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Health-related quality of life and its determinants during and after treatment for paediatric acute lymphoblastic leukaemia: a national, prospective, longitudinal study in the Netherlands

Emily R Schwartz,[1] Niki Rensen ,[1,2] Lindsay M H Steur,[1] Reinoud Gemke,[1] Natasha K A van Eijkelenburg,[2] Inge M van der Sluis,[2,3] Natasja Dors,[2,4] Cor van den Bos,[1,2] Wim J E Tissing,[2,5] Martha A Grootenhuis,[2] Gertjan J L Kaspers,[1,2] Raphaele R L Van Litsenburg[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Raphaele R L Van Litsenburg; R.R.L.vanLitsenburg@prinsesmaximacentrum.nl

ABSTRACT

Objectives Health-related quality of life (HRQoL) is impaired in paediatric patients with acute lymphoblastic leukaemia (ALL). Over the past decades, ALL treatment has successfully been adjusted to the risk of relapse, which is now reflected by the stratification of patients into three risk groups who receive treatment of differing intensities. This study is the first to evaluate the longitudinal course of HRQoL in light of these adjustments and identify determinants of HRQoL.

Design Two prospective, national cohort studies (add-on studies within the two most recent treatment protocols for children with ALL (ALL-10 and ALL-11)).

Setting Dutch paediatric oncology hospitals between October 2006 and October 2009 (ALL-10) and between August 2013 and July 2017 (ALL-11).

Participants Patients with ALL (2–18 years) are treated according to the ALL-10 or ALL-11 treatment protocol. Patients treated according to the ALL-10 protocol only completed a cancer-specific QoL measure and patients treated according to the ALL-11 protocol completed both a cancer-specific and generic QoL measure (see below).

Outcome measures HRQoL, assessed with parent-proxy questionnaires (PedsQL Generic and Cancer module) within the first 5 months (T0), at 1 year (T1), 2 years (T2) and 3 years (T3) after diagnosis. The proportion of patients with clinically relevant generic HRQoL impairment was compared with healthy norm values. Multivariable mixed model analyses were used to evaluate the development of HRQoL over time and its medical and sociodemographic determinants (collected on enrolment).

Results Of the ALL-10 cohort, 132 families participated and of the ALL-11 cohort, 136 families participated (268 total). Thus, cancer-specific HRQoL assessments were available for 268 patients (median age 5.3 years (IQR 6.15), 56.0% boys, 69.0% medium-risk ALL), and generic HRQoL assessments for 136 patients (median age 4.8 years (IQR 6.13), 60.3% boys, 75.0% medium-risk ALL). Generic HRQoL improved between timepoints T0 and T3 (total score B 16.1, 95% CI 12.2 to 20.1, p<0.001), but did not restore to normal 1 year after the end of treatment: 28.0% of children remained impaired compared with 16% in the general population (p=0.003). Cancer-specific HRQoL generally improved from T0 to T2 (Pain B 11.3, 95% CI 7.1 to 15.5; Nausea B 11.7, 8.4 to 15.1; Procedural Anxiety B 19.1, 14.8 to 23.4; Treatment Anxiety B 12.8, 9.5 to 16.0; Worry B 3.5, 0.6 to 6.3; Communication B 8.5, 5.0 to 11.9; all p<0.001 except for Worry (p=0.02)), while Physical Appearance and Cognitive Functioning remained stable. Higher treatment intensity and experiencing pain or simultaneous chronic illness were associated with lower HRQoL over time for multiple subscales.

Conclusions HRQoL impairment is prevalent during and after ALL treatment. Patients with standard-risk ALL and reduced treatment intensity have better HRQoL than patients in higher risk groups. Systematic monitoring of HRQoL is of utmost importance in order to provide timely psychosocial interventions and supportive care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study longitudinally assesses the development of health-related quality of life (HRQoL) in a large, national sample of paediatric patients with acute lymphoblastic leukaemia across two Dutch treatment protocols.
⇒ The large sample of patients allowed for the evaluation of multiple predictive determinants of HRQoL.
⇒ A limitation of this study is that results are based on parent-proxy reports, as the numbers of self-reports were too low to be used to detect associations.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common type of childhood cancer.[1 2] Treatment is intensive, requiring frequent chemotherapy administration and procedural interventions over a 2–3 year course.[2] Survival rates are now exceeding 90% due to treatment refinement and improved

supportive care practices over the past decades.[3] Attaining optimal psychosocial outcomes during and after treatment is therefore of the utmost importance.

Health-related quality of life (HRQoL) characterises an individual's perception of the impact of their health status on their ability to live a fulfilling life.[4] HRQoL assessment in paediatric oncology can thus illuminate the multidimensional impact of a cancer diagnosis and the treatment burden on the patients', and their families', perception of well-being.[5] Several studies describe physical, psychosocial and emotional HRQoL impairment in this population.[5–9] Despite HRQoL improvement over the course of the disease, a significant proportion of this population does not demonstrate restoration to normal at the end of treatment.[7 10 11] Findings with regards to HRQoL in long term ALL survivors are mixed, with a large review concluding that HRQoL is still reduced in the long term but a recent study showed better HRQoL in ALL survivors than controls.[12 13]

