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PERINATAL AND FAMILIAL RISK FACTORS FOR ACUTE LYMPHOBLASTIC LEUKEMIA IN A SWEDISH NATIONAL COHORT

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Precis: We conducted the largest population-based cohort study to date to examine perinatal and familial risk factors for acute lymphoblastic leukemia (ALL) among ~3.5 million individuals

born in Sweden during 1973-2008. High fetal growth was associated with an increased risk of ALL in childhood through young adulthood, independently of gestational age at birth, suggesting that growth factor pathways may play an important long-term role in the etiology of ALL.

Abbreviations: ALL (acute lymphoblastic leukemia), CI (confidence interval), DOB (date of birth), ICD (International Classification of Diseases), IGF (insulin-like growth factor), IRR (incidence rate ratio), SD (standard deviation)

Key words: cohort studies; fetal development; gestational age; leukemia; risk factors

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ABSTRACT

Background: Perinatal factors including high birth weight have been associated with acute lymphoblastic leukemia (ALL) in case-control studies. However, these findings have seldom been examined in large population-based cohort studies, and the specific contributions of gestational age and fetal growth remain unknown.

Methods: We conducted a national cohort study of 3,569,333 persons without Down syndrome who were born in Sweden in 1973-2008, followed up for ALL incidence through 2010 (maximum age 38 years) to examine perinatal and familial risk factors.

Results: There were 1,960 ALL cases in 69.7 million person-years of follow-up. After adjusting for potential confounders, risk factors for ALL included high fetal growth (incidence rate ratio [IRR] per additional 1 standard deviation, 1.07; 95% CI, 1.02-1.11, P=0.002; IRR for large vs. appropriate for gestational age, 1.22; 95% CI, 1.06-1.40; P=0.005), first-degree family history of ALL (IRR, 7.41; 95% CI, 4.60-11.95, P<0.001), male sex (IRR, 1.20; 95% CI, 1.10-1.31; P<0.001), and parental country of birth (IRR for both parents born in Sweden vs. other countries, 1.13; 95% CI, 1.00-1.27, P=0.045). These risk factors did not appear to vary by age at ALL diagnosis. Gestational age at birth, season of birth, birth order, multiple birth, parental age, and parental education level were not associated with ALL.

Conclusions: In this large cohort study, high fetal growth was associated with an increased risk of ALL in childhood through young adulthood, independently of gestational age at birth, suggesting that growth factor pathways may play an important long-term role in the etiology of ALL.

INTRODUCTION

Leukemia is the most common cancer in childhood (age <15 years), and acute lymphoblastic leukemia (ALL) accounts for ~80% of all cases in this age range.[1, 2] Established risk factors for ALL such as ionizing radiation, Down syndrome, and other genetic disorders account for only a minority of cases, whereas the etiology of most cases remains unknown.[3] Because most ALL cases are diagnosed in early childhood, perinatal factors may be etiologically important, and their identification may provide insights into mechanisms. Case-control studies have reported that high birth weight is associated with ALL, possibly through growth factor pathways involving insulin-like growth factors (IGF) 1 and 2.[4, 5] However, few studies have examined the specific components of birth weight—gestational age at birth and fetal growth—and their results have been inconsistent. Some[6, 7] but not all[8] have reported that large-for-gestational-age infants have increased risk of childhood ALL, hence the specific contributions of gestational age and fetal growth remain unclear. Also, most studies have examined ALL risk only in childhood, without examining longer-term risk into adolescence or young adulthood. These issues have not been addressed in large population-based cohort studies, which have the potential to provide more robust and generalizable risk estimates and to clarify susceptible population subgroups.

We conducted the largest population-based cohort study to date to examine perinatal and familial risk factors for ALL among ~3.5 million individuals born in Sweden during 1973-2008. Detailed information on perinatal and familial factors and ALL incidence were obtained from birth and cancer registries that are nearly 100% complete nationwide. Our aims were to examine

whether fetal growth, gestational age at birth, and other perinatal and familial factors are associated with ALL in a large national cohort.

