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Early life exposure to infections and risk of childhood acute lymphoblastic leukemia

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Abstract

Evidence from a growing number of studies indicates that exposure to common infections early in life may be protective against childhood acute lymphoblastic leukemia (ALL). We examined the relationship between three measures of early life exposure to infections—daycare attendance, birth order and common childhood infections in infancy—with the risk of ALL in non-Hispanic white and Hispanic children, two ethnicities that show sociodemographic differences. The analysis included 669 ALL cases (284 non-Hispanic whites and 385 Hispanics) and 977 controls (458 non-Hispanic whites and 519 Hispanics) ages 1–14 years enrolled in the Northern California Childhood Leukemia Study (NCCLS). When the three measures were evaluated separately, daycare attendance by the age of 6 months (odds ratio [OR] for each thousand child-hours of exposure = 0.90, 95% confidence interval [CI]: 0.82–1.00) and birth order (OR for having an older sibling = 0.68, 95% CI: 0.50–0.92) were associated with a reduced risk of ALL among non-Hispanic white children but not Hispanic children, whereas ear infection before age 6 months was protective in both ethnic groups. When the three measures were assessed simultaneously, the influence of daycare attendance (OR = 0.83, 95% CI: 0.73–0.94) and having an older sibling (OR = 0.59, 95% CI: 0.43–0.83) became stronger for non-Hispanic white children. In Hispanic children, a strong reduction in risk associated with ear infections persisted (OR = 0.45, 95% CI: 0.25–0.79). Evidence of a protective role for infection-related exposures early in life is supported by findings in both the non-Hispanic white and Hispanic populations within the NCCLS.

Keywords

childhood leukemia; infection; daycare; birth order; risk factor

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Introduction

There is growing evidence supporting a role for infection and immunologic mechanisms in the etiology of acute lymphoblastic leukemia (ALL) in children, but the involvement of specific infectious agents has not yet been demonstrated.[1] The confirmation of an infectious etiology is complicated by the challenges associated with quantifying a child's exposure and/or response to infections in epidemiologic studies which by nature of the case-control design, usually collect this information retrospectively. Nonetheless, indirect evidence is mounting which suggests childhood ALL may result from an adverse immunologic response to a delay in exposure to nonspecific common infections.[2] Evidence to date in support of this "delayed infection" hypothesis derives from a substantial body of literature based on surrogate measures of exposure to infections which show a reduced risk of ALL, particularly precursor B-cell ALL (common ALL or c-ALL), associated with increasing birth order, child's history of infections and child's daycare and play group attendance.[3–5] However, uncertainty still remains regarding these associations in childhood leukemia largely because of unresolved inconsistencies between study results that may have been affected by design issues, such as biases in control selection and/or exposure assessment.

In addition, inconsistencies between study results may be partly because of between-study variation in the degree to which surrogate measures, alone or in combination, accurately reflect a child's "true" exposure to infectious agents early in life. For example, a nationwide survey conducted in the United States showed that among children aged 18–35 months, childcare attendance was a statistically significant risk factor for respiratory tract illness only among children who did not have an older sibling.[6] Also, a previous analysis conducted within the Northern California Childhood Leukemia Study (NCCLS) indicated a differential risk associated with daycare attendance between non-Hispanic white and Hispanic children.[7] The two ethnic groups differed with respect to several sociodemographic characteristics, as well as Hispanic children generally living with more children (siblings and non-siblings) in a household, and utilizing daycare in a formal setting less often, at a later age and for a shorter duration. Given these differences, the absence of an association in Hispanics compared to non-Hispanic whites may reflect the weakness of the measure, presence in a daycare setting, to predict early exposure to infections among Hispanic children.

Diversity in the potential sources and nature of exposure to infection between populations illustrates the importance of simultaneously considering different indicators of exposure to infections. Our analysis examined the multivariable relationships between multiple indicators of early life exposure to infections to clarify the role of infection in the etiology of childhood ALL in non-Hispanic whites and Hispanics separately.

Material and Methods

Study population

The NCCLS is a case-control study designed to investigate the etiology of pediatric leukemias. Beginning in 1995, newly diagnosed childhood leukemia cases were rapidly ascertained from major pediatric hospitals located in the 17-county San Francisco Bay Area study region, which was expanded in 1999 to 35 counties in Northern and Central California. For each eligible case, the statewide birth registry maintained by the Center for Health Statistics of the California Department of Public Health was utilized to generate a list of randomly selected controls that matched the case on date of birth, sex, maternal race and Hispanic status (has a biological parent who is Hispanic). Information obtained through birth certificates and commercially available search tools was used in the tracing effort to identify one or two matched controls for each case.

Cases and controls were considered eligible if they were under 15 years of age, resided in the study area at the date of diagnosis (or corresponding reference date for controls), had a parent or guardian who spoke either English or Spanish, and had no prior history of malignancy. Approximately 85% of eligible cases have consented to participate. Among all eligible controls contacted, 86% consented to participate. The overall participation for the control subjects was 59% (the number of enrolled controls divided by the total number of control searches excluding the known and presumed ineligibles). A detailed description of control selection in the NCCLS is reported elsewhere.[8] This evaluation showed that participating controls in the NCCLS are representative of the sampled population with respect to parental age, parental education and mother's reproductive history.[8]

The demographic composition of the pediatric population of the study area included approximately 42% Hispanic (at least one parent self-reported as Hispanic) with an equivalent proportion of non-Hispanic whites (both parents self-reported as non-Hispanic white). Our analysis focused on these two race/ethnicity groups which together comprised greater than 85% of all subjects enrolled. Cases diagnosed under one year of age were excluded as infant leukemias may be etiologically distinct compared to leukemia diagnosed at a later age.[9,10] In total, this analysis included 669 cases of ALL (284 non-Hispanic white and 385 Hispanic) including 334 confirmed c-ALL cases (defined as CD10+ and CD19+ ALL, aged 2–5 years; 142 non-Hispanic white and 192 Hispanic) and 977 controls (458 non-Hispanic white and 519 Hispanic) enrolled between August 1995 and July 2008. The distribution of cALL cases remained consistent over this period comprising about half of all ALL cases.

