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Systematic Reviews and Meta- and Pooled Analyses

Childhood Acute Lymphoblastic Leukemia and Indicators of Early Immune Stimulation: A Childhood Leukemia International Consortium Study

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The associations between childhood acute lymphoblastic leukemia (ALL) and several proxies of early stimulation of the immune system, that is, day-care center attendance, birth order, maternally reported common infections in infancy, and breastfeeding, were investigated by using data from 11 case-control studies participating in the Childhood Leukemia International Consortium (enrollment period: 1980–2010). The sample included 7,399 ALL cases and 11,181 controls aged 2–14 years. The data were collected by questionnaires administered to the parents. Pooled odds ratios and 95% confidence intervals were estimated by unconditional logistic regression adjusted for age, sex, study, maternal education, and maternal age. Day-care center attendance in the first year of life was associated with a reduced risk of ALL (odds ratio = 0.77, 95% confidence interval: 0.71, 0.84), with a marked inverse trend with earlier age at start ($P < 0.0001$). An inverse association was also observed with breastfeeding duration of 6 months or more (odds ratio = 0.86, 95% confidence interval: 0.79, 0.94). No significant relationship with a history of common infections in infancy was observed even though the odds ratio was less than 1 for more than 3 infections. The findings of this large pooled analysis reinforce the hypothesis that day-care center attendance in infancy and prolonged breastfeeding are associated with a decreased risk of ALL.

breastfeeding; childhood leukemia; day care; infections

Abbreviations: ALL, acute lymphoblastic leukemia; AUS_ALL, Australian Study of Causes of Acute Lymphoblastic Leukemia in Children; CA_QCLS, Quebec Childhood Leukemia Study (Canada); CI, confidence interval; FR_ADELE, Adele Study (France); FR_ELECTRE, Electre Study (France); FR_ESCALE, Epidemiologic Study on Childhood Cancer and Leukemia (France); GR_NARECHEM, Nationwide Registration for Childhood Hematological Malignancies (Greece); IT_SETIL, Study on the Etiology of Childhood Lymphohematopoietic Malignancies (Italy); NZ_NZCCS, New Zealand Childhood Cancer Study; OR, odds ratio; UK_UKCCS, United Kingdom Childhood Cancer Study; US_COG15, Children's Oncology Group Study (United States); US_NCCLS, Northern California Childhood Leukemia Study (United States).

Acute lymphoblastic leukemia (ALL) accounts for 80% of childhood acute leukemia, the most common cancer before the age of 15 years. ALL is frequently initiated in utero, with preleukemic cells often detectable at birth (1–3). Subsequent events during childhood are believed to be necessary for progression from covert preleukemia to clinical leukemia (4, 5). One area that has been the subject of much interest, but still controversial, is the role of the immune system and exposure to infections in early life in relation to the etiology of ALL (4–7). However, immunological development is difficult to assess, and the interpretation of published studies in this area is complex. A number of proxies for exposure to infectious agents have been used, including day care, birth order, and self-reported and clinical reported infections. Several studies based on maternal interviews reported inverse associations between risk of ALL and a history of common infections in

infancy (8–14). Summarizing these results is difficult because of the heterogeneity of definitions across the studies. In contrast, studies based on medical records or health claims databases reported null (15, 16) or positive associations (17, 18), suggesting that children who develop leukemia are more likely to have had clinically diagnosed infections in infancy. Day-care attendance and birth order are the proxies most often used to measure early exposure to infectious agents. Most of the studies published so far have reported inverse associations between day-care attendance and childhood leukemia (8–10, 12, 19–27). A meta-analysis of published data reported a summary odds ratio of 0.76 (95% confidence interval (CI): 0.67, 0.87) (28), with significant between-study heterogeneity possibly influenced by the variability of the day-care definition and age at entrance, as well as variability in day-care provision between countries. Non-firstborn children are also likely to be exposed more frequently to infectious agents in infancy through contacts with their older siblings. However, the association between increasing birth order and leukemia is inconsistent, with inverse (12, 13, 25, 29–32), positive (8, 21), or null associations (9, 10, 20, 22, 26, 33–40) reported. Breastfeeding promotes adequate maturation of the immune system in infants and has also been inversely associated with ALL. Two meta-analyses reported summary odds ratios of 0.76 (95% CI: 0.68, 0.84) for breastfeeding duration >6 months (41) and 0.81 (95% CI: 0.72, 0.91) for duration ≥6 months (42).

The aim of the present study was to investigate the association between childhood ALL and day-care center attendance, birth order, breastfeeding, and maternally reported common infections in infancy, taken as proxies for early stimulation of the immune system, using the large set of studies from the Childhood Leukemia International Consortium (https://clic.berkeley.edu/).

