



Original Contribution

Childhood Acute Leukemia, Early Common Infections, and Allergy: The ESCALE Study

Jérémy Rudant, Laurent Orsi, Florence Menegaux, Arnaud Petit, André Baruchel, Yves Bertrand, Anne Lambilliotte, Alain Robert, Gérard Michel, Geneviève Margueritte, Julie Tandonnet, Françoise Mechinaud, Pierre Bordigoni, Denis Hémon, and Jacqueline Clavel*

* Correspondence to Dr. Jacqueline Clavel, CESP Environmental Epidemiology of Cancer, INSERM U1018, 16, AV. Paul Vaillant Couturier, F-94807 Villejuif Cedex, France (e-mail: jacqueline.clavel@inserm.fr).

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This study investigated the role of factors considered related to early stimulation of the immune system in the etiology of childhood acute leukemia. The national registry-based case-control study ESCALE was carried out in France in 2003–2004. Population controls were frequency matched to cases on age and gender. Data were obtained from structured telephone questionnaires administered to mothers. Odds ratios were estimated using unconditional regression models adjusted for potential confounders. Included were 634 acute lymphoblastic leukemia cases, 86 acute myeloblastic leukemia cases, and 1,494 controls aged ≥ 1 year. Negative associations were observed between acute lymphoblastic leukemia and birth order (P for trend < 0.0001), attendance at a day-care center before age 1 year (odds ratio (OR) = 0.8, 95% confidence interval (CI): 0.6, 1.1), prolonged breastfeeding (OR = 0.7, 95% CI: 0.5, 1.0), repeated early common infections (OR = 0.7, 95% CI: 0.6, 0.9), regular contact with farm animals (OR = 0.6, 95% CI: 0.5, 0.8), frequent farm visits in early life (OR = 0.4, 95% CI: 0.3, 0.6), and history of asthma (OR = 0.7, 95% CI: 0.4, 1.0) or eczema (OR = 0.7, 95% CI: 0.6, 0.9). Results support the hypothesis that repeated early infections and asthma may play a role against childhood acute leukemia.

allergy and immunology; animals, domestic; breast feeding; child; infant; infections; leukemia

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CI, confidence interval; OR, odds ratio.

Childhood acute leukemia is the most common cancer in children, accounting for approximately one-third of all childhood neoplasms in developed countries (1). In France, about 470 new cases of acute leukemia are diagnosed each year. Except for high-level ionizing radiation, certain chemotherapeutic agents, Down's syndrome, and a few rare genetic disorders, the etiology of acute leukemia in children remains largely unknown.

Greaves (2) hypothesized that acute lymphoblastic leukemia (ALL) may result from a 2-step process, with the first step occurring in utero and the second during childhood, enabled by the lack of infections in early childhood. This hypothesis is considered to apply mainly to the B-cell precursor subtype, responsible for the peak in incidence observed at about 2 years of age in developed countries. By contributing to normal maturation of the immune sys-

tem, early common infections would protect the child against leukemia, while a situation of relative isolation would make the child more vulnerable and liable to overreact to later infections. This parallels the hygiene hypothesis developed to explain the rising prevalence of allergies in Western populations: fewer infections and less contact with dirt or soil in early life, and thus less exposure to bacteria and endotoxins, may lead to less effective maturation of the immune system and to overreactive T-helper 2 cells, and subsequently to allergy (3, 4). Epidemiologic studies have shown a lower risk of allergy for children exposed to animals in infancy (5–7) and for children living on farms (8). Recently, it has also been hypothesized that the increase in cortisol levels induced by early infections may eliminate preleukemic cells and reduce the risk of acute leukemia (9).

