



Parental age and the risk of childhood acute myeloid leukemia: results from the Childhood Leukemia International Consortium

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ARTICLE INFO

Keywords:

Infant acute myeloid leukemia
Childhood cancer
Epidemiology
Maternal age
Paternal age
Risk factors

ABSTRACT

Background: Parental age has been associated with several childhood cancers, albeit the evidence is still inconsistent.

Aim: To examine the associations of parental age at birth with acute myeloid leukemia (AML) among children aged 0–14 years using individual-level data from the Childhood Leukemia International Consortium (CLIC) and non-CLIC studies.

Material/methods: We analyzed data of 3182 incident AML cases and 8377 controls from 17 studies [seven registry-based case-control (RCC) studies and ten questionnaire-based case-control (QCC) studies]. AML risk in association with parental age was calculated using multiple logistic regression, meta-analyses, and pooled-effect

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLIC, Childhood Leukemia International Consortium; RCC, registry-based case-control study; QCC, questionnaire-based case-control study; CI, confidence interval; OR, Odds ratio; COG, Children's Oncology Group

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<https://doi.org/10.1016/j.canep.2019.01.022>

Received 10 November 2018; Received in revised form 29 January 2019; Accepted 31 January 2019

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estimates. Models were stratified by age at diagnosis (infants < 1 year-old vs. children 1–14 years-old) and by study design, using five-year parental age increments and controlling for sex, ethnicity, birthweight, prematurity, multiple gestation, birth order, maternal smoking and education, age at diagnosis (cases aged 1–14 years), and recruitment time period.

Results: Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) derived from RCC, but not from the QCC, studies showed a higher AML risk for infants of mothers ≥ 40 -year-old (OR = 6.87; 95% CI: 2.12–22.25). There were no associations observed between any other maternal or paternal age group and AML risk for children older than one year.

Conclusions: An increased risk of infant AML with advanced maternal age was found using data from RCC, but not from QCC studies; no parental age-AML associations were observed for older children.

1. Introduction

Acute myeloid leukemia (AML) is very rare in children accounting for about 15% of all childhood leukemia cases [1]. Its incidence varies significantly between and within countries, continents and ethnic groups [1,2]. This variability could be due to genetic, environmental [3] or socioeconomic factors, although underascertainment of cases likely plays a role. AML incidence is higher in infants less than one year of age, dropping in childhood to gradually increase again in adolescents and young adults [3]. Heterogeneity by disease subtype and biologic characteristics is noticeable, especially among infants [4].

Large collaborative studies have examined the association of AML with several potential risk factors such as demographic and genetic characteristics [3], socioeconomic indices [5], environmental exposures (e.g. solvents [6], ambient air pollution [7], pesticides [8]), vitamins [9], infections, and birth characteristics [including anthropometrics [10], gestational age [11], birth order, and method of delivery (vaginal vs. cesarean) [12]], with findings that vary across studies for most factors. In contrast, associations of genetic syndromes (i.e., Down syndrome, Fanconi anemia, Bloom syndrome) with AML have been well established [3], but explain only a small percentage of all cases.

Several studies have examined the association between parental age and increased risk of various types of childhood cancer [13–16], acute leukaemia [17,18] and infant AML [19] in particular, with inconsistent results. We sought to elucidate this association by using the largest existing individual-level AML dataset. Here we report combined analyses of data from 17 studies; 13 participating in the Childhood Leukemia International Consortium (CLIC) across nine countries in Europe, America, and New Zealand and another four non-CLIC studies. To take into account the possible selection bias of some included case-control (CC) studies which required active participation [20], we analysed the data of registry-based case-control (RCC) studies separately from those of questionnaire-based case-control (QCC) studies.

2. Methods

2.1. Study designs and availability of data

CLIC was established in 2007 to promote investigations on the association of childhood leukemia with rare exposures and gene-environment interactions through pooling of data from independent studies internationally. Thirteen CLIC studies provided data. In order to further increase the size of our data four non-CLIC registry-based studies were also included (US, California State, CCLRP; US, Minnesota State; US, New York State; US, Texas State) and provided individual-level data from large-scale record-linkage of national or statewide population-based administrative registries. Overall, seven registry-based CC and 10 questionnaire-based CC studies were included in this pooling project. Of note, some of the questionnaire-based CC studies involve also subjects from population-based registries, at least with regards to case recruitment.

Adjusted summary estimates were provided by the California State registry-based CC study, whereas three State cancer registries

(Minnesota, New York -excluding New York City-, Texas) provided pooled analysis-derived estimates (Supplementary Table 1). Questionnaire-based CC studies conducted in Brazil, Costa Rica, Germany, Greece, Italy, New Zealand, UK, and the U.S. (California State, COG-E14, Texas State) provided individual-level data on the exposures of interest for cases and controls and disease-related information. The term QCC studies refers to the method of data collection via questionnaire and includes interview-based studies. Details on data collection for each study are reported elsewhere [21].

The age range of cases and controls at diagnosis or recruitment was 0–14 years. Children with Down syndrome –known to be associated with advanced maternal age- and an established strong risk factor for the development of leukemia [22,23] - were excluded from these analyses from both cases and controls, especially because this was an exclusion criterion for control enrollment in some studies.