The study protocol was available in English and Spanish and was approved by the institutional review boards of the University of California, Berkeley and all collaborating institutions, and a written informed consent was obtained for all study participants.

Data collection

In the NCCLS, a detailed account of the child's history of exposure to infection was obtained through various measures. Respondents, usually the biological mothers, were asked for a history of all infectious illnesses the child had during the first year of life, including severe diarrhea/vomiting, ear infection, persistent cough, mouth infection, eye infection, influenza and unspecified "other infections." These data were collected with an emphasis on the timing of exposure, specifically whether the child had the illness at the age of <3 months, 3–5 months, and/or 6–12 months.

Other measures of exposure to infections included child's social contacts both inside and outside the home. Specifically, information was obtained regarding the number of other children present in the household before the index child went to first grade (usually occurring around age 6 years), including both siblings and non-siblings. The child's birth order was determined based on a detailed pregnancy history obtained for the biological mother. Information on the child's social contacts outside the home was obtained through a history of daycare and preschool attendance before the reference date (date of diagnosis for cases and corresponding date for matched controls) or before age 6, whichever occurred first. For each daycare and/or preschool the child attended, information on age attended, duration of time attended, hours per week and number of other children was obtained. Under the assumption that exposure to infections is primarily through the child's social contacts with other children, a quantitative summary measure, total child-hours of exposure, was calculated for each child.[7,11] Child-hours at each daycare facility were calculated as follows: (number of months attending the daycare) × (mean hours per week at this daycare) × (number of other children at this daycare) × (4.35 weeks per month).

For each child, the child-hours in each daycare setting were summed to obtain the total child-hours of exposure. For children who never attended daycare, 72 months (6 years) was assigned as the age when first started daycare and 0 was assigned for the duration of stay, mean hours per week, mean number of children, total number of children, and total child-hours. To examine the influence of daycare attendance during a specific time window of exposure, data for daycare attendance and total child-hours were censored at 1 year and 6 months of age. Censoring at a specific age means that only exposures occurring before that age of the child were considered in the analysis.

Statistical analysis

Cases and controls were compared with respect to sociodemographic characteristics and other potential confounding factors for the research question under study using the Pearson chi-square test. All analyses were performed separately in non-Hispanic whites and Hispanics because of observed differences in sociodemographic characteristics and daycare utilization patterns between these race/ethnicity groups. Specific daycare characteristics including age first started, months of stay, mean hours per week, mean number of other children and total thousand child-hours of exposure were compared between cases and controls using the Wilcoxon rank-sum test. To evaluate the risk associated with the three measures of exposure to infections—child-hours of exposure in daycare settings, birth order and infections during the first year of life—odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression adjusting for child's age and annual household income. The total child-hours variable was evaluated as a continuous measure per thousand child-hours unit increase and as a categorical variable where the median value of child-hours in controls was used as the cut-off point. Specific childhood infections experienced during the first year of life were evaluated as dichotomous (yes *versus* no) variables, in addition to categories of when the infection occurred: none during the first year of life, at less than 6 months of age only, between 6 to 12 months only, or during both time periods.

The joint effects of the measures of exposure to infections on risk of childhood ALL were examined using logistic regression with interaction terms describing the two-way multiplicative interactions between daycare child-hours by age 6 months, having an older sibling, and ear infections. The influence of several covariates (*i.e.*, child's age, sex, maternal education, maternal age, annual household income, mother's smoking status, breastfeeding and birth weight) on risk estimates for the three infection-related exposure measures were evaluated. With the exception of two potential confounding variables, child's age and annual household income, other covariates were not included in the final multivariable models because of their minimal influence on risk for the three measures of exposure to infections.

Results

In this study, differences were observed between non-Hispanic white and Hispanic children with respect to several characteristics (Table 1). Among control participants, Hispanic children had mothers who were younger at child's birth and who had less formal education compared to non-Hispanic white children. Hispanic control children had, on average, lower birth weight, more other children living in the household, and lower annual household income. In addition, Hispanic children had a lower proportion of mothers who had ever smoked and a higher proportion who had ever breastfed compared to non-Hispanic white controls. However, case-control differences in these select characteristics were similar between non-Hispanic white and Hispanic children (Table 1). Among both non-Hispanic white and Hispanic children, mothers of cases tended to be younger and have less formal education than mothers of controls, and cases resided in homes with lower annual household income.

Differences in daycare attendance patterns were observed between non-Hispanic white and Hispanic children. A comparison among controls (Table 2) showed that compared to Hispanic children, non-Hispanic white children tended to start daycare at an earlier age, attended for a longer period of time, for more hours each week, and attended daycare settings with a greater number of children present. Twenty-seven percent of non-Hispanic white control children attended daycare before 6 months of age, whereas only 9% of Hispanic control children attended daycare during this age (Table 3).

The relationship between common infection during the first year of life and the social contact variables also appeared to differ by race/ethnicity. In non-Hispanic white controls, compared to children who did not attend daycare by age 6 months, a larger proportion of children who attended day-care during that time were reported as having any infection (p = 0.102) or ear infection (p = 0.002) before age 6 months. This association was not observed in Hispanic children, neither was an association with birth order in both non-Hispanic whites and Hispanics (data not shown).

