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

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The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Ethics Statement

All participating studies were approved by relevant ethics committees or institutional review boards. Due to the large study population, registry-based studies were approved with waiver of consent while questionnaire-data had written informed consent from either parent(s) or guardian(s) at the time of data collection.

Disclaimer

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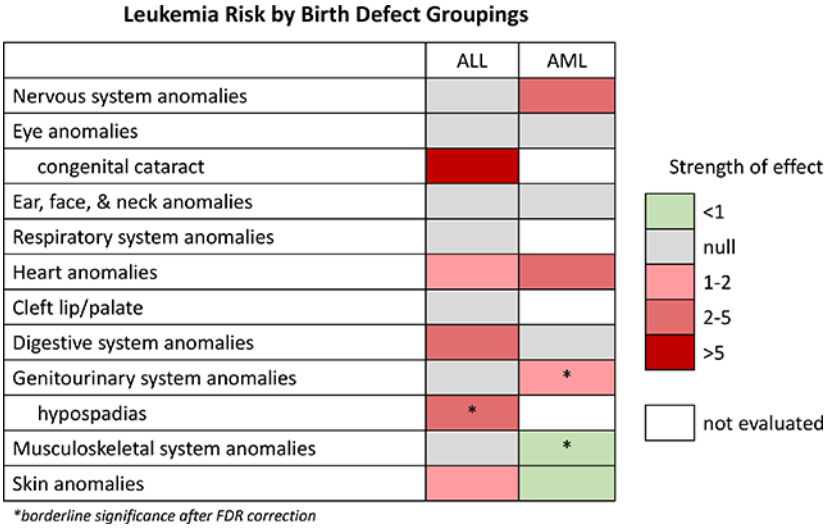
Abstract

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 consortium data from 18 questionnaire-based and three registry-based case-control 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.

Graphical Abstract



Keywords

Epidemiology; childhood leukemia; birth defects; acute lymphoblastic leukemia; acute myeloid leukemia

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]

Methods

CLIC

CLIC is a consortium of leukemia-focused questionnaire- and registry-based case-control studies (which is now open to other pediatric tumors as well). It 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. Further comprehensive descriptions of CLIC have been published previously.[25–31]

Study Subjects

Data for our pooled analyses were provided from 18 questionnaire-based and three registry-based case-control 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). Additional information on each study site is provided in Supplemental Table 1.

Leukemia and Birth Defects Diagnoses

As noted, leukemia diagnoses were ascertained by study site and included both ALL and AML cases. 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.[32, 33] For this assessment, we evaluated major birth defects included as part of the NBDPN annual report or the National Birth Defects Prevention Study.[34, 35]

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. No frequency matching was conducted for the pooled analysis; however, all models were adjusted for study site.

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 [≥37 weeks]), maternal age (<25; 25–29; 30–34; 35–39; ≥40 years), birth year, and child's race/ethnicity (non-Hispanic White; non-Hispanic Black; Hispanic; and other – these categories varied by study and were harmonized based on previous CLIC assessments).[29, 30, 36] 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] Additionally, the categorical variables were designed similarly to what was used in previous CLIC assessments [27–30]. However, unadjusted ORs and 95% CIs were also calculated and presented. In these models, we also included study site. Additionally, we evaluated the impact of missing data on results in unadjusted models and found no differences. Based on that, unadjusted models include all cases.

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 ≥5 co-occurring cases. We used the false discovery rate (FDR) to account for multiple comparisons.[37] 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, and ≥2 defects) and leukemia risk. Logistic regression models were used for all analyses. All statistical analyses were performed using Stata 15.0 (StataCorp LP, College Station, TX).

Results

Overall, there were 46,172 controls and 15,235 cases: 13,115 ALL; 2,120 AML; 1,152 infant (Table 1). The distribution of demographic characteristics across cases and controls was largely consistent with some exceptions. Overall, the prevalence of non-chromosomal birth defects was 5.7% and 5.8% in cases and controls, respectively (Table 2). Prevalence in each study was also calculated by case-control status and histology. 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 (Supplemental Table 2). Across these groups, prevalence was largely the same in each study but prevalence did vary across studies (Supplemental Table 2). Moreover, as described below, there were some notable differences for ALL, AML, and infant leukemia by birth defect group and by specific birth defects.

