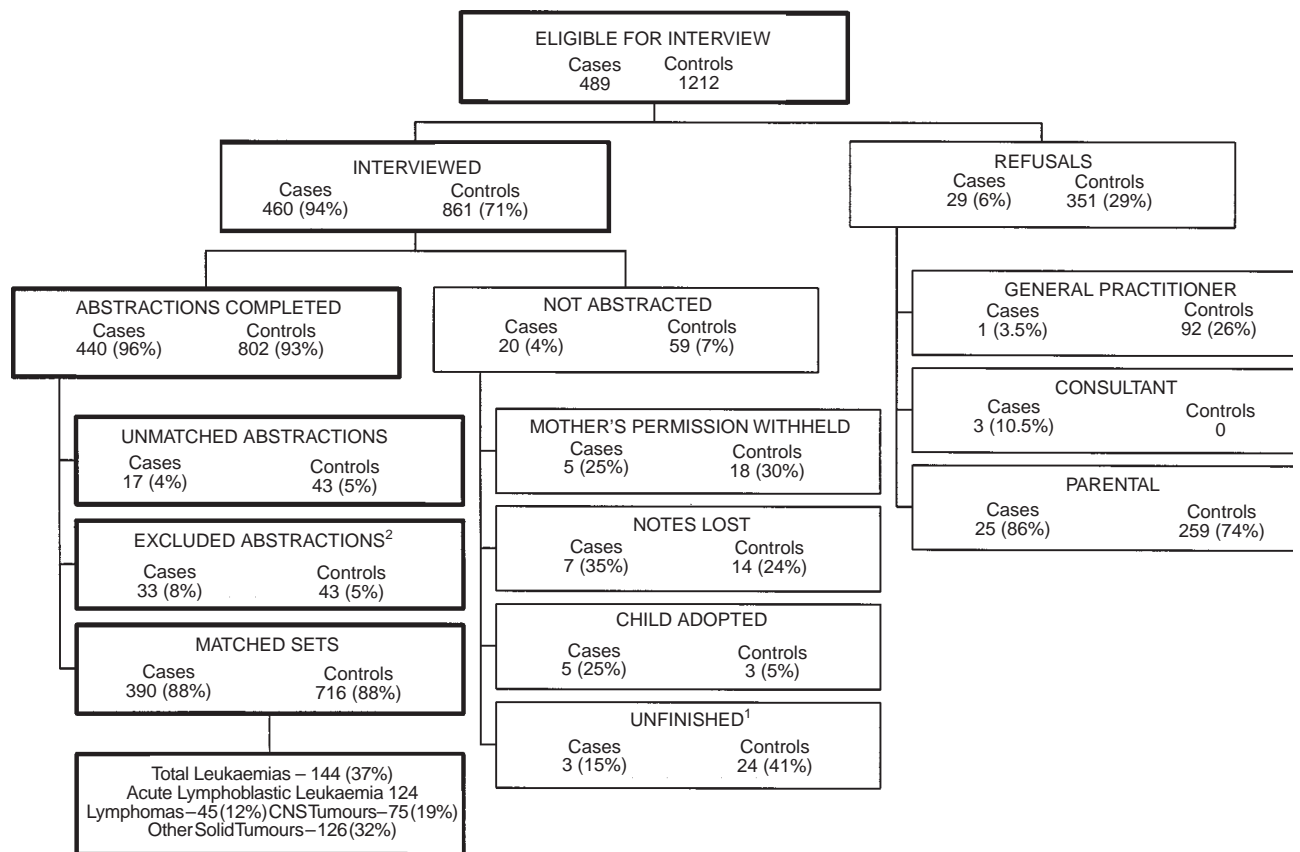


Figure 1 Frequency of case and control interviews and obstetric abstractions. ¹Incomplete at end of study period. ²Exclusions: Down's syndrome, multiple birth, diagnosed under 3 months

hepatic, bone and germ cell tumours, soft tissue sarcomas and carcinomas) and a subset of the leukaemias, acute lymphoblastic leukaemia (ALL).