In the analysis of the social contact variables among non-Hispanic whites, the risk of ALL and c-ALL associated with child-hours of exposure varied depending on the time in which daycare censoring occurred (Table 3). Evidence of an association was observed for daycare child-hours by age 6 months showing a reduced risk of childhood ALL associated with each thousand child-hours (OR = 0.90, 95% CI: 0.82–1.00; p = 0.046). Evaluation of c-ALL showed similar evidence of a reduced risk, but lacked statistical precision (Table 3). Daycare child-hours by 1 year of age also showed evidence of a reduced risk of ALL and c-ALL (data not shown), but no association was observed for daycare child-hours by the reference date. In non-Hispanic white children, being third-born (OR = 0.62, 95% CI: 0.40–0.97) or fourth-born or higher (OR = 0.44, 95% CI: 0.21–0.92) when compared to first-borns, was associated with a statistically significant reduced risk of childhood ALL (Table 3) with evidence of a linear trend (p = 0.004). Similar risk estimates and trend were also observed for c-ALL. Analysis of the social contact variables among Hispanic children did not show daycare child-hours or birth order to be associated with ALL or cALL risk (Table 3).

In the evaluation of common childhood infections (Table 4), the occurrence of an ear infection during the first year of life was associated with a reduced risk of childhood c-ALL (OR = 0.66, 95% CI: 0.44–1.00) in non-Hispanic whites. The analysis by specific time periods within the first year of life showed a reduced risk of ALL associated with a history of ear infection at <6 months of age among both non-Hispanic whites (OR = 0.39, 95% CI: 0.19–0.91) and Hispanics (OR = 0.48, 95% CI: 0.27–0.83). Associations with each of the other assessed infections (*i.e.*, severe diarrhea and vomiting, persistent cough, mouth infection, eye infection, influenza and “other infections”) were not observed. In addition, no associations were found in an analysis of “any infections” by time period during the first year of life (data not shown).

The multivariable analysis (Table 5) evaluating the joint effects between the two social contact variables (model 1), daycare child-hours by age 6 months and having an older sibling, showed no evidence of interactions in either non-His-panic white (p = 0.590) or Hispanic (p = 0.659) children. In the additive model (model 2), both daycare child-hours by age 6 months and older sibling were independently associated with childhood ALL risk among non-Hispanic whites, whereas no association was observed in Hispanics.

The joint influence of ear infections together with the social contact variables showed no evidence of two-way interactions among the three measures of exposure to infections (data not shown). The additive model containing all three measures of infectious exposure and adjusting for child’s age and annual household income (model 3) showed daycare child-

hours by age 6 months (OR = 0.83, 95% CI: 0.73–0.94), having an older sibling (OR = 0.59, 95% CI: 0.43–0.83), and ear infections before age 6 months (OR = 0.44, 95% CI: 0.19–1.02) to be independently associated with a reduced risk of childhood ALL in non-Hispanic whites (Table 5). Among Hispanic children, the multivariable model con-firmed the lack of association for daycare child-hours and having an older sibling, but ear infections before age 6 months compared to no ear infections during infancy was associated with a strong reduced risk of childhood ALL (OR = 0.45, 95% CI: 0.25–0.79).

Discussion

For non-Hispanic white and Hispanic children enrolled in the NCCLS, we conducted an analysis examining the individual and joint effects of three widely recognized measures of early exposure to infection. In non-Hispanic white children, a reduced risk of childhood ALL was associated with daycare attendance (measured by child-hours) by 6 months of age, higher birth order and history of ear infection with similar associations found when limited to c-ALL. The multivariable analysis confirmed these results showing separate additive effects associated with all three measures. Based on these data, it is difficult to conclude whether the association applies specifically to c-ALL only or more generally to ALL of varying subtypes. In Hispanic children, a reduced risk was associated with ear infection by age 6 months, but not with the social contact measures.

A recently conducted meta-analysis of 14 studies suggested that daycare attendance is associated with a reduced risk of childhood ALL overall (summary OR = 0.76, 95% CI: 0.67–0.87)[12] and similarly with c-ALL (summary OR = 0.83, 95% CI: 0.70–0.98), even after a thorough evaluation of several sources of study heterogeneity. In our analysis, the strongest evidence of a reduced risk was found when daycare attendance was censored at 6 months of age, demonstrating the importance of timing of early exposure to infection. A few individual studies have also shown that the strongest reduction in risk occurs when daycare attendance is started before 6 months of age.[13–15]

Several studies have reported reduced risks associated with increasing birth order or parity.[16–23] In contrast, a few studies observed a risk estimate in the opposite direction,[14,24,25] whereas a large majority showed no effect.[13,15,26–33] Among the few studies that demonstrated an increased risk associated with higher birth order, one showed an effect only for a birth order of four or higher,[14] and another study attributed the finding to possible selection bias.[24] Two large registry-based studies provided strong evidence supporting an inverse association between birth order and risk of childhood ALL.[16,17] In one of these studies conducted among 2,942 childhood ALL cases and 1:1 matched controls residing in England and Wales, Dockerty *et al*.[16,34] reported a decreased risk of ALL associated with increasing parity (OR = 0.90, 95% CI: 0.86–0.95; p trend <0.001). Similar findings were reported in another large study conducted with 1,817 ALL cases and 8,827 matched controls in Denmark, Sweden, Nor-way and Iceland.[17] The use of population-based registries in the identification of study subjects, the record-based data collection, and the large sample sizes are obvious strengths of these two studies, which included predominantly white children.