METHODS

Study Population

We identified 3,595,055 individuals in the Swedish Birth Registry who were born from 1973 through 2008. We excluded all 2,262 (0.06%) individuals with Down syndrome (a strong established risk factor for ALL),[9] 10,424 (0.3%) others who had missing information for birth weight, and 7,702 (0.2%) others who had missing information for gestational age at birth. To remove possible coding errors, we also excluded 5,334 (0.1%) others who had a reported birth weight more than four standard deviations (SD) above or below the mean birth weight for gestational age and sex based on a Swedish reference growth curve.[10] A total of 3,569,333 individuals (99.3% of the original cohort) remained for inclusion in the study. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

ALL Ascertainment

The study cohort was followed up for ALL incidence from birth through December 31, 2010 (maximum attained age was 38 years). All incident ALL cases were identified using the *International Classification of Diseases (ICD), revisions 8, 9, and 10*, in the Swedish Cancer Registry (code 204.0 in *ICD*-8 and *ICD*-9, and code C91.0 in *ICD*-10). This registry includes all primary incident cancers in Sweden since 1958, with compulsory reporting nationwide. Data on immunophenotypic or cytogenetic subtypes of ALL were unavailable.

Perinatal and Familial Variables

Perinatal and familial characteristics that may be associated with ALL were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number.[11] The following variables were examined as predictors of interest or adjustment variables: sex (male or female); birth year (modeled simultaneously as a continuous variable and a categorical variable by decade to allow for a non-linear effect); fetal growth (a standardized variable defined as the number of SD from the mean birth weight for gestational age and sex based on a Swedish reference growth curve,[10] modeled alternatively as a categorical [<-1; -1 to <1; ≥1 SD] or continuous variable); gestational age at birth (based primarily on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s; modeled alternatively as a categorical [<37, 37-41, ≥42 weeks] or continuous variable); season of birth (modeled alternatively as a categorical variable [Dec-Feb, Mar-May, Jun-Aug, Sep-Nov] or a sinusoidal function as described below); birth order (1, 2, ≥3); multiple birth (singleton vs. twin or higher order); maternal and paternal age at birth (<20, 20-24, 25-29, 30-34, ≥35 years; examined separately for mothers and fathers); parental country of birth (both parents born in Sweden vs. 1 or both foreign-born; note that other specific information on ethnicity was unavailable); maternal and paternal education level (compulsory high school or less [≤9 years], practical high school or some theoretical high school [10-11 years], theoretical high school and/or some college [12-14 years], college and/or post-graduate study [≥15 years]; examined separately for mothers and fathers); and family history of ALL in a parent or sibling (yes or no; identified from the Swedish Cancer Registry from 1958 through 2010, not self-reported, thus enabling highly complete and unbiased ascertainment during this time period).

As alternatives to the standardized fetal growth variable, we also examined birth weight (modeled alternatively as a categorical [<2500, 2500-3999, ≥4000 g] or continuous variable); birth length (crown-heel length in cm, modeled alternatively as a categorical [<48, 48-52, ≥53 cm] or continuous variable); and size for gestational age (based on a Swedish reference growth curve[10] and categorized as small [<10th percentile], appropriate [10th-90th percentile], or large [>90th percentile]).

Statistical Analysis

Poisson regression with robust standard errors was used to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for associations between perinatal or familial variables and ALL.[12] Two different adjusted models were used: The first was adjusted for birth year, and the second was further adjusted for other variables that were found to be associated with ALL (sex, fetal growth, parental country of birth, and family history of ALL in a parent or sibling). Missing data for covariates were imputed using a standard multiple imputation procedure.[13, 14] Poisson models were a better fit for these data than Cox proportional hazards models, which did not meet the proportional hazards assumption. Poisson goodness-of-fit was assessed using deviance and Pearson chi-squared tests, which showed a good fit in all models.

