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Childhood leukaemia and infectious exposure: A report from the United Kingdom Childhood Cancer Study (UKCCS)

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ABSTRACT

Data from a national case-control study are used to explore the relationships between childhood leukaemia, infant infection and three markers of infectious exposure – birth order, infant-activity group attendance and area-based deprivation. Amongst controls, clinically diagnosed infection in the first year varied little with birth order and infant-activity group attendance – with 4 in 5 children having at least one infection, and each child averaging around 2.9 (2.8–3.0). Amongst cases of acute lymphoblastic leukaemia (ALL), the levels of infection increased as the indices of infectious exposure increased – for example, odds ratios associated with at least one infection in the first year being 0.9 (95% confidence interval (CI): 0.6–1.4) for birth order one and 1.6 (95% CI: 1.1–2.2) for birth order two or more. By contrast, interview data were misleading, with mothers – particularly case mothers – consistently under-reporting. We conclude that the findings based on clinical data, combined with the markers of infectious exposure, confirm the observation that immune dysregulation among children who develop ALL is detectable from an early age.

1. Introduction

The potential aetiological role of infection in the development of childhood leukaemia has been the subject of many epidemiological studies and reports. To date, however, no specific agents have been identified and the mechanism by which infectious exposures might influence subsequent leukaemia risk remains a much debated topic.[1,2] A key reason for this uncertainty is the lack of consistency between study findings, and the present paper explores some of the reasons why this may occur.

Unravelling the relationship between disease risk and previous infectious exposure is not straightforward. With a view to quantifying children's likely exposure to infectious agents at various time-points, a wide range of proxies have been employed including family measures of socio-economic status and residential location[3,4]; parental indicators of social contact outside the home[1,5]; markers of the child's social activity such as birth order[6–8] and pre-school group attendance[9–11]; as well as infectious illness histories of both the child[8,12–17] and their mothers.[17–22]

In order to investigate the relationship between leukaemia and infection as comprehensively as possible, the United Kingdom Childhood Cancer Study (UKCCS) collected information on a number of markers of infectious exposure from multiple sources (www.ukccs.org). A unique facet of the UKCCS is that, in addition to asking mothers about their child's health, systematic abstractions of primary-health care

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data contemporaneously compiled before diagnosis/interview were also undertaken.[12,23] Using these data we have already demonstrated that children who develop leukaemia between the peak ages of 2 and 5 years have more infectious illness episodes in the first year of life than children who do not.[12] The present paper expands on this work by examining the relationship between childhood leukaemia, infectious illness episodes and three commonly used markers of childhood infectious exposure – birth order, maternal reports of infant social activity outside the home and a census-derived measure of deprivation. In addition, results based on clinical diagnoses of infection are compared with those based on maternal self-report.

2. Material and methods

The UKCCS is a national population-based case-control study, and full details of its conduct and ethical approvals have been previously described.[24] Briefly, children aged 0–14 years diagnosed with leukaemia between 1991 and 1996 in Great Britain were eligible. For each case, two controls matched by sex, month and year of birth and region of residence at diagnosis were randomly recruited from primary care population registers.

At interview, mothers were asked a series of structured questions about the infectious illnesses that their child had during their first year of life. This included general questions about colds, diarrhoea, vomiting, ear infections, eye infections and mouth infections; as well as more specific ones about illnesses such as measles and chicken pox. For each infectious illness episode, mothers were asked whether or not they had consulted a doctor and, if so, whether any medications had been prescribed. At the end of this section, mothers were also asked whether or not their child had any infections that they had not been asked about, and about other factors that may have influenced their child's exposure to infection during infancy. Mothers were also asked about their child's social activity with other infants and children outside the home in the first year of life. In particular they were asked whether they regularly (at least once a week) attended a nursery, play group, mother and toddler group, childminder, swimming, gym group or any other group. For each positive response, mother's were asked how old their child was when they first attended.[9]

At interview, consent to access the child's primary care (general practice – GP) records was also requested; and all information contained within these routinely compiled health records from birth until diagnosis (pseudo-diagnosis date for control children) was subsequently abstracted onto specially designed forms by centrally trained research staff. These data, which included all symptoms, diagnoses and drugs recorded at each consultation, were centrally coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)[25] and drugs to a schema based on the British National Formulary.[26]

