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Birth weight and other perinatal characteristics and childhood leukemia in California

S Oksuzyan¹, CM Crespi², M Cockburn³, G Mezei⁴, and L Kheifets⁵

¹Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, California, soksuzyan@ucla.edu

²Department of Biostatistics, UCLA Fielding School of Public Health, Los Angeles, California, ccrespi@ucla.edu

³Department of Preventive Medicine, University of Southern California, Los Angeles, California, myles@med.usc.edu

⁴Environment Department, Electric Power Research Institute, Palo Alto, California, gmezei@epri.com

⁵Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, California, kheifets@ucla.edu.

Abstract

Aims—We conducted a large registry-based study in California to investigate the association of perinatal factors and childhood leukemia with analysis of two major subtypes, acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML).

Methods—We linked California cancer and birth registries to obtain information on 5788 cases and 5788 controls matched on age and sex (1:1). We examined the association of birth weight, gestational age, birth and pregnancy order, parental ages, and specific conditions during pregnancy and risk of total leukemia, ALL and AML using conditional logistic regression, with adjustment for potential confounders.

Results—The odds ratio (OR) per 1000 gram increase in birth weight was 1.11 for both total leukemia and ALL. The OR were highest for babies weighing 4,500g with reference <2,500g: 1.59 (95% CI: 1.05-2.40) and 1.70 (95% CI: 1.08-2.68) for total leukemia and ALL, respectively. For AML, increase in risk was also observed but the estimate was imprecise due to small numbers. Compared to average-for-gestational age (AGA), large-for-gestational age (LGA) babies were at slightly increased risk of total childhood leukemia (OR=1.10) and both ALL and AML (OR=1.07 and OR=1.13, respectively) but estimates were imprecise. Being small-for-gestational age (SGA) was associated with reduced risk of childhood leukemia (OR=0.81, 95% CI: 0.67-0.97) and ALL (OR=0.77, 95% CI: 0.63-0.94), but not AML. Being first-born was associated with decreased risk of AML only (OR=0.70; 95% CI: 0.53-0.93). Compared to children with paternal age <25 years, children with paternal age between 35 and 45 years were at increased risk of total childhood leukemia (OR=1.12; 95% CI: 1.04-1.40) and ALL (OR=1.23; 95% CI: 1.04-1.47). None of conditions during pregnancy examined or maternal age were associated with increased risk of childhood leukemia or its subtypes.

Conclusions—Our results suggest that high birth weight and LGA were associated with increased risk and SGA with decreased risk of total childhood leukemia and ALL, being first-born was associated with decreased risk of AML, and advanced paternal age was associated with increased risk of ALL. These findings suggest that associations of childhood leukemia and perinatal factors depend highly on subtype of leukemia.

Keywords

childhood leukemia; birth weight; birth order; parental age; perinatal factors; pregnancy complications

Introduction

Childhood leukemia is the most common malignant disease in children worldwide and in the United States.[1] The incidence of childhood leukemia in California is 5.2 and 4.3 per 100,000 for males and females, respectively. Incidence is highest among the youngest age group (0-4 years), with 8.2 and 6.8 cases per 100,000 for males and females, respectively, then incidence declines with age until late adolescence.[2]

The etiology of childhood leukemia remains largely unknown. Several perinatal characteristics have been linked to childhood leukemia but the relation of others to leukemia and particularly to its subtypes remains to be elucidated. Birth weight is one of a few perinatal factors that have been consistently reported to be related to childhood leukemia risk,[3] with over 30 studies examining the association. Most reported positive association between birth weight and ALL; less consistent associations have been reported for AML. [3-14] Few studies have taken into account gestational age in the analysis of birth weight. Of those that did, most showed that large-for-gestational age babies were at increased risk of childhood leukemia.[12, 15]

Birth order is another perinatal factor that has been examined with regard to childhood leukemia risk. Most studies have found that high birth order was associated with decreased risk of ALL compared with first-born babies (OR varied from 0.57 to 0.95).[10, 16] A few studies reported increased risk of ALL with increasing birth.[3, 13] For AML, studies have detected either positive association or no association with birth order.[3, 10-12, 16, 17]

