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Age-, sex- and disease subtype- fetal growth differentials in childhood acute myeloid leukemia risk: results from 22 studies participating in a Childhood Leukemia International Consortium analysis

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ABSTRACT

Background: Evidence for an association of fetal growth with acute myeloid leukemia (AML) is inconclusive. AML is a rare childhood cancer, relatively more frequent in girls, with distinct features in infancy. In the context of the Childhood Leukemia International Consortium (CLIC), we examined an *a priori* hypothesis that the association may vary by age, sex and disease subtype using data comprising 22 studies and a total of 3564 AML cases.

Methods: Pooled estimates by age, sex and overall for harmonized fetal growth measures in association with AML risk were calculated using the INTERGROWTH 21st project for 17 studies contributing individual-level data; thereafter, meta-analyses were conducted with effect estimates provided *ad hoc* due to administrative constraints by five more studies. Sub-analyses by AML subtype were also performed.

Findings: A nearly 50% greater risk was observed among large for gestational age (LGA) infant boys <1 year [odds ratio (OR): 1.49, 95% confidence intervals (CI): 1.03-2.14], reduced to 34% among boys <2 years (OR: 1.34, 95% CI: 1.05-1.71) and 25% for all age boys (OR: 1.25, 95% CI: 1.06-1.46). The association became stronger among boys with M0/M1subtype (OR: 1.80, 95% CI: 1.15-2.83). The association among boys with large birth length for gestational age was 1.38 (95% CI: 1.00-1.92). No index of decelerated fetal growth was associated with AML risk.

Interpretation: Greater fetal growth was associated with AML, especially in infant boys and those with minimally differentiated myeloid leukemia. Further cytogenetic research would help inform the underlying mechanisms.

Keywords: fetal growth; birthweight; birthweight for gestational age; birth length; weight-for-length ratio; acute myeloid leukemia; subtypes; childhood; sex; meta-analysis

Research in context

Evidence before this study

Fetal growth reflects a complex array of underlying mechanisms, including genetic and epigenetic factors, environmental exposures, maternal pathology and nutritional status. Evidence for an association of fetal growth with acute myeloid leukemia (AML) is inconclusive. AML is a rare childhood cancer with distinct features in infancy and is relatively more frequent in girls as contrasted with other childhood cancers.

Added value of this study

The pooled analysis and meta-analysis of the largest international dataset (N=3564 AML cases and 9584 controls) comprising 22 studies participating in the Childhood Leukemia International Consortium analysis provide evidence for a positive association of excess fetal growth with childhood AML. The association was robust among large for gestational age newborns, specifically infant boys and those with minimally differentiated myeloid cells subtypes. The impact of accelerated fetal growth on AML risk was attenuated among older ages. A positive association of large birth length for gestational age was also found, confined also to boys, whereas the positive association of the large weight-for-height ratio adjusted for gestational age did not reach statistical significance. Neither low birthweight nor smaller for gestational age were associated with AML risk.

Implications of all the available evidence

Our results showing accelerated fetal growth age-, sex- and disease subtype-related differentials in AML risk, if replicated in future cytogenetic research could further refine our understanding of the biological pathways through which fetal growth environment may be implicated in the risk of childhood AML and its specific subtypes.

INTRODUCTION

Fetal growth is one of the most commonly studied perinatal risk factors of childhood cancer (1-5). Measures of fetal growth reflect a complex array of underlying mechanisms including genetic and epigenetic factors, environmental exposures, maternal pathology and nutritional status (6).

Numerous publications have examined the potential association between high birthweight (HBW), as a gross indicator of fetal growth and childhood acute lymphoblastic leukemia (ALL); however, their results remain inconclusive for acute myeloid leukemia (AML) (1, 4, 7, 8). AML is a rare childhood cancer with distinct features in infancy and relatively more frequent in girls as contrasted with other childhood cancers (9, 10). A U-shape association of AML risk has been reported with birthweight (7); yet, fewer studies have explored the potential relationship of more robust fetal growth measures, such as birthweight adjusted for gestational age, birth length, weight-for-length ratio and proportion of optimal birthweight (POBW) (11, 12). A recent pooled study from the Childhood Leukemia International Consortium (CLIC) (4) and a German study (13), which was also included in the CLIC pooled analysis showed that fetal growth rate, rather than birthweight *per se* may be more strongly associated with childhood leukemia, especially ALL.

Biological mechanisms underlying the possible effect of HBW on AML risk remain indecisive and may involve growth factors and epigenetics with chromatin modifiers (14). Birthweight is, partially, determined by the intrauterine environment and has been linked to cord blood levels of insulin-like growth factors (IGF) I and II, as well as sex steroid hormones (14, 15). Any association between low birthweight and AML is speculated to be due to fetal programming and genomic stability determined by epigenetic pathways, which affect the growth hormone-IGF axis through hyperinsulinemia, according to the “thrifty phenotype” hypothesis (4, 11, 16, 17).

Given the rarity of the disease, its distinct age and sex characteristics and the inconclusive results of published literature, we aimed to assess whether measures of fetal growth are related to the risk of AML using data from questionnaire-based case-control (QCC) and registry-based case-control (RCC) studies in an international Childhood Leukemia International Consortium (CLIC) analysis. Specifically, we focused on the potential associations between AML and available fetal growth markers, namely birthweight, birthweight for gestational age, as well as birth length and weight-for-length ratio for gestational age by age, sex and overall, including subgroup analyses by disease subtype.