Sociodemographic, psychosocial and medical risk factors for HRQoL impairment in children with ALL have been identified. For example, older age and female sex are associated with HRQoL reduction during ALL treatment.[5 6] Certain psychosocial risk factors, such as parent-reported child sleep problems and problematic family functioning are also associated with reduced HRQoL.[10 14] Additionally, previous research has shown that several medical factors are related to HRQoL. Pain is experienced by the vast majority of ALL patients undergoing treatment, and has been associated with lower quality of life.[15–17] Fardell *et al* discuss tentative evidence for an association between corticosteroid therapy, increased toxicity and intensive chemotherapy phases with worse HRQoL.[5] With regards to the latter, it is unclear how adjusted treatment intensity affects HRQoL, and whether there is a reflected benefit in HRQoL outcomes from treatment reduction in standard risk (SR) patients. The two most recent national Dutch Childhood Oncology Group (DCOG) treatment protocols ALL-10 (2004–2012) and ALL-11 (2012–2020) stratified primary patients with ALL ((≥1 year of age) according to therapy response and cytogenetics into three groups—SR, medium risk (MR) and high risk (HR), reflecting the risk of relapse.[18 19] Treatment intensity was adjusted accordingly. SR patients underwent a reduction in treatment intensity and MR and HR patients underwent higher treatment intensity (given some HR patients were transplanted after initial chemotherapy), without compromising the survival rate.[2 20] There were minimal differences in the chemotherapy regimens between the two treatment protocols. As of yet, longitudinal studies incorporating change in ALL treatment and known risk factors are sparse.[7 10 11]

It is necessary to better understand the landscape of HRQoL for paediatric patients with ALL—the progression of HRQoL over the course of the illness experience, the impact of the cancer illness and treatment intensity on HRQoL, and the risk factors associated with worse HRQoL outcomes. This could allow for early detection, supportive interventions and prevention of worse HRQoL. Therefore, the aims of this study were to:

1. Describe longitudinal development in HRQoL of paediatric patients with ALL treated according to ALL-10 (cancer-specific HRQoL from diagnosis until the end of treatment) and ALL-11 treatment protocols (cancer-specific HRQoL from diagnosis until the end of treatment and generic HRQoL from diagnosis up to 1 year post-treatment).
2. Provide the percentage of patients with clinically impaired HRQoL for each timepoint.
3. Identify determinants for the course of HRQoL.

METHODS

Data collection

Patients were recruited during two longitudinal prospective multicentre cohort studies with a psychosocial focus which were add-ons to the national ALL-10[8 21] and ALL-11 treatment protocols.[22] Patients were identified from the DCOG registry, the national childhood cancer database. They were recruited between October 2006 and October 2009 (ALL-10) and between August 2013 and July 2017 (ALL-11) from seven Dutch paediatric oncology centres (operating at the time of the study).

Inclusion criteria

Patients were eligible if they met the following criteria: (1) diagnosed with primary ALL and treated according to ALL-10 or ALL-11 treatment protocol, and (2) 2–18 years of age at assessment since the questionnaires used have not been validated for children under the age of two. An exclusion criterion for the ALL-10 study was Down syndrome. Therefore, we excluded the measurements of three patients with Down syndrome in the ALL-11 cohort as well. Parents were eligible if they had sufficient command of the Dutch language to independently complete the questionnaires.

Follow-up

Figure 1 illustrates the timing of study assessments. The first measurement (T0) occurred during induction or consolidation therapy (together comprising approximately the first 5 months after diagnosis). The details of ALL therapy during this period have been previously published.[8 22 23] The second measurement (T1) occurred around 1 year after diagnosis, during maintenance therapy. Patients in the MR group were administered cyclic dexamethasone during this period. Due to the known adverse effects of corticosteroids on HRQoL, our analyses here only include assessments during periods without dexamethasone treatment.[5] The third measurement (T2) occurred 2 years after diagnosis, which constitutes the end of treatment for the far majority of patients.[20 24] The final measurement (T3) was only done for generic HRQoL in ALL-11 patients and occurred 3 years after diagnosis, which was 1 year after the end of treatment.[20 24] We removed the T3 generic HRQoL data from the MR patients with an IKZF1-deletion since these

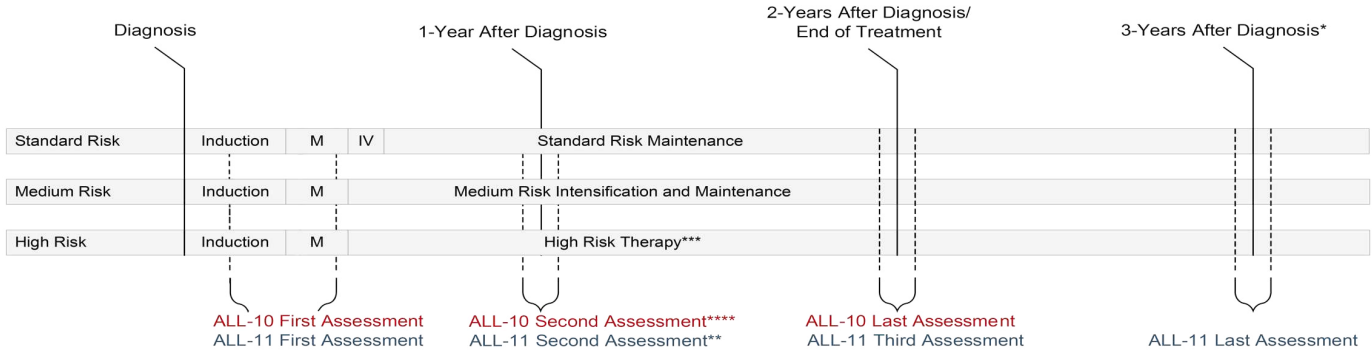

Figure 1 Schematic overview of ALL treatment and study assessments. *End of treatment for patients with IKZF-1 deletion. **Additional assessment with dexamethasone for medium risk patients. ***Includes stem cell transplantation for the majority of patients. ****Assessment not conducted for high risk patients. ALL, acute lymphoblastic leukaemia.

children received an additional year of treatment, and are thus just concluding treatment at this timepoint (eight patients in our study sample).

Measures

The valid and reliable parent-proxy questionnaires described below were used to assess child HRQoL. One parent completed the questionnaires per timepoint. Parents provided general sociodemographic information for themselves as well as sociodemographic and medical information for their child through a survey. Questionnaires were completed via paper and pencil (ALL-10), or participants could opt for online questionnaires (ALL-11).

