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Non-chromosomal birth defects and risk of childhood leukemia: an assessment in 15,000 leukemia cases and 46,000 controls from the Childhood Cancer and Leukemia International Consortium

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Manuscripts

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3 **Non-chromosomal birth defects and risk of childhood leukemia: an assessment in 15,000**
4 **leukemia cases and 46,000 controls from the Childhood Cancer and Leukemia**
5 **International Consortium**
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17 acute myeloid leukemia
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20 **Abbreviations:** ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CI:
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22 confidence interval; CLIC: Childhood Cancer and Leukemia International Consortium; FDR:
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24 false discovery ratio; NBDPN: National Birth Defects Prevention Network; OR: odds ratio
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26 **Conflict of interest:** The authors declare no potential conflicts of interest
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33 34 **Novelty and Impact**

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36 Little is known about the potential etiologic role non-chromosomal birth defects have on
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38 childhood leukemia risk. Therefore, we sought to identify associations between leukemia and
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40 non-chromosomal birth defects in a pooled cohort from studies participating in the Childhood
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42 Cancer and Leukemia International Consortium. Certain birth defects were strongly associated
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44 with increased leukemia risk. These associations could point to novel genetic and environmental
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46 factors associated with birth defects that could also increase leukemia susceptibility.
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Abstract

Although recent studies have demonstrated associations between non-chromosomal birth defects and several pediatric cancers, less is known about their role on childhood leukemia susceptibility. Using data from the Childhood Cancer and Leukemia International Consortium, we evaluated associations between non-chromosomal birth defects and childhood leukemia. Pooling data from 18 questionnaire-based studies and three registry-based studies across 13 countries, we used multivariable logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between a spectrum of birth defects and leukemia. Our analyses included acute lymphoblastic leukemia (ALL, n=13,115) and acute myeloid leukemia (AML, n=2,120) cases, along with 46,172 controls. We used the false discovery rate to account for multiple comparisons. In the questionnaire-based studies, the prevalence of birth defects was 5% among cases versus 4% in controls, whereas, in the registry-based studies, the prevalence was 11% among cases versus 7% in controls. In pooled adjusted analyses, there were several notable associations, including: 1) digestive system defects and ALL (OR=2.70, 95% CI: 1.46-4.98); 2) congenital anomalies of the heart and circulatory system and AML (OR=2.86, 95% CI: 1.81-4.52); and 3) nervous system defects and AML (OR=4.23, 95% CI: 1.50-11.89). Effect sizes were generally larger in registry-based studies. Overall, our results could point to novel genetic and environmental factors associated with birth defects that could also increase leukemia susceptibility. Additionally, differences between questionnaire- and registry-based studies point to the importance of complementary sources of birth defect phenotype data when exploring these associations.

Introduction

Leukemia accounts for around a third of all cancers diagnosed in individuals younger than 15 years of age, with acute lymphoblastic leukemia (ALL) as the most common (~75%) subtype and acute myeloid leukemia (AML) as the second most common (~15%).^{1, 2} While five-year survival for children with ALL and AML has improved over the past several decades approaching 90% in some settings,^{3, 4} survival remains poor for those with relapsed disease. Furthermore, survivors experience an excess risk of adverse health outcomes related to their cancer diagnosis and treatment.⁵ Despite the incidence and clinical importance of these malignancies, outside of the approximately 5% of cases that are due to genetic syndromes, a majority of cases are of unknown etiologies.⁶

One of the strongest genetic risk factors for developing ALL and AML is being born with trisomy 21 (i.e., Down syndrome).⁷⁻⁹ Compared to their contemporaries, children with Down syndrome are 20-times more likely to develop ALL and 200-times more likely to develop AML, respectively.¹⁰ This and certain other chromosomal anomalies are well-established risk factors for ALL and AML; however, much less is known about the potential etiologic role of non-chromosomal birth defects, which affect approximately 6% of pregnancies worldwide.¹¹

There is strong evidence indicating non-chromosomal birth defects are associated with a range of pediatric solid tumors.^{10, 12-24} However, associations between specific non-chromosomal birth defects and leukemia are less clear. Therefore, we sought to comprehensively evaluate the association between non-chromosomal birth defects and leukemia using data from the Childhood Cancer and Leukemia International Consortium (CLIC).²⁵ This is a consortium of leukemia-focused questionnaire- and registry-based case-control studies (which is now open to other pediatric tumors as well). CLIC was established in 2007 with the goal of overcoming the limitations of single epidemiological studies and allowing the assessment of relatively infrequent potential risk factors, including specific non-chromosomal birth defects.