METHODS

Study population

Fourteen QCC and eight RCC studies provided data for this collaborative CLIC analysis. Registration process and data collection in each study reported elsewhere (18), are summarized in Supplementary Table 1. Information for the RCC studies conducted in Denmark, Finland, Taiwan, and five States of the U.S. (California, Minnesota, New York-excluding New York City, Texas and Washington State) was derived from linkage of nationwide or statewide population-based cancer registries with administrative registries (Supplementary Table 1).

Due to administrative constraints, the CLIC Californian RCC study, as well as the non-CLIC RCC studies from Minnesota, New York, Texas and Taiwan contributed only adjusted summary effect estimates for the meta-analyses. Pooled estimates were derived from the remaining 17 studies, which provided individual-level data, namely the RCC CLIC studies from Denmark, Finland and Washington State, as well as the QCC CLIC studies conducted in Brazil, Costa Rica, France (ADELE, ELECTRE, ESCALE and ESTELLE), Germany, Greece, Italy, New Zealand, UK, and the U.S. [Children's Oncology Group (COG)-AE24,

COG-E14 and Texas]. All 22 studies used the same variables (birth characteristics, potential confounders and disease-related information) and the same statistical analysis program.

Cases and controls (0-14 years) from the QCC COG-AE24 study born in California, Washington, Minnesota, New York and Texas (40 cases and 84 controls) were excluded due to overlap with the remaining U.S. studies. Children with Down syndrome were also excluded given the particular biological mechanisms of AML leukemogenesis in these patients (19). A total of 3564 AML cases and 9584 controls from the 22 participating studies (19 CLIC studies and 3 non-CLIC studies) were included in this analysis.

Data collection and harmonization

Information on socio-demographic and birth characteristics of cases and controls including fetal growth measures was harmonized across the studies. Whenever controls were frequency-matched to cases on age and sex (Brazil, Costa Rica, Denmark, France, Germany, New Zealand, Texas QCC study, Taiwan and the U.S. California, Minnesota, New York, Texas and Washington RCC studies), a maximum of three controls were randomly selected from the respective study databases.

Data on primary exposures were provided by birth certificates, medical birth records or maternal self-reports, depending on the study. Birthweight for gestational age was examined using the 10^{th} and 90^{th} percentiles of the International Fetal and Newborn Growth Consortium for the 21^{st} Century (INTERGROWTH-21^{st}) birthweight standard (20). Three categories for birthweight for gestational age were used: Small for Gestational Age (SGA) for neonates weighing below the 10^{th} percentile of the reference population, Appropriate for Gestational Age (AGA) for neonates weighing between the 10^{th} and 90^{th} percentile, and Large for Gestational Age (LGA) for neonates weighing above the 90^{th} percentile. The same process was used to categorize the other fetal growth markers, namely birth length for gestational age and weight-for-length adjusted for gestational age ratio. Applying this procedure to our data resulted in approximately 20% of newborn categorized as LGA and 6-7% as SGA. We

therefore label them as accelerated fetal growth (AFG) and low fetal growth (LFG) instead. Seeing that INTERGROWTH resulted in such a large number of children in the two extreme categories, for sensitivity analyses, we also calculated the joint growth distribution based on the pooled set of our controls and then applied to the study-specific cases.

Statistical analysis

The overall analysis model included the matching factors and potential confounders, selected *a priori* based on the existing literature: child's age at diagnosis (<1, 1-4, 5-9, 10-14 years), sex (male, female), maternal age at birth (<25, 25-29, 30-34, ≥35years), birth order (1^{st}, 2^{nd}, ≥3^{rd}), index child's ethnicity (Caucasian, other) (18), plurality (yes, no), study of origin and prematurity (gestational age <37 weeks: yes, no) whenever appropriate to be introduced as an independent variable. The primary exposures of interest were birthweight, birthweight for gestational age, birth length and weight-for-length ratio adjusted for gestational age and they were alternatively introduced into the overall analysis model. Additionally, in order to provide comparable estimates with previous studies, which showed a U-shape association (6), the standard birthweight categories [<2500, 2500-3999 (reference), ≥4000 grams] were used to examine the impact of birthweight alone. The proportion of missing data for each variable per study is presented in Supplementary Table 2.

Given the different biological characteristics of AML during infancy and the first two years of age, as well as the increasing incidence of the disease in girls as contrasted with other childhood cancers (10, 21), we initially assessed the associations of birthweight and birthweight for gestational age with AML risk separately for each gender (boys, girls) and for the age groups <1 year and 1-14 years or alternatively <2 years and 2-14 years. A formal test for interaction of birthweight or birthweight for gestational age with age or sex was thereafter applied in the pooled dataset as to explore this *a priori* hypothesis. In addition, we explored the potential effect modification of sex on the associations above by calculating the relative

excess risk due to interaction (RERI), the proportion attributable to the interaction (AP) and the synergy index (S) (22) in the total dataset (0-14 years), as well as in the age groups <2 and 2-14 years. Given the borderline significant interactions observed, multivariable logistic regression models were fitted in the total pooled set of individual-level data. These pooled odds ratios (OR) and 95% confidence intervals (CI) for each exposure were thereafter meta-analyzed using random-effect models (23) with the readily contributed adjusted effect estimates from studies not allowed to contribute individual-level data in order to obtain overall risk estimates for the total of 22 studies. Between-study heterogeneity was assessed using the Cochran Q and I^2 statistics. The Z-test was applied for the overall effect and statistical significance was set at $p<0.10$. Study-specific meta-analyses comprising the 17 studies which provided individual-level data, as well as sensitivity meta-analyses excluding a study per time were also performed.

Sub-analyses were conducted by study design, namely pooled analyses of RCC and meta-analyses of QCC studies. In addition, subgroup meta-analyses by French-American-British (FAB) subtype (M0-M1, M2, M3, M4-M5 and M6-M7) (24) were also performed.