2.2. Data collection and harmonization

Variables contributed by the individual studies were reviewed and harmonized. Whenever controls were frequency-matched on age [Brazil, Costa Rica, Denmark, Germany, New Zealand, Texas CC study, and the five RCC studies from the U.S. (States of California, Minnesota, New York, Texas, and Washington)], a maximum of three controls per case were randomly selected. Percentages of missing values for each variable per study were mostly small (Supplementary Table 2). For Denmark and Finland where ethnicity was not available, the data provider assigned the category Caucasian whereas for Costa Rica the category non-Caucasian was used.

2.3. Statistical analyses

Associations of childhood AML with paternal and maternal age were first examined using cubic spline models for each study with individual-level data but results were inconsistent across studies. Based on two recent publications [17,19] in order to explore the impact of extremely young and very advanced parental ages, six age categories were defined (< 20, 20–24, 25–29 [reference], 30–34, 35–39, ≥ 40 years) for maternal and paternal age.

Covariates included in the multivariable models were literature-derived, determined *a priori*, and categorized as follows: index child's age at diagnosis (< 1, 1–4, 5–9, 10–14 years) (used as a covariate only for analyses among 1–14 year olds); sex (male/female); child's ethnicity (Caucasian/non-Caucasian), birthweight (500 g increments; lowest and highest recorded weights were 501 g and 6001 g respectively); maternal education (low: secondary education not completed, intermediate: secondary education completed, high: college, university or higher degree); maternal smoking during pregnancy (yes/no); preterm birth (gestational age < 37 weeks: yes/no), multiple gestation (yes/no), birth order (1, 2, ≥ 3), and time period of diagnosis/recruitment (1968–1993, 1994–2003, 2004–2015). Paternal and maternal age variables were first included in the models separately and then simultaneously (i.e., mutual adjustment).

Risk estimates were calculated using maximally-adjusted logistic

regression models. Because of the known different biological characteristics of infant AML, models were stratified by age at diagnosis (< 1 year of age vs. 1–14 years) and also by study design (RCC vs. QCC) and analyses were conducted separately. Variables with > 20% missing values were excluded from study-specific models [17]. Data from the 10 questionnaire-based CC studies were pooled using unconditional logistic regression models controlling for individual study. Meta-analysis of individual study-effect estimates was not feasible in several CC studies due to paucity of data for some parental age groups for the analysis of infant AML cases (< 1 year-old). For the tabulated, registry-based case control, linkage-derived data meta-analysis was performed.

Among the seven registry-based CC studies, two effect estimates were supplied: one for the California State RCC study, a second for the combined effect estimate for Minnesota, New York and Texas States RCC studies. A third effect estimate was calculated from the pooled individual-level data for the remaining three registry-based CC studies (Washington State, Finland and Denmark). The three effect estimates were then combined using a random-effects meta-analysis, with heterogeneity of the estimates tested using Cochran Q and I^2 statistic (statistical significance was set at p -value < 0.10, derived from the Cochran Q test). The supplied effect estimates were adjusted for the same variables as those that we used in the raw data. Statistical analyses were conducted with SAS 9.4 version and STATA 14.1 version.

3. Results

3.1. Characteristics of the study population

A total of 3182 childhood (0–14 years) AML cases and 8377 controls were included in the analyses. The seven registry-based CC studies contributed data for 1888 cases (285 infants) and 6102 controls (922 infants); the 10 questionnaire-based CC studies contributed 1294 cases (186 infants) and 2275 controls (402 infants). Enrollment periods of diagnosis or recruitment varied by study and spanned from 1968 to 2015. Characteristics of cases and controls stratified by age group (< 1 year vs. 1–14 years) and by study design (RCC vs. QCC) are presented in Table 1. Differences in the distributions by sex, ethnicity, and time period at diagnosis in the infant dataset could be attributed to the differential distributions of these characteristics among subjects from Brazil, during the 1998–2015 period. When the Brazilian data were excluded (data not shown), the distributions became similar. Overall, boys outnumbered girls in the 1–14 year age group. Caucasians represented 65% and 73% of participants (cases and controls together) in RCC studies and QCC studies, respectively. The distribution of maternal and paternal age at childbirth of the controls was highly variable across studies (Supplementary Fig. 1).

3.2. Results by study design

Table 2 shows the results from the meta-analysis of the RCC studies and the multivariable analysis of the QCC studies. The meta-analysis of RCC studies indicated an almost seven-fold increase in AML risk for infants whose mothers were older than 40 years-old compared to infants whose mothers were 25–29 years-old ($OR_{RCC} = 6.87$, 95% CI = 2.12–22.25 - adjusted for paternal age). An increased AML risk for infants whose mothers were 40 years-old or older was also observed in the multivariable analysis of the QCC studies, but did not reach statistical significance and confidence intervals were wide ($OR_{QCC} = 3.31$, 95% CI = 0.64–16.98). None of the remaining maternal age groups were associated with AML risk neither among infants nor among older children. Analyses of the effect of paternal age showed no statistically significant associations with the risk for childhood AML in infants or in older children.

4. Discussion

In this study, the effect of parental age -a well-defined exposure variable- on the incidence of childhood AML was assessed using the largest dataset of newly diagnosed children with AML worldwide. A seven-fold increase in risk of AML before the age of one year was found for children born to mothers older than 40 years compared to mothers aged 25–29 years. No association of paternal age with AML risk was found in RCC or QCC studies.

