Published in final edited form as:

Eur J Epidemiol. 2015 December ; 30(12): 1277–1285. doi:10.1007/s10654-015-0063-0.

PERINATAL RISK FACTORS FOR ACUTE MYELOID LEUKEMIA

Casey Crump, M.D., Ph.D.,

Stanford University, Department of Medicine, 1265 Welch Road, MSOB X212, Stanford, California 94305-5411, USA. Tel: (650) 721-2400. Fax: (650) 498-7750

Jan Sundquist, M.D., Ph.D.,

Lund University, Center for Primary Health Care Research, Clinical Research Centre (CRC), building 28, floor 11, Jan Waldenströms gata 35, Skåne University Hospital, SE-205 02 Malmö, Sweden

Weiva Sieh, M.D., Ph.D.,

Stanford University, Department of Health Research and Policy, HRP Redwood Building, T254B, Stanford, California 94305-5405, USA

Marilyn A. Winkleby, Ph.D., and

Stanford University, Stanford Prevention Research Center, Medical School Office Building, 251 Campus Drive, Room X318, Stanford, California 94305-5411, USA

Kristina Sundquist, M.D., Ph.D.

Lund University, Center for Primary Health Care Research, Clinical Research Centre (CRC), building 28, floor 11, Jan Waldenströms gata 35, Skåne University Hospital, SE-205 02 Malmö, Sweden

Casey Crump: kccrump@stanford.edu

Abstract

Infectious etiologies have been hypothesized for acute leukemias because of their high incidence in early childhood, but have seldom been examined for acute myeloid leukemia (AML). We conducted the first large cohort study to examine perinatal factors including season of birth, a proxy for perinatal infectious exposures, and risk of AML in childhood through young adulthood. A national cohort of 3,569,333 persons without Down syndrome who were born in Sweden in 1973–2008 were followed up for AML incidence through 2010 (maximum age 38 years). There were 315 AML cases in 69.7 million person-years of follow-up. We found a sinusoidal pattern in AML risk by season of birth ($P < 0.001$), with peak risk among persons born in winter. Relative to

Correspondence to: Casey Crump, kccrump@stanford.edu.

There were no conflicts of interest.

Author Contributions: Dr. Jan Sundquist had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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.

Drafting of the manuscript: Crump.

Critical revision of the manuscript for important intellectual content: Crump, J. Sundquist, Sieh, Winkleby, K. Sundquist.

Statistical analysis: Crump, J. Sundquist.

Obtained funding: Crump, J. Sundquist, K. Sundquist.

persons born in summer (June–August), incidence rate ratios for AML were 1.72 (95% CI, 1.25–2.38; $P=0.001$) for winter (December–February), 1.37 (95% CI, 0.99–1.90; $P=0.06$) for spring (March–May), and 1.27 (95% CI, 0.90–1.80; $P=0.17$) for fall (September–November). Other risk factors for AML included high fetal growth, high gestational age at birth, and low maternal education level. These findings did not vary by sex or age at diagnosis. Sex, birth order, parental age, and parental country of birth were not associated with AML. In this large cohort study, birth in winter was associated with increased risk of AML in childhood through young adulthood, possibly related to immunologic effects of early infectious exposures compared with summer birth. These findings warrant further investigation of the role of seasonally varying perinatal exposures in the etiology of AML.

Keywords

cohort studies; fetal development; gestational age; leukemia; risk factors; seasons

INTRODUCTION

Leukemia is the most common cancer in childhood, accounting for about 30% of all cancers diagnosed before age 15 years (1). Although acute lymphoblastic leukemia (ALL) is the most common subtype, acute myeloid leukemia (AML) accounts for 15–20% of all leukemia in this age range (1–3). AML has a bimodal age distribution with a peak in early childhood and again in older adulthood (4). Established risk factors for childhood AML, such as *in utero* ionizing radiation exposure (5), Down syndrome (6, 7), and other genetic disorders (8), account for only a small proportion of cases (4). The identification of other risk factors has been elusive and limited by small sample sizes. Infectious etiologies have been hypothesized for both ALL and AML (9) because of the high incidence of these cancers in early childhood, coinciding with common early infections and immune system immaturity (10). This hypothesis has been supported for ALL by some (11–15) but not all (16–18) studies reporting associations with season of birth, a proxy for perinatal infectious exposures. However, season of birth has rarely been studied in relation to AML risk, and has never been examined in large population-based cohort studies with the potential to provide more robust and generalizable risk estimates. Such studies may shed light on potential mechanisms for this relatively common and often fatal cancer that still has largely unknown causes.

