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Short Report

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)

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The "delayed infection hypothesis" states that a paucity of infections in early childhood may lead to higher risks of childhood leukemia (CL), especially acute lymphoblastic leukemia (ALL). Using prospectively collected data from six population-based birth cohorts we studied the association between birth order (a proxy for pathogen exposure) and CL. We explored whether other birth or parental characteristics modify this association. With 2.2×10^6 person-years of follow-up, 185 CL and 136 ALL cases were ascertained. In Cox proportional hazards models, increasing birth order (continuous) was inversely associated with CL and ALL; hazard ratios (HR) = 0.88, 95% confidence interval (CI): (0.77–0.99) and 0.85: (0.73–0.99), respectively. Being later-born was associated with similarly reduced hazards of CL and ALL compared to being first-born; HRs = 0.78: 95% CI:

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0.58–1.05 and 0.73: 0.52–1.03, respectively. Successive birth orders were associated with decreased CL and ALL risks (P for trend 0.047 and 0.055, respectively). Multivariable adjustment somewhat attenuated the associations. We found statistically significant and borderline interactions between birth weight (p = 0.024) and paternal age (p = 0.067), respectively, in associations between being later-born and CL, with the lowest risk observed for children born at <3 kg with fathers aged 35+ (HR = 0.18, 95% CI: 0.06–0.50). Our study strengthens the theory that increasing birth order confers protection against CL and ALL risks, but suggests that this association may be modified among subsets of children with different characteristics, notably advanced paternal age and lower birth weight. It is unclear whether these findings can be explained solely by infectious exposures.

What's new?

Can birth order affect childhood leukemia risk? Children with older siblings encounter more infectious pathogens than first-born children, and fewer childhood infections might contribute to increased risk of childhood leukemia. Here, the authors studied birth order as a proxy for childhood infections. They conducted a prospective study and found that later-born children had reduced risk of childhood leukemia compared with first-borns. The effect was strongest in children with fathers age 30 or older, and in children with birth weight less than 3 kg.

Introduction

Childhood leukemia is thought to be related to environmental exposures during the prenatal, postnatal, and possibly the preconception periods. Current theories on the etiology of childhood leukemia, especially acute lymphoblastic leukemia (ALL), include the "delayed infection hypothesis", which states that reduced exposure to infection in early childhood results in an abnormal response to common pathogens, leading to lymphoproliferation and clonal expansion of B or T cell clones.[1] There is limited direct evidence for reduced exposure to specific infections among children who develop leukemia[2] as early childhood exposure to multiple pathogens is difficult to measure precisely, particularly in retrospective studies relying on maternal recall. Therefore, proxy measures have been evaluated, including daycare attendance, breastfeeding, vaccination history, hospitalization or prescriptions for infection, as well as birth order or sibship size[3–5] among others. In fact, later-born children have increased serological evidence of several common infections.[6]

The association between family size and childhood cancer was first raised in 1962 by MacMahon and Newill, who showed a monotonic decrease in childhood cancer mortality for birth order 1–5.[7] Since then, studies from many countries have explored the relationship between birth order and childhood cancer in general or leukemia in particular, with inconsistent results[3,8–10] among others. These inconsistencies may be due to differences in study design or heterogeneity regarding sociodemographic or perinatal characteristics among populations studied.

International data demonstrate secular trends of increasing birth weight,[11] increasing average paternal age[12] as well as decreased total fertility rates and family size.[13] The current and future effects of these recent developments on childhood leukemia risk have received little attention. Birth weight has emerged as a clear and consistent risk factor for childhood leukemia.[14] Furthermore, increased paternal age has been raised as a potential risk factor for childhood ALL.[15] In most epidemiologic studies, these two factors have been considered as potential confounders of the association between birth order and leukemia, but have not been assessed as modifiers of this relationship. The search for modifiers may uncover specific subgroups in which biological or environmental determinants have differential impacts; this knowledge may enhance the investigation of the etiologic pathways leading to childhood leukemia.

Since childhood cancers are rare and risk factors assessed to date explain only a small part of their etiology, large collaborative efforts are required to accumulate sufficient cases for epidemiologic studies. Most epidemiologic evidence for the etiology of childhood cancer is based on retrospective studies or birth registries. The International Childhood Cancer Cohort Consortium (I4C) includes birth cohorts spanning four continents and 50 years of data collection,[16] each cohort providing rich and detailed perinatal and postnatal data (see Supporting Information data). Our study aims to explore the association between birth order and childhood leukemia in the I4C and to determine whether other etiologic factors, such as birth weight, paternal age, child sex and age at diagnosis modify the effect of birth order on childhood leukemia risk.