The majority of studies that looked at the relationships of maternal and paternal age to childhood leukemia detected an increased risk for older paternal age. [5, 13, 17-19] Some of these also reported an increased risk for older maternal age.[18, 19]

Conflicting results have been reported for the association between childhood leukemia and several perinatal and reproductive factors such as history of fetal loss, preeclampsia, polyhydramnios, anemia and genital herpes.[7] The majority of studies found no association but a few reported positive associations. [11, 20]

In a large case-control study linking data from the California Cancer Registry (1988-2008) and Birth Registry (1986-2007), we examined the association of childhood leukemia with perinatal factors, including birth weight, birth order and history of pregnancy terminations;

maternal and paternal age as well as the difference between them; and complications during pregnancy. The large size of the sample allowed for detailed analysis by two major subtypes of leukemia, ALL and AML, which was not possible in most previous studies.

Materials and methods

The California Cancer Registry (CCR), a population-based statewide cancer registry, was used to obtain information on all childhood leukemia cases diagnosed between 1988 and 2008 in children younger than 16 years who were born in California and resided in California at the time of diagnosis. The CCR is recognized as one of the leading cancer registries in the world with almost complete registration (99%). It routinely records age, race/ethnicity, sex, and residence at the time of diagnosis as well as information on almost all cancers, cancer subtypes and characteristics.[21] Controls were individuals randomly selected from the California Birth Registry who had not been diagnosed in California with any type of cancer and were matched to cases (1 to 1) on the basis of date of birth (± 6 months) and sex.

Information on birth weight, maternal and paternal age, history of pregnancy terminations before and after 20 weeks of gestation, number of live births living, number of live births deceased and maternal complications during pregnancy, as well as child's date of birth, gender, father's education, and ethnicity were extracted from California birth records. Gestational age was calculated based on last menstrual period and date of birth. Birth order was inferred from the number of live births living and number of live births deceased; first pregnancy was inferred from the number of live births living, number of live births deceased, and number of terminations before and after 20 weeks of gestation.

Birth weight was evaluated as a categorical variable with reference <2500 g, a continuous variable with units of 1000 g, and as a dichotomous variable with cut points at $<$ or $\geq 3,500$ g and $<$ or $\geq 4,000$ g. Some authors suggested that birth weight for gestational age as an indicator for fetal growth could be a better predictor for childhood leukemia. [15] Birth weight-for-gestational age was constructed using U.S. national reference for fetal growth and was classified into three categories: small-for-gestational age (SGA), average-for-gestational age (AGA) and large-for-gestational age (LGA).[22] To evaluate dose-response relationships between birth weight and childhood leukemia we obtained odds ratios using a moving window of birth weight. These analyses used birth weight categories (windows) of 2500 to <3500 g, 3000 to <4000 g, 3500 to <4500 g, 4000-5000 g, and >4500 g with a reference category <2500 g.

Gestational age, maternal and paternal ages, and history of terminations were analyzed as dichotomous and as categorical variables. Birth and pregnancy orders, maternal complications during pregnancy were used as dichotomous variables (first vs. other, or yes vs. no).

The primary analysis method was conditional logistic regression using the one-to-one age and gender matched case-control pairs.[23] Analyses were conducted with and without subjects with Down's syndrome, which is known to be associated with increased risk of

childhood leukemia. [10, 11, 17, 24] Results of those analyses were similar. Here we present analyses that include subjects with Down's syndrome (46 subjects: 42 cases and 4 controls). We confirmed the absence of unduly influential observations by fitting a variety of models with different subsets of covariates and examining the results for outliers and influence. Covariates in the models were chosen based on information about known or potential confounders and model fit statistics. Models with minimal Akaike information criterion (AIC) value and the lowest number of potential confounders were chosen as main models presented in this paper. Father's education and payment source for delivery were used in all models as proxies for socioeconomic status (SES), a known confounder. For payment source for delivery, governmental programs such as Medicare, Medi-Cal and others as well as 'No care' were coded as low SES; private insurance and other sources of payment were coded as middle-high SES. For father's education, 12 years of education was considered low SES, 13-17 years as middle SES, and 17 years as high SES.

