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Title: Number of siblings and survival from childhood leukaemia: a national register-based cohort study from Sweden

Running title: Siblings and childhood leukaemia survival

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Abstract

Background: Previous studies suggest worse leukaemia survival for children with siblings, but the evidence is sparse, inconsistent and does not consider clinical factors. We explored the associations between number of siblings in the household, birth order, and survival from childhood acute lymphoid leukaemia (ALL) and acute myeloid leukaemia (AML).

Methods: In this nationwide register-based study we included all children aged 1-14, diagnosed with ALL and AML between 1991-mid 2015 in Sweden (n=1692). Using Cox regression models, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs) according to number of siblings and birth order, adjusting for known prognostic and sociodemographic factors.

Results: A tendency towards better ALL survival among children with one, or ≥2, siblings was observed, $_{adj}$HRs (95% CI): 0.73 (0.49-1.10) and 0.63 (0.40-1.00), respectively. However, this was mainly limited to children with low risk profiles. An indication of better AML survival among children with siblings was seen, $_{adj}$HRs (95% CI) 0.68 (0.36-1.29) and 0.71 (0.34-1.48) but diminished after adjusting for birth order.

Conclusion: Our results do not support previous findings that a larger number of siblings is associated with poorer survival. Inconsistencies might be explained by underlying mechanisms that differ between settings, but chance cannot be ruled out.

Background

Leukaemia is the most common type of childhood cancer in most parts of the world.[1, 2] Even though the prognosis has improved substantially over the past decades, not all children have benefited equally from these improvements and survive their disease.[3, 4] In Europe, five-year survival from the two most common leukaemia types, acute lymphoid leukaemia (ALL) and acute myeloid leukaemia (AML), are 88% and 64% respectively.[4] To further increase survival, it is important to identify vulnerable patient groups and factors related to a poor prognosis.

Besides the well-established clinical prognostic factors including disease subtype, sex, age at diagnosis, presenting white blood cell count, cytogenetic and molecular markers and response to initial therapy,[5-9] socioeconomic and sociodemographic factors have been suggested to impact survival from childhood leukaemia.[10-12] One hypothesized mechanism by which socioeconomic status (SES) could affect survival is through treatment adherence which is suggested to be lower among families of low SES; however, the empirically observed associations differ depending on the population and the social factors studied.[13-16] Number of siblings reflects one aspect of familial social circumstances, and one can hypothesize that a larger number of siblings and more parental obligations could have a negative impact on for example treatment adherence and thereby potentially affecting survival negatively.[10, 17] However, the few studies assessing the association between number of siblings and leukaemia survival do not yield consistent results.[10, 18-21] The largest of these studies is based on Danish registry data, includes 1011 children with ALL and 213 children with AML (diagnosed from 1973 to 2006), and suggests a lower survival in ALL and AML for children with a larger number of siblings and of higher birth order.[10] Previous studies have focused on biological siblings, while considering all siblings (biological and non-biological) in the household at time of diagnosis might better reflect the social situation. In addition, biological birth order has been discussed in relation to the risk of childhood leukaemia,[22, 23] but more seldom in relation to survival.[10, 19] Examining the association between both the number of siblings in the household and biological birth order, and survival, is needed to increase the understanding of underlying mechanisms.

Prognosis and treatment do not only differ largely between ALL and AML but also within these leukaemia types where subtypes are defined by immunophenotyping, genetic information and morphology. As an example, children with B-cell precursor ALL have a favourable prognosis compared to children with T-cell ALL.[8] In addition, the aetiology of leukaemia subtypes

remains poorly understood, but amongst the most discussed environmental risk factor is exposure to infections early in life, of particular importance for B-cell precursor ALL.[24, 25] The number of siblings and birth order are often used as proxies for such exposure. Therefore, a potential association between number of siblings and leukaemia survival may be explained by differences in the risk of subtypes with different prognosis. Moreover, having siblings might have different implications depending on the severity of disease or type of treatment. Clinical prognostic factors are therefore highly relevant to study as potential mediators or effect modifiers but have not been considered in previous studies on siblings and leukaemia survival.