The data analysed in this report are from the six UKCCS administrative areas that systematically abstracted GP records – one region routinely abstracted data on each case and both controls, whilst others opted for one control per case at varying times as the study progressed – three doing so almost from the outset, and two changing tack part-way through.[12] Importantly, in common with other components of the UKCCS that only collected additional data on one of the two individually matched controls, this control – the lowest numbered (first randomly selected) interviewed control in the series – was identified in advance of abstraction.[24,27]

Enumeration district 'deprivation' indices at birth were calculated using the same methods as described for the UK as a whole.[3] As in previous UKCCS publications,[12] in order to increase precision and statistical power all available controls were used as the comparison group. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression with adjustment for UKCCS administrative area of residence at diagnosis, sex and age at diagnosis (in single years).[28] The analyses presented here focus on the first 12 months of life, and cases diagnosed before 15 months of age and their corresponding controls are excluded. Also excluded are children who had Down's syndrome because of the known relationship between Down's syndrome and leukaemia and between Down's syndrome and infection.[29] All analyses were conducted using STATA.[30]

3. Results

Socio-demographic characteristics of the 811 leukaemia cases and 1288 controls are compared in Table 1. As expected, the sex and age distributions at diagnosis/pseudo-diagnosis were similar – the marginal non-significant differences reflecting the fact that in this dataset some cases were matched to one control and others were matched to two. The interval between the child's diagnosis/pseudo-diagnosis and parental interview was, on average, greater for controls than cases; and control children were around 6–10 months older than case children at the time of interview. With respect to indicators of infectious exposure, participating cases and controls were similar with respect to their birth order, but controls were significantly more likely ($P < 0.05$) to have regularly attended social groups outside the home and to live in more affluent areas at the time the child was born.

The relationship between infectious illness frequency in the first year of life and birth order, infant social activity outside the home and deprivation is summarised in Table 2. Control children received an infectious diagnosis from their GP an average of 2.9 (95% CI 2.8–3.0) times in their first year of life. This varied little with birth order or social activity outside the home. However, controls living in the most deprived areas (those in the highest deprivation quintile) had significantly more infectious illnesses diagnosed than those residing in more affluent areas. In comparison to controls, case children averaged significantly more infectious illness episodes overall (3.2; 95% CI 3.1–3.3; $P < 0.01$). Moreover, children with acute lymphoblastic leukaemia of birth order two or more tended to have more infectious illness episodes diagnosed in the first year of life (3.6; 95% CI 3.4–3.7) than controls (2.9; 95% CI 2.8–3.0) and cases of birth order one (2.7; 95% CI 2.5–2.9). The pattern was similar for children with all who regularly attended infant activity groups outside the home (3.3; 95% CI 3.1–3.5) and those in the lowest deprivation category (3.8; 95% CI 3.5–4.1).

Table 1 – Characteristics of leukaemia cases and their controls with primary-care records, UKCCS, 1991–1996

	Controls	Leukaemia	
		Total[a]	Acute lymphoblastic (ALL)
Total	1288 (100)	811 (100)	703 (100)
Sex			
Male	711 (55.2)	442 (54.5)	387 (55.0)
Female	577 (44.8)	369 (45.5)	316 (45.0)
Age (years) at diagnosis			
1	94 (7.3)	58 (7.2)	43 (6.1)
2–5	726 (56.4)	455 (56.1)	425 (60.5)
6–9	208 (16.2)	132 (16.3)	108 (15.4)
10+	260 (20.2)	166 (20.5)	127 (18.1)
Mean (95% confidence interval (CI))	5.9 (5.7–6.1)	6.0 (5.7–6.2)	5.7 (5.5–6.0)
Age (years) at interview			
1	15 (1.2)	25 (3.1)	16 (2.3)
2–5	689(53.5)	454 (56.0)	421 (59.9)
6–9	294 (22.8)	156 (19.2)	132 (18.8)
10+	290 (22.5)	176 (21.7)	134 (19.1)
Mean (95% CI)	7.0 (6.7–7.2)	6.5 (6.2–6.7)	6.2 (6.0–6.5)
Birth order[b]			
1	561(43.7)	343 (42.5)	301(43.0)
2+	723 (56.3)	465 (57.5)	399 (57.0)
Pre-school activity[c]			
No	606 (47.0)	452 (55.7)	387 (55.0)
Yes	682 (53.0)	359 (44.3)	316 (45.0)
Deprivation at birth[d]			
Low/intermediate	1093 (85.1)	648 (80.1)	565 (80.6)
High[e]	192 (14.9)	161(19.9)	136 (19.4)

a 440 (54%) cases had two controls.
b Because of adoption, birth order was not available for three cases and 4 controls.
c Regular social activity (at least once a week) outside the home in the first year of life.
d Because of adoption birth address was missing for 2 cases and 3 controls.
e Top 20%, most deprived areas in Great Britain.