Sociodemographic and medical information

For all patients, the following variables were available: age, sex, time since diagnosis, ALL treatment protocol and risk group. Additionally, in patients from the ALL-11 cohort, parents reported on their child's pre-existent chronic illness and pain. Parents were asked, 'Did your child experience pain at some point during the last 7 days?' and were allowed to respond on a scale of 0–10, 0 representing 'no pain at all' and 10 representing 'very much pain'.

For all parents, information on the following variables was collected: age and sex. The highest education level for both parents was only available in the ALL-11 cohort.

Generic HRQoL

Generic HRQoL was measured via the Pediatric Quality of Life Inventory 4.0 (PedsQL) Generic Core Scale in the ALL-11 cohort. The reliability and validity of this instrument have been previously demonstrated.[25] This 23-item, 1 week recall questionnaire measures Physical, Emotional, Social and School Functioning. The sum of these four subscale scores is used to calculate the Total score. Furthermore, the Psychosocial Health Summary (PSHS) score includes the Emotional, Social and School Functioning subscales. A score of 100 represents the highest quality of life, and 0 represents the worst.[26] When at least 50% of the scale items were answered, missing values were calculated by imputing the mean of the completed items in that scale according to the scoring manual. Parents were instructed to skip the school subscale if their child did not attend school in the past week, to not overwhelm or burden them.

Cancer-specific HRQoL

The PedsQL 3.0 Acute Cancer Version is a 27-item multidimensional questionnaire used to measure cancer-specific HRQoL that was collected in the ALL-10 and the ALL-11 cohort at timepoints, T0, T1 and T2.[27] The instrument comprises eight subscales to determine issues relevant to cancer treatment: Pain, Nausea, Procedural Anxiety, Treatment Anxiety, Physical Appearance, Worry, Communication and Cognitive Function. The PedsQL Cancer has satisfactory psychometric properties. Scoring and handling of missing values are similar to the PedsQL Generic.

Statistical analysis

Study population

Baseline characteristics were evaluated using descriptive statistics. For each timepoint, similar descriptive characteristics were performed for generic and cancer-specific HRQoL subscales.

Longitudinal development of HRQoL over time

The longitudinal development of HRQoL was evaluated with linear mixed model analyses, with a random intercept on child level for each subscale of both questionnaires. Linear mixed models are very effective in handling missing data in the outcomes. To specifically assess change between the different measurements, timepoints were added as categorical covariates. Analyses were corrected for parental sex, since questionnaires were not necessarily completed by the same parent throughout the study course, and differences between parental proxy reports have been previously documented.[28] Results were presented as regression coefficients (B) with 95% CI.

Clinically impaired HRQoL

The percentage of patients with clinically impaired generic HRQoL was calculated per timepoint for each subscale. Clinical impairment was defined as a proxy

Table 1 Baseline characteristics

	Parent-reported generic HRQoL (ALL-11) n=136	Parent-reported cancer-specific HRQoL (ALL-10 and ALL-11) n=268
Patient characteristics		
Sex, n (%)		
Male	82 (60.3)	150 (56.0)
Female	54 (39.7)	118 (44.0)
Age at diagnosis (years), median (IQR)	4.8 (6.13)	5.3 (6.15)
Medical characteristics		
Risk group stratification, n (%)		
Standard risk	32 (23.5)	62 (23.1)
Medium risk	102 (75.0)	185 (69.0)
High risk	1 (0.7)	20 (7.5)
Unknown*	1 (0.7)	1 (0.4)
Chronic illness (other than ALL),† n (%)		
Yes	6 (4.4)	6 (4.4)
No	124 (91.2)	124 (91.2)
Unknown‡	6 (4.4)	138 (51.5)
Family characteristics		
Family education level,§ n (%)		
Low–middle	42 (30.9)	42 (30.9)
High	87 (64.0)	87 (64.0)
Unknown‡	7 (5.1)	139 (51.9)

Percentages may not equal 100% due to rounding.
*Deceased before risk group stratification.
†Weaver Syndrome (n=1), autism (n=1), hypermobility (n=1), coeliac disease (n=1), anorectal malformation (n=1) and cavernomas in the brain (n=1).
‡Chromic illness and family education level were unknown for ALL-10.
§Educational level was dichotomised as low/middle (no education up to pre-university education and intermediate vocational education) and high (higher vocational education, university).
ALL, acute lymphoblastic leukaemia; HRQoL, health-related quality of life.

generic HRQoL score of more than one SD below the reference value (=16% in the general population).[27] We used χ^2 goodness-of-fit tests to determine if the proportions of patients with clinically impaired HRQoL were significantly different between the study population and the general population. As norm data for PedQL cancer scale do not exist, the percentage of patients with clinically impaired cancer-specific HRQoL was not calculated. We did calculate the proportion of patients per timepoint with 'never' (score 100), 'almost never' (75–100), 'sometimes' (50–74), 'often' (25–49) or 'almost always' (0–24) problems for each subscale.

Determinants of longitudinal development of HRQoL

Sociodemographic and medical factors associated with the longitudinal development HRQoL scores were determined with linear mixed model analyses with a random intercept on child level. The following variables were analysed: patient age (continuous), patient sex and ALL risk group. Risk group was dichotomised into SR versus MR/HR due to a low number of HR participants. Additionally, parent highest education level, patient pain and patient pre-existent chronic illness were also included for generic HRQoL. Parent highest educational level was interpreted as a derivative of familial socioeconomic status and defined according to Statistics Netherlands.[23 29] Due to the small number of low educated parents, educational level was dichotomised as low/middle (no education up to pre-university education and intermediate vocational education) and high (higher vocational education, university). For pain, we dichotomised clinically relevant versus non-clinically relevant pain with a cut-off score of 4 or higher as pre-established in the literature.[30] For chronic illness, a yes/no dichotomisation was used due to the low number of reported comorbidities.