In this nationwide population-based register study, we aimed to examine the association between number of siblings in the household and birth order, and survival from childhood ALL and AML in Sweden. Moreover, we assessed if these potential associations can be explained or modified by disease subtype, white blood cell count, or treatment regimen.

Methods

This study is based on information from Swedish nationwide health and population registries. Accurate linkage between the high-quality data is possible due to the unique personal identification number that is used in all registries.[26]

All children, 1–14 years old, with a first, primary diagnosis of ALL or AML, registered in the Swedish Cancer Register[27] or the Swedish Childhood Cancer Register[28] from 1st of January 1991 until 30th of June 2015, and registered in Sweden at the time of diagnosis, were eligible for inclusion (n=1838). Since 1958, reporting to the national Swedish Cancer Register is compulsory,[27] while the Swedish Childhood Cancer Register is a health care quality register which started in 1982 and contains more detailed clinical information.[28] ALL and AML were defined as either registered in the Swedish Childhood Cancer Register as ALL or AML, or registered in the Swedish Cancer Register as lymphoid leukaemia or acute myeloid leukaemia according to the International Classification of Childhood Cancer 3rd edition (ICCC-3).[29] From the coding used in the Cancer Register we recoded the diagnoses according to ICCC-3 (Supplementary table 1). Most children were found in both registers (n=1751, 95%), 32 (2%) were found only in the Swedish Cancer Register and 55 (3%) only in the Swedish Childhood Cancer Register. We used the earliest date of diagnosis in either of the two registers to define the date of leukaemia diagnosis. If the dates of diagnosis differed more than one month between the registers, the child was excluded (n=18). We also excluded children with Down syndrome, identified from the national Patient Register and the Medical Birth Register (n=78), since they

have a different survival profile.[30] Further, children for whom no biological mother or no parents in the household could be identified were excluded (n=27).

Information in the Swedish Childhood Cancer Register for ALL (available for 1485 children), was used to exclude children with mature B-cell or bi-linage ALL (n=23) to make the study population more homogenous. We also used this register to obtain additional information regarding disease subtype, characterized by immunophenotype (B-cell precursor, T-cell) and genotype (favourable; high hyperdiploidy-HeH or ETV6-RUNX1, other, available 1992 onwards); white blood cell count at diagnosis (<10, 10-50, >50 (x 10^9/L)); and treatment information, including treatment protocol (low risk (including standard and intermediate), high risk) and stem cell transplantation (yes, no).

The study population was followed from the date of diagnosis for up to 10 years, until death, emigration, or end of follow-up (31st of December 2015), whichever occurred first.

Number of siblings in the household

We derived information on siblings as well as parents living together with the child from the Total Population Register at the end of the year before diagnosis. In the Total Population Register the household includes individuals registered at the same residence who are related through marriage, common children or parenthood (not restricted to biological parenthood).[31] We defined all children (biological, adoptive, or other children), irrespective of age, to someone in the household as siblings, and categorized into none, one, and two or more. Using the same definition and categorization, we obtained information about the number of siblings younger than the index child.

Birth order

We identified the biological mother and obtained information about birth order from the Swedish Multi-generation Register.[32] Birth order was defined by counting all live-births of the same mother before the birth month of the index child, and categorized into first, second, and third or higher.

Other covariates used for adjustment

In addition to sex, age (1–4, 5–9, 10–14 years) and year of diagnosis (1991–1995, 1996–2000, 2001–2005, 2006–2010, 2011–2015), we also obtained information on parental sociodemographic factors. Highest achieved education (compulsory or less, upper-secondary,

postsecondary education) the year before the diagnosis was obtained from the Longitudinal integration database for health insurance and labour market studies,[31] for one parent in the household (household mother if available, otherwise household father) as well as for the biological mother. We also included age of the parent that provided information on educational level (in 5-year categories), and parental cohabitation (yes, no) for the parents in the household.

For children identified in the national Cancer Register, information on health care region at diagnosis was also available.