Among the various common infections assessed in the NCCLS, occurrence of ear infections during the first year of life was associated with a reduced risk of childhood ALL and c-ALL. An evaluation of timing within the first year suggested a greater importance of exposure before 6 months of age, which is consistent with the findings for timing of day-care attendance. Two other studies have also reported a reduced risk associated with ear infections.[23,28] The Children's Cancer Group study reported a reduction in risk of cALL associated with two to four occurrences of ear infections during the first year of life

compared to none (OR = 0.65, 95% CI: 0.43–1.00) and a statistically significant trend with increasing occurrences ($p = 0.016$).[28] Several other studies provide evidence of a reduced risk associated with other types of common infections including the common cold,[23] gastrointestinal infections,[14,26,35] Roseola[36] and a non-specific category referred to as "any infections."[14,15,20,23] In contrast, some studies have reported no association[37,38] or an increased risk of childhood ALL.[26,39,40] Two of the three studies reporting an increased risk of childhood ALL associated with early infection were conducted in the United Kingdom and utilized general practitioner records to identify clinically diagnosed infections rather than self-reported infections.[39,40] The authors explain that their findings may indicate that a dysregulated immune response to infections during the first few months of life leads to an increased risk of ALL.[40] This may be one of many mechanisms through which infections may be involved in the etiology of childhood ALL.

From a methodological perspective, however, it has been suggested that these contrasting results may be an indication that previous studies using self-reported data for infections and social contacts, many of which have found a reduction in risk, may be biased because of differential recall or reporting between cases and controls.[41] Although more studies are needed to evaluate this discrepancy, it may be important to note that clinically diagnosed infections are likely different from self-reported infectious diseases, as parents/caretakers may not seek medical attention for all common infections experienced by a child. The decision to seek the help of medical professionals may be influenced by socioeconomic status, access to care, child's overall health status, and many other factors. Although still susceptible to recall bias, surrogate measures of exposure to infections such as daycare attendance and birth order are recognized as strong alternative measures to testing the "delayed infection" hypothesis, because they are highly associated with common childhood infections and have the added advantage of capturing a child's asymptomatic infections.[42]

Another alternative interpretation of the observed association between clinically diagnosed infections and an increased risk of childhood ALL has been suggested.[43] Dorak *et al*. suggested that frequent infectious episodes very early in life may be an indicator of inherent deficiencies in immune response that may play a role in neoplastic development independent of the influence of infection. A previous United Kingdom study showed that, among controls, the average number of practitioner diagnosed infections was very similar between the different levels of birth order and social activity outside the home, but was markedly different among leukemia cases.[41] This observation could also suggest that children destined to develop leukemia may have preexisting immunodeficiencies that make them more susceptible to developing active infection after exposure.

The characteristics observed in the NCCLS Hispanic children compared to non-Hispanic whites are consistent with our current understanding of familial and cultural practices among Hispanic populations in the U.S. In general, Hispanic populations have been associated with a tendency for earlier childbearing, larger family households that extend beyond nuclear members, and a greater tendency to live with family rather than with unrelated individuals or alone.[44,45] In our study, non-Hispanic white and Hispanic children showed marked differences in a broad range of characteristics including maternal age, socioeconomic indicators, children in the household, birth weight, breast-feeding and maternal smoking status, all of which can be envisioned to play some role in the child's exposure pattern and response to infections.

Given these observations, the interpretation of the findings in the NCCLS Hispanic children should consider the potential inadequacies of the surrogate measures used in this study to evaluate the "delayed infection" hypothesis in this population. For instance, as an indirect measure of exposure to infections, the ability of daycare attendance to serve as a strong

measure may vary depending on several characteristics of the facility attended and the child's pattern of attendance. This is well-documented in the epidemiologic literature on childcare facilities and infections in children,[46,47] indicating that the transmission and development of infectious disease are highly influenced by the age of the child, frequency and duration of attendance, structure and size of the facility. In the NCCLS, Hispanic children, compared to non-Hispanic white children, attended daycare at a later age, less often, for a fewer number of hours per week, and were at facilities with fewer children. In addition, results relating to daycare attendance can be influenced by birth order, another major source of exposure to infections. It has been shown that the effect of daycare attendance on occurrence of respiratory illnesses is most pronounced among those without older siblings.[6,48] Compared to non-Hispanic whites, Hispanic children appeared to live with a greater number of other children, both sibling and non-sibling, in the household before they started first grade (at approximately 6 years). Given these observations, it seems probable that the lack of association for daycare attendance and birth order within Hispanics is not evidence against a role for early infectious exposures in leukemia risk. Rather, a more likely explanation may be that these two social contact measures are not good indicators of early infections for Hispanic children in the study. From a social contacts perspective, a more refined measure of exposure to infections among Hispanics may be to additionally consider the total number of people living in the household at the time of child's birth including non-sibling children and adults.

This conclusion is also supported by strong statistically significant findings observed in Hispanics for ear infections during the first year of life. Unlike daycare attendance and birth order, which are indirect measures that assume a strong correlation with actual infection-related exposures, maternally reported childhood infection is a direct measure of exposure. Such a consistent finding for both non-Hispanic whites and Hispanics provides important support for the "delayed infection" hypothesis.