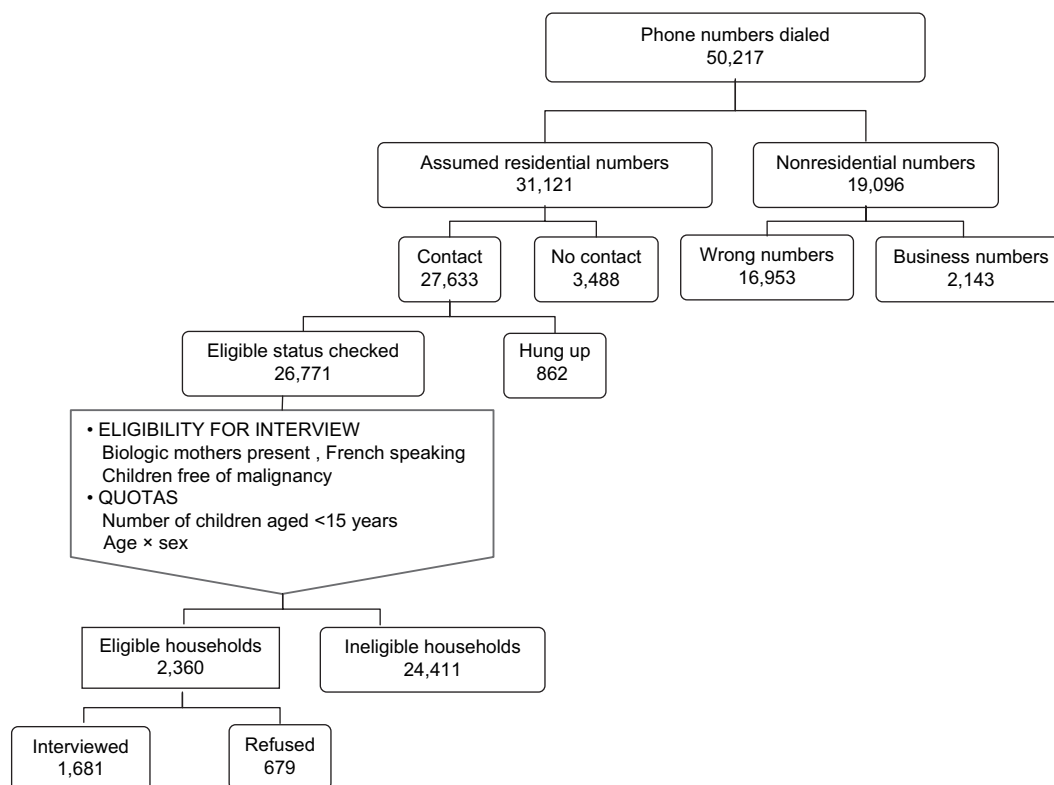


Figure 1. Diagram of the procedure used to select population controls in the ESCALE study, France, 2003–2004.

The national, population-based, case-control study ESCALE investigated the relation between acute leukemia and factors related to early stimulation of the immune system. This paper reports on that study.

MATERIALS AND METHODS

The ESCALE study was conducted to investigate the role of infectious, environmental, and genetic factors in childhood acute leukemia, lymphoma, neuroblastoma, and brain tumor. This paper focuses on acute leukemia.

Case and control ascertainment

The cases were identified directly by the investigators of the French National Registry of Childhood Blood Malignancies (10). Cases resided in mainland France at the time of diagnosis, were less than age 15 years, and were diagnosed in 2003 and 2004. Of the 938 acute leukemia cases identified during the study period, 843 were eligible to participate, 765 of whom consented (91%). The reasons for noneligibility were the child's death (34 cases), hospital palliative care (7 cases), the biologic mother's death (10 cases), a non-French-speaking mother (29 cases), and a mother with a serious psychiatric disorder (15 cases).

Population controls were randomly selected during 2003–2004 by using a quota sampling method. A base of 60,000 phone numbers representative of French telephone sub-

scribers was randomly extracted from the telephone directory. By increasing the last digit of each number by 1, we obtained a new set of 60,000 numbers, including unlisted numbers, with the same distribution of municipalities (same first 6 digits) as the previous set. The first 50,217 randomly dialed numbers were used to complete control sampling. The quotas were designed to make the age and gender distributions of the controls similar to those of all ESCALE cases, based on rates from the French National Registry of Childhood Blood Malignancies (10) and the Regional Childhood Cancer Registries (1). Additional quotas ensured that the control group had the same distribution as the general population of number of children aged less than 15 years living in the household, conditional on age (11). Thus, there were 48 quota strata of age (0–1, 2, 3, 4, 5–6, 7–8, 9–11, 12–14 years), sex, and number of children by household (1, 2, ≥3). Each call session had to balance the numbers for each quota stratum being filled progressively over the study period. The controls were selected among children free of cancer; who had not been adopted; and whose biologic mother was alive, free from serious psychiatric disorders, and French speaking.

Figure 1 shows the procedure for control selection. Calls unanswered after 12 attempts at different times of the day were submitted to the reverse phone directory to eliminate wrong numbers (not allocated, no longer in use, fax) and business numbers. The participation rate was 71% (interviewed mothers/eligible households), and the overall response rate

was 61% (participation rate $\times$ proportion of households whose eligibility could be established (86%) (12)).

Data collection

The same trained interviewers carried out the telephone interviews with the mothers of both cases and controls using structured questionnaires. Half of the cases' mothers were interviewed less than 4 months after the diagnosis. The questionnaire elicited information on demographic and socioeconomic characteristics; childhood environment; life-style; familial history of cancer; child-care history; duration of breastfeeding; history of tonsillitis, otitis, upper respiratory tract infections, gastroenteritis, bronchiolitis and other lower respiratory tract infections, and urinary tract infections; history of surgical procedures for early ear-nose-throat infections; and history of asthma, eczema, and wheezing bronchitis. "Repeated early common infections" was defined as 4 or more episodes of infection of at least one given site or 1–3 episodes of infection of at least 4 sites in infancy. Mothers were also asked how often the child visited a farm and whether the child had been in contact with animals at least once a week in infancy.

Statistical analysis

The analyses were restricted to children aged 1 year or older so that cases and controls both had a maximum opportunity to encounter the exposures of interest, which take place in the first year of life. Odds ratios and their 95% confidence intervals were estimated by using polytomous unconditional logistic regression models including the stratification variable age $\times$ gender used for quota sampling. Systematic adjustment was conducted for parental professional category, urban/rural status of the place of residence (1999 census (11)), and maternal age. Models including animal contacts were also adjusted for housing during the first year of life (only apartment vs. house). The stability of the results was tested after additional adjustments for parental education, paternal smoking, and household exposure to pesticides (13, 14) and after exclusion of 18 cases and 6 controls with chromosomal abnormalities. Analyses were also carried out by ALL subtype. The SAS software package (version 9; SAS Institute, Inc., Cary, North Carolina) was used for all analyses.

RESULTS

A total of 765 incident cases and 1,681 controls were included. Of these children, 734 cases (634 ALL, 86 acute myeloblastic leukemia (AML), and 14 undifferentiated or biphenotypic acute leukemia) and 1,494 controls were aged 1 year or older (Table 1).