As noted, season of birth was examined alternatively as a categorical variable or a sinusoidal function. In the sinusoidal analysis, date of birth (DOB, coded as an integer from 1 to 365) was modeled as a sinusoidal function in the Poisson regression model, using an iterative method to identify the peak date for ALL relative risk and to test for an overall seasonal association, as previously described.[15] In the case of a leap year, February 29 was recoded as

calendar day 59 so that the respective year had 365 days. Specifically, the trigonometric term entered into the Poisson model was

$$x = \cos[2 \times \arccos(-1) \times ((DOB-t_{max})/365)]$$

where t_{max} (the peak birthdate for ALL risk) was determined iteratively by finding the value from 1 to 365 that maximized the model coefficient.[15]

First-order interactions between sex and other variables were explored by examining risk estimates after stratifying by sex and formally testing for interactions using likelihood ratio tests. Multinomial logistic regression was used to test for heterogeneity in the association between each risk factor and earlier-onset (age <15 years) vs. later-onset (age ≥15 years) ALL. All statistical tests were 2-sided and used an α-level of 0.05. All analyses were conducted using Stata version 13.0.[13]

RESULTS

Among the 3,569,333 persons in this cohort, 1,960 (0.05%) ALL cases were identified in 69.7 million person-years of follow-up. The median age at ALL diagnosis was 4.7 years (mean 6.9, SD 5.9). ALL incidence rates by age and sex are shown in Table 1.

Males had a higher risk of ALL than females (fully adjusted IRR, 1.20; 95% CI 1.10-1.31; $P<0.001$) (Table 2). However, the associations between any other variables and ALL did not vary by sex ($P>0.05$ for each interaction), hence non-stratified risk estimates are presented in Table 2. The strongest risk factor for ALL was a first-degree family history of ALL, which was associated with a >7-fold risk of ALL in the proband (fully adjusted IRR, 7.41; 95% CI, 4.60-11.95; $P<0.001$). There was no evidence that this association varied by whether the affected family member was male or female ($P=0.37$), or by whether the affected family member was the

same or opposite sex as the proband (P=0.87). Only 17 ALL cases had a first-degree family history of ALL (12 with an affected sibling and 5 with an affected parent), which were too few for a more detailed analysis of family history in parents vs. siblings.

Other risk factors for ALL included high fetal growth (fully adjusted IRR per additional 1 SD, 1.07; 95% CI, 1.02-1.11; P=0.002). In addition, individuals whose parents were both Swedish-born had a borderline increased risk of ALL relative to those with at least 1 foreign-born parent (fully adjusted IRR, 1.13; 95% CI, 1.00-1.27; P=0.045). Further stratification of foreign-born parents into Europe/U.S./Canada vs. other countries yielded similar risk estimates, hence they were modeled as a single category.

Birth weight, birth length, and size for gestational age (as a categorical variable) were also examined as alternatives to the standardized fetal growth variable. High birth weight was associated with an increased risk of ALL (fully adjusted P_{trend}=0.005; IRR for ≥4000 vs. 2500-3999 g, 1.19; 95% CI, 1.06-1.32; P=0.003). Birth length had risk estimates in the same direction but without a detectable trend (P_{trend}=0.24). Persons who were born large for gestational age also had an increased risk of ALL relative to those who were appropriate for gestational age (fully adjusted IRR, 1.22; 95% CI, 1.06-1.40; P=0.005). Gestational age at birth, season of birth, birth order, multiple birth, parental age, and parental education level were not associated with ALL (Table 2). Season of birth was alternatively examined as a sinusoidal function (rather than 4 categories) but was still not associated with ALL (fully adjusted P=0.69; not shown in the table).

There was no evidence of heterogeneity in the associations between the predictor variables and ALL by age at diagnosis. Comparing point estimates, high fetal growth appeared to be an equally strong risk factor for ALL with onset at age ≥15 years (fully adjusted odds ratio per additional 1 SD, 1.08; 95% CI, 0.95-1.22; P=0.24; based on 210 cases) compared with age

<15 years (fully adjusted odds ratio per additional 1 SD, 1.07; 95% CI, 1.02-1.12; *P*=0.004; based on 1,041 cases) ($P_{heterogeneity}$=0.88; not shown in the table).