Table 2 – Mean number of primary care visits for infection systematically extracted per child in the first year, UKCCS, 1991–1996

		Controls		Leukaemia			
				Total		ALL	
		N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
Infectious diagnosis[a]		1288	2.9 (2.8–3.0)	811	3.2 (3.1–3.3)	703	3.2 (3.1–3.3)
– Birth order[b]	1	561	2.9 (2.7–3.0)	343	2.8 (2.7–3.0)	301	2.7 (2.5–2.9)
	2+	723	2.9 (2.8–3.0)	465	3.4 (3.3–3.6)	399	3.6 (3.4–3.7)
– Regular social activity	No	606	2.9 (2.7–3.0)	452	3.0 (2.9–3.2)	387	3.1 (2.9–3.3)
outside the home[c]	Yes	682	2.9 (2.8–3.1)	359	3.4 (3.2–3.6)	316	3.3 (3.1–3.5)
– Deprivation at birth[d]	Low/intermediate	1093	2.8 (2.7–2.9)	648	3.0 (2.9–3.1)	565	3.0 (2.9–3.2)
	High[e]	192	3.3 (3.0–3.6)	161	3.9 (3.6–4.3)	136	3.8 (3.5–4.1)

a International Classification of Diseases 10th revision = A00–B99, H10, H66, J00–J11, J18–J22, L00–L03, L08, P35–P39.
b Because of adoption, birth order was not available for three cases and four controls.
c Regular social activity (at least once a week) outside the home in the first year of life.
d Because of adoption, birth address was not available for two cases and three controls.
e Top 20%, most deprived areas in Great Britain.

For acute lymphoblastic leukaemia, odds ratios distributed by birth order, social activity outside the home and deprivation are presented in Table 3. As well as findings for the totality of infection, results for the five most common infections recorded in primary care records – upper respiratory tract infection (URTI), conjunctivitis, gastro-intestinal, otitis media and fungal infection – are also given. The proportions with at least one infections illness were 83.1% and 82.4% for controls and cases, respectively, for birth order one (OR = 0.9, 95% CI = 0.6–1.4), and 80.9% and 87.2% for birth order two or more (OR = 1.6 95% CI = 1.1–2.2). This disparity is reflected in the individual infections, with all of the odds ratios for birth order two or more being greater than one.

Similarly, amongst children who did not regularly attend infant activity groups, infection levels were comparable for cases and controls – 81.4% of controls and 82.2% of cases (OR = 1.0; 95% CI 0.7–1.4) having at least one infection in the first year of life. By contrast, among those who regularly attended social groups outside the home, infection levels were significantly higher for cases than for controls – 82.4% of controls and 88.3% of cases (OR = 1.7; 95% CI 1.1–2.5) having at least one infection in the first year of life. Likewise, more cases than controls in the lowest deprivation quintile had at least one infectious illness episode diagnosed (OR = 2.7; 95% CI 1.2–6.0).

For comparative purposes, mothers' reports about infectious illnesses in their children during infancy are presented in Table 4. As well as maternal reports for all infections, findings for infections of the eye and ear – both of which are relatively easily characterised and were specifically asked about at interview – are also presented. Overall, the levels of maternally reported infection were consistently lower than those recorded in primary care records (Table 3) – even when the infections were not judged severe enough to engender a GP visit. Furthermore, in contrast to the findings for clinically diagnosed infection, the odds ratios based on maternal report tended to be reduced, some significantly so, and showed little variation with either birth order, infant activity outside the home or deprivation. For example, the odds ratios for maternally reported eye infection (with a GP visit) for first and subsequently born children were 0.9 (95% CI = 0.6–1.3) and 0.7 (95% CI = 0.5–1.0), respectively.