Case-control comparability

The controls were similar to the whole case group with respect to age and gender (data not shown) but not to the leukemia cases considered alone because of overrepresentation of the age group 2–4 years (Table 2). Nevertheless, all strata included at least one control per case.

Table 1. Numbers of Acute Leukemia Cases and Controls Included in the ESCALE Study (Aged 0–14 Years), France, 2003–2004, and Selected for the Present Analysis (Aged ≥ 1 Year)

Subjects	All ESCALE Children Aged 0–14 Years	Selected for the Present Analysis, Aged 1–14 Years
Controls	1,681	1,494
Acute leukemia cases	765	734
ALL	647	634
Pro-B ALL	22	17
Pre-B ALL or common B-cell ALL	524	517
B mature ALL	30	30
T-cell ALL	67	67
Unspecified	4	3
Acute myeloblastic leukemia	102	86
Undifferentiated or biphenotypic acute leukemia	16	14

Abbreviation: ALL, acute lymphoblastic leukemia.

The parents of the controls were slightly more educated and had a qualified job significantly more often than the parents of the cases, but they were similar with regard to urban/rural status of their place of residence and number of children in the household (Table 3). Maternal age at the child's birth was significantly higher for the controls than for the cases.

Birth order, day-care attendance, breastfeeding, and early common infections

Nonfirstborn status was negatively associated with ALL (Table 4); the odds ratios decreased with increasing birth order (P trend < 0.0001). The inverse association was no longer observed among children at least 6 years younger than their youngest elder sibling. Full-time day-care center attendance in infancy was slightly negatively associated with ALL (odds ratio (OR) = 0.8, 95% confidence interval (CI): 0.6, 1.1) and AML (OR = 0.5, 95% CI: 0.2, 1.4) but not significantly, with no trend with age at the start of day care. We found no association with other child care (parents, nanny) (not shown). Prolonged breastfeeding for at least 6 months was negatively associated with ALL (OR = 0.7, 95% CI: 0.5, 1.0).

Overall, repeated early common infections were significantly negatively associated with ALL (OR = 0.7, 95% CI: 0.6, 0.9) but not with AML (Table 5). ALL was negatively and significantly associated with early repeated bronchiolitis (OR = 0.3, 95% CI: 0.2, 0.6), gastroenteritis (OR = 0.3, 95% CI: 0.1, 0.8), and otitis (OR = 0.7, 95% CI: 0.5, 1.0). Extending the time window of infections to the second or third year of life removed the association with ALL.

Contacts with farm animals, farm visits

Regular contacts with farm animals in the first year of life were significantly and negatively associated with ALL

Table 2. Distribution of Cases and Controls by the Stratification Variable Age × Gender (16 Categories) Used for Quota Sampling in the ESCALE Study, France, 2003–2004

Age, years	Controls (<i>n</i> = 1,681)		Acute Leukemia Cases			
			ALL (<i>n</i> = 647)		AML (<i>n</i> = 102)	
	No.	%	No.	%	No.	%
Boys						
<1	107	6	3	1	8	8
1	94	6	31	4	9	9
2	79	5	49	8	5	5
3	87	5	56	9	2	2
4	89	5	42	6	4	4
5–6	126	8	51	8	7	7
7–8	96	6	29	5	5	5
9–11	137	8	49	8	9	9
12–14	117	7	37	6	6	6
Girls						
<1	80	5	10	2	8	8
1	88	5	32	4	10	10
2	74	4	46	7	3	3
3	79	5	47	7	2	2
4	56	3	35	5	3	3
5–6	102	6	55	9	5	5
7–8	67	4	33	5	6	6
9–11	88	5	26	4	7	7
12–14	115	7	16	2	3	3

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia.

(OR = 0.6, 95% CI: 0.5, 0.8) and AML (OR = 0.4, 95% CI: 0.2, 1.0) (Table 6). There was no association with regular contacts with cats or dogs. The proportion of children who visited a farm before age 2 years was lower for the ALL cases than for the controls, and the odds ratio decreased with increasing visit frequency.

Allergy

ALL was negatively associated with a history of asthma (OR = 0.7, 95% CI: 0.4, 1.0), bronchitis with wheezing (OR = 0.7, 95% CI: 0.6, 1.0), and eczema (OR = 0.7, 95% CI: 0.6, 0.9). Any treatment for asthma was reported for 84% of the controls and 86% of the cases who were reported to have asthma, whereas a more specific treatment with a combination of 3 drugs (salbutamol + corticosteroids + antihistamines) was reported for 27% and 20% of them, respectively (Table 7). The report of treatment for asthma was also negatively associated with ALL (Table 7).

Subtype analysis

The odds ratios for pre-B and common ALL were similar to those for all ALL (Table 8) and for the 1–5-year and 6–14-year age groups (not shown). The relation with prolonged breastfeeding was not observed with the other ALL subtypes.

Repeated early common infections were not associated with mature B-cell or pro-B ALL, based on small numbers.

Adjustments and sensitivity analyses

The associations were very similar when the analysis was stratified by socioeconomic status or rural/urban status; after adjustment for education, maternal age at birth, and paternal smoking; and after exclusion of the children with chromosomal abnormalities. The results were not substantially changed when all variables of interest were adjusted for each other. However, the association between ALL and repeated early common infections was restricted to non-breastfed children (OR = 0.5, 95% CI: 0.4, 0.7) (breastfeeding for <6 months: OR = 0.9, 95% CI: 0.4, 1.9; breastfeeding for ≥6 months: OR = 1.0, 95% CI: 0.7, 1.3).