A profile of the study sample showing the original eligible cases and controls and the proportion of those who were interviewed, along with the proportion of interviewed subjects participating in

Table 2 Odds ratios (OR), 95% confidence intervals (CI) and numbers of exposed cases (ca) and controls (co) for maternal pregnancy related risk factors by diagnostic subgroup

Factor	Category ^a	Total leukaemias	Acute lymphoblastic leukaemia (subset)	Lymphomas	CNS tumours	Other solid tumours	
		OR (95% CI) Ca 144, Co 271	OR (95% CI) Ca 124, Co 236	OR (95% CI) Ca 45, Co 82	OR (95% CI) Ca 75, Co 133	OR (95% CI) Ca 26, Co 230	
Mother's age at birth (years)	≤19	1.86 (0.84–4.10) 14, 15	1.63 (0.69–3.85) 11, 14	3.14 (0.76–13.0) 6, 5	1.73 (0.49–6.10) 6, 7	0.85 (0.40–1.80) 10, 23	
	20–34	1.00 120, 234	1.00 104, 204	1.00 36, 75	1.00 65, 114	1.00 108, 185	
	≥35	0.90 (0.41–1.95) 10, 22	0.98 (0.43–2.24) 9, 18	2.30 (0.38–14.1) 3, 2	0.60 (0.19–1.92) 4, 12	0.66 (0.28–1.55) 8, 22	
Parity	0 vs 1 or more	0.82 (0.55–1.23) 72, 148	0.81 (0.52–1.25) 61, 127	1.11 (0.51–2.39) 29, 51	0.88 (0.50–1.55) 40, 77	1.19 (0.78–1.81) 71, 119	
Gravidity	1 vs more than 1	1.01 (0.67–1.51) 87, 162	0.95 (0.62–1.47) 73, 140	1.05 (0.49–2.27) 29, 52	1.20 (0.66–2.18) 49, 84	0.95 (0.61–1.48) 77, 144	
Prior miscarriage	No vs yes	1.28 (0.68–2.40) 17, 26	1.09 (0.54–2.17) 13, 23	0.26 (0.03–2.10) 1, 7	1.71 (0.66–4.44) 8, 9	0.51 (0.23–1.11) 9, 29	
Infections: Any	None vs 1 or more	1.43 (0.85–2.42) 33, 46	1.44 (0.81–2.55) 26, 36	0.82 (0.28–2.41) 5, 12	0.64 (0.30–1.34) 13, 31	1.81 ^b (1.07–3.06) 30, 32	
		:Respiratory tract	1.46 (0.58–3.67) 9, 12	1.64 (0.60–4.46) 8, 10	– 1, 3	0.38 (0.08–1.97) 2, 9	14.1 ^c (1.76–113.7) 8, 1
		:Viral	– 5, 8	– 4, 8	– 0, 1	– 0, 1	– 2, 3
		:Genitourinary	1.36 (0.66–2.83) 13, 18	1.18 (0.50–2.79) 9, 14	1.50 (0.34–6.70) 3, 4	0.91 (0.38–2.18) 8, 14	2.20 (0.95–5.08) 13, 11
		:Fungal	– 2, 13	– 2, 11	– 1, 2	– 2, 4	– 5, 8
Pre-eclampsia	No vs yes	1.09 (0.66–1.82) 34, 57	1.19 (0.69–2.05) 28, 45	0.53 (0.19–1.51) 6, 17	0.77 (0.38–1.54) 16, 34	1.05 (0.61–1.82) 26, 46	
Excessive vomiting	No vs yes	0.49 (0.17–1.43) 5, 17	0.42 (0.13–1.35) 4, 16	0.64 (0.10–4.16) 2, 5	1.25 (0.46–3.43) 7, 10	0.92 (0.33–2.52) 6, 12	
Ultrasound scans	None vs 1 or more	1.07 (0.57–1.99) 121, 228	1.08 (0.56–2.09) 104, 198	0.32 ^d (0.11–0.92) 28, 65	2.47 (0.86–7.08) 69, 112	2.01 (0.98–4.12) 114, 192	
Abdominal X-rays	None vs 1 or more	2.26 (0.69–7.45) 6, 5	2.50 (0.67–9.31) 5, 4	0.71 (0.17–2.97) 3, 7	1.11 (0.24–5.05) 3, 4	1.20 (0.29–5.02) 3, 5	
Mode of delivery	Normal	1.00 100, 98	1.00 84, 169	1.00 33, 59	1.00 59, 94	1.00 92, 163	
		Assisted	1.05 (0.58–1.91) 20, 38	1.06 (0.56–2.00) 18, 34	0.89 (0.28–2.91) 5, 11	0.59 (0.24–1.45) 8, 21	0.61 (0.31–1.18) 14, 41
		Caesarean	1.43 (0.79–2.59) 24, 35	1.43 (0.77–2.67) 22, 33	1.03 (0.36–3.01) 7, 12	0.68 (0.27–1.72) 8, 18	1.35 (0.71–2.57) 20, 26

