

Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study

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Abstract

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

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

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

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

Results Increasing levels of social activity were associated with consistent reductions in risk of ALL; a dose-response trend was seen. When children whose mothers reported no regular activity outside the family were used as the reference group, odds ratios for increasing levels of activity were 0.73 (95% confidence interval 0.62 to 0.87) for any social activity, 0.62 (0.51 to 0.75) for regular day care outside the home, and 0.48 (0.37 to 0.62) for formal day care (attendance at facility with at least four children at least twice a week) (P value for trend < 0.001).

Although not as striking, results for non-ALL malignancies showed a similar pattern (P value for trend < 0.001). When children with non-ALL malignancies were taken as the reference group, a significant protective effect for ALL was seen only for formal day care (odds ratio = 0.69, 0.51 to 0.93; P = 0.02). Similar results were obtained for B cell precursor common ALL and other subgroups, as well as for cases diagnosed above and below age 5 years.

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

Introduction

The UK childhood cancer study (UKCCS), a large population based case-control study,¹ was designed to test several hypotheses, one of which was that leukaemias and lymphomas may be caused by abnormal responses to common infectious agents. Here, we focus on Greaves's hypothesis that immunological isolation in infancy increases the risk of B cell precursor common acute lymphoblastic leukaemia (cALL).² Proxy variables for exposure to infection must be used; the literature on infectious illnesses occurring in day care settings suggests that social interactions with other children outside the home may be

important,³⁻⁵ and several studies of childhood leukaemia have used such proxies.⁶⁻¹⁰

Precise molecular subclassification of cALL is potentially important for these analyses. The two largest subgroups are those with hyperdiploidy (hyperdiploid ALL) and with fusion of the *TEL* and *AML1* genes (TEL-AML1 ALL). Most (possibly all) children with these lesions have affected clones present at the time of birth,^{11 12} so initiation usually occurs in utero. However, at least one postnatal event also occurs in the development of cALL. Greaves's hypothesis relates to the promotional factors that affect the frequency of this second event.

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

Methods

Participants

This case-control study was conducted in 10 regions across the United Kingdom between 1991 and 1996. Details of the UKCCS study are described elsewhere.^{1 13} Briefly, children diagnosed as having a confirmed malignancy were ascertained through paediatric oncology units, and two controls matched to each case for sex, month and year of birth, and region of residence at diagnosis were randomly selected from population registers. Age at diagnosis of the case was designated as the age at "pseudodiagnosis" of the matched control. A structured questionnaire was used to interview parents of 3838 cases and 7629 controls face to face. Questions about social activity focused on activity with other infants and children, and included information on the number of sessions a week and the number of children attending for specific activities before starting school.

Exposure variables

We defined "social activity" as regular activity (at least once a week) with other infants who were not members of the same household. We defined "day care" as attendance (at least once a week) at a day nursery, nursery school, play group, mother and toddler group, or



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childminder. We defined “formal day care” as any attendance at a day nursery or nursery school, at least two half day sessions a week at a playgroup or mother and toddler group, or at least two half day sessions a week at a childminder with a minimum of four children attending.

Statistical analysis

We excluded children given a diagnosis or pseudodiagnosis before the age of 2 years (649 cases and 1320 controls), as well as children with Down's syndrome (49 cases and 4 controls), which left 9445 eligible children (3140 cases and 6305 controls) (see bmj.com). We analysed data for all cancers combined and separately for ALL, cALL, TEL-AML1 ALL, hyperdiploid ALL, and non-ALL malignancies. To increase precision, we compared each case subgroup with all controls. We also did a case-case comparison of ALL and cALL versus non-ALL malignancies.

Results

Most (86%) mothers of controls reported some social activity with children outside the family in the first year of life (table). Any such activity was associated with a reduced risk of ALL (odds ratio = 0.66; $P < 0.001$). The risk ratios for cALL alone and for the cytogenetic subgroups TEL-AML1 and hyperdiploidy were similarly reduced. Analyses of non-ALL malignancies combined gave a similar result; the only individually statistically significantly reduced risk was for the largest group—central nervous system tumours. With respect to the

case-case comparison (ALL *v* non-ALL malignancies), the dichotomous variable “any social activity” was not significantly reduced. Analyses restricted to 2-5 year olds produced similar results, but we found no evidence that the association was stronger in the childhood peak (2-5 years) than at older ages.

Each category of malignancy showed a significant inverse trend as level of social activity increased. The statistically significant trend ($P = 0.04$) for the comparison of ALL with non-ALL malignancies (right hand column of table) is due largely to the reduced odds ratio for formal day care. Analyses restricted to cases aged 2-5 years gave similar results, although statistical significance was reduced.