DISCUSSION

In the present study, ALL was negatively associated with several factors considered to stimulate the immune system in infancy: having an older sibling, day-care attendance, breastfeeding, repeated infections, and regular contacts with farm animals. ALL was also negatively related to child allergies. The associations tended to be more marked for B-cell precursor ALL.

The size of the study generated sufficient statistical power for most of the associations under study, but it was limited for subgroup analyses. For AML, minimum odds ratios of 0.6 and 0.3 for exposure prevalences of 50% and 10%, respectively, could be evidenced (power of 80%, alpha error of 5%).

The cases were identified in all pediatric cancer units through the data collection system of the French National Registry of Childhood Blood Malignancies. Thus, very few diagnosed cases likely escaped inclusion because of non-identification. Moreover, the case-mother participation rate was very high (91%).

The controls were recruited from the overall French population at the time of case diagnosis using the national telephone directory as the basis for random selection. Unlisted numbers were randomly generated to prevent selection on socioeconomic category or related factors that might influence the decision not to be listed in the telephone directory. The randomly selected numbers had to be dialed as many as 12 times at different times of the day to maximize the proportion of the population contacted and prevent overrepresentation of mothers spending more time at home. The screening response rate (86%) and overall response rate (61%) were higher than those reported in the recent US studies based on random digit dialing (approximately 70% and 40%, respectively) (12, 15).

The distribution of the responding controls by birth order, region, and maternal education was close to that of the French national perinatal surveys (15,000 births each) carried out in 1995, 1998, and 2003 (16–18). In these surveys, 42.6% of the newborns were firstborn, 34.3% were second born, and 22.6% were third born and subsequent compared with 40.9%, 36.8%, and 22.3%, respectively, of the controls born between 1995 and 2003. Refusal to take part could have been related to parental socioeconomic status or

Table 3. Socioeconomic Characteristics of Cases and Controls in the ESCALE Study, France, 2003–2004

	No. of Controls (<i>n</i> = 1,681)	Acute Lymphoblastic Leukemia			Acute Myeloblastic Leukemia		
		No. of Cases (<i>n</i> = 647)	OR ^a	95% CI	No. of Cases (<i>n</i> = 102)	OR ^a	95% CI
Maternal educational level							
≤High school	979	391	1.0		62	1.0	
>High school	701	256	0.9	0.8, 1.1	38	0.8	0.5, 1.2
Parental professional category ^b at interview							
Intellectual/scientific jobs, managers and intermediate-level professions	715	238	1.0		36	1.0	
Administrative and sales workers	477	197	1.3	1.0, 1.6	24	1.0	0.6, 1.7
Service workers	215	78	1.1	0.8, 1.5	15	1.4	0.8, 2.8
Factory and agricultural workers, unemployed	274	134	1.4	1.1, 1.8	27	2.0	1.2, 3.3
Place of residence at diagnosis							
Rural	601	216	1.0		32	1.0	
Semiurban	391	148	1.1	0.8, 1.4	29	1.4	0.8, 2.4
Urban	689	280	1.1	0.9, 1.4	39	1.1	0.7, 1.8
Maternal age at child's birth, years							
<25	163	101	1.8	1.3, 2.4	17	2.0	1.1, 3.8
25–29	664	231	1.0		37	1.0	
30–34	571	220	1.0	0.8, 1.3	31	1.0	0.6, 1.7
≥35	283	95	0.9	0.7, 1.2	17	1.1	0.6, 2.0
No. of children aged <15 years in the household at diagnosis							
1	546	199	1.0		35	1.0	
2	710	297	1.0	0.8, 1.3	43	1.0	0.6, 1.6
≥3	425	151	0.9	0.7, 1.2	24	0.9	0.5, 1.6

^a Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by polytomous unconditional regression, adjusted for the stratification variable age × gender.

^b Professional category was considered the higher of maternal and paternal professional categories.

education, which were slightly higher for the controls than for the leukemia cases, as reported in the literature (15), but the results were unchanged when the analyses were stratified by, or adjusted for, those factors. Compared with the mothers of the cases, the mothers of the controls were less often younger than age 25 years, which may be related to the fact that the households with cell phones only could not be accessed by our selection procedure. According to the French national statistics department, in 2003, 13% of households were not equipped with a land line (19). Despite an imbalance regarding the youngest mothers, maternal age was very similar for the cases and controls, and the impact of potential bias due to selection on maternal age was small. Finally, the mothers of 11.1% of the controls aged 11–14 years reported asthma in their child, which is very similar to the 12.7% history of asthma at the same age reported in a French survey in 2003 (20).

The mothers of the cases and controls were interviewed by the same interviewers using closed questions. Misclassification is likely to have occurred since the exposures were

described retrospectively and were reported by maternal interview. However, birth order, breastfeeding, and day-care attendance are well-defined, nonsporadic events and should be less prone to recall bias than history of early common infections or allergies. In the United Kingdom Childhood Cancer Study (21, 22), medical information contemporaneously recorded in medical records differed from maternal recall of allergies and infections confirmed by a general practitioner: an episode of any infection recorded by the general practitioner was slightly more underreported by the mothers of cases (66%) than by the mothers of controls (72%) (22). Depending on the allergy, the odds ratios calculated from the records were 1.0 and 0.9 for asthma and eczema; the corresponding odds ratios calculated from the interview data were 0.7 and 0.8 (21).