We conducted the largest population-based cohort study to date to examine perinatal factors including season of birth and risk of AML among ~3.5 million individuals born in Sweden during 1973–2008. Detailed information on perinatal factors and AML incidence were obtained from birth and cancer registries that are nearly 100% complete nationwide. Our aims were to examine whether season of birth and other perinatal factors are associated with AML in childhood through young adulthood 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. For the primary analyses, we excluded all 2,262 (0.06%) individuals with Down syndrome (a strong established risk factor for AML) (6, 7), 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%) individuals 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 (19). A total of 3,569,333 individuals (99.3% of the original cohort) remained for inclusion in these analyses. For a secondary analysis, we included all 2,262 (0.06%) individuals with Down syndrome and made the same other exclusions as above. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

AML Ascertainment

The study cohort was followed up for AML incidence from birth through December 31, 2010 (maximum attained age was 38 years). All incident AML cases were identified using the *International Classification of Diseases (ICD), revisions 8, 9, and 10*, in the Swedish Cancer Registry (code 205.0 in *ICD-8* and *ICD-9*, and code C92.0 in *ICD-10*), and were verified using morphology codes according to the International Classification of Childhood Cancer, Third Edition (20). The Swedish Cancer Registry includes all primary incident cancers in Sweden since 1958, with compulsory reporting nationwide. Morphology codes are assigned according to Systemized Nomenclature of Medicine (SNOMED) codes since 1993 and synonymous definitions provided by the World Health Organization prior to this period. Data on cytogenetic subtypes of AML were unavailable.

Perinatal and Familial Variables

Perinatal and familial characteristics that may be associated with AML were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number (21). The following variables were available for all birth years and 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); season of birth (modeled alternatively as a categorical variable [Dec-Feb, Mar-May, Jun-Aug, Sep-Nov] or a sinusoidal function as described below); fetal growth (a standardized fetal growth variable defined as the number of standard deviations from the mean birth weight for gestational age and sex based on a Swedish reference growth curve (19), 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); 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); multiple birth (singleton vs. twin or higher order); birth order

(1, 2, 3); 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. at least 1 foreign-born; note that other information on ethnicity was unavailable); and 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).

We also examined family history of AML in a parent or sibling (yes or no; identified using the Swedish Cancer Registry from its inception in 1958 through 2010; diagnoses prior to 1958 were unavailable) and multiple birth (singleton vs. twin or higher order), but they were too infrequent among AML cases to obtain stable risk estimates. Only 1 of the 315 AML cases had a first-degree family history of AML (which was in the father), and only 6 AML cases were from twin pregnancies (and for each case the twin sibling did not have AML).

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 AML (22). Two different adjusted models were used: The first was adjusted for birth year and sex, and the second was further adjusted for other variables that were found to be associated with AML (season of birth, fetal growth, gestational age at birth, and maternal education level). 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 AML relative risk and to test for an overall seasonal association, as previously described (23). 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:

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

where $t_{\max}$ (the peak birthdate for AML risk) was determined iteratively by finding the value from 1 to 365 that maximized the model coefficient (23). After identifying the peak date in this manner, the 3-month period of maximum risk was identified by centering on this date.

An interaction between sex and season of birth in relation to AML risk has been reported previously (11). We evaluated for interaction between sex and season of birth by examining sex-stratified risk estimates and formally testing for interaction using a likelihood ratio test. Multinomial logistic regression was also used to test for heterogeneity in the association between each risk factor and earlier-onset (age <15 years) vs. later-onset (age ≥ 15 years) AML. All statistical tests were 2-sided and used an α -level of 0.05. All analyses were conducted using Stata version 13.0 (24).

RESULTS

Among the 3,569,533 persons in this cohort, 315 AML cases were identified in 69.7 million person-years of follow-up. The mean age at AML diagnosis was 13.7 years (SD 9.7, median 13.3, range 0.1 to 35.7). Incidence rates by age and sex are presented in Table 1.

Table 2 shows AML incidence rates by season and month of birth. Incidence rates (per million person-years) were highest among persons born in winter (5.8), lowest among those born in summer (3.4), and intermediate among those born in spring (4.6) or fall (4.4). In the Poisson model, we found a sinusoidal pattern in AML risk by season of birth ($P<0.001$, adjusted for birth year and sex), with peak risk corresponding to a birthdate of January 26, and lowest risk corresponding to a birthdate of July 28. Figure 1 shows the seasonal pattern in AML risk by birthdate from the sinusoidal model. Adjusted for birth year and sex, the IRR for the 3-month peak (Dec 12–Mar 12) relative to the 3-month nadir (Jun 13–Sep 11) was 1.82 (95% CI, 1.33–2.49, $P<0.001$; not shown in the tables).

Associations between other variables and AML risk from childhood through young adulthood are shown in Table 3. The association between fetal growth and AML appeared U-shaped, with highest risk occurring among persons with fetal growth ± 1 SD relative to -1 to 1 SD (fully adjusted IRR, 1.49; 95% CI, 1.11–1.98; $P=0.007$) (Table 3, Adjusted Model 2). High gestational age at birth appeared linearly associated with increased risk of AML (fully adjusted IRR per additional 1 week, 1.11; 95% CI 1.04–1.19; $P=0.002$). Maternal (but not paternal) education level was inversely associated with risk of AML (fully adjusted IRR per each higher category, 0.81; 95% CI, 0.72–0.92; $P=0.001$). No associations were found between sex, birth weight, birth length, birth order, maternal or paternal age, or parental country of birth and AML (Table 3). With the exception of birth year (included to adjust for follow-up time), adjustment for any combination of other variables had minimal effect on the risk estimates.