Multivariable models were created via backward selection to determine which of the aforementioned factors were associated with the longitudinal development of HRQoL scores. Variables with the highest p value were

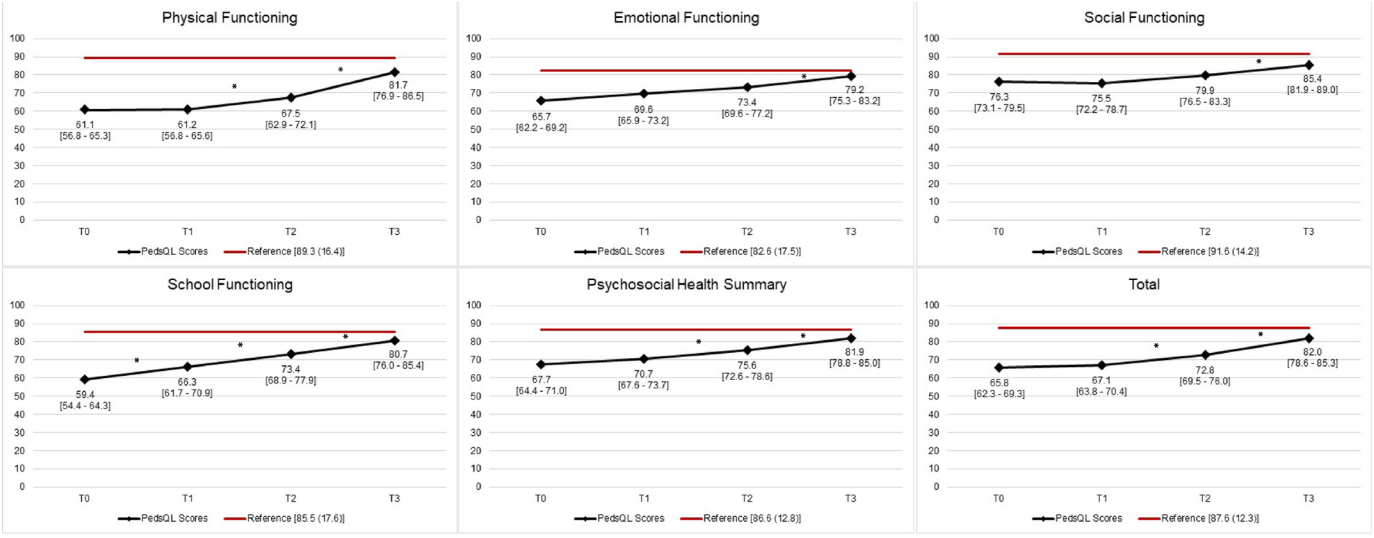

Figure 2 Longitudinal development of generic HRQoL scores.[25] *p<0.05. HRQoL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory.

deleted from the multivariable model in a stepwise approach until only variables with a p value below 0.10 remained. All models were corrected for parent sex. Effects were shown as regression coefficients (B) with SE and 95% CI. for all linear mixed models.

Patient and public involvement

None.

RESULTS

Study population

Informed consent was obtained from 159 families (82% response rate) in the ALL-10 cohort[8] and 151 families (67% response rate) in the ALL-11 cohort,[22] of which 132 and 136 provided HRQoL data at one or more timepoints, respectively. Hence, 268 families provided cancer-specific and 136 families generic HRQoL data at one or more timepoints. The main reasons for families to not participate were illness severity, study burden and organisational issues.[8 22] Sociodemographic characteristics of patients are provided in table 1. Mean time since diagnosis for the generic HRQoL cohort at each assessment timepoint (in months) was as follows: T0 4.7 (SD 1.3), T1 13.6 (SD 1.3), T2 24.2 (SD 1.8), T3 36.7 (SD 1.8); and for the cancer HRQoL cohort: T0 3.0 (SD 1.9), T1 13.8 (SD 1.6), T2 25.5 (SD 4.1). Parent-reported clinically relevant pain of the child for the generic HRQoL cohort was as follows: T0 n=54 (45.4%), T1 n=36 (33.6%), T2 n=31 (31.3%), T3 n=17 (21.0%). Most proxy respondents were mothers at each timepoint for both generic and cancer HRQoL cohorts.

Longitudinal development of HRQoL

Generic HRQoL

HRQoL significantly improved over time, with the most consistent improvement observed between T2 and T3 for all scales (figure 2, online supplemental table 1). School Functioning scores significantly improved across all timepoints (T0–T3). Physical Functioning, PSHS and Total scores were stable between T0 and T1 but significantly improved from T1 onwards. Social Functioning and Emotional Functioning scores significantly improved only during the third year (between T2 and T3).

Cancer-specific HRQoL

Nausea and Communication scores significantly improved across all timepoints (between T0 and T2). Procedural Anxiety and Treatment Anxiety only significantly improved from T0 to T1, but not from T1 to T2. Pain did not improve from T0 to T1 but did significantly improve from T1 to T2. There was a small but significant improvement in Worry between T0 and T2. Physical Appearance and Cognitive Functioning did not significantly improve across any timepoints (figure 3, online supplemental table 2).

Clinically impaired HRQoL

Unadjusted generic HRQoL scores and percentage clinically impaired by timepoint are provided in online supplemental table 1. For Physical Functioning, the percentage clinically impaired went down from 61.9% (T0) to 21.2% (T3); for Emotional Functioning 59.2% (T0) to 23.5% (T3); for Social Functioning 48.7% (T0) to 24.7% (T3); for School Functioning 62.6% (T0) to 22.0% (T3); for PSHS 64.4% (T0) to 25.6% (T3) and for Total 71.2% (T0) to 28.0% (T3). Thus at T3, Total score was the subscale with the greatest percentage of patients with clinically impaired HRQoL (28.0% compared with 16% in the general population, p=0.003). Unadjusted cancer HRQoL scores (proxy-reported) by timepoint are provided in online supplemental table 2. The proportion of patients with parent-reported problems on each cancer-specific subscale is shown in figure 4, per timepoint.