In ESCALE, odds ratios greater than 1 were observed for 1–3 infections for most sites, which was an unexpected finding. Differential recall of common infections might have been greater for less frequent infections, for which episodes may have seemed less noteworthy. Regarding asthma, the

Table 4. Birth Order, Day-care Attendance, Breastfeeding, and Childhood Acute Leukemia (Analyses Restricted to Children Aged ≥ 1 Year) in the ESCALE Study, France, 2003–2004

	Controls (<i>n</i> = 1,494)	Acute Lymphoblastic Leukemia			Acute Myeloblastic Leukemia		
		No. of Cases (<i>n</i> = 634)	OR ^a	95% CI	No. of Cases (<i>n</i> = 86)	OR ^a	95% CI
Birth order							
1	628	321	1.0		37	1.0	
2	536	198	0.7	0.6, 0.9**	29	1.0	0.6, 1.8
3	239	91	0.7	0.5, 1.0*	12	1.0	0.5, 2.1
≥ 4	91	24	0.5	0.3, 0.8**	8	1.3	0.5, 3.3
<i>P</i> trend				<0.0001			
Interval to birth of the next older sibling, years ^b							
≤ 2	214	74	0.7	0.5, 0.9**	18	1.5	0.8, 2.7
3–5	462	142	0.6	0.5, 0.8***	22	0.9	0.5, 1.6
≥ 6	190	97	1.1	0.8, 1.5	9	0.8	0.4, 1.9
Full-time day-care attendance in the first year of life							
No	1,348	583	1.0		82	1.0	
Yes	146	51	0.8	0.6, 1.1	4	0.5	0.2, 1.4
Age at start of day-care attendance, months							
7–12	30	10	0.8	0.4, 1.6	0		
4–6	66	20	0.7	0.4, 1.2	3	0.9	0.3, 2.9
≤ 3	50	21	1.0	0.6, 1.6	1	0.4	0.0, 2.7
Breastfeeding							
No	740	317	1.0		41	1.0	
Yes	754	317	1.0	0.8, 1.2	45	1.2	0.8, 1.9
Breastfeeding duration, months ^c							
<6	554	256	1.1	0.9, 1.4	29	1.0	0.6, 1.7
≥ 6	193	59	0.7	0.5, 1.0*	16	1.7	0.9, 3.2
≤ 2	296	151	1.3	1.0, 1.6	16	1.0	0.6, 1.9
3–5	258	101	0.9	0.7, 1.2	13	1.0	0.5, 2.0
6–11	137	44	0.7	0.5, 1.1	12	1.9	0.9, 3.6
≥ 12	56	15	0.6	0.3, 1.0	4	1.3	0.5, 4.4

* $0.01 \leq P < 0.05$; ** $0.001 \leq P < 0.01$; *** $P < 0.001$.

^a Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by polytomous unconditional logistic regression, adjusted for age, gender, parental professional category, degree of urbanization, and maternal age at child's birth.

^b Reference group: birth order 1.

^c Reference group: no breastfeeding.

disease had a prevalence very close to that in the general population during the same period, which suggests that our questions did not lead to a major overreport or underreport of asthma in controls. Reports of treatment with salbutamol, corticosteroids, or antihistamines in children with asthma were very similar between cases and controls, suggesting no, or little, differential bias. In addition, the more specific variable “asthma with specific treatment” was still negatively associated with acute leukemia.

The distribution of birth order among the controls may be biased if the probability of a control being selected depends on the size of the sibship, which may happen if the statistical unit for control sampling is a family rather than individuals

(23). It is noteworthy that the cohort studies and the case-control studies based on birth registries, not subject to such bias, reported null or negative associations between birth order and ALL (24–37), whereas the results were more inconsistent for the other studies (24, 38–48). In the present study, the number of children younger than age 15 years in the household was forced to reflect that of the population because quotas were used.

To our knowledge, 13 studies have reported results regarding day-care attendance in early childhood and acute leukemia (29, 30, 39, 41, 43, 45, 48–55). All except 2 of those studies reported negative associations between acute leukemia and day-care attendance (29, 30, 39, 41, 43, 45, 49–52,

Table 5. Number of Common Infections in the First Year of Life and Childhood Acute Leukemia (Analyses Restricted to Children Aged ≥ 1 Year) in the ESCALE Study, France, 2003–2004