There was no evidence of statistical or biologically meaningful interaction between sex and season of birth or any other variables in relation to AML risk ($P>0.05$ for each interaction). There also was no evidence of heterogeneity in the associations between any of these variables and AML by age at diagnosis, comparing <15 to ≥ 15 years (data not shown).

Down syndrome is already a well-established strong risk factor for AML (6, 7), 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 >100 -fold risk of AML (fully adjusted IRR, 154.6; 95% CI, 100.5–237.9; $P<0.001$; based on 24 persons with Down syndrome who were diagnosed with AML). This association did not vary by sex or any other variables in Table 3 ($P>0.05$ for each interaction).

DISCUSSION

In this large national cohort study, we found that persons who were born in winter had an increased risk of AML in childhood through young adulthood, relative to those born in summer. We also identified other independent risk factors for AML, including high fetal

growth, high gestational age at birth, and low maternal education level. Sex, birth order, parental country of birth, and paternal education level were not associated with AML.

Season of birth as a proxy for perinatal infectious exposures has rarely been examined in relation to AML. A UK study of 128 children with AML (ages <15 years) reported a sinusoidal pattern by season of birth for males only ($P=0.04$), with peak risk among those with birthdates in September (11). Another UK study of 463 adolescents and young adults with AML (ages 15–24 years) found no association between season of birth and AML ($P=0.50$) (25). A Swedish case-control study of 74 children with AML and an equal number of matched controls found no association between maternal infection and AML, but statistical power was low and season of birth was not examined (26). Our study was the first to use a population-based cohort design with the ability to estimate relative risks for AML by season of birth. We found a strong seasonal pattern, irrespective of sex or age at diagnosis, with peak risk corresponding to birthdates in January. We previously reported a similar seasonal pattern in this cohort for non-Hodgkin lymphoma, with peak risk among birthdates in April ($P=0.04$), but not for Hodgkin lymphoma (27).

The observed association between season of birth and AML suggests a possible etiologic role of seasonally varying perinatal exposures such as infections. Leukemogenesis is a multistep process involving susceptibility of a hematopoietic progenitor cell to inductive agents at multiple stages that may begin prenatally (4, 10). Known risk factors for AML, including genetic disorders (6–8), ionizing radiation (5), benzene exposure (28), and chemotherapy (29), account for only a small percentage of cases (4). Infectious etiologies have been hypothesized because of an incidence peak in early childhood (before a larger peak later in life), coinciding with common early infections and immune system immaturity (9, 10). Viruses, particularly RNA retroviruses, have been reported to cause leukemia in animal studies by disturbing hematopoietic regulatory mechanisms in genetically susceptible hosts (30). Associations between certain viruses such as parvovirus B19 and acute leukemias in humans have also been suggested (31) but not confirmed (9). Most studies to date have been limited by small sample sizes. The present study's findings warrant further investigation in other large cohorts to elucidate the role of perinatal infectious exposures in the etiology of AML. Other seasonally varying environmental exposures such as pesticides also cannot be excluded as possible contributors.

We also found that high fetal growth and high gestational age at birth (but not birth weight and birth length) appeared independently associated with AML. Most previous studies have focused on birth weight without examining its specific components—fetal growth and gestational age. The largest meta-analysis to date included a total of 1,832 AML cases from 7 case-control and 2 cohort studies and reported an increased risk of AML for both low birth weight (odds ratio, 1.50; 95% CI, 1.05–2.13) and high birth weight (odds ratio, 1.24; 95% CI, 1.16–1.33) that were variably defined (32). A large case-control study reported a similar U-shaped relationship between birth weight and risk of childhood AML in the UK, and risk of AML among older (5–14 years) but not younger (<5 years) children in the US (33). In the present study, we also found a possible U-shaped relationship between fetal growth and AML risk, with highest risk occurring among those with high rather than low fetal growth. High fetal growth also has been associated with other hematologic cancers in this cohort,

including Hodgkin lymphoma (34) and non-Hodgkin lymphoma (35). Our findings extend those of previous studies (32, 36) by suggesting that high fetal growth is associated with increased risk of AML independently of gestational age, and not only with early-onset but also late-onset disease into young adulthood. The underlying mechanisms may involve growth factors including insulin-like growth factor 1 and 2, which are highly correlated with birth weight and have been shown to inhibit cellular apoptosis and promote tumor growth (37). High levels of these growth factors may augment fetal sensitivity to carcinogenic exposures by increasing cell division and growth rates, or prevent apoptosis in cell populations that have already begun leukemic transformation (32, 38). In addition, we found that high gestational age at birth appeared independently and linearly associated with increased risk of AML. The few previous studies that specifically examined gestational age at birth reported no association with AML, but were based on case-control data with small sample sizes (7, 39–42). This relationship warrants confirmation in other large cohort studies.

