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RESEARCH ARTICLE

Quality of life in children and adolescents after treatment for acute lymphoblastic leukemia according to the NOPHO ALL2008 protocol

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Abstract

Background: The improved outcome of childhood acute lymphoblastic leukemia (ALL) over the last decades has increased the importance of assessing late effects and health-related quality of life (HRQoL), particularly when evaluating and comparing outcomes in clinical trials. This study aimed to assess HRQoL in children treated for ALL according to the NOPHO ALL2008 protocol.

Procedure: Children, aged 1 to less than 18 years at diagnosis, alive in first remission, and their parents, were asked to complete PedsQL 4.0 Generic Core Scales (self- and proxy-report) at ≥6 months after end of therapy. Data on socioeconomic factors and parent-reported toxicity were collected through a study-specific questionnaire, and the NOPHO ALL2008 database was used to identify eligible families and add additional disease- and treatment-related data. HRQoL data were collected during 2013–2019 in Sweden, Finland, and Denmark.

Results: A total of 299 children were included. The older children (8 years and older) reported similar HRQoL scores compared to Finnish reference data, except lower scores for School Functioning in high-risk patients. Scores from the parent-proxy and self-reports from 5–7-year olds were notably lower than reference. Parent-reported toxicity was associated with lower total and physical HRQoL scores in adjusted models for younger as well as older children in the self-report and parent-proxy versions, and also with lower psychosocial score in the parent-proxy.

Conclusions: Self-reported HRQoL was similar to reference population. The most important determinant for HRQoL after end of ALL treatment was parent-reported toxicity during treatment. Thus, minimizing complications is an obvious focus for future treatment protocols.

KEYWORDS
acute lymphoblastic leukemia, childhood cancer, clinical trials, quality of life, toxicity

Abbreviations: 6MP, 6-mercaptopurine; ALL, acute lymphoblastic leukemia; ANOVA, analysis of variance; ASP, PEG-asparaginase; CI, confidence interval; HR, high risk; HRQoL, health-related quality of life; IR, intermediate risk; MCID, minimal clinically important difference; NOPHO, Nordic Society of Paediatric Haematology and Oncology; PedsQL, Pediatric Quality of Life Inventory Generic Core Scales version 4.0; RCT, randomized clinical trial; SCT, stem cell transplantation; SR, standard risk.

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most common childhood cancer, has today a generally favorable prognosis, with an overall survival exceeding 90%.[1] The cure may come at a cost, however, and complications during and after treatment, as well as psychosocial effects of treatment, may significantly impact quality of life. Health-related quality of life (HRQoL) is an individual's perception of their own health, and encompasses multiple aspects attributed to health, illness, and its treatment,[2] such as physical, psychological, and social health.[3] Perceived quality of life may also be affected by personal coping strategies, cultural context, and family functioning.[4–6] In pediatric oncology, it is generally recommended to use self-reports for assessment of HRQoL,[7,8] but age or condition of the child sometimes necessitates the use of parent-proxy reports only. Notably, parent-proxy tends to underestimate a child's HRQoL in general, both during and after treatment,[9–15] and may also correlate with the parent's own HRQoL[16,17] and be influenced by the parent's gender.[18]

Findings from longitudinal and cross-sectional studies regarding HRQoL during ALL treatment usually indicate worse HRQoL shortly after diagnosis and during more intense treatment phases, but it usually improves over time[19,20] and becomes similar to that of reference population or controls around the end of treatment,[12,21–25] although some of these studies indicate remaining deficits in HRQoL.[12,23–26] A limitation of previous studies focusing on the first years after treatment includes small numbers of patients or use of parent-proxy reports only, as reviewed by Garas et al.[27] For HRQoL after treatment, published findings tend to vary, with some studies indicating a better HRQoL,[28–30] while other studies have observed worse HRQoL than healthy controls or reference data,[31–34] usually in psychosocial domains[35] or if assessed by parent-proxy.[25,36] The end of treatment is a major transition, and the early post-treatment period, when the child and family are usually seen frequently at the clinic, poses a unique opportunity for interventions and early assessment.[27,37] This study aimed to use both self- and parent-proxy reports to evaluate children's HRQoL after ALL treatment, in relation to risk group, randomization arm, and parent-reported toxicity, in a large, population-based setting in Denmark, Finland, and Sweden.