	Controls (<i>n</i> = 1,494)	Acute Lymphoblastic Leukemia			Acute Myeloblastic Leukemia		
		No. of Cases (<i>n</i> = 634)	OR ^a	95% CI	No. of Cases (<i>n</i> = 86)	OR ^a	95% CI
Early common infections							
None	347	127	1.0		26	1.0	
Rare ^b	312	174	1.5	1.1, 2.0**	19	0.8	0.4, 1.5
Intermediate ^c	230	115	1.3	1.0, 1.8	7	0.4	0.2, 0.9*
Repeated ^d	546	192	0.9	0.7, 1.2	19	0.7	0.4, 1.2
Missing	59	26			3		
Repeated early common infections ^d							
No	889	416	1.0		52	1.0	
Yes	546	192	0.7	0.6, 0.9**	31	0.9	0.6, 1.5
Missing	59	26			3		
Tonsillitis							
No infection	1,282	534	1.0		72	1.0	
1–3	136	67	1.2	0.9, 1.6	8	1.0	0.5, 2.2
≥ 4	52	17	0.8	0.5, 1.5	2	0.7	0.2, 2.8
Missing	24	16			4		
Otitis							
No infection	1,074	456	1.0		63	1.0	
1–3	236	122	1.3	1.0, 1.6	16	1.1	0.6, 1.9
≥ 4	168	50	0.7	0.5, 1.0*	6	0.6	0.3, 1.4
Missing	16	6			1		
Upper respiratory tract infections							
No infection	591	211	1.0		37	1.0	
1–3	473	269	1.6	1.3, 2.0***	24	0.8	0.5, 1.4
≥ 4	411	144	0.9	0.7, 1.2	24	0.9	0.5, 1.6
Missing	19	10			1		
Bronchiolitis and other lower respiratory tract infections							
No infection	1,152	528	1.0		76	1.0	
1–3	254	88	0.7	0.5, 0.9**	7	0.4	0.2, 0.9*
≥ 4	76	13	0.3	0.2, 0.6***	3	0.5	0.2, 1.7
Missing	12	5			0		
Gastroenteritis							
No infection	1,180	526	1.0		70	1.0	
1–3	255	92	0.8	0.6, 1.0	15	0.9	0.5, 1.7
≥ 4	33	4	0.3	0.1, 0.8*	0		
Missing	26	12			1		
Urinary tract infections							
No infection	1,444	615	1.0		82	1.0	
1–3	40	17	1.0	0.5, 1.7	3	1.2	0.4, 4.2
≥ 4	5	2	1.0	0.2, 5.3	0		
Missing	5	0			1		
Surgical operation for ear infections before age 3 years							
No	1,463	628	1.0		84	1.0	
Yes	31	6	0.4	0.2, 1.0*	2	1.4	0.3, 6.1
Missing	0	0			0		
Surgical operation for ear-nose-throat infections before age 3 years							
No	1,407	598	1.0		79	1.0	
Yes	85	36	1.0	0.7, 1.6	6	1.4	0.6, 3.4
Missing	2	0			1		

* $0.01 \leq P < 0.05$; ** $0.001 \leq P < 0.01$; *** $P < 0.001$.^a Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by polytomous unconditional logistic regression, adjusted for age, gender, parental professional category, and degree of urbanization.^b 1–3 episodes of infection of only 1 site.^c 1–3 episodes of infection of 2 or 3 sites.^d 4 or more episodes of infection of at least 1 given site or 1–3 episodes of infection of at least 4 sites.

Table 6. Farm Visits, Contacts With Animals, and Childhood Acute Leukemia (Analyses Restricted to Children Aged ≥ 1 Year) in the ESCALE Study, France, 2003–2004

	Controls (<i>n</i> = 1,494)	Acute Lymphoblastic Leukemia			Acute Myeloblastic Leukemia		
		No. of Cases (<i>n</i> = 634)	OR ^a	95% CI	No. of Cases (<i>n</i> = 86)	OR ^a	95% CI
Regular contacts with animals before age 1 year (at least once/week)							
Cats	501	188	0.9	0.7, 1.1	26	0.9	0.6, 1.5
Dogs	680	294	1.1	0.9, 1.3	40	1.0	0.6, 1.6
Rodents	49	16	0.8	0.4, 1.4	5	1.8	0.7, 4.9
Birds	140	28	0.4	0.3, 0.7***	8	0.9	0.4, 1.9
Cows	78	13	0.3	0.2, 0.7**	1	0.2	0.0, 1.5
Sheep	47	8	0.4	0.2, 0.9*	1	0.4	0.1, 2.9
Horses	59	23	1.0	0.6, 1.6	0		
Pigs	24	6	0.7	0.3, 1.7	0		
Rabbits	111	31	0.6	0.4, 1.0*	4	0.6	0.2, 1.7
Poultry	131	34	0.6	0.4, 0.9*	3	0.4	0.1, 1.3
Regular contact with farm animals ^b before age 1 year							
No	1,270	570	1.0		80	1.0	
Yes	224	64	0.6	0.5, 0.8**	6	0.4	0.2, 1.0*
Lived on a farm during the first year of life							
No	1,470	624	1.0		85	1.0	
Yes	24	10	0.8	0.4, 1.8	1	0.6	0.1, 4.8
Farm visits before age 2 years							
No	1,071	499	1.0		67	1.0	
Several days/year	198	76	0.8	0.6, 1.1	8	0.7	0.3, 1.5
Several days/month	84	30	0.7	0.5, 1.2	6	1.2	0.5, 3.0
Several days/week	141	29	0.4	0.3, 0.6***	5	0.6	0.2, 1.5

* $0.01 \leq P < 0.05$; ** $0.001 \leq P < 0.01$; *** $P < 0.001$.^a Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by polytomous unconditional logistic regression, adjusted for age, gender, parental professional category, degree of urbanization, and housing.^b Farm animals: cows, sheep, horses, pigs, rabbits, and poultry.