Maternal education level was inversely associated with risk of AML in this cohort, in contrast to smaller case-control studies that reported no association (41, 43, 44). This finding will need confirmation in other population-based studies and identification of pertinent environmental exposures that may be related to maternal education. Also in contrast to some (39, 41, 45) but not all (7, 43, 46–48) studies, we found no link between advanced maternal age and AML.

Important strengths of this study are its national population-based cohort design, large sample size providing excellent statistical power, and lengthy follow-up with the ability to examine disease risk from birth into young adulthood. This study design enabled risk estimation for an entire national population, which can yield more robust and generalizable inferences than those based on a selected sample. Linkage of birth and cancer registries provided detailed information on perinatal factors and AML diagnoses that was nearly 100% complete nationwide (49, 50). The use of registry-based data prevented bias that may potentially result from self-reporting.

Limitations included insufficient subtype information to enable subtype-specific analyses. Family history of AML was examined but was too infrequent among AML cases to obtain meaningful risk estimates. Although we used season of birth as a proxy for early infectious exposures, we were unable to directly assess specific infections, infectious exposures later in life, or other seasonally varying exposures such as pesticides that may potentially influence disease risk. Information on other environmental exposures such as radiation and smoking was also unavailable. Additional cohort studies with more specific information on seasonally varying environmental exposures in the perinatal period and beyond will be needed to examine more complex pathways and other age windows of susceptibility.

In summary, this large national cohort study found that birth in winter, high fetal growth, high gestational age at birth, and low maternal education level were associated with increased risk of AML in childhood through young adulthood among persons born in Sweden during 1973–2008. The association with winter birth suggests that seasonally varying perinatal exposures such as infections may play an important role in the etiology of AML.

Additional studies with more detailed information on infections and other seasonally varying environmental exposures are warranted to further delineate the specific risk factors and mechanisms.

Acknowledgments

FUNDING

This work was supported by the National Cancer Institute at the National Institutes of Health [grant number R03 CA171017]; the Swedish Research Council; and ALF project grant, Region Skåne/Lund University, Sweden. The funding agencies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
CI	confidence interval
DOB	date of birth
ICD	International Classification of Diseases
IRR	incidence rate ratio
SD	standard deviation

References

1. Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992–2004). *Cancer*. 2008; 112(2):416–32.10.1002/cncr.23169 [PubMed: 18074355]
2. Eden T. Aetiology of childhood leukaemia. *Cancer treatment reviews*. 2010; 36(4):286–97.10.1016/j.ctrv.2010.02.004 [PubMed: 20223594]
3. Kaatsch P. Epidemiology of childhood cancer. *Cancer treatment reviews*. 2010; 36(4):277–85. S0305-7372(10)00023-X [pii]. 10.1016/j.ctrv.2010.02.003 [PubMed: 20231056]
4. Deschler B, Lubbert M. Acute myeloid leukemia: epidemiology and etiology. *Cancer*. 2006; 107(9):2099–107.10.1002/cncr.22233 [PubMed: 17019734]
5. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *The British journal of radiology*. 1997; 70:130–9.10.1259/bjr.70.830.9135438 [PubMed: 9135438]
6. Bruwier A, Chantrain CF. Hematological disorders and leukemia in children with Down syndrome. *European journal of pediatrics*. 2012; 171(9):1301–7.10.1007/s00431-011-1624-1 [PubMed: 22113227]
7. Cnattingius S, Zack M, Ekblom A, Gunnarskog J, Linet M, Adami HO. Prenatal and neonatal risk factors for childhood myeloid leukemia. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 1995; 4(5):441–5.
8. Pui CH. Childhood leukemias. *The New England journal of medicine*. 1995; 332(24):1618–30.10.1056/NEJM199506153322407 [PubMed: 7753142]
9. McNally RJ, Eden TO. An infectious aetiology for childhood acute leukaemia: a review of the evidence. *British journal of haematology*. 2004; 127(3):243–63.10.1111/j.1365-2141.2004.05166.x [PubMed: 15491284]
10. Greaves M. Childhood leukaemia. *Bmj*. 2002; 324(7332):283–7. [PubMed: 11823363]