Despite the large number of cases and controls, sample sizes for some analyses were reduced due to missing data that was attributable largely to differences in the information collected on birth certificates from year to year. No differences in patterns of missingness were detected between cases and controls. Missing data were multiply imputed using Monte Carlo Markov chain full-data imputation under a missing at random assumption [25, 26] implemented by the MI procedure in SAS 9.1.[27] The imputation model included all variables used in models (except abnormal fetal conditions and pregnancy complications) and auxiliary variables likely to be correlated with variables of interest (number of pregnancy visits, month prenatal care began, type of birth, planned place of birth, number of ever born children, number of children born alive, and number of children born alive now deceased). Analyses were repeated on the multiply imputed data using the MIANALYZE procedure.

Analyses were conducted using statistical software SAS 9.1.[27]

The study was approved by University of California, Los Angeles Office for the Protection of Research Subjects.

Results

A total of 6645 childhood leukemia cases were identified from the California cancer registry. Linkage to birth records was successful for 87.1% (5788/6645) of cases. Of the 5788 cases (55.8% males and 44.2% females) included in this analysis, 4721 were ALL cases (56.2% males and 43.8% females), 852 were AML cases (53.3% males and 46.7% females), and 215 were other childhood leukemia types. The mean age at diagnosis was 4.9 years with a range of 0 to 15.6 years. Table 1 shows additional characteristics of study subjects.

We assessed the association of childhood leukemia and variables of interest in unadjusted and adjusted conditional logistic regressions matched for child's age and sex. Results of these analyses were not materially different; therefore we present adjusted results only.

Birth weight

In Table 2 we show results for conditional logistic regression for the association of childhood leukemia and birth weight and birth weight-for-gestational age. We observed an increased risk of total childhood leukemia and ALL for high birth weight babies using increments by 1000g (OR=1.11, 95% CI: 1.01-1.21 and OR=1.11, 95% CI: 1.01-1.23, respectively). Increased risk of total leukemia and ALL was also detected in all categories of birth weight with a reference category of < 2500g; the highest increase was noted for the heaviest babies, weighing 4500g (OR=1.59, 95% CI: 1.05-2.40 and OR=1.70, 95% CI: 1.08-2.68, respectively). Increased risk using cutpoints of 3500g and 4000 g for birth weight and birth weight-for-gestational age was less pronounced.

To address concerns about exposure misclassification due to chosen cut points for birth weight and to further examine trend, we obtained odds ratios for total leukemia and subtypes using a moving window for birth weight categorized as 2500- <3500g, 3000- <4000g, 3500- <4500g, 4000- >5000g, and 4500g with a reference category <2500g, with adjustment for potential confounders (see Figure 1). These showed elevated risk for ALL but not for AML, compared to the reference category.

Moving window analysis for total leukemia is available online (Figure 1a).

Models with interactions between birth weight and birth order, mother's age, child's race and source of payment for care were also considered. All of these factors are potentially associated with childhood leukemia and could act as effect modifiers. None of the models suggested interaction between the examined variables (results not presented).

Gestational age

Gestational age adjusted for birth weight, birth order, mother's age, father's education, child's race, and payment source for delivery when entered in the model as a continuous variable with 1-week and 2-week increments had an OR of 0.97 (95% CI: 0.95-1.00) and an OR of 0.95 (95% CI: 0.90-1.00), respectively. Gestational age entered into the model as a categorical variable gave similar results (not presented).

Birth order

We found that first-born babies were at decreased risk for AML (OR: 0.70, 95% CI 0.53-0.93), but not for total leukaemia or ALL (Table 3). Similar results were obtained for pregnancy order with OR=0.73 and 95% CI 0.55-0.96 for AML.