Statistical analyses

We compared overall survival among children with different number of siblings in the household, and children of different birth order. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards model with time since diagnosis as the underlying time scale. We conducted adjusted analyses with covariates included determined *a priori*. In addition to sex, age and time period of diagnosis, the models examining number of siblings were adjusted for sociodemographic factors related to the parents in the household, and for birth order. The models assessing the association between birth order and survival were, together with the basic characteristics, adjusted for sociodemographic information related to the biological mother. As an additional analysis, we adjusted the models of birth order also for number of siblings in the household, a potential mediator, to assess the direct association between birth order and survival. We conducted all analyses separately for ALL and AML. We also conducted additional analyses including only the number of siblings in the household younger than the index child, since younger children usually require more attention from the parents.

Among children with ALL included in the Childhood Cancer Register we assessed if immunophenotype, genotype, white blood cell count, treatment protocol or stem cell transplantation were associated with number of siblings or with birth order, using Pearson's Chi-squared test. This was done in the total population and within age strata. Further, we stratified our analyses on these clinical factors to assess potential effect modification. We compared the HRs across strata using the method suggested by Altman et al.[33]

In a sensitivity analysis we adjusted the main analyses also for health care region at diagnosis (six regions) to control for potential regional differences in practices related with cancer registration, particularly regarding date of diagnosis.

Results

We identified 1481 children with ALL of which 166 (11%) died within 10 years after diagnosis. The corresponding number for the 211 children with AML was 74 (35%). Table 1 shows baseline characteristics of the study population according to number of siblings. For children with ALL, as expected, the most common age at diagnosis was 1–4 years. It was most common to have one sibling (47%) and to be firstborn (46%). For children with AML, it was most common to have one sibling (50%), but to be second born (41%).

Survival in ALL patients

For children with ALL, a tendency towards better survival among children with siblings compared to children without siblings was observed in the model adjusted for sex, age, and time of diagnosis (Table 2). Additional adjustments for parental education, age, and cohabitation did not change the results; having one, or two or more, siblings was associated with better survival, adjusted HR 0.73 (95% CI 0.49-1.10) and 0.63 (95% CI 0.40-1.00), respectively. Also when adjusting for birth order the effect estimates remained virtually the same (Table 2). When only younger siblings were accounted for, a similar association pointing in the direction of better survival among children with one (adjusted HR 0.84; 95% CI 0.59-1.20), and two or more (adjusted HR 0.57; 95% CI 0.29-1.12) siblings, compared to none, was observed (Supplementary Table 2). A weak association between higher birth order and better survival from ALL was indicated by the point estimates but the confidence intervals were wide (Table 3). When additionally adjusting for number of siblings, a potential mediator, the association disappeared (data not shown).

Table 4 shows disease subtype, white blood cell count, and treatment information across stratum of number of siblings among children with ALL. There was an indication that children without siblings more often had B-cell precursor ALL and genotype HeH/ETV6-RUNX, but these associations disappeared when stratifying by age group (data not shown). No associations between the clinical factors and birth order were observed (p-values from non-stratified analyses ranging between 0.16 and 0.99, data not shown). When stratifying the analysis by the clinical factors (Table 5), the suggested better survival among children with siblings was mainly seen among children with B-cell precursor ALL, genotype HeH/ ETV6-RUNX1, white blood cell count <50, and treated with protocols according to low risk. However, most of the HRs did not differ statistically significantly (Table 5).

Survival in AML patients

For children with AML, we also observed a tendency towards better survival for children with siblings compared to children without, however, this association disappeared when birth order was adjusted for (Table 2). When including only younger siblings, the results differed and pointed in the direction of poorer survival from AML among children with younger siblings, however, due to small numbers these estimates are imprecise (Supplementary table 2). Focusing on birth order, better survival was observed among second born children compared to first born (Table 3).

Additional adjustment for health care region did not change the results for either children with ALL or AML (data not shown).