2 | METHODS

2.1 | Study design and population

The Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL2008 database was used to identify all patients aged 1 to less than 18 years old at diagnosis in Denmark, Finland (from January 1, 2010), and Sweden who were treated according to the NOPHO ALL2008 protocol, which was in use during 2008–2019. Eligibility criteria included diagnosis before March 2016 and being alive in first remission without any secondary malignancy at the time of data collection (2013–2019). Patients who had Down syndrome, mixed phenotype acute leukemia (MPAL), or those who underwent stem cell transplantation (SCT) in first remission were excluded from this study. Study eligibility ($n = 826$) was cross-checked with staff at each local center before questionnaires were sent (Figure 1).

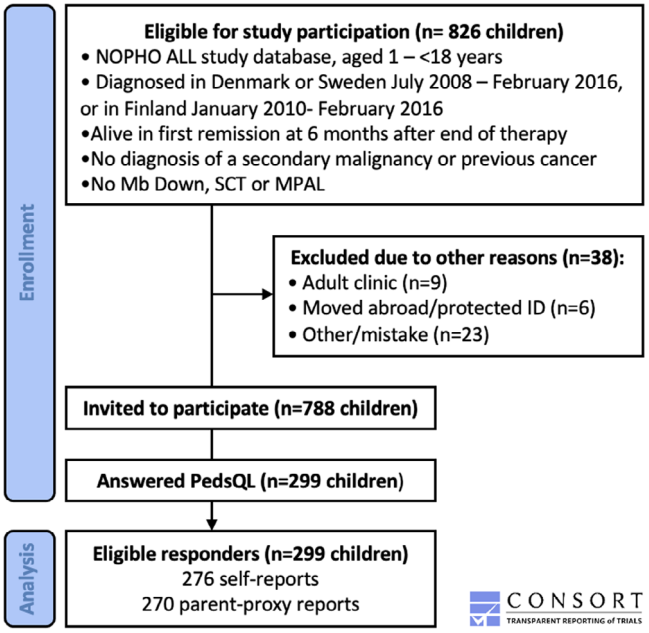

FIGURE 1 Consort diagram of study population. Numbers shown refer to children unless otherwise indicated. ALL, acute lymphoblastic leukemia; MPAL, mixed phenotype acute leukemia; NOPHO, Nordic Society of Paediatric Haematology and Oncology; SCT, stem cell transplantation.

Questionnaire packets including an invitational letter and informed consent forms were sent by mail at least 6 months after end of therapy (e.g., ≥3 years from diagnosis). Up to two reminders were sent if parents had not responded after at least 3 months from the initial invitation. The study was conducted according to the Declaration of Helsinki, and was approved by the Ethical Review Board of Stockholm (reference number 2013/1470-31) and Ethical Committee of the South-West Finland Hospital District (reference number ETMK:17/1801/2015). No additional ethical approval, apart from participation in the clinical study NOPHO ALL2008 (EudraCT 2008-003235-20), was required in Denmark.

2.2 | NOPHO ALL2008 treatment protocol and its randomized clinical trials

The NOPHO ALL2008 protocol was in use during 2008–2019 in the Nordic and Baltic countries. Treatment duration was 2.5 years, and depending on leukemia characteristics and treatment response after induction (Day 29) and consolidation (Day 79), patients were assigned to either standard- (SR), intermediate- (IR), or high-risk (HR) treatment arms. SR and IR arms were similar in treatment intensity, except for the use of either one (SR) or two (IR) delayed intensifications, while the HR

arm comprised seven to nine very intensive chemotherapy blocks, followed by delayed intensification and maintenance.[38] Only HR patients who underwent allogenic SCT received radiotherapy; however, no transplanted patients were included in this study. Two randomized clinical trials (RCTs) were open for patients in the SR and IR arms. The first of those compared fixed dose of 6-mercaptopurine (6MP) as standard arm to two dose increments if toxicity allowed (experimental arm) during consolidation,[39] and the second one investigated de-escalation of PEG-asparaginase (ASP) by increasing the interval between doses from every second week (standard arm) to every sixth week after the first five injections, also reducing the total number of ASP doses from 15 to eight in the experimental arm.[40] A third RCT (DepoCyte study) investigated the substitution of triple (methotrexate, cytarabine, prednisolone) intrathecal therapy with liposomal cytarabine for HR patients in the first part of the maintenance phase, but closed prematurely due to withdrawal of the investigational drug from the market, and only few patients were included.[41]

