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ORIGINAL PAPER

Quality of life in mothers and fathers of children treated for acute lymphoblastic leukaemia in Sweden, Finland and Denmark

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Summary

Acute lymphoblastic leukaemia (ALL) has a high survival rate, but treatment is lengthy with risk of severe side-effects, which may also impact parents' health-related quality of life (HRQOL). We present data on 526 parents of 310 children treated for ALL according to the NOPHO ALL2008-protocol, in Sweden, Finland and Denmark. Parents were asked to complete the 36-Item Short Form Survey (SF-36) at least 6 months after end of treatment and data were compared with Norwegian reference data. Parental background factors were collected via a study-specific questionnaire. Participating parents scored significantly lower than the reference population on both physical and mental summary indexes, but only surpassed a minimal clinically important difference for the mental summary index (Mental Component Summary [MCS]). Mothers scored lower than fathers in the MCS and stopped working and took care of the affected child more often than the fathers. Higher mental HRQOL was associated with male gender and living in Finland or Denmark (compared to Sweden). Correlations within spouses in physical and mental scores were weak to moderate. In conclusion, ALL negatively affects parental HRQOL, especially the mental domains, even after treatment. Findings suggest that mothers are more affected than fathers and may require extra support.

KEYWORDS
acute lymphoblastic leukaemia, cancer, childhood, parents, quality of life, questionnaire

INTRODUCTION

Survival rates in acute lymphoblastic leukaemia (ALL) have improved remarkably during the last decades, with 5-year overall survival >90% in most contemporary protocols.[1] The treatment causes severe adverse events in most patients, which may lead to long-term complications. In the Nordic and Baltic countries, children diagnosed with ALL between 2008 and 2019 were treated according to the NOPHO ALL2008 protocol. This protocol had a long treatment duration of 2.5 years with high overall survival rates, but treatment-related complications were frequent; almost half of treated children were reported to have one or more predefined severe treatment-related complication, excluding infections, during treatment post induction, and about one-fifth required intensive care.[2]

Being a parent of a child with a life-threatening malignancy negatively affects their health-related quality of life (HRQOL). Factors associated with worse HRQOL during treatment have been identified, e.g., being a mother (vs. father), more complex cancer diagnoses (e.g., brain tumours),

treatment intensity and family functioning before diagnosis.[3] High levels of anxiety and depression of parents have been shown to correlate with significantly lower HRQOL of the child during treatment.[4,5] Parental well-being strongly influences the well-being of their children, stressing the importance of identifying and supporting parents in distress also for the sake of the child.[6–8]

Most studies regarding parents of children previously treated for cancer have focused on mental health, coping strategies and post-traumatic stress (PTS).[9–14] Few studies have investigated overall HRQOL in parents after treatment with regard to social and physical functioning.[15,16] Previous studies have often included heterogenous patient groups treated according to diverse protocols, which limits their generalisability for children treated for ALL. Mainly due to a lack of data regarding fathers, comparisons of the impact of having a child treated for cancer between mothers and fathers are scarce.

This study is a part of a population-based questionnaire study in which parents of children treated according to the NOPHO ALL2008 protocol in Denmark, Finland and Sweden were asked to participate after end of treatment. Here, we aimed to analyse HRQOL in mothers and fathers, and to identify potential predictive factors of poor HRQOL. In order to better support these families, it is important to understand how their HRQOL is affected, and to identify individuals at increased risk of impaired HRQOL.

SUBJECTS, PATEINTS AND METHODS

Study design and population

All patients aged 1–17 years at diagnosis who were treated according to the NOPHO ALL2008 protocol, which was in use from 2008–2019 in Finland, Denmark and Sweden, were identified in the NOPHO ALL2008 registry. Parents and their child were eligible if the child was alive in first remission and if no secondary malignancy had occurred. Study eligibility was cross-checked with staff at each local centre before questionnaires were sent. Data were collected from 2013–2019. In Sweden and Denmark, all eligible patients since the start of the treatment protocol in 2008 were invited to participate, and in Finland from 2010 and onwards. From 2013, questionnaire packets including an invitational letter and informed consent forms were sent by mail ≥6 months after end of therapy (e.g., ≥3 years from diagnosis). Families who consented were asked to complete three different questionnaires (described below) in the same questionnaire packets. Up to two reminders were sent if parents had not responded after at least 3 months from the initial invitation. This questionnaire study 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.