The large number of subjects enrolled in the NCCLS, the very detailed exposure assessment, and the ability to conduct separate analyses among non-Hispanic white and Hispanic children represent strengths of our analysis. As with any case–control study that relies on retrospectively collected self-reported data, there is a potential for bias because of differential case–control recall of past exposures. The results of this study consistently showed reduced risk estimates among three different measures of exposures to infections as hypothesized. There was likely very little, if any, influence of recall bias on the birth order findings. The manner in which recall bias may affect the daycare results is difficult to predict since it is not certain how respondents perceive the role of daycare in childhood leukemia risk. However, if recall bias were a major contributor in the childhood infections analysis, we would expect to see a pattern of consistently elevated (or reduced) risk estimates for multiple conditions. Instead, the only remarkable finding was for ear infections, a condition for which recall is thought to be more accurate since the pain is acute, medical attention is often sought, and diagnosis is usually made by a clinician with treatment often requiring use of antibiotics.

Potential selection biases resulting in systematic differences between cases and controls are a concern. In the NCCLS, population-based controls are selected from the statewide birth registry among all children born within the study region. A previous methodological evaluation has shown that controls enrolled in the NCCLS are comparable to "ideal" controls who could have been enrolled under the optimal circumstances (*i.e.*, no difficulty in tracing, no refusal of participation).[8] In our analysis, cases and controls appeared to differ in maternal age, maternal education and annual household income among both non-Hispanic whites and Hispanics separately. The influence of these and other potential confounders were evaluated and addressed accordingly in all analyses, but the influence of uncontrolled

or residual confounding on risk estimates is always a possibility. Consistent findings persisted even when limiting the analysis to those cases and controls within the highest levels of annual household income.

Understanding the potential heterogeneity in risk by ALL subtypes (*e.g.*, T-lineage, *TEL-AML1* positive and high-hyperdiploidy ALL) is of ongoing interest, but is constrained by insufficient sample sizes after stratification and limitations in the availability of refined subtype-specific disease classification. Future studies will be able to address this question, and perhaps more efficiently through a combined effort within the Childhood Leukemia International Consortium (http://ccls.berkeley.edu/clic).

Study results on daycare attendance, birth order and infections during the first year of life are consistent with the hypothesis that exposure to infections early in life is associated with a reduced risk of childhood ALL. The consideration of these multiple indicators simultaneously suggests that exposures through daycare attendance and older siblings in the household may have independent effects on childhood ALL risk in non-Hispanic whites. The reduced risks associated with ear infection early in life, a direct indicator of exposure to infection, in non-Hispanic whites and Hispanics provide evidence that the “delayed infection” hypothesis may be operative in both ethnic populations.

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Abbreviations

ALL	acute lymphoblastic leukemia
c-ALL	common acute lymphoblastic leukemia
CI	confidence interval
mo	month
NCCLS	Northern California Childhood Leukemia Study
NH-white	non-Hispanic White
OR	odds ratio
SD	standard deviation
SE	standard error

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Table 1

Demographic and select characteristics of non-Hispanic white and Hispanic acute lymphoblastic leukemia cases and controls, Northern California Childhood Leukemia Study, 1995–2008

	Non-Hispanic White		Hispanic		
	Cases *N* (%)	Controls *N* (%)	Cases *N* (%)	Controls *N* (%)	*p* value[1] NH-White *vs*. Hispanic controls
All	284 (100)	458 (100)	385 (100)	519 (100)	
Child's gender					
Male	161 (56.7)	269 (58.7)	208 (54.0)	27 (53.4)	0.092
Female	123 (43.3)	189 (41.3)	177 (46.0)	242 (46.6)	
Child's age					
12–23.9 months	19 (6.7)	41 (9.0)	30 (7.8)	53 (10.2)	0.454
2–5 years	170 (59.9)	239 (52.2)	225 (58.4)	282 (54.3)	
6–10 years	61 (21.5)	110 (24.0)	86 (22.3)	124 (23.9)	
11–14 years	34 (12.0)	68 (14.8)	44 (11.4)	60 (11.6)	
Mean (SE)	5.6 (0.2)	6.0 (0.2)	5.7 (0.2)	5.7 (0.2)	
Mother's age at child's birth					
<20 years	17 (6.0)	10 (2.2)	47 (12.2)	62 (11.9)	<0.001
20–24.9 years	38 (13.4)	46 (10.0)	131 (34.0)	146 (28.1)	
25–29.9 years	69 (24.3)	125 (27.3)	90 (23.4)	161 (31.0)	
30–34.9 years	106 (37.3)	156 (34.1)	69 (17.9)	100 (19.3)	
≥35 years	54 (19.0)	121 (26.4)	46 (11.9)	50 (9.6)	
Missing	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	
Mean (SE)	30.2 (0.3)	31.4 (0.3)	26.6 (0.3)	26.9 (0.3)	
Mother's education					

	Non-Hispanic White		Hispanic		
	Cases *N* (%)	Controls *N* (%)	Cases *N* (%)	Controls *N* (%)	*p* value[1] NH-White *vs.* Hispanic controls
High school or less	66 (23.2)	77 (16.8)	261 (67.8)	317(61.1)	<0.001
Some college	92 (32.4)	155 (33.8)	88 (22.9)	138 (26.6)	
College or postgraduate	125 (44.0)	226 (49.3)	36 (9.4)	63 (12.1)	
Missing	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	
Annual household income					
<$15,000	16 (5.6)	18 (3.9)	101 (26.2)	85 (16.4)	<0.001
$15,000–$29,999	26 (9.2)	19 (4.1)	101 (26.2)	114 (22.0)	
$30,000–$44,999	34 (12.0)	32 (7.0)	76 (19.7)	102 (19.7)	
$45,000–$59,999	47 (16.5)	53 (11.6)	49 (12.7)	77 (14.8)	
$60,000–$74,999	33 (11.6)	58 (12.7)	18 (4.7)	50 (9.6)	
≥$75,000	128 (45.1)	278 (60.7)	40 (10.4)	91 (17.5)	
Other children in household[2]					
0	44 (15.5)	54 (11.8)	47 (12.2)	49 (9.4)	<0.001
1	134 (47.2)	202 (44.1)	97 (25.2)	151 (29.1)	
2	61 (21.5)	123 (26.9)	98 (25.5)	136 (26.2)	
3	22 (7.8)	42 (9.2)	52 (13.5)	91 (17.5)	
≥4	23 (8.1)	36 (7.9)	91 (23.6)	92 (17.7)	
Missing	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	
Child's birth weight (grams)					
<2,500	15 (5.3)	20 (4.4)	18 (4.7)	34 (6.6)	0.019
2,500–3,999	206 (72.5)	340 (74.2)	295 (76.6)	407 (78.4)	