Methods

Study Subjects

Comprehensive descriptions of CLIC have been published previously.²⁵⁻³¹ Data for our pooled analyses were provided from 18 case-control and three registry linkage studies in 13 countries. Each eligible study provided both birth defect and leukemia data. Depending on the study design, questionnaires, hospital records, birth records, population-based birth defect registries, and cancer registries were used to identify cases and select controls. Children born with recognized chromosomal anomalies and/or single gene disorders (as defined below) were excluded from this assessment. Our overall study population consisted of 46,172 controls and 15,235 acute leukemia cases (ALL n=13,115 and AML n=2,120). In separate analyses, we evaluated all cases (ALL or AML) diagnosed at ≤ 12 months of age (i.e., infant leukemia, n=1,152). Prior to contributing data, all studies were approved by their respective institutional review boards or ethics committees.

Birth Defects Diagnoses

Birth defect diagnoses were provided by: 1) diagnosis name; 2) codes using the Eighth, Ninth, or Tenth Revisions of the World Health Organization's International Classification of Diseases, Clinical Modification (i.e., ICD-8, ICD-9, and ICD-10); or 3) codes using the Western Australian Register of Developmental Anomalies (WARDA).³² All diagnoses were converted to the Centers for Disease Control and Prevention (CDC) modification of the British Paediatric Association Classification of Diseases (BPA) using coding-specific crosswalks obtained from the National Birth Defects Prevention Network (NBDPN) and WARDA. For this assessment, we evaluated major birth defects included as part of the NBDPN annual report or the National Birth Defects Prevention Study.^{33, 34}

Study Variables

In addition to data on birth defects and leukemia, the following variables were obtained from each study: child's sex, age at leukemia diagnosis (cases), age at study entry (controls) histological subtype, ALL immunophenotype, year of birth, birthweight, gestational age, child's race/ethnicity, plurality, as well as maternal age at child's birth and maternal education. Data were standardized across studies.

Statistical Methods

We used frequencies and percentages to describe demographic and clinical characteristics among the study population. We used logistic regression models to calculate odds ratios (OR) and 95% confidence intervals (CI) for each birth defect-leukemia combination, while adjusting for the following variables: study site, sex, birthweight (<2,500; 2,500-3,999; >3,999 grams), gestational age (preterm [<37 weeks]; term [\geq 37 weeks]), maternal age (<25; 25-29; 30-34; 35-39; \geq 40 years), birth year, and child's race/ethnicity (non-Hispanic White; non-Hispanic Black; Hispanic; and other). These variables were selected based on previous assessments and to be consistent with other studies evaluating associations between non-chromosomal birth defects and pediatric cancer.^{10, 26-31} However, unadjusted ORs and 95% CIs were also calculated and presented.

We first evaluated the associations between leukemia subtypes of interest (ALL, AML, and infant leukemia) and specific birth defects (e.g., ventricular septal defect), as well as larger birth defect groupings (e.g., congenital anomalies of the heart and circulatory system). Based on standard data suppression rules,¹⁰ our analyses were restricted to patterns where there were \geq 5 co-occurring cases. We used the false discovery rate (FDR) to account for multiple comparisons.³⁵ To evaluate the impact of differences in birth defect reporting, candidate associations were stratified by study design (i.e., questionnaire- vs. registry-based studies). Lastly, we evaluated the association between number of birth defects (0 defects, 1 defect, \geq 2

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3 defects) and leukemia risk. All statistical analyses were performed using Stata 15.0 (StataCorp
4 LP, College Station, TX).
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9 **Results**

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11 Overall, there were 46,172 controls and 15,235 cases: 13,115 ALL; 2,120 AML; 1,152
12 infant (Table 1). The distribution of demographic characteristics across cases and controls was
13 largely consistent with some exceptions. Overall, the prevalence of non-chromosomal birth
14 defects was 5.8% in both cases and controls (Table 2). However, as described below, there
15 were some notable differences for ALL, AML, and infant leukemia by birth defect group and by
16 specific birth defects.
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26 *Non-Chromosomal Birth Defects and ALL*

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28 Among the 10 non-chromosomal birth defect groups evaluated (Table 2), three were
29 significantly associated with ALL in adjusted models after correcting for multiple comparisons: 1)
30 congenital anomalies of the heart and circulatory system (OR=1.46, 95% CI: 1.10-1.95); 2)
31 congenital anomalies of the digestive system (OR=2.70, 95% CI: 1.46-4.98); and 3) congenital
32 anomalies of the skin (OR=1.43, 95% CI: 1.11-1.85). While hypospadias was associated with
33 ALL (OR=2.12, 95% CI: 1.16-3.85), it was not statistically significant after correcting for multiple
34 comparisons ($p_{\text{FDR}}=0.066$). The only specific birth defect associated with ALL after correcting for
35 multiple comparisons was congenital cataracts (OR=18.62, 95% CI: 4.36-79.49, $p_{\text{FDR}}=0.002$).
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45 To account for differences in birth defect reporting, associations were then stratified by
46 study design (i.e., questionnaire- vs. registry-based). The direction and magnitude of the effect
47 estimates were consistent for congenital anomalies of the digestive system and congenital
48 anomalies of the skin (Table 3). This was not the case for congenital anomalies of the heart and
49 circulatory system where the OR in questionnaire-based studies was 0.84 (95% CI: 0.55-1.28)
50 compared to 2.36 (95% CI: 1.66-3.34) in registry-based studies.
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Non-Chromosomal Birth Defects and AML