Non-Chromosomal Birth Defects and ALL

Among the 10 non-chromosomal birth defect groups evaluated (Table 2), three were significantly associated with ALL in adjusted models after correcting for multiple comparisons: 1) congenital anomalies of the heart and circulatory system (OR=1.46, 95% CI: 1.10–1.95); 2) congenital anomalies of the digestive system (OR=2.70, 95% CI: 1.46–4.98); and 3) congenital anomalies of the skin (OR=1.43, 95% CI: 1.11–1.85). While hypospadias was associated with ALL (OR=2.12, 95% CI: 1.16–3.85), it was not statistically significant after correcting for multiple comparisons (p_{FDR}=0.066). The only specific birth defect associated with ALL after correcting for multiple comparisons was congenital cataracts (OR=18.62, 95% CI: 4.36–79.49, p_{FDR}=0.002).

To account for differences in birth defect reporting, associations were then stratified by study design (i.e., questionnaire- vs. registry-based). The direction and magnitude of the effect estimates were consistent for congenital anomalies of the digestive system and congenital anomalies of the skin (Table 3). This was not the case for congenital anomalies of the heart and circulatory system and muscoskeletal system where the OR in questionnaire-based studies was 0.84 (95% CI: 0.55–1.28) and 0.66 (95% CI: 0.44–0.99), respectively compared to 2.36 (95% CI: 1.66–3.34) and 1.23 (95% CI: 0.83–1.82) in registry-based studies.

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) (Table 2), 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) within questionnaire-based studies. There were no 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_{trend}=0.006), the association was neither strong nor statistically significant for children with ≥2 defects (OR_{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_{AML}=1.96, 95% CI: 1.10–3.46 and $OR_{infant\ leukemia}$=1.71, 95% CI: 0.93–1.35) compared to children with 1 defect (OR_{AML}=0.92, 95% CI: (0.72–1.18 and $OR_{infant\ leukemia}$=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 registry-based studies were generally stronger compared to questionnaire-based studies. This suggests to the likelihood of underreporting in questionnaire-based studies, as well as the potential for differential reporting. In fact, there are reported differences in birth defect reporting across many modalities (e.g., birth certificates, questionnaires, active surveillance).[38–41] Because of that, it is important to leverage multiple sources of data when evaluating these conditions and their impact on cancer risk. Future studies of leukemia risk in children with non-chromosomal birth defects should utilize data from expanded registry linkages. Nevertheless, our assessment yielded new insights regarding birth defect-leukemia associations.

We found generally consistent associations for congenital anomalies of the digestive system and ALL (while not statistically significant, similar patterns were seen for AML and infant leukemia); congenital cataracts and ALL; congenital anomalies of the nervous system and AML; and congenital anomalies of the heart and circulatory system for both ALL and AML. These observed associations could be due to a range of factors. First, each of these structural birth defects is more common in children with Down syndrome.[42] Although we excluded children with Down syndrome from this assessment, it is possible that genetic variation on

chromosome 21 could explain the co-occurrence of these conditions, or that cases of Down syndrome were misclassified.[7, 43] Second, it is also possible that these associations could be due to other known syndromes that were not diagnosed in these individuals. For example, children with Fanconi anemia, an AML predisposition syndrome, are more likely to have heart and gastrointestinal defects compared to unaffected children.[44] Third, it is possible that these associations could represent "yet-to-be-discovered" cancer predisposition syndromes or shared genetic effects across phenotypes (i.e., pleiotropy) that could be leveraged to discover novel genetic variants underlying the occurrence of both birth defects and leukemia.

A largely unexplored potential explanation for the overlap between non-chromosomal birth defects and leukemia, as well as other pediatric cancers, is the role of non-genetic *in utero* factors and exposures that could lead to both phenotypes (e.g., maternal diabetes) or postnatal exposures that children with birth defects are more likely to receive (e.g., diagnostic procedures that involve radiation).[21] However, outside of a recent assessment evaluating the impact of *in vitro* fertilization (IVF) on the co-occurrence of birth defects and pediatric cancer, which reported that IVF-exposed children were more likely to develop both birth defects and cancer compared to naturally conceived children,[45] there have been few attempts to evaluate the role of various exposures on the overlap between these conditions.