METHODS

Data from 11 Childhood Leukemia International Consortium case-control studies conducted in 8 countries from 1980 to 2010 were used (Table 1): Australian Study of Causes of Acute Lymphoblastic Leukemia in Children (AUS_ALL) (43); Quebec Childhood Leukemia Study, Canada (CA_QCLS) (44); Adele Study, France (FR_ADELE) (45); Electre Study, France (FR_ELECTRE) (8); Epidemiologic Study on Childhood Cancer and Leukemia, France (FR_ESCALE) (12); Nationwide Registration for Childhood Hematological Malignancies, Greece (GR_NARECHEM) (46); Study on the Etiology of Childhood Lymphohematopoietic Malignancies, Italy (IT_SETIL) (47); New Zealand Childhood Cancer Study (NZ_NZCCS) (33); United Kingdom Childhood Cancer Study (UK_UKCCS) (18); Children's Oncology Group Study, United States (US_COG15) (48); and Northern California Childhood Leukemia Study (United States) (US_NCCLS) (49). The study design and participant characteristics for each study have been summarized previously (50).

Data collection

All the data were collected with questionnaires that were administered to the parents face-to-face (FR_ADELE, GR_NARECHEM, IT_SETIL, NZ_NZCCS, UK_UKCCS, US_NCCLS) or by telephone (CA_QCLS, FR_ESCALE, US_COG15) or were self-administered (AUS_ALL, FR_ELECTRE). The questionnaires included information on demographic and socioeconomic characteristics and factors potentially associated with childhood leukemia. For the purpose of the present analysis, birth order, number and age of siblings, breastfeeding, history of common infections in the first year of life, and day-care attendance of the index child were provided by the investigators, as were sex, age at diagnosis or recruitment, and any other variables used for matching, as well as parental age at child's birth, parental education, and other indicators of socioeconomic status. All the studies included both B-cell and T-cell ALL.

Data harmonization

Parental education and socioeconomic status. Maternal and paternal levels of education were classified by using the same categories in all the studies: none or primary education, secondary education, and tertiary education (university). A heterogeneous 3-class (low, medium, high) indicator of socioeconomic status was also derived from the deprivation index based on address at diagnosis or interview (UK_UKCCS), household income (AUS_ALL, CA_QCLS, US_COG15, US_NCCLS), parental professional status (FR_ADELE, FR_ELECTRE, FR_ESCALE, GR_NARECHEM, NZ_NZCCS), or maternal education (IT_SETIL), depending on the data available (Web Table 1 available at http://aje.oxfordjournals.org/).

Breastfeeding. Breastfeeding was classified by using the ever/never variable provided by the investigators. Children breastfed 1 month or less were also classified in the never breastfed group in some sensitivity analyses. The duration of breastfeeding was available for all the studies.

Day care. Information on day-care center attendance was available for all the studies, and age at start of attendance was available for 10 studies (Web Table 1). Attendance was considered full-time when attendance was at least 6 half-days per week, except in the French and Italian studies, which reported the frequency of attendance as full-time or part-time with no further details. Care by a child minder was also available in 5 studies.

Early common infections. History of common infections in the first year of life, as reported by mothers, was available in 8 studies (FR_ADELE, FR_ELECTRE, FR_ESCALE, GR_NARECHEM, IT_SETIL, NZ_NZCCS, UK_UKCCS, US_NCCLS). Web Table 1 shows the sites of infections that were collected in the different studies. Four studies provided the total number of episodes for each site and, in the 3 French studies, a 3-class variable was available: no infection for the given site, between 1 and 3 episodes, and 4 or more episodes. The history of ear, nose, and throat surgery before age 3 years was available in 5 studies.

Statistical analysis

The analyses were restricted to children aged at least 2 years, first, to ensure that all the cases and controls had had the opportunity of having been breastfed for a prolonged

Table 1. Summary of the 11 Studies Included in the Pooled Analysis (1980–2010) and Numbers of Acute Lymphoblastic Leukemia Cases and Controls Contributing to the Present Study Sample, Childhood Leukemia International Consortium

First Author, Year (Reference No.)	Study	Country	Period	Participation Fraction, %[a]		Source of Controls	Children 0–14 Years of Age		Children 2–14 Years of Age	
				Cases	Controls		ALL	Controls	ALL	Controls
Milne, 2009 (43)	AUS_ALL	Australia	2002–2006	75	64	Random digit dialing	389	871	355	796
Infante-Rivard, 2005 (44)	CA_QCLS	Canada	1980–2000	93	86	Health insurance file population-based registry (province wide)	790	790	697	697
Clavel, 2005 (45)	FR_ADELE	France	1994–1999	95	99	Hospitals (same as cases)	240	288	219	237
Jourdan-Da Silva, 2004 (8)	FR_ELECTRE	France	1995–1998	73	70	Phone subscribers (population quotas by age, sex, region; nationwide)	408	567	379	489
Rudant, 2010 (12)	FR_ESCALE	France	2003–2005	91	71	Phone subscribers (population quotas by age, sex, region; nationwide)	648	1,681	573	1,312
Petridou, 2008 (46)	GR_NARECHEM	Greece	1996–2010	83	96	Hospital, age, and sex matched	880	993	794	872
Magnani, 2014 (47)	IT_SETIL	Italy	1998–2001	91	69	Population based National Health Service registry	601	1,044	527	888
Dockerty, 1999 (33)	NZ_NZCCS	New Zealand	1989–1994	92	69	Birth registry (nationwide)	97	119	86	105
Roman, 2007 (18)	UK_UKCCS	United Kingdom	1991–1996	93	64	General practitioner/primary care (nationwide)	1,461	3,448	1,315	3,010
Zierhut, 2012 (48)	US_COG15	United States	1989–1993	87	70	Random digit dialing	1,914	1,987	1,706	1,717
Bartley, 2010 (49)	US_NCCLS	United States	1995–2008	86	68	Birth registry (statewide)	839	1,226	748	1,058
Total							8,267	13,014	7,399	11,181