2.3 | Study-specific questionnaire and outcome measures

The study-specific questionnaire was prepared by the authors[42] with input from families with children previously treated for ALL. Each parent within the study was asked to complete the questionnaire, which included items on socioeconomic factors before and after treatment, and their experience of different treatment-related factors and side effects. Parents were asked to estimate to what extent their child was affected by complications overall compared to other children with ALL. The possible answers on disposable income and education were based on the Swedish median for annual disposable income and ISCED-97 (the International Standard Classification of Education 1997), respectively,[43,44] and has been described elsewhere.[45]

Treatment-related factors (treatment intensity, categorized as SR, IR, or HR) and the birth year of the child were retrieved from the NOPHO ALL2008 database.

2.4 | HRQoL

The Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales version 4.0 is a widely used instrument[35,46] that has been successfully validated in children, adolescents,[47,48] and young adults,[49] including in children with cancer[50,51] and in Nordic settings.[52,53] It has parallel self-report forms from age 5 years, parent-proxy versions for ages 2–4, 5–7, 8–12, and 13–18 years, and self-report only from 19–25 years. The questionnaire consists of 23 items (questions on how much of a problem the child has experienced over the last month, e.g., "I have trouble getting along with other kids") that are categorized into four scales: Physical, Emotional, Social, and School Functioning. From these, Total Score (all subscales, 23 items) and Psychosocial Health Summary Score (PSHS, from Emotional, Social, and School Functioning subscales, 15 items) can be computed. Recall period is 1 month, and responses are made on a five-point Likert scale (or three-point scale for the 5–7 years self-report) that translates into a score, ranging from 0 (almost always a problem) to 100 (never a problem), so that a higher score corresponds with a higher HRQoL. To avoid attributing too much importance to small and clinically meaningless changes in HRQoL, even if statistically significant, the concept of minimal clinically important difference (MCID) is applied, and is, for example, regarded as 4.36 for self-report and 4.50 for parent-proxy versions of the PedsQL Total Score.[54]

It was noted that answers on the two last questions of the PedsQL School Functioning scale on both the self-report and parent-proxy versions for all ages had a highly divergent pattern in Denmark compared to Sweden and Finland, which was likely due to discrepancies in translation (i.e., asking for absence from school/daycare *when* sick or *when* having appointments at hospitals, not *due to* being sick or having hospital appointments). It was also noted that Questions 1 and 5 on the Social Functioning scale of the Finnish parent-proxy version for 5–7 years old had significantly different answers compared to the other countries. Many parents commented that the wording was ambiguous, resulting in Finnish parents answering "almost always" (50.0% and 29.6% on Question 1 and 5, respectively) when probably not intended. Thus, all of these items (Items 4 and 5 on School Functioning in the Danish versions, and Items 1 and 5 on Social Functioning in the Finnish parent-proxy version for 5–7 years old) were removed before analysis.

2.5 | Statistics

The PedsQL was scored according to the copyright holder's instructions. As the self-report version for 5–7-year olds only had three-point Likert scales, and this group had statistically significantly lower scores than other age groups (analyzed with analysis of variance [ANOVA] and Tukey as post hoc analysis), self-report results for this group were analyzed and presented separately. This group is referred to as "younger" children and the remaining participants (8–25-year olds) are referred to as "older" children. These two groups, together with parent-proxy reports, are collectively referred to as "study groups".

Mean differences in HRQoL scores between the different treatment arms were analyzed using ANOVA. One sample *T*-test was used to compare study population scores to Finnish reference data (from a general population of school children).[53] Simple linear regression analysis was used to evaluate association between each different treatment-related and socioeconomic factor in this study and outcome in HRQoL scores separately. Multiple linear regression analysis was used to model these associations while adjusting for all the other socioeconomic and treatment-related factors that were associated with HRQoL in any domain in any group (self- or proxy reports) at $p < .05$. No adjustment for multiple testing was done.