Methods

Study population

We pooled data from six I4C-member population-based birth cohorts (Table 1 and Supporting Information data), ALSPAC, CPP, DNBC, JPS, MoBa and TIHS, as detailed in our previous

work on birth weight.[16] All childhood leukemia cases ascertained to date from participating cohorts were included in the analysis. Regarding noncases, for four of the cohorts all children were included, while for Scandinavian cohorts, MoBa and DNBC, a random 10% sample of noncases contributed person-time (due to cohort data-sharing policies). Children with Down syndrome and nonsingleton births were excluded.

Outcome assessment

Cancer was ascertained using national or regional cancer registries, where available, or by clinical follow-up as previously described.[16] We calculated time to leukemia onset from birth to date of first cancer diagnosis, censoring at date of last follow-up (or age 15 years) or date of death for noncases (see Table 1). The dependent variables were all leukemia and acute lymphoblastic leukemia (ALL), in particular, as ascertained using ICD-0-3 morphology codes 9800–9946 and 9820–9837, respectively. Sample sizes were insufficient to assess other subtypes.

Exposure assessment

Using data recorded at baseline in the cohorts, the main independent variable was birth order analyzed as three metrics: later-born versus first-born (dichotomous); continuous; and ordinal categories. Due to outliers in family size, we performed a sensitivity analysis curtailing continuous birth order at ≤6. Previous multiple births were counted as the number of resultant live births. Previous stillbirths were included as previous births. Paternal age and birth weight were modeled as continuous variables and, in separate analyses, as categorical variables.

The covariates assessed included sex of child, year of birth, gestational age, and birth weight, in addition to parental ages, age difference (father's age minus mother's age), maternal smoking and maternal education. Criteria for covariate entry into the models were their importance in the literature or change in the birth-order-cancer or birth-order-leukemia hazard ratios (HR) by more than 10% in either direction. Covariates with missing data (proportions shown in Supporting Information Table S1) were imputed using a chained multiple [$N = 20$] imputation procedure. The final set of covariates for the full dataset included birth weight (continuous), sex of the child, maternal secondary education (yes vs. no), maternal age (continuous), and paternal age (continuous). Since only 23.2% of the children in the JPS had information on gestational age, an additional analysis was performed for the subcohort with information on this covariate.

Statistical analysis

Analysis was performed using Cox proportional hazards models, stratified by cohort. We examined whether there was heterogeneity of the association between leukemia and birth order by cohort, and found none. The pooled associations between birth order and leukemia are expressed as hazard ratios (HR) and their corresponding 95% confidence intervals (95% CI). For all analyses, $p \leq 0.05$ was considered statistically significant. After testing the main-effects of birth order, we looked for first-order interactions between birth order*paternal age, and birth order*birth weight, and birth order*child sex on their relationship with leukemia and ALL, respectively. We explored the relation between birth order and leukemia diagnosed at successive ages.

Proportional hazards assumptions were confirmed using a test of the Schoenfeld residuals and by graphically observing that the transformed survival probabilities plotted over the natural log of the analysis time for both later-born and first-born were roughly parallel.

Power

A sample size of 185 cases of leukemia was sufficient to detect a hazard ratio of 0.645 for later-born versus first-born, with alpha = 0.05 and power of 80%, assuming that two-thirds of children would be later-born.

Results

A total of 180,549 children were followed from birth until first cancer diagnosis, death, or end of follow-up. This resulted in a total of 2,210,600 person-years of follow-up and 643 incident cases of childhood cancer, of which 185 were leukemia and 136 were ALL. Years of recruitment and baseline parameters for the cohorts are shown in Table 1. We note differences in characteristics and contribution of cases depending on the size and the age of the cohort. In particular, the Scandinavian cohorts were characterized by later recruitment periods, older paternal age at birth, higher birth weights and higher numbers of incident cancer cases compared to the earlier cohorts; TIHS was predominantly male, with lowest mean parental ages.

Table 2 shows the unadjusted and multivariable-adjusted relationships between leukemia and birth order using the various metrics. Increasing birth order (continuous) was associated with a decreased risk of leukemia as well as ALL. The results for leukemia and ALL were especially marked after truncating birth order to ≤6 (adjusted HR 0.81 and 0.78, respectively, $p = 0.017$).