Abbreviations: ALL, acute lymphoblastic leukemia; AUS_ALL, Australian Study of Causes of Acute Lymphoblastic Leukemia in Children; CA_QCLS, Quebec Childhood Leukemia Study (Canada); FR_ADELE, Adele Study (France); FR_ELECTRE, Electre Study (France); FR_ESCALE, Epidemiologic Study on Childhood Cancer and Leukemia (France); GR_NARECHEM, Nationwide Registration for Childhood Hematological Malignancies (Greece); IT_SETIL, Study on the Etiology of Childhood Lymphohematopoietic Malignancies (Italy); NZ_NZCCS, New Zealand Childhood Cancer Study; UK_UKCCS, United Kingdom Childhood Cancer Study; US_COG15, Children's Oncology Group Study (United States); US_NCCLS, Northern California Childhood Leukemia Study (United States).

[a] Participation fractions are those for children aged 0–14 years and are based on information available from published studies or obtained directly from study personnel. Definition of the participation fraction may vary across studies.

period, of day-care attendance, and of contracting infections in their first year of life; and second, because common infections occurring before 1 year of age may have been related to a prediagnostic phase of the disease in the ALL cases aged less than 2 years at diagnosis (51).

Meta-analysis. Meta-analyses based on study-specific odds ratios were conducted for the main exposures of interest. The odds ratios were estimated by using either unconditional or conditional logistic regression, depending on the design of each study, and including study-specific matching variables in the models. The sociodemographic characteristics significantly associated with both case-control status and the exposure were also included in the study-specific models. Between-study heterogeneity was assessed by using Cochran's Q and I^2 statistics. Summary odds ratios and 95% confidence intervals were implemented by using the inverse variance method, with random effects in the event of heterogeneity.

Pooled analysis. Pooled odds ratios were estimated from individual data by unconditional logistic regression systematically adjusted for age, sex, and study. Maternal education and maternal age at the child's birth were also included in the models, as they were significantly associated with both case-control status and exposures.

Trend for breastfeeding duration, age at start of day care, and birth order were investigated. In line with validation studies, which showed that mothers tend to round reported breastfeeding durations (52, 53), the dose-response relationships with breastfeeding duration were estimated with cutoffs centered on digits 3, 6, 9, and 12 months. The analysis of age at the start of day care was also undertaken with cutoffs centered on these rounded values. The tests for trend were computed from categorical variables. The subjects of each class of the categorical variables were assigned the median value of that class. Deviation from linearity was tested by a likelihood ratio test, comparing the model having the quantitative variable with that having the categorical variable. If linearity was not rejected, the P value of the trend was obtained by testing the slope of the quantitative variable.

Stratified analyses were also conducted to investigate the association between ALL and each of the exposures of interest by the strata of the other exposures. P values for the interaction between each pair of variables were estimated in the logistic models by using the Wald χ^2 statistic.

Subgroup analysis. The analyses were performed for B-cell and T-cell ALL subtypes by using polytomous logistic models and by age (2–5 years corresponding to the peak of incidence and 6–14 years).

Sensitivity analysis. The robustness of the results was tested by excluding each study in turn and then 2 studies in turn. The analyses were also repeated after adjustment for socioeconomic status instead of maternal education, as well as for age at start of day care and breastfeeding duration, after consideration of alternative categorizations. For each exposure of interest, the potential for participation bias was investigated by estimating the difference in participation between exposed controls and unexposed controls that would have generated an odds ratio of the magnitude observed, under the assumption of no true effect, and assuming no difference in participation between exposed and unexposed cases.

Ethics

All of the studies were approved by institutional ethics committees, and informed consent was provided by all participants.

RESULTS

The 11 participating studies provided 7,399 ALL cases and 11,181 controls aged 2–14 years (Table 1).

Participant characteristics

Overall, the cases' parents were less educated, in a lower socioeconomic status category, and younger at the index child's birth than the controls' parents (Table 2).

The controls whose parents belonged to higher socioeconomic status categories or had a higher educational level were more likely to have attended a day-care center in infancy and to have been breastfed for 6 months or more than the controls with parents in a lower socioeconomic status category or with a lower educational level (Web Table 2). Firstborn children were slightly more likely to have attended a day-care center and slightly less likely to have been breastfed for 6 months or more than were non-firstborns. A history of common infections in infancy was also more likely to be reported for children who had attended a day-care center and less likely among children breastfed for 6 months or more; such a history was not significantly associated with birth order.