Questionnaires and outcome measures

A total of six questionnaires were used. A study-specific questionnaire was constructed by the authors with input from seven families from Stockholm, Sweden, with children previously treated for ALL. Each parent was asked to complete the questionnaire that included questions on socioeconomic factors before and after treatment, their experience of different treatment-related factors and side-effects, as well as of being asked to participate in any of the randomised clinical trials (RCTs) within the protocol (Appendix S1). The socioeconomic questions concerned, e.g., occupational status before and after treatment, education, disposable income, marital status, number of siblings and sibling support, birth year of the parents, absence from school or day-care, and country of birth and residency of parents and the child.

The question on total annual disposable household income had three options: <165 000 SEK (~17 200 EUR), >412 800 SEK (~43 100 EUR) or in-between these two values (or the equivalent in local currency), which at the time of study design corresponded to >60% and <150% of the Swedish national median for annual total disposable household income, respectively, which were then regarded as cut-offs for the low and high economic standard respectively.[17] For analysis, the categories for low and intermediate income were combined to achieve comparable group sizes.

Level of education was based on the International Standard Classification of Education (ISCED)-97[18] and comprised the categories: compulsory school, upper secondary school/vocational school, post-secondary education (<3 years) and university/tertiary education (>3 years). These categories were later combined into primary/secondary and post-secondary/tertiary education respectively.

Data on year of birth of the child and treatment arm (standard risk, intermediate risk or high risk) were retrieved from the NOPHO registry.

Health-related quality of life

Parental HRQOL was measured using the 36-Item Short Form Survey (SF-36) version 2, which is a standardised, validated and widely used patient-reported outcome questionnaire.[19–24] The questionnaire comprises 36 items categorised into eight separate health domains. The scores on individual scales range from zero to 100, with higher scores corresponding to higher HRQOL. By use of factor score coefficients, the domain scores can be combined into two summary scores, namely Physical Component Summary (PCS) and Mental Component Summary (MCS), both of which are reported as norm-based T-scores. SF-36 data for each participating country was not available, thus Norwegian SF-36 normative data was used as the reference population.[25] The 30–39-year-old age group was chosen for the reference population as the majority of the participating mothers and fathers fell into this age group (62.4% and 58.0% respectively) at diagnosis.

Minor changes in HRQOL may be statistically significant but not meaningful for the subject, and the concept of minimal clinically important difference (MCID) has hence been introduced.[26,27] A MCID is usually defined as the smallest change in outcomes that the subject perceives as clinically important,[26,28] and cut-offs may differ slightly between different instruments, method of calculation (distribution or anchor) and study populations.

For SF-36 summary scores the MCID is usually considered to be between 4 to 5 points for PCS and MCS, which corresponds to a change of 0.5 SD,[29–31] which we have used as the cut-off in this study.

There were also questionnaires to assess the child's own HRQOL (self and proxy). Families could choose whether one or two (if applicable) parents/caregivers would participate in the study and whether they would complete all or selected questionnaires, which was stated in the invitation letter. For this study, only parents who responded both to the socioeconomic part of the study-specific questionnaire and the SF-36 were included.

Statistics

The SF-36 data were scored with instructions provided by M.E. Maruish.[24] The PCS and MCS scores were calculated by using the individual health-domain scores, normative population data, and factor score coefficients. Mean differences between study population and normative data were compared using one-sample *t*-tests. Linear mixed models with a random intercept per child, taking into account the dependencies between scores of parents of the same child, were used to evaluate the association between covariates and the MCS and PCS respectively.

Correlations of scores within couples were analysed with Pearson correlation. Cross-tabulations were used to compare the frequency of mothers and fathers leaving full- or part-time jobs, as well as absence from work or studies, tested with the chi-square test and Mann–Whitney *U*-test. Absence from work and MCS score were analysed using independent samples median test and independent samples *t*-test. Statistical significance was defined as two-sided $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 28.0.

