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Age-, sex- and disease subtype–related foetal growth differentials in childhood acute myeloid leukaemia risk: A Childhood Leukemia International Consortium analysis

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Abstract ***Aim:*** Evidence for an association of foetal growth with acute myeloid leukaemia (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 the hypothesis that the association may vary by age, sex and disease subtype using data from 22 studies and a total of 3564 AML cases.

Methods: Pooled estimates by age, sex and overall for harmonised foetal growth markers in association with AML were calculated using the International Fetal and Newborn Growth Consortium for the 21st Century Project for 17 studies contributing individual-level data; meta-analyses were, thereafter, conducted with estimates provided *ad hoc* by five more studies because of administrative constraints. Subanalyses by AML subtype were also performed.

Results: A nearly 50% increased risk was observed among large-for-gestational-age infant boys (odds ratio [OR]: 1.49, 95% confidence interval [CI]: 1.03–2.14), reduced to 34% in boys aged <2 years (OR: 1.34, 95% CI: 1.05–1.71) and 25% in boys aged 0–14 years (OR: 1.25, 95% CI: 1.06–1.46). The association of large for gestational age became stronger in boys with M0/M1subtype (OR: 1.80, 95% CI: 1.15–2.83). Large birth length for gestational age was also positively associated with AML (OR: 1.38, 95% CI: 1.00–1.92) in boys. By contrast, there were null associations in girls, as well as with respect to associations of decelerated foetal growth markers.

Conclusions: Accelerated foetal growth was associated with AML, especially in infant boys and those with minimally differentiated leukaemia. Further cytogenetic research would shed light into the underlying mechanisms.

1. Introduction

Foetal growth is one of the most commonly studied perinatal risk factors of childhood cancer [1–5]. Measures of foetal 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 foetal growth, and childhood acute lymphoblastic leukaemia (ALL); however, their results remain inconclusive for acute myeloid leukaemia (AML) [1,4,7,8]. AML is a rare childhood cancer with distinct features in infancy and is relatively more frequent in girls as contrasted with other childhood cancers [9,10]. A U-shaped association of birthweight with AML risk has been reported [7]; yet, fewer studies have explored the potential relationship of more robust foetal growth measures, such as birthweight 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 the foetal growth rate, rather than birthweight *per se*, may be more strongly associated with childhood leukaemia, 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 (IGFs) I and II, as well as sex steroid hormones [14,15]. Any association between low birthweight and AML is speculated to be due to foetal programming and genomic stability determined by epigenetic pathways, which affect the growth hormone-IGF axis through hyperinsulinaemia, as per 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 the published literature, we sought to assess the association of measures of foetal growth with the risk of childhood AML by pooling and analysing international data from the CLIC. Specifically, we focused on the potential associations between AML and available foetal 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.

2. Methods

2.1. Study population

The CLIC, established in 2007, invests in childhood cancer etiologic research to identify preventive factors and promote research translation by pooling and met-analysing international data from independent studies [18]. Fourteen questionnaire-based case-control (QCC) and eight registry-based case-control (RCC) studies provided data for this collaborative CLIC analysis. Registration process and data collection in the study reported by Panagopoulou et al. [19] are summarised in eTable 1. Information for the RCC studies conducted in Denmark, Finland, Taiwan, and five states of the US (California, Minnesota, New York, excluding New York City, Texas and Washington) was derived from linkage of nationwide or statewide population-based cancer registries with administrative registries (eTable 1).

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 owing to administrative constraints. Pooled estimates were derived from the remaining 17 studies, which provided individual-level data, namely, the RCC CLIC studies from Denmark, Finland and Washington as well as the QCC CLIC studies conducted in Brazil, Costa Rica, France (ADELE, ELECTRE, ESCALE and ESTELLE), Germany, Greece, Italy, New Zealand, the United Kingdom and the US (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 (aged 0–14 years) from the QCC COG-AE24 study who were born in California, Washington, Minnesota, New York and Texas (40 cases and 84 controls) were excluded based on the diagnosis year because of overlap with the remaining US studies. Children with Down syndrome were also excluded, given the particular biological mechanisms of acute myeloid leukaemogenesis in these patients [20]. A total of 3564 AML cases and 9584 controls from the 22 participating studies (19 CLIC and 3 non-CLIC studies) were eventually included in this analysis.