Discussion

In this nationwide register study, we observed a tendency towards better survival among children with siblings after a diagnosis of ALL. The association was not explained by differences in subtype of disease but seemed to be limited to children with a low risk profile. We also found an indication of better survival from AML among children with siblings, although the association diminished when adjusting for birth order and was not observed when only younger siblings were accounted for.

Few previous studies have examined the association between number of siblings and childhood cancer survival, including survival from leukaemia, with inconsistent findings being reported even across European studies.[10, 17, 19-21, 34] When combining all childhood cancer types, two previous studies suggested an inverse association between number of siblings and survival,[17, 18] while another reported no association.[34] However, due to the heterogeneity regarding prognosis and treatment, combining all cancer types makes the interpretation and comparability with our results difficult. Focusing on leukaemia, a Danish register study indicated, in contrast to our findings, that children with siblings or of higher birth order had worse survival in both the ALL- and AML groups; however, in mutually adjusted analyses only the associations with birth order remained.[10] The Danish study included children diagnosed as early as 1973, a period when both treatment and prognosis of leukaemia was very different from today. When restricting the analysis to children diagnosed 1990 and onwards (n=661 for ALL; n=150 for AML), a similar trend of worse survival from ALL and AML among children with siblings was observed, although estimates were imprecise.[10] On the contrary, in line with our findings, a

smaller Greek study (n=293) reported lower mortality in ALL among children with siblings.[20] However, this association was not found when the study was updated by including leukaemia cases from the whole country and extending both the inclusion period and the follow-up time.[21] A German study on survival from ALL has reported better survival among second born children, compared to first and third or later born.[19] Further, their estimates indicated slightly better survival among children with one or two siblings and poorer survival among children with three or more siblings, all compared to no siblings, even if not statistically significant.[19]As pointed out before,[10] it is not clear if the diverse result across studies reflect a different association in diverse societies or if it is a consequence of different study design and methods. However, all studies report rather weak, non-statistically significant associations. This is also the case for the current study, even though it is, to our knowledge, the largest study including children diagnosed with ALL and AML after 1990 investigating this topic in depth. Also in our study, we cannot rule out chance as an explanation for the observed findings.

Although some of our results are imprecise, they do not support the hypothesis that parents with many children and thereby more parental obligations have difficulties in handling complex leukaemia treatments which could affect survival negatively. Similar hypotheses have been discussed earlier as potential mechanisms for findings of worse cancer survival among children from families of low SES,[12] and among children with a larger number of siblings.[10, 17] However, studies assessing treatment adherence are rare. One small study (based on 64 in-depth interviews) investigating factors associated with adherence to ALL treatment did not find an association with number of siblings, although adherence tended to be better in homes where a larger number of persons were living.[16] Another small study conducted in the U.S. among 46 children and adolescents with cancer and their caregivers showed that compliance was worse among patients with a larger number of siblings.[35] It seems like siblings can act as a support as well as an additional obligation in families of children with cancer, and that this might depend on the age of the siblings.[36] This is also reflected in our findings which suggests subgroup specific associations between number of siblings and survival. When restricting the analyses to younger siblings, no superior survival from AML among children with siblings was seen. Moreover, among children with ALL, the better survival among children with siblings was mainly limited to children with low risk profiles (B-cell precursor ALL, favourable genotype HeH/ ETV6-RUNX1, white blood cell count ≤50, treated with protocols according to low risk).

Number of siblings reflects one aspect of family circumstances and are sometimes used as one of several indicators when operationalizing SES. To understand the underlying mechanisms of a potential association with childhood cancer survival it is, however, important to investigate different social factors separately.[37, 38] A previous study by our group has shown an association between higher parental education and increased survival in childhood cancer; the results for ALL were less pronounced but in the same direction.[11] We therefore adjusted for parental education in the present study and it can be ruled out as an explanation for the observed associations.