RESULTS

Background characteristics of study participants

A total of 526 parents (296 mothers, 230 fathers) of 310 children were included (Figure 1). Study participant characteristics are summarised in Table 1. Most (53.0%) of the participants were from Sweden, while 24.0% were from Denmark and 23.0% from Finland (Table 1). The mean age at diagnosis for fathers was 38.4 years and 36.2 years for mothers, and mean (SD, range) time since diagnosis was 4.3 (1.2, 2.6–8.6) years. Children were classified according to age at diagnosis into two groups: 1–6 years and 7–17 years. Most of the children (232/310, 74.8%) were in the younger age group and had been treated according to the standard- or intermediate-risk arms in the protocol.

TABLE 1 Study participant characteristics

	Category	Value
Parents' characteristics ($N = 526$)		
Relation to the child, *n* (%)	Mothers	296 (56.3)
	Fathers	230 (43.7)
Country of residence during treatment, *n* (%)	Sweden	279 (53.0)
	Denmark	126 (24.0)
	Finland	121 (23.0)
Time since diagnosis, years, mean (SD)		4.3 (1.2)
Parents age at diagnosis, years, mean (SD)	Fathers	38.4 (6.3)
	Mothers	36.2 (5.9)
Highest achieved education level, *n* (%)	Primary or secondary education	205 (39.0)
	Post-secondary or tertiary education	291 (55.3)
	Not reported	30 (5.7)
Total annual disposable household income (before diagnosis), *n* (%)	Low-intermediate (<412 800 SEK/43 100 euro)	228 (43.3)
	High (>412 800 SEK/43 100 euro)	284 (54.0)
	Not reported	14 (2.7)
Childs' characteristics ($N = 310$)		
Treatment group, *n* (%)	SR or IR	281 (90.6)
	HR	29 (9.4)
Child's age at diagnosis, *n* (%)	1–6 years	232 (74.8)
	7–17 years	78 (25.2)

Abbreviations: HR, high risk; IR, intermediate risk; SD, standard deviation; SR, standard risk.

Physical Component Summary and MCS scores of SF-36

Mean scores for the PCS and MCS were lower in the study population compared to normative data, PCS −1.16 (95% confidence interval [CI] −1.88, −0.45; $p = 0.001$) and MCS −7.72 (95% CI −8.84, −6.61; $p < 0.001$) respectively. For the PCS, the difference from reference population did not exceed the previously reported MCID[29–31] and thus these results should be interpreted with caution.[26–28] Regarding the MCS, the difference in mean scores compared to the reference population was statistically significant for both mothers and fathers (MCS in mothers −9.12 [95% CI −10.63, −7.61], in fathers −5.81 [95% CI −7.42, −4.19], $p < 0.001$ for both) and exceeded MCID (Figure 2).

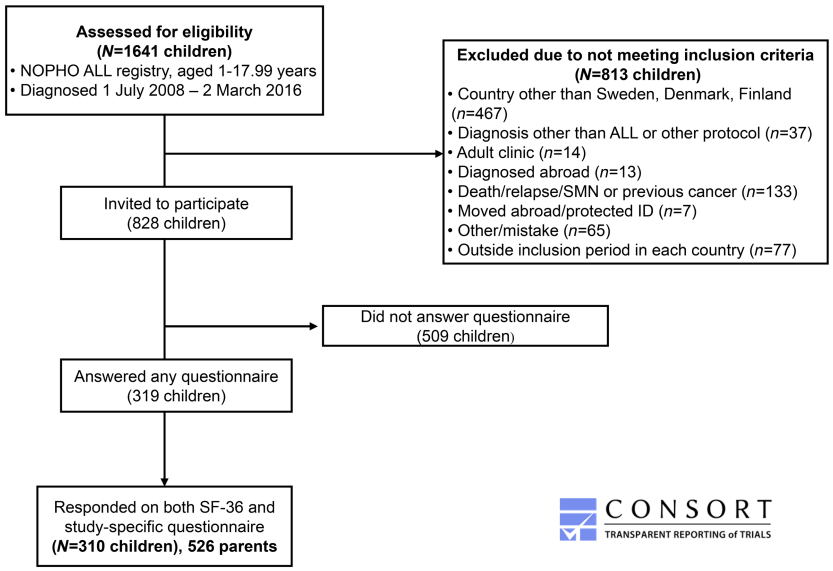

FIGURE 1 Study population flow chart, presented as a Consolidated Standards for Reporting Trials (CONSORT) diagram, for the present study. [Colour figure can be viewed at wileyonlinelibrary.com]