^aReference category stated first; ^b $P = 0.028$; ^c $P = 0.013$; ^d $P = 0.034$.

the obstetric data study, is shown in Figure 1. The other solid tumour group comprises 33 neuroblastomas, seven retinoblastomas, 23 renal, three hepatic, 13 bone and 23 germ cell tumours, 13 soft tissue sarcomas and 11 carcinomas and other cancers. Further details of the numbers of case and control mothers interviewed and response rates are published elsewhere (McKinney et al, 1998).

The statistical analysis excluded cases diagnosed under 3 months ($n = 16$), with Down's syndrome ($n = 5$) or from a multiple birth ($n = 12$) which resulted in the loss of 33 cases and their 43 matched controls. In addition, as the analysis was restricted to matched sets, information was lost for a further 17 cases (4%) lacking controls and 43 controls (5%) without a matched case. These were distributed equally across the diagnosis groups. A standard case control analysis (Breslow and Day, 1980) of 390 matched case control sets (326 triplets, 64 pairs) was performed using Stata (StataCorp, 1997). Odds ratios (OR), 95% confidence intervals (CI) and P -values were estimated using conditional logistic regression. The presentation of ORs is restricted to when the prevalence of an exposure was at least 5% in either cases or

controls. When appropriate and unless otherwise stated, missing values were included in the reference category.

RESULTS

Table 1 shows results for demographic factors. There was a reduction in the risk of CNS tumours and other solid tumours, the latter reaching statistical significance, both with increased levels of education and school-leaving age; the children of mothers who were more highly educated were at lower risk. There was no evidence of any trend in risk of any of the malignancies studied in relation to levels of deprivation.

Results for pregnancy-related factors are shown in Table 2. The only statistically significant risks were a positive association with infections during pregnancy for the other solid tumours and an OR < 1 for the lymphomas with ultrasound examinations. The infections were accounted for by respiratory tract infections, of which the majority (5/8 cases) occurred in the third trimester. There was no association of risk with increasing age of mother in any subgroup. Drugs ingested during pregnancy (Table 3) reflected the

Table 3 Odds ratios (OR), 95% confidence intervals (CI) and numbers of exposed cases (ca) and controls (co) for drugs taken in pregnancy