Findings that exceeded MCID (described above under HRQoL section) and that were statistically significant were considered important.

Statistical significance was defined as two-sided $p < .05$. All statistical analyses were performed in SPSS Statistics version 28.0 (IBM).

3 | RESULTS

3.1 | Participant characteristics

A total of 299 children (self-report from 276 children and parent-proxy from 270 parents) of the eligible families answered the PedsQL questionnaire (Figure 1). Child and parent characteristics are presented in Table 1. Most of the children were in the age groups 5–7 or 8–12 years, and had been treated according to the SR or IR treatment arms. A little more than a fourth (28%) of all parents rated the overall impact of toxicity during treatment for their child as higher than for fellow ALL patients. There were no significant differences between responders and non-responders regarding age at diagnosis or risk group, although fewer parents than expected were born outside any Nordic country, and had higher level of education compared to the general population (data not shown).[55,56]

3.2 | HRQoL, risk groups, and socioeconomic factors

There were no differences in HRQoL between age groups, except 5–7 years self-report as previously described, nor were there any significant differences between countries. When comparing HRQoL between risk groups, no statistically or clinically significant differences were observed, except for lower scores for School Functioning in the self-report from older patients (8–25 years) belonging to the HR group (Table S1).

Female gender was associated with worse total self-reported HRQoL in the older children (−4.85 ± 2.13; $p = .024$), which was not observed in younger children or in parent-proxy reports. The parental level of education did not impact reported HRQoL, neither in self- nor in parent-proxy reports. Household income was associated with higher self-reported total HRQoL in the older children 8–25 years (4.45 ± 2.17; $p = .042$), as well as statistically higher scores for Physical Functioning in this group, and in parent-proxy, but not exceeding MCID (Table S2). A tendency to a lower HRQoL was seen in all domains and study groups (i.e., 5–7 years self-report, 8–25 years self-report, and 2–18 years parent-proxy reports) related to "parents not living together." Statistically and clinically significantly lower HRQoL scores related to this background variable were seen in Total Scale Scores (all study groups), Physical Functioning (8–25 years, self-report), and PSHS (5–7 years self-report; and parent-proxy). Having any parent born outside of the Nordic countries was associated with better total self-reported HRQoL in the younger children (7.48 ± 3.54; $p = .037$), but not in the other study groups. Parent-reported toxicity was significantly associated with lower total and physical HRQoL in older children, and with lower total and psychosocial HRQoL in parent-proxy reports; however, ten-

TABLE 1 Baseline characteristics of children and parents.

	Total children ($N = 299$)	
	n	%
Sex		
Male	158	52.8
Female	141	47.2
Age at diagnosis in years, mean (SD)	5.3 (3.7)	
Age group for PedsQL		
2–4 years	7	2.3
5–7 years	120	40.1
8–12 years	132	44.1
13–18 years	34	11.4
19–25 years	6	2.0
Any parent born outside Nordic countries	36	12.0
Treatment arm		
Standard risk	160	53.5
Intermediate risk	114	38.1
High risk	25	8.4
Any toxicity in registry	154	51.5
Parent-rated toxicity		
Less/same as other patients with ALL	193	64.5
More/a lot more	83	27.8
Don't know/missing	23	7.7
Participation in randomized clinical trial		
6MP standard	110	36.8 (50.0)
6MP dose increments	110	36.8 (50.0)
ASP standard	89	29.8 (50.3)
ASP exp. (every 6th week)	88	29.4 (49.7)
Country of residence		
Sweden	150	50.2
Denmark	71	23.7
Finland	78	26.1
Parents' civil status		
Living together with other parent	230	76.9
Not living with other parent	63	21.1
Unknown/missing	6	2.0
Parents' highest achieved education level		
Primary or secondary education	113	37.8
Post-secondary or tertiary education	176	58.9
Other/not reported	10	3.3
Disposable income for household		
Low–intermediate (<412,800 SEK/43,100 €)	131	43.8
High (>412,800 SEK/43,100 €)	157	52.5
Not reported	11	3.7

Abbreviations: 6MP, 6-mercaptopurine; ASP, PEG-asparaginase; SEK, Swedish Krona.