Our study must be considered in the light of certain limitations. First, and as noted, it is possible that birth defects may have been incompletely ascertained. Our study relied separately on self-reported birth defects (questionnaire-based studies) and independent assessment of birth defects (registry-based studies). Each of these approaches has limitations.[21] However, for defects with sufficient numbers to evaluate associations by study design, the direction of effects were largely consistent, with findings from registry-based studies being stronger. Also, while incomplete ascertainment of birth defects may bias our effect estimates, most studies of birth defects and cancer risk (independent of birth defect ascertainment method) have comparable findings.[21] Related to this, it is possible that selection bias could influence results derived from the case-control studies. However, the inclusion of data from registry-based studies aided in the evaluation of this potential bias across study types. Even in our large study, sample size issues or data availability limited our ability to evaluate subtypes based on immunophenotype, cytogenetic features, or other genomic characteristics. This could be particularly important as there is evidence that etiologic factors differ by tumor characteristics.[46] Finally, an issue inherit in studies of birth defects and cancer is that children diagnosed with cancer may undergo additional diagnostic scrutiny compared to children without a malignancy, which results in the increased identification of birth defects in cases compared to controls.[10] However, previous assessments have indicated this is likely not a driver of observed birth defect-pediatric cancer associations.[10]

The present study has considerable strengths, most notably its large sample size (>15,000 cases), which enabled us to evaluate specific non-chromosomal birth defects that have not been included in previous assessments. Another strength of our assessment is the inclusion of different study designs (questionnaire- versus registry-based) as well as leukemia types (ALL, AML, and infant acute leukemia), which allowed us to conduct sensitivity analyses to evaluate differences by case ascertainment method, helping us to confirm associations.

Lastly, as this is an international study, we included diverse populations from multiple settings and geographical locations.[25]

In conclusion, while associations between non-chromosomal birth defects and leukemia risk were observed, they were not as numerous or strong as those reported for other less common pediatric cancers. However, these findings contribute to our understanding of leukemia risk. Future assessments should evaluate the mediating effects of key variables, including birthweight and gestational age. Additionally, we recommend leveraging associations related to the role of anomalies of the heart, skin, and digestive system to evaluate the role of shared genetic effects and non-genetic exposures, thereby yielding new insights into the overlap between non-chromosomal birth defects and acute leukemia, as well as acute leukemia susceptibility in general.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

Supporting data may be obtained by formal application to each of the participating Principal Investigators and the relevant ethical and regulatory bodies. Further information is available from the corresponding author upon request.

Abbreviations:

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
CI	confidence interval
CLIC	Childhood Cancer and Leukemia International Consortium
FDR	false discovery ratio
NBDPN	National Birth Defects Prevention Network
OR	odds ratio

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Novelty and Impact

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

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 [d]					
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

	Controls (N=46,172)	Cases (N=15,235)	ALL[a] (N=13,115)	AML[b] (N=2,120)	Infant[c] (N=1,152)
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					
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 [e]					
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)

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	Controls (N=46,172)	Cases (N=15,235)	ALL[a] (N=13,115)	AML[b] (N=2,120)	Infant[c] (N=1,152)
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 Diagnosis/Inclusion (Mean/SD)	5.7 (4.2)	5.5 (4.0)	5.4 (3.7)	6.2 (5.3)	0.5 (0.4)
Year of Birth					
1965–1976	9,137 (19.9)	968 (6.4)	757 (5.8)	211 (9.9)	38 (3.3)
1977–1986	9,423 (20.6)	2,895 (19.0)	2,434 (18.6)	461 (21.8)	28 (2.4)
1987–1996	14,964 (32.7)	5,344 (35.1)	4,661 (35.5)	683 (32.2)	271 (23.5)
1997–2006	9,963 (21.8)	4,592 (30.1)	3,997 (30.5)	595 (28.1)	678 (58.9)
2007–2016	2,310 (5.0)	1,436 (9.4)	1,266 (9.7)	170 (8.0)	137 (11.9)
Missing	375	0	0	0	0

[a] Acute lymphoblastic leukemia

[b] Acute myeloid leukemia

[c] Infant leukemia includes any leukemia case diagnosed at ≤12 months of age

[d] The studies in Denmark, Italy(MORE), and Washington are registry based, all others are questionnaire-based

[e] Preterm: <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**	**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]**
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
Right ventricular outflow tract defects	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

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		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**
Septal defects	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)	--	--	--	--
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	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

		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}**
musculoskeletal system																
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

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

[a]Acute lymphoblastic leukemia

[b]Acute myeloid leukemia

[c]Infant leukemia includes any leukemia case diagnosed at ≤12 months of age

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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, gestational age, and race/ethnicity

[a]Acute 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

[a]Acute myeloid leukemia

Table 5.

Risk of Childhood Leukemia by Number of Birth Defects and Leukemia Subtype

		ALL[a]				AML[b]				Infant[c]			
	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)**	**p_{trend}**
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, gestational age, and race/ethnicity

[a]Acute lymphoblastic leukemia

[b]Acute myeloid leukemia

[c]Infant leukemia includes any leukemia case diagnosed at ≤12 months of age