	Total leukaemias OR (95% CI) (Ca 144, Co 271)	Acute lymphoblastic leukaemia (subset) OR (95% CI) (Ca 124, Co 236)	Lymphomas OR (95% CI) (Ca 45, Co 82)	CNS tumours OR (95% CI) (Ca 75, Co 133)	Other solid tumours OR (95% CI) (Ca 126, Co 230)
Antacids	1.15 (0.52–2.55) 11, 17	1.24 (0.50–3.06) 9, 13	1.11 (0.24–5.20) 3, 5	1.27 (0.39–4.14) 6, 9	0.97 (0.42–2.22) 9, 17
Hypnotics and anxiolytics	1.45 (0.67–3.14) 13, 17	2.04 (0.88–4.74) 13, 13	0.43 (0.11–1.63) 3, 12	1.36 (0.57–3.24) 9, 12	0.88 (0.41–1.90) 11, 23
Analgesics	1.33 (0.68–2.62) 15, 21	1.30 (0.60–2.82) 11, 16	0.58 (0.14–2.35) 3, 9	0.86 (0.29–2.55) 5, 10	0.97 (0.45–2.11) 12, 24
Antibiotics	1.60 (0.92–2.80) 26, 34	1.74 (0.95–3.20) 23, 28	0.75 (0.20–2.83) 3, 8	0.65 (0.28–1.46) 9, 23	2.16 ^b (1.10–4.25) 21, 19
Topical anti-fungals	0.10 ^a (0.01–0.75) 1, 18	0.14 (0.02–1.09) 1, 14	1.00 (0.25–4.00) 3, 6	0.74 (0.24–2.23) 5, 12	1.74 (0.82–3.68) 14, 15
Iron preparations	0.95 (0.62–1.45) 75, 143	0.80 (0.51–1.25) 57, 120	0.79 (0.36–1.73) 20, 41	0.89 (0.51–1.58) 39, 75	1.03 (0.66–1.60) 70, 129
Anti-nauseants	– 6, 4	– 4, 2	1.88 (0.39–8.92) 4, 5	– 2, 1	2.02 (0.67–6.12) 7, 7
General anaesthetics	– 4, 2	– 4, 2	– 0, 1	– 3, 0	– 2, 0

^a $P = 0.025$; ^b $P = 0.026$.

observed increase in the risk of infections for the solid tumour group with a raised risk for antibiotics. An inverse association was observed for use of topical antifungals in the leukaemias and ALL groups, although the OR was not statistically significant for the ALLs. Adjustment for maternal age, which is potentially associated with increased attendance at hospital, showed no evidence of confounding this result.

For drugs taken in labour (not tabulated), which included analgesia, there were no significantly positive or negative ORs with the exception of a reduced risk for antacid use for the CNS tumours (cases 14, controls 39, OR 0.33, 95% CI 0.13–0.89).

Neonatal risk factors are presented in Table 4. A significantly reduced risk for neonatal infections is observed for ALL, accounted for by 'skin infections' which mainly comprise omphalitis or infection of the umbilical cord. For ALL, 15 (12.1%) cases and 52 (22.0%) controls were recorded with 'any infection' and two (1.6%) cases and 19 (8.1%) controls with 'skin infections'. For 'any infection' in the ALLs, 7/15 (47%) cases and 24/52 (46%) were confirmed by positive swab test results. Separate adjustment of the significant OR for 'any infection' and skin infections by the other significant associated variables, Apgar scores and birth asphyxiation had no effect on the magnitude or significance of the OR. Adjusting by deprivation score (five categories) and maternal school leaving age (< 16 vs 16 or older), on the grounds that the occurrence of leukaemia may be influenced by social class, had little effect on the significance or magnitude of the OR. The appearance of neonatal infections may be related to mode of delivery with fewer infections expected for caesarean deliveries. Adjustment for mode of delivery did not affect any neonatal infections results for the leukaemia group. The risk of skin infections is significantly raised for the 'other solid tumours' with 6/14 cases being diagnosed with Wilm's tumour.

Two linked exposures, poor Apgar scores (4–6) at 1 min, and birth asphyxia (ICD-10 P21), had significantly raised OR for the leukaemias and ALLs, except for Apgars 4–6 for the ALLs which only approached significance (see Table 4). Proportions of cases and controls exposed for leukaemias were: Apgars 4–6 cases

18.8%, controls 11.1%; birth asphyxia cases 11.1%, controls 4.8%; and correspondingly for ALL cases 19.4%, controls 11.4% and cases 10.5%, controls 4.7% respectively. At 5 min, no children had an Apgar score of 3 or less and for 4–6 the OR was close to unity and non-significant.

Table 5 shows details of infectious exposure in the leukaemias. For all infections taken together, the protective effect is seen to be significant in the 0 to 4-year-old ALLs, but not in those aged 5–14 years. The high proportion of exposed controls in the 0 to 4-year-olds (25.3%) compared to the 5–14 group (16.3%) was reversed for the CNS tumours (0–4, 14.0%; 5–14, 19.3%), reduced for the 'other solid tumours' (0–4, 21.1%; 5–14, 15.9%) and similar for the smaller group of lymphomas (0–4, 23.8%; 5–14, 16.4%).