It is also important to clarify if a potential association between number of siblings and survival is explained by differences in subtypes or other clinical prognostic factors. This mediation has also been discussed as a potential mechanism behind the association between SES and survival in childhood cancer,[10, 11, 17, 34, 39, 40] but since this information is seldom recorded within national cancer registers it is rarely possible to study. A study from northern England has assessed the association between white blood cell count and parental social class, in addition to the impact on childhood leukaemia survival.[39] White blood cell count did not explain the socioeconomic differences in survival observed in that study.[39] In the current study we did not observe an association between white blood cell count and number of siblings or birth order. Neither did we observe any differences in subtypes or other clinical prognostic factors according to number of siblings or birth order within age groups.

This study is the first investigation on this topic in Sweden and one of the very few from Europe. The reliability of the findings is strengthened by the use of population-based register data, not influenced by non-participation or lost to follow-up. Moreover, compared to earlier studies, we included a larger number of children with ALL and AML, diagnosed after 1990 — a time period which is relevant for the situation of today. A great advantage is also the use of a health care quality register in addition to the national Cancer Register. By including this information, we could investigate potential mechanisms that have been hypothesized but not empirically tested in earlier studies, for example by assessing the potential associations in well-defined sub-groups according to clinical characteristics.

For the aim of this study, it was more relevant to identify the number of all siblings living in the household at the time of diagnosis, in comparison to several other studies with information only on biological siblings which might not reflect the social situation. In addition, we also assessed biological birth order. Only siblings born no later than the calendar year before the

child's diagnosis were included because the severity of an ill child's diagnosis could potentially influence the choice of having another child, which would have led to a systematic error. However, the drawback is that some of the siblings born around the time of diagnosis are not included — siblings that usually requires more attention from the parents in the first year of life. Consequently, the definition of siblings differs slightly in comparison to earlier studies but is unlikely to fully explain the different results. Another limitation is that only siblings in the household where the child was registered were counted. This means that if children had separated parents, the influence of the other parent's household was not considered.

Conclusion

This study is, to our knowledge, the largest study on this topic considering leukaemia diagnosis after 1990. We have taken birth order into account and, as one of the first studies, also clinical prognostic factors. Our results from Sweden do not support the hypothesis and previous findings from other European settings that a larger number of siblings is associated with poorer survival from childhood leukaemia. In summary, the evidence of an association between number of siblings and leukaemia survival is overall conflicting and inconclusive. This might partly be explained by underlying mechanisms that differ between study populations and settings; however, we cannot rule out chance as a potential reason for the diverse findings across studies.

Disclaimer

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Additional information

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Authors' contributions: GT, MF, KM, HM designed this study. MF and MH acquired the data, HM, MT, GT did the data management and HM conducted the analyses with supervision from GT, MF, MT. All authors contributed to the interpretation of the results. HM drafted the

manuscript, all authors contributed to the revision of it and approved the final version. All authors take responsibility for the accuracy and integrity of the work.

Ethics approval and consent to participate: This study was approved by the Regional Ethical Review Board in Stockholm, Sweden, dnr 2011/634-31/4 and 2014/417-32, and did not require individual consent from participants. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable

Data availability: This study were conducted using register data from Statistics Sweden (https://www.scb.se/vara-tjanster/bestalla-mikrodata/), the Swedish National Board of Health and Welfare (https://bestalladata.socialstyrelsen.se/data-for-forskning/) and the Swedish Childhood Cancer Register (http://child3.ki.se/wordpress/index.php/for-vardpersonal-forskare/for-forskning/). These data are only available from each register holder after ethical review and secrecy assessment.

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Table 1. Characteristics of children diagnosed with ALL and AML in Sweden during 1991-mid 2015, according to number of siblings in the household.