For the different domains, both mothers and fathers of previous ALL patients scored below the reference population especially in the mental health domain and general health perception domain (Figure 3). Mothers had in general lower mean scores in most domains than fathers and compared to the general population, most notably in vitality and social functioning. Exceptions were physical functioning and role physical, where the mean scores of both mothers and fathers were equal or slightly above reference values. However, it should be noted, that role physical and role emotional domains should be interpreted with care, as the scaling system differs from the previous SF-36 version.

The relationship of background factors to PCS and MCS

Results from unadjusted and adjusted linear mixed model are shown in Table 2. For the PCS, being a father, having a higher disposable household income and having a higher level of education were all associated with a higher PCS in both unadjusted and adjusted models. Statistically significant factors that were associated with a higher MCS were being a father and, in the adjusted model only, living in Denmark or Finland compared to Sweden. The child's age at diagnosis and treatment arm were not associated with different outcomes in the PCS or MCS, nor was parents' civil status when added to the model (data not shown).

Correlation within couples

For 77.5% (n = 241) of all children included (N = 310), their parents were either married to each other or living

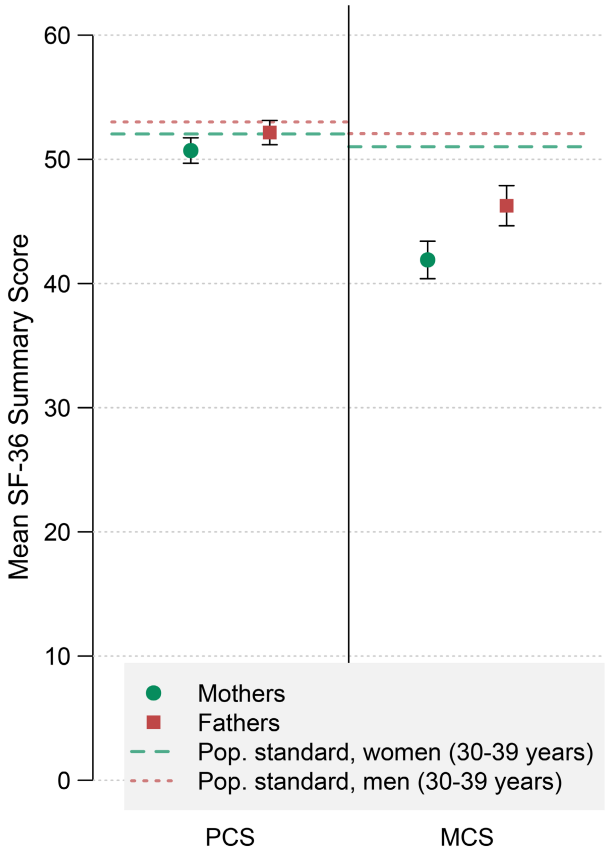

FIGURE 2 Mean scores for summary indexes for mothers and fathers in the study, compared to reference population standards. Difference between study and reference population exceeded minimal clinically important difference (MCID) for the MCS. PCS, Physical Component Summary T-score; MCS, Mental Component Summary T-score; SF-36, 36-Item Short-Form Survey. [Colour figure can be viewed at wileyonlinelibrary.com]