DISCUSSION

A key strength of the population-based Scottish case control study was the use of medical records as the principal source of information thus avoiding reliance on self-reporting of illness, which is particularly susceptible to recall bias. A very high proportion of notes were abstracted both for case and control mothers, despite elapsed times of up to 20 years between birth and data collection.

Data abstraction was restricted to two trained researchers, one of whom was a midwife. Although not blind to case control status, the abstractors had no knowledge of the case diagnosis and were unaware of the hypotheses under investigation. The use of a specifically designed highly structured and previously validated data collection form (Roman et al, 1997) reduced the likelihood of systematic bias. The method of analysis was conservative, using only matched sets, resulting in the loss of a small amount of data, but this was proportionately distributed between the cases and controls and across diagnostic groups.

The entire study was designed to collect interview data along with further independent sets of information from obstetric and general practitioner records. Recruitment into the interview phase of the study may have been subject to bias as the refusal rate for eligible cases was 6% compared to 26% for controls. However,

Table 4 Odds ratios (OR), 95% confidence intervals (CI) and numbers of exposed cases (ca) and controls (co) for neonatal risk factors by diagnostic subgroup

Factor	Category ^a	Total leukaemias OR (95% CI) Ca 144, Co 271	Acute lymphoblastic leukaemia (subset) OR (95% CI) Ca 124, Co 236	Lymphomas OR (95% CI) Ca 45, Co 82	CNS tumours OR (95% CI) Ca 75, Co 133	Other solid tumours OR (95% CI) Ca 126, Co 230
Gestation (weeks)	38–42 vs < 38	1.00 (0.49–2.03) 14, 26	0.93 (0.44–1.97) 12, 24	0.51 (0.13–1.93) 4, 12	1.00 (0.42–2.40) 9, 16	0.93 (0.43–2.01) 12, 24
Birthweight (g)	< 2500	1.84 (0.67–5.04) 9, 10	1.52 (0.52–4.43) 7, 10	2.03 (0.42–9.75) 4, 4	1.36 (0.35–5.26) 4, 5	– 5, 11
	2500–3499	1.00 74, 149	1.00 64, 131	1.00 21, 40	1.00 39, 69	1.00 70, 119
	≥ 3500	1.12 (0.73–1.73) 60, 112	1.17 (0.74–1.85) 52, 95	0.99 (0.43–2.28) 19, 38	0.99 (0.54–1.83) 32, 58	0.84 (0.54–1.33) 51, 100
	Admitted to special care Unit	No vs yes 40, 58	1.53 (0.93–2.50) 36, 52	1.56 (0.93–2.62) 36, 52	0.70 (0.29–1.69) 10, 22	0.85 (0.38–1.89) 12, 24
Jaundice	No vs yes 49, 109	0.79 (0.51–1.20) 49, 109	0.77 (0.49–1.21) 44, 100	0.67 (0.32–1.44) 20, 44	0.87 (0.48–1.58) 30, 58	1.04 (0.66–1.63) 46, 82
Initially breastfed	No vs yes 52, 99	0.96 (0.62–1.49) 52, 99	0.92 (0.58–1.47) 44, 87	0.86 (0.41–1.84) 18, 36	1.39 (0.72–2.67) 31, 47	0.73 (0.44–1.19) 38, 82
Neonatal Infections	No vs yes	0.62 (0.34–1.11) 19, 55	0.49 ^d (0.26–0.95) 15, 52	1.18 (0.50–2.80) 10, 15	0.91 (0.38–2.15) 12, 23	0.97 (0.55–1.71) 22, 43
	Any	0.76 (0.38–1.51) 13, 33	0.63 (0.29–1.36) 10, 30	1.43 (0.55–3.68) 9, 11	0.81 (0.30–2.21) 7, 15	0.56 (0.27–1.16) 11, 34
	Conjunctivitis	No vs yes 2, 19	0.20 ^b (0.05–0.87) 2, 19	0.20 ^b (0.05–0.87) 2, 19	– 2, 4	0.40 (0.08–2.10) 2, 8
Skin	No vs yes	1.00 111, 225	1.00 97, 195	1.00 38, 67	1.00 65, 109	1.00 106, 185
	7+	1.81 ^c (1.03–3.19) 27, 30	1.79 (0.99–3.24) 24, 27	0.63 (0.19–2.09) 4, 10	0.66 (0.22–1.96) 6, 15	0.66 (0.30–1.44) 10, 27
	4–6	– 4, 8	– 2, 7	– 0, 3	– 3, 4	– 5, 9
1–3	–	–	–	–	–	
Problems at birth						
Complications of cord	No vs yes 17, 23	1.36 (0.69–2.68) 17, 23	1.10 (0.52–2.33) 13, 22	1.84 (0.46–7.41) 4, 4	1.21 (0.43–3.44) 7, 10	0.61 (0.29–1.26) 11, 31
Cyanosis	No vs yes 9, 28	0.57 (0.26–1.24) 9, 28	0.53 (0.23–1.22) 8, 26	1.90 (0.57–6.39) 6, 6	0.48 (0.15–1.51) 4, 15	0.87 (0.41–1.83) 11, 23
Vomiting	No vs yes 5, 15	0.63 (0.22–1.77) 5, 15	0.63 (0.20–1.97) 4, 12	1.56 (0.24–10.1) 3, 4	1.08 (0.28–4.18) 5, 7	1.36 (0.57–3.26) 9, 13
Cephalohaematoma	No vs yes 7, 15	0.88 (0.34–2.33) 7, 15	0.77 (0.26–2.34) 5, 12	1.79 (0.36–8.97) 3, 3	1.15 (0.32–4.14) 4, 6	– 1, 8
scalp injury	No vs yes 16, 13	2.44 ^g (1.15–5.20) 16, 13	2.41 ^h (1.05–5.52) 13, 11	1.79 (0.36–8.97) 3, 3	– 3, 4	1.21 (0.52–2.80) 10, 15
Birth asphyxiation	No vs yes					