11. Basta NO, James PW, Craft AW, McNally RJ. Season of birth and diagnosis for childhood cancer in Northern England, 1968–2005. *Paediatric and perinatal epidemiology*. 2010; 24(3):309–18. PPE1112 [pii]. 10.1111/j.1365-3016.2010.01112.x [PubMed: 20415761]
12. Feltbower RG, Pearce MS, Dickinson HO, Parker L, McKinney PA. Seasonality of birth for cancer in Northern England, UK. *Paediatric and perinatal epidemiology*. 2001; 15(4):338–45. [PubMed: 11703681]
13. Sorensen HT, Pedersen L, Olsen J, Rothman K. Seasonal variation in month of birth and diagnosis of early childhood acute lymphoblastic leukemia. *JAMA: the journal of the American Medical Association*. 2001; 285(2):168–9. [PubMed: 11176808]
14. Yaniv I, Lewy H, Avrahami G, Jeison M, Stark B, Laron Z. Possible link between month of birth and childhood leukemia supports the hypothesis of an infectious etiology. *The Israel Medical Association journal: IMAJ*. 2010; 12(12):776. [PubMed: 21348411]
15. Nyari TA, Kajtar P, Bartyik K, Thurzo L, McNally R, Parker L. Seasonal variation of childhood acute lymphoblastic leukaemia is different between girls and boys. *Pathology oncology research: POR*. 2008; 14(4):423–8. 10.1007/s12253-008-9017-0 [PubMed: 18409021]
16. Kajtar P, Fazekasne KM, Mehes K. Month of birth in childhood acute lymphoblastic leukemia. *Orvosi hetilap*. 2003; 144(38):1869–71. [PubMed: 14596025]
17. Meltzer AA, Annegers JF, Spitz MR. Month-of-birth and incidence of acute lymphoblastic leukemia in children. *Leukemia & lymphoma*. 1996; 23(1–2):85–92. 10.3109/10428199609054805 [PubMed: 9021689]
18. Higgins CD, dos-Santos-Silva I, Stiller CA, Swerdlow AJ. Season of birth and diagnosis of children with leukaemia: an analysis of over 15 000 UK cases occurring from 1953–95. *British journal of cancer*. 2001; 84(3):406–12. 10.1054/bjoc.2000.1575 [PubMed: 11161408]
19. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta paediatrica*. 1996; 85(7):843–8. [PubMed: 8819552]
20. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. *International Classification of Childhood Cancer*, third edition. *Cancer*. 2005; 103(7):1457–67. 10.1002/cncr.20910 [PubMed: 15712273]
21. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *JAMA: the journal of the American Medical Association*. 2011; 306(11):1233–40. [PubMed: 21934056]
22. Zou G. A modified poisson regression approach to prospective studies with binary data. *American journal of epidemiology*. 2004; 159(7):702–6. [PubMed: 15033648]
23. Efrid JT, Nielsen SS. A method to model season of birth as a surrogate environmental risk factor for disease. *International journal of environmental research and public health*. 2008; 5(1):49–53. [PubMed: 18441405]
24. StataCorp. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP; 2013.
25. van Laar M, Kinsey SE, Picton SV, Feltbower RG. First description of seasonality of birth and diagnosis amongst teenagers and young adults with cancer aged 15–24 years in England, 1996–2005. *BMC cancer*. 2013; 13:365. 10.1186/1471-2407-13-365 [PubMed: 23902746]
26. Naumburg E, Bellocco R, Cnattingius S, Jonzon A, Ekblom A. Perinatal exposure to infection and risk of childhood leukemia. *Medical and pediatric oncology*. 2002; 38(6):391–7. 10.1002/mpo.10084 [PubMed: 11984799]
27. Crump C, Sundquist J, Sieh W, Winkleby MA, Sundquist K. Season of birth and risk of Hodgkin and non-Hodgkin lymphoma. *International journal of cancer. Journal international du cancer*. 2014; 1002/ijc.28909
28. Savitz DA, Andrews KW. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. *American journal of industrial medicine*. 1997; 31(3):287–95. [PubMed: 9055951]
29. Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *The New England journal of medicine*. 1991; 325(24):1682–7. 10.1056/NEJM199112123252402 [PubMed: 1944468]
30. Ben-David Y, Bernstein A. Friend virus-induced erythroleukemia and the multistage nature of cancer. *Cell*. 1991; 66(5):831–4. [PubMed: 1889087]