Three non-chromosomal birth defect groups were significantly associated with AML in adjusted models after correcting for multiple comparisons (Table 2): 1) congenital anomalies of the nervous system (OR=4.23, 95% CI: 1.50-11.89); 2) congenital anomalies of the heart and circulatory system (OR=2.86, 95% CI: 1.81-4.52); and 3) congenital anomalies of the skin (OR=0.36, 95% CI: 0.18-0.70). The OR for congenital anomalies of the skin was <1.0, suggesting children with AML were less likely to have these non-chromosomal birth defects compared to controls. None of the specific birth defects with ≥ 5 co-occurring cases was significantly associated with AML.

When numbers were sufficient to conduct sensitivity analyses for AML stratified by study design, results were consistent in terms of direction of effect (Table 4); however, effect estimates from the registry-based studies were larger. For example, associations with congenital anomalies of the heart and circulatory system were stronger in registry-based studies (OR=5.39, 95% CI: 3.14-9.24) compared to questionnaire-based studies (OR=1.28, 95% CI: 0.61-2.67).

Non-Chromosomal Birth Defects and Infant Leukemia

While there were no significant associations between non-chromosomal birth defects and infant leukemia after correcting for multiple comparisons, there was a strong association with congenital anomalies of the digestive system and infant leukemia (OR=4.55, 95% CI: 1.06-19.62), which was stronger when evaluating effects in questionnaire-based studies (OR=7.31, 95% CI: 1.20-44.63) (data not shown). However, these associations were based on a small number of co-occurring cases ($n=6$). There were not enough observations to evaluate specific associations in registry-based studies.

Risk of Leukemia by Number of Birth Defects

While there was a significant p-for-trend when evaluating the association between increasing number of non-chromosomal birth defects and ALL ($p_{\text{trend}}=0.006$), the association was neither strong nor statistically significant for children with ≥ 2 defects ($OR_{\text{ALL}}=1.32$, 95% CI: 0.90-1.94; Table 5). For both AML and infant leukemia, risk was greater for children with ≥ 2 birth defects ($OR_{\text{AML}}=1.96$, 95% CI: 1.10-3.46 and $OR_{\text{infant leukemia}}=1.71$, 95% CI: 0.93-1.35) compared to children with 1 defect ($OR_{\text{AML}}=0.92$, 95% CI: (0.72-1.18 and $OR_{\text{infant leukemia}}=0.97$, 95% CI: 0.69-1.35) (Table 5).

Discussion

In this large assessment of leukemia risk among children with non-chromosomal birth defects, which included >15,000 cases and >46,000 controls, we report several birth defect-leukemia associations including: 1) congenital anomalies of the digestive system-ALL; 2) congenital cataracts-ALL; 3) anomalies of the skin-ALL; 4) congenital anomalies of the heart-ALL; 5) congenital anomalies of the heart-AML; and 6) congenital anomalies of the nervous system-AML. Several of our observations are consistent with previous findings,¹⁰ including anomalies of the skin-ALL and congenital anomalies of the heart and circulatory system-AML.

While these associations are notable, our study points to two important findings in relation to non-chromosomal birth defects and leukemia susceptibility. First, there are not as many associations reported for leukemia as with some solid tumors (e.g., germ cell tumors are associated with a larger spectrum of birth defects).^{10, 21} Second, associations are not as strong as reported for other pediatric cancers (e.g., neuroblastoma).^{10, 17, 19, 20} However, some of these differences could be due to the variability in birth defect reporting between questionnaire-based studies and registry-based studies.

In our assessment, the prevalence of birth defects was higher in registry-based studies compared to questionnaire-based studies. Additionally, birth defect-leukemia associations from