^aReference category stated first. ^b $P = 0.032$; ^c $P = 0.038$; ^d $P = 0.034$; ^e $P = 0.032$; ^f $P = 0.008$; ^g $P = 0.020$; ^h $P = 0.039$.

66% of the controls were the 'first choice' mothers to be interviewed and the geographical pattern and age distribution of the refusers did not differ between cases and controls.

The testing of case control differences in over 200 variables, resulted in 13 ORs significantly greater or less than unity. Multiple testing and small numbers mean these results could potentially be explained by chance. However, interpretation of their significance will depend on the existence of a prior hypothesis, biological plausibility, the presence of a 'dose-response' and consistency with other published reports of the same effect. The results from the present study are described by subgroup and discussed in the context of findings from other studies. A study of neonatal exposure to Vitamin K is already published (McKinney et al, 1998).

Leukaemias and acute lymphoblastic leukaemia

One striking finding was the significant deficit of neonatal infections for children who later developed ALL, applying especially to those diagnosed between the ages of 0 and 4 years. Protection appears to be most prominent for children diagnosed in the 'childhood peak' of

ALL, which mainly comprises the common pre-B-cell immunophenotype. The negative association for neonatal infections supports the hypothesis proposed by Greaves and Alexander (1993). This postulates that a lack of exposure to infections in infancy and immunological isolation increases the risk of common ALL, because in the absence of early exposure the immune system may remain 'unprogrammed' and unable to respond appropriately later in life (Greaves, 1997).

The restriction of the protective effect of infections to the young leukaemias is unlikely to be artefactual. The differential frequency of infections by age group in the ALLs is clearly not present in the CNS group, although it is seen to a lesser extent in the small lymphoma group and the heterogeneous 'other solid tumours'.

A significant excess of control children had 'any infection', mainly accounted for by skin infections. Clinical observations of an infection were accompanied by confirmed positive laboratory swab tests for approximately half of all the infections for both cases and controls.