Down syndrome is already a well-established strong risk factor for ALL,[9] and therefore was not a primary focus of this study. In a secondary analysis that included individuals with Down syndrome (n=2,262; 0.06%), Down syndrome was associated with a >20-fold risk of ALL in this cohort (fully adjusted IRR, 22.04; 95% CI, 14.58-33.32; *P*<0.001). This association did not vary by sex or any other variables in Table 2 (*P*>0.05 for each interaction).

DISCUSSION

In this large national cohort study, we found that high fetal growth was associated with an increased risk of ALL in childhood through young adulthood, independently of gestational age at birth, and irrespective of age at ALL onset. A first-degree family history of ALL was also associated with more than a 7-fold risk of ALL. Other risk factors included male sex and having Swedish-born parents compared with those born in other countries. Gestational age at birth, season of birth, birth order, multiple birth, parental age, and parental education level were not associated with ALL.

The association we found with high fetal growth is overall consistent with previous evidence for high birth weight derived mainly from case-control studies. A meta-analysis of 23 ALL studies (19 case-control and 4 smaller cohort studies) with a total of 10,974 ALL cases reported an odds ratio of 1.23 (95% CI, 1.15-1.32) for high relative to normal birth weight (defined as ≥4000 and 2500-3999 g, respectively, in most studies).[4] High birth weight has also been associated with an increased risk of various other cancers,[16] including Hodgkin lymphoma[17] and non-Hodgkin lymphoma[18] in this Swedish cohort. The current study suggests that high fetal

growth is associated with increased risk of ALL independently of gestational age, and not only with early-onset but also late-onset ALL into young adulthood. The underlying mechanisms are not well-established but may involve growth factors including IGF-1 and/or IGF-2, which are correlated with birth weight and have been shown to inhibit cell apoptosis and promote tumor growth.[19] High levels of these growth factors may increase cell division and growth rates, thereby augmenting fetal sensitivity to carcinogenic exposures, or may prevent apoptosis in cell populations that have already begun leukemic transformation.[4, 20] Epigenetic assessments of polymorphisms in the IGF family may help further elucidate these pathways and their potential carcinogenic effects on lymphoblasts *in utero*.

We also found that a first-degree family history of ALL was associated with a strong (>7-fold) risk of ALL in this cohort. This is consistent with a previous risk estimate for ALL among persons with an affected sibling in Sweden,[21] but to our knowledge has not been examined in other large cohort studies. Most studies have had insufficient cases to examine family history of ALL specifically, and instead have examined family history of hematopoietic cancers more broadly, with relative risk estimates for ALL in the ~1-2 range.[22-24] We were able to examine family history of ALL more precisely using registry-based (not self-reported) diagnoses that are nearly 100% complete for a national population. The strong association that we found may reflect genetic factors as well as shared environmental exposures. Recent genome-wide association studies have reported strong associations between variant polymorphisms located in the *ARID5B*, *IKZF1*, and *CEBPE* genes and ALL among persons of European ancestry.[25-28] A large Nordic study of twins, however, found that inherited genetic factors make only a small contribution to leukemia susceptibility, compared with environmental factors that are still largely unknown.[29]

The modest associations we found between male sex or having Swedish-born parents and ALL are broadly consistent with previous findings.[1] A slight male preponderance for childhood ALL has been previously described,[30, 31] as well as higher ALL incidence in Sweden than in Asia, Africa, South America, or among U.S. blacks.[31] These relationships are still not well understood, but may be partly explained by a more protective effect of estradiol compared with testosterone on leukemic cell proliferation,[32] as well as ethnic differences in genetic variants that predispose to ALL.[33] These relationships warrant further investigation in experimental and epidemiologic studies with the ability to examine subtype-specific mechanisms that potentially vary by sex and ethnicity.