Parental age

For maternal age, slightly increased risk for total childhood leukaemia and both subtypes were observed for ages greater than 35 years old but none of the estimates was precise (Table 3). For paternal age, results were similar but estimates were more precise, with increased risk of total childhood leukaemia and ALL for 5-year increase in age (OR=1.01, 95% CI 1.00-1.02), for fathers aged 35 years and older compared to younger fathers (OR=1.13, 95% CI 1.01-1.26 and OR=1.12, 95% CI 0.99-1.27, respectively), and for fathers aged 35-45 years compared to <25 years old (OR=1.12, 95% CI 1.04-1.40 and OR=1.23,

95% CI 1.04-1.47, respectively). The difference between paternal and maternal ages was not associated with childhood leukaemia nor its subtypes.

Other prenatal factors

Neither history of pregnancy termination before or after 20 weeks of gestation nor maternal complications/conditions during pregnancy (Table 3) were associated with increased risk of childhood leukaemia or its subtypes.

Multiple imputations

In analyses repeated using multiply imputed data, the association between birth weight and childhood leukemia was slightly weaker than the same association using complete case analyses, with narrower confidence intervals and a similar trend. The association between birth weight-for-gestational age and childhood leukemia was slightly stronger and more precise. No other important differences were observed between complete case and multiply imputed data analyses. Table 4 with results of the association between birth weight and childhood leukemia estimated using multiple imputation is available online.

Discussion

Consistent with other studies, we observed an increased risk of childhood leukemia for high birth weight babies. We observed an 11% increase in risk of total childhood leukemia and acute lymphocytic leukemia per 1-kg increase in birth weight. For acute myeloid leukemia, no such risk increase was observed. In analyses with birth weight as a categorical variable with a reference category <2500g, increased risk was present for all babies above 2500g. The highest increase in risk for all types of leukemia (1.59-fold) and ALL (1.70-fold) was observed for the heaviest babies (≥ 4500g). For AML, results were consistent with increased risk for the highest weight category but estimates were less precise. In general, statistical power to detect associations with AML was more limited due to smaller numbers.

Results of a moving window analysis suggested a slightly positive trend of increasing risk with increasing birth weight for total leukemia and ALL compared to <2500g birth weight; for AML no trend was observed.

When we examined birth weight-for-gestational age, results suggested that large for gestational age babies were at slightly increased risk of total childhood leukemia and both ALL and AML compared to average for gestational age babies, but the estimates were imprecise. Being small for gestational age was associated with reduced risk of total childhood leukemia and ALL, but not for AML. Our findings confirm results of other studies that looked at birth weight-for-gestational age [12].

There are two main theories explaining the association between high birth weight and childhood cancers, including childhood leukemia. The first theory is related to insulin-like growth factor 1 (IGF-1), a known procarcinogenic agent. IGF-1 level is associated with birth weight and could play a role in the development of childhood leukemia through the induction of pre-leukemic cell division.[16, 28] Another hypothesis suggests that, because there is an association between birth weight and bone marrow volume, i.e., the number of

bone marrow cells, children with a higher birth weight have more cells at risk of malignant transformation, and thus are at a greater risk of leukemia.[16, 29-31] These two hypotheses are not mutually exclusive, e.g., pre-leukemic cells may secrete growth factors that increase birth weight.[28]

We observed decrease in risk of AML for first-born babies but no association with total leukemia and ALL. Some previous studies found an increased risk of total childhood leukemia and ALL with increasing birth order;[13, 32] a few reported an increased risk of childhood leukemia for first-born babies.[3, 10, 13, 16] Other studies found very weak or no association of birth order and childhood leukemia.[11, 18] For AML, most studies detected either increase in risk or no change in risk with increasing birth order.[3, 10-12, 16, 17] In developed countries, birth order is considered a proxy for exposure to infections in early childhood. [11] In recent years, use of day care facilities for first-born babies has increased due to growing numbers of working mothers. Day care use is associated with exposure to infections in early childhood.[11, 16, 33] These factors could explain the conflicting results of studies on birth order and childhood leukemia in recent years.

Our results for analysis of the association of maternal and paternal ages and childhood leukemia were very similar to findings of another study conducted in California.²² We observed a small risk associated with older paternal age: for 5-year increase in paternal age, for father's aged 35 compared to younger fathers, and for father's aged 35-45 compared to father's 25 years of age. Small increase in risk was observed for older maternal age but estimates were imprecise. We also considered a difference between paternal and maternal ages but we observed no associations with childhood leukemia.

