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## Article:

Lupo, Philip J, Chambers, Tiffany M, Mueller, Beth A et al. (24 more authors) (2023) Nonchromosomal 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. *International Journal of Cancer*. ISSN: 1097-0215

<https://doi.org/10.1002/ijc.34720>

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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**

Journal:	<i>International Journal of Cancer</i>
Manuscript ID	Draft
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	n/a
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Key Words:	Epidemiology, childhood leukemia, birth defects, acute lymphoblastic leukemia, acute myeloid leukemia

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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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**Manuscript Type:** Cancer Epidemiology

**Key Words:** Epidemiology, childhood leukemia, birth defects, acute lymphoblastic leukemia,  
acute myeloid leukemia

**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

**Conflict of interest:** The authors declare no potential conflicts of interest

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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.

**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%).<sup>1, 2</sup> While five-year survival for children with ALL and AML has improved over the past several decades approaching 90% in some settings,<sup>3, 4</sup> 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.<sup>5</sup> 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.<sup>6</sup>

One of the strongest genetic risk factors for developing ALL and AML is being born with trisomy 21 (i.e., Down syndrome).<sup>7-9</sup> 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.<sup>10</sup> 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.<sup>11</sup>

There is strong evidence indicating non-chromosomal birth defects are associated with a range of pediatric solid tumors.<sup>10, 12-24</sup> 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).<sup>25</sup> 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.<sup>25-31</sup> 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  $\leq 12$  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).<sup>32</sup> 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.<sup>33, 34</sup>

### *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.<sup>10, 26-31</sup> 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,<sup>10</sup> 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.<sup>35</sup> 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

defects) and leukemia risk. 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 5.8% in both cases and controls (Table 2). However, 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 where the OR in questionnaire-based studies was 0.84 (95% CI: 0.55-1.28) compared to 2.36 (95% CI: 1.66-3.34) 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  $\geq 5$  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  $\geq 2$  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  $\geq 2$  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,<sup>10</sup> 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).<sup>10, 21</sup> Second, associations are not as strong as reported for other pediatric cancers (e.g., neuroblastoma).<sup>10, 17, 19, 20</sup> 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).<sup>36-39</sup> 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.<sup>40</sup> 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.<sup>7, 41</sup> 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.<sup>42</sup> 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).<sup>21</sup> 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,<sup>43</sup> 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.<sup>21</sup> 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.<sup>21</sup> 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.<sup>44</sup> Finally, an issue inherent 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.<sup>10</sup> However, previous assessments have indicated this is likely not a driver of observed birth defect-pediatric cancer associations.<sup>10</sup>

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.

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. Specifically, future assessments could leverage 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.



**Author Contributions**

**Philip J. Lupo:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, and Writing – review & editing; **Tiffany M. Chambers:** Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, and Writing – review & editing; **Beth A. Mueller:** Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, and Writing – review & editing; **Jacqueline Clavel:** Methodology, Resources, Validation, and Writing – review & editing; **John D. Dockerty:** Methodology, Resources, Validation, and Writing – review & editing; **David R. Doody:** Resources, and Writing – review & editing; **Friederike Erdmann:** Methodology, Resources, and Writing – review & editing; **Sameera Ezzat:** Methodology, Resources, Validation, and Writing - review & editing; **Tommaso Filippini:** Resources, and Writing – review & editing; **Johnni Hansen:** Resources, and Writing – review & editing; **Julia E. Heck:** Methodology, Resources, Validation, and Writing – review & editing; **Claire Infante-Rivard:** Methodology, Resources, Validation, and Writing – review & editing; **Alice Y. Kang:** Funding acquisition, Project administration, Resources, and Writing – review & editing; **Corrado Magnani:** Methodology, Resources, Validation, and Writing – review & editing; **Carlotta Malagoli:** Methodology, Resources, Validation, and Writing – review & editing; **Catherine Metayer:** Funding acquisition, Methodology, Resources, and Writing – review & editing; **Helen D. Bailey:** Funding acquisition, Methodology, Resources, and Writing – review & editing; **Ana M. Mora:** Methodology, Resources, and Writing – review & editing; **Evangelia Ntzani:** Methodology, Resources, Validation, and Writing – review & editing; **Eleni Th Petridou:** Funding acquisition, Methodology, Resources, Validation, and Writing – review & editing; **Maria S. Pombo-de-Oliveira:** Methodology, Resources, Validation, and Writing – review & editing; **Wafaa M. Rashed:** Methodology, Resources, and Writing – review & editing; **Eve Roman:** Methodology, Resources, Validation, and Writing – review & editing; **Joachim Schüz:** Methodology, Resources, Validation, and Writing – review & editing; **Catharina Wesseling:**