	ALL				AML			
	Total, n=1481	0 siblings, n=337	1 sibling, n=693	≥2 siblings, n=451	Total, n=211	0 siblings, n=37	1 sibling, n=106	≥2 siblings, n=68
	n %	n %	n %	n %	n %	n %	n %	n %
Sex								
Boys	840 57	183 54	408 59	249 55	111 53	18 49	53 50	40 59
Girls	641 43	154 46	285 41	202 45	100 47	19 51	53 50	28 41
Age at diagnosis								
1-4 years	820 55	253 75	366 53	201 45	74 35	22 59	38 36	14 21
5-9 years	405 27	53 16	202 29	150 33	56 27	6 16	27 25	23 34
10-14 years	256 17	31 9	125 18	100 22	81 38	9 24	41 39	31 46
Time period of diagnosis								
1991-1995	280 19	62 18	135 19	83 18	29 14	6 16	16 15	7 10
1996-2000	316 21	72 21	149 22	95 21	45 21	11 30	26 25	8 12
2001-2005	309 21	60 18	149 22	100 22	47 22	9 24	22 21	16 24
2006-2010	281 19	66 20	134 19	81 18	55 26	7 19	23 22	25 37
2011-2015	295 20	77 23	126 18	92 20	35 17	4 11	19 18	12 18
Birth order								
First	688 46	312 93	298 43	78 17	76 36	32 86	30 28	14 21
Second	490 33	16 5	364 53	110 24	87 41	2 5	71 67	14 21
Third or later	303 20	9 3	31 4	263 58	48 23	3 8	5 5	40 59
Number of younger siblings in the household								
0	944 64	337 100	385 56	222 49	141 67	37 100	76 72	28 41
1	440 30		308 44	132 29	54 26		30 28	24 35
≥2	97 7			97 22	16 8			16 24
Parental education*								
Compulsory or less	175 12	28 8	57 8	90 20	43 20	9 24	13 12	21 31
Upper secondary	734 50	173 51	353 51	208 46	108 51	18 49	61 58	29 43
Post secondary	563 38	135 40	280 40	148 33	60 28	10 27	32 30	18 26

Children with Down syndrome are excluded.

*Highest achieved maternal education if available, otherwise paternal education.

The numbers do not add up to the total because of missing values.

Abbreviations: ALL: Acute lymphoid leukaemia; AML: Acute myeloid leukaemia

Table 2. Mortality after childhood ALL and AML, diagnosed in Sweden 1991-mid 2015, according to number of siblings in the household.

	Deaths, n	**Adjusted model 1***	**Adjusted model 2†**	**Adjusted model 3‡**
		HR (95%CI)	HR (95%CI)	HR (95%CI)
ALL				
Number of siblings		n=1481	n=1472	n=1472
0	40	1	1	1
1	78	0.74 (0.50-1.09)	0.73 (0.49-1.10)	0.75 (0.48-1.17)
≥2	48	0.65 (0.42-1.00)	0.63 (0.40-1.00)	0.62 (0.36-1.08)
AML				
Number of siblings		n=211	n=211	n=211
0	19	1	1	1
1	33	0.53 (0.29-0.95)	0.68 (0.36-1.29)	0.97 (0.46-2.07)
≥2	22	0.59 (0.30-1.16)	0.71 (0.34-1.48)	0.88 (0.37-2.12)

* Model 1: adjusted for sex, age at diagnosis, and year of diagnosis

† Model 2: adjusted as model 1 plus parental education, parental age, and parental cohabitation

‡ Model 3: adjusted as model 2 plus birth order

Abbreviations: ALL: Acute lymphoid leukaemia; AML: Acute myeloid leukaemia; CI: Confidence interval; HR: Hazard ratio

Table 3. Mortality after childhood ALL and AML, diagnosed in Sweden 1991-mid 2015, according to birth order.

	Deaths, n	Adjusted model 1* HR (95% CI)	Adjusted model 2† HR (95% CI)
ALL			
Birth order		n=1481	n=1460
First	81	1	1
Second	52	0.83 (0.58-1.17)	0.85 (0.59-1.23)
Third or later	33	0.85 (0.56-1.27)	0.85 (0.54-1.33)
AML			
Birth order		n=211	n=208
First	33	1	1
Second	25	0.52 (0.31-0.88)	0.55 (0.31-0.99)
Third or later	16	0.69 (0.38-1.27)	0.67 (0.33-1.34)

* Model 1: adjusted for sex, age at diagnosis, and year of diagnosis

† Model 2: adjusted as model 1 plus maternal education, and maternal age

Abbreviations: ALL: Acute lymphoid leukaemia; AML: Acute myeloid leukaemia; CI: Confidence interval; HR: Hazard ratio

Table 4. Clinical characteristics of children with ALL identified in the Swedish Childhood Cancer Registry 1991-mid 2015, according to number of siblings in the household.