2.2. Data collection and harmonisation

Information on sociodemographic and birth characteristics of cases and controls including foetal growth measures was harmonised across studies. Whenever controls were frequency matched to cases by age and sex in the original studies (those conducted in Brazil, Costa Rica, Denmark, France, Germany, New Zealand and Taiwan, the QCC and RCC studies conducted in Texas and the RCC studies conducted in the US: California, Minnesota, New York and Washington), a maximum of three controls were randomly selected from the respective study databases.

Information on birth characteristics was obtained from birth certificates, medical birth records or maternal self-reports, depending on the study design. Birthweight for gestational age was examined using the 10th and 90th percentiles of the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) birthweight standard [21]. Three categories for birthweight for gestational age were used: small for gestational age (SGA) for neonates weighing below the 10th percentile of the reference population, appropriate for gestational age for neonates weighing between the 10th and 90th percentiles and large for gestational age (LGA) for neonates weighing above the 90th percentile. The same process was used to categorise the other foetal growth markers, namely, birth length for gestational age and weight-for-length ratio for gestational age. Applying this procedure to our data resulted in approximately 20% of newborns categorised as LGA and 6–7% as SGA. We therefore label them as accelerated foetal growth (AFG) and low foetal 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.

2.3. Statistical analysis

The overall analysis model included the matching factors and potential confounders, selected *a priori* based on the existing literature: the 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, ≥ 35 years), birth order (1st, 2nd, ≥3rd), the child's ethnicity (Caucasian, other) [19], plurality (yes, no), study of origin and prematurity (gestational age <37 weeks: yes, no; only in the analyses of birthweight alone), whenever appropriate to be introduced as an independent variable. The primary exposures of interest were birthweight for gestational age, birth length for gestational age and weight-for-length ratio for gestational age, and they were alternatively introduced into the overall analysis model. In addition, to provide comparable estimates with previous studies, which showed a U-shaped association [6], the standard birthweight categories (<2500, 2500–3999 [reference] and ≥4000 g) were used to examine the impact of birthweight alone on AML risk. The proportion of missing data for each variable per study is presented in eTable 2.

Given the different biological characteristics of AML during infancy and the first two years of life, as well as the increasing incidence of the disease in girls as contrasted with other childhood cancers [10,22], we initially examined the associations of birthweight and birthweight for gestational age with AML risk separately for each sex (boys and girls) and for the age groups <1 year and 1–14 years, or alternatively <2 years and 2–14 years. Formal testing for interaction of birthweight or birthweight for gestational age with age or sex was thereafter applied in the pooled data set as to explore this *a priori* hypothesis. In addition, we explored the potential effect modification of sex on the aforementioned associations by calculating the relative excess risk due to interaction (RERI), the proportion attributable to the interaction (AP) and the synergy index (S) [23] in the total data set (0–14 years), as well as in the two age groups separately (<2 and 2–14 years). Given the borderline significant interactions observed, we fitted multivariable logistic regression models in the total pooled set of individual-level data. These pooled odds ratios (ORs) and 95% confidence intervals (CIs) for each exposure were thereafter meta-analysed using random-effect models [24] with the readily contributed adjusted effect estimates from studies not allowed to contribute individual-level data to obtain overall risk estimates for the total of 22 studies. Between-study heterogeneity was assessed using the Cochran's Q and I^2 statistics. Study-specific meta-analyses comprising the 17 studies that provided individual-level data and sensitivity meta-analyses excluding a study per time were also performed.

Subanalyses 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) [25] were also performed.

