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Health-related quality of life in young survivors of childhood cancer

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Abstract
Purpose Childhood cancer and its treatment may affect health-related quality of life (HRQoL) in childhood cancer survivors, but population-based studies in young survivors are scarce. We aimed to: (1) compare HRQoL between young survivors and population norms and (2) find factors that influence parent-reported HRQoL in survivors.
Methods As part of the Swiss Childhood Cancer Survivor Study, a questionnaire was mailed to parents of survivors aged 8–16 years, registered in the Swiss Childhood Cancer Registry, ≥5 years after diagnosis. We used the KIDSCREEN-27 instrument to compare self- and parent-reported HRQoL between survivors ($N = 425$) and standardized norms in the five dimensions of *physical well-being*, *psychological well-being*, *autonomy*, *peers* and *school environment* (mean = 50, SD = 10). We then used multivariable linear regressions to test the influence of socio-demographic and cancer-related factors on HRQoL.
Results Self-reported *physical well-being* was comparable to norms. Other HRQoL dimensions were higher than norms, with the highest mean = 52.2 ($p < 0.001$) for *school environment*. Parent-reported HRQoL in survivors was comparable to population norms; only *physical well-being* was lower (mean = 47.1, $p < 0.001$), and *school environment* was higher (mean = 51.1, $p = 0.035$). Parent-reported HRQoL was lower for survivors of CNS tumors (*physical well-being*: $\beta = -5.27$, $p = 0.007$; *psychological well-being*: $\beta = -4.39$, $p = 0.044$; *peers* $\beta = -5.17$, $p = 0.028$), survivors of neuroblastoma (*psychological well-being* $\beta = -5.20$, $p = 0.047$), and survivors who had had a relapse (*physical well-being* $\beta = -5.41$, $p = 0.005$).
Conclusions Assessing HRQoL during follow-up care, with a focus on physical well-being, specific diagnoses (e.g., CNS tumor) and late complications (e.g., relapse) might help to early identify problems and offer support to survivors with reduced HRQoL.

Keywords Childhood cancer · Health-related quality of life · Cohort study · Children · KIDSCREEN

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Introduction

Continuous improvements in therapy have increased 5-year survival of childhood cancer to over 80 % [1, 2], leading to a growing population of long-term survivors. Each year around 200 children receive a diagnoses of cancer in Switzerland. Currently, more than 5000 survivors diagnosed in Switzerland from 1976 until today are registered in the Swiss Childhood Cancer Registry (SCCR) [3]. Although most childhood cancer patients survive, they have to face late effects from the harsh treatment and the cancer itself for the rest of their lives. More than one out of four adult childhood cancer survivors

suffer from a severe or life-threatening late effect [4]. More survivors than siblings report poor general health, adverse mental health, functional impairment or activity limitations [5]. Such late effects can affect health-related quality of life (HRQoL) in survivors [6–11].

HRQoL in adult long-term survivors of childhood cancer [6–9, 12–15] is extensively studied, but little is known about the HRQoL of young long-term survivors, who are still children or teenagers. Sample sizes in published studies tended to be small ($n = 68$) [16], were limited to specific diagnoses such as tumors of the central nervous system (CNS) [17, 18] or retinoblastoma [19], or focus on HRQoL during [10], or shortly after treatment ended [11, 20]. Some larger studies assessed HRQoL in populations of survivors with various diagnostic groups: a study from the USA used the Child Health and Illness Profile-Adolescent Edition in 307 survivors and found that the overall health profiles of survivors were similar to siblings, but survivors of CNS tumors scored lower in terms of satisfaction with health and had more health disorders [21]. However, the study only focused on survivors diagnosed before the age of 4 years. A study including 110 survivors of various diagnostic groups from Korea showed that physical and psychosocial HRQoL assessed with the PedsQL questionnaire [22] including disease-specific modules were reduced compared to healthy controls [23]. However, the analysis did not distinguish HRQoL for different diagnostic groups.

In order to understand how HRQoL is affected in young long-term survivors of childhood cancer, we need a large population-based study including all diagnostic groups of survivors, as well as comparison data from healthy peers. In our large population-based sample of childhood cancer survivors, we aimed to (1) quantify and compare self- and parent-reported HRQoL between young survivors and population norms and (2) find socio-demographic and cancer-related factors associated with HRQoL in survivors.

Materials and methods

The Swiss Childhood Cancer Survivor Study

The Swiss Childhood Cancer Survivor Study (SCCSS) is a population-based long-term follow-up study. It includes all patients registered in the SCCR, diagnosed between 1976 and 2005 at age <16 years, who survived ≥5 years after initial diagnosis [24]. Currently, the SCCSS includes questionnaire data of 2542 survivors with an overall response rate of 72 % [25]. The SCCR is a population-based cancer registry and includes all children and adolescents in Switzerland diagnosed with leukemia, lymphoma, CNS tumors, malignant solid tumors or Langerhans cell histiocytosis (LCH) before age 21 [26].