Few studies looked at the relationships of childhood leukemia and perinatal factors such as pregnancy terminations and complications/conditions during pregnancy. Most found no association; only two studies found a small increase in risk of childhood leukemia in children of women with polyhydramnios and anemia [11] and genital herpes during index pregnancy.[3] In our study we found no association of pregnancy terminations or complications during pregnancy either with total leukemia risk or with ALL and AML. An unexpected finding was a decrease in risk with tobacco smoking for total leukemia and ALL, but these results did not stand for AML. Similar results were observed in Danish study by Westergaard. [10] These results could be related to the association of tobacco smoking and small-for-gestational age birth weight. [34] Mothers who smoke are at increased risk of having SGA babies [34] and SGA has a protective effect for childhood leukemia. Alternative explanations for these findings could include random error due to small numbers, misclassification issues, and probably very poor and inconsistent reporting of this variable on birth certificates. Therefore, our results on tobacco smoking and childhood leukemia should be interpreted with great caution.

The large size of the dataset allowed us to conduct separate analyses for two main subtypes of childhood leukemia, AML and ALL. The risk patterns were quite different for the two subtypes, which supports a theory that they have different etiology.

One of the major advantages of the current study was that our data were based on population registries with almost complete registration of births and cancers in California and controls were randomly selected from birth registry rather than by recruiting volunteers as in many case-control studies. Since these registries are independent of each other and participation of subjects was not required for our data collection, selection bias was unlikely in this study. Misclassification of outcome status was also unlikely in this study due to the completeness and high accuracy of the California Cancer Registry. Misclassification of birth weight was possible but unlikely. We think that birth weight is usually recorded fairly accurately. For other perinatal factors such as complications during pregnancy and abnormal fetal conditions, misclassification was possible due to many missing values and questionable accuracy of reporting.

We adjusted for potential confounders that were available in registries. There was no information available on such potential confounders as maternal and paternal occupation, diet, and alcohol and drug abuse, maternal health conditions before pregnancy, fertility treatments and procedures and child's birth defects. Therefore, residual confounding was possible. Maternal occupation and alcohol and drug use are inversely associated with birth weight [35-37] but positively associated with childhood leukemia. [38-40] Therefore, confounding due to such variables would most likely pull estimates toward the null.

One of the limitations of the study was missing data. However, since information was missing mainly due to differences in the information collected on birth certificates from year to year rather than non-response, the potential for biases was probably small, and the impact was mainly on the precision of the estimates. There were no differences in the pattern of missingness between cases and controls. We repeated all analyses using multiply imputed dataset and obtained similar results but with narrower confidence intervals.

In summary, we found that high birth weight and LGA were associated with increased risk and SGA was associated with decreased risk of total childhood leukemia and ALL. For AML, increased risk was found for heaviest babies but estimates were imprecise. We also found that being first-born was associated with decreased risk of all leukemia types combined and AML, but not ALL. Increased risk of total leukemia and ALL was observed for advanced paternal age. These findings suggest that associations of childhood leukemia and perinatal factors depend highly on subtype of leukemia, which needs further evaluation.

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Figure 1.

Odds ratios (OR) and 95% confidence intervals (CI) for acute lymphocytic leukemia and acute myeloid leukemia at moving windows of birth weight matched on age and sex and adjusted for child's race, gestational age, mother's age, birth order, father's education and source of payment for delivery. Reference level: < 2500g.

Figure 1a.

Odds ratios (OR) and 95% confidence intervals (CI) for childhood leukemia at moving windows of birth weight, matched on age and sex and adjusted for child's race, gestational age, mother's age, birth order, father's education and source of payment for delivery. Reference level: < 2500g.

Table 1

Socio-demographic and perinatal characteristics of study subjects, California birth registry, 1986-2007.