	Non-Hispanic White		Hispanic		
	Cases *N* (%)	**Controls *N* (%)**	**Cases *N* (%)**	**Controls *N* (%)**	***p* value[1] NH-White *vs*. Hispanic controls**
4,000+	58 (20.4)	89 (19.4)	66 (17.1)	70 (13.5)	
Missing	5 (1.8)	9 (2.0)	6 (1.6)	8 (1.5)	
Mean (SE)	3509 (35.3)	3508 (27.1)	3466 (32.8)	3395 (26.1)	
Child breast-fed					
Yes	37 (13.0)	41 (9.0)	63 (16.4)	79 (15.2)	0.003
No	246 (86.6)	414 (90.4)	321 (83.4)	440 (84.8)	
Missing	1 (0.4)	3 (0.7)	1 (0.3)	0 (0.0)	
Mean duration, months (SE)	7.2 (0.4)	8.2 (0.4)	5.7 (0.4)	6.4 (0.3)	
Mother ever smoked					
Yes	111 (39.1)	153 (33.4)	76 (19.7)	115 (22.2)	<0.001
No	173 (60.9)	304 (66.4)	309 (80.3)	404 (77.8)	
Missing	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	

[1] *p*-values were estimated using the Pearson chi-squared test not including missings. Infants (age <1 year) and non-Hispanic other race/ethnicity were excluded.

[2] Number of other children in household before the index child went to 1st grade (includes siblings and non-sibling children).

Table 2

Characteristics of daycare attendance in non-Hispanic white and Hispanic case and control subjects, Northern California Childhood Leukemia Study, 1995–2008

	Non-Hispanic White					Hispanic					*p* value[1]
	ALL		Controls			ALL		Controls			
	Mean (SD)	Median	Mean (SD)	Median	*p* value[1] Case *vs.* Control	Mean (SD)	Median	Mean (SD)	Median	*p* value[1] Case *vs.* Control	NH-white *vs.* Hispanic controls
Age first started[2] daycare (months)	33.0 (25.1)	30	31.1 (25.3)	28.5	0.190	50.8 (24.3)	55.5	49.2 (24.5)	54.0	0.320	<0.001
Months of stay[2] (regardless of hours)	22.5 (21.4)	18.4	23.5 (21.1)	19.0	0.402	10.4 (15.5)	1.0	10.8 (15.3)	3.1	0.424	<0.001
Mean hours per week[2]	14.0 (13.5)	10.0	17.2 (15.1)	13.3	0.008	12.1 (14.7)	4.0	12.6 (14.8)	6.0	0.424	<0.001
Mean number of other children at each daycare[2]	10.3 (8.2)	9.7	10.2 (7.7)	10.0	0.940	7.3 (8.6)	3.0	7.9 (9.0)	5.0	0.333	<0.001
Total child-hours[2,3] (thousands)	24.5 (37.8)	8.7	28.3 (40.8)	12.3	0.103	16.1 (35.0)	0.4	15.5 (30.8)	2.1	0.535	<0.001

[1] *p* values were derived using Wilcoxon rank-sum tests.

[2] For children who never attended daycare, 72 months (6 years) was assigned as the age when first started daycare and 0 was assigned for the duration of stay, mean hours per week, mean number of children, and total child-hours.

[3] The child-hours in each daycare setting were summed to obtain the total child-hours for each child. Child-hours = (number of months attending the daycare) × (mean hours per week at this daycare) × (number of other children at this daycare) × (4.35 weeks per month).

Table 3

Social contact measures [daycare attendance (thousand child-hours) and birth order] and risk of ALL in non-Hispanic white and Hispanic children, Northern California Childhood Leukemia Study, 1995–2008

	ALL	c-ALL	Controls	OR (95% CI)[1]	
	n (%)	*n* (%)	*n* (%)	ALL	c-ALL
Non-Hispanic White[2]	284	142	458		
Daycare child-hours by reference date[3]					
0	63 (22.3)	33 (23.2)	90 (19.7)	1.00 (Ref)	1.00 (Ref)
>0 and <15	107 (38.0)	63 (44.4)	158 (34.5)	1.11 (0.73–1.68)	1.69 (0.99–2.88)
≥15	112 (39.7)	46 (32.4)	205 (44.8)	0.99 (0.64–1.51)	1.43 (0.80–2.55)
Continuous				1.00 (0.99–1.00)	1.00 (0.99–1.01)
				$p = 0.733$	$p = 0.878$
Daycare child-hours by age 6 months					
0	230 (81.0)	111 (78.2)	332 (72.7)	1.00 (Ref)	1.00 (Ref)
>0 and <2	33 (11.6)	19 (13.4)	70 (15.3)	0.78 (0.50–1.23)	0.93 (0.52–1.66)
≥2	21 (7.4)	12 (8.4)	55 (12.0)	0.59 (0.34–1.01)	0.63 (0.32–1.27)
Continuous				0.90 (0.82–1.00)	0.86 (0.74–1.01)
				$p = 0.046$	$p = 0.071$
Birth order					
First	131 (46.8)	67 (47.5)	171 (38.1)	1.00 (Ref)	1.00 (Ref)
Second	93 (33.2)	43 (30.5)	164 (36.5)	0.75 (0.53–1.06)	0.65 (0.41–1.04)
Third	45 (16.1)	25 (17.7)	84 (18.7)	0.62 (0.40–0.97)	0.68 (0.39–1.20)
≥Fourth	11 (3.9)	6 (4.3)	30 (6.7)	0.44 (0.21–0.92)	0.43 (0.17–1.14)