Statistical analyses were conducted using SAS version 9.4 (Cary, NC) and Stata version 14.1 (College Station TX).

Role of the funding source

Funding sources of individual studies had no involvement in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

RESULTS

Characteristics of the study population

A total of 3564 cases with AML and 9584 controls were included. Table 1 shows the distributions of the study variables for cases and controls. Among the exposures of interest, the proportions of prematurity and LGA labelled as accelerated fetal growth (AFG) for the purposes of this study, were larger among AML cases than controls (9.0% versus 7.7% and 23.6% versus 21.2%, respectively).

Birthweight and birthweight for gestational age

Based on the *a priori* hypothesis of age- and sex-differentials in the association of fetal growth with AML risk, we found a borderline significant additive effect modification of sex on the association of AFG with AML risk (RERI: 0.27, p=0.10; AP: 18%, p=0.10; S: 2.4), which reached statistical significance in the age group 2-14 years (RERI: 0.41, p=0.03; AP: 31%, p=0.02; S: -2.9). Formal testing yielded statistically significant interactions only with age for HBW (≥4000 grams; p for interaction=0.04) and LFG (p for interaction=0.04). The pooled age- and sex-specific analyses showed positive associations of AML with the gross indicator of fetal growth, namely HBW among boy infants ($OR_{boys<1y;\ HBW}$: 1.34, 95% CI: 1.01-1.79; Supplementary Table 3). A nearly 50% higher risk was found among male infants, when the more accurate measure of AFG, namely birthweight for gestational age (Table 2) was used ($OR_{boys<1y;\ AFG}$: 1.49, 95% CI: 1.03-2.14), reduced to 34% among young boys <2 years ($OR_{boys<2ys;\ AFG}$: 1.34, 95% CI: 1.05-1.71) and to 23% among boys 1-14 years ($OR_{boys;\ 1-14yrs;\ AFG}$: 1.23, 95% CI: 1.00-1.51). By contrast, none of the associations among girls reached statistical significance. Likewise, we observed null associations of either low birthweight (<2500 grams) or LFG with the risk of AML.

The overall analysis (0-14 years) replicated the positive associations of AML with HBW (OR_{HBW}: 1.15, 95% CI: 0.98-1.34; Supplementary Table 3), whereas a 20% statistically significant increased risk was noted for AFG (OR_{AFG}: 1.20, 95% CI: 1.03-1.39; Table 2). Of note, the impact of HBW and AFG on AML risk was stronger among boys ($OR_{boys;\ 0-14yrs;\ HBW}$: 1.21, 95% CI: 1.03-1.43; $OR_{boys;\ 0-14yrs;\ AFG}$: 1.25, 95% CI: 1.06-1.46). More importantly, the association of AFG became stronger among children with AML FAB-M0 or -M1 subtype

(OR: 1.53, 95% CI: 1.08-2.16), again confined only to boys (OR: 1.80, 95% CI: 1.15-2.83; Table 4). Of note, null associations were observed between birthweight and AML FAB specific subtypes (Supplementary Table 4).

The findings remained robust in the analyses of birthweight for gestational age based on the 10% and 90% distribution of the pooled set of controls (Supplementary Table 5). Overall, there was no evidence of heterogeneity across studies regarding the findings on infant boys or both genders, except for the meta-analyses on AFG 0-14 (p=0.09) and <2 years girls (p=0.04), as well as LFG 2-14 (p=0.08) and 1-14 years (p=0.06) boys. Excluding the combined effect estimates provided by the RCC studies of Minnesota, New York and Texas, the heterogeneity became statistically non-significant (p=0.18-0.84), whereas the results of the main analyses did hardly change. Likewise, the study-specific meta-analyses and sub-analyses by study design (not shown in Tables) showed essentially similar results with the main-analyses without evidence of significant between-study heterogeneity.

Other fetal growth measures

Analyses of alternative fetal growth measures, namely birth length and weight-for-length ratio adjusted for gestational age were based on smaller numbers of AML cases and controls derived only from studies providing individual-level data (Supplementary Table 6). The positive associations of accelerated birth length adjusted for gestational age ($OR_{\text{larger for gestational age birth length}}$: 1.14, 95% CI: 0.91-1.42) and accelerated weight-for-length adjusted for gestational age ratio ($OR_{\text{larger for gestational age weight-for-length}}$: 1.16, 95% CI: 0.88-1.52) with AML reached statistical significance only among boys with accelerated birth length for gestational age (OR: 1.38, 95% CI: 1.00-1.92); by contrast, null associations were again observed in girls.

DISCUSSION

Main findings

The pooled analysis and meta-analysis of the largest international dataset contributed to this CLIC study provide evidence for a positive association of accelerated fetal growth with childhood AML, more marked in boys. Specifically, a robust association was found for AFG newborns, larger in size among male infants and those with minimally differentiated myeloid cell subtypes. Indeed, the impact of AFG on AML risk remained unchanged, though attenuated, after infancy among boys. A positive association of large for gestational age birth length was also found, again stronger in boys, whereas the positive association of the large for gestational age weight-for-length ratio did not reach statistical significance. By contrast, neither low birthweight (<2500 grams) nor LFG were associated with risk of AML in any sex or age group.