	Total, n=1462		0 siblings, n=335		1 siblings, n=679		≥2 siblings, n=448		P for association
	n	%	n	%	n	%	n	%	
Immunophenotype									
B-cell precursor	1286	88	308	92	592	87	386	86	0.053
T-cell	170	12	27	8	83	12	60	13	
Genotype*									
HeH/ETV6-RUNX1	679	46	174	52	307	45	198	44	0.056
Other	636	44	128	38	303	45	205	46	
White blood cell count									
<10	734	50	158	47	345	51	231	52	0.421
10-50	421	29	103	31	201	30	117	26	
>50	306	21	74	22	132	19	100	22	
Treatment protocol†									
Low risk	1092	75	257	77	512	75	323	72	0.240
High risk	343	23	75	22	150	22	118	26	
Treatment with stem cell transplantation									
No	1256	86	297	89	579	85	380	85	0.252
Yes	206	14	38	11	100	15	68	15	

Children with mature B-cell and bi-linage ALL are excluded.

The numbers do not always add up to the total because of missing values.

* Missing includes children diagnosed before 1992.

† Missing includes protocols outside Nordic Society of Pediatric Hematology and Oncology.

Abbreviations: ALL: Acute lymphoid leukaemia; HeH: High hyperdiploidy

Table 5. Mortality after childhood ALL in Sweden 1991-2015 according to number of siblings in the household and birth order, within strata of clinical characteristics.

		Number of siblings			**Birth order**		
		0	1	≥2	First	Second	Third or later
	n	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*
Immunphenotype							
B-cell precursor	1286	1	0.62 (0.39-0.98)	0.59 (0.35-0.98)	1	0.84 (0.55-1.29)	0.90 (0.55-1.45)
T-cell	170	1	1.08 (0.46-2.51)	0.68 (0.27-1.69)	1	0.64 (0.32-1.27)	0.64 (0.29-1.43)
P for difference			*0.260*	*0.791*		*0.511*	*0.474*
Genotype							
HeH/ETV6-RUNX1	679	1	0.65 (0.34-1.27)	0.59 (0.28-1.27)	1	0.47 (0.23-0.96)	0.77 (0.38-1.59)
Other	636	1	0.90 (0.52-1.57)	0.81 (0.45-1.47)	1	1.09 (0.69-1.73)	1.06 (0.62-1.82)
P for difference			*0.458*	*0.518*		*0.052*	*0.484*
White blood cell count							
<10	734	1	0.53 (0.27-1.03)	0.71 (0.36-1.41)	1	0.68 (0.37-1.25)	0.83 (0.43-1.60)
10-50	421	1	0.65 (0.31-1.33)	0.37 (0.14-0.95)	1	0.75 (0.35-1.58)	1.01 (0.46-2.24)
>50	306	1	1.43 (0.71-2.87)	0.86 (0.39-1.87)	1	1.05 (0.61-1.82)	0.69 (0.34-1.42)
P for difference			*<10 vs 10-50: p=0.686*	*<10 vs 10-50: p=0.277*		*<10 vs 10-50: p=0.843*	*<10 vs 10-50: p=0.708*
			<10 vs >50: p=0.044	*<10 vs >50: p=0.718*		*<10 vs >50: p=0.298*	*<10 vs >50: p=0.709*
			10-50 vs >50: p=0.126	*10-50 vs >50: p=0.182*		*10-50 vs >50: p=0.479*	*10-50 vs >50: p=0.484*
Treatment protocol							
Low risk	1092	1	0.46 (0.26-0.81)	0.42 (0.22-0.81)	1	0.60 (0.35-1.06)	0.53 (0.27-1.05)
High risk	343	1	1.42 (0.77-2.61)	1.03 (0.53-1.99)	1	1.00 (0.61-1.64)	1.36 (0.79-2.33)
P for difference			*0.008*	*0.058*		*0.178*	*0.033*
Treatment with stem cell transplantation							
No	1256	1	0.78 (0.47-1.32)	0.52 (0.28-0.96)	1	0.54 (0.32-0.90)	0.67 (0.38-1.18)
Yes	206	1	0.68 (0.37-1.25)	0.76 (0.41-1.43)	1	1.06 (0.64-1.78)	1.14 (0.62-2.09)
P for difference			*0.736*	*0.397*		*0.069*	*0.210*