	ALL	c-ALL	Controls	OR (95% CI)[1]	
	n (%)	*n* (%)	*n* (%)	ALL	c-ALL
p trend				0.004	0.038
Non-firstborn	149 (53.2)	74 (52.5)	278 (61.9)	0.68 (0.50–0.92)	0.64 (0.42–0.96)
Hispanic[2]	385	192	519		
Daycare child-hours by reference date[3]					
0	187 (49.5)	105 (55.6)	232 (45.3)	1.00 (Ref)	1.00 (Ref)
>0 and <15	92 (24.3)	48 (25.4)	144 (28.1)	0.92 (0.65–1.28)	1.02 (0.66–1.57)
≥15	99 (26.2)	36 (19.0)	136 (26.6)	1.02 (0.72–1.44)	1.12 (0.69–1.82)
Continuous				1.00 (0.99–1.01)	1.00 (0.99–1.01)
				p = 0.458	*p* = 0.403
Daycare child-hours by age 6 months					
0	348 (90.9)	175 (91.1)	472 (91.3)	1.00 (Ref)	1.00 (Ref)
>0 and <2	21 (5.5)	10 (5.2)	24 (4.6)	1.69 (0.90–3.17)	1.52 (0.66–2.51)
≥2	14 (3.6)	7 (3.7)	21 (4.1)	1.13 (0.56–2.29)	1.12 (0.44–2.86)
Continuous				1.08 (0.94–1.24)	1.072 (0.90–1.28)
				p = 0.309	*p* = 0.446
Birth order					
First	143 (37.6)	69 (36.5)	182 (35.5)	1.00 (Ref)	1.00 (Ref)
Second	117 (30.8)	56 (29.6)	177 (34.6)	0.86 (0.62–1.19)	0.81 (0.53–1.25)
Third	73 (19.2)	44 (23.3)	88 (17.2)	1.02 (0.69–1.50)	1.15 (0.71–1.87)
≥Fourth	47 (12.4)	20 (10.6)	65 (12.7)	0.80 (0.51–1.25)	0.72 (0.39–1.31)
p trend				0.490	0.641

	ALL	c-ALL	Controls	OR (95% CI)[1]	
	n (%)	*n* (%)	*n* (%)	ALL	c-ALL
Non-firstborn	237 (62.4)	120 (63.5)	330 (64.5)	0.89 (0.67–1.18)	0.89 (0.61–1.28)

[1] OR and 95% CI calculated using logistic regression adjusting for child's age and annual household income.

[2] These totals include subjects with missing data which vary between analyses.

[3] The child-hours in each daycare setting were summed to obtain the total child-hours (thousands) for each child. Child-hours = (number of months attending the daycare) × (mean hours per week at this daycare) × (number of other children at this daycare) × (4.35 weeks per month).

Table 4

Age of common infections during the first year of life and risk of ALL in non-Hispanic white and Hispanic children, Northern California Childhood Leukemia Study, 1995–2008

	ALL	c-ALL	Controls	OR (95% CI)[1]	
	n (%)	*n* (%)	*n* (%)	ALL	c-ALL
Non-Hispanic White[2]	284	142	458		
Severe diarrhea/vomiting					
Not during 1st year	232 (84.4)	117 (83.6)	393 (87.3)	1.00 (Ref)	1.00 (Ref)
Age <6 mo. Only	16 (5.8)	9 (6.4)	22 (4.9)	1.33 (0.68–2.60)	1.66 (0.69–4.00)
Age 6–11 mo. only	18 (6.5)	11 (7.9)	29 (6.4)	1.08 (0.58–2.00)	1.27 (0.60–2.72)
Both time periods	9 (3.3)	3 (2.1)	6 (1.3)	2.39 (0.82–6.95)	2.23 (0.46–10.7)
1st year (yes *vs.* no)[3]	43 (15.6)	23 (16.4)	57 (12.7)	1.14 (0.74–1.76)	1.47 (0.85–2.54)
Ear infection					
Not during 1st year	152 (59.8)	79 (61.2)	227 (53.8)	1.00 (Ref)	1.00 (Ref)
Age <6 mo. only	8 (3.2)	4 (3.1)	26 (6.2)	0.39 (0.17–0.91)	0.35 (0.11–1.08)
Age 6–11 mo. only	46 (18.1)	27 (20.9)	100 (23.7)	0.70 (0.46–1.06)	0.82 (0.48–1.38)
Both time periods	48 (18.9)	19 (14.7)	69 (16.4)	1.06 (0.69–1.63)	0.71 (0.39–1.31)
1st year (yes *vs.* no)[3]	117 (43.5)	57 (41.9)	223 (49.2)	0.78 (0.58–1.07)	0.66 (0.44–1.00)
Persistent cough					
Not during 1st year	258 (93.1)	128 (92.8)	414 (91.0)	1.00 (Ref)	1.00 (Ref)
Age <6 mo. only	5 (1.8)	2 (1.4)	13 (2.9)	0.57 (0.20–1.64)	0.33 (0.70–1.55)
Age 6–11 mo. only	8 (2.9)	5 (3.6)	19 (4.2)	0.69 (0.29–1.62)	0.77 (0.27–2.18)
Both time periods	6 (2.2)	3 (2.2)	9 (2.0)	1.06 (0.37–3.07)	1.04 (0.26–4.20)