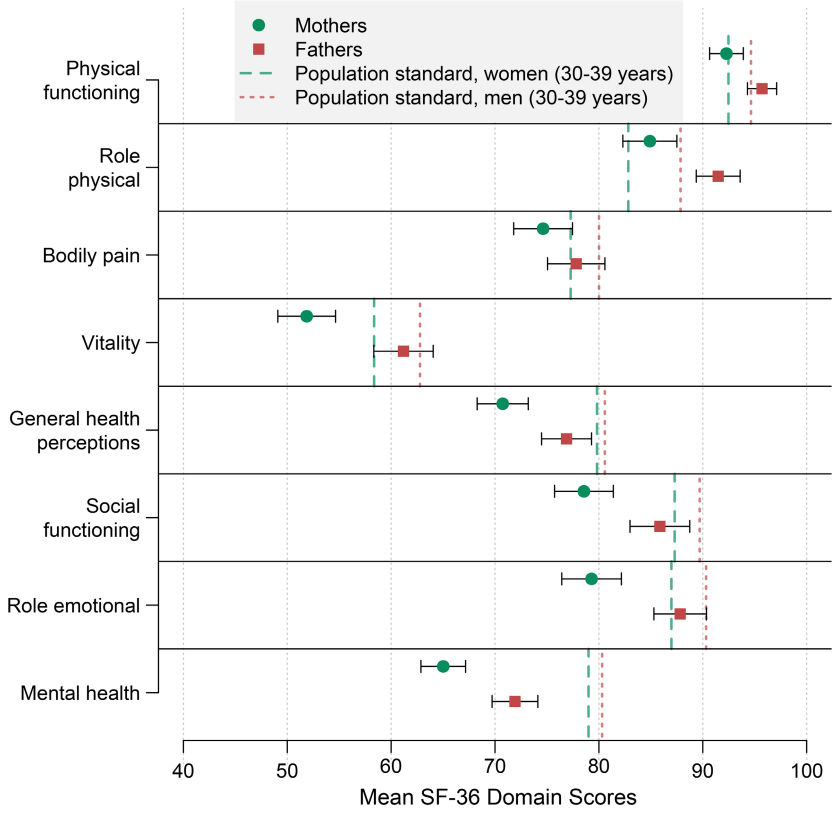

FIGURE 3 Mean SF-36 health domain scores for mothers and fathers in the study, compared to reference population standards. SF-36, 36-item Short-Form Survey. [Colour figure can be viewed at wileyonlinelibrary.com]

together at the time of study participation. A total of 70.1% (n = 170) of these parents had both answered the SF-36 questionnaires. The correlation in the PCS and MCS within these couples were weak to moderate with a correlation coefficient for the PCS and MCS of $r = 0.28$ ($p < 0.001$) for the PCS and $r = 0.38$ ($p < 0.001$) for the MCS.

Absence from work or studies

Almost half (45.8%) of the participating mothers left a full- or part-time job because of their child's illness, compared to 20.2% of fathers. This difference was statistically significant ($p < 0.001$). Similar percentages of mothers and fathers (17.6% and 18.8% respectively) reduced their work hours. Regarding overall absence from work, more mothers (79.9%) than fathers (50.5%) were away from work or studies for at least 6 months because of their child's illness ($p < 0.001$). Absence from work was associated with worse MCS in mothers, with mean scores being highest in the group with lowest absence (MCS 46.7 in mothers absent for <6 months due to child's illness) and highest absence (>24 months) had the lowest mean score at 39.0 ($p = 0.01$). No differences were observed for the PCS in mothers or in any of the scores for fathers.

DISCUSSION

This study investigates HRQOL and its determinants in mothers and fathers of children who had completed treatment for ALL. Both mothers and fathers in this study experienced impaired mental HRQOL, with significantly lower scores compared to the reference population. This difference was even more pronounced in mothers. No clinically relevant impact was observed for physical HRQOL. Our findings of significantly impaired mental (including psychosocial) HRQOL is consistent with some of the previous studies investigating HRQOL in parents during active treatment for childhood cancer.[32–35] Generally, psychological distress[36] and HRQOL tends to improve with longer time since diagnosis,[32] although more severe symptoms of general psychological distress and PTS seem to persist in a subset of parents.[12] Our study population had a mean time since diagnosis of slightly over 4 years, which corresponds to a mean of 1.5 years after active treatment, allowing time for the parents and child to have adjusted back to their daily activities. Despite this, a significant impact of the child's illness on parental mental HRQOL was still observed.