Breastfeeding

Overall, 62.7% of the ALL cases and 65.0% of the controls were reported to have been breastfed (Table 3). Breastfeeding for less than 6 months was not associated with ALL (odds ratio (OR) = 1.01, 95% confidence interval (CI): 0.94, 1.08). On the contrary, breastfeeding for 6 months or more was inversely associated with ALL in both the meta-analysis (OR = 0.85, 95% CI: 0.74, 0.98) (Web Figure 1) and the pooled analysis (OR = 0.86, 95% CI: 0.79, 0.94) (Table 3). There was no linear decreasing trend with increasing breastfeeding duration.

Birth order

Higher birth order was inversely associated with ALL (pooled OR = 0.94, 95% CI: 0.88, 1.0; $P = 0.05$) (Table 3), but the meta-analysis showed significant between-study heterogeneity ($I^2 = 71\%$) (Web Figure 2), with a spectrum of associations ranging from significantly increased odds ratios in CA_QCLS to significantly decreased odds ratios in AUS_ALL, FR_ESCALE, and US_NCCLS.

Day care

Day-care center attendance in the first year of life was associated with a reduced risk of ALL (OR = 0.77, 95% CI: 0.71, 0.84) (Table 3), with no between-study heterogeneity ($I^2 = 0\%$) (Web Figure 3). The odds ratios decreased with the age at start of day-care center attendance (P for trend < 0.0001).

Table 2. Sociodemographic Characteristics of Acute Lymphoblastic Leukemia Cases and Controls, Pooled Analyses of 11 Studies (1980–2010), Restricted to Children Aged ≥2 Years, Childhood Leukemia International Consortium

	ALL		Controls		OR[a]	95% CI
	No.	%	No.	%		
Maternal education						
Did not complete secondary education	1,620	21.9	2,336	20.9	1.00	Referent
Completed secondary education	3,548	48.0	5,281	47.2	0.81	0.74, 0.88
Completed tertiary education	2,195	29.7	3,518	31.5	0.77	0.70, 0.84
Missing	36	0.5	46	0.4		
Paternal education						
Did not complete secondary education	1,651	22.3	2,407	21.5	1.00	Referent
Completed secondary education	3,213	43.4	4,612	41.2	0.85	0.78, 0.93
Completed tertiary education	2,131	28.8	3,421	30.6	0.78	0.72, 0.85
Missing	404	5.5	741	6.6		
Socioeconomic status						
Low	1,956	26.4	2,605	23.3	1.00	Referent
Medium	3,046	41.2	4,628	41.4	0.86	0.79, 0.93
High	2,329	31.5	3,876	34.7	0.81	0.75, 0.88
Missing	68	0.9	72	0.6		
Maternal age at child's birth						
<25 years	2,023	27.3	2,729	24.4	1.00	Referent
25–29 years	2,553	34.5	4,063	36.3	0.87	0.81, 0.94
30–34 years	1,940	26.2	3,015	27.0	0.90	0.83, 0.98
≥35 years	860	11.6	1,348	12.1	0.91	0.82, 1.01
Missing	22	0.3	26	0.2		
Total	7,399		11,181			

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; OR, odds ratio.
[a] Pooled odds ratio and 95% confidence interval were estimated by unconditional logistic models adjusted for age, sex, and study center.

The results were similar for part-time (OR = 0.75, 95% CI: 0.67, 0.84) and full-time (OR = 0.79, 95% CI: 0.70, 0.90) attendance, based on 10 studies. No association was observed for child care by a child minder (OR = 1.02, 95% CI: 0.88, 1.18), based on 5 studies.

Early common infections

No association between a history of at least 1 common infection before age 1 year and ALL was observed (OR = 0.95, 95% CI: 0.87, 1.04) (Table 4, Web Figure 4). The odds ratio was slightly less than 1 for a history of 4 or more common infections (pooled OR = 0.88, 95% CI: 0.79, 0.98) (Table 4) and meta-analysis (OR = 0.89, 95% CI: 0.73, 1.07; $I^2 = 52\%$) (Web Figure 4). Regarding the sites of infection, a history of lower respiratory tract infections was significantly associated with ALL in the pooled analysis (OR = 0.84, 95% CI: 0.73, 0.97) (Table 4), but not in the random effects model accounting for between-study heterogeneity (Web Figure 5). The odds ratios decreased with the numbers of episodes. Repeated history of infections at other sites and history of ear, nose, and throat surgery before age 3 years (OR = 0.80, 95% CI: 0.63, 1.03) were also inversely associated with ALL, but not significantly so.

Stratified analyses

The associations between ALL and birth order, day-care center attendance, prolonged breastfeeding, and history of common infections did not significantly differ according to the strata of the other exposures (Web Table 3). In particular, the odds ratios for the association between ALL and day-care center were always significantly less than 1. The multivariate analysis including birth order, day-care center, and prolonged breastfeeding in a single model yielded estimates very close to those of the univariate models shown in Table 3 (day-care center: OR = 0.77, 95% CI: 0.70, 0.84; breastfeeding ≥6 months: OR = 0.88, 95% CI: 0.80, 0.96; birth order ≥2: OR = 0.93, 95% CI: 0.87, 0.99) (not shown).