Table 4 also shows that mothers were more likely to report infections for first born children than for later births. The proportions of controls and cases with at least one report of an infection being 76.5% and 75.1% (OR = 0.9, 95% CI = 0.6–1.2) for birth order one, and 75.1% and 71.7% (OR = 0.8, 95% CI = 0.6–1.1) for birth order two or more. The slight deficit amongst cases compared to controls was more pronounced amongst those whose mother reported taking their child to

Table 3 – Numbers of ALL cases with at least one episode of an infectious illness in the first year of life, as recorded in their primary care records and related odds ratios[a]: stratified by birth order, social activity outside the home in the first year of life and deprivation at birth

Infection proxy	Infection (ICD-10)	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)
Birth order[b]		One			Two or more		
	Total	561 (100)	301 (100)	–	723 (100)	399 (100)	–
	At least one	466 (83.1)	248 (82.4)	0.9 (0.6.1.4)	585 (80.9)	348 (87.2)	**1.6 (1.1–2.2)**
	– URTI (J00–J06, J11.1)	346 (61.7)	194 (64.5)	1.1 (0.8–1.5)	453 (62.7)	259 (64.9)	1.1 (0.8–1.4)
	– Conjunctivitis (H10, P39.1)	145 (25.9)	71 (23.6)	0.9 (0.6–1.2)	234 (32.4)	141 (35.3)	1.1 (0.9–1.5)
	– Gastro-intestinal (A02–A09)	171 (30.5)	96 (31.9)	1.0 (0.8–1.4)	178 (24.6)	111 (27.8)	1.2 (0.9–1.6)
	– Otitis media (H66)	90 (16.0)	44 (14.6)	0.9 (0.6–1.4)	148 (20.5)	92 (23.1)	1.2 (0.9–1.6)
	– Fungal (B35, B37, P37.5)	91 (16.2)	40 (13.3)	0.8 (0.5–1.2)	87 (12.0)	66 (15.5)	**1.4 (1.0–2.1)**
Regular social activity outside the home		No			Yes		
	Total	606 (100)	387 (100)	–	682 (100)	316 (100)	–
	At least one	493 (81.4)	318 (82.2)	1.0 (0.7–1.4)	562 (82.4)	279 (88.3)	**1.7 (1.1–2.5)**
	– URTI (J00–J06, J11.1)	386 (63.7)	246 (63.6)	0.9 (0.7–1.2)	416 (61.0)	207 (65.5)	1.2 (0.9–1.6)
	– Conjunctivitis (H10, P39.1)	173 (28.6)	107 (27.7)	0.9 (0.7–1.2)	206 (30.2)	105 (33.2)	1.2 (0.9–1.6)
	– Gastro-intestinal (A02–A09)	172 (28.4)	105 (27.1)	0.9 (0.7–1.2)	178 (26.1)	102 (32.3)	**1.4 (1.0–1.8)**
	– Otitis media (H66)	94 (15.5)	70 (18.1)	1.2 (0.8–1.7)	144 (21.1)	66 (20.9)	1.0 (0.7–1.4)
	– Fungal (B35, B37, P37.5)	94 (15.5)	54 (14.0)	0.9 (0.6–1.3)	84 (12.3)	52 (16.5)	1.4 (0.9–2.0)
Deprivation at birth[c]		Low/intermediate			High[d]		
	Total	1093 (100)	565 (100)		192 (100)	136 (100)	
	At least one	896 (82.0)	471 (83.4)	1.1 (0.9–1.3)	155 (81.3)	125 (91.9)	**2.7 (1.2–6.0)**
	– URTI (J00–J06, J11.1)	680 (62.2)	361 (63.9)	1.0 (0.8–1.3)	120 (62.5)	92 (67.7)	1.2 (0.7–2.1)
	– Conjunctivitis (H10, P39.1)	323 (29.6)	175 (31.0)	1.1 (0.9–1.3)	56 (29.2)	37 (27.2)	0.7 (0.4–1.3)
	– Gastro-intestinal (A02–A09)	296 (27.1)	157 (27.8)	1.0 (0.8–1.3)	53 (27.6)	50 (36.8)	1.4 (0.8–2.4)
	– Otitis media (H66)	209 (19.1)	106 (18.8)	1.0 (0.7–1.3)	29 (15.1)	30 (22.1)	1.6 (0.9–3.0)
	– Fungal (B35, B37, P37.5)	139 (12.7)	76 (13.5)	1.1 (0.8–1.5)	39 (20.3)	30 (22.1)	1.0 (0.5–1.7)

a Adjusted for sex, age at diagnosis (single years).
b Because of adoption birth order was not available for three cases and four controls.
c Because of adoption birth address was not available for two cases and three controls.
d Top 20%, most deprived areas in Great Britain.