31. Kerr JR, Barah F, Cuniffe VS, et al. Association of acute parvovirus B19 infection with new onset of acute lymphoblastic and myeloblastic leukaemia. *Journal of clinical pathology*. 2003; 56(11): 873–5. [PubMed: 14600138]
32. Caughey RW, Michels KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. *International journal of cancer Journal international du cancer*. 2009; 124(11):2658–70.10.1002/ijc.24225 [PubMed: 19173295]
33. O'Neill KA, Murphy MF, Bunch KJ, et al. Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. *International journal of epidemiology*. 2015; 44(1):153–68.10.1093/ije/dyu265 [PubMed: 25626438]
34. Crump C, Sundquist K, Sieh W, Winkleby MA, Sundquist J. Perinatal and family risk factors for Hodgkin lymphoma in childhood through young adulthood. *American journal of epidemiology*. 2012; 176(12):1147–58.10.1093/aje/kws212 [PubMed: 23171883]
35. Crump C, Sundquist K, Sieh W, Winkleby MA, Sundquist J. Perinatal and family risk factors for non-Hodgkin lymphoma in early life: a Swedish national cohort study. *Journal of the National Cancer Institute*. 2012; 104(12):923–30.10.1093/jnci/djs225 [PubMed: 22623506]
36. Hjalgrim LL, Westergaard T, Rostgaard K, et al. Birth weight as a risk factor for childhood leukemia: a meta-analysis of 18 epidemiologic studies. *American journal of epidemiology*. 2003; 158(8):724–35. [PubMed: 14561661]
37. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nature reviews. Cancer*. 2004; 4(7):505–18. nrc1387 [pii]. 10.1038/nrc1387 [PubMed: 15229476]
38. Tower RL, Spector LG. The epidemiology of childhood leukemia with a focus on birth weight and diet. *Crit Rev Clin Lab Sci*. 2007; 44(3):203–42. 776296428 [pii]. 10.1080/10408360601147536 [PubMed: 17453918]
39. McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. Birth weight, maternal weight and childhood leukaemia. *British journal of cancer*. 2006; 94(11):1738–44.10.1038/sj.bjc.6603173 [PubMed: 16736025]
40. Hjalgrim LL, Rostgaard K, Hjalgrim H, et al. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. *Journal of the National Cancer Institute*. 2004; 96(20): 1549–56. 96/20/1549 [pii]. 10.1093/jnci/djh287 [PubMed: 15494605]
41. Johnson KJ, Soler JT, Puumala SE, Ross JA, Spector LG. Parental and infant characteristics and childhood leukemia in Minnesota. *BMC pediatrics*. 2008; 8:7.10.1186/1471-2431-8-7 [PubMed: 18298855]
42. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. *American journal of epidemiology*. 2002; 155(7):603–13. [PubMed: 11914187]
43. Ma X, Metayer C, Does MB, Buffler PA. Maternal pregnancy loss, birth characteristics, and childhood leukemia (United States). *Cancer causes & control: CCC*. 2005; 16(9):1075–83.10.1007/s10552-005-0356-9 [PubMed: 16184473]
44. Rudant J, Orsi L, Monnereau A, et al. Childhood hodgkin's lymphoma, non-Hodgkin's lymphoma and factors related to the immune system: the Escale study (SFCE). *International journal of cancer. Journal international du cancer*. 2010.10.1002/ijc.25862
45. Johnson KJ, Carozza SE, Chow EJ, et al. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiology*. 2009; 20(4):475–83.10.1097/EDE.0b013e3181a5a332 [PubMed: 19373093]
46. Zack M, Adami HO, Ericson A. Maternal and perinatal risk factors for childhood leukemia. *Cancer research*. 1991; 51(14):3696–701. [PubMed: 2065325]
47. Shu XO, Gao YT, Brinton LA, et al. A population-based case-control study of childhood leukemia in Shanghai. *Cancer*. 1988; 62(3):635–44. [PubMed: 3164642]
48. Westergaard T, Andersen PK, Pedersen JB, et al. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. *Journal of the National Cancer Institute*. 1997; 89(13):939–47. [PubMed: 9214673]
49. Centre for Epidemiology. The Swedish Medical Birth Registry--a summary of content and quality. The National Board of Health and Welfare; Stockholm: 2003.
50. Centre for Epidemiology. Cancer Incidence in Sweden 2011. The National Board of Health and Welfare; Stockholm: 2011.

Figure 1. Sinusoidal Poisson regression results for association between birthdate and acute myeloid leukemia (AML) in childhood through young adulthood, adjusted for birth year and sex ($P<0.001$ for overall seasonal association). Harmonic displacement represents the log rate ratio for a given time point relative to the mean rate over the entire calendar year.

Table 1
Incidence rates for acute myeloid leukemia (AML) by age and sex (1973–2010)

Age (years)	Total			Males			Females		
	Cases	P-Y ^a	Rate ^b	Cases	P-Y ^a	Rate ^b	Cases	P-Y ^a	Rate ^b
0–4	84	17.2	4.8	34	8.8	3.7	50	8.4	6.0
5–9	40	14.8	2.7	17	7.6	2.2	23	7.2	3.2
10–14	54	12.5	4.3	37	6.4	5.8	17	6.1	2.8
15–19	50	10.1	4.9	34	5.2	6.5	16	4.9	3.3
20–24	37	7.3	5.1	20	3.7	5.4	17	3.5	4.8
25–29	28	4.8	5.8	18	2.5	7.3	10	2.3	4.3
30–38	22	3.0	7.3	8	1.6	5.1	14	1.5	9.6
0–14	178	44.5	4.0	88	22.8	3.8	90	21.6	4.2
15–38	137	25.2	5.4	80	13.0	6.2	57	12.2	4.7
Overall	315	69.7	4.5	168	35.8	4.7	147	33.9	4.3

^aPerson-years in millions.