Examining later-born versus first-born we noted a borderline significant inverse relation for leukemia and ALL after adjusting for covariates. Successive birth order was associated with decreased leukemia and ALL risk (P for linear trend 0.047 and 0.055, respectively in unadjusted analyses), Table 2 and Supporting Information Figure S1. The association was attenuated slightly in the subcohort with available gestational age (Supporting Information Fig. S2). The peak inverse effect of birth order on leukemia (HR = 0.62. 95% CI: 0.38–1.02) and ALL (HR = 0.46, 95% CI: 0.24–0.87) was particularly noted at birth order 3. Adjustment for parental age, maternal education, birth weight and child sex did not materially change the HRs but slightly affected the precision of the findings (Table 2 and Supporting Information Fig. S1). Maternal

Table 1. Participating cohorts,* baseline characteristics[1] and incident childhood cancer cases

	Collaborative Perinatal Project—CPP[4]	Jerusalem Perinatal Study—JPS	Tasmanian Infant Health Survey—TIHS	Avon Longitudinal Study of Parents and Children—ALSPAC	Danish National Birth Cohort—DNBC[3]	Norwegian Mother and Child Cohort Study—MoBa[3]	Total
Recruitment years	1959–1966	1964–1976	1987–1995	1991–1992	1996–2003	1999–2009	1959–2009
Total number of live births in cohort	58,000	92,408	10,628	14,062	96,860	108,487	380,445′ (180,549 included in analysis)
Years follow-up, mean (range)	5.6 (0.0–8.0)	15.0 (15–15)	14.7 (12.7–15.0)	14.9 (0.5–15)	14.0 (11.6–15.0)	9.5 (5.6–15.0)	12.3 (0–15)
Person-years	322,414	1,317,498	137,514	204,819	129,370	98,986	2,210,600
% Later-born	71.6	70.8	53.1	56.2	67.5	55.2	68.0
Mean sibship size [SD] (range)	2.0 [2.1] (0–21)	2.0 [2.3] (0–16)	N/A	0.8 [1.0] (0–13)	0.9 [0.8] (0–6)	0.8 [0.9] (0–4)	1.8 [2.1] (0–21)
% Male	50.7	51.5	71.3	51.6	51.0	50.2	52.2
Mean birth weight [SD]	3,177 [531]	3,272 [523]	3,195 [751]	3,410 [551]	3,586 [567]	3,604 [561]	3,288 [560]
Mean Paternal Age at Birth [SD] (range)	28.3 [7.0] (14–66)	31.6 [6.8] (16–80)	26.5 [5.6] (14–63)	30.7 [5.8] (15–65)	32.7 [5.2] (18–64)	32.7 [5.3] (19–50)	30.6 [6.8] (14–80)
Mean Maternal Age at birth [SD] (range)	24.1 [5.9] (12–48)	27.6 [5.7] (13–59)	23.6 [4.4] (13–45)	28.0 [5.0] (15–44)	30.5 [4.3] (18–47)	30.2 [4.6] (16–47)	26.8 [5.9] (12–59)
% Maternal secondary education	41.4	42.4	18.1	35.3[2]	65.5	79.7	43.2
Total number of cancer cases	49	168	24	22	190	190	643
Leukemia	16	39	4	3	61	62	185
ALL	11	27	2	3	44	49	136

*Reference describing each cohort can be found in Supporting Information A. ALL = Acute lymphoblastic leukemia; SD = Standard Deviation; N/A = Not available.
[1]Proportion with missing values shown in Supporting Information Table S1.
[2]Proportion staying in secondary education after compulsory school-leaving age.
[3]Follow-up not complete to age 15; 10% sample of "noncases" included in analysis.
[4]Follow-up for cancer to age 8 only.

Table 2. Hazard ratios for childhood leukemia, and acute lymphoblastic leukemia (ALL) by birth order as a continuous, dichotomous or ordinal variable

Cancer type	Number of cases	Unadjusted hazard ratio	95% confidence interval	*p*-value	Adjusted[2] hazard ratio	95% confidence interval	*p*-value
Continuous birth order (*N* = 180,549)[3]							
Leukemia	185	0.88	0.77–0.99	0.037	0.88	0.76–1.02	0.091
ALL	136	0.85	0.73–0.99	0.038	0.84	0.70–1.01	0.067
Continuous birth order truncated at 6 (*N* = 170,894)							
Leukemia	177	0.82	0.70–0.95	0.009	0.81	0.68–0.96	0.017
ALL	131	0.80	0.66–0.95	0.013	0.78	0.63–0.96	0.017
Later born vs. first born where first born is the referent group (*N* = 180,549)							
Leukemia	185	0.78	0.58–1.05	0.097	0.80	0.58–1.11	0.180
ALL	136	0.73	0.52–1.03	0.077	0.74	0.51–1.09	0.129
Successive birth order (*N* = 180,549)							
Leukemia	185						
1	79	1.00	---	---	1.00	---	---
2	68	0.86	0.61–1.19	0.357	0.84	0.59–1.18	0.309
3	22	0.62	0.38–1.02	0.058	0.61	0.36–1.04	0.068
4	16	0.60	0.33–1.07	0.082[1]	0.61	0.31–1.20	0.152
ALL	136						
1	60	1.00	---	---	1.00	---	---
2	53	0.87	0.60–1.27	0.481	0.85	0.57–1.26	0.407
3	12	0.46	0.24–0.87	0.016	0.44	0.23–0.87	0.018
4	11	0.61	0.31–1.20	0.154[1]	0.59	0.27–1.31	0.197