Between 2007 and 2012, we traced addresses of eligible survivors for the SCCSS and sent them an extensive questionnaire that included the KIDSCREEN-27 instrument which measures HRQoL. The questionnaire was available in German, French and Italian to cover the different language regions in Switzerland. Non-responders were mailed a second copy of the questionnaire and, if they again failed to respond, were contacted by phone. Questionnaires were similar to those used in USA and UK childhood cancer survivor studies [27, 28]. We added questions about health behaviors and socio-demographic measures from the Swiss Health Survey 2007 [29] and the Swiss Census 2000 [30]. Ethics approval was granted through the general cancer registry permission of the SCCR (The Swiss Federal Commission of Experts for Professional Secrecy in Medical Research) and we obtained a *non obstat* statement from the ethics committee of the canton of Bern.

For this study, we sent two questionnaires to the families of all survivors aged 8–16 years at survey. The first questionnaire was addressed to parents, who were asked to evaluate HRQoL of their child who survived cancer, and included the KIDSCREEN-27 version for parents. The second questionnaire was addressed to the survivor, who was asked to evaluate his or her HRQoL, and included the KIDSCREEN-27 version for children. Pre-paid return envelopes were included with the questionnaires. Survivors and parents were told that participation was voluntary and that they did not have to show their completed questionnaire to anybody, before sending it back.

Assessment of health-related quality of life (HRQoL)

We assessed self- and parent-reported HRQoL with the generic KIDSCREEN-27 instrument. The validated KIDSCREEN-27 instrument [31] was tested in 22,827 children from different European countries [32]. It assesses self- and parent-reported HRQoL in children and adolescents aged 8–18 years and offers country-adjusted normative reference values. It is applicable for healthy children [33] as well as for children with chronic diseases such as mental illnesses [34, 35], congenital lower limb deficiencies [36], stroke, [37] or cerebral palsy [38]. So far, the KIDSCREEN-27 instrument was tested in a small group of young childhood cancer survivors ($n = 63$, aged 12–22 years) [39, 40]. It was found to be a valid instrument to measure HRQoL in young survivors [39] and to identify children in need of additional support [40].

The KIDSCREEN-27 instrument includes five dimensions of HRQoL [32]: *physical well-being* (five questions on physical activities and health), *psychological well-being* (seven questions about general moods and feelings), *autonomy and parents* (seven questions about family and leisure time), *peers and social support* (four questions about relations to friends) and *school environment* (four

questions about school and learning). For each item, children and parents rate the child's HRQoL for the past week on a Likert scale. For each dimension, a Rasch score ranging from 0 to 100 is calculated, with a higher score indicating higher HRQoL. The scores of each dimension are then compared to age- and gender-stratified normative scores of 50 (SD = 10). In our study, we sent the German, French or Italian version of the KIDSCREEN-27 to families, based on the language region where the family lived. We compared HRQoL of all survivors from our study to Swiss norm data of 1701 children coming from the German-speaking region of Switzerland [41].

Assessment of socio-demographic and clinical data

The parent questionnaire assessed the following socio-demographic variables of survivors: gender; age at survey; migration background; language region of Switzerland; parents' educations; living situation; and having siblings. For the regression models, we created a binary variable for age: children (aged 8–12 years) and adolescents (aged 13–16 years). Survivors were coded as having a migration background if they were not born in Switzerland, had no Swiss citizenship at birth or had at least one parent without Swiss citizenship. Parents' education was classified into three categories: primary education (compulsory schooling only; ≤9 years); secondary education (vocational training or upper secondary education); or, tertiary education (university or technical college education). If parents achieved different levels of education, we selected the parent with the highest education. For the regression models, we created a binary variable for parents' education. Tertiary education was considered to be high parental education, while compulsory and secondary education was considered low parental education. There were four categories of living situation: survivor lives with both parents; survivor lives with one parent and partner of parent; survivor lives with one parent; and survivor lives in an institution (home for children or adolescents).

Cancer-related variables were retrieved from the SCCR, from which we extracted diagnosis, treatment modalities (surgery, chemotherapy, radiotherapy, bone marrow transplantation), age at diagnosis, duration of treatment in days, time since diagnosis and relapse status. We coded diagnoses according to the international classification of childhood cancer—third edition (ICCC-3) [42].