Subgroup analysis

A significant heterogeneity between B-cell and T-cell ALL was observed only for a history of gastroenteritis ($P = 0.01$),

Table 3. Association Between Acute Lymphoblastic Leukemia and Breastfeeding, Birth Order, and Day Care, Pooled Analyses of 11 Studies (1980–2010), Restricted to Children Aged ≥2 Years, Childhood Leukemia International Consortium

	No. of Studies	ALL		Controls		OR[a]	95% CI
		No.	%	No.	%		
Breastfeeding	11	7,399		11,181			
No		2,696	36.4	3,798	34.0	1.00	Referent
Yes		4,639	62.7	7,264	65.0	0.95	0.89, 1.02
Missing		64	0.9	119	1.0		
<6 months		2,899	39.2	4,324	38.7	1.01	0.94, 1.08
≥6 months		1,717	23.2	2,892	25.9	0.86	0.79, 0.94
Missing		87	1.2	167	1.5		
Breastfeeding duration							
1 month or less		1,318	17.8	1,896	17.0	1.06	0.97, 1.16
2–4 months		1,284	17.4	1,894	16.9	0.99	0.90, 1.08
5–7 months		793	10.7	1,303	11.7	0.90	0.81, 1.01
8–10 months		439	5.9	831	7.4	0.78	0.69, 0.89
11–13 months		393	5.3	690	6.2	0.83	0.72, 0.96
14 months or more		389	5.3	602	5.4	0.92	0.79, 1.06
Missing		87	1.2	167	1.5		
Birth order	11	7,399		11,181			
1		3,393	45.9	4,982	44.6	1.00	Referent
≥2		3,944	53.3	6,119	54.7	0.94	0.88, 1.00
2		2,500	33.8	3,872	34.6	0.95	0.88, 1.01
3		992	13.4	1,518	13.6	0.95	0.87, 1.05
4		293	4.0	485	4.3	0.86	0.73, 1.00
5		92	1.2	144	1.3	0.92	0.70, 1.21
≥6		67	0.9	100	0.9	0.93	0.68, 1.29
Missing		62	0.8	80	0.7		
P for trend							0.07
Day-care center attendance at <1 year of age	11	7,399		11,181			
No		6,116	82.7	8,713	77.9	1.00	Referent
Yes		1,021	13.8	2,169	19.4	0.77	0.71, 0.84
Missing		262	3.5	299	2.7		

Table continues

with an inverse association for B-cell ALL and a positive one for T-cell ALL (Web Table 4). The associations were similar by subgroups of age.

Sensitivity analyses (pooled analysis)

The sensitivity analyses excluding each study and then 2 studies in turn led to odds ratio estimates for breastfeeding and day-care center attendance that were very close to those based on the 11 studies. In particular, the trend in risk reduction with earlier age at the start of day-care center attendance always remained significant (*P* values ranging from 0.007 to less than 0.0001). Alternative categorizations (0–3 months, 4–6 months, 7–11 months; 0–2 months, 3–5 months, 6–11 months; and 0–2 months, 3–5 months, 6–8 months, 9–11 months) also led to a similar trend in risk reduction. Including children breastfed 1 month or less in the reference group did not change the results (OR = 0.85, 95% CI: 0.78, 0.91 for breastfeeding of 6 months or more).

The magnitude of possible bias induced by better participation of the control mothers who breastfed for at least 6 months or who made use of a day-care center was estimated. Assuming no association, for such a bias to generate an odds ratio of the magnitude observed for breastfeeding for 6 months or more (OR = 0.86), the participation fractions would have to have been equal to 80% for the prolonged breastfed controls and 68% for the non-breastfed or shorter breastfed controls, considering the average participation fraction of 71% for controls and the 26% prevalence of prolonged breastfeeding observed in the present study. Similarly, for the bias to

Table 3. Continued

	No. of Studies	ALL		Controls		OR[a]	95% CI
		No.	%	No.	%		
Frequency	10[b]	6,605		10,309			
Part-time		553	8.4	1,416	13.7	0.75	0.67, 0.84
Full-time		453	6.9	737	7.1	0.79	0.70, 0.90
Missing		262	4.0	299	2.9		
Age at start of day-care center attendance	10[c]	7,044		10,385			
≥24 months or never		5,273	74.9	7,287	70.2	1.00	Referent
14–23 months		400	5.7	583	5.6	1.03	0.89, 1.18
11–13 months		200	2.8	353	3.4	0.92	0.77, 1.10
8–10 months		175	2.5	342	3.3	0.82	0.68, 0.99
5–7 months		232	3.3	477	4.6	0.79	0.67, 0.93
0–4 months		506	7.2	1,086	10.5	0.75	0.66, 0.84
Missing		262	3.7	300	2.5		
P for trend						<0.0001	
Any day care at <1 year of age	5[d]	2,572		5,153			
No day care		1,597	62.1	3,038	59.0	1.00	Referent
Child minder and no day-care center		399	15.5	686	13.3	1.02	0.88, 1.18
Day-care center		487	18.9	1,340	26.0	0.71	0.63, 0.81
Missing		89	3.5	89	1.7		

Abbreviations: ALL, acute lymphoblastic leukemia; AUS_ALL, Australian Study of Causes of Acute Lymphoblastic Leukemia in Children; CA_QCLS, Quebec Childhood Leukemia Study (Canada); CI, confidence interval; FR_ADELE, Adele Study (France); FR_ELECTRE, Electre Study (France); FR_ESCALE, Epidemiologic Study on Childhood Cancer and Leukemia (France); GR_NARECHEM, Nationwide Registration for Childhood Hematological Malignancies (Greece); IT_SETIL, Study on the Etiology of Childhood Lymphohematopoietic Malignancies (Italy); NZ_NZCCS, New Zealand Childhood Cancer Study; OR, odd ratio; UK_UKCCS, United Kingdom Childhood Cancer Study; US_COG15, Children's Oncology Group Study (United States); US_NCCLS, Northern California Childhood Leukemia Study (United States).