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

Estimated risks for children starting day care in the first year of life showed no marked trends with age at

Levels of social activity in the first year of life for acute lymphoblastic leukaemia (ALL), ALL subgroups, and non-ALL malignancies

Activity level	Controls No (%)	ALL		cALL		TEL-AML1		Hyperdiploid ALL		Non-ALL malignancies		ALL <i>v</i> non-ALL malignancy: Odds ratio* (95% CI)
		No (%)	Odds ratio* (95% CI)	No (%)	Odds ratio* (95% CI)	No (%)	Odds ratio* (95% CI)	No (%)	Odds ratio* (95% CI)	No (%)	Odds ratio* (95% CI)	
Aged over 2 years												
Total No†	6238	1272		791		138		417		1825		
Any social activity	5343 (85.7)	1020 (80.2)	0.66 (0.56 to 0.77)	640 (80.9)	0.67 (0.55 to 0.82)	110 (79.7)	0.59 (0.38 to 0.90)	335 (80.3)	0.64 (0.50 to 0.83)	1496 (82.0)	0.78 (0.68 to 0.90)	0.88 (0.73 to 1.06)
No social activity	895 (14.4)	252 (19.8)	1.00	151 (19.1)	1.00	28 (20.3)	1.00	82 (19.7)	1.00	329 (18.0)	1.00	1.00
Social activity, but no day care	2840 (45.5)	587 (46.1)	0.73 (0.62 to 0.87)	358 (45.3)	0.74 (0.60 to 0.91)	60 (43.5)	0.61 (0.38 to 0.97)	199 (47.7)	0.76 (0.58 to 1.00)	880 (48.2)	0.83 (0.71 to 0.96)	0.91 (0.74 to 1.11)
Informal day care only	1768 (28.3)	325 (25.6)	0.62 (0.51 to 0.75)	218 (27.6)	0.67 (0.53 to 0.84)	38 (27.5)	0.60 (0.36 to 1.00)	105 (25.2)	0.57 (0.42 to 0.78)	435 (23.8)	0.72 (0.61 to 0.85)	0.90 (0.71 to 1.13)
Formal day care	735 (11.8)	108 (8.5)	0.48 (0.37 to 0.62)	64 (8.1)	0.44 (0.32 to 0.60)	12 (8.7)	0.47 (0.24 to 0.94)	31 (7.4)	0.38 (0.24 to 0.59)	181 (9.9)	0.73 (0.59 to 0.90)	0.69 (0.51 to 0.93)
P for trend‡			<0.001		<0.001		0.04		<0.001		<0.001	0.04
Aged 2-5 years												
Total No†	2475	671		471		81		248		546		
Any social activity	2156 (87.1)	545 (81.2)	0.63 (0.50 to 0.79)	387 (82.2)	0.67 (0.51 to 0.88)	68 (84.0)	0.73 (0.39 to 1.35)	198 (79.8)	0.57 (0.40 to 0.80)	447 (81.9)	0.66 (0.51 to 0.85)	0.98 (0.73 to 1.31)
No social activity	319 (12.9)	126 (18.8)	1.00	84 (17.8)	1.00	13 (16.0)	1.00	50 (20.2)	1.00	99 (18.1)	1.00	1.00
Social activity, but no day care	1023 (41.3)	294 (43.8)	0.70 (0.54 to 0.89)	195 (41.4)	0.69 (0.52 to 0.93)	35 (43.2)	0.74 (0.38 to 1.43)	115 (46.4)	0.69 (0.48 to 0.99)	234 (42.9)	0.70 (0.53 to 0.91)	1.03 (0.75 to 1.42)
Informal day care only	778 (31.4)	182 (27.1)	0.59 (0.45 to 0.77)	142 (30.1)	0.71 (0.52 to 0.96)	25 (30.9)	0.76 (0.38 to 1.53)	63 (25.4)	0.51 (0.34 to 0.76)	139 (25.5)	0.59 (0.44 to 0.79)	1.01 (0.71 to 1.43)
Formal day care	355 (14.3)	69 (10.3)	0.49 (0.35 to 0.68)	50 (10.6)	0.52 (0.35 to 0.77)	8 (9.9)	0.62 (0.25 to 1.53)	20 (8.1)	0.33 (0.19 to 0.58)	74 (13.6)	0.68 (0.48 to 0.96)	0.73 (0.48 to 1.13)
P for trend‡			<0.001		0.004		0.4		<0.001		0.01	0.2

cALL=B cell precursor common ALL; TEL-AML1=ALL with fusion of the *TEL* and *AML1* genes.

*Odds ratio for cases compared with all controls, or with non-ALL malignancies where stated, adjusted for age at diagnosis/pseudodiagnosis, sex, region, maternal age, mother working at time of birth, and deprivation.

†Excluding missing values.

‡Trend test across categories: none through to formal day care.

first attendance. The greatest reduction in risk of ALL, however, was seen in children who attended formal day care during the first three months of life, for whom the odds ratio remained statistically significant when we used non-ALL malignancies as the reference group (odds ratio = 0.52, 0.32 to 0.83; $P = 0.007$).