	ALL	c-ALL	Controls	OR (95% CI)[1]	
	n (%)	*n* (%)	*n* (%)	ALL	c-ALL
1st year (yes *vs.* no)[3]	21 (7.5)	12 (8.6)	43 (9.4)	0.77 (0.44–1.33)	0.75 (0.37–1.51)
Hispanic[2]	385	192	519		
Severe diarrhea/vomiting					
Not during 1st year	297 (81.1)	149 (81.4)	425 (84.8)	1.00 (Ref)	1.00 (Ref)
Age <6 mo. only	24 (6.6)	14 (7.7)	25 (5.0)	1.26 (0.70–2.27)	1.58 (0.77–3.25)
Age 6–11 mo. only	34 (9.3)	15 (8.2)	36 (7.2)	1.23 (0.74–2.02)	1.16 (0.59–2.27)
Both time periods	11 (3.0)	5 (2.7)	15 (3.0)	0.92 (0.41–2.04)	0.71 (0.24–2.11)
1st year (yes *vs.* no)[3]	82 (21.6)	43 (22.4)	88 (17.1)	1.24 (0.88–1.74)	1.36 (0.88–2.11)
Ear infection					
Not during 1st year	221 (64.1)	111 (63.4)	282 (58.6)	1.00 (Ref)	1.00 (Ref)
Age <6 mo. only	20 (5.8)	8 (4.6)	49 (10.2)	0.48 (0.27–0.83)	0.40 (0.18–0.91)
Age 6–11 mo. only	60 (17.4)	34 (19.4)	93 (19.3)	0.80 (0.55–1.16)	0.93 (0.57–1.49)
Both time periods	44 (12.8)	22 9 (12.6)	57 (11.9)	1.07 (0.69–1.65)	1.13 (0.64–2.00)
1st year (yes *vs.* no)[3]	150 (40.4)	75 (40.3)	223 (44.2)	0.84 (0.64–1.11)	0.87 (0.61–1.25)
Persistent cough					
Not during 1st year	319 (86.2)	153 (83.6)	435 (86.1)	1.00 (Ref)	1.00 (Ref)
Age <6 mo. only	14 (3.8)	8 (4.4)	18 (3.6)	0.91 (0.44–1.87)	1.16 (0.47–2.88)
Age 6–11 mo. only	25 (6.8)	16 (8.7)	37 (7.3)	0.81 (0.47–1.38)	0.96 (0.50–1.84)
Both time periods	12 (3.2)	6 (3.3)	15 (3.0)	1.05 (0.48–2.32)	1.00 (0.36–2.74)
1st year (yes *vs.* no)[3]	58 (15.3)	35 (18.5)	76 (14.8)	0.94 (0.64–1.37)	1.12 (0.70–1.79)

[1] OR and 95% CI calculated using logistic regression adjusting for child's age and annual household income.

[2] These totals include subjects with missing data which vary between analyses.

[3] May not equal the sum of individuals listed by time period. Data for 1st year (yes/no) may be more complete.

Table 5

Multivariable analyses of social contact measures, ear infections during the first year of life, and risk of childhood ALL, Northern California Childhood Leukemia Study, 1995–2008

	Model 1[1]		Model 2[1]		Model 3[1]	
Social contacts and ear infection variables	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Non-Hispanic White						
Daycare child-hours[2] by age 6 months	0.91 (0.80–1.03)	0.142	0.89 (0.80–0.98)	0.024	0.83 (0.73–0.94)	0.004
Older siblings (yes *vs.* no)	0.67 (0.48–0.93)	0.016	0.65 (0.48–0.89)	0.006	0.59 (0.43–0.83)	0.002
Daycare child-hours*older siblings interaction	0.94 (0.75–1.18)	0.590	–	–	–	–
Ear infections (*vs.* none during 1st year)						
Age <6 months only	–	–	–	–	0.44 (0.19–1.02)	0.056
Age 6–11 months only	–	–	–	–	0.71 (0.46–1.08)	0.110
Both time periods (<6 and 6–11 months)	–	–	–	–	1.32 (0.83–2.11)	0.247
Hispanic						
Daycare child-hours[2] by age 6 months	1.16 (0.81–1.66)	0.416	1.08 (0.94–1.24)	0.289	1.06 (0.91–1.23)	0.443
Older siblings (yes *vs.* no)	0.88 (0.66–1.18)	0.402	0.87 (0.66–1.16)	0.340	0.84 (0.62–1.13)	0.250
Daycare child-hours*older siblings interaction	0.92 (0.62–1.35)	0.659	–	–	–	–
Ear infections (*vs.* none during 1st year)						
Age <6 months only	–	–	–	–	0.45 (0.25–0.79)	0.006
Age 6–11 months only	–	–	–	–	0.82 (0.56–1.20)	0.304
Both time periods (<6 and 6–11 months)	–	–	–	–	1.05 (0.67–1.64)	0.839

[1] Variables for which OR and 95% CI are provided were included in a single multivariable logistic regression model adjusting for child's age and annual household income.

[2] The child-hours in each daycare setting were summed to obtain the total child-hours (thousands) for each child. Child-hours = (number of months attending the daycare) × (mean hours per week at this daycare) × (number of other children at this daycare) × (4.35 weeks per month).