To address the issue of confounding, adjustment was made for the other significant variables and those considered to an appro-

Table 5 Frequencies, odds ratios (OR) and 95% confidence intervals (CI) of neonatal infections for the leukaemias and acute lymphoblastic leukaemias by age

Infection	Age group	Total leukaemias (n = 144)			Acute lymphoblastic leukaemias (n = 124)		
		Cases n (%)	Controls n (%)	OR (95% CI)	Cases n (%)	Controls n (%)	OR (95% CI)
Any (1 or more)	0-4	10 (11.8)	39 (23.6)	0.40 ^a (0.17-0.90)	9 (11.7)	38 (25.3)	0.35 ^b (0.15-0.83)
	5-14	9 (15.3)	16 (15.1)	1.10 (0.47-2.59)	6 (12.8)	14 (16.3)	0.85 (0.32-2.27)
Respiratory tract	0-4	0	1	-	0	1	-
	5-14	0	1	-	0	1	-
Gastrointestinal tract	0-4	0	0	-	0	0	-
	5-14	0	1	-	0	1	-
Fungal	0-4	1	3	-	1	3	-
	5-14	1	0	-	0	0	-
Skin	0-4	2 (2.4)	14 (8.5)	0.27 (0.06-1.21)	2 (2.6)	14 (9.3)	0.27 (0.06-1.21)
	5-14	0	5	-	0	5	-
Conjunctivitis	0-4	7 (8.2)	23 (13.9)	0.55 (0.22-1.40)	6 (7.8)	22 (14.7)	0.47 (0.17-1.30)
	5-14	6 (10.2)	10 (9.4)	1.22 (0.43-3.47)	4 (8.5)	8 (9.3)	1.00 (0.30-3.32)
Other ^c	0-4	1	3	-	1	3	-
	5-14	3	1	-	2	1	-

^aP = 0.027; ^bP = 0.017; ^cIncludes ICD-10 P36 Bacterial sepsis of newborn and P39.9 Infection specific to the perinatal period, unspecified.

appropriate proxy for social class, i.e. deprivation and maternal school-leaving age. The results remained unaffected and therefore unexplained by social class, which is perhaps not surprising as neither deprivation nor school-leaving age are significant in the univariate analysis. If lower social class is related to higher infectious exposure the general direction of the results are not supportive of the infections hypothesis. Caesarean delivery is likely to result in reduced exposure to infection compared to vaginal delivery, but the neonatal infections remained independent of this potential confounder.

A negative association was observed for maternal use of topical antifungals, primarily pessaries prescribed for vaginal thrush/candidiasis, for the all leukaemia category. This was not explained by maternal age, a possible indicator of increased levels of hospital care and, consequently, increased frequency of recording. The presence of candida may act as a marker for other vaginal infections (Cotch et al, 1998) and increase exposure to infections in vaginally delivered babies. Adjustment for type of delivery did not alter the OR for antifungal medication, which provides limited support for the theory that exposure to infectious agents reduces the risk of childhood ALL.

Few other studies have reported on neonatal or early infections. Exposure to specific viral infections under 6 months of age, as reported at interview, has been noted to increase the risk of leukaemia/lymphoma (McKinney et al, 1987). This is in contrast to a Dutch study from a postal questionnaire showing that children with leukaemia experienced fewer infections in the first year of life (van Steensel-Moll et al, 1986).

Reports of increased risk of leukaemia for first-born children have been inconsistent (Fasal et al, 1971; Shaw et al, 1984; Roman et al, 1997; Westergaard et al, 1997). Our results for neither first pregnancies nor first live births were statistically significant for leukaemia (or ALL). Children born first in a family are likely to

have lower exposure to infections than those of a higher birth order and our findings of lowered risk for not being first born are weakly supportive of the delayed infectious exposure hypothesis.

The following observations summarize the evidence consistent with the prior hypothesis of a low frequency of infections increasing risk. Significantly reduced ORs for neonatal infections, particularly in the 0 to 4-year-olds, and the lowered risk for antifungal use in pregnancy are the strongest signals of support, with parity providing weaker corroboration.