Variables	Total #	Cases (%)	Controls (%)	ALL # cases/controls ^a	AML # cases/controls ^a
All	11576	5788	5788	4721	852
Child's age					
< 1 year	791	(6.7)	(7.1)	178/196	156/161
1-5 years	7381	(64.1)	(63.7)	3196/3182	413/407
6-9 years	2007	(17.4)	(17.3)	849/845	131/130
10-15 years	1373	(11.9)	(11.9)	497/497	152/154
Missing #	24	12	12	1/1	0/0
Mother's age					
< 25 years	3952	(32.6)	(35.7)	1530/1689	296/301
25-35 years	5998	(52.3)	(51.4)	2495/2430	415/435
35-45 years	1603	(14.9)	(12.8)	687/594	136/116
45 years	21	(0.2)	(0.1)	9/7	5/0
Missing #	2	1	1	0/1	0/0
Father's age					
< 25 years	2354	(20.7)	(22.4)	925/993	175/179
25-35 years	5808	(53.1)	(53.2)	2405/2373	405/407
35-45 years	2443	(23.5)	(21.2)	1041/933	191/170
45 years	323	(2.8)	169 (3.1)	121/140	27/22
Missing #	648	286	362	228/281	46/66
Child's race					
White	8889	(81.6)	(78.6)	3777/3559	610/622
Black	780	(5.2)	(8.9)	198/399	76/68
Asian	1214	(11.3)	(10.6)	494/474	107/88
Other	209	(1.9)	(1.9)	81/82	21/18
Missing #	484	214	270	171/207	38/56
Father's education					
12 years	6352	(77.9)	(77.6)	2600/2582	484/461
13-17 years	1307	(15.8)	(16.2)	554/562	68/76
17 years	509	(6.3)	(6.2)	213/208	35/36
Missing [Not collected] # ^b	3408 [3014]	1691 [1509]	1717 [1505]	1354/1369	265/279
Source for payment for delivery					
Governmental programs	4457	(44.0)	(46.4)	1741/1861	346/350
Other insurance	5397	(56.0)	(53.6)	2296/2166	378/367
Missing [Not collected] # ^b	1722 [1695]	853 [845]	869 [850]	684/694	128/135

Variables	Total #	Cases (%)	Controls (%)	ALL # cases/controls ^a	AML # cases/controls ^a
All	11576	5788	5788	4721	852
Birth weight					
<2500 g	620	(5.8)	(4.9)	219/274	52/53
2500-3000 g	1654	(14.8)	(13.8)	634/695	138/127
3000-3500 g	4377	(38.2)	(37.4)	1783/1782	313/355
3500-4000 g	1654	(30.1)	(30.7)	1449/1435	252/235
4000-4500 g	1170	(9.2)	(11.0)	527/441	83/71
4500 g	238	(1.9)	(2.2)	109/94	14/11
Missing #	2	1	1	1/1	0/0
Gestational age					
<28 weeks	47	(0.3)	(0.5)	13/23	4/6
28-37 weeks	1103	(10.8)	(9.4)	453/418	116/81
37-42 weeks	8842	(80.6)	(81.4)	3629/3602	619/657
>42 weeks	927	(8.3)	(8.7)	376/385	62/60
Missing/implausible values #	657	311	346	250/293	51/48
Birth weight for gestational age					
SGA	862	(7.0)	(8.8)	295/386	70/71
AGA	8593	(78.4)	(79.0)	3516/3492	627/646
LGA	1464	(14.6)	(12.2)	660/550	104/87
Missing/implausible values #	657	311	346	250/293	51/48
Birth order					
First	4556	(38.7)	(40.7)	1840/1896	309/356
Other	7008	(61.3)	(59.3)	2878/2819	496
Missing #	12	6	6	3/6	1/0
History of terminations before 20 weeks					
No	9685	(83.4)	(84.1)	3923/3964	724/720
Yes	1880	(16.6)	(16.0)	795/749	128/132
Missing #	11	3	8	3/8	0/0
History of terminations after 20 weeks					
No	11392	(98.5)	(98.6)	4652/4643	832/844
Yes	170	(1.5)	(1.4)	66/69	20/8
Missing #	14	4	10	3/9	0/0
Maternal conditions during index pregnancy ^c					
Preeclampsia/Eclampsia	182	(1.6)	(1.5)	78/69	13/15
Anemia	82	(0.7)	(0.7)	32/35	5/5