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

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

Variables	Cases		Controls	
	N	%[a]	N	%[b]
Age at diagnosis/index date (years)				
<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[b]	1	0.0	1	0.0
Sex				
Male	1854	52.0	4981	52.0
Female	1710	48.0	4603	48.0
Missing[b]	0	–	0	–
Maternal age (years)				
<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[b]	12	0.3	22	0.2
Birth order				
1st	1321	37.6	3542	37.9
2nd	1203	34.2	3392	36.3
≥3rd	991	28.2	2407	25.8
Missing[b]	49	1.4	243	2.5
Child's ethnicity				
Caucasian	2463	69.3	6398	66.9
Other	1093	30.7	3171	33.1
Missing[b]	8	0.2	15	0.2
Plurality				
No	3429	98.2	9145	97.5
Yes	63	1.8	233	2.5
Missing[b]	72	2.0	206	2.1
Prematurity (<37 weeks)				
No	3036	91.0	8215	92.3
Yes	300	9.0	686	7.7
Missing[b]	228	6.4	683	7.1
Birthweight (grams)				
<2500	208	6.0	549	6.0
2500–3999	2844	81.4	7632	82.6
≥4000	439	12.6	1055	11.4
Missing[b]	73	2.0	348	3.6
Birthweight for gestational age[c]				
SGA	228	7.0	561	6.6
AGA	2261	69.4	6159	72.2
LGA	771	23.6	1810	21.2
Missing[b]	304	8.5	1054	11.0
Birth length for gestational age[c]				
SGA	23	4.0	56	4.4
AGA	292	50.9	645	50.2
LGA	259	45.1	583	45.4
Missing[b]	2985	83.7	8300	86.6
Birth weight-for-length ratio (WLR) for gestational age[c]				
SGA	49	8.5	104	8.1
AGA	413	72.1	970	75.5
LGA	111	19.4	210	16.4
Missing[b]	2991	83.9	8300	86.6

[a] Proportions after exclusion of missing values.
[b] Percentage of total.
[c] Based on the intergrowth curve (IC): SGA, small for gestational age (<10th of IC); AGA, appropriate for gestational age (10th–90th of IC) and LGA, large for gestational age (>90th of IC).

3. Results

3.1. 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 AFG for the purposes of this study were larger among AML cases than among controls (9.0% versus 7.7% and 23.6% versus 21.2%, respectively).

3.2. Birthweight and birthweight for gestational age

Based on the *a priori* hypothesis of age and sex differentials in the association of foetal 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 of 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 g; p for interaction = 0.04) and LFG (p for interaction = 0.04). Indeed, the age- and sex-specific meta-analyses showed positive associations of AML with the gross indicator of foetal growth, namely, HBW, among boy infants ($\mathrm{OR}_{\mathrm{boys}<1\mathrm{y};\ \mathrm{HBW}}$: 1.34, 95% CI: 1.01–1.79; data not shown). As shown in Table 2, a nearly 50% higher risk was observed among boy infants, when the more accurate measure, namely, birthweight for gestational age, was used ($\mathrm{OR}_{\mathrm{boys}<1\mathrm{y};\ \mathrm{AFG}}$: 1.49, 95% CI: 1.03–2.14); the risk was reduced to 34% among young boys aged <2 years ($\mathrm{OR}_{\mathrm{boys}<2\mathrm{ys};\ \mathrm{AFG}}$: 1.34, 95% CI: 1.05–1.71) and to 23% among boys aged 1–14 years ($\mathrm{OR}_{\mathrm{boys};\ 1-14\mathrm{yrs};\ \mathrm{AFG}}$: 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 g) or LFG with the risk of AML.

Table 3
Meta-analysis–derived disease subtype– and sex-specific summary effect estimates (odds ratio [OR] and 95% confidence interval [95% CI]) on the association of birthweight for gestational age[a] with childhood (age: 0–14 years) acute myeloid leukaemia (AML) risk.