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3 registry-based studies were generally stronger compared to questionnaire-based studies. This
4 suggests to the likelihood of underreporting in questionnaire-based studies, as well as the
5 potential for differential reporting. In fact, there are reported differences in birth defect reporting
6 across many modalities (e.g., birth certificates, questionnaires, active surveillance).³⁶⁻³⁹ Because
7 of that, it is important to leverage multiple sources of data when evaluating these conditions and
8 their impact on cancer risk. Future studies of leukemia risk in children with non-chromosomal
9 birth defects should utilize data from expanded registry linkages. Nevertheless, our assessment
10 yielded new insights regarding birth defect-leukemia associations.
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20 We found generally consistent associations for congenital anomalies of the digestive
21 system and ALL (while not statistically significant, similar patterns were seen for AML and infant
22 leukemia); congenital cataracts and ALL; congenital anomalies of the nervous system and AML;
23 and congenital anomalies of the heart and circulatory system for both ALL and AML. These
24 observed associations could be due to a range of factors. First, each of these structural birth
25 defects is more common in children with Down syndrome.⁴⁰ Although we excluded children with
26 Down syndrome from this assessment, it is possible that genetic variation on chromosome 21
27 could explain the co-occurrence of these conditions, or that cases of Down syndrome were
28 misclassified.^{7, 41} Second, it is also possible that these associations could be due to other known
29 syndromes that were not diagnosed in these individuals. For example, children with Fanconi
30 anemia, an AML predisposition syndrome, are more likely to have heart and gastrointestinal
31 defects compared to unaffected children.⁴² Third, it is possible that these associations could
32 represent “yet-to-be-discovered” cancer predisposition syndromes or shared genetic effects
33 across phenotypes (i.e., pleiotropy) that could be leveraged to discover novel genetic variants
34 underlying the occurrence of both birth defects and leukemia.
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51 A largely unexplored potential explanation for the overlap between non-chromosomal
52 birth defects and leukemia, as well as other pediatric cancers, is the role of non-genetic *in utero*
53 factors and exposures that could lead to both phenotypes (e.g., maternal diabetes) or postnatal
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3 exposures that children with birth defects are more likely to receive (e.g., diagnostic procedures
4 that involve radiation).²¹ However, outside of a recent assessment evaluating the impact of *in*
5 *vitro* fertilization (IVF) on the co-occurrence of birth defects and pediatric cancer, which reported
6 that IVF-exposed children were more likely to develop both birth defects and cancer compared
7 to naturally conceived children,⁴³ there have been few attempts to evaluate the role of various
8 exposures on the overlap between these conditions.
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16 Our study must be considered in the light of certain limitations. First, and as noted, it is
17 possible that birth defects may have been incompletely ascertained. Our study relied separately
18 on self-reported birth defects (questionnaire-based studies) and independent assessment of
19 birth defects (registry-based studies). Each of these approaches has limitations.²¹ However, for
20 defects with sufficient numbers to evaluate associations by study design, the direction of effects
21 were largely consistent, with findings from registry-based studies being stronger. Also, while
22 incomplete ascertainment of birth defects may bias our effect estimates, most studies of birth
23 defects and cancer risk (independent of birth defect ascertainment method) have comparable
24 findings.²¹ Even in our large study, sample size issues or data availability limited our ability to
25 evaluate subtypes based on immunophenotype, cytogenetic features, or other genomic
26 characteristics. This could be particularly important as there is evidence that etiologic factors
27 differ by tumor characteristics.⁴⁴ Finally, an issue inherent in studies of birth defects and cancer is
28 that children diagnosed with cancer may undergo additional diagnostic scrutiny compared to
29 children without a malignancy, which results in the increased identification of birth defects in
30 cases compared to controls.¹⁰ However, previous assessments have indicated this is likely not a
31 driver of observed birth defect-pediatric cancer associations.¹⁰
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49 The present study has considerable strengths, most notably its large sample size
50 (>15,000 cases), which enabled us to evaluate specific non-chromosomal birth defects that
51 have not been included in previous assessments. Another strength of our assessment is the
52 inclusion of different study designs (questionnaire- versus registry-based) as well as leukemia
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3 types (ALL, AML, and infant acute leukemia), which allowed us to conduct sensitivity analyses
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5 to evaluate differences by case ascertainment method, helping us to confirm associations.
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7 Lastly, as this is an international study, we included diverse populations from multiple settings
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9 and geographical locations.
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11 In conclusion, while associations between non-chromosomal birth defects and leukemia
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13 risk were observed, they were not as numerous or strong as those reported for other less
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15 common pediatric cancers. However, these findings contribute to our understanding of leukemia
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17 risk. Specifically, future assessments could leverage associations related to the role of
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19 anomalies of the heart, skin, and digestive system to evaluate the role of shared genetic effects
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21 and non-genetic exposures, thereby yielding new insights into the overlap between non-
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23 chromosomal birth defects and acute leukemia, as well as acute leukemia susceptibility in
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25 general.
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47 Where authors are identified as personnel of the International Agency for Research on Cancer/
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Table 1. Demographics of Subjects from the Childhood Cancer and Leukemia International Consortium