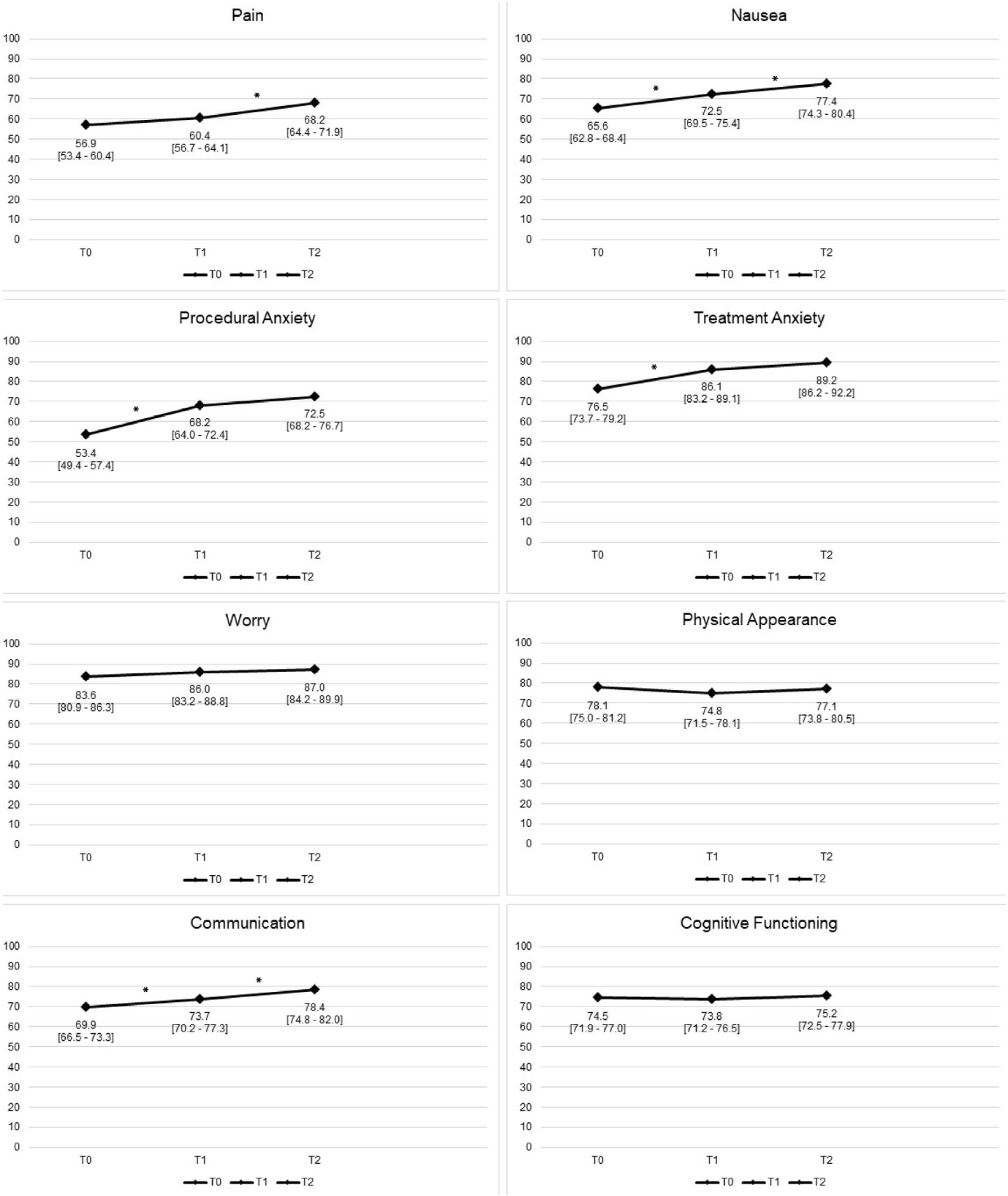

Figure 3 Longitudinal development of cancer-specific HRQoL scores. *p<0.005. HRQoL, health-related quality of life.

Determinants of HRQoL development

Generic HRQoL

Experiencing pain or simultaneous chronic illness was independently associated with lower HRQoL on all subscales over time (table 2). Additionally, higher treatment intensity was independently associated with decreased Physical Functioning, Social Functioning, PSHS and Total scores. Sex was independently associated with Social Functioning and the