Previous studies of infectious etiologies and ALL have yielded discrepant results. Although no specific virus has been consistently associated with ALL, maternal infections during pregnancy have been linked with increased risks, whereas daycare attendance in early childhood has appeared to be protective.[34] Season of birth has also been examined as a proxy for perinatal infectious exposures, and birth order as a proxy for infectious exposures in early childhood from siblings. Previous findings for season of birth and ALL have been inconsistent, including positive associations with peak risk occurring among persons born in spring[35, 36] or summer[37], a bimodal summer/winter peak among all children[38] or only boys[39], or no association.[40-42] Results for birth order based mainly on case-control data have also been inconclusive, with null findings in most studies.[34] We did not confirm a link between season of birth or birth order and ALL in this large national cohort.

Important strengths of this study are its population-based national cohort design and large sample size, enabling more robust and generalizable inferences, and the ability to examine disease risk into young adulthood. Linkage of birth and cancer registries provided detailed

information on perinatal factors and ALL incidence that was nearly 100% complete nationwide.[43, 44] A cohort design prevented selection bias that may potentially occur in case-control studies, and the use of registry-based data prevented bias that may result from self-reporting. Family history of ALL was also based on registry data with virtually complete ascertainment, thus improving the reliability of those risk estimates.

Study limitations included the unavailability of cytogenetic data to examine ALL subtypes. Although we examined season of birth and birth order as proxies for early infectious exposures, we were unable to directly assess specific infections or infectious exposures later in life that may potentially influence disease risk. We also lacked data on other environmental exposures such as radiation, pesticides, other chemicals, and smoking. Additional cohort studies with information on perinatal as well as other environmental factors are needed to examine more complex etiologic pathways and age windows of susceptibility.

In summary, this large national cohort study identified several risk factors for ALL among persons born in Sweden during 1973-2008, including high fetal growth, family history of ALL, male sex, and having Swedish-born parents. High fetal growth was associated with an increased risk of ALL independently of gestational age at birth, and irrespective of age at disease onset. These findings suggest that growth factor pathways may play an important role in the etiology of ALL from childhood into young adulthood.

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Study concept and design: Crump, J. Sundquist, Sieh, Winkleby, K. Sundquist.

Acquisition of data: J. Sundquist, K. Sundquist.

Analysis and interpretation of data: Crump, J. Sundquist, Sieh, Winkleby, K. Sundquist.

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Table 1. Incidence rates for acute lymphoblastic leukemia (ALL) by age and sex (1973-2010)

	Total			Males			Females		
Age (years)	**Cases**	**Person-years[a]**	**Rate[b]**	**Cases**	**Person-years[a]**	**Rate[b]**	**Cases**	**Person-years[a]**	**Rate[b]**
Overall	1,960	69.7	28.1	1,097	35.8	30.7	863	33.9	25.5
0-4	1,041	17.2	60.6	549	8.8	62.2	492	8.4	58.9
5-9	469	14.8	31.8	279	7.6	36.8	190	7.2	26.4
10-14	240	12.5	19.2	148	6.4	23.0	92	6.1	15.1
15-19	130	10.1	12.9	72	5.2	13.9	58	4.9	11.8
20-24	45	7.3	6.2	28	3.7	7.5	17	3.5	4.8
25-38	35	7.8	4.5	21	4.1	5.1	14	3.8	3.7

[a]Person-years in millions.
[b]Incidence rate per million person-years.

Table 2. Adjusted incidence rate ratios for associations between perinatal or familial characteristics and acute lymphoblastic leukemia (ALL) in 1973-2010