[a] Pooled odds ratio and 95% confidence interval were estimated by unconditional logistic models adjusted for age, sex, study center, maternal education, and maternal age at child's birth.

[b] AUS_ALL, CA_QCLS, FR_ADELE, FR_ELECTRE, FR_ESCALE, IT_SETIL, NZ_NZCCS, UK_UKCCS, US_COG15, and US_NCCLS.

[c] CA_QCLS, FR_ADELE, FR_ELECTRE, FR_ESCALE, GR_NARECHEM, IT_SETIL, NZ_NZCCS, UK_UKCCS, US_COG15, and US_NCCLS.

[d] FR_ADELE, FR_ELECTRE, FR_ESCALE, NZ_NZCCS, and UK_UKCCS.

explain the odds ratio observed for day-care center attendance (OR = 0.77), participation fractions would have had to have been equal to 88% for the controls who attended a day-care center and 68% for those who did not, considering the 19% prevalence of day-care center attendance observed for the controls in the present study.

DISCUSSION

We examined the association between proxies for exposure to infections and risk of childhood ALL in the Childhood Leukemia International Consortium that included data on 7,399 ALL cases and 11,181 controls aged 2–14 years. This analysis confirms the inverse association between ALL and day-care center attendance during infancy and reveals a marked trend in risk reduction with earlier age at the start of day-care center attendance, a finding made possible by the enhanced statistical power of this pooled analysis. A significant inverse association with breastfeeding for 6 months or more was also observed. Overall, there was no clear association between ALL and common infections in infancy as reported by mothers and between ALL and birth order.

One of the challenges faced in this area of research is the ability to accurately quantify indicators for early immune stimulation. In the present study, the proxies were based on maternally reported data and as such possibly subject to recall bias. With respect to breastfeeding, the available validity studies suggest that mothers tend to round breastfeeding duration and to report slightly increased durations of short-term breastfeeding and slightly decreased durations of long-term breastfeeding, with inaccuracies becoming more marked for recall after a long period (52–55). In a large Norwegian study, 64% of the women recalled their breastfeeding duration to within 1 month and 83% to within 2 months 20 years after delivery, with a median overestimation of about 2 weeks (54). In a US study including 140 college-educated women aged

Table 4. Association Between Acute Lymphoblastic Leukemia and History of Early Common Infections, Pooled Analysis of 8 Studies (1989–2010), Restricted to Children Aged ≥2 Years, Childhood Leukemia International Consortium

	No. of Studies	ALL		Controls		OR[a]	95% CI
		No.	%	No.	%		
Common infections in the first year of life							
2-class variable	8[b]	4,641		7,971			
1 or more vs. none		2,746	59.2	5,146	64.6	0.95	0.87, 1.04
Missing		183	3.9	174	2.2		
3-class variable	7[c]	4,555		7,866			
1–3 vs. none		1,737	38.1	3,151	40.0	0.98	0.90, 1.08
4 or more vs. none		928	20.4	1,876	23.8	0.88	0.79, 0.98
Missing		187	4.1	203	2.6		
Specific sites of infection							
Ear, nose, throat infections[d]							
2-class variable	6[e]	3,895		6,846			
1 or more vs. none		1,797	46.1	3,514	51.3	0.99	0.91, 1.09
Missing		132	3.4	124	1.8		
3-class variable	5[f]	3,809		6,741			
1–3 vs. none		1,241	32.6	2,374	35.2	1.02	0.93, 1.12
4 or more vs. none		501	13.1	1,080	16.0	0.90	0.79, 1.03
Missing		132	3.5	124	1.8		
Otitis							
2-class variable	3[g]	1,407		2,475			
1 or more vs. none		476	3.4	839	3.4	0.94	0.81, 1.08
Missing		37	2.7	41	1.7		
3-class variable	2[h]	1,321		2,370			
1–3 vs. none		333	25.2	561	23.7	0.98	0.83, 1.16
4 or more vs. none		118	8.9	244	10.3	0.87	0.68, 1.10
Missing		37	2.8	41	1.7		
Lower respiratory tract infections[i]							
2-class variable	5[j]	2,728		4,235			
1 or more vs. none		552	20.2	1,023	24.2	0.84	0.73, 0.97
Missing		53	1.4	68	1.6		
3-class variable	4[k]	2,642		4,130			
1–3 vs. none		440	16.7	758	18.4	0.90	0.77, 1.04
4 or more vs. none		109	4.1	258	4.1	0.67	0.52, 0.87
Missing		53	2.0	68	1.6		