^bIncidence rate per million person-years.

Table 2

Incidence of acute myeloid leukemia (AML) in 1973–2010 by season or month of birth

	Total Births		AML cases	
	N (%)	P-Y ^a	n (%)	Rate ^b
Overall	3,569,333 (100.0)	69.7	315 (100.0)	4.5
Spring	990,165 (27.7)	19.8	90 (28.6)	4.6
March	334,590 (9.4)	6.7	42 (13.3)	6.2
April	331,325 (9.3)	6.6	22 (7.0)	3.3
May	324,250 (9.1)	6.4	26 (8.3)	4.1
Summer	915,319 (25.6)	17.6	60 (19.0)	3.4
June	305,058 (8.6)	5.9	24 (7.6)	4.0
July	309,857 (8.7)	5.9	20 (6.3)	3.4
August	300,404 (8.4)	5.8	16 (5.1)	2.8
Fall	821,829 (23.0)	15.7	69 (21.9)	4.4
September	291,008 (8.2)	5.6	26 (8.3)	4.6
October	278,367 (7.8)	5.3	25 (7.9)	4.7
November	252,454 (7.1)	4.8	18 (5.7)	3.8
Winter	842,020 (23.6)	16.6	96 (30.5)	5.8
December	253,414 (7.1)	4.8	26 (8.3)	5.4
January	297,035 (8.3)	5.9	32 (10.2)	5.4
February	291,571 (8.2)	5.8	38 (12.1)	6.5

^aPerson-years in millions.^bIncidence rate per million person-years.

Adjusted incidence rate ratios for associations between perinatal or familial characteristics and acute myeloid leukemia (AML) in 1973–2010

Table 3

	Total population N (%)	AML cases n (%)	Adjusted Model 1 ^a			Adjusted Model 2 ^b		
			IRR	95% CI	P	IRR	95% CI	P
Age at diagnosis (years)								
<10		124 (39.4)						
10–19		104 (33.0)						
20		87 (27.6)						
Sex								
Female	1,734,966 (48.6)	147 (46.7)	1.00			1.00		
Male	1,834,367 (51.4)	168 (53.3)	1.08	0.87, 1.35	0.49	1.08	0.87, 1.35	0.50
Season of birth								
Spring (Mar–May)	990,165 (27.7)	90 (28.6)	1.36	0.98, 1.89	0.06	1.37	0.99, 1.90	0.06
Summer (Jun–Aug)	915,319 (25.6)	60 (19.1)	1.00			1.00		
Fall (Sep–Nov)	821,829 (23.0)	69 (21.9)	1.28	0.90, 1.80	0.17	1.28	0.90, 1.80	0.17
Winter (Dec–Feb)	842,020 (23.6)	96 (30.5)	1.72	1.25, 2.38	0.001	1.73	1.25, 2.39	0.001
Fetal growth (SD)								
<−1	647,584 (18.1)	68 (21.6)	1.26	0.96, 1.67	0.10	1.22	0.92, 1.62	0.16
−1 to <1	2,384,285 (66.8)	186 (59.1)	1.00			1.00		
1	537,464 (15.1)	61 (19.4)	1.54	0.98, 2.43	0.06	1.49	1.11, 1.98	0.007
Per SD (trend test)			0.98	0.88, 1.09	0.69	0.99	0.89, 1.10	0.80
Gestational age at birth (weeks)								
<37	206,387 (5.8)	14 (4.4)	0.80	0.47, 1.37	0.41	0.77	0.45, 1.33	0.35
37–41	3,064,550 (85.9)	263 (83.5)	1.00			1.00		
42	298,396 (8.4)	38 (12.1)	1.37	0.97, 1.93	0.07	1.38	0.98, 1.95	0.06
Per week (trend test)			1.11	1.03, 1.18	0.003	1.11	1.04, 1.19	0.002
Birth weight (g)								
<2500	149,020 (4.2)	10 (3.2)	0.78	0.41, 1.47	0.44	0.85	0.41, 1.79	0.68
2500–3999	2,777,911 (77.8)	242 (76.8)	1.00			1.00		
4000	642,402 (18.0)	63 (20.0)	1.16	0.88, 1.53	0.29	1.11	0.83, 1.47	0.48
Per 1000 g (trend test)			1.16	0.95, 1.41	0.15	1.10	0.88, 1.38	0.40