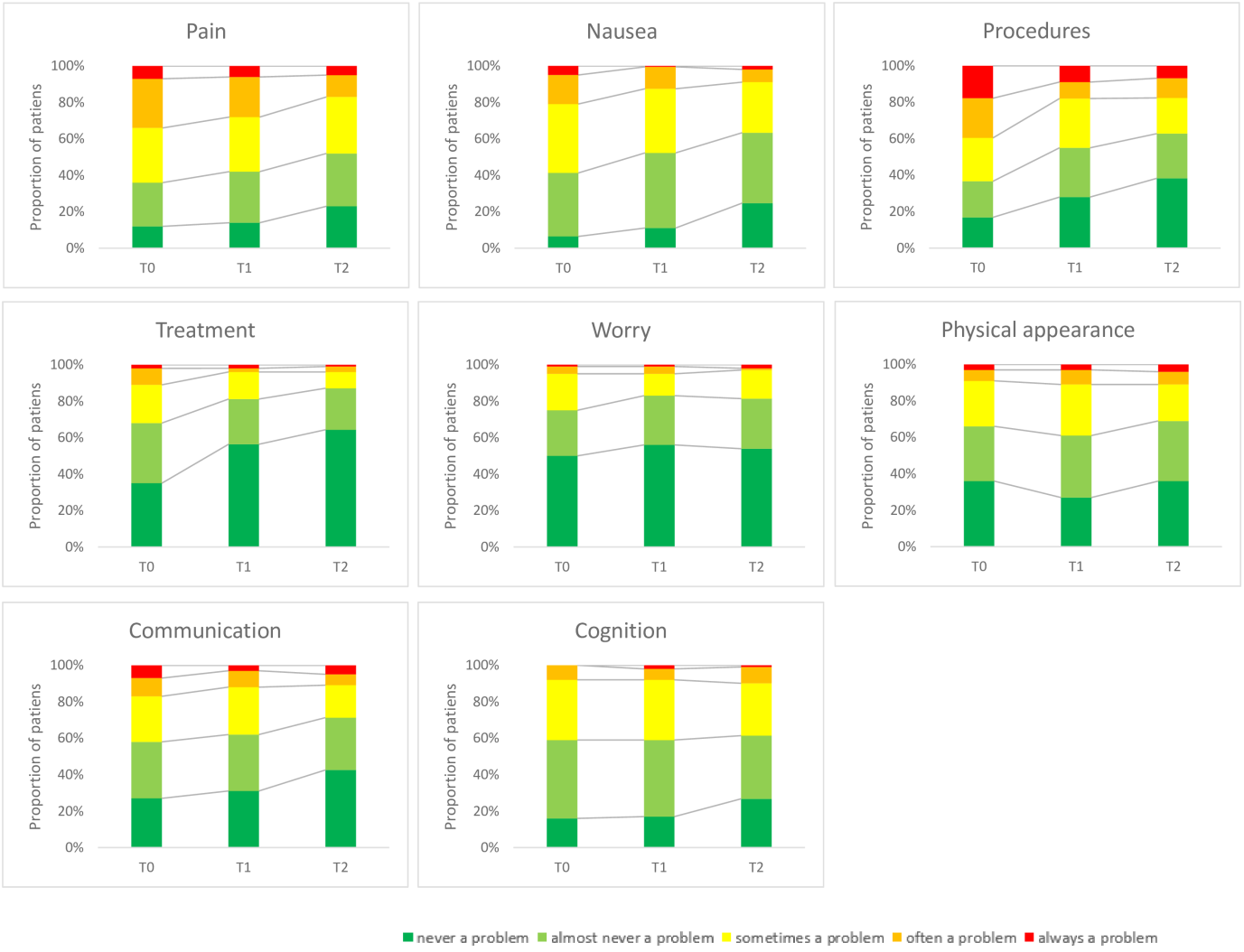

Figure 4 Proportion of patients reporting problems ('never' to 'always') on the PedsQL Cancer scales. PedsQL, Pediatric Quality of Life Inventory.

Total score, with parents reporting worse HRQoL for boys than girls. Older patient age was independently associated with better Emotional Functioning and better PSHS scores. High family education was independently associated with better Social Functioning, PSHS and Total scores (table 2).

Cancer-specific HRQoL

Patient age was independently associated with seven of the eight subscales, as older patients experienced more Worry, concern about Physical Appearance, and worse Cognitive Functioning but less Nausea, Procedural Anxiety, Treatment Anxiety and better Communication than younger patients. Male patient sex was independently associated with less Procedural Anxiety, less concern about Physical Appearance, better Communication, but more Nausea. Higher treatment intensity was independently associated with worse HRQoL, as patients experienced more Pain and Nausea (table 2).

DISCUSSION

This study is one of the few to longitudinally assess the development of HRQoL in children with ALL and thus provides new insights into the field. With regards to our three aims, we found that generic HRQoL showed longitudinal improvement in all subscales and cancer-specific HRQoL showed longitudinal improvement in all subscales except Physical Appearance and Cognitive Functioning. Despite longitudinal improvement, generic HRQoL of paediatric patients with ALL remained impaired compared with healthy children up to 3 years after diagnosis. Chronic illness and pain were the most consistently associated risk factors for lower generic HRQoL. In addition, treatment intensity was significantly associated with the longitudinal course of generic HRQoL: children in the SR group with reduced treatment intensity experienced a better HRQoL than children with higher risk ALL. They also experienced less Pain and Nausea on the cancer-specific subscales.

Cancer-specific HRQoL improved over the course of treatment on most subscales, although Physical Appearance and Cognitive Functioning remained stable over the course of time. An explanation could be that HRQoL on these scales, to begin with, was not very impaired. In a

Table 2 Determinants of HRQoL

	Generic HRQoL (multivariable regression coefficient (95% CI)†)					
	Physical functioning	Emotional functioning	Social functioning	School functioning	Psychosocial health summary score	Total
Patient age (per year increase)		1.1 (0.5 to 1.6)****			0.4 (–0.1 to 0.8)*	
Male patient sex			–5.0 (–9.3 to –0.7)**			–3.8 (–8.0 to 0.4)*
Higher treatment intensity (MR or HR ALL)	–8.8 (–14.9 to –2.7)***		–4.9 (–9.7 to –0.2)**		–4.7 (–9.1 to –0.3)**	–6.0 (–10.6 to –1.4)***
Clinically relevant pain of the child‡	–20.6 (–24.9 to –16.2)****	–9.6 (–13.2 to –6.0)****	–6.6 (–9.9 to –3.3)****	–12.4 (–17.6 to –7.3)****	–8.4 (–11.6 to –5.2)****	–11.6 (–15.1 to –8.1)****
Presence of chronic illness (other than ALL)	–18.2 (–30.9 to –5.6)***	–15.0 (–26.5 to –3.5)**	–13.2 (–23.6 to –2.7)**	–22.5 (–35.5 to –9.4)****	–12.6 (–22.1 to –3.1)**	–14.1 (–24.0 to –4.2)***
Highly educated families			5.2 (0.5 to 10.0)**		5.5 (1.1 to 9.8)**	3.9 (–0.7 to 8.6)*

	Cancer-specific HRQoL (multivariable regression coefficient (95% CI)†)							
	Pain	Nausea	Procedural Anxiety	Treatment Anxiety	Worry	Physical Appearance	Communication	Cognitive Functioning
Patient age (per year increase)		0.5 (0.08 to 0.9)**	2.9 (2.3 to 3.6)****	1.2 (0.8 to 1.7)****	–1.6 (–2.0 to –1.2)****	–2.0 (–2.5 to –1.5)****	0.8 (0.1 to 1.4)**	–0.6 (–1.0 to –0.1)**
Male patient sex		–4.1 (–8.1 to 0.03)*	5.5 (–0.4 to 11.5)*			5.1 (0.6 to 9.7)**	5.0 (–0.6 to 10.7)*	
Higher treatment intensity (MR or HR ALL)	–9.9 (–15.8 to –3.9)***	–6.7 (–11.4 to –2.0)***						

*p<0.1, **p<0.05, ***p<0.01, ****p<0.001.
†Models are adjusted for parent sex.
‡The cut-off used for designating clinically relevant pain was a score of 4 or higher.[30]
ALL, acute lymphoblastic leukaemia; HR, high risk; HRQoL, health-related quality of life; MR, medium risk.