54), and, in 6 studies, the association was significant (41, 43, 45, 49–51). Three studies showed evidence of dose-response effects, with a decreasing risk of acute leukemia with increasing child-hours of day-care attendance (50), time spent outside the home (52), or level of childhood social activity (49). In the present study, the negative association was restricted to full-time attendance at day-care centers, which involves more exposure to contact with other children than other kinds of child care do. Five studies reported a risk of acute leukemia at a very early age, at the start of day care, before age 3 or 6 months (29, 39, 43, 45, 49). Only 2 studies reported stronger negative associations for day-care beginning before age 3 (45) or 6 (43) months compared with later.

With regard to breastfeeding, Martin et al. (56) included 26 studies in a meta-analysis carried out in 2005 and reported meta-odds ratios of 0.9 (95% CI: 0.8, 1.0) for acute leukemia. The associations were slightly more marked when breastfeeding lasted 6 months or more (OR = 0.8, 95% CI: 0.7, 0.9 for ALL and OR = 0.7, 95% CI: 0.6, 0.9 for AML). Studies published since then have reported odds ratios close to unity (46, 57).

About 10 studies have addressed the relation between acute leukemia and early common infections (30, 34, 39, 40, 43, 45, 52, 53, 58–61). Two previous independent French studies showed negative and significant associations between acute leukemia and 4 or more common infections per year before the age of 1 (45) or 2 (43) years. The questionnaire used in the present study was also designed to identify the children with the highest frequency of common infections in early life. Similar to this study, one of the previous studies showed a stronger association for gastrointestinal infections in infancy (45). Van Steensel-Moll et al. (58) observed a significant negative association between common colds in infancy and ALL. Neglia et al. (39) observed a significant negative trend in acute leukemia risk with increasing number of episodes of otitis before age 1 year. McKinney et al. (40) observed a significant negative association between ALL and neonatal infections based on information from neonatal records.

In contrast, 2 United Kingdom studies evidenced significant positive associations between ALL and infections of

Table 7. Child History of Allergy and Childhood Acute Leukemia (Analyses Restricted to Children Aged ≥ 1 Year) in the ESCALE Study, France, 2003–2004

	Controls (<i>n</i> = 1,494)	Acute Lymphoblastic Leukemia			Acute Myeloblastic Leukemia		
		No. of Cases (<i>n</i> = 634)	OR ^a	95% CI	No. of Cases (<i>n</i> = 86)	OR ^a	95% CI
Asthma							
No	1,365	598	1.0		81	1.0	
Yes	128	35	0.7	0.4, 1.0*	5	0.6	0.3, 1.6
Bronchitis with wheezing							
No	1,196	537	1.0		68	1.0	
Yes	295	95	0.7	0.6, 1.0*	17	1.0	0.6, 1.8
Eczema							
No	1,160	518	1.0		66	1.0	
Yes	329	112	0.7	0.6, 0.9*	20	1.1	0.7, 1.9
Any allergy (asthma, bronchitis with wheezing, eczema)							
None of the 3	935	444	1.0		54	1.0	
Eczema with no history of asthma or bronchitis with wheezing	220	81	0.8	0.6, 1.0*	12	1.0	0.5, 1.9
Asthma or bronchitis with wheezing with no history of eczema	222	74	0.7	0.6, 1.0*	12	0.9	0.5, 1.7
Both asthma or bronchitis with wheezing and eczema	108	29	0.5	0.4, 0.8**	8	1.4	0.6, 3.1
Asthma and any treatment with antihistamines, salbutamol, or corticosteroids							
No	1,385	603	1.0				
Yes	108	30	0.7	0.4, 1.0			
Asthma and treatment with antihistamines, salbutamol, and corticosteroids							
No	1,459	626	1.0				
Yes	34	7	0.6	0.3, 1.4			

* $10^{-2} \leq P < 0.05$; ** $10^{-3} \leq P < 10^{-2}$; *** $P < 10^{-3}$.

^a Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by polytomous unconditional logistic regression, adjusted for stratification variables, age, gender, parental professional category, and degree of urbanization.

the upper respiratory tract during infancy recorded by the general practitioner (59, 60). The United Kingdom studies also showed positive, albeit nonsignificant, associations with consultation for any common infection in infancy. In the United Kingdom Childhood Cancer Study, mothers tended to underreport a history of at least one infection recorded by their general practitioners during the first year of the child's life, and mothers of cases were more prone to do so than mothers of controls for second-born or subsequent children (22). Overall, it is likely that all infections do not necessarily lead to a consultation, particularly for non-firstborn children, and that recall for common infections may be less impaired for firstborn children. However, it is not clear why underreporting should be differential for only nonfirstborn children. In the present study, cases were more frequently firstborn than controls were (51% vs. 42%), which should have lowered the impact of this bias if such a bias really existed in the study population. The other stud-

ies have shown nonsignificant negative (34, 52, 53, 61) or positive (30) associations between acute leukemia and early common infections.

Interestingly, in this study, the negative relation between acute leukemia and frequent early common infections was more pronounced in children who had not been breastfed. In addition, it was not even discernible in children breastfed for more than 6 months, as if a child could not benefit fully from both breastfeeding and early infections.