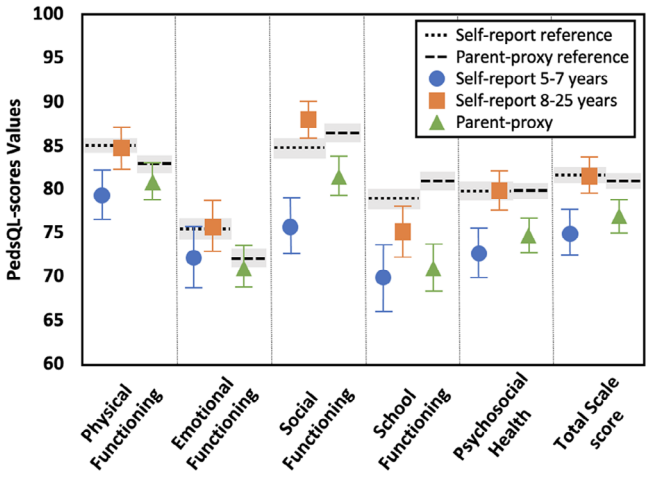

FIGURE 2 PedsQL scores in different responder groups, and reference data.

dencies to lower HRQoL scores were seen in all domains and study groups.

3.3 | PedsQL scores from multiple linear regression

In the multiple linear regression model, parent-reported toxicity was associated with lower total and physical HRQoL in all study groups, and for parent-proxy also regarding psychosocial HRQoL. Parents not living together was associated with lower total and psychosocial summary scores in the younger children, exceeding MCID (Table 2). Having any parent born outside of the Nordic countries was associated with better self-reported total, physical, and psychosocial HRQoL in the younger children. Younger children in the HR group also reported a better total and physical HRQoL than other treatment arms. None of these findings were seen in the older children, nor in parent-proxy reports. High household income was associated with higher reported physical functioning in parent-proxy reports, but not exceeding MCID. Parent-reported toxicity was the only factor that was associated with lower HRQoL in all study groups.

3.4 | HRQoL in children treated for ALL compared to reference data

The scores from the PedsQL self-reports in the older children (8–25 years) did not significantly differ from reference data from Finland (Figure 2), when analyzed with one-sample *T*-tests. However, they reported significantly lower scores in School Functioning (mean difference between mean for 8–25 years and reference mean in Table S1: −3.66, 95% confidence interval [CI]: −6.64 to −0.68; $p = .016$), but this difference did not exceed MCID. For younger children (5–7 years), self-reported HRQoL scores were lower in all domains, and exceeded MCID for total and psychosocial HRQoL scores. In the parent-proxy responses, scores were significantly lower in the Social Functioning, School Functioning, and Psychosocial domains as well as for total HRQoL, but exceeded MCID only for School Functioning (mean difference between parent-proxy and reference mean in S1: −9.96, 95% CI: −12.63 to −7.30; $p < .001$) compared to reference data.

3.5 | HRQoL for children according to self- versus parent-proxy reports

The Pearson correlations between self- and parent-proxy reports were moderate to high, with *r* ranging from .56 (for both School and Social Functioning among 5–7-year olds) to .82 (Total Scale scores for 8–18-year olds), and were generally higher in the older than the younger children. However, a lower correlation between self- and parent-proxy reports was observed for Social Functioning ($r = .60$) in older children.

3.6 | HRQoL and RCTs

For the 6MP study, significant differences were seen in School Functioning and PSHS for 5–7-year-old self-reports and Social Functioning in older children's self-reports (8–25 years), with higher scores for those in the experimental arm (Table S3). These differences only exceeded MCID for School Functioning among younger children. No significant differences were seen in the parent-proxy versions. For the ASP study, no differences between the standard and experimental arms were seen in any of the study groups.