Discussion

In this report, one of the principal hypotheses tested was that immunological isolation in infancy increases the risk of cALL. We assessed immunological isolation indirectly, mainly by lack of social activity as indicated by day care attendance in the first year of life. The overall results for ALL show a consistent and statistically significant reduction in risk for each level of social activity in the first year of life and a dose-response trend across increasing levels of activity. Results were similar for cALL and other ALL subgroups, although the numbers for TEL-AML1 ALL were small. The findings were similar when we restricted the analysis to children aged 2-5 years at diagnosis. However, because we also saw similar trends for non-ALL malignancies, we repeated the analyses for ALL with non-ALL malignancies as the comparison group. The estimated risk for formal day care attendance in the first year of life remained significant (odds ratio = 0.69, 95% confidence interval 0.51 to 0.93; $P = 0.02$); the effect was most marked for formal day care within the first three months of life (odds ratio = 0.52, 0.32 to 0.83; $P = 0.007$).

Potential limitations

Participants who respond may differ from those who do not; some responses may systematically differ between cases and controls; and behavioural variables, such as social activity outside the home, may be affected by the preclinical effects of incipient disease.

Some systematic differences between cases and controls existed in this study. Analysis of census data revealed that controls who agreed to take part were living in more affluent areas, and some control parents were interviewed when their children were older than their matched cases. The average interval from diagnosis or pseudodiagnosis to interview was six months for cases and 14 months for controls. Children destined to develop a malignancy may also have more periods of ill health in early life, leading to lower attendance at day care.

Interpretation of our findings depends crucially on whether the protective effect of social activity for non-ALL malignancies is real or due to bias, as the protective effect for ALL is both smaller and less significant when non-ALL malignancies are used as the reference group. Despite this uncertainty, we believe that the difference between ALL and non-ALL malignancies may well be real. A prior hypothesis was that the risk of leukaemia would be increased by a lack of early social activity, and the effect of day care is particularly marked during the first three months of life ($P = 0.007$ for ALL *v* non-ALL malignancies), as was seen in another recent study.¹⁰

Our data for "any social activity" are, inevitably, subjective. At interview, parents were offered a range of activities to describe groups that their children might have attended. We used the responses to these

What is already known on this topic

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

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

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

What this study adds

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

questions to derive the variables used in our analyses. We investigated the possibility of under-reporting by combining the two lowest categories in the combined exposure variable, and this did not affect the results.

Comparison with other studies

Other case-control studies of childhood leukaemia have looked at social activity and day care.⁶⁻¹⁰ Diversity exists for both ages at diagnosis and ages of day care attendance, as well as the definition of day care used. The only study that quantified exposure to other children reported a significant protective effect.¹⁰ Most other studies suggest a reduction in risk of around 30-40% for day care attendance or social activity, though lack of statistical power often leads to imprecise risk estimates.

Although reduced risks in children with several older siblings have been seen in some studies, most studies, like ours, have found no such effects.¹⁴ Other studies have also considered different proxies for exposure to the spectrum of infectious agents. The only European study with comparable numbers of ALL cases to our series inferred social contact from parents' employment status and found no association.¹⁵ Several investigators have reported reduced risks of ALL or cALL in children with many infections,^{8, 15} or with specific infections in infancy, such as frequent otitis media or roseola,^{6, 7} but others have not found such associations.¹⁶

Evidence of inherited susceptibility to ALL associated with HLA and alleles of other immune system genes is consistent with the suggestion that infection may be associated with ALL. The UKCCS has reported statistically significant associations between cALL and specific HLA-DPB1 variants.¹⁷ This is further supported by evidence that immunisation of infants may protect against ALL.¹⁶

Conclusion

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

this protection comes from exposure to common infections.

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Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials

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Abstract

Objective To determine the cost utility of medical co-prescription of heroin compared with methadone maintenance treatment for chronic, treatment resistant heroin addicts.

Design Cost utility analysis of two pooled open label randomised controlled trials.

Setting Methadone maintenance programmes in six cities in the Netherlands.

Participants 430 heroin addicts.

Interventions Inhalable or injectable heroin prescribed over 12 months. Methadone (maximum 150 mg a day) plus heroin (maximum 1000 mg a day) compared with methadone alone (maximum 150 mg a day).

Psychosocial treatment was offered throughout.

Main outcome measures One year costs estimated from a societal perspective. Quality adjusted life years

(QALYs) based on responses to the EuroQol EQ-5D at baseline and during the treatment period.

Results Co-prescription of heroin was associated with 0.058 more QALYs per patient per year (95% confidence interval 0.016 to 0.099) and a mean saving of €12 793 (£8793, \$16 122) (€1083 to €25 229) per patient per year. The higher programme costs (€16 222; lower 95% confidence limit €15 084) were compensated for by lower costs of law enforcement (-€4129; upper 95% confidence limit -€486) and damage to victims of crime (-€25 374; upper 95% confidence limit -€16 625). The results were robust for the use of national EQ-5D tariffs and for the exclusion of the initial implementation costs of heroin treatment. Completion of treatment is essential;

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