	Total population	ALL cases	Adjusted Model 1[a]			Adjusted Model 2[b]		
	N (%)	n (%)	IRR	95% CI	*P*	IRR	95% CI	*P*
Age at diagnosis (years)								
<5		1,041 (53.1)						
5-9		469 (23.9)						
10-14		240 (12.2)						
≥15		210 (10.7)						
Sex								
Female	1,734,966 (48.6)	863 (44.0)	1.00			1.00		
Male	1,834,367 (51.4)	1,097 (56.0)	1.20	1.10, 1.31	<0.001	1.20	1.10, 1.31	<0.001
Fetal growth (SD)								
<-1	647,584 (18.1)	357 (18.2)	0.99	0.88, 1.12	0.92	1.00	0.89, 1.13	0.97
-1 to <1	2,384,285 (66.8)	1,275 (65.1)	1.00			1.00		
≥1	537,464 (15.1)	328 (16.7)	1.35	1.12, 1.63	0.01	1.15	1.02, 1.30	0.02
Per SD (trend test)			1.07	1.03, 1.12	0.001	1.07	1.02, 1.11	0.002
Gestational age at birth (weeks)								
<37	206,387 (5.8)	111 (5.7)	1.00	0.83, 1.21	0.99	1.00	0.83, 1.22	0.97
37-41	3,064,550 (85.9)	1,657 (84.5)	1.00			1.00		
≥42	298,396 (8.4)	192 (9.8)	1.14	0.98, 1.33	0.09	1.14	0.98, 1.33	0.08
Per week (trend test)			1.01	0.98, 1.03	0.60	1.01	0.98, 1.03	0.60
Birth weight (g)								
<2500	149,020 (4.2)	83 (4.2)	1.06	0.85, 1.32	0.62	1.06	0.85, 1.32	0.61
2500-3999	2,777,911 (77.8)	1,470 (75.0)	1.00			1.00		
≥4000	642,402 (18.0)	407 (20.8)	1.22	1.09, 1.36	<0.001	1.19	1.06, 1.32	0.003
Per 1000 g (trend test)			1.15	1.06, 1.24	0.001	1.12	1.04, 1.21	0.005
Birth length (cm)								
<48	359,182 (10.1)	185 (9.4)	0.97	0.83, 1.13	0.72	0.98	0.84, 1.15	0.81
48-52	2,600,085 (72.9)	1,402 (71.5)	1.00			1.00		
≥53	576,918 (16.2)	363 (18.5)	1.14	1.02, 1.28	0.03	1.09	0.96, 1.24	0.16

Unknown	33,148 (0.9)	10 (0.5)						
Per cm (trend test)			1.02	1.01, 1.04	0.009	1.01	0.99, 1.03	0.24
Size for gestational age								
Small (<10th percentile)	356,521 (10.0)	202 (10.3)	1.01	0.87, 1.17	0.88	1.02	0.88, 1.18	0.80
Appropriate (10th-90th percentile)	2,854,197 (80.0)	1,528 (78.0)	1.00			1.00		
Large (>90th percentile)	356,655 (10.0)	230 (11.7)	1.23	1.07, 1.41	0.003	1.22	1.06, 1.40	0.005
Season of birth								
Spring (Mar-May)	990,165 (27.7)	558 (28.5)	1.05	0.93, 1.19	0.40	1.05	0.93, 1.19	0.42
Summer (Jun-Aug)	915,319 (25.6)	484 (24.7)	1.00			1.00		
Fall (Sep-Nov)	821,829 (23.0)	464 (23.7)	1.07	0.94, 1.21	0.32	1.07	0.94, 1.21	0.31
Winter (Dec-Feb)	842,020 (23.6)	454 (23.2)	1.01	0.89, 1.15	0.86	1.01	0.89, 1.15	0.86
Birth order								
1	1,827,129 (51.2)	1,060 (54.1)	1.00			1.00		
2	1,200,398 (33.6)	620 (31.6)	0.93	0.84, 1.03	0.15	0.91	0.82, 1.01	0.07
≥3	541,806 (15.2)	280 (14.3)	0.96	0.83, 1.10	0.52	0.93	0.81, 1.06	0.29
Per higher category (trend test)			0.98	0.93, 1.04	0.58	0.97	0.92, 1.03	0.32
Multiple birth								
Singleton	3,484,910 (97.6)	1,907 (97.3)	1.00			1.00		
Twin or higher order	84,423 (2.4)	53 (2.7)	1.21	0.92, 1.59	0.17	1.23	0.94, 1.62	0.14
Maternal age at birth (years)								
<20	83,987 (2.4)	51 (2.6)	1.04	0.78, 1.39	0.77	1.06	0.80, 1.41	0.70
20-24	678,027 (19.0)	396 (20.2)	1.03	0.91, 1.17	0.65	1.04	0.91, 1.17	0.58
25-29	1,251,348 (35.1)	677 (34.5)	1.00			1.00		
30-34	1,033,763 (29.0)	562 (28.7)	1.09	0.97, 1.22	0.15	1.08	0.97, 1.21	0.16
≥35	518,097 (14.5)	272 (13.9)	1.10	0.95, 1.27	0.19	1.10	0.95, 1.27	0.19
Unknown	4,111 (0.1)	<5 (0.1)						
Per higher category (trend test)			1.03	0.98, 1.08	0.23	1.02	0.98, 1.07	0.29
Paternal age at birth (years)								
<20	16,943 (0.5)	10 (0.5)	1.05	0.56, 1.96	0.89	1.06	0.57, 1.98	0.86
20-24	326,974 (9.2)	202 (10.3)	1.09	0.92, 1.27	0.32	1.09	0.93, 1.28	0.29
25-29	1,021,644 (28.6)	564 (28.8)	1.00			1.00		
30-34	1,161,177 (32.5)	625 (31.9)	1.05	0.93, 1.17	0.43	1.05	0.93, 1.17	0.44