a doctor (OR = 0.7, 95% CI = 0.5–1.0, for birth order one, and 0.8, 95% CI = 0.6–1.0, for birth order two or more). Unlike the findings for birth order, the broad direction of the effect for maternal report is as expected for infant activity outside the home - infection levels appearing generally higher among those with more social contact. This is also true for deprivation, where those in the bottom quintile had more infectious diagnoses than those in the remaining 80%.

At the individual level, agreement between the illness episodes recorded in GP records and maternal recall at interview

Table 4 – Numbers of ALL cases with at least one episode of an infectious illness in the first year of life, as reported by their mother and related odds ratios[a]: stratified by birth order, social activity outside the home in the first year of life and deprivation at birth

Infection proxy	Maternal self-report	Infection	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)
Birth order[b]			One			Two or more		
		Total	561 (100)	301 (100)	–	723 (100)	399 (100)	–
	Illness	At least one	429 (76.5)	226 (75.1)	0.9 (0.6–1.2)	543 (75.1)	286 (71.7)	0.8 (0.6–1.1)
		– Eye	139 (24.8)	67 (22.3)	0.8 (0.6–1.2)	168 (23.2)	68 (17.0)	**0.7 (0.5–0.9)**
		– Ear	106 (18.9)	44 (14.6)	0.7 (0.5–1.0)	127 (17.6)	72 (18.1)	1.0 (0.7–1.4)
	Illness	At least one	395 (70.4)	196 (65.1)	**0.7 (0.5–1.0)**	479 (66.3)	244 (61.2)	**0.8 (0.6–1.0)**
	+GP visit	– Eye	118 (21.0)	60 (19.9)	0.9 (0.6–1.3)	152 (21.0)	63 (15.8)	**0.7 (0.5–1.0)**
		– Ear	106 (18.9)	44 (14.6)	0.7 (0.5–1.0)	124 (17.2)	70 (17.5)	1.0 (0.7–1.4)
Regular social activity outside the home			No			Yes		
		Total	606 (100)	387 (100)	–	682 (100)	316 (100)	–
	Illness	At least one	423 (69.8)	277 (71.6)	1.1 (0.8–1.4)	551 (80.8)	236 (74.7)	**0.7 (0.5–0.9)**
		– Eye	124 (20.5)	55 (14.2)	**0.6 (0.4–0.9)**	184 (27.0)	80 (25.3)	0.9 (0.7–1.2)
		– Ear	91 (15.0)	64 (16.5)	1.1 (0.8–1.6)	142 (20.8)	52 (16.5)	0.8 (0.5–1.1)
	Illness	At least one	372 (61.4)	234 (60.5)	0.9 (0.7–1.2)	504 (73.9)	207 (65.5)	**0.6 (0.5–0.9)**
	+GP visit	– Eye	111(18.3)	50 (12.9)	**0.6 (0.4–0.9)**	160 (23.5)	73 (23.1)	1.0 (0.7–1.4)
		– Ear	89 (14.7)	63 (16.3)	1.1 (0.8–1.6)	141 (20.7)	51 (16.1)	0.7 (0.5–1.1)
Deprivation at birth[c]			Low/intermediate			High[d]		
		Total	1093 (100)	565 (100)		192 (100)	136 (100)	
	Illness	At least one	824 (75.4)	409 (72.4)	0.8 (0.7–1.1)	148 (77.1)	103 (75.7)	0.9 (0.5–1.5)
		– Eye	266 (24.3)	115 (20.4)	0.8 (0.6–1.0)	41 (21.4)	20 (14.7)	0.6 (0.3–1.2)
		– Ear	195 (17.8)	93 (16.5)	0.9 (0.7–1.2)	38 (19.8)	23 (16.9)	0.8 (0.4–1.5)
	Illness	At least one	739 (67.6)	349 (61.8)	**0.7 (0.6–0.9)**	135 (70.3)	91 (66.9)	0.8 (0.5–1.4)
	+GP visit	– Eye	236 (21.6)	104 (18.4)	0.8 (0.6–1.1)	34 (17.7)	19 (14.0)	0.8 (0.4–1.5)
		– Ear	193 (17.7)	92 (16.3)	0.9 (0.7–1.2)	37 (19.3)	22 (16.2)	0.8 (0.4–1.4)

a Adjusted for sex, age at diagnosis (single years).
b Because of adoption birth order was not available for three cases and four controls.
c Because of adoption birth address was not available for two cases and three controls.
d Top 20%, most deprived areas in Great Britain.