Table continues

69–79 years at the time of interview, the mean reporting difference of breastfeeding duration was 0.0 months, but durations of 9 and 12 months were reported 1.8 and 5.0 times more frequently, respectively, in the questionnaires than in the original diaries (53). In the present study, cutoffs for breastfeeding and day care were centered on rounded values to limit misclassifications due to the tendency to report the nearest preferred digit. Although it is difficult to quantify precisely the magnitude of misclassification in the set of studies included in this analysis, previous validation studies appear to suggest that breastfeeding can be recalled with reasonable accuracy. Although maternal recall is assumed to be better for the more recent births, the results of the analyses limited to the cases and controls aged less than 6 years were consistent with the main analyses.

The potential for recall bias is likely to be greater when looking at a history of common infections, which are sporadic events, and the few available validity studies have shown systematic underreporting of medically diagnosed infections (56–58). In the United Kingdom Childhood Cancer Study, a history of clinically diagnosed common infections was underreported more often by the cases' mothers than by the controls' mothers (58, 59), leading to an inverse association

Table 4. Continued

	No. of Studies	ALL		Controls		OR[a]	95% CI
		No.	%	No.	%		
Gastroenteritis							
2-class variable	6[e]	3,895		6,846			
1 or more vs. none		496	12.7	1,046	15.2	0.90	0.80, 1.01
Missing		123	3.2	123	1.8		
3-class variable	5[f]	3,809		6,741			
1–3 vs. none		435	11.4	929	13.8	0.91	0.80, 1.03
4 or more vs. none		49	12.9	95	1.4	0.89	0.62, 1.26
Missing		123	3.2	123	1.8		
Ear, nose, throat surgery at <3 years of age	5[l]	2,708		5,010			
Yes vs. no		99	1.2	218	4.4	0.80	0.63, 1.03
Missing		26	0.4	12	0.3		

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; FR_ADELE, Adele Study (France); FR_ELECTRE, Electre Study (France); FR_ESCALE, Epidemiologic Study on Childhood Cancer and Leukemia (France); GR_NARECHEM, Nationwide Registration for Childhood Hematological Malignancies (Greece); IT_SETIL, Study on the Etiology of Childhood Lymphohematopoietic Malignancies (Italy); NZ_NZCCS, New Zealand Childhood Cancer Study; OR, odds ratio; UK_UKCCS, United Kingdom Childhood Cancer Study; US_NCCLS, Northern California Childhood Leukemia Study (United States).

[a] Pooled odds ratio and 95% confidence interval estimated by unconditional logistic models adjusted for age, sex, study center, maternal education, and maternal age at child's birth.

[b] FR_ADELE, FR_ELECTRE, FR_ESCALE, GR_NARECHEM, IT_SETIL, NZ_NZCCS, UK_UKCCS, and US_NCCLS.

[c] FR_ADELE, FR_ELECTRE, FR_ESCALE, GR_NARECHEM, IT_SETIL, UK_UKCCS, and US_NCCLS; 4 or more episodes were defined as 4 or more episodes of any common infection in the 4 studies that had provided the total number of episodes (GR_NARECHEM, IT_SETIL, UK_UKCCS, US_NCCLS), and by 4 or more episodes of infection at a particular site or 1–3 episodes of infection of a minimum of 4 sites occurring in infancy, for the 3 French studies (FR_ADELE, FR_ELECTRE, FR_ESCALE).

[d] Including tonsillitis and mouth infections, otitis, upper respiratory tract infections, and cold.

[e] FR_ELECTRE, FR_ESCALE, GR_NARECHEM, UK_UKCCS, US_NCCLS, and NZ_NZCCS.

[f] FR_ELECTRE, FR_ESCALE, GR_NARECHEM, UK_UKCCS, and US_NCCLS.

[g] FR_ESCALE, US_NCCLS, and NZ_NZCCS.

[h] FR_ESCALE and US_NCCLS.

[l] Including bronchiolitis, pneumonia, and persistent cough.

[j] FR_ESCALE, GR_NARECHEM, IT_SETIL, US_NCCLS, and NZ_NZCCS.

[k] FR_ESCALE, GR_NARECHEM, IT_SETIL, and US_NCCLS.

[l] FR_ADELE, FR_ELECTRE, FR_ESCALE, GR_NARECHEM, and UK_UKCCS, with analysis restricted to children aged 3 years or more.

between ALL and history of clinically diagnosed common infections as reported by the mothers but to a positive association when relying on information from medical records. The present pooled analysis focused on maternal reports of any episode of infection, medically diagnosed or not, and the influence of the case-control status on that recall and the direction of this bias remain difficult to predict.

Another important issue in case-control studies is that the procedure for control selection may distort the representativeness of controls with respect to the exposure in the source population of the cases, in particular if no complete roster of children contemporaneous with case diagnosis was available. However, the procedures varied between studies, and the sensitivity analyses excluding each study and then 2 studies in turn did not reduce the associations with breastfeeding or day care, suggesting that, overall, these associations were not unduly affected by biases inherent in 1 or 2 of the studies. In particular, the estimates were unchanged after exclusion of the 2 studies using random digit dialing (AUS_ALL, US_COG15), the 2 hospital-based studies (FR_ADELE, GR_NARECHEM), and the 2 studies relying on phone subscriber listings (FR_ELECTRE, FR_ESCALE).