Previous literature

Our findings are consistent with recent studies that reported a positive association of AML with AFG, which relied, however, on smaller number of cases and less comprehensive list of markers used (1, 25, 26) compared to our analysis. We found no U-shaped association as contrasted to the recent meta-analysis comprising highly heterogeneous studies regarding the birthweight cut-off points (OR_{HBW}: 1.24, 95% CI: 1.16-1.33; $OR_{lowbirthweight}$: 1.50, 95% CI 1.05, 2.13)(6) or previous studies (7, 8). A preceding meta-analysis reported a weak, of similar effect size, association between HBW and AML (OR: 1.27, 95% CI: 0.70-2.20) (27), whereas a case-control study in England and Wales suggested that the association with birthweight could be U-shaped, as increased risks were found for both high and low birthweight children and a weak association when birthweight was treated as a continuous variable (OR: 1.04, 95% CI: 0.98-1.12 per 500g increase) (28). Our study did not support an association with decelerated fetal growth, either with low birthweight (<2500 grams) *per se* or with the more accurate markers, namely smaller for gestational age weight or length.

Interpretation of findings

The physiology of fetal growth is complex, involving genetic and environmental factors. Specifically, determinants of fetal macrosomia include maternal and paternal overweight/obesity, previous macrosomic birth, Hispanic ethnicity, multiparity, maternal obesity and nutritional status, gestational diabetes and hypertension, non-smoking and advanced maternal age (29, 30).

Growth factors seem to be the biologically plausible mechanisms underlying the association of AFG with AML (14, 31). *In utero*, growth factors are considered to stimulate an increase in the total number of stem cells, with a subsequent expansion of the populations of tumorigenic and preleukemic cells with pre-existing genetic abnormalities (32). In vitro, IGF-1 stimulates the growth of lymphoid and myeloid cells and it may also have antiapoptotic properties (33). The IGF-2 imprinted gene is normally expressed from the paternally inherited allele (34). The biallelic expression of IGF-2 attributed to epigenetic changes is likely to lead to fetal overgrowth, which might explain the association between AFG and AML incidence (35). The effects of growth factors and their binding proteins on fetal macrosomia are more pronounced among diabetic mothers, but have also been observed among non-diabetic pregnant women, highlighting the importance of normal weight gain during pregnancy (34, 36). Indeed, the robustness of our results on AFG based on the broader definition of the intergrowth curves and the upper 10% growth percentile of the controls' pooled set provides implications about the crucial role of determinants of high fetal growth rate, such as maternal pre-existing obesity, diabetes and weight gain during pregnancy which may result in increased maternal basal metabolic rate and IGF levels (37).

The stronger association of AFG with AML among infants compared to older age groups of children strengthens support for the hypothesis that the IGF system may be associated with birthweight, especially during infancy, given the shorter interval between birth and the disease outcome (28). In addition, infant AML is characterized by a particularly high prevalence of histone lysine-methyl transferase 2 (KMT2A/MLL) gene rearrangements,

which are also present in umbilical cord blood of healthy individuals and may predispose to hematological malignancies later in life (38, 39). In this context, the fetal exposure to topoisomerase II inhibitors through maternal diet, another suspected risk factor for childhood AML, in addition to deregulated DNA methylation as a result of gestational weight gain and accelerated fetal growth could both act as an early mechanism modulating later susceptibility to AML onset during infancy (40-44). Moreover, genetic aberrations, such as epigenetic dysfunction, sister chromatid exchange and unbalanced distribution of the chromosomes or incorrect repair of DNA double-strand breaks are common in AML (45). These aberrations seem to occur more frequently in aging cells due to shortening of telomeres and less efficient DNA repair capacity in immature cells. Therefore, the age-specific distribution of specific changes in hematopoiesis and pools of hematopoietic precursors as targets for leukemogenesis might be explained by earlier effects of environmental growth factors (46).

The subtype-specific associations in our study could be due to the presence of distinct feature genes, crucial for fetal growth, which are expressed in specific AML subtypes (47). In particular, AML without maturation (M1) is characterized by morphologically and phenotypically immature AML blasts associated with recurrent mutations of epigenetic regulators, such as IDH1, IDH2, TET2, DNMT3A, MLL-PTD, ASXL1, and EZH2 (48). Gene expression profiling studies have shown that the growth factor-binding protein-2 (GFBP-2) gene, which has been implicated in fetal growth, is down-regulated in FAB-M1 AML (47); these findings could be related to the association between AFG and AML onset among cases with FAB-M0 or -M1 subtype. In the same context, the myeloid differentiated cells in AML FAB-M3 have been associated with distinct biology at the genetic level, namely with a unique PML-RARα gene fusion and chimeric protein, which prevail in certain countries, such as Italy, Spain and South America (48).

Lastly, the sex-associated findings of our study could be employed in the context of fetal sex as a modifier of fetoplacental growth. Indeed, recent studies show that male fetuses may grow faster than females confirming the known mean 150 grams difference of male birthweight

compared to that of females (49, 50). Hence, the consistent male-specific associations of AFG with AML in our study might be due to differential sex-hormonal interactions, namely higher concentrations of circulating androgens synthesized by the testes and sex-related differences in growth rate before differentiation of the fetal gonads (51, 52), which may lead among others to a higher mean weight of boys at birth as a result of the IGF axis activation, despite the fact that males as a rule are born one week earlier than girls (43, 53). The significant effect modification of sex on the association of AFG with AML risk in the older age group of children (2-14 years) in combination with the small gradual increase in the incidence of the disease in girls (annual percent change: +1.0%) as contrasted with the male preponderance characterizing other childhood cancers (9, 10) provide some evidence for the reliability of our results; nevertheless, the sex-related differentials of our study merit further consideration given the borderline significant interactions of sex with AFG in the total age group (0-14 years). To this end, further research is needed given that sex-specific associations of fetal growth with risk of other cancers, including ALL and central nervous system tumors, have also been described (3, 4).