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Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, and Writing  
– review & editing; **Michael E. Scheurer:** Conceptualization, Data curation, Investigation,  
Methodology, Resources, Supervision, Visualization, and, Writing – review & editing

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

### **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.

### **Ethics Statement**

All participating studies were approved by relevant ethics committees or institutional review  
boards.

### **Acknowledgements**

**AUS-ALL:** The AUS-ALL consortium conducted the AUS-ALL study and the Telethon Kids  
Institute (formerly Telethon Institute for Child Health Research; TICHHR), University of Western  
Australia, was the coordinating center. Bruce Armstrong (Sydney School of Public Health),  
Elizabeth Milne (TICHHR), Frank van Bockxmeer (Royal Perth Hospital), Michelle Haber  
(Children's Cancer Institute Australia), Rodney Scott (University of Newcastle), John Attia

(University of Newcastle), Murray Norris (Children’s Cancer Institute Australia), Carol Bower (TICHR), Nicholas de Klerk (TICHR), Lin Fritschi (WA Institute for Medical Research, WAIMR), Ursula Kees (TICHR), Margaret Miller (Edith Cowan University), Judith Thompson (WA Cancer Registry) were the research investigators, and Helen Bailey (TICHR) was the project coordinator. The clinical investigators were: Frank Alvaro (John Hunter Hospital, Newcastle); Catherine Cole (Princess Margaret Hospital for Children, Perth); Luciano Dalla Pozza (Children’s Hospital at Westmead, Sydney); John Daubenton (Royal Hobart Hospital, Hobart); Peter Downie (Monash Medical Centre, Melbourne); Liane Lockwood (Royal Children’s Hospital, Brisbane); Maria Kirby (Women’s and Children’s Hospital, Adelaide); Glenn Marshall (Sydney Children’s Hospital, Sydney); Elizabeth Smibert (Royal Children’s Hospital, Melbourne); Ram Suppiah (previously Mater Children’s Hospital, Brisbane). AUS-ALL was funded by the National Health and Medical Research Council of Australia Grant Number 254539.

**Baylor College of Medicine:** Research reported in this publication was supported by the U.S. Department of Defense under award number CA190214 (PJ Lupo).

**California Childhood Leukemia Study:** The CCLS thanks the families for their participation and the clinical investigators at the following collaborating hospitals for help in recruiting patients: University of California Davis Medical Center (Dr. J. Ducore), University of California San Francisco (Drs. M. Loh and K. Matthay), Children’s Hospital of Central California (Dr. V. Crouse), Lucile Packard Children’s Hospital (Dr. G. Dahl), Children’s Hospital Oakland (Dr. J. Feusner), Kaiser Permanente Roseville (former Sacramento; Drs. K. Jolly and V. Kiley), Kaiser Permanente Santa Clara (Drs. C. Russo, A. Wong, and D. Taggart), Kaiser Permanente San Francisco (Dr. K. Leung), and Kaiser Permanente Oakland (Drs. D. Kronish and S. Month). Finally, the CCLS thanks the entire study staff and former University of California, Berkeley Survey Research Center for their effort and dedication. This work was supported by the National Institute for Environmental Health Sciences (NIEHS) grants R01ES009137, P42ES004705,

R24ES028524, and P01ES018172, the United States Environmental Protection Agency grant RD83451101, and with the additional support from the Children with Cancer UK (CWCUK). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the funding sponsors.