≥35	1,014,007 (28.4)	541 (27.6)	1.10	0.97, 1.24	0.14	1.10	0.98, 1.24	0.12
Unknown	28,588 (0.8)	18 (0.9)						
Per higher category (trend test)			1.02	0.97, 1.07	0.40	1.02	0.97, 1.07	0.40
Both parents born in Sweden								
Yes	2,852,520 (79.9)	1,622 (82.8)	1.13	1.01, 1.28	0.04	1.13	1.00, 1.27	0.045
No	716,813 (20.1)	338 (17.2)	1.00			1.00		
Maternal education (years)								
≤9	674,884 (18.9)	390 (19.9)	1.00			1.00		
10-11	1,149,737 (32.2)	694 (35.4)	1.04	0.92, 1.19	0.52	1.03	0.91, 1.17	0.64
12-14	1,044,760 (29.3)	520 (26.5)	1.01	0.88, 1.16	0.88	1.00	0.87, 1.15	0.99
≥15	554,418 (15.5)	288 (14.7)	1.13	0.96, 1.32	0.15	1.11	0.95, 1.31	0.19
Unknown	145,534 (4.1)	68 (3.5)						
Per higher category (trend test)			1.03	0.98, 1.08	0.29	1.02	0.97, 1.08	0.35
Paternal education (years)								
≤9	767,366 (21.5)	454 (23.2)	1.00			1.00		
10-11	1,128,568 (31.6)	610 (31.1)	0.98	0.86, 1.11	0.73	0.97	0.85, 1.11	0.67
12-14	959,668 (26.9)	518 (26.4)	1.06	0.93, 1.21	0.38	1.06	0.93, 1.20	0.41
≥15	537,725 (15.1)	294 (15.0)	1.07	0.92, 1.24	0.39	1.06	0.92, 1.23	0.42
Unknown	176,006 (4.9)	84 (4.3)						
Per higher category (trend test)			1.03	0.98, 1.08	0.21	1.03	0.99, 1.08	0.18
ALL in a parent or sibling								
No	3,565,267 (99.9)	1,943 (99.1)	1.00			1.00		
Yes	4,066 (0.1)	17 (0.9)	7.61	4.64, 12.09	<0.001	7.41	4.60, 11.95	<0.001

[a]Adjusted for birth year (modeled simultaneously as continuous and categorical variables).
[b]Adjusted for birth year (as noted above), sex, fetal growth, parental country of birth, and family history of ALL in a parent or sibling. Birth weight, birth length, and size for gestational age were each examined in separate models as alternatives to the standardized fetal growth variable. The reference category for all variables is indicated by an IRR of 1.00. Multiple imputation was used for missing data.
ALL = acute lymphoblastic leukemia, CI = confidence interval, IRR = incidence rate ratio, SD = standard deviation.