	Controls (N=46,172)	Cases (N=15,235)	ALL^a (N=13,115)	AML^b (N=2,120)	Infant^c (N=1,152)
Study Site					
Australia (Aus-ALL)	1,246 (2.7)	387 (2.5)	387 (2.6)	0 (0.0)	10 (0.9)
Brazil	541 (1.3)	578 (3.8)	428 (3.2)	150 (7.1)	135 (11.7)
Canada	790 (1.7)	753 (4.9)	753 (5.7)	0 (0.0)	24 (2.1)
Costa Rica	578 (1.2)	291 (1.9)	251 (1.9)	40 (1.9)	13 (1.1)
Denmark	15,871 (34.4)	1,582 (10.4)	1,333 (10.1)	249 (11.8)	86 (7.5)
Egypt	351 (0.8)	296 (1.9)	296 (2.2)	0 (0.0)	5 (0.4)
France (Adele)	288 (0.6)	275 (1.8)	240 (1.8)	35 (1.7)	16 (1.4)
France (Electre)	567 (1.2)	458 (3.0)	399 (3.0)	59 (2.8)	11 (0.9)
France (Escale)	1,681 (3.6)	738 (4.8)	641 (4.8)	97 (4.6)	29 (2.5)
France (Estelle)	1,420 (3.1)	727 (4.8)	628 (4.7)	99 (4.7)	34 (2.9)
Germany	2,056 (4.5)	720 (4.7)	622 (4.7)	98 (4.6)	44 (3.8)
Greece (NARECHEM-ST)	1,433 (3.1)	1,297 (8.5)	1,233 (9.3)	64 (3.0)	41 (3.6)
Italy (MORE)	528 (1.1)	110 (0.7)	106 (0.8)	4 (0.2)	7 (0.6)
Italy (SETIL)	1,044 (2.2)	677 (4.4)	596 (4.5)	81 (3.8)	30 (2.6)
New Zealand (NZCCS)	303 (0.7)	118 (0.8)	96 (0.7)	22 (1.0)	5 (0.4)
United Kingdom (UKCCS)	7,610 (16.5)	1,672 (11.0)	1,437 (10.9)	235 (11.1)	90 (7.8)
USA (California Childhood Leukemia Study)	1,225 (2.7)	944 (6.2)	813 (6.1)	131 (6.2)	45 (3.9)
USA (Children's Cancer Group)	2,596 (5.6)	2,428 (15.9)	1,911 (14.4)	517 (24.3)	34 (2.9)
USA (Children's Cancer Group – AE24)	324 (0.7)	433 (2.8)	262 (2.0)	171 (8.0)	440 (38.2)
USA (Texas)	426 (0.9)	347 (2.3)	334 (3.3)	13 (0.8)	35 (3.0)
USA (Washington)	5,294 (11.5)	404 (2.7)	349 (2.6)	55 (2.6)	18 (1.6)
Sex					
Male	24,909 (53.9)	8,380 (55.0)	7,283 (55.5)	1,097 (51.8)	563 (48.9)
Female	21,262 (46.1)	6,854 (45.0)	5,831 (44.5)	1,023 (48.2)	589 (51.1)
Missing	1	1	1	0	0
Birthweight (in grams)					
<2500 grams	2,515 (5.9)	768 (5.2)	659 (5.2)	109 (5.3)	55 (4.9)
2500-3999 grams	34,835 (81.0)	11,927 (81.1)	10,241 (80.9)	1,686 (82.3)	915 (81.7)
>3999 grams	5,636 (13.1)	2,009 (13.7)	1,756 (13.9)	253 (12.4)	150 (13.4)
Missing	3,186	531	459	72	32
Maternal Age					
<25 years	12,410 (27.2)	4,170 (27.7)	3,522 (27.2)	648 (30.8)	295 (26.4)
25-29 years	16,268 (35.6)	5,147 (34.2)	4,431 (34.3)	716 (34.0)	341 (30.5)
30-34 years	11,647 (25.5)	3,907 (26.0)	3,408 (26.3)	499 (23.7)	324 (28.9)
35-39 years	4,52 (9.9)	1,516 (10.1)	1,314 (10.2)	202 (9.6)	129 (11.5)
≥40 years	872 (1.9)	303 (2.0)	264 (2.0)	39 (1.9)	31 (2.8)
Missing	473	192	176	16	32
Child Race/Ethnicity					

	Controls (N=46,172)	Cases (N=15,235)	ALL^a (N=13,115)	AML^b (N=2,120)	Infant^c (N=1,152)
Non-Hispanic White	38,145 (89.3)	11,247 (80.5)	9,644 (80.6)	1,603 (79.8)	810 (76.0)
Non-Hispanic Black	718 (1.7)	350 (2.5)	269 (2.3)	81 (4.0)	60 (5.6)
Hispanic	1,693 (4.0)	1,207 (8.6)	1,036 (8.7)	171 (8.5)	114 (10.7)
Other	2,181 (5.1)	1,170 (8.4)	1,015 (8.5)	155 (7.7)	82 (7.7)
Missing	3,435	1,261	1,151	110	86
Gestational Age^d					
Preterm	2,425 (6.4)	952 (7.3)	827 (7.4)	125 (6.7)	68 (6.7)
Term	35,421 (93.6)	12,047 (92.7)	10,295 (92.6)	1,752 (93.3)	942 (93.3)
Missing	8,326	2,236	1,993	243	142
Maternal Education					
Less than Secondary Education	7,471 (30.1)	4,042 (32.2)	3,499 (32.3)	543 (31.6)	231 (22.9)
Completed Secondary Education	9,360 (37.7)	4,289 (34.2)	3,586 (33.1)	703 (40.9)	292 (28.9)
Above Secondary Education	7,983 (32.2)	4,227 (33.7)	3,752 (34.6)	475 (27.6)	489 (48.3)
Missing	21,358	2,677	2,278	399	140
Plurality					
Singleton	42,740 (96.8)	13,423 (95.9)	11,541 (95.5)	1,882 (98.5)	944 (97.4)
Multiple	1,408 (3.2)	568 (4.1)	539 (4.5)	29 (1.5)	25 (2.6)
Missing	2,024	1,244	1,035	209	183
Age at Dx./Inclusion (Mean/SD)	5.7 (4.2)	5.5 (4.0)	5.4 (3.7)	6.2 (5.3)	0.5 (0.4)