**NARECHEM-ST:** The authors wish to acknowledge the contribution of the network (narechem.gr) of pediatric hematologists-oncologists, radiologists, immunologists, and pediatricians who made this study possible; the field coordinator Evanthia Bouka, MPH and the statisticians Nick Dessypris M.Sc., Ph.D and George Markozannes M.Sc., Ph.D. Continuous clinical support by Margarita Baka M.D. (Department of Pediatric Hematology–Oncology, “P&A Kyriakou” Children’s Hospital, Athens), Maria Moschovi M.D., Sophia Polychronopoulou M.D.(Departments of Pediatric Hematology–Oncology, “A. Sophia” Children’s Hospital, Athens); Emmanuel Hatzipantelis M.D., Ph.D (Pediatric Hematology Oncology Unit, 2nd Pediatric Department of Aristotle University, AHEPA General Hospital, Thessaloniki); Maria Kourti M.D.(Pediatric Oncology Department, Hippokration Hospital, Thessaloniki); Eftychia Stiakaki M.D.(Department of Pediatric Hematology-Oncology, University Hospital of Heraklion, Heraklion); Maria Karalexi and Ioannis Matsoukis M.D. (Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, 11527 Athens) should be also acknowledged. The Study has been supported in part since 1996 by the Hellenic Society for Social Pediatrics and Health Promotion.

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**Table 1. Demographics of Subjects from the Childhood Cancer and Leukemia International Consortium**

	<b>Controls (N=46,172)</b>	<b>Cases (N=15,235)</b>	<b>ALL<sup>a</sup> (N=13,115)</b>	<b>AML<sup>b</sup> (N=2,120)</b>	<b>Infant<sup>c</sup> (N=1,152)</b>
<b>Study Site</b>					
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)
<b>Sex</b>					
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
<b>Birthweight (in grams)</b>					
<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
<b>Maternal Age</b>					
<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
<b>Child Race/Ethnicity</b>					

	Controls (N=46,172)	Cases (N=15,235)	ALL <sup>a</sup> (N=13,115)	AML <sup>b</sup> (N=2,120)	Infant <sup>c</sup> (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
<b>Gestational Age<sup>d</sup></b>					
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
<b>Maternal Education</b>					
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
<b>Plurality</b>					
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
<b>Age at Dx./Inclusion (Mean/SD)</b>	5.7 (4.2)	5.5 (4.0)	5.4 (3.7)	6.2 (5.3)	0.5 (0.4)

<sup>a</sup>Acute lymphoblastic leukemia

<sup>b</sup>Acute myeloid leukemia

<sup>c</sup>Infant leukemia includes any leukemia case diagnosed at ≤12 months of age

<sup>d</sup>Preterm: <37 weeks; Term: ≥37 weeks

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

	ALL <sup>a</sup>						AML <sup>b</sup>					Infant <sup>c</sup>				
	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 <sup>FDR</sup>	Exposed N=129	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p	p <sup>FDR</sup>	Exposed N=124	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p	p <sup>FDR</sup>
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)	<b>4.23</b> <b>(1.50-11.89)</b>	<b>0.006</b>	<b>0.024</b>	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)	<b>8.22</b> <b>(2.12-31.79)</b>	<b>18.62</b> <b>(4.36-79.49)</b>	<b>&lt;0.001</b>	<b>0.002</b>	0 (0.0)	--	--	--	--	0 (0.0)	--	--	--	--
Congenital anomalies of the ear, face and neck	241 (9.1)	30 (3.9)	<b>0.44</b> <b>(0.30-0.64)</b>	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)	<b>1.46</b> <b>(1.10-1.95)</b>	<b>0.009</b>	<b>0.050</b>	31 (24.0)	<b>1.66</b> <b>(1.15-2.40)</b>	<b>2.86</b> <b>(1.81-4.52)</b>	<b>&lt;0.001</b>	<b>0.001</b>	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)	<b>1.72</b> <b>(1.26-2.34)</b>	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)	<b>1.73</b> <b>(1.27-2.36)</b>	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
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)	<b>0.39</b> <b>(0.18-0.85)</b>	0.68 (0.30-1.56)	0.359	0.590	1 (0.8)	--	--	--	--	1 (0.8)	--	--	--	--