The association of childhood cancer and leukemia with parental age has been previously investigated [13–15]. It has been shown that advanced parental age is associated with increased ALL risk in the offspring [17]. However, fewer studies have focused solely on the risk of AML. Recently, Marcotte et al, studied this association and found that maternal age > 40 years significantly increased the risk of infant AML ($OR:4.8$, 95%CI:1.8–12.76), whereas paternal age < 20 years was associated with an increased risk of infant ALL ($OR:3.69$, 95%CI: 1.62–8.41) [19]. The size of the effect of advanced maternal age was similar to that in the present study. Moreover, despite the relatively high effect magnitude when using multiplicative measures of association, the absolute risk increase as well as the derived attributable fractions remain small.

Similarly, in a recent study by Sergentanis et al, maternal age was found to be significantly associated with an increased risk of childhood AML in a U-shaped manner as both oldest (> 40 years) and youngest (< 20 years) ages were associated with a 23% increase in AML risk [18]. Also in these analyses, only fathers in the youngest age-group had a 28% increase in risk of having a child with AML[18]. In contrast to the study by Sergentanis et al, where results derived from the meta-analysis of 77 published case-control studies, in the current analysis, the participating studies contributed individual-level data which allowed more detailed analyses with simultaneous adjustment for maternal and paternal age. It also allowed subgroup analyses by age at diagnosis, which proved to be particularly important given the striking association of infant AML with advanced maternal age that emerged. The fact that the association of younger paternal age with AML reported by Sergentanis et al. was not replicated in the present study, could be attributed to methodological differences such as the use of data from RCC studies and not QCC studies which require active participation, the use of adjusted estimates, and the availability of primary data regarding age.

The association of advanced maternal age with infant AML may be explained by several mechanisms. Infant leukemia is characterized by high prevalence of MLL gene rearrangements (50–80% of infant ALL and 34–50% of infant AML compared to 6% and 14% in older children, respectively) [4,24,25]. In addition, secondary AML after chemotherapy with DNA topoisomerase-II inhibitors (e.g. epipodophyllotoxins) usually harbors a large number of MLL mutations [26]. It has been suggested that dietary exposure of pregnant women to naturally occurring topoisomerase-II inhibitors (e.g. in beans, fresh and canned vegetables, fruit, soy, coffee, tea, cocoa, and wine) [27] may contribute to the increased incidence of AML among their infants [28]. In the present study, no data on the MLL gene status of the cases were available, so it was not possible to assess this association. Further research incorporating genetic information should be conducted to better elucidate associations of maternal and paternal age with MLL mutation status.

Other carcinogenic effects and *de novo* mutations, associated with advanced maternal age, could also be involved in the etiology of infant AML. In a study of MLL-negative infant leukemia, where whole genome sequencing was performed for infant-mother pairs, a high burden of germline genetic variation in the MLL3 gene was found [29]. More specifically, it was shown that 100% of infant AML and 50% of infant ALL cases were compound heterozygotes of MLL3 [29]. Nearly half of the germline variation in the infants could be tracked to maternal alleles, and it was suggested that the additional germline variation was

Table 1
 Characteristics of acute myeloid leukemia (AML) cases and controls by study design and age at diagnosis (< 1 year, 1–14 years).