	Total population N (%)	AML cases n (%)	Adjusted Model 1 ^a			Adjusted Model 2 ^b		
			IRR	95% CI	P	IRR	95% CI	P
Birth length (cm)								
<48	359,182 (10.1)	26 (8.3)	0.82	0.55, 1.23	0.34	0.86	0.55, 1.34	0.51
48–52	2,600,085 (72.9)	231 (73.3)	1.00			1.00		
53	576,918 (16.2)	56 (17.8)	1.11	0.83, 1.48	0.50	1.06	0.79, 1.43	0.70
Unknown	33,148 (0.9)	2 (0.6)	0.78	0.19, 3.13	0.72	0.83	0.20, 3.42	0.79
Per cm (trend test)			1.03	0.99, 1.08	0.17	1.02	0.97, 1.08	0.38
Birth order								
1	1,827,129 (51.2)	171 (54.3)	1.00			1.00		
2	1,200,398 (33.6)	107 (34.0)	1.05	0.82, 1.34	0.72	1.05	0.82, 1.34	0.72
3	541,806 (15.2)	37 (11.8)	0.87	0.60, 1.25	0.44	0.87	0.60, 1.25	0.44
Per higher category (trend test)			0.99	0.86, 1.14	0.87	0.99	0.86, 1.14	0.87
Maternal age at birth (years)								
<20	83,987 (2.4)	15 (4.8)	1.76	1.02, 3.02	0.04	1.48	0.85, 2.56	0.17
20–24	678,027 (19.0)	67 (21.3)	1.02	0.76, 1.39	0.87	0.94	0.69, 1.27	0.67
25–29	1,251,348 (35.1)	112 (35.6)	1.00			1.00		
30–34	1,033,763 (29.0)	82 (26.0)	0.98	0.74, 1.31	0.90	1.03	0.77, 1.37	0.87
35	518,097 (14.5)	38 (12.1)	0.97	0.67, 1.40	0.86	1.00	0.69, 1.46	0.98
Unknown	4,111 (0.1)	1 (0.3)	6.03	0.82, 44.33	0.08	6.59	0.88, 49.41	0.07
Per higher category (trend test)			0.94	0.84, 1.05	0.28	0.99	0.88, 1.11	0.89
Paternal age at birth (years)								
<20	16,943 (0.5)	3 (1.0)	1.75	0.55, 5.52	0.34	1.51	0.48, 4.79	0.48
20–24	326,974 (9.2)	31 (9.8)	0.92	0.61, 1.37	0.67	0.84	0.56, 1.27	0.41
25–29	1,021,644 (28.6)	100 (31.8)	1.00			1.00		
30–34	1,161,177 (32.5)	101 (32.1)	0.98	0.74, 1.29	0.87	1.03	0.78, 1.36	0.86
35	1,014,007 (28.4)	77 (24.4)	0.92	0.68, 1.25	0.61	0.97	0.71, 1.32	0.84
Unknown	28,588 (0.8)	3 (1.0)	1.26	0.40, 3.97	0.70	1.27	0.40, 4.03	0.68
Per higher category (trend test)			0.97	0.87, 1.09	0.67	1.01	0.90, 1.14	0.81
Both parents born in Sweden								
Yes	2,852,520 (79.9)	254 (80.6)	1.00			1.00		
No	716,813 (20.1)	34 (10.8)	1.04	0.79, 1.38	0.77	1.03	0.76, 1.38	0.87

	Total population N (%)	AML cases n (%)	Adjusted Model 1 ^a			Adjusted Model 2 ^b		
			IRR	95% CI	P	IRR	95% CI	P
Maternal education (years)								
9	674,884 (18.9)	86 (27.3)	1.23	0.93, 1.63	0.15	1.24	0.93, 1.64	0.14
10–11	1,149,737 (32.2)	114 (36.2)	1.00			1.00		
12–14	1,044,760 (29.3)	71 (22.5)	0.81	0.60, 1.10	0.18	0.81	0.60, 1.09	0.17
15	554,418 (15.5)	30 (9.5)	0.67	0.45, 1.01	0.06	0.67	0.44, 1.01	0.05
Unknown	145,534 (4.1)	14 (4.4)	0.93	0.54, 1.63	0.81	0.95	0.54, 1.65	0.85
Per higher category (trend test)			0.82	0.72, 0.92	0.001	0.81	0.72, 0.92	0.001
Paternal education (years)								
9	767,366 (21.5)	89 (28.3)	1.14	0.86, 1.53	0.36	1.10	0.82, 1.47	0.53
10–11	1,128,568 (31.6)	101 (32.1)	1.00			1.00		
12–14	959,668 (26.9)	67 (21.3)	0.84	0.62, 1.15	0.28	0.91	0.66, 1.25	0.57
15	537,725 (15.1)	41 (13.0)	0.90	0.63, 1.30	0.58	1.14	0.76, 1.70	0.54
Unknown	176,006 (4.9)	17 (5.4)	0.97	0.58, 1.63	0.92	0.99	0.58, 1.68	0.96
Per higher category (trend test)			0.90	0.80, 1.01	0.08	0.97	0.85, 1.10	0.62

^aAdjusted for birth year (modeled simultaneously as continuous and categorical variables) and sex.

^bAdjusted for birth year (as noted above), sex, season of birth, fetal growth (categorical), gestational age at birth (continuous), and maternal education. Birth weight and birth length 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. Missing data were excluded for trend tests.

CI = confidence interval, IRR = incidence rate ratio.