^aAcute lymphoblastic leukemia

^bAcute myeloid leukemia

^cInfant leukemia includes any leukemia case diagnosed at ≤12 months of age

^dPreterm: <37 weeks; Term: ≥37 weeks

Table 2. Risk of Childhood Leukemia by Birth Defect Group and Leukemia Subtype

	ALL ^a						AML ^b					Infant ^c				
	Controls N=46,172	Cases N=13,115					Cases N=2,120					Cases N=1,152				
	Exposed N=2,662	Exposed N=753	Unadjust ed OR* (95% CI)	Adjusted OR* (95% CI)	p	p ^{FDR}	Exposed N=129	Unadjust ed OR* (95% CI)	Adjusted OR* (95% CI)	p	p ^{FDR}	Exposed N=124	Unadjust ed OR* (95% CI)	Adjusted OR* (95% CI)	p	p ^{FDR}
Congenital anomalies of the nervous system	49 (1.8)	13 (1.7)	0.93 (0.51-1.72)	1.60 (0.77-3.31)	0.207	0.570	5 (3.9)	2.23 (0.89-5.59)	4.23 (1.50-11.89)	0.006	0.024	3 (2.4)	--	--	--	--
Congenital anomalies of the eye	73 (2.7)	31 (4.1)	1.50 (0.98-2.28)	1.55 (0.93-2.58)	0.095	0.299	5 (3.9)	1.49 (0.60-3.70)	1.75 (0.65-4.59)	0.258	0.387	2 (1.6)	--	--	--	--
Anophthalmia or microphthalmia	25 (1.0)	6 (0.7)	0.84 (0.35-2.06)	0.58 (0.17-1.98)	0.384	0.590	1 (0.8)	--	--	--	--	0 (0.0)	--	--	--	--
Congenital cataract	3 (0.1)	7 (0.9)	8.22 (2.12-31.79)	18.62 (4.36-79.49)	<0.001	0.002	0 (0.0)	--	--	--	--	0 (0.0)	--	--	--	--
Congenital anomalies of the ear, face and neck	241 (9.1)	30 (3.9)	0.44 (0.30-0.64)	0.91 (0.57-1.45)	0.684	0.836	6 (4.7)	0.54 (0.24-1.22)	1.28 (0.54-3.02)	0.570	0.664	5 (4.1)	0.83 (0.34-2.02)	1.27 (0.38-4.23)	0.700	0.900
Congenital anomalies of the respiratory system	39 (1.5)	9 (0.1)	0.81 (0.39-1.68)	0.93 (0.34-2.58)	0.894	0.790	3 (2.3)	--	--	--	--	3 (2.4)	--	--	--	--
Congenital anomalies of the heart and circulatory system	408 (15.3)	129 (17.1)	1.11 (0.91-1.36)	1.46 (1.10-1.95)	0.009	0.050	31 (24.0)	1.66 (1.15-2.40)	2.86 (1.81-4.52)	<0.001	0.001	16 (13.0)	1.58 (0.96-2.61)	1.57 (0.75-3.27)	0.227	0.681
<i>Right ventricular outflow tract defects</i>	123 (4.6)	60 (7.9)	1.72 (1.26-2.34)	0.72 (0.35-1.48)	0.366	0.590	10 (7.8)	1.77 (0.93-3.39)	1.30 (0.47-3.59)	0.608	0.664	8 (6.5)	2.62 (1.28-5.37)	1.35 (0.38-4.74)	0.641	0.900
Pulmonary valve atresia and stenosis	122 (4.6)	60 (7.9)	1.73 (1.27-2.36)	0.73 (0.35-1.50)	0.381	0.590	10 (7.8)	1.79 (0.94-3.41)	1.32 (0.48-3.64)	0.594	0.664	8 (6.5)	2.64 (1.29-5.41)	1.40 (0.39-4.98)	0.605	0.900
<i>Septal defects</i>	90 (3.4)	15 (2.0)	0.59 (0.34-1.01)	1.11 (0.60-2.04)	0.743	0.861	5 (3.9)	1.21 (0.49-2.98)	2.37 (0.85-6.66)	0.100	0.172	1 (0.8)	--	--	--	--
Ventricular septal defect	63 (2.4)	7 (0.9)	0.39 (0.18-0.85)	0.68 (0.30-1.56)	0.359	0.590	1 (0.8)	--	--	--	--	1 (0.8)	--	--	--	--