Age at diagnosis																
Study design →	< 1 year								1-14 years							
	Registry-based CC ^a				Questionnaire-based CC				Registry-based CC			Questionnaire-based CC				
	(no of studies = 7)				(no of studies = 10)				(no of studies = 7)			(no of studies = 10)				
Variables ↓	AML cases N = 285		Controls N = 922		AML cases N = 186		Controls N = 402		AML cases N = 1603		Controls N = 5180		AML cases N = 1108		Controls N = 1873	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Index child's age at diagnosis/recruitment (years)																
< 1	285	100.0	922	100.0	186	100.0	402	100.0								
1–4									766	47.8	2468	47.7	456	41.2	814	43.5
5–9									389	24.3	1260	24.3	331	29.9	579	30.9
10–14									448	27.9	1452	28.0	321	28.9	480	25.6
Index child's sex																
Male	131	46.0	423	45.9	100	53.8	243	60.5	836	52.2	2719	52.5	595	53.7	977	52.2
Female	154	54.0	499	54.1	86	46.2	159	39.5	767	47.8	2461	47.5	513	46.3	896	47.8
Time period at diagnosis/recruitment																
1968–1993	96	33.7	297	32.2	67	36.0	110	27.4	493	30.8	1551	29.9	508	45.9	785	41.9
1994–2003	122	42.8	400	43.4	62	33.3	216	53.7	725	45.1	2356	45.5	390	35.2	821	43.8
2004–2015	67	23.5	225	24.4	57	30.7	76	18.9	387	24.1	1273	24.6	210	18.9	267	14.3
Index child's race																
Caucasian	181	63.5	576	62.6	149	80.1	266	66.2	1072	67.0	3395	65.6	823	74.4	1367	73.0
Non-Caucasian	104	36.5	344	37.4	37	19.9	136	33.8	529	33.0	1779	34.4	283	25.6	505	27.0
Missing	0	0.0	2	0.2	0	0.0	0	0.0	2	0.1	6	0.1	2	0.2	1	0.1
Birthweight (g)																
< 2500	23	8.2	48	5.3	7	3.8	43	10.9	93	6.0	264	5.2	55	5.1	126	6.9
2500–2999	44	15.8	133	14.6	32	17.5	89	22.5	234	15.1	742	14.7	182	16.7	316	17.3
3000–3499	102	36.5	323	35.5	60	32.8	131	33.1	514	33.2	1784	35.5	368	33.8	670	36.6
3500–3999	78	28.0	287	31.6	66	36.1	105	26.5	489	31.6	1567	31.2	336	30.8	533	29.1
≥ 4000	32	11.5	118	13.0	18	9.8	28	7.0	219	14.1	673	13.4	148	13.6	184	10.1
Missing	6	2.1	13	1.4	3	1.6	6	1.5	54	3.4	150	2.9	19	1.7	44	2.4
Maternal education^b																
Low	42	17.4	118	14.6	42	22.8	130	32.4	170	15.5	503	14.2	294	26.8	520	28.1
Intermediate	131	54.4	462	57.1	97	52.7	210	52.4	655	59.6	2121	59.6	589	53.8	933	50.4
High	68	28.2	229	28.3	45	24.5	61	15.2	274	24.9	933	26.2	212	19.4	398	21.5
Missing	44	15.4	113	12.3	2	1.1	1	0.3	504	31.4	1623	31.3	13	1.2	22	1.2
Maternal smoking during pregnancy																
No	156	92.9	536	95.0	150	81.1	297	74.2	721	92.7	2373	92.3	856	77.9	1437	77.1
Yes	12	7.1	28	5.0	35	18.9	103	25.8	57	7.3	199	7.7	243	22.1	428	22.9
Missing	117	41.1	358	38.8	1	0.5	2	0.5	825	51.5	2608	50.3	9	0.8	8	0.4
Preterm birth^c																
No	223	86.1	772	91.6	135	91.8	208	92.9	1287	89.0	4318	91.6	908	94.1	1440	92.9
Yes	36	13.9	71	8.4	12	8.2	16	7.1	159	11.0	394	8.4	57	5.9	110	7.1
Missing	26	9.1	79	8.6	39	21.0	178	44.3	157	9.8	468	9.0	143	12.9	323	17.3
Multiple pregnancy																
No	266	97.4	865	97.6	176	96.7	385	97.5	1460	98.1	4709	97.4	1046	98.9	1695	97.7
Yes	7	2.6	21	2.4	6	3.3	10	2.5	28	1.9	124	2.6	12	1.1	39	2.3
Missing	12	4.2	36	3.9	4	2.2	7	1.7	115	7.2	347	6.7	50	4.5	139	7.4
Birth order																
1	111	39.2	370	40.3	81	44.2	174	46.6	599	38.0	2065	40.4	491	45.2	777	44.9
2	82	29.0	315	34.3	64	35.0	107	28.7	528	33.4	1705	33.3	356	32.8	584	33.8
≥ 3	90	31.8	233	25.4	38	20.8	92	24.7	451	28.6	1343	26.3	239	22.0	368	21.3
Missing	2	0.7	4	0.4	3	1.6	29	7.2	25	1.6	67	1.3	22	2.0	144	7.7
Maternal age at birth (years)																
< 20	30	10.5	62	6.7	15	8.1	51	12.8	139	8.6	431	8.3	110	10.0	170	9.2
20–24	57	20.1	196	21.3	38	20.6	99	24.8	375	23.4	1267	24.5	285	25.9	449	24.2
25–29	73	25.7	307	33.3	59	31.9	134	33.6	503	31.4	1640	31.7	373	33.9	613	33.0
30–34	69	24.3	229	24.8	47	25.4	78	19.5	365	22.8	1229	23.7	237	21.5	435	23.4
35–39	36	12.7	109	11.8	20	10.8	31	7.8	179	11.2	507	9.8	84	7.6	162	8.7
≥ 40	19	6.7	19	2.1	6	3.2	6	1.5	42	2.6	106	2.0	12	1.1	27	1.5
Missing	1	0.4	0	0	1	0.5	3	0.8	0	0.0	0	0.0	7	0.6	17	0.9
Mean ± SD	28.5 ± 6.79		28.1 ± 5.66		27.9 ± 6.09		26.4 ± 5.84		27.6 ± 5.99		27.4 ± 5.73		26.8 ± 5.53		27.2 ± 5.66	
Paternal age at birth (years)																
< 20	9	3.3	25	2.8	7	3.9	14	3.7	44	2.9	163	3.2	40	3.9	34	2.0
20–24	43	15.8	131	14.3	26	14.4	75	19.6	250	16.2	896	17.5	169	16.2	303	17.4
25–29	69	25.4	255	27.9	45	25.0	110	28.7	452	29.4	1512	29.5	321	30.8	503	28.9
30–34	72	26.5	256	28.0	50	27.8	103	26.9	415	27.0	1407	27.5	276	26.5	495	28.5
35–39	40	14.7	160	17.5	33	18.3	53	13.8	246	16.0	763	14.9	165	15.8	257	14.8
≥ 40	39	14.3	87	9.5	19	10.6	28	7.3	131	8.5	379	7.4	71	6.8	147	8.4
Missing	13	4.6	8	0.9	6	3.2	19	4.7	65	4.1	60	1.2	66	6.0	134	7.2

(continued on next page)

Table 2
 Association of maternal and paternal age with the risk of childhood (0–14 years) acute myeloid leukemia (AML): Meta-analysis derived Odds Ratios (OR) and 95% Confidence Intervals (95% CI) of the registry based case-control (RCC) studies and multiple logistic regression derived ORs of pooled data of the questionnaire based case-control (QCC) studies; maternal and paternal age are both adjusted for in the models.