[1]p for trend = 0.047 and 0.055 for leukemia and ALL, respectively.
[2]The hazard ratio is adjusted for birth weight (continuous), sex of the child, maternal secondary education (yes vs. no), maternal age (continuous) and paternal age (continuous).
[3]For TIHS cohort birth order beyond first-born was imputed.

smoking (both imputed and not imputed) was not found to be a confounder or modifier of the birth order-leukemia relationship (not shown).

A statistically significant interaction was found between birth order and continuous birth weight (p = 0.024), and a borderline interaction between birth order and continuous paternal age (p = 0.067), in their association with time to leukemia. In a model containing main effects of birth order as well as interactions between later-born and continuous paternal age and between later-born and continuous birth weight, the interaction P-values were 0.033 and 0.015, respectively (Supporting Information Table S2).

In order to evaluate these interactions further, we conducted a stratified analysis. We examined the effect of birth order in strata of birth weight and paternal age categories individually, with a further analysis combining strata of both these variables (Table 3). In these analyses, we observe that the effect of birth order was strongest among children with lower birth weight (<3 kg), in those with older fathers (≥30 years old), and the strongest inverse relations (HR = 0.26 and 0.18) was seen in children with birth weights <3 kg with older fathers (aged 30–35 and > 35 years, respectively). This pattern of effect modification was unchanged after adjusting for covariates. We did not find any evidence of a time-varying relationship between birth order and age at diagnosis, using cut-offs of 1, 2, 3, 4, or 5 years of age, nor of effect modification by child's sex (not shown).

Discussion

In this pooled analysis of six cohort studies spanning the globe and over 40 years of recruitment, we found a clear inverse relation between childhood leukemia (and ALL) and birth order. Being a later-born child conferred a reduction in childhood leukemia risk that did not appear to be confounded by parental age, maternal education, child's sex or birth weight. The relation did not vary by age at diagnosis. The pattern of decreased ALL risk with increasing birth order is similar to those reported in a pooled analysis from five U.S. states.[8] Being a later-born rather than a first-born child implies increased early opportunities for exposure to pathogens post-partum. In general, these findings support the delayed infection hypothesis, although it is important to note that later-born children also have a different immunologic intrauterine milieu than first-borns, with evidence of differences in T-cell programming.[17] There may also be other

Table 3. Unadjusted hazard ratios and 95% confidence interval (CI) for leukemia association with birth order (later-born vs. first-born [reference category]) stratified by paternal age and birth weight categories

Stratification variables				Hazard ratio for later-born vs. first-born		
Paternal age, years	Birth weight, kg	Observations *N*	Leukemia *N*		95% CI	*p*-value
Stratified by paternal age						
25		36,628	20	0.91	0.37–2.25	0.833
25–30		49,585	68	1.15	0.71–1.87	0.560
30–35		38,507	49	0.70	0.39–1.25	0.226
›35		**36,881**	**41**	**0.49**	**0.26–0.96**	**0.037**
Stratified by birth weight						
	‹3.0	**49,539**	**26**	**0.31**	**0.14–0.72**	**0.006**
	3.0 to ‹4.0	115,545	199	0.83	0.57–1.26	0.316
	4.0	14,733	40	0.97	0.48–1.94	0.922
Stratified by both paternal age and birth weight						
25	‹3.0	11,755	6	0.39	0.12–1.23	0.109
	3.0 to ‹4.0	22,780	10	1.08	0.43–2.74	0.870
	4.0	1,991	4	1.31	0.42–4.06	0.639
25–30	‹3.0	13,233	11	0.44	0.18–1.11	0.082
	3.0 to ‹4.0	32,443	43	1.23	0.72–2.08	0.449
	4.0	3,719	14	1.49	0.67–3.29	0.326
30–35	**‹3.0**	**8,995**	**4**	**0.26**	**0.10–0.70**	**0.008**
	3.0 to ‹4.0	25,521	30	0.73	0.39–1.35	0.311
	4.0	3,841	15	0.88	0.38–2.04	0.766
›35	**‹3.0**	**8,451**	**4**	**0.18**	**0.06–0.50**	**0.001**
	3.0 to ‹4.0	24,054	31	0.50	0.25–1.00	0.051
	4.0	4,234	6	0.61	0.25–1.50	0.280

environmental and biological exposures associated with birth order, such as fetal microchimerism.