Swedish sample of children with different types of cancer, HRQoL on these subscales was more impaired than in our population.[31] Regarding Physical Appearance, this finding might relate to the age of our population: younger children might be less concerned with their appearance than teenagers.[32] Similarly, most studies do not show major neurocognitive defects during ALL treatment with chemotherapy only and a stability over time, but results are mixed due to differences in design, tests, treatment protocols, etc.[33–36] ALL survivors typically have greater impairments in sustained attention, working memory and processing speed, although the PedsQL likely does not detect subtle difficulties.

The finding that proxy-reported generic HRQoL improves over time but a large proportion of children still demonstrate clinical impairment 1 year after treatment is in line with results of previous longitudinal studies conducted in this same population.[10 11 37 38] For parents, the initial period after the end of their child's treatment is notoriously difficult. In addition to time needed for the child to recover physically, there is a loss of security and regularity given that after leaving the hospital there are less clinical check-ups. Parents can experience distress and impaired HRQoL themselves during this vulnerable period, which can influence how they report on their child's functioning.[28 39 40]

The most consistently associated determinants of lower proxy-reported generic HRQoL were chronic illness and pain. Having an ongoing chronic illness in conjunction with an ALL diagnosis was associated with lower HRQoL, which was notable given that the number of patients with chronic illness was low and the diagnoses were not acutely life threatening (table 1). This finding may be representative of the ALL disease burden, and its impact on a family's ability to handle other/additional stressors.[39 41 42] This is further supported by the known negative association between parental distress and proxy-reported HRQoL.[28] With regards to pain, this has been ranked among the most common, severe and burdensome treatment-related symptoms of children with cancer.[15 16 43] A negative association between pain and HRQoL has been previously demonstrated,[17] which is in line with our findings that pain is one of the most significant and consistent predictors of lower HRQoL in all subscales.

An important determinant of generic as well as cancer-specific HRQoL was higher treatment intensity, with lower HRQoL in children who received higher intensity treatments on most subscales. Patients stratified to the SR group had reduced treatment intensity, which not only resulted in improved survival in this population,[2] but as our results show also in better HRQoL compared with the higher risk groups. In addition to a lower physical burden due to treatment reduction, fewer hospital visits for scheduled treatments and perhaps the knowledge of a lower risk of recurrence may also explain this result. Higher treatment intensity was also predictive of worse Pain and Nausea HRQoL according to the cancer-specific scores, similar to findings in an earlier study.[11] More days in the hospital and more treatment-related toxicities have been associated with reduced overall HRQoL scores,[5] which may offer a potential explanation for this finding.

Regarding age and sex as determinants of both generic and cancer-specific HRQoL, we found some inconsistencies across different subscales and questionnaires. There is also relative inconsistency in the literature however, as a number of studies included in the Fardell *et al* review showed no association between age or sex with HRQoL.[5] Age was the most consistently associated determinant of cancer-specific HRQoL, and our findings were in line with expectations.

Study limitations

Our study must be interpreted in light of certain limitations. First, results are based on parent-proxy reports, as we had a too low number of self-reports to detect associations. While self-report data is very valuable, the peak age of ALL is quite young. Thus, self-report data is difficult to obtain from children during treatment. Similarly, we only assessed general HRQoL in the ALL-11 cohort and not in the ALL-10 cohort. However, these protocols were very similar in terms of treatment; hence, we believe that it did not affect generalisability. We also did not take psychosocial factors into account, such as psychosocial functioning of child or parent, when interpreting HRQoL, while previous research has shown that psychosocial factors are relevant.[10 14 28] Second, we used US reference data with which we compared our Dutch population's proxy-HRQoL subscale scores of the PedsQL generic because such data on Dutch healthy norms does not exist for children 8 years and older. Third, our population was not ideally generalisable as there was a lack of HR patients in the PedsQL generic group, and the majority of our population was of high socioeconomic status and of Dutch nationality. This could indicate participation bias. Finally, pain was found to be an important determinant of HRQoL, but we did not measure it elaborately, and only by proxy reports. Future perspectives are warranted to better evaluate the relationship between pain and HRQoL in order to provide effective intervention.

Clinical implications

Assessment of HRQoL and changes throughout the course of treatment can enhance both family and patient HRQoL.[5 44] This is also recommended by the Psychosocial Standards of Care, which were developed by an interdisciplinary expert group.[45] Our findings suggest that HRQoL should be routinely monitored both during and after the end of treatment given that the generic HRQoL of paediatric patients with ALL does not normalise compared with healthy children. At the Princess Máxima Center for Pediatric Oncology, we do so through the KLIK PROM Portal, where clinicians and the psychosocial care team monitor patient HRQoL throughout follow-up into survivorship.[46] It is difficult to interpret cancer-specific scores, as there is no norm to which comparisons can be made. Therefore, it is unclear what change in score can be

considered clinically meaningful. Future research should aim to evaluate the longitudinal course of cancer-specific HRQoL in a large sample in order to create a 'normal' cancer cohort in which relevant determinants of progression are taken into account. In comparison to the results from this established cohort, it may be possible to identify children who deviate from this course. Furthermore, appropriate pharmacological and non-pharmacological pain management, additional supportive care measures and psychosocial support for children with simultaneous chronic illnesses are imperative to optimise the HRQoL of children with ALL diagnoses. Our findings also suggest an important need for ongoing psychosocial support after the end of treatment to ensure restoration of HRQoL in all patients. It is important to devote attention to parental well-being, given that parental distress is a significant predictor of impaired proxy-reported HRQoL for their child.[39 40 47] For example, an educational intervention for parents with regards to ALL treatment, communication and ways to improve their child's HRQOL has shown to be effective in improving proxy-reported HRQoL.[48] This implies that ongoing psychosocial screening of parents, as well as of the child, is important for a comprehensive understanding of the patient's HRQoL.