Table 5 – Comparison between infectious episodes contemporaneously recorded in GP notes and maternal recall of infection that was confirmed by a GP

Maternal report of illness with confirmatory GP visit	GP infection record							
	Controls				Cases			
	Yes	No	Sensitivity (%)	PPV[a] (%)	Yes	No	Sensitivity (%)	PPV[a] (%)
Any infection								
Yes	758	118	71.9	86.5	450	56	66.1	88.9
No	297	115			231	74		
Eye infection								
Yes	149	122	39.3	55.0	78	64	32.0	54.9
No	230	787			166	503		
Ear infection								
Yes	84	146	35.3	36.5	61	77	37.4	44.2
No	154	904			102	571		

a PPV, positive predictive value.

was poor, as can be seen from Table 5 . Even for ear infections, where GP confirmation was reported to be high at interview, nearly two-thirds of mothers (cases and controls) whose children had a clinical entry for otitis media did not report an episode with a GP visit at interview – the mothers of only 84 (35.3%) of 238 control children and 61 (37.4%) of 163 case children with recorded diagnoses reporting an ear-infection during the first year of life. As with sensitivity, the predictive value of a positive interview report was similarly disappointing, even for overtly obvious conditions such as infections of the eye where only around 55.0% of case and control mothers' reports were confirmed. In general, however, case mothers' positive reports at interview were marginally more accurate than those of control mothers' – the positive predictive values tending to be slightly higher.

4. Discussion

In the UKCCS we have previously demonstrated that children who develop leukaemia between the peak ages of 2 and 5 years have more infectious illness episodes in the first year of life than children who do not .[12] This paper explores the relationship between childhood leukaemia, infectious illness episodes and three of the most commonly used markers of childhood infectious exposure – birth order,[6–8] attendance at infant activity groups outside the home[9–11] and area-based deprivation.[3,4] In addition, it examines the relationship between clinically diagnosed infections and maternal reports at interview.

Amongst controls, we found that clinically diagnosed levels of infection varied little with birth order and infant group attendance – with the average number of GP visits for infection being 2.9 (2.8–3.0) in the first year, and around 4 in every 5 children having at least one infectious illness diagnosed. There was, however, some indication that children in the bottom deprivation quintile averaged more infectious illness diagnoses than other children (3.3; 3.0–3.6). Patterns were far more pronounced amongst children with ALL than amongst controls, where, for all three markers, the level of infection appears to consistently increase as the index of infectious exposure increases – those of birth two or more, those who regularly attended infant groups and those in the lowest deprivation quintile all having more infectious episodes diagnosed than those in the lower exposure categories.

With respect to the association between ALL and birth order alone, proportions of children from second and subsequent births are similar for controls (56.3%) and cases (57.0%), confirming previous UKCCS findings.[7,9] By contrast, more control mothers than case mothers reported attendance at infant activity groups outside the home (53.0% controls, 45% cases; $P < 0.05$), whereas fewer controls than cases lived in deprived areas (15.0 % controls, 19.3 cases; $P < 0.05$). The latter two findings reflect the fact that participants in epidemiological studies are often more affluent than non-participants – apparent associations arising purely as a result of differential case-control participation.[3,9] Nonetheless, when taken together with more robust estimates such variables can prove useful. In the present case, for example, the association between infectious exposure and the risk of ALL appears consistently raised in the most highly exposed groups - the risks being increased in children with at least one primary care visit for an infection in the first year of life for all high exposure categories; birth order two or more (OR = 1.6 95% CI = 1.1–2.2), regular attendance at infant activity groups (OR = 1.7 95% CI = 1.1–2.5) and living in a deprived area at birth (OR = 2.7 95% CI = 1.2–6.0).