Strengths and limitations

Main strengths of the present study include the sound methodological approach including the availability of the largest set of harmonized individual study data for this rare form of childhood cancer -especially infant AML- contributed by 22 studies around the globe, which were pooled and meta-analyzed as appropriate in comprehensively-adjusted models. Indeed, low power was a substantial limitation of previous studies (54). Despite the proportion of missing values, we assessed several fetal growth markers beyond the gross marker of birthweight, overall and within informative sub-groups. In particular, we performed analyses using alternative fetal growth markers, such as birthweight, birth length and weight-for-length ratio adjusted for gestational age. Moreover, intergrowth standardized curves, based on a population-based, multiethnic, multi-country and sex-specific prospective study, were used (20, 55). Furthermore, results from population-based record linkage studies were materially

the same as those springing from QCC studies and they were thus presented jointly. Finally, we performed stratified analyses by sex and AML morphological FAB-subtype, given the different endometrial environments and levels of growth factors by sex of embryos, as well as by age given the differential biological profile of infant AML as contrasted to the disease among older age groups of children.

Regarding limitations in the assessment of exposures of interest and despite maternal self-reports of birthweight being considered reliable (56) different methods were used to report/record gestational age depending on the study; diverse were also the diagnostic periods across studies. Yet, the between-study heterogeneity was minimal and any inaccuracies in reporting between cases and the comparison groups are expected to be non-differential, since gestational age is not widely considered as a risk factor for childhood leukemia (57). Several CLIC-QCC studies are nationwide or region-wide easing concerns of control selection. It is true, however, that most studies provide partial or no information on cytogenetic recurrent aberrations according to the International Classification of Diseases for Oncology (ICD)-O-3 coding, especially for the KMT2A/MLL rearrangement status that could have allowed to explore a possible association with fetal growth. Additionally, there have been inherent limitations in application of the POBW formula (12) in this international study beyond the high proportion of missing data mainly on maternal height. Moreover, possible confounding factors, such as maternal smoking, diabetes and weight gain during pregnancy, were not included in the models due to high proportions of missing data leaving room for residual confounding. Lastly, there is no gold standard in defining AFG when comparing across populations and the use of the INTERGROWTH 21st standard international distribution did not only capture the top 10% of babies according to the traditional categorization of LGA, but the approximately top 20%, while the low fetal growth category encompassed roughly 6-7% of babies instead of 10%. There is, however, no reason to assume that increased AML risk was confined to only the top 10% so that AML risk is increased within the top 20% is merely an observation of our study. Future studies in larger samples, i.e. in countries with birth

registries, should explore in more detail the dose-response function, if any. Besides that, alternative analyses employing the empirical 10% and 90% distribution within our controls had no impact on the results of the main analyses.

Conclusion

This is the largest study to-date to explore the association between fetal growth and childhood AML risk using robust markers and *a priori* designed age and sex sub-analyses. Our results are in line with those of previous studies showing a positive association with indices of accelerated fetal growth, such as HBW. The findings further specify, however, that the association is confined to boys known have a more accelerated fetal growth compared to girls, especially in infancy and with undifferentiated (M0) or with minimal maturation (M1) myeloid leukemia. By contrast, there seems to be no support for an association with decelerated fetal growth. Sub-group analyses on cytogenetics could further refine our understanding of the mechanisms through which accelerated fetal growth may increase childhood leukemia risk.

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Table 1. Distribution of the study variables among 3564 children (0-14 years) with acute myeloid leukemia (AML) and 9584 controls

Variables	**Cases**		**Controls**		
	N	%*	N	%	*p*-value (chi-square)
Age at diagnosis/index date (years)					0.81
<1	656	18.4	1751	18.3	
1-4	1323	37.1	3646	38.0	
5-9	779	21.9	2065	21.5	
10-14	805	22.6	2121	22.1	
*Missing***	*1*	*0.0*	*1*	*0.0*	
Sex					0.96
Male	1854	52.0	4981	52.0	
Female	1710	48.0	4603	48.0	
*Missing***	*0*	--	*0*	--	
Maternal age (years)					0.07
<25	1102	31.0	2883	30.1	
25-29	1139	32.1	3157	33.0	
30-34	841	23.7	2386	25.0	
≥35	470	13.2	1136	11.9	
*Missing***	*12*	*0.3*	*22*	*0.2*	
Birth order					0.08
1st	1321	37.6	3542	37.9	
2nd	1203	34.2	3392	36.3	
≥3rd	991	28.2	2407	25.8	

*Missing***	*49*	*1.4*	*243*	*2.5*	
Child's ethnicity					0.01
Caucasian	2463	69.3	6398	66.9	
Other	1093	30.7	3171	33.1	
*Missing***	*8*	*0.2*	*15*	*0.2*	
Plurality					0.02
No	3429	98.2	9145	97.5	
Yes	63	1.8	233	2.5	
*Missing***	*72*	*2.0*	*206*	*2.1*	
Prematurity (<37 weeks)					0.02
No	3036	91.0	8215	92.3	
Yes	300	9.0	686	7.7	
*Missing***	*228*	*6.4*	*683*	*7.1*	
Birthweight (grams)					0.19
<2500	208	6.0	549	6.0	
2500-3999	2844	81.4	7632	82.6	
≥4000	439	12.6	1055	11.4	
*Missing***	*73*	*2.0*	*348*	*3.6*	
Birthweight for gestational age****					0.008
SGA	228	7.0	561	6.6	
AGA	2261	69.4	6159	72.2	
LGA	771	23.6	1810	21.2	
*Missing***	*304*	*8.5*	*1054*	*11.0*	
Birth length for gestational age****					0.92