* All analyses are adjusted for sex, age at diagnosis, and time period of diagnosis.
Abbreviations: ALL: Acute lymphoid leukaemia; CI: Confidence interval; HeH: High hyperdiploidy; HR: Hazard ratio

Supplementary Table 1. Definition of ALL and AML.

Year of diagnosis	Register	ALL	AML
2005-2015	The national Swedish Cancer Register	ICCC-3 Group Ia according to Steliarova-Foucher et al (2005), additionally ICD-O-3 morphology codes 9812-9818.	ICCC-3 Group Ib according to Steliarova-Foucher et al (2005), additionally ICD-O-3 morphology codes 9865, 9869, 9898, 9911.
	The Swedish Childhood Cancer Register	Registered in the Swedish Childhood Cancer Register for ALL.	Registered in the Swedish Childhood Cancer Register for AML.
1993-2004	The national Swedish Cancer Register	ICCC-2 Group Ia according to Kramarova & Stiller (1996).	ICCC-2 Group Ib according to Kramarova & Stiller (1996), additionally ICD-O-2 morphology code 9984.
	The Swedish Childhood Cancer Register	Registered in the Swedish Childhood Cancer Register for ALL.	Registered in the Swedish Childhood Cancer Register for AML.
1991-1992	The national Swedish Cancer Register	ICD-9: 204	ICD-9: 205.0, 205.1 (morphology 296), 206.0 (morphology 256), 207.0 (morphology 286), 207.2 (morphology 296)
	The Swedish Childhood Cancer Register	Registered in the Swedish Childhood Cancer Register for ALL.	Registered in the Swedish Childhood Cancer Register for AML.

Children are included at their first registered date of diagnosis if the diagnosis correspond to either the definition from the national Swedish Cancer Register or the Swedish Childhood Cancer Register.

Abbreviations: ALL: Acute lymphoid leukaemia; AML: Acute myeloid leukaemia; ICCC: International classification of childhood cancer; ICD: International classification of diseases; ICD-O: International classification of diseases for oncology

Supplementary Table 2. Mortality after childhood ALL and AML according to number of younger siblings in the household.

	Deaths, n	Adjusted model 1* HR (95% CI)	Adjusted model 2† HR (95% CI)	Adjusted model 3‡ HR (95% CI)
ALL				
Number of younger siblings		n=1481	n=1472	n=1472
0	105	1	1	1
1	50	0.86 (0.61–1.22)	0.84 (0.59–1.20)	0.74 (0.50–1.09)
≥2	11	0.61 (0.32–1.16)	0.57 (0.29–1.12)	0.50 (0.25–0.99)
AML				
Number of younger siblings		n=211	n=211	n=211
0	47	1	1	1
1	22	1.62 (0.96–2.75)	1.81 (1.04–3.15)	1.57 (0.88–2.82)
≥2	5	1.16 (0.44–3.09)	1.17 (0.39–3.49)	0.94 (0.30–2.90)

*Model 1: adjusted for sex, age at diagnosis, and year of diagnosis

†Model 2: adjusted as model 1 plus parental education, parental age, and parental cohabitation

‡Model 3: adjusted as model 2 plus birth order

Abbreviations: ALL: Acute lymphoid leukaemia; AML: Acute myeloid leukaemia; CI: Confidence interval; HR: Hazard ratio