	Total	Boys	Girls
	OR (95% CI)[b]	OR (95%CI)[b]	OR (95% CI)[b]
M0–M1 cases (N = 212) versus controls (N = 2244)			
SGA	1.16 (0.65–2.07)	1.86 (0.92–3.79)	0.55 (0.19–1.61)
AGA	Reference	Reference	Reference
LGA	1.53 (1.08–2.16)	1.80 (1.15–2.83)	1.22 (0.69–2.17)
M2 cases (N = 265) versus controls (N = 2345)			
SGA	1.11 (0.66–1.88)	0.71 (0.22–2.29)	2.18 (0.38–12.54)[c]
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)			
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 = 605) versus controls (N = 2915)			
SGA	1.04 (0.71–1.50)	1.01 (0.56–1.81)	1.05 (0.64–1.71)
AGA	Reference	Reference	Reference
LGA	1.18 (0.93–1.50)	1.28 (0.94–1.75)	1.13 (0.83–1.55)
M6–M7cases (N = 224) versus controls (N = 2542)			
SGA	1.05 (0.56–1.98)	1.07 (0.46–2.50)	0.86 (0.31–2.35)
AGA	Reference	Reference	Reference
LGA	1.11 (0.78–1.59)	0.85 (0.50–1.45)	1.45 (0.88–2.39)

[a] Based on the intergrowth curve (IC): SGA, small for gestational age (<10th of IC); AGA, appropriate for gestational age (10th–90th of IC) and LGA, large for gestational age (>90th of IC).

[b] Adjusted for child's age, sex, ethnicity, maternal age at birth, plurality, birth order and study of origin.

[c] Statistically significant heterogeneity: $I^2 = 76.2\%$, $p = 0.04$; Crump et al. [1].

Table 2
Meta-analysis–derived[a] age- and sex-specific summary effect estimates (odds ratio [OR] and 95% confidence interval [95% CI]) on the association of birthweight for gestational age[b] with childhood (age: 0–14 years) acute myeloid leukaemia (AML).

Variables	Total	Boys	Girls	Total	Boys	Girls
	OR (95% CI)[c]	OR (95% CI)[c]	OR (95% CI)[c]	OR (95% CI)[c]	OR (95% CI)[c]	OR (95% CI)[c]
	Age: 0–14 years			Age: 2–14 years		
SGA	1.05 (0.88–1.25)	0.99 (0.72–1.35)	1.07 (0.83–1.37)	1.14 (0.92–1.41)	0.94 (0.53–1.68)[d]	1.19 (0.88–1.61)
AGA	Reference	Reference	Reference	Reference	Reference	Reference
LGA	1.20 (1.03–1.39)	1.25 (1.06–1.46)	1.22 (0.94–1.58)[d]	1.15 (1.01–1.31)	1.22 (1.02–1.46)	1.10 (0.90–1.34)
	Age < 2 years			Age: 2–14 years		
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)[d]	1.19 (0.88–1.61)
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)[d]	1.15 (1.01–1.31)	1.22 (1.02–1.46)	1.10 (0.90–1.34)
	Age < 1 year			Age: 1–14 years		
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)[d]	1.17 (0.88–1.54)
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 (0.96–1.46)

[a] Meta-analysis comprising the pooled analysis–derived estimates from the studies providing individual-level data along with the adjusted estimates provided ad hoc.

[b] Based on the intergrowth curve (IC): SGA, small for gestational age (<10th of IC); AGA, appropriate for gestational age (10th–90th of IC) and LGA, large for gestational age (>90th of IC).

[c] Adjusted for child's age, sex, ethnicity, maternal age at birth, plurality, birth order and study of origin.

[d] Statistically significant heterogeneity: $\mathrm{LGA}_{\mathrm{female};\ 0-14\mathrm{yrs}}$: $I^2 = 57.5\%$, $p = 0.09$; $\mathrm{LGA}_{\mathrm{females};\ <2\mathrm{y}}$: $I^2 = 68.7\%$, $p = 0.04$; $\mathrm{SGA}_{\mathrm{males};\ 2-14\mathrm{yrs}}$: $I^2 = 59.8\%$, $p = 0.08$; $\mathrm{SGA}_{\mathrm{males};\ 1-14\mathrm{yrs}}$: $I^2 = 65.1\%$, $p = 0.06$.