Design→ Variable↓	1–14 years											
	< 1 year				RCC studies ^a				QCC studies ^b			
	AML cases N	Controls N	OR (95% CI)	OR (95% CI)	AML cases N	Controls N	OR (95% CI)	OR (95% CI)	AML cases N	Controls N	OR (95% CI)	OR (95% CI)
Maternal age (years)	< 20	23	62	1.44 (0.65–3.20)	12	44	0.47 (0.16–1.34)	0.47 (0.16–1.34)	112	399	0.93 (0.55–1.59) ^c	0.93 (0.55–1.59) ^c
	20–24	54	185	1.13 (0.70–1.82)	35	80	1.01 (0.54–1.86)	1.01 (0.54–1.86)	344	1202	0.92 (0.62–1.38) ^c	0.92 (0.62–1.38) ^c
	25–29	69	298	Reference	55	123	Reference	Reference	463	1579	Reference	Reference
	30–34	66	229	1.53 (0.81–2.88)	45	74	1.23 (0.69–2.17)	1.23 (0.69–2.17)	351	1183	0.98 (0.83–1.17)	0.98 (0.83–1.17)
	35–39	35	106	2.01 (0.78–5.20)	20	26	1.46 (0.63–3.35)	1.46 (0.63–3.35)	173	499	1.14 (0.90–1.44)	1.14 (0.90–1.44)
≥40	19	18	6.87 (2.12–22.25)	5	3	3.31 (0.64–16.98)	3.31 (0.64–16.98)	39	103	1.26 (0.56–2.81) ^c	1.26 (0.56–2.81) ^c	
Paternal age (years)	< 20	8	25	0.86 (0.29–2.62) ^d	7	13	2.33 (0.62–8.78)	2.33 (0.62–8.78)	44	162	0.91 (0.60–1.38)	0.91 (0.60–1.38)
	20–24	43	128	1.16 (0.68–1.98)	23	65	1.11 (0.54–2.29)	1.11 (0.54–2.29)	237	841	1.01 (0.75–1.36)	1.01 (0.75–1.36)
	25–29	68	248	Reference	42	104	Reference	Reference	432	1471	Reference	Reference
	30–34	70	253	0.84 (0.45–1.56)	49	99	0.96 (0.54–1.70)	0.96 (0.54–1.70)	402	1362	0.97 (0.82–1.15)	0.97 (0.82–1.15)
	35–39	39	158	0.60 (0.26–1.42)	32	44	1.29 (0.61–2.70)	1.29 (0.61–2.70)	243	740	1.04 (0.84–1.29)	1.04 (0.84–1.29)
≥40	38	86	0.85 (0.42–1.74)	19	25	1.21 (0.52–2.83)	1.21 (0.52–2.83)	124	389	0.95 (0.69–1.30)	0.95 (0.69–1.30)	

RCC: registry-based case control studies; QCC: questionnaire-based case control studies; AML: acute myeloid leukemia.

In bold: statistically significant results at 0.05 level.

^a Meta-analysis derived OR comprising (a) pooled OR of the raw data from Denmark, Finland and Washington State adjusted for Caucasian vs. non-Caucasian ethnicity, birth weight, birth order and study, (b) provided pooled OR for Minnesota, New York and Texas States adjusted for Caucasian vs. non-Caucasian ethnicity, birth weight, birth order, pre-term birth, multiple pregnancy and study period.

^b (Applies only to the 1–14 years-old study group) Pooled Odds Ratios, maximally adjusted for age (categorical; 1–4 [reference], 5–9, 10–14 years), sex, Caucasian vs. non-Caucasian ethnicity, birth weight, birth order, maternal education, maternal smoking during pregnancy and study.

^c Meta-analyses with statistically significant heterogeneity: maternal age < 20: I²:60.9% p = 0.08; maternal age 20–24: I²:78.8% p = 0.01; maternal age 40 + : I²:66.1% p = 0.05.

^d Based on the meta-analysis of the CGRLP California study OR and the provided pooled OR for the Minnesota, New York, and Texas States studies.

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Approval of final version: All authors.

Study supervision: Eleni Th. Petridou had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analysis.

Conflict of interest

The authors declare that they have no conflict of interest.

Declarations of interest

None.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

Where applicable, informed consent was obtained from all individual participants included in the studies.

Acknowledgements

The CLIC studies thank the families for their consent and participation, the study staff, interviewers and pediatric oncologists for their support. Acknowledgements by study site as well as sources of funding are shown in Supplementary Table 3.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.canep.2019.01.022>.