No association for all leukaemias or ALL was found with high birthweight, in common with some (McKinney et al, 1987; Golding et al, 1990; Zack et al, 1991; Roman et al, 1997), but not all studies (Fasal et al, 1971; Daling et al, 1984; Shu et al, 1988; Kaye et al, 1991; Cnattingius et al, 1995; Ross et al, 1996; Westergaard et al, 1997), although high birthweight has been linked to acute myeloid leukaemia (Roman et al, 1997; Westergaard et al, 1997) and children diagnosed with cancers under 2 years (Yeazel et al, 1997). Ross and colleagues (Ross et al, 1996) argue for a biological mechanism involving insulin-like growth factor (IGF-1) to explain risks correlated with high birthweight.

Perinatal hypoxia was not associated with childhood leukaemia but was linked to 'other and unspecified solid tumours' in a Swedish birth registry study (Forsberg and Kallen, 1990). This contrasts with the present results where both poor Apgar scores and birth asphyxia recorded in the notes raised the risk for leukaemias. The reason for these associations is not clear and it is notable the effect did not persist to the Apgars at 5 min.

Childhood leukaemia and maternal use of drugs in pregnancy and during labour have been extensively studied with links observed for the following labour drugs - inhaled nitrous oxide anaesthesia (Zack et al, 1991), narcotic analgesia (McKinney et al, 1987; Gilman et al, 1989; Golding et al, 1990) and sedatives and tranquillizers in pregnancy (McWhirter and Chant, 1990). The

present study lent little support to the concept of transplacental leukaemogenesis effected by maternal drug use.

Lymphomas

The finding that significantly more mothers of control children received ultrasound scans is not supported by other published literature (McKinney et al, 1987; Shu et al, 1994). The majority of examinations were conducted in the second trimester and increasing numbers of scans conferred greater protection. The explanation for this is unlikely to be biological and ultrasound examinations may well be markers of other exposures. The separate ORs for Hodgkin's disease and non-Hodgkin's lymphoma are both less than unity, but neither are statistically significant. A recent study of non-Hodgkin's lymphoma revealed few maternal or perinatal risk factors (Adami et al, 1996).

Central nervous system tumours

The only maternal or neonatal factor associated with risk of developing a CNS tumour was an inverse association with use of antacids during labour. The absence of any other significant risks is consistent with the findings of McCredie et al (1994a, 1994b). No association was found for anti-nausea medication during pregnancy, thus failing to support the findings from an American study of children with astrocytomas (Kuijten et al, 1990). N-nitrosatable drugs have been postulated as transplacental carcinogens, but neither this or another study (Carozza et al, 1995) found an elevated risk. Use of narcotic analgesics during pregnancy and labour have been linked specifically to childhood CNS tumours (Linet et al, 1996), but our study results were non-significant. Neonatal infections and neonatal distress observed as increasing risk by Linet et al (1996) had non-significant ORs close to unity in the current study.

Other solid tumours

The analysis of a solid tumour group was pragmatic, as, although subtypes within this subgroup may have differing aetiologies, the consequence of further subdivision would have been unacceptably low power. Some infections in pregnancy are known to have teratogenic consequences; for example, rubella and cytomegalovirus, but the search for in-utero infections which may be transplacental carcinogens has been unsuccessful. The current study has shown a significantly raised risk of infections in pregnancy for the other solid tumours, accounted for by the respiratory tract. Interpretation is difficult as the confidence intervals are wide, particularly for the respiratory tract infections, and the infections relate to a mixed group of tumour types, none of which predominated, indicating a causal link is improbable.

Neonatal skin infections were associated with a significantly increased risk for the other solid tumours. This was unsupported by other results in this exposure category as the finding was not restricted to any particular tumour type and the OR for 'any neonatal infection' was in the opposite direction.

CONCLUSIONS

Overall, few specific maternal or neonatal risks were statistically significant for individual disease subgroups. This may represent a real effect implying that early exposures are not important

determinants of risk or simply reflect a lack of statistical power. The possibility remains of there being risks associated with factors which either are unmeasured or were represented by insufficient numbers in the current study; for example, maternal ingestion of a specific drug. The most notable finding was a negative association with neonatal infections and leukaemia and ALL. This supports the concept of infectious exposure in early life conferring protection against these malignancies. The combination of data from this and other similar population-based studies will improve power and, crucially, improved size will permit examination by diagnostic groups that are more clearly defined both at the histological and molecular level.

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