SGA	23	4.0	56	4.4	
AGA	292	50.9	645	50.2	
LGA	259	45.1	583	45.4	
*Missing***	*2985*	*83.7*	*8300*	*86.6*	
Birth weight-for-length ratio for gestational age***					0.24
SGA	49	8.5	104	8.1	
AGA	413	72.1	970	75.5	
LGA	111	19.4	210	16.4	
*Missing***	*2991*	*83.9*	*8300*	*86.6*	

*Proportions after exclusion of missing values; **Percent of total; ***Intergrowth Curve: IC; SGA: Small for gestational age (<10th of IC), AGA: Appropriate for gestational age (10th-90th of IC), LGA: Large for gestational age (>90th of IC)

Table 2. Overall and sex-specific meta-analysis-derived Odds Ratios (OR) and 95% Confidence Intervals (95% CI) [*] on the association of birthweight and birthweight for gestational age with childhood (0-14 years) acute myeloid leukemia (AML)

Variables	Total OR (95% CI)[**]	Males OR (95% CI)	Females OR (95% CI)
Birthweight (grams)			
<2500	0.97 (0.78-1.20)	0.90 (0.57-1.42)	1.03 (0.77-1.39)
2500-3999	reference	reference	reference
≥4000	1.15 (0.98-1.34)	**1.21 (1.03-1.43)**	1.02 (0.74-1.41)
Birthweight for gestational age[a]			
SGA	1.05 (0.88-1.25)	0.99 (0.73-1.36)	1.07 (0.83-1.37)
AGA	reference	reference	reference
LGA	**1.20 (1.03-1.39)**	**1.25 (1.06-1.46)**	1.22 (0.94-1.58)[b]

In bold: statistically significant associations; *Meta-analysis comprising pooled analysis-derived estimates from the studies providing primary data along with the provided adjusted estimates; **Adjusted for index child's age, sex, ethnicity, maternal age at birth, plurality, birth order, prematurity and study of origin; [a] Intergrowth Curve: IC; SGA: Small for gestational age (<10^{th} of IC), AGA: Appropriate for gestational age (10^{th}-90^{th} of IC), LGA: Large for gestational age (>90^{th} of IC); [b] Statistically significant heterogeneity: $LGA_{female;}$: I^2=57.5%, p=0.09

Table 3. Age and sex-specific meta-analysis-derived Odds Ratios (OR) and 95% Confidence Intervals (95% CI)* on the association of birthweight and birthweight for gestational age with childhood (0-14 years) acute myeloid leukemia (AML)

Variables	Total OR (95% CI)**	Males OR (95% CI)	Females OR (95% CI)	Total OR (95% CI)**	Males OR (95% CI)	Females OR (95% CI
	Age<2 years			*Age: 2-14 years*		
Birthweight (grams)						
<2500	0.99 (0.69-1.42)	1.06 (0.61-1.85)	0.92 (0.55-1.52)	0.96 (0.73-1.26)	0.80 (0.51-1.25)	1.15 (0.79-1.6
2500-3999	reference	reference	reference	reference	reference	reference
≥4000	1.20 (0.97-1.66)	**1.34 (1.01-1.79)**	1.16 (0.74-1.82)	1.13 (0.91-1.41)	1.17 (0.96-1.44)	1.03 (0.78-1.3
Birthweight for gestational age[a]						
SGA	0.87 (0.63-1.19)	1.04 (0.67-1.62)	0.72 (0.45-1.15)	1.14 (0.92-1.41)	0.94 (0.53-1.68)[b]	1.19 (0.88-1.6
AGA	reference	reference	reference	reference	reference	reference
LGA	**1.24 (1.01-1.53)**	**1.34 (1.05-1.71)**	1.32 (0.80-2.17)[b]	**1.15 (1.01-1.31)**	**1.22 (1.02-1.46)**	1.10 (0.90-1.3
	Age<1 year			*Age: 1-14 years*		
Birthweight (grams)						
<2500	1.26 (0.77-2.06)	1.88 (0.88-4.03)	0.78 (0.32-1.88)	0.93 (0.73-1.18)	0.75 (0.48-1.17)	1.12 (0.81-1.5
2500-3999	reference	reference	reference	reference	reference	reference
≥4000	1.36 (0.83-2.24)	1.21 (0.71-2.07)	1.22 (0.57-2.61)	**1.16 (1.01-1.34)**	**1.22 (1.02-1.46)**	1.08 (0.77-1.5
Birthweight for gestational age[a]						
SGA	0.91 (0.99-1.39)	1.25 (0.65-2.42)	0.77 (0.41-1.45)	1.08 (0.89-1.31)	0.89 (0.51-1.54)[b]	1.17 (0.88-1.5
AGA	reference	reference	reference	reference	reference	reference
LGA	1.21 (0.95-1.55)	**1.49 (1.03-2.14)**	1.01 (0.66-1.58)	**1.20 (1.03-1.41)**	**1.23 (1.00-1.51)**	1.19 (0.96-1.4

In bold: statistically significant associations; *Meta-analysis comprising pooled analysis-derived estimates from the studies providing primary data along with the provided adjusted estimates; **Adjusted for index child's age, sex, ethnicity, maternal age at birth, plurality, birth order, prematurity and study of origin; [a] Intergrowth Curve: IC; SGA: Small for gestational age (<10th of IC), AGA: Appropriate for gestational age (10th-90th of IC), LGA: Large for gestational age (>90th of IC); [b] Statistically significant heterogeneity: $LGA_{females;\ <2y}$: I^2=68.7%, p=0.04; $SGA_{males;\ 2\text{-}14yrs}$: I^2=59.8%, p=0.08; $SGA_{males;\ 1\text{-}14yrs}$: I^2=65.1%, p=0.06

Table 4. Meta-analysis derived, subtype- and sex- specific effect estimates [Odds Ratios (OR) and 95% Confidence Interval (95% CI)] on the association of birthweight and birthweight for gestational age with childhood (0-14 years) acute myeloid leukemia (AML) risk