			ALL ^a				AML ^b					Infant ^c				
	Controls N=46,172	Cases N=13,115					Cases N=2,120					Cases N=1,152				
	Exposed N=2,662	Exposed N=753	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p	p ^{FDR}	Exposed N=129	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p	p ^{FDR}	Exposed N=124	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p	p ^{FDR}
Atrial septal defect	35 (1.3)	8 (1.0)	0.80 (0.37-1.73)	2.17 (0.89-5.25)	0.090	0.299	4 (3.1)	--	--	--	--	0 (0.0)	--	--	--	--
Cleft palate and cleft lip	70 (2.6)	13 (1.7)	0.65 (0.36-1.18)	0.71 (0.34-1.22)	0.348	0.590	2 (1.6)	--	--	--	--	0 (0.0)	--	--	--	--
Cleft palate without cleft lip	35 (1.3)	10 (1.3)	1.01 (0.50-2.03)	0.70 (0.29-1.62)	0.402	0.590	2 (1.6)	--	--	--	--	0 (0.0)	--	--	--	--
Congenital anomalies of the digestive system	48 (1.8)	25 (3.3)	1.84 (1.13-2.98)	2.70 (1.46-4.98)	0.002	0.022	5 (3.9)	2.27 (0.90-5.71)	3.09 (0.97-9.91)	0.057	0.114	6 (4.9)	5.03 (2.15-11.78)	4.55 (1.06-19.62)	0.042	0.378
Congenital anomalies of the genitourinary system	623 (23.4)	123 (16.3)	0.69 (0.57-0.84)	1.00 (0.78-1.27)	0.979	0.979	28 (21.7)	0.98 (0.67-1.43)	1.60 (1.02-2.51)	0.041	0.099	17 (13.8)	1.10 (0.67-1.78)	0.84 (0.40-1.76)	0.645	0.900
Renal agenesis and hypoplasia	71 (2.7)	35 (4.6)	1.74 (1.16-2.61)	1.20 (0.64-2.25)	0.572	0.787	6 (4.7)	1.84 (0.80-4.25)	0.75 (0.16-3.51)	0.719	0.719	5 (4.1)	2.83 (1.14-7.02)	0.76 (0.09-6.59)	0.804	0.905
Obstructive genitourinary defects	43 (1.6)	9 (1.1)	0.74 (0.36-1.51)	1.23 (0.55-2.74)	0.610	0.790	2 (1.6)	--	--	--	--	1 (0.8)	--	--	--	--
Hypospadias	57 (2.1)	18 (2.4)	1.08 (0.64-1.84)	2.12 (1.16-3.85)	0.015	0.066	0 (0.0)	--	--	--	--	0 (0.0)	--	--	--	--
Congenital anomalies of the musculoskeletal system	461 (17.3)	92 (12.2)	0.70 (0.56-0.88)	0.88 (0.66-1.17)	0.381	0.590	10 (7.8)	0.47 (0.25-0.88)	0.42 (0.18-0.97)	0.041	0.099	6 (4.9)	0.52 (0.23-1.16)	0.44 (0.16-1.18)	0.101	0.455
Congenital hip dislocation	79 (3.0)	12 (1.6)	0.53 (0.29-0.98)	1.01 (0.51-2.02)	0.967	0.979	1 (0.8)	--	--	--	--	1 (0.8)	--	--	--	--
Congenital anomalies of the skin	221 (8.3)	135 (17.9)	2.16 (1.74-2.68)	1.43 (1.11-1.85)	0.006	0.044	16 (12.4)	1.58 (0.95-2.63)	0.36 (0.18-0.70)	0.003	0.018	32 (26.0)	5.94 (4.08-8.65)	1.02 (0.54-1.90)	0.959	0.959

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*Adjusted for study site, sex, maternal age, birth year, birthweight, prematurity, and race/ethnicity