References

- [1] E. Steliarova-Foucher, M. Colombet, L.A.G. Ries, P. Hesselting, F. Moreno, H.Y. Shin, C.A. Stiller (Eds.), International Incidence of Childhood Cancer, Volume III International Agency for Research on Cancer, Lyon, France, 2017 <http://iicc.iarc.fr/results/> (electronic version), Available from, (Accessed 30 June 2018).
- [2] A. Redner, R. Kessel, Chapter 19: Acute myeloid leukemia, in: P. Lanzkowsky, J.M. Lipton, J.D. Fish (Eds.), Lanzkowsky's Manual of Paediatric Hematology and Oncology, sixth edition, Academic Press, London, 2016, pp. 390–406.
- [3] S.E. Puumala, J.A. Ross, R. Aplenc, L.G. Spector, Epidemiology of childhood acute myeloid leukemia, *Pediatr. Blood Cancer* 60 (2013) 728–733, <https://doi.org/10.1002/pcb.24464>.
- [4] J.D.E. De Rooij, C.M. Zwaan, M. van den Heuvel-Eibrink, Pediatric AML: from biology to clinical management, *J. Clin. Med.* 4 (2015) 127–149, <https://doi.org/10.3390/jcm4010127>.
- [5] M. Adam, C.E. Kuehni, A. Spoerri, K. Schmidlin, F. Gumy-Pause, P. Brazzola, N. Probst-Hensch, M. Zwahlen, Socioeconomic status and childhood leukemia incidence in Switzerland, *Front. Oncol.* 5 (2015) 139, <https://doi.org/10.3389/fonc.2015.00139>.
- [6] G. Scélo, C. Metayer, L. Zhang, J.L. Wiemels, M.C. Aldrich, S. Selvin, S. Month, M.T. Smith, P.A. Buffler, Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia, *Environ. Health Perspect.* 117 (2009) 133–139, <https://doi.org/10.1289/ehp.11927>.
- [7] O. Raaschou-Nielsen, U.A. Hvidtfeldt, N. Roswall, O. Hertel, A.H. Poulsen, M. Sørensen, Ambient benzene at the residence and risk for subtypes of childhood leukemia, lymphoma and CNS tumor, *Int. J. Cancer* 143 (2018) 1367–1373, <https://doi.org/10.1002/ijc.31421>.
- [8] H.D. Bailey, L. Fritsch, C. Infante-Rivard, D.C. Glass, L. Miligi, J.D. Dockerty, T. Lightfoot, J. Clavel, E. Roman, L.G. Spector, P. Kaatsch, C. Metayer, C. Magnani, E. Milne, S. Polychronopoulou, J. Simpson, J. Rudant, V. Sidi, R. Rondelli, L. Orsi, A.Y. Kang, E. Petridou, J. Schüz, Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium, *Int. J. Cancer* 135 (2014) 2157–2172, <https://doi.org/10.1002/ijc.28854>.
- [9] C. Metayer, E. Milne, J.D. Dockerty, J. Clavel, M.S. Pombo-de-Oliveira, C. Wesseling, L.G. Spector, J. Schüz, E. Petridou, S. Ezzat, B.K. Armstrong, J. Rudant, S. Koifman, P. Kaatsch, M. Moschovi, W.M. Rashed, S. Selvin, K. McCauley, R.J. Hung, A.Y. Kang, C. Infante-Rivard, Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a Childhood Leukemia International Consortium study, *Epidemiology* 25 (2014) 811–822, <https://doi.org/10.1097/EDE.0000000000000141>.
- [10] S. Okuszyn, C.M. Crespi, M. Cockburn, G. Mezei, L. Kheifets, Birth weight and other perinatal characteristic and childhood leukemia in California, *Cancer Epidemiol.* 36 (2012) e359–65, <https://doi.org/10.1016/j.canep.2012.08.002>.
- [11] Y.F. Wang, L.Q. Wu, Y.N. Liu, Y.Y. Bi, H. Wang, Gestational age and childhood leukemia: a meta-analysis of epidemiologic studies, *Hematology* 23 (2018) 253–262, <https://doi.org/10.1080/10245332.2017.1396056>.
- [12] E.L. Marcotte, T.P. Thomopoulos, C. Infante-Rivard, J. Clavel, E.T. Petridou, J. Schüz, S. Ezzat, J.D. Dockerty, C. Metayer, C. Magnani, M.E. Scheurer, B.A. Mueller, A.M. Mora, C. Wesseling, A. Skalkidou, W.M. Rashed, S.S. Francis, R. Ajrouche, F. Erdmann, L. Orsi, L.G. Spector, Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC), *Lancet Haematol.* 3 (2016) e176–85, [https://doi.org/10.1016/S2352-3026\(16\)00002-8](https://doi.org/10.1016/S2352-3026(16)00002-8).
- [13] K.J. Johnson, S.E. Carozza, E.J. Chow, E.E. Fox, S. Horel, C.C. McLaughlin, B.A. Mueller, S.E. Puumala, P. Reynolds, J. Von Behren, L.G. Spector, Parental age and risk of childhood cancer: a pooled analysis, *Epidemiology* 20 (2009) 475–483, <https://doi.org/10.1097/EDE.0b013e3181a5a332>.