The overall analysis (0−14 years of age) replicated the positive associations of AML with HBW (OR_{HBW}: 1.15, 95% CI: 0.98−1.34; not shown in Tables), whereas a 20% statistically significant increased risk was found 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). The association of AFG became stronger among children with AML FAB-M0 or FAB-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 3). By contrast, null associations were observed between birthweight and AML FAB-specific subtypes (not shown in Tables).

The findings remained robust in the sensitivity analyses of birthweight for gestational age based on the 10% and 90% distribution of the pooled set of controls (eTable 3). Overall, there was no evidence of heterogeneity across studies regarding the findings on infant boys or both sexes, except for the meta-analyses on AFG in girls aged 0−14 ($p = 0.09$) and <2 years ($p = 0.04$), as well as on LFG in boys aged 2−14 ($p = 0.08$) and 1−14 years ($p = 0.06$). Excluding the combined effect estimates provided by the RCC studies of Minnesota, New York and Texas, the heterogeneity became non-significant ($p = 0.18$−0.84), whereas the results of the main analyses did hardly change. Likewise, the study-specific meta-analyses and subanalyses by study design (not shown in Tables) showed essentially similar results with the main analyses without evidence of significant between-study heterogeneity.

3.3. Other foetal growth measures

Analyses of alternative foetal 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 (eTable 4). The positive associations of large birth length for gestational age ($OR_{larger\ for\ gestational\ age\ birth\ length}$: 1.14, 95% CI: 0.91−1.42) and large weight-for-length ratio for gestational age ($OR_{larger\ for\ gestational\ age\ weight-for-length}$: 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.

4. Discussion

4.1. Main findings

The pooled analysis and meta-analysis of the largest international data set contributed to this CLIC study provide evidence for a positive association of AFG with childhood AML, more marked in boys. Specifically, a robust association was found for newborns with AFG, larger in size among boy infants and those with minimally differentiated myeloid cell subtypes. Indeed, the impact of AFG on AML risk remained unchanged, although 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 g) nor LFG was associated with risk of AML in any sex or age group.

4.2. Previous literature

Our findings are consistent with recent studies that reported a positive association of AML with AFG, which relied, however, on a smaller number of cases and less comprehensive list of markers used [1,26,27] than those in 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; $OR_{low\ birthweight}$: 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) [28], 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 was found when birthweight was treated as a continuous variable (OR: 1.04, 95% CI: 0.98−1.12 per 500 g of increase) [29]. Our study did not support an association with decelerated foetal growth, either with low birthweight (<2500 g) *per se* or with the more accurate markers, namely, small-for-gestational-age weight or length.

4.3. Interpretation of the findings

The physiology of foetal growth is complex, involving genetic and environmental factors. Specifically, determinants of foetal 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 [30,31].

Growth factors seem to be the biologically plausible mechanisms underlying the association of AFG with AML [14,32]. *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 preleukaemic cells with pre-existing genetic abnormalities [33]. In vitro, IGF-1 stimulates the growth of lymphoid and myeloid cells, and it may also have antiapoptotic properties [34]. The IGF-2 imprinted gene is normally expressed from the paternally inherited allele [35]. The biallelic expression of IGF-2 attributed to epigenetic changes is likely to lead to foetal overgrowth, which might explain the association between AFG and AML incidence [36]. The effects of growth factors and their binding proteins on foetal macrosomia are more pronounced among mothers with diabetes but have also been observed among pregnant women without diabetes, highlighting the importance of normal weight gain during pregnancy [35,37]. 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 foetal growth rate, such as maternal pre-existing obesity, diabetes and weight gain during pregnancy, which may result in an increased maternal basal metabolic rate and IGF levels [38].

The stronger association of AFG with AML among infants compared with 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 [29]. In addition, infant AML is characterised 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 haematological malignancies later in life [39,40]. 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 [41]. These aberrations seem to occur more frequently in ageing cells because of shortening of telomeres and less efficient DNA repair capacity in immature cells. Therefore, the age-specific distribution of specific changes in haematopoiesis and pools of haematopoietic precursors as targets for leukaemogenesis might be explained by earlier effects of environmental growth factors [42].