	ALL <sup>a</sup>						AML <sup>b</sup>					Infant <sup>c</sup>				
	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 <sup>FDR</sup>	Exposed N=129	Unadjus ted OR* (95% CI)	Adjusted OR* (95% CI)	p	p <sup>FDR</sup>	Exposed N=124	Unadjus ted OR* (95% CI)	Adjusted OR* (95% CI)	p	p <sup>FDR</sup>
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

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

<sup>a</sup>Acute lymphoblastic leukemia

<sup>b</sup>Acute myeloid leukemia

<sup>c</sup>Infant leukemia includes any leukemia case diagnosed at  $\leq 12$  months of age

For Peer Review



Table 3. Risk of ALL<sup>a</sup> 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

<sup>a</sup>Acute lymphoblastic leukemia

**Table 4. Risk of AML<sup>a</sup> 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
<b>Congenital anomalies of the nervous system</b>	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)	--	--	--
<b>Congenital anomalies of the heart and circulatory system</b>	239 (14.7)	16 (40.0)	<b>2.62</b> <b>(1.99-3.49)</b>	<b>5.39</b> <b>(3.14-9.24)</b>	<b>&lt;0.001</b>	169 (16.3)	15 (16.9)	1.16 (0.91-1.48)	1.28 (0.61-2.67)	0.514
<b>Congenital anomalies of the digestive system</b>	27 (16.6)	1 (2.5)	--	--	--	21 (2.0)	4 (4.5)	--	--	--
<b>Congenital anomalies of the genitourinary system</b>	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)	--	--	--
<b>Congenital anomalies of the musculoskeletal system</b>	169 (10.4)	4 (10)	--	--	--	142 (13.7)	6 (6.7)	0.84 (0.63-1.13)	<b>0.28</b> <b>(0.85-0.91)</b>	<b>0.035</b>
<b>Congenital anomalies of the skin</b>	86 (5.2)	1 (2.5)	--	--	--	135 (13.0)	15 (16.9)	<b>1.85</b> <b>(1.46-2.35)</b>	<b>0.42</b> <b>(0.22-0.79)</b>	<b>0.007</b>

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

<sup>a</sup>Acute myeloid leukemia

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

		ALL <sup>a</sup>					AML <sup>b</sup>					Infant <sup>c</sup>			
	Controls (n=46,172)	Cases (n=13,115)	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p <sub>trend</sub>		Cases (n=2,120)	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p <sub>trend</sub>		Cases (n=1,152)	Unadjusted OR* (95% CI)	Adjusted OR* (95% CI)	p <sub>trend</sub>
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)	<b>1.15</b> <b>(1.03-1.28)</b>	0.006		108 (5.1)	1.01 (0.93-1.10)	0.92 (0.72-1.18)	0.442		94 (8.2)	<b>1.63</b> <b>(1.31-2.02)</b>	0.97 (0.69-1.35)	0.270
≥2 Defects	226 (0.5)	49 (0.4)	0.96 (0.73-1.25)	<b>1.32</b> <b>(0.90-1.94)</b>			21 (1.0)	0.96 (0.73-1.24)	<b>1.96</b> <b>(1.10-3.46)</b>			30 (2.6)	<b>5.62</b> <b>(3.82-8.26)</b>	1.71 (0.93-1.35)	

<sup>a</sup>Adjusted for study site, sex, maternal age, birth year, birthweight, prematurity, and race/ethnicity  
<sup>a</sup>Acute lymphoblastic leukemia  
<sup>b</sup>Acute myeloid leukemia  
<sup>c</sup>Infant leukemia includes any leukemia case diagnosed at ≤12 months of age