Our findings for clinically diagnosed infection were not replicated by the data recorded at interview. Both case and control mothers consistently under-reported the frequency of infectious illness experienced by their children in the first year of life – more than one in four mothers who took their child to a GP with an infectious illness did not report doing so at interview. The levels of accuracy were even lower when specific infections were considered, for example, only one in every three ear infections diagnosed by a GP was recalled at interview. The degree of under-reporting appeared greater for case mothers than for control mothers with odds ratios for infectious illness estimated from the interview data all tending to be below one, many significantly so ($P < 0.05$). Furthermore, this case-control disparity was unaffected by the likely level of infectious exposure as measured by the proxy variables of birth order, attendance at infant-activity groups and area-based deprivation. For children who attended regular social activity groups outside the home, the two data sources (primary care and interview) yielded statistically significant results in the opposite direction. The odds of developing ALL was significantly raised when based on GP data (OR = 1.7, 95% CI = 1.1–2.5, $P = 0.014$), but reduced when based on mothers report (OR = 0.7, 95% CI = 0.5–0.9, $P = 0.02$).

Underreporting and inaccurate recall of historical events is an acknowledged problem in interview-based epidemiological research, and since the children were around 6–7 years old when their mothers were interviewed such inaccuracies are, perhaps, not surprising. Indeed, with respect to maternal recollections about their children's health, the available evidence suggests that whilst serious health events are reported reasonably accurately[31], common childhood illness and minor complaints, such as those investigated in the present report, are not .[32–34] The reasons behind the differential case-control under-reporting are, however, unclear, but it is possible that minor childhood infections may be even less well remembered by mothers of seriously ill children.

Our novel analyses of primary health-care data suggest that early infectious illness patterns of children who subsequently develop ALL differ from those of children who do not. The evidence for this is twofold. Firstly, our previous analysis which was based on a subset of the data presented here demonstrated that from birth onwards children diagnosed with ALL between the ages of 2 and 5 years had more infections than unaffected children.[12] Secondly, the present analysis shows that amongst infants who are exposed to infection via other children, those who develop ALL after 15 months of age tend to have more clinically diagnosed infections than unaffected controls. In the context of the hygiene hypothesis, our observations have parallels with recent findings on children who subsequently develope allergic disorders.[35,36]

In summary, our analyses of UKCCS data suggest that the findings based on maternal reports of minor illnesses in their children should be interpreted with extreme caution. By contrast, findings based on clinical data combined with markers of infectious exposure confirm the observation that immune

dysregulation in children who develop ALL is detectable from an early age.

Conflict of interest statement

None declared.