Finally, the sex-associated findings of our study could be used in the context of foetal sex as a modifier of foetoplacental growth. Indeed, recent studies show that male foetuses may grow faster than female foetuses, confirming the known mean 150-g difference of male birthweight compared with that of female foetuses [43,44]. 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 synthesised by the testes and sex-related differences in the growth rate before differentiation of the foetal gonads [45,46], which may lead among others to a higher mean weight of boys at birth as a result of activation of the IGF axis, despite the fact that boys as a rule are born one week earlier than girls [47,48]. 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 characterising other childhood cancers [9,10] provides 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, future research is needed, given that sex-specific associations of foetal growth with risk of other cancers, including ALL and central nervous system tumours, have also been described [3,4].

4.4. Strengths and limitations

Main strengths of the present study include the sound methodological approach including the availability of the largest set of harmonised individual-level data for this rare type of childhood cancer—especially infant AML—contributed by 22 studies around the globe, which were pooled and meta-analysed as appropriate in comprehensively adjusted models. Indeed, low power was a substantial limitation of previous studies [49]. Despite the proportion of missing values, we assessed several foetal growth measures beyond the gross marker of birthweight, overall and within informative subgroups. In particular, we performed analyses using alternative foetal growth markers, such as birthweight for gestational age, birth length for gestational age and weight-for-length ratio for gestational age. Moreover, intergrowth standardised curves, based on a population-based, multiethnic, multicountry and sex-specific prospective study, were used [21,50,56]. Furthermore, results from population-based record linkage RCC studies were materially the same as those springing from QCC studies. 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 [51,57], different methods were used to report/record gestational age depending on the study design; the diagnostic periods were also diverse across studies. However, the between-study heterogeneity was minimal, and any inaccuracies in reporting between cases and the comparison groups are expected to be non-differential because gestational age is not widely considered as a risk factor for childhood leukaemia [52,58]. Several CLIC QCC studies are nationwide or region-wide, easing concerns of control selection. Moreover, it is true that most studies provided partial or no information on cytogenetic recurrent aberrations as per the International Classification of Diseases for Oncology (ICD-O-3) coding, especially for the KMT2A/MLL rearrangement status that could have allowed exploring a possible association with foetal growth. In addition, there have been inherent limitations in the 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 because of high proportions of missing data, leaving room for residual confounding. Finally, there is no gold standard in defining AFG when comparing across populations, and the use of the INTERGROWTH 21st standard international distribution captured not only the top 10% of babies as per the traditional categorisation of LGA but also the approximately top 20%, whereas the LFG 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 using the empirical 10% and 90% distribution within our controls had no impact on the results of the main analyses.

5. Public health perspective and conclusions

Over the last decades, temporal increases in mean birthweight have been reported in Western countries [53]. It is, thus, challenging to explore whether the approximately 10% of infants currently born macrosomic may have contributed to the overall increase in childhood cancer incidence [54]; in addition, given the consistent global increase in obesity rates and the positive association of overweight during pregnancy with AFG, this proportion might further increase [55]. In the same context, if the present results are replicated in future research, it would be also interesting to explore whether decelerated foetal growth due to socioeconomic restraints may negatively impact AML incidence. To this end, although the absolute risk seems to be low at a population level, given the rarity of childhood AML, it would be worth exploring whether modifiable factors leading to macrosomia may also affect AML risk to stimulate future monitoring and preventive interventions before and during pregnancy.

This is the largest study to date to explore the association between foetal growth and childhood AML risk using robust markers and *a priori* designed age and sex subanalyses. Our results are in line with those of previous studies showing positive associations with indices of AFG, such as HBW. The findings further specify, however, that the association is confined to boys known to have larger foetal growth than girls, especially in infancy and with undifferentiated (M0) or with minimal maturation (M1) myeloid leukaemia. By contrast, there seems to be no support for an association with decelerated foetal growth. Further cytogenetic research could further refine our understanding of the mechanisms through which AFG may increase childhood leukaemia risk.

Disclaimer

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Conflict of interest statement

The authors state that there is no personal, financial or other conflict of interest related to this study.

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Appendix A. Supplementary data

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Appendix 1

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