	Total	Males	Females
	OR (95% CI)*	OR (95%CI)	OR (95% CI)
M0-M1 cases (N=210) versus controls (N=2244)			
Birthweight (grams)			
<2500	0.83 (0.41-1.68)	0.87 (0.34-2.22)	0.74 (0.25-2.23)
2500-3999	reference	reference	reference
≥4000	1.32 (0.86-2.05)	1.28 (0.75-2.19)	1.40 (0.66-2.99)
Birthweight for gestational age**			
SGA	1.18 (0.66-2.10)	1.93 (0.95-3.92)	0.55 (0.19-1.61)
AGA	reference	reference	reference
LGA	**1.55 (1.09-2.20)**	**1.85 (1.18-2.91)**	1.22 (0.69-2.17)
M2 cases (N=265) versus controls (N=2345)			
Birthweight (grams)			
<2500	1.03 (0.37-2.81)	0.99 (0.36-2.72)[a]	0.50 (0.14-1.82)[a]
2500-3999	reference	reference	reference
≥4000	1.17 (0.79-1.77)	1.16 (0.69-1.94)	1.17 (0.59-2.34)
Birthweight for gestational age			
SGA	1.11 (0.66-1.88)	0.71 (0.22-2.29)	2.18 (0.38-12.54)[b]
AGA	reference	reference	reference
LGA	1.04 (0.74-1.46)	0.96 (0.61-1.52)	1.23 (0.62-2.44)
M3 cases (N=155) versus controls (N=2340)			
Birthweight (grams)			

<2500	1.47 (0.63-3.42)	2.09 (0.50-8.78)[a]	2.14 (0.77-5.95)
2500-3999	reference	reference	reference
≥4000	0.85 (0.42-1.74)	0.47 (0.14-1.56)[a]	1.90 (0.92-3.93)
Birthweight for gestational age			
SGA	1.14 (0.56-2.29)	0.95 (0.32-2.78)	1.52 (0.58-4.02)
AGA	reference	reference	reference
LGA	1.10 (0.71-1.69)	0.59 (0.25-1.44)	1.76 (0.99-3.13)
	M4-M5 cases (N=600) versus controls (N=2915)		
Birthweight (grams)			
<2500	0.99 (0.51-1.91)	0.60 (0.29-1.27)	1.14 (0.67-1.96)
2500-3999	reference	reference	reference
≥4000	1.00 (0.74-1.34)	1.23 (0.75-2.01)	0.80 (0.48-1.33)
Birthweight for gestational age			
SGA	1.04 (0.72-1.52)	1.03 (0.57-1.84)	1.05 (0.64-1.72)
AGA	reference	reference	reference
LGA	1.18 (0.95-1.50)	1.30 (0.96-1.77)	1.12 (0.82-1.54)
	M6-M7 cases (N=223) versus controls (N=2542)		
Birthweight (grams)			
<2500	0.90 (0.45-1.80)	1.21 (0.34-4.27)	0.70 (0.25-1.94)
2500-3999	reference	reference	reference
≥4000	1.08 (0.68-1.72)	0.95 (0.50-1.80)	1.22 (0.57-2.62)
Birthweight for gestational age			
SGA	1.06 (0.56-1.99)	1.08 (0.46-2.52)	0.86 (0.31-2.35)
AGA	reference	reference	reference
LGA	1.12 (0.79-1.61)	0.87 (0.51-1.48)	1.45 (0.88-2.39)

In bold statistically significant associations; *Adjusted for index child's age, sex, ethnicity, maternal age at birth, plurality, birth order, prematurity and study of origin; ** Intergrowth Curve: IC; SGA: Small for gestational age (<10th of IC), AGA: Appropriate for gestational age (10th-90th of IC), LGA: Large for gestational age (>90th of IC); [a] No meta-analysis performed: estimates derived from the studies providing primary data; [b] Statistically significant heterogeneity: I^2=76.2%, *p*=0.04

Supplementary Table 1. Studies participating in the Childhood Leukemia International Consortium analysis of fetal growth markers and risk of childhood (0-14 years) acute myeloid leukemia (AML)

Study location, Acronym	Recruitment	Cases source	Controls source/recruitment type	Cases, N	Controls, N
Registry-based case-control studies					
Denmark	1968-2016	National Cancer Registry	Central Population Register/ Electronic linkage	249	747
Finland	1989-2011	National Cancer Registry	National Central Population Register/ Electronic linkage	127	381
Taiwan	2004-2014	National Cancer Registry	Taiwan Maternal and Child Health Database	112	336
US, California State, CCLRP[1]	1988-2011	Statewide Cancer Registry	Linked State birth-hospital discharge records	846	2976
US, Minnesota, State US, New York, State US, Texas, State	1988-2004 1985-2001 1990-1998	National Cancer Registry National Cancer Registry National Cancer Registry	State birth certificates State birth certificates State birth certificates	489	1467
US, Washington State	1974-2014	Cancer Registry (regional 1974-1993; statewide 1994-onwards)	Linked State birth-hospital discharge records	177	531