Variables	Total #	Cases (%)	Controls (%)	ALL # cases/controls ^a	AML # cases/controls ^a
All	11576	5788	5788	4721	852
Genital herpes	129	(1.1)	(1.2)	54/51	5/15
Chronic diseases	305	(2.7)	(2.6)	133/128	16/16
Polyhydramnios	51	(0.5)	(0.4)	19/17	10/3
Blood and immune disorders	105	(0.8)	(1.0)	38/46	9/9
Tobacco use	162	(1.1)	(1.7)	49/78	14/16
Missing #	10	5	5	3/5	2/0

^a Number of cases and controls for ALL and AML do not add up for the total number of cases and controls for childhood leukemia because there were few other subtypes in the dataset.

^b Patterns of missingness varied by variable and by year due to differences in data collection for different years.

^c Conditions are not mutually exclusive and thus frequencies exceed the totals. Information was not routinely collected for many of these conditions prior 1990.

Table 2

Conditional odds ratios (OR) and 95% confidence intervals (CI) for childhood leukemia associated with birth weight and birth weight-for-gestational age matched on age and sex and adjusted for gestational age, birth order, mother's age, father's education, child's race, and payment source for delivery. California birth registry, 1986-2007.

	All types (3334 cases/3334 controls)			ALL (2744 cases/2744 controls)			AML (462 cases/462 controls)		
	95% Confidence			95% Confidence			95% Confidence		
	OR	Intervals		OR	Intervals		OR	Intervals	
Birth weight (g)									
Reference <2500	1	-	-	1	-	-	1	-	-
2500-3500	1.39	1.09	1.77	1.51	1.15	1.98	1.03	0.54	1.98
3500-4500	1.47	1.14	1.88	1.50	1.13	1.98	1.26	0.65	2.44
4500	1.59	1.05	2.40	1.70	1.08	2.68	1.45	0.45	4.70
Birth weight (3,500g vs <3,500g)	1.08	0.98	1.20	1.03	0.92	1.15	1.23	0.93	1.63
Birth weight (4,000g vs <4,000g)	1.05	0.90	1.22	1.04	0.89	1.23	1.03	0.66	1.61
Birth weight, 1000g increase	1.11	1.01	1.21	1.11	1.01	1.23	1.01	0.80	1.28
Birth weight- forgestational age									
SGA	0.81	0.67	0.97	0.77	0.63	0.94	1.15	0.71	1.88
AGA	1	-	-	1	-	-	1	-	-
LGA	1.10	0.95	1.27	1.07	0.91	1.25	1.13	0.75	1.68

Table 3

Conditional odds ratios (OR) and 95% confidence intervals (CI) for childhood leukemia associated with several perinatal factors matched on age and sex and adjusted for confounders. California birth registry, 1986-2007.