Our study showed a clear gender difference, with mothers having significantly lower MCS scores than fathers. This difference was also seen in five of the eight domains, where mothers had lower mean scores in vitality, general health

TABLE 2 Associations between different covariates and Physical Component Score (PCS) and Mental Component Score (MCS) respectively. Results from linear mixed model

Covariate	Categories	Unadjusted β	95% CI for β	*p*-value	Adjusted β	95% CI for β	*p*-value
PCS Score							
Gender	Mothers	REF			REF	-	-
	Fathers	**1.45**	**0.01, 2.89**	**0.049**	**1.66**	**0.15, 3.15**	**0.031**
Child age	1–6 years	REF			REF	-	-
	7–17 years	0.27	−1.42, 1.96	0.754	0.33	−1.43, 2.09	0.713
Education	Primary or secondary	REF			REF	-	-
	Post-secondary or tertiary	**1.99**	**0.49, 3.49**	**0.009**	**1.82**	**0.26, 3.38**	**0.023**
Total annual disposable household income before diagnosis	Low-intermediate (<412 800 SEK 43 100 euro)	REF			REF	-	-
	High (>412 800 SEK 43 100 euro)	**2.38**	**0.94, 3.81**	**0.01**	**1.79**	**0.19, 3.38**	**0.029**
Country of residence	Sweden	REF			REF	-	-
	Denmark	0.42	−1.25, 2.1	0.622	0.18	−1.67, 2.02	0.850
	Finland	−1.33	−3.03, 0.38	0.127	−0.33	−2.39, 1.50	0.652
Risk group	SR or IR	REF			REF		
	HR	−1.09	−3.54, 1.36	0.382	−0.65	−3.16, 1.86	0.610
MCS Score							
Gender	Mothers	REF			REF	-	-
	Fathers	**4.36**	**2.14, 6.59**	**<0.001**	**4.34**	**2.02, 6.65**	**<0.001**
Child age	1–6 years	REF			REF	-	-
	7–17 years	1.37	1.26, 4.01	0.306	0.87	−1.84, 3.58	0.529
Education	Primary or secondary	REF			REF	-	-
	Post-secondary or tertiary	0.77	−1.55, 3.10	0.515	0.76	−1.65, 3.17	0.535
Total annual disposable household income before diagnosis	Low-intermediate (<412 800 SEK 43 100 euro)	REF			REF	-	-
	High (>412 800 SEK 43 100 euro)	1.26	−1.01, 3.53	0.276	1.35	−1.11, 3.81	0.283
Country of residence	Sweden	REF			REF	-	-
	Denmark	2.28	−0.32, 4.88	0.850	**3.45**	**0.61, 6.29**	**0.017**
	Finland	1.83	−0,82, 4.49	0.176	**3.24**	**0.24, 6.23**	**0.034**
Risk group	SR or IR	REF			REF		
	HR	−0.59	−4.41, 3.24	0.882	−0.49	−4.36, 3.36	0.800

Abbreviations: HR, high risk; IR, intermediate risk; SD, standard deviation; SR, standard risk.
Bold indicates *p*-values <0.05 are statistically significant.

perceptions, social functioning, role emotional and mental health domains. A French study by Vercasson et al.[15] that investigated HRQOL in parents of previous acute leukaemia patients made a similar observation regarding lower psychosocial relationship scores in the parents compared to the general population, as well as lower psychological HRQOL scores in mothers compared to fathers. In contrast to our findings, psychological HRQOL scores were higher for the parents, and physical scores lower, than for the reference population in their study. This disparity could be due to a longer follow-up time since diagnosis (mean [SD] 7.3 [3.2] years) in the French study or the use of a different instrument to measure HRQOL (WHOQOL-BREF).