Questionnaire-based case-control studies					
Brazil	1998-2015	Hospitals	Hospitals/Interviews	151	453
Costa Rica, CRCLS	2001-2003	Nationwide Cancer Registry	Nationwide Birth registry/Interviews	39	117
France, ADELE France, ELECTRE France,ESCALE France, ESTELLE	1994-1999 1995-1998 2003-2005 2010-2012	Hospitals of Lille, Lyon, Nancy & Paris National Blood Malignancy Registry National Blood Malignancy Registry National Blood Malignancy Registry	Same hospitals as cases National Random digit dialing National Random digit dialing National Random digit dialing	291	873
Germany, GCCR	1991-1994	Childhood Cancer Registry (nationwide)	German Registries of residents (regional with national coverage)/ Interviews	98	294
Greece, NARECHEM-ST[2]	1996-2015	Nationwide Clinical Cancer Registry	Hospitals/Interviews	138	138
Italy, SETIL	1998-2001	Nationwide Cancer Registry	National health system rosters/Interviews	69	97
New Zealand, NZCCS	1989-1994	National Cancer Registry, Children's Cancer Registry; Hospital Admission/Discharge system	Nationwide Birth Registry/ Interviews	22	66
UK, UKCCS	1991-1997	Nationwide General Practitioners' Registry	Nationwide General Practitioners' registry/ Interviews	235	465

US, Texas State	1997-2015	Hospitals	Hospital/Interviews	8	24
US, COG[3]-AE24[4]	1996-2006	COG institutions; US and Canada	Random digit dialing/Birth registries	132	240
US,COG-E14	1989-1993	CCG clinical trials	Random digit dialing/Interviews	401	469

[1] Effect estimates were provided for the meta-analyses by the registry-based case-control studies of Taiwan, US, California State and US, Minnesota/New York/Texas States; [2] Nationwide Registry for Childhood Hematological Malignancies and Solid Tumors; [3]Children's Oncology Group; 4: Overlapping cases with the remaining US studies have been excluded

Supplementary Table 2. Proportion of missing values (overall % for cases and controls) of the study variables by participating study

Study location, Name	Birthweight	Birthweight for GA*	Birth length for GA	Weight-for-length for GA	POBW**	AML FAB	Child's age	Child's sex	Child's ethnicity	Birth plurality	Preterm birth	Birth order	Maternal age
Registry-based case-control studies													
Denmark	9.2	9.3	9.9	9.9	3.6	84.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Finland	16.7	16.7	17.1	17.1	85.8	9.5	0.0	0.0	0.0	16.5	16.7	16.9	0.2
Taiwan	0.0	0.0	100.0	100.0	100.0	47.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
US, California State CCLRP	0.0	0.0	100.0	100.0	100.0	41.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
US, Minnesota/ New York/Texas States	8.8	10.4	100.0	100.0	100.0	100.0	0.0	0.0	0.0	0.1	1.9	0.1	0.0
US, Washington State	0.3	11.4	100.0	100.0	77.4	100.0	0.0	0.0	1.4	0.1	11.4	1.6	0.0
Questionnaire-based case-control studies													
Brazil	4.8	70.4	75.7	75.8	100.0	5.3	0.0	0.0	0.0	0.0	67.4	25.7	1.0
Costa Rica, CRCLS	11.5	100.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	100.0	0.6	0.6	0.6
France, ADELE/ ELECTRE/ESCALE/ESTELLE	0.7	4.8	100.0	100.0	100.0	7.9	0.2	0.0	0.8	0.1	4.2	0.3	0.3
Germany, GCCR	1.0	2.3	100.0	100.0	100.0	100.0	0.0	0.0	0.0	0.0	1.5	0.0	0.3
Greece, NARECHEM-ST*	1.1	63.0	71.0	71.0	68.5	1.5	0.0	0.0	0.0	0.0	62.7	0.0	0.0
Italy, SETIL	0.0	38.0	100.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	38.0	0.0	0.6

New Zealand, NZCCS	1.1	2.3	100.0	100.0	100.0	4.6	0.0	0.0	0.0	0.0	1.1	0.0	0.0
UK, UKCCS	1.7	1.9	100.0	100.0	100.0	9.8	0.0	0.0	0.4	0.4	0.6	0.4	0.9
US, Texas State	3.1	15.3	40.6	40.6	100.0	100.0	0.0	0.0	0.0	100.0	15.6	100.0	31.3
US, COG*-AE24	0.0	0.0	1.6	1.6	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.5
US, COG-E14	0.3	0.3	100.0	100.0	100.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2

* Abbreviations: GA, Gestational age; NARECHEM-ST, Nationwide Registry for Childhood Hematological Malignancies and Solid Tumors; COG, Children's Oncology Group POBW, **Proportion of optimal birthweight: approximate estimation based on the % of missing values on maternal height

Supplementary Table 3. Overall and sex-specific multiple logistic regression-derived Odds Ratios (OR) and 95% Confidence Intervals (95% CI) on the association of birth length and weight-for-length ratio adjusted for gestational age with childhood (0-14 years) acute myeloid leukemia (AML)

Variables	Total (N=564 cases/1265 controls) OR (95% CI)*	Males (N=277 cases/605 controls) OR (95% CI)	Females (N=287 cases/660 controls) OR (95% CI)
Birth length**:			
SGA	0.69 (0.40-1.20)	0.47 (0.20-1.12)	0.91 (0.43-1.90)
AGA	reference	reference	reference
LGA	1.14 (0.91-1.42)	**1.38 (1.00-1.92)**	1.00 (0.74-1.35)
Weight-for-length ratio**:			
SGA	0.98 (0.67-1.45)	0.74 (0.39-1.39)	1.23 (0.74-2.02)
AGA	reference	reference	reference
LGA	1.16 (0.88-1.52)	1.17 (0.79-1.74)	1.18 (0.80-1.72)

In bold: statistically significant associations; *Adjusted for index child's age, sex, ethnicity, maternal age, plurality, birth order and study of origin; **Intergrowth Curve: IC; SGA: Small for gestational age (<10th of IC), AGA: Appropriate for gestational age (10th-90th of IC), LGA: Large for gestational age (>90th of IC)