A few studies have reported either positive (54, 62, 63) or null (30, 64, 65) associations between acute leukemia and contacts with pets during childhood. Two of these studies also reported results for animals other than cats and dogs during childhood, and they showed positive, significant associations (64, 65), although not specifically for exposure in early life. Lastly, one paper reported a negative association with living on a farm during childhood (30). To our knowledge, the present study is the first to focus on contacts with

Table 8. Birth Order, Day-care Attendance, Breastfeeding, Repeated Common Infections, Farm Animal Contacts, Farm Visits, and Child Allergy by Childhood ALL Subtype (Analyses Restricted to Children Aged ≥ 1 Year) in the ESCALE Study, France, 2003–2004

	ALL Subtype											
	Pro-B (<i>n</i> = 17)			Pre-B/Common B (<i>n</i> = 517)			B Mature ^a (<i>n</i> = 30)			T-cell (<i>n</i> = 67)		
	No.	OR ^b	95% CI	No.	OR ^b	95% CI	No.	OR ^b	95% CI	No.	OR ^b	95% CI
Birth order												
1	11	1.0		259	1.0		18	1.0		32	1.0	
2	4	0.5	0.1, 1.5	163	0.7	0.6, 1.0*	6	0.3	0.1, 0.8*	25	0.9	0.5, 1.6
≥ 3	2	0.8	0.1, 1.8	95	0.7	0.5, 0.9*	6	0.4	0.1, .1	9	0.5	0.2, 1.1
Full-time day-care attendance in the first year of life												
No	17	1.0		474	1.0		25	1.0		63	1.0	
Yes	0			43	0.8	0.6, 1.2	5	1.9	0.7, 5.4	3	0.5	0.1, 1.6
Breastfeeding												
No	5	1.0		266	1.0		12	1.0		32	1.0	
<6 months	11	3.0	1.0, 9.1	200	1.0	0.8, 1.3	16	2.0	0.9, 4.5	28	1.4	0.8, 2.4
≥ 6 months	1	1.0	0.1, 9.2	49	0.6	0.4, 0.9*	2	0.7	0.1, 3.2	6	1.0	0.4, 2.5
Repeated early common infections												
No	9	1.0		341	1.0		19	1.0		42	1.0	
Yes ^c	8	1.6	0.6, 4.4	158	0.7	0.6, 0.9**	11	0.9	0.4, 1.9	16	0.6	0.3, 1.1
Regular contact with farm animals ^c before age 1 year												
No	16	1.0		456	1.0		24	1.0		61	1.0	
Yes	1	0.4	0.1, 3.4	52	0.6	0.5, 0.9**	6	1.6	0.6, 4.1	5	0.4	0.1, 1.0*
Farm visits before age 2 years												
No	13	1.0		407	1.0		25	1.0		51	1.0	
A few days/year	3	1.4	0.4, 5.1	66	0.9	0.7, 1.2	2	0.4	0.1, 1.7	4	0.5	0.2, 1.1
A few days/month	0			25	0.7	0.5, 1.2	0			5	1.1	0.4, 3.1
Several days/week	1	0.7	0.1, 6.1	19	0.3	0.2, 0.6***	3	0.8	0.2, 2.8	6	0.7	0.3, 1.7
Any allergy (asthma, bronchitis with wheezing, eczema)												
No allergy	15	1.0		355	1.0		24	1.0		49	1.0	
Eczema with no history of asthma or bronchitis with wheezing	0			66	0.8	0.6, 1.0	4	0.8	0.3, 2.4	9	0.9	0.4, 1.9
Asthma or bronchitis with wheezing with no history of eczema	1	0.3	0.0, 2.2	65	0.9	0.6, 1.2	0			7	0.5	0.2, 1.1
Both asthma and bronchitis with wheezing	1	0.6	0.1, 4.8	26	0.6	0.4, 1.0	1	0.2	0.0, 1.8	1	0.2	0.0, 1.2

Abbreviation: ALL, acute lymphoblastic leukemia.

* $10^{-2} \leq P < 0.05$; ** $10^{-3} \leq P < 10^{-2}$; *** $P < 10^{-3}$.^a Analyses were restricted to children older than age 1 year.^b Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by polytomous unconditional logistic regression, adjusted for stratification variables, age, gender, parental professional category, and degree of urbanization.^c 4 episodes or more of infection of at least 1 given site or 1–3 episodes of infection of at least 4 sites.

farms and farm animals during infancy. Such exposures may enable effective maturation of the immune system and thus prevent acute leukemia, as has been hypothesized for allergies.

Eight (21, 45, 53, 54, 63, 66–68) of 9 (21, 44, 45, 53, 54, 63, 66–68) studies found an inverse association between allergy and acute leukemia, which was significant in most of the studies (21, 45, 53, 63, 66–68). This finding suggests that allergy and acute leukemia may share some underlying biologic mechanisms (3), for instance, a positive effect of

the allergic reaction on destruction of neoplastic blood and lymphatic cells.

The literature on early infections and acute leukemia is heterogeneous, with various definitions of common infections and various quantifying indices. Useful discussions will be possible in the framework of the Childhood Leukemia International Consortium (<http://cllc.berkeley.edu/>). Future research will also benefit from the prospective data on the International Childhood Cancer Cohort Consortium

(I4C) birth cohorts. Finally, genes involved in the immune system, such as human lymphocyte antigen polymorphisms, have been associated with childhood acute leukemia (69), and investigation of the way in which those polymorphisms interact with early common infections, breastfeeding, and other factors linked to early stimulation of the immune system is also a promising prospect.

Overall, our findings support the hypothesis that some conditions promoting the maturation of the immune system, such as prolonged breastfeeding, repeated common infections in infancy, and related factors, may play a protective role with respect to ALL. The early farm exposure findings are new and also support this hypothesis.

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