Most previous studies on parental HRQOL in paediatric cancer have focused on mothers. One study by Rensen et al.[16] investigated HRQOL in both mothers and fathers during and shortly after active treatment and showed that mothers tend to have worse HRQOL than fathers. Some studies indicate that this gap narrows over time, and that the well-being regarding psychological distress or HRQOL of mothers improves and becomes equivalent to the level of fathers after some years.[37,38]

Another factor associated with impaired MCS scores, besides being a mother, was country of residence. Parents in Sweden had lower MCS scores than in Finland and Denmark. This difference could reflect the already existing difference in happiness and perceived well-being between the countries. According to the World Happiness Report (2020), Finnish people are the world's happiest, followed closely by those living in Denmark in second and Sweden in seventh place.[39]

In line with previous studies, we found that being a father, having a higher disposable income and having a higher level of education were all associated with higher PCS.[40] No associations were seen between MCS or PCS scores and age of the child or treatment intensity. Notably, the high-risk group was small, comprising a little <10% of children and parents. This was expected as this group has a higher risk of relapse and death, which were reasons for exclusion.

The study design and large cohort size enabled within-couple comparisons of mothers and fathers. The correlation between HRQOL was weak to moderate in parents living together. The present study shows that mothers were away from work due to their child's illness substantially more than fathers. They were also twice as likely to have left a full- or part-time job. This is in line with the existing literature, where primary caregiver status traditionally falls more on mothers.[38] This is likely to lead to further imbalance in income, as a national Swedish cohort study has shown.[41] In that study, mothers to children previously treated for cancer had persistently lower income in the years after treatment than mothers to healthy children and this income gap increased over time. Interestingly, in our study, absence from work during treatment due to child's illness was associated with lower mental HRQOL in mothers, with highest MCS scores in those absent for <6 months, and lowest for those absent >24 months. The reason for this is unknown and could reflect burden of disease, but still warrants attention.

Despite the population-based approach of our study, parents born outside of the Nordic countries and parents with lower education are underrepresented among responders compared to the general population. Another limitation is that Norwegian reference data, and not reference data from the countries included in the study, were used due to the advantage of available references for gender and age groups to enable more precise comparisons. However, when comparing national SF-36 overall population scores on the different domain scores from the validation publications, no major differences were seen between the countries.[20–22,25] For income, Swedish national reference was used, which differs slightly from Danish and Finnish references and should be considered when interpreting the impact of disposable household income.

Regarding generalisability between treatment protocols, comparing overall toxicity between different protocols is challenging due to differences in reporting. In NOPHO ALL2008, 19 pre-defined toxicities were reported at 3-month intervals during therapy with high coverage, which we believe may contribute to the high prevalence of reported toxicities. It cannot be ruled out though that treatment-related toxicity were slightly higher in this protocol compared to other contemporary ALL protocols.

Strengths of this study include the population-based setting and the large cohort of both mothers and fathers often from the same family, which enabled within-couple comparisons between mothers and fathers. Also, rather than evaluating only psychological/mental domains of HRQOL, a generic instrument with several domains was used. Furthermore, the study cohort only included parents of children treated for ALL and in first remission, making it less heterogenous than previous studies that have often contained mixed paediatric cancer populations or included other types of leukaemia and/or relapsed ALL. This facilitates generalisability to other parents of children with ALL, as for instance relapse is associated with higher levels of distress.[3] Our study also provides socioeconomic data including how the parents' work situations were affected during the time of treatment, which contributes to our understanding of the parents' psychosocial situation both during and after treatment.

In conclusion, parents of children recently treated for ALL had impaired mental HRQOL, especially mothers. This highlights the importance of assessing parental needs for individual support. The connection between high absence from work during treatment and worse outcomes in mental HRQOL after treatment in mothers calls for further attention.

AUTHOR CONTRIBUTIONS

Nina Mogensen, Arja Harila-Saari, Mats Heyman and Ulrika Kreicbergs designed the research study and interpreted the data. Birgitte Klug Albertsen and Päivi M. Lähteenmäki contributed to the conception and design and data collection. Nina Mogensen, Ella Saaranen and Erik Olsson analysed and interpreted the data. Nina Mogensen and Ella Saaranen wrote the draft of the paper. All the authors drafted and revised the paper critically and accepted the final version.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest to disclose.

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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