Variables	All leukemia types			ALL			AML		
	OR	95% CI		OR	95% CI		OR	95% CI	
Birth order (1st vs Other) ^a	0.93	0.84	1.03	0.97	0.87	1.08	0.70	0.53	0.93
Pregnancy order (1st vs Other) ^a	0.96	0.87	1.07	1.00	0.89	1.12	0.73	0.55	0.96
History of terminations before week 20 ^d	0.95	0.83	1.09	0.97	0.83	1.12	0.94	0.65	1.37
History of termination after week 20 ^d	1.13	0.74	1.73	1.02	0.65	1.62	2.81	0.74	10.66
Mother's age ^b									
By 5-year increase	1.01	0.99	1.02	1.00	0.98	1.02	1.02	0.98	1.06
35 years vs < 35 years	1.14	0.88	1.49	1.07	0.80	1.45	1.52	0.81	2.87
40 years vs < 40 years	1.10	0.82	1.74	0.92	0.52	1.64	2.18	0.77	6.14
25-35 years vs < 25 years	1.00	0.85	1.32	1.13	0.88	1.44	0.84	0.48	1.48
35-45 years vs < 25 years	1.13	0.87	1.61	1.19	0.83	1.68	1.31	0.64	2.70
45 years vs < 25 years	1.52	0.33	6.93	0.76	0.12	4.71	-	-	-
Father's age ^c									
By 5-year increase	1.01	1.00	1.02	1.01	1.00	1.02	1.00	0.98	1.02
35 years vs < 35 years	1.13	1.01	1.26	1.12	0.99	1.27	1.11	0.90	1.27
40 years vs < 40 years	1.11	0.95	1.30	1.10	0.92	1.31	1.02	0.74	1.61
25-35 years vs < 25 years	1.03	0.91	1.17	1.07	0.93	1.23	0.80	0.57	1.12
35-45 years vs < 25 years	1.12	1.04	1.40	1.23	1.04	1.47	0.90	0.60	1.35
45 years vs < 25 years	0.90	0.68	1.20	0.89	0.65	1.22	0.92	0.44	1.94
Difference between paternal and maternal age ^c									
5-10 years vs < 5 years	0.95	0.81	1.11	0.97	0.82	1.15	0.95	0.58	1.54
10 years vs < 5 years	0.84	0.65	1.08	0.87	0.65	1.15	0.78	0.41	1.46
Conditions during index pregnancy ^d									
Eclampsia	1.08	0.75	1.57	1.19	0.78	1.80	0.84	0.33	2.15
Anemia	1.09	0.64	1.87	1.13	0.62	2.05	1.16	0.22	6.17
Blood disorders	0.76	0.48	1.23	0.84	0.50	1.42	0.61	0.17	2.18
Chronic conditions	1.07	0.80	1.43	0.99	0.72	1.36	1.24	0.48	3.21
Tobacco use	0.59	0.38	0.92	0.56	0.33	0.93	0.84	0.31	2.33
Polyhydramnios	1.10	0.59	2.06	0.95	0.46	1.94	2.32	0.44	12.28

Variables	All leukemia types			ALL			AML		
	OR	95% CI		OR	95% CI		OR	95% CI	
Genital herpes	0.81	0.43	1.54	0.87	0.43	1.78	0.46	0.09	2.44

^a Adjusted for child's race, mother's age, source of payment for delivery

^b Adjusted for child's race, birth order, father's education, terminations after 20 weeks of gestation, source of payment for delivery

^c Adjusted for child's race, birth order, father's education, and source of payment for delivery

^d Adjusted for child's race, birth weight, gestational age, birth order, mother's age, source of payment for delivery

Table 4

Conditional odds ratios for childhood leukemia associated with birth weight and birth weight for gestational age matched on age and sex and adjusted for gestational age, birth order, mother's age, father's education, child's race, and payment source for delivery based on multiple imputation of missing data. California birth registry, 1986-2007.

	All leukemia types			ALL			AML			
	OR	95% CI		OR	95% CI		OR	95% CI		
Birth weight (g)										
Reference <2500	1	-	-	1	-	-	1	-	-	
2500-3500	1.25	1.04	1.50	1.27	1.04	1.56	1.22	0.76	1.94	
3500-4500	1.36	1.13	1.64	1.35	1.09	1.67	1.46	0.90	2.34	
>4500	1.45	1.06	1.98	1.48	1.05	2.08	1.79	0.71	4.52	
Birth weight (3,500g vs <3,500g)	1.11	1.03	1.20	1.08	0.99	1.18	1.22	1.00	1.50	
Birth weight (4,000g vs <4,000g)	1.19	1.06	1.34	1.19	1.05	1.34	1.20	0.87	1.66	
Birth weight, 1000g increase	1.16	1.09	1.24	1.17	1.08	1.25	1.12	0.95	1.34	
Birth weight-for-gestational age										
SGA vs AGA	0.82	0.71	0.94	0.78	0.66	0.92	0.93	0.63	1.37	
LGA vs AGA	1.19	1.06	1.32	1.18	1.04	1.33	1.23	0.90	1.68	