Little attention has been given to possible modifiers of the effect of birth order on leukemia risk. An exception is a study by Marcotte *et al.*[3] which reported that birth order effects were modified by ethnicity. A novel finding in our study is the apparent modifying effect of increasing paternal age on the relation between birth order and childhood leukemia and a strong modifying effect of birth weight. Although based on small numbers, it appears that the "protective" effect of having siblings is most pronounced in children of lower birth weight and those with older fathers.

Older paternal age is associated with a variety of offspring outcomes including single gene and chromosomal abnormalities, complex disorders such as autism, schizophrenia, and type I diabetes and low birth weight.[18] Oksuzyan *et al.*[19] reported a significant association between paternal age (odds ratio 1.23) and childhood ALL in offspring of fathers aged 35–45 compared with fathers aged <25 years, however, no analysis of interactions was reported. Yip *et al.* also reported an increased risk of leukemia, specifically ALL, among older fathers.[20]

Older fathers, besides the obvious fact that they are likely to have more offspring, more experience in childrearing, and higher incomes than younger fathers, may also bear a higher lifetime burden of environmental exposures along with higher risk of germ cell spontaneous mutations. These factors should seemingly increase the child's leukemia risk, not the converse. Furthermore, older fathers give birth to offspring with longer telomeres,[21] and telomere length may, in itself, be related to childhood ALL risk.[22] However, increased paternal age has also been associated with increased rates of fetal loss, both spontaneous abortion and stillbirths,[18] this may imply that there is enhanced prenatal loss of infants at risk for leukemia or cancer conceived by older fathers, and raises the possibility of "live-birth bias."[23]

As for birth weight, most research has focused on high birth weight as a risk factor for childhood leukemia, especially ALL. However Roman and colleagues[24] have drawn attention to the paucity of childhood ALL cases among children with low birth weight. Whether these children are "protected" from leukemia due to low somatic growth, or whether the low leukemia rates also reflect in utero loss of fetuses with poor growth characteristics is unclear. That older siblings may be further protected by having lower birth weight is intriguing, especially since they are at lower risk for impaired fetal growth. It is known that several types of neonatal infection

are increased in low birth weight or small-for-gestational-age babies, and this increased risk may persist throughout childhood.[25] Infection may trigger preterm birth, itself a cause of low birth weight, however controlling for gestational age did not materially affect our results. Is it plausible that the enhanced "protection" conferred by lower birth weight in children with at least one older sibling is due to the compounding effect of increased early exposure to infectious agents, both in utero and post-partum, resulting in a broader immune repertoire? Ongoing studies in our consortium aim to identify DNA-based molecular signatures of infection and how they relate to childhood cancer. Once identified, these signatures may help determine to what extent the associations observed between birth order and leukemia are mediated by infection *versus* other mechanisms or other exposures.

The strengths of our study are the prospective nature of data collection spanning several countries and several decades. Birth weight, paternal age and birth order were ascertained in all cohorts in an unbiased fashion without reference to later cancer onset. Adjustment for multiple potential confounders did not substantially alter our findings nor did analysis by age of leukemia onset.

Our study is limited by relatively low numbers of events, with insufficient power to examine leukemia subtypes other than ALL. In the earlier cohorts misclassification of leukemia subtype may have occurred due to lack of immunophenotyping. Moreover, we had no information on immune or genetic subtypes of ALL, which may have distinct etiologies. We were not always able to distinguish previous live- from still-births. In some of the included cohorts, children have not all reached 15 years of age, so some findings may change when complete case ascertainment data become available. Further studies undertaken when all the cohorts have matured will provide more information on the entire spectrum of childhood leukemia through to adolescence as well as providing new opportunities for analyses within sibships, and regarding birth spacing.

In conclusion, we have found a clear protective association between having older siblings on childhood leukemia risk and two previously unreported possible effect modifiers. Recent large population-based registry studies reporting null or weak associations between birth order and leukemia[9,10] may not have discerned the modifying effects suggested in the current analysis because paternal age and birth weight were examined as covariates and not as potential modifiers. We look forward to efforts to determine whether our findings can be replicated in other populations. Additionally, it would be important to examine whether specific molecular or clinical subtypes of childhood leukemia are associated with these striking inverse relations.

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