CONCLUSION

HRQoL impairment for children with ALL is prevalent during treatment despite gradual improvement and generic HRQoL remains impaired post-treatment for a significant proportion of children. Children with SR ALL and reduced treatment intensity have better HRQoL than children with higher risk ALL. Systematic attention to both child and parental HRQoL throughout and after treatment, and recognition of vulnerable populations that exhibit risk factors for worse HRQoL are all of major importance to improve the quality of patient survival in the long term.

Author affiliations
[1]Department of Pediatric Oncology, Emma Childrens' Hospital UMC, Amsterdam, The Netherlands
[2]Department of Hematology-oncology, Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands
[3]Department of Pediatric Oncology, Erasmus MC Sophia Children Hospital, Rotterdam, The Netherlands
[4]Department of Pediatric Oncology, Radboudumc, Nijmegen, The Netherlands
[5]Department of Pediatric Oncology, University Medical Centre Groningen, Groningen, The Netherlands

Contributors ERS, NR and LMHS contributed to data curation, analysis, investigation, methodology, administration and writing. RG, MAG and GJLK contributed to conceptualisation, methodology, resources, validation and writing. NKAvE, IMvdS, ND, CvdB and WJET contributed to conceptualisation and writing. RRLVL contributed to conceptualisation, data curation, analysis, investigation, methodology, supervision, validation and writing and is responsible for the overall content as guarantor.

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ORCID iD
Niki Rensen http://orcid.org/0000-0003-1683-6331

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Supplemental table 1. Pediatric Quality of Life Inventory Generic Core scale scores

		T0	T1	T2	T3	Change T0-T3[e], B (95% C.I.)
		N=122[a]	N=114[b]	N=99[c]	N=85[d]	
Physical Functioning	Mean (SD)	62.6 (24.0)	62.7 (23.9)	69.5 (24.7)	84.3 (17.9)	20.7 (15.5 – 25.8) P<0.001
	Clinically Impaired (%)	61.9	67.3	50.5	21.2	-
Emotional Functioning	Mean (SD)	66.7 (19.2)	70.8 (20.1)	74.7 (18.6)	80.5 (17.9)	13.5 (9.3 – 17.8) P<0.001
	Clinically Impaired (%)	59.2	46.3	34.4	23.5	-
Social Functioning	Mean (SD)	76.9 (17.3)	75.8 (17.2)	80.2 (17.4)	86.0 (16.2)	9.1 (5.2 – 13.0) P<0.001
	Clinically Impaired (%)	48.7	49.5	46.4	24.7*	-
School Functioning	Mean (SD)	60.5 (24.9)	67.7 (22.7)	74.6 (20.0)	82.0 (18.5)	21.3 (15.2 – 27.4) P<0.001
	Clinically Impaired (%)	61.6	44.3	34.4	22.0	-
Psychosocial Health Summary	Mean (SD)	68.8 (14.4)	72.0 (15.9)	76.6 (14.9)	82.9 (12.9)	14.2 (10.4 – 18.0) P<0.001
	Clinically Impaired (%)	64.4	61.4	41.8	25.6*	-
Total	Mean (SD)	67.2 (15.6)	68.3 (17.0)	74.1 (16.8)	83.5 (13.7)	16.1 (12.2 – 20.1) P<0.001
	Clinically Impaired (%)	71.2	67.4	50.5	28.0*	-

[a]N=73-118 with proxy QoL data across the different scales at T0; [b]N=86-109 with proxy QoL data at T1; [c]N=91-97 with proxy QoL data at T2; [d]N=82-85 with proxy QoL data at T3
[e]Mixed linear model with intercept on child level, adjusted for parental sex
*significantly different from 16% in general population (Chi-square goodness-of-fit test)

Supplemental table 2. Pediatric Quality of Life Inventory Cancer module scores (Mean (SD))

	T0 N=250[a]	**T1 N=242[b]**	**T2 N=228[c]**	**Change T0-T2[d] B (95% C.I.)**
Pain	56.8 (27.1)	60.3 (27.1)	68.4 (26.2)	11.3 (7.1 – 15.5) P<0.001
Nausea	65.7 (22.5)	72.4 (20.0)	77.6 (21.1)	11.7 (8.4 – 15.1) P<0.001
Procedural Anxiety	53.6 (32.2)	68.1 (29.7)	72.7 (30.3)	19.1 (14.8 – 23.4) P<0.001
Treatment Anxiety	76.5 (24.8)	86.7 (19.6)	89.7 (17.5)	12.8 (9.5 – 16.0) P<0.001
Worry Score	83.6 (21.8)	86.7 (20.3)	87.9 (18.3)	3.5 (0.6 – 6.3) P=0.02
Physical Appearance	78.1 (23.7)	75.4 (23.5)	77.7 (24.7)	-0.9 (-4.2 – 2.4) P=0.58
Communication	70.6 (27.8)	75.0 (24.6)	80.0 (24.7)	8.5 (5.0 – 11.9) P<0.001
Cognitive Functioning	74.6 (19.1)	74.6 (19.5)	76.3 (21.3)	0.72 (-1.9 – 3.3) P=0.59

[a]N=233-248 with proxy QoL data across the different scales at T0; [b]N=196-206 with proxy QoL data at T1; [c]N=193-196 with proxy QoL data at T2
[d]Mixed linear model with intercept on child level, adjusted for parental sex