4 | DISCUSSION

Our population-based study of HRQoL in 299 children and adolescents after ALL treatment from 276 self-reports and 270 parent-proxy reports found that HRQoL in general was similar to reference data for children 8 years and older. However, parent-proxy scores were lower than reference data in general, and for School Functioning they exceeded MCID. This finding of lower proxy scores is in line with previous studies, in which parents of children with cancer tend to rate their child's HRQoL lower than the child itself[9–11] during and shortly after treatment, while they tend to overestimate HRQoL in healthy children or siblings.[9,11] It has also been found that while both the child and parents rate the child's HRQoL low shortly after ALL diagnosis and during the first phases of treatment, the children's self-reports indicate improving HRQoL over time, while parent-proxy scores, although increasing, tend to remain lower than the self-reports.[23,27] The reasons for this could be several. First, parents with high levels of distress or low HRQoL themselves tend to rate their child's HRQoL as low,[7,18,57–61] and parents, especially mothers, of children recently treated for cancer have been shown to have impaired HRQoL,[59,62] which is true also for this cohort.[45] Second, after a life-altering event such as being diagnosed with a life-threatening disease, a phenomenon referred to as *response shift* often occurs. This means that the individual adapts in different ways, sometimes by lowering expectations (internal standards)

TABLE 2 Associations between different factors and Total Scale Score, Physical Functioning, and Psychosocial Health Score.

	Total Scale Score		Physical Functioning		Psychosocial Health Score	
	B ± SE	*p*	*B* ± SE	*p*	*B* ± SE	*p*
Self-report, 5–7 years old						
Gender						
Male	Ref					
Female	2.61 ± 2.64	.325	2.28 ± 3.04	.455	2.90 ± 2.85	.312
Civil status						
Parents living together	Ref					
Parents not living together	**−9.87 ± 3.68**[a,b]	**.009**	−7.16 ± 4.24[b]	.094	**−11.34 ± 3.98**[a,b]	**.005**
Total annual disposable household income						
Low–intermediate (<412,800 SEK/43,100 €)	Ref					
High (>412,800 SEK/43,100 €)	4.16 ± 2.67	.122	2.45 ± 3.07	.428	5.20 ± 2.88	.074
Parent born outside Nordic countries	**8.55 ± 3.45**[a,b]	**.015**	**8.72 ± 3.98**[a,b]	**.031**	**8.53 ± 3.74**[a,b]	**.025**
Treatment arm						
Standard/intermediate risk	Ref					
High risk	**9.33 ± 4.42**[a,b]	**.037**	**10.33 ± 5.10**[a,b]	**.045**	8.71 ± 4.78[b]	.072
Parent-rated overall toxicity						
Equal or less	Ref					
Slightly more/more	**−7.24 ± 2.95**[a,b]	**.016**	**−9.67 ± 3.40**[a,b]	**.005**	−5.76 ± 3.19[b]	.074
Self-report, 8–25 years old						
Gender						
Male	Ref		Ref		Ref	
Female	−3.54 ± 2.29	.125	−3.31 ± 2.58	.203	−3.62 ± 2.39	.133
Civil status						
Parents living together	Ref		Ref		Ref	
Parents not living together	−4.64 ± 2.68[b]	.085	−6.50 ± 3.02[a]	.033	−3.60 ± 2.79	.199
Total annual disposable household income[1]						
Low–intermediate (<412,800 SEK/43,100 €)	Ref		Ref		Ref	
High (>412,800 SEK/43,100 €)	3.25 ± 2.31	.161	3.11 ± 2.60	.234	3.41 ± 2.41	.160
Parent born outside Nordic countries	−6.12 ± 4.47[b]	.174	−7.70 ± 5.04[b]	.129	−5.46 ± 4.67[b]	.244
Treatment arm						
Standard/intermediate risk	Ref		Ref		Ref	
High risk	−2.56 ± 4.53	.573	−3.95 ± 5.10	.440	−1.73 ± 4.73	.715
Parent-rated overall toxicity						
Equal or less	Ref		Ref		Ref	
Slightly more/more	**−5.85 ± 2.65**[a,b]	**.029**	**−8.47 ± 2.99**[a,b]	**.005**	−4.30 ± 2.77	.123
Parent-proxy, 2–18 years old						
Gender						
Male	Ref		Ref		Ref	
Female	0.51 ± 1.97	.798	−0.56 ± 2.20	.799	1.02 ± 2.11	.629
Civil status						
Parents living together	Ref				Ref	
Parents not living together	−4.20 ± 2.44	.087	−3.06 ± 2.73	.264	−4.84 ± 2.61	.065

(Continues)

TABLE 2 (Continued)