- [14] R. Wang, C. Metayer, L. Morimoto, J.L. Wiemels, J. Yang, A.T. DeWan, A. Kang, X. Ma, Parental age and risk of pediatric cancer in the offspring: a population-based record-linkage study in California, *Am. J. Epidemiol.* 186 (2017) 843–856, <https://doi.org/10.1093/aje/kwx160>.
- [15] Z.A. Contreras, J. Hansen, B. Ritz, J. Olsen, F. Yu, J.E. Heck, Parental age and childhood cancer risk: a Danish population-based registry study, *Cancer Epidemiol.* 49 (2017) 202–215, <https://doi.org/10.1016/j.canep.2017.06.010>.
- [16] S.K. Urhoj, O. Raaschou-Nielsen, A.V. Hansen, L.H. Mortensen, P.K. Andersen, A.M. Nybo Andersen, Advanced paternal age and childhood cancer in offspring: a nationwide register-based cohort study, *Int. J. Cancer* 140 (2017) 2461–2472, <https://doi.org/10.1002/ijc.30677>.
- [17] E.T. Petridou, M.K. Georgakis, F. Erdmann, X. Ma, J.E. Heck, A. Auvinen, B.A. Mueller, L.G. Spector, E. Roman, C. Metayer, C. Magnani, M.S. Pombo-de-Oliveira, S. Ezzat, M.E. Scheurer, A.M. Mora, J.D. Dockerty, J. Hansen, A.Y. Kang, R. Wang, D.R. Doody, E. Kane, W.M. Rashed, N. Dessypris, J. Schüz, C. Infante-Rivard, A. Skalkidou, Advanced parental age as risk factor for childhood acute lymphoblastic leukemia: results from studies of the Childhood Leukemia International Consortium, *Eur. J. Epidemiol.* (2018), <https://doi.org/10.1007/s10654-018-0402-z> May 14, [Epub ahead of print].
- [18] T.N. Sergentanis, T.P. Thomopoulos, S.P. Gialamas, M.A. Karalexi, S.I. Biniaris-Georgallis, E. Kontogeorgi, P. Papatoma, G. Tsilimidos, A. Skalkidou, A.N. Iliadou, E.T. Petridou, Risk for childhood leukemia associated with maternal and paternal age, *Eur. J. Epidemiol.* 30 (2015) 1229–1261, <https://doi.org/10.1007/s10654-015-0089-3>.
- [19] E.L. Marcotte, T.E. Druley, K.J. Johnson, M. Richardson, J. von Behren, B.A. Mueller, S. Carozza, C. McLaughlin, E.J. Chow, P. Reynolds, L.G. Spector, Parental age and risk of infant leukaemia: a pooled analysis, *Paediatr. Perinat. Epidemiol.* 31 (2017) 563–572, <https://doi.org/10.1111/ppe.12412>.
- [20] J. Schüz, Non-response bias as a likely cause of the association between young maternal age at the time of delivery and the risk of cancer in the offspring, *Paediatr. Perinat. Epidemiol.* 17 (2003) 106–112.
- [21] C. Metayer, E. Milne, J. Clavel, C. Infante-Rivard, E. Petridou, M. Taylor, J. Schüz, L.G. Spector, J.D. Dockerty, C. Magnani, M.S. Pombo-de-Oliveira, D. Sinnett, M. Murphy, E. Roman, P. Monge, S. Ezzat, B.A. Mueller, M.E. Scheurer, B.K. Armstrong, J. Birch, P. Kaatsch, S. Koifman, T. Lightfoot, P. Bhatti, M.L. Bondy, J. Rudant, K. O'Neill, L. Miligi, N. Dessypris, A.Y. Kang, P.A. Buffler, The childhood leukemia international consortium, *Cancer Epidemiol.* 37 (2013) 336–347, <https://doi.org/10.1016/j.canep.2012.12.011>.
- [22] A.B. Cantor, Myeloid proliferations associated with Down syndrome, *J. Hematop.* 8 (2015) 169–176, <https://doi.org/10.1007/s12308-014-0225-0>.
- [23] D. Tomizawa, E.A. Kolb, Down syndrome and AML: where do we go from here? *Blood* 129 (Jun) (2017) 3274–3275, <https://doi.org/10.1182/blood-2017-04-780031>.
- [24] M.F. Greaves, J. Wiemels, Origins of chromosome translocations in childhood leukemia, *Nat. Rev. Cancer* 3 (2003) 639–649, <https://doi.org/10.1038/nrc1164>.
- [25] J.A. Ross, A.M. Linabery, C.N. Blommer, E.K. Langer, L.G. Spector, J.M. Hilden, N.A. Heerema, G.A. Radloff, R.L. Tower, S.M. Davies, Genetic variants modify susceptibility to leukemia in infants: a Children's Oncology Group report, *Pediatr. Blood Cancer* 60 (Jan) (2013) 31–34, <https://doi.org/10.1002/pcb.24131>.