^aAcute lymphoblastic leukemia

^bAcute myeloid leukemia

^cInfant leukemia includes any leukemia case diagnosed at ≤ 12 months of age

For Peer Review

Table 3. Risk of ALL^a by Birth Defect Group and Study Design

	Registry-Based Studies					Questionnaire-Based Studies				
	Controls N=21,693	Cases N=1,788				Controls N=24,479	Cases N=11,327			
	Exposed N=1,623	Exposed N=186	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p	Exposed N=1,039	Exposed N=567	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p
Congenital anomalies of the nervous system	32 (2.0)	7 (3.8)	3.22 (1.58-6.56)	2.30 (0.88-6.05)	0.089	17 (1.6)	6 (1.1)	0.87 (0.37-2.01)	1.13 (0.41-3.09)	0.815
Congenital cataract	2 (0.1)	6 (3.2)	30.88 (6.23-153.11)	31.85 (6.10-166.17)	<0.001	1 (0.1)	1 (0.2)	--	--	--
Congenital anomalies of the heart and circulatory system	239 (14.7)	44 (23.7)	2.62 (1.97-3.49)	2.36 (1.66-3.35)	<0.001	169 (16.3)	85 (15.0)	1.16 (0.91-1.48)	0.84 (0.55-1.28)	0.418
Congenital anomalies of the digestive system	27 (16.6)	10 (5.4)	4.20 (2.08-8.48)	3.88 (1.63-9.19)	0.002	21 (2.0)	15 (2.6)	1.75 (0.95-3.23)	2.00 (0.89-4.52)	0.094
Congenital anomalies of the genitourinary system	445 (27.4)	41 (22.0)	1.18 (0.88-1.58)	1.08 (0.76-1.54)	0.656	178 (17.1)	82 (14.5)	1.05 (0.82-1.34)	0.92 (0.66-1.28)	0.724
Hypospadias	36 (2.2)	8 (4.3)	2.29 (1.06-4.93)	2.92 (1.33-6.40)	0.007	21 (2.0)	10 (1.8)	0.92 (0.45-1.90)	1.50 (0.64-3.53)	0.356
Congenital anomalies of the musculoskeletal system	169 (10.4)	18 (9.7)	1.26 (0.90-1.76)	1.23 (0.83-1.82)	0.295	142 (13.7)	57 (10.1)	0.84 (0.63-1.13)	0.66 (0.44-0.99)	0.046
Congenital anomalies of the skin	86 (5.2)	15 (8.1)	1.92 (1.12-3.27)	1.83 (0.97-3.48)	0.063	135 (13.0)	120 (21.2)	1.85 (1.46-2.35)	1.36 (1.04-1.80)	0.025

*Adjusted for study site, sex, maternal age, birth year, birthweight, prematurity, and race/ethnicity

^aAcute lymphoblastic leukemia

Table 4. Risk of AML^a by Birth Defect Group and Study Design

	Registry-Based Studies					Questionnaire-Based Studies				
	Controls N=21,693	Cases N=308				Controls N=24,479	Cases N=1,812			
	Exposed N=1,623	Exposed N=40	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p	Exposed N=1,039	Exposed N=89	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p
Congenital anomalies of the nervous system	32 (2.0)	3 (7.5)	--	--	--	17 (1.6)	2 (2.2)	--	--	--
Congenital cataract	2 (0.1)	0 (0.0)	--	--	--	1 (0.1)	0 (0.0)	--	--	--
Congenital anomalies of the heart and circulatory system	239 (14.7)	16 (40.0)	2.62 (1.99-3.49)	5.39 (3.14-9.24)	<0.001	169 (16.3)	15 (16.9)	1.16 (0.91-1.48)	1.28 (0.61-2.67)	0.514
Congenital anomalies of the digestive system	27 (16.6)	1 (2.5)	--	--	--	21 (2.0)	4 (4.5)	--	--	--
Congenital anomalies of the genitourinary system	445 (27.4)	10 (25)	1.18 (0.88-1.58)	1.73 (0.87-3.45)	0.118	178 (17.1)	18 (20.2)	1.05 (0.81-1.34)	1.58 (0.86-2.88)	0.139
Hypospadias	36 (2.2)	0 (0.0)	--	--	--	21 (2.0)	0 (0.0)	--	--	--
Congenital anomalies of the musculoskeletal system	169 (10.4)	4 (10)	--	--	--	142 (13.7)	6 (6.7)	0.84 (0.63-1.13)	0.28 (0.85-0.91)	0.035
Congenital anomalies of the skin	86 (5.2)	1 (2.5)	--	--	--	135 (13.0)	15 (16.9)	1.85 (1.46-2.35)	0.42 (0.22-0.79)	0.007

*Adjusted for study site, sex, maternal age, birth year, birthweight, gestational age, and race/ethnicity

^aAcute myeloid leukemia

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Table 5. Risk of Childhood Leukemia by Number of Birth Defects and Leukemia Subtype

	ALL ^a					AML ^b				Infant ^c			P _{trend}
	Controls (n=46,172)	Cases (n=13,115)	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	P _{trend}	Cases (n=2,120)	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	P _{trend}	Cases (n=1,152)	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	
No Defects	43,510 (94.2)	12,362 (94.3)	1.00 (Ref)	1.00 (Ref)		1,991 (93.9)	1.00 (Ref)	1.00 (Ref)		1,028 (89.2)	1.00 (Ref)	1.00 (Ref)	
1 Defect	2,436 (5.3)	704 (5.4)	1.01 (0.93-1.10)	1.15 (1.03-1.28)	0.006	108 (5.1)	1.01 (0.93-1.10)	0.92 (0.72-1.18)	0.442	94 (8.2)	1.63 (1.31-2.02)	0.97 (0.69-1.35)	0.270
≥2 Defects	226 (0.5)	49 (0.4)	0.96 (0.73-1.25)	1.32 (0.90-1.94)		21 (1.0)	0.96 (0.73-1.24)	1.96 (1.10-3.46)		30 (2.6)	5.62 (3.82-8.26)	1.71 (0.93-1.35)	

*Adjusted for study site, sex, maternal age, birth year, birthweight, prematurity, and race/ethnicity

^aAcute lymphoblastic leukemia

^bAcute myeloid leukemia

^cInfant leukemia includes any leukemia case diagnosed at ≤12 months of age