	Total Scale Score		Physical Functioning		Psychosocial Health Score	
	B ± SE	*p*	*B* ± SE	*p*	*B* ± SE	*p*
Total annual disposable household income						
Low–intermediate (<412,800 SEK/43,100 €)	Ref		Ref		Ref	
High (>412,800 SEK/43,100 €)	3.46 ± 2.02	.080	5.51 ± 2.25[a]	.015	2.51 ± 2.16	.245
Parent born outside Nordic countries	−1.90 ± 3.19	.552	0.33 ± 3.57	.926	−2.98 ± 0.38	.384
Treatment arm						
Standard/intermediate risk	Ref		Ref		Ref	
High risk	1.85 ± 3.72	.619	2.24 ± 4.15	.590	1.47 ± 3.98	.712
Parent-rated overall toxicity						
Equal or less	Ref				Ref	
Slightly more/more	**−7.19 ± 2.21**[a,b]	**.001**	**−7.52 ± 2.46**[a,b]	**.003**	**−6.81 ± 2.36**[a,b]	**.004**

Note: Results from multiple linear regression (adjusted for sex, parents living together, income, parent born outside Nordic countries, parent-rated overall toxicity, all $p < .05$ in any of the outcomes in simple linear regression). Results that were both statistically significant and exceeded MCID are shown in bold.
Abbreviations: *B*, regression coefficient; SE, standard error; SEK, Swedish Krona.
[a]Statistical significance ($p > .05$).
[b]Clinical significance (exceeds minimal clinically important difference, MCID). MCID for self-report: Total 4.36, Physical Functioning 6.66, Psychosocial Health Score 5.30. MCID for parent-proxy: Total 4.50, Physical Functioning 6.92, Psychosocial Health Score 5.49.

or change their reference values, resulting in an improvement in perceived HRQoL.[63,64] For a parent, who may compare the child's situation with before treatment, or with healthy peers, this adjustment might be more difficult than for their child.

The HRQoL scores in the younger children's self-report were significantly different from the older children, with lower scores that exceeded MCID in many domains, and higher HRQoL for patients in the HR group, and for those with a parent born outside the Nordic countries. Younger children also reported lower scores in general compared to the parent-proxy. This may in part be due to the different methods of measurement, with only three rather than five options (three-grade Likert scale instead of five-grade) per item in the self-report form. In fact, also when evaluated in healthy children, the PedsQL results for younger children had a low agreement and significant differences in scores between parent-proxy and self-reports.[16] It cannot be ruled out, however, that the observed differences in HRQoL indeed reflect a different situation for the younger children, with different impact of gender and family background. For example, higher HRQoL in the young HR children could reflect a more pronounced response shift after previous intensive treatment. Despite these differences in HRQoL between younger and older children and parent-proxy reports, parent-rated toxicity was associated with worse Total Summary and Physical Functioning scores according to all reports, and for parent-proxy, also with Psychosocial Health Summary scores. No differences were seen between treatment groups, except for the perhaps surprising finding of better HRQoL in HR patients in the self-report for younger children (5–7 years), nor were any relevant differences seen between the different arms in the randomizations, despite differences in treatment intensity among the arms.

Limitations of this study include the relatively low response rate, and that despite the population-based approach, children to parents born outside the Nordic countries and with lower education were underrepresented compared to the general population. Strengths of this study are the relatively large cohort from a population-based setting and the use of both self- and proxy reports. Furthermore, the study population only comprised children/AYAs (adolescents and young adults) treated for ALL in first remission and without any radiotherapy, which makes it less heterogenous compared to several previous study populations. This together with the fact that a generic instrument was used, facilitates comparisons.

In conclusion, children 8 years or older assessed at least 6 months after end of ALL treatment reported HRQoL at levels similar to reference data, while children aged 5–7 years and parent-proxy responses for all age groups reported worse HRQoL than reference data. The tendency toward lower School Functioning scores requires further attention, as several studies indicate that leukemia survivors do less well in school than the general population,[65–67] and the first years post treatment offer an opportunity to improve re-integration and to support both the family and the school.[33,36] Parent-reported toxicity was the most important determinant for lower HRQoL observed in this study, and highlights the need to include toxicity data in future studies. Thus, to minimize complications and side effects is of paramount importance when trying to achieve optimal short- and long-term HRQoL after ALL treatment.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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