- [26] E.S. Sandler, D.J. Friedman, M.M. Mustafa, N.J. Winick, W.P. Bowman, G.R. Buchanan, Treatment of children with epipodophyllotoxin-induced secondary acute myeloid leukemia, *Cancer* 79 (1997) 1049–1054.
- [27] J.A. Ross, J.D. Potter, G.H. Reaman, T.W. Pendergrass, L.L. Robison, Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): a report from the Children's Cancer Group, *Cancer Causes Control* 7 (1996) 581–590.
- [28] L.G. Spector, Y. Xie, L.L. Robison, N.A. Heerema, J.M. Hilden, B. Lange, C.A. Felix, S.M. Davies, J. Slavin, J.D. Potter, C.K. Blair, G.H. Reaman, J.A. Ross, Maternal diet and infant leukemia. The DNA topoisomerase II inhibitor hypothesis: a report from the children's oncology group, *Cancer Epidemiol. Biomarkers Prev.* 14 (2005) 651–655, <https://doi.org/10.1158/1055-9965.EPI-04-0602>.
- [29] M.C. Valentine, A.M. Linabery, S. Chasnoff, A.E. Hughes, C. Mallaney, N. Sanchez, J. Giacalone, N.A. Heerema, J.M. Hilden, L.G. Spector, J.A. Ross, T.E. Druley, Excess congenital non-synonymous variation in leukemia-associated genes in *MLL* – infant leukemia: a Children's Oncology Group report, *Leukemia* 28 (2014) 1235–1241, <https://doi.org/10.1038/leu.2013.367>.
- [30] E.T. Petridou, T.N. Sergentanis, P. Panagopoulou, M. Moschovi, S. Polychronopoulou, M. Baka, A. Pourtsidis, F. Athanassiadou, M. Kalmanti, V. Sidi, N. Dessypris, C. Frangakis, I.L. Matsoukis, C. Stefanadis, A. Skalkidou, O. Stephansson, H.O. Adami, H. Kieler, In vitro fertilization and risk of childhood leukemia in Greece and Sweden, *Pediatr. Blood Cancer* 58 (2012) 930–936, <https://doi.org/10.1002/pbc.23194>.
- [31] M. Hargreave, A. Jensen, T.S. Nielsen, E.P. Colov, K.K. Andersen, A. Pinborg, S.K. Kjaer, Maternal use of fertility drugs and risk of cancer in children—a nationwide population-based cohort study in Denmark, *Int. J. Cancer* 136 (2015) 1931–1939, <https://doi.org/10.1002/ijc.29235>.
- [32] J.A. Martin, B.E. Hamilton, M.J. Osterman, A.K. Driscoll, T.J. Mathews, Births: final data for 2015, *Vital Stat. Rep.* 66 (2017) 1.
- [33] A.M. Nybo-Andersen, S.K. Urhoj, Is advanced paternal age a health risk for the offspring? *Fertil. Steril.* 107 (2017) 312–318, <https://doi.org/10.1016/j.fertnstert.2016.12.019>.
- [34] W.S. Wong, B.D. Solomon, D.L. Bodian, P. Kothiyal, G. Eley, K.C. Huddlestone, R. Baker, D.C. Thach, R.K. Iyer, J.G. Vockley, J.E. Niederhuber, New observations on maternal age effect on germline de novo mutations, *Nat. Commun.* 7 (2016) 10486, <https://doi.org/10.1038/ncomms10486>.
- [35] R. Rahbari, A. Wuster, S.J. Lindsay, R.J. Hardwick, L.B. Alexandrov, S.A. Turki, A. Dominiczak, A. Morris, D. Porteous, B. Smith, M.R. Stratton, UK10K Consortium, M.E. Hurles, Timing, rates and spectra of human germline mutation, *Nat. Genet.* 48 (Feb (2)) (2016) 126–133, <https://doi.org/10.1038/ng.3469>.
- [36] R.M. Adkins, F. Thomas, F.A. Tyllavsky, J. Krushkal, Parental ages and levels of DNA methylation in the newborn are correlated, *BMC Med. Genet.* 12 (2011) 47, <https://doi.org/10.1186/1471-2350-12-47>.
- [37] A.J. Wilcox, D.P. Sandler, R.B. Everson, Using father's age to explore the role of germcell mutation as a cause of human cancer, *Int. J. Epidemiol.* 17 (1988) 469–471.
- [38] M.A. Bellis, K. Hughes, S. Hughes, J. Ashton, Measuring paternal discrepancy and its public health consequences, *J. Epidemiol. Community Health* 59 (2005) 749–754, <https://doi.org/10.1136/jech.2005.036517>.
- [39] M.M. Maule, L. Vizzini, F. Merletti, C. Magnani, G. Pastore, L. Richiardi, Parental age and risk of acute lymphocytic leukaemia and embryonal tumours in the Piedmont Region, Italy, *Int. J. Epidemiol.* 36 (2007) 691–692, <https://doi.org/10.1093/ije/dym115>.
- [40] O. Paltiel, S. Lemeshow, G.S. Phillips, G. Tikellis, M.S. Linet, A.L. Ponsoyby, P. Magnus, S.E. Håberg, S.F. Olsen, C. Granström, M. Klebanoff, J. Golding, Z. Herceg, A. Ghantous, J.E. Hirst, A. Borkhardt, M.H. Ward, S. Holst Søegaard, T. Dwyer, The association between birth order and childhood leukemia may be modified by paternal age and birth weight. Pooled results from the International Childhood Cancer Cohort Consortium (I4C), *Int. J. Cancer* (2018), <https://doi.org/10.1002/ijc.31635> Aug 11, [Epub ahead of print].