Overall, the controls' parents were slightly more educated and had higher socioeconomic status than the cases' parents, and the former were slightly older at the index child's birth than the cases' parents. This may suggest that participating controls were selected on these factors, which is consistent with the usual characteristics of respondents in epidemiologic studies (60). Greater participation among eligible controls of higher socioeconomic status may have led to overrepresentation of day-care center attendance and breastfeeding among participating controls and, then, to overestimation of the inverse associations

with ALL. All analyses were adjusted for education or socioeconomic status, and adjustment for these factors had little impact on the estimates (4% less), but residual confounding cannot be excluded. However, the sensitivity analysis showed that participation fractions would have to have been 20% higher for controls attending a day-care center than for the other controls in order for differential participation to explain the relationship with day-care center attendance. Additionally, a Danish registry-based study, based on 176 ALL cases and 1,571 controls with complete child-care registration, free from participation bias, also showed an inverse association between ALL and child-care attendance during the first 2 years of life (22). Regarding breastfeeding, the participation fractions of the studies would have to have been reduced by 12%, on average, in the non-breastfed or short-term breastfed controls compared with the long-term breastfed controls to produce biased results, a possibility that cannot be ruled out.

Because day-care center attendance strongly increases the likelihood of being exposed to infectious agents in infancy (61–64), day care in early life has been considered a good surrogate to test the role of early immune system stimulation. In the present study, a significant trend with age at the start of day-care center attendance was observed. The trend has not been reported previously, but a slightly lower ALL risk for children attending day care in the first 3 months of life than for later attendance was reported in United Kingdom (20) and French (8) studies. In the Northern California Childhood Leukemia Study, the strongest association with day-care attendance was observed before 6 months of age, with odds ratios decreasing with increasing number of child-hours (13, 23). In the present pooled analysis, a significant decrease in ALL risk was observed for attendance at a day-care center and not for day care by a child minder. Reverse causality is not a likely explanation for the inverse relationship between ALL and the day-care center attendance observed in this pooled analysis, because the cases were not reported to have had more infections than the controls. However, the severity of infections and the timing of infectious episodes and day-care entrance were not available. In the event that severe infectious episodes delay entrance into a day-care center and that they are more frequent in infants who will develop ALL, reverse causality cannot be ruled out.

The fact that the association with ALL was more marked for day-care center attendance than for infection may reflect the existence of 2 coexisting mechanisms, the first being that the exposure to infectious agents in infancy, even asymptomatic or weakly symptomatic, would protect against ALL through immune system stimulation (4), and the second being that the infections may be more symptomatic in the children who will develop ALL if a deregulated immune response already exists in infancy (5). Indeed, in 2 medical record–based studies, children with ALL had more clinically diagnosed infections in the first year of life than the control children (17, 18), and another study reported that children with ALL had a lower neonatal level of interleukin 10, a key regulator for modeling the intensity and duration of immune response to infections, compared with healthy children (65). With the hypothesis that there are 2 coexisting mechanisms, the proxies for exposure to infectious agents may be inversely associated with ALL, while the overall direction of the association between ALL and symptomatic infections would be less predictable and may depend on the intensity of the symptoms considered.

An important issue is how infection and immune modulation might operate in influencing ALL risk. One possible explanation is that an abnormal or dysregulated immune response to an infection, favored by little previous exposure to infectious agents during infancy and, possibly, inherited variants in immunity genes, may promote leukemia among children who are carriers of a persistent preleukemic clone generated prenatally (4, 66). However, the biological mechanisms underlying this process remain to be established (4, 7, 67, 68), and more evidence based on experimental studies modeling the transition of silent preleukemic stem cells to overt ALL, in an inflammatory context, is needed (69).

In conclusion, the findings of this large pooled analysis reinforce the hypothesis that breastfeeding for at least 6 months and day-care center attendance are associated with a decreased risk of ALL. They also suggest that the effect of day-care center attendance may be more marked with an earlier age at the start of attendance. Early exposure to common infectious agents may be responsible for the association with day care, but the lack of consistency in results for infections during the first year of life calls for further elucidation of potential mechanisms through refined exposure assessment strategies that consider both the severity and the timing of infections.

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This study was conducted by 12 teams of investigators (10 clinical and epidemiologic, 2 biological) based in university departments, research institutes, and the National Health Service in Scotland. Its work is coordinated by a management committee. Further information can be found on the website: www.ukccs.org. US_COG15. The E14 and E15 cohorts of the Children's Oncology Group were identified by Children's Cancer Group principal and affiliate member institutions. CA_QCLS. The Québec Childhood Leukemia Study was conducted in the province over a 20-year period in all university-affiliated pediatric center hospitals designated to diagnose and treat pediatric cancers, under the direction of Claire Infante-Rivard. Main support collaborators were Alexandre Cusson, Marcelle Petitclerc, and Denyse Hamer.

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