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REFERENCES

1. Kinlen L. Infections and immune factors in cancer: the role of epidemiology. *Oncogene* 2004;**23**(38):6341–8.
2. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer* 2006(Feb 9).
3. Smith A, Roman E, Simpson J, Ansell P, Fear NT, Eden T. Childhood leukaemia and socioeconomic status: fact or artefact? A report from the United Kingdom childhood cancer study (UKCCS). *Int J Epidemiol* 2006;**35**(6):1504–13.
4. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G. Socioeconomic status and childhood leukaemia: a review. *Int J Epidemiol* 2006;**35**(2):370–84.
5. Fear NT, Simpson J, Roman E. Childhood Cancer and Social Contact: the Role of Paternal Occupation (United Kingdom). *Cancer Causes Control* 2005;**16**(9):1091–7.
6. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. *Int J Epidemiol* 2001;**30**(6):1428–37.
7. Roman E, Simpson J, Ansell P, Lightfoot T, Mitchell C, Eden TO. Perinatal and reproductive factors: a report on haematological malignancies from the UKCCS. *Eur J Cancer* 2005;**41**(5):749–59.
8. Jourdan-Da Silva N, Perel Y, Mechinaud F, et al. Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. *Br J Cancer* 2004;**90**(1):139–45.
9. Gilham C, Peto J, Simpson J, et al. Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study. *Br Med J* 2005;**330**(7503):1294–9.
10. Neglia JP, Linet MS, Shu XO, et al. Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukaemia. *Br J Cancer* 2000;**82**(1):234–40.
11. Ma X, Buffler PA, Selvin S, et al. Daycare attendance and risk of childhood acute lymphoblastic leukaemia. *Br J Cancer* 2002;**86**(9):1419–24.
12. Roman E, Simpson J, Ansell P, et al. Childhood acute lymphoblastic leukemia and infections in the first year of life: a report from the United Kingdom Childhood Cancer Study. *Am J Epidemiol* 2007;**165**(5):496–504.
13. Dockerty JD, Skegg DCG, Elwood JM, Herbison GP, Becroft ME, Lewis ME. Infections, vaccinations, and the risk of childhood leukaemia. *Br J Cancer* 1999;**80**(9):1483–9.
14. Rosenbaum PF, Buck GM, Brecher ML. Allergy and infectious disease histories and the risk of childhood acute lymphoblastic leukaemia. *Paediatr Perinat Epidemiol* 2005;**19**(2):152–64.
15. Steensel-Moll HA, Valkenburg HA, van Zanen GE. Childhood leukemia and infectious diseases in the first year of life: a register-based case-control study. *Am J Epidemiol* 1986;**124**(4):590–4.
16. Schuz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Association of childhood leukaemia with factors related to the immune system. *Br J Cancer* 1999;**80**(3–4):585–90.
17. Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. *Br Med J* 1958;**30**(5086):1495–507.
18. Fedrick J, Alberman ED. Reported influenza in pregnancy and subsequent cancer in the child. *Br Med J* 1972;**2**(812):485–8.
19. Lehtinen M, Koskela P, Ogmundsdottir HM, et al. Maternal herpesvirus infections and risk of acute lymphoblastic leukemia in the offspring. *Am J Epidemiol* 2003;**158**(3):207–13.
20. Hakulinen T, Hovi L, Karkinen J, Penttinen K, Saxen L. Association between influenza during pregnancy and childhood leukaemia. *Br Med J* 1973;**4**(5887):265–7.
21. Smith MA, Simon R, Strickler HD, McQuillan G, Ries LA, Linet MS. Evidence that childhood acute lymphoblastic leukemia is associated with an infectious agent linked to hygiene conditions. *Cancer Causes Control* 1998;**9**(3):285–98.
22. Naumburg E, Bellocco R, Cnattingius S, Jonzon A, Ekbom A. Perinatal exposure to infection and risk of childhood leukemia. *Med Pediatr Oncol* 2002;**38**(6):391–7.
23. Hughes AM, Lightfoot T, Simpson J, et al. Allergy and risk of childhood leukaemia: results from the UKCCS. *Int J Cancer* 2007(Mar 27).
24. UK Childhood Cancer Study Investigators. The United Kingdom Childhood Cancer Study: objectives, materials and methods. *Br J Cancer* 2000;**82**(5):1073–102.
25. World Health Organization. International Statistical Classification of Diseases and Health Related Problems; 1992.

26. British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary – number 24 (September 1992). London, British Medical Association and The Pharmaceutical Press; 1992.
27. Day N, Skinner J, Roman E, Allen SG, Maslanyj MP, Mee TJ. Exposure to power-frequency magnetic fields and the risk of childhood cancer. UK Childhood Cancer Study Investigators. *Lancet* 1999;**354**(9194):1925–31.
28. Breslow NE, Day NE. *Statistical Methods in Cancer Research. The analysis of case-control studies*, vol. 1. Lyon: International Agency for Research on Cancer; 1980.
29. Roizen NJ, Patterson D. Down's syndrome. *Lancet* 2003;**361**(9365):1281–9.
30. Stata Statistical Software: Release 9 [computer program]. College Station, Texas: Stata Corporation; 2005.
31. Souza-Vazirani D, Minkovitz CS, Strobino DM. Validity of maternal report of acute health care use for children younger than 3 years. *Arch Pediatr Adolesc Med* 2005;**159**(2):167–72.
32. McKinney PA, Alexander FE, Nicholson C, Cartwright RA, Carrette J. Mothers' reports of childhood vaccinations and infections and their concordance with general practitioner records. *J Public Health Med* 1991;**13**(1):13–22.
33. Alho OP. The validity of questionnaire reports of a history of acute otitis media. *Am J Epidemiol* 1990;**132**(6):1164–70.
34. Miller JE, Gaboda D, Davis D. Early childhood chronic illness: comparability of maternal reports and medical records. *Vital Health Stat 2* 2001(131):1–10.
35. Harris JM, Mills P, White C, et al. Recorded infections and antibiotics in early life: associations with allergy in UK children and their parents. *Thorax* 2007;**20**(62):631–7.
36. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? *Br J of Dermatology* 2005;**152**:202–16.