Statistical analysis

We calculated data completeness, floor and ceiling effects and internal consistency to measure data quality of the KIDSCREEN-27 in Swiss childhood cancer survivors, (Supplemental Table 1). If more than one question in a dimension was missing, the HRQoL of this dimension could not be calculated and was missing. Data completeness was good with <1–2 % of missings per dimension in survivors and 1–6 % in parents. Floor effects were low with 0–2 % in survivors and parents. This means that 0–2 % of survivors and parents always answered with the lowest category (indicating lower HRQoL) within one or more of the five dimensions. Ceiling effects were higher in survivors (8–21 %) compared to parents (5–9 %). This means that 8–21 % of survivors and 5–9 % of parents always answered using the highest category (indicating high HRQoL) within one or more of the five dimensions. Reliability was good with Cronbach's alpha ranging from 0.73 to 0.87 in self-reported and from 0.78 to 0.90 in parent-reported dimensions of HRQoL.

First, we compared the mean self- and parent-reported HRQoL to age and gender-adjusted Swiss population norms using *t* tests. We also compared the mean self-reported to the mean parent-reported HRQoL using paired *t* tests. Second, we analyzed the proportion of survivors with a score of self- and parent-reported HRQoL ≤ 45. Third, we tested the association of self- and parent-reported HRQoL for each of the five KIDSCREEN-27 dimensions with socio-demographic and cancer-related factors using univariable linear regressions. Factors associated with at least one of the five self- or parent-reported HRQoL dimensions ($p < 0.05$) in univariable linear regressions were then tested in multivariable linear regressions for each of the five parent-reported dimensions. We chose to analyze risk factors for the parent-reported HRQoL because parents reported lower HRQoL for survivors than survivors for themselves and parents do have less ceiling effect than survivors. Supplemental Table 4 includes the multivariable linear regression for self-reported HRQoL. We then used Bonferroni correction in multivariable linear regressions in order to adjust for multiple comparison. We had five different models and therefore the Bonferroni corrected *p* value turned out to be $p < 0.05/5 = 0.01$.

Results

Characteristics of Study Population

Questionnaire data from 425 survivors were included (response rate 74 %; Fig. 1). Non-responders did not significantly differ from responders in terms of age ($p = 0.115$), gender ($p = 0.787$) or diagnosis ($p = 0.365$). Survivors for whom only the parent completed the questionnaire, tended to be younger than the survivors who also completed the questionnaire ($p < 0.001$) themselves. In two cases, only an abridged questionnaire was filled in, not including the KIDSSCREEN-27 questions. In 12 cases only survivors' questionnaires and in 23 cases only parents' questionnaires were sent back. Of the survivors, 43 % were female, mean age

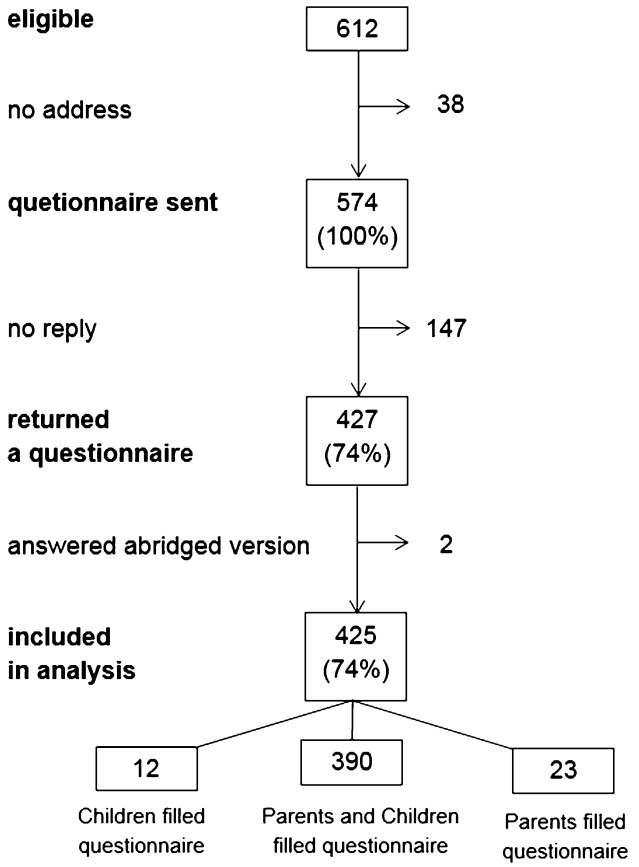


Fig. 1 The response in study participants. Eligible were survivors who were diagnosed ≥5 years ago with leukemia, lymphoma, CNS tumors, malignant solid tumors or Langerhans cell histiocytosis (LCH), aged 8–16 years at time of survey

of survivors at survey was 13.3 years (SD = 2.2), and 8 % of survivors had a migration background (Table 1). Most families came from the German-speaking region of Switzerland (69 %). Two-thirds of parents of survivors had secondary education (67 %); 24 % had tertiary education; and 9 % had primary education. Most children lived with both parents (81 %); 13 % lived with one parent, 5 % with one parent and partner, and 1 % lived in an institution. Most survivors had one or more siblings (85 %).

Leukemia was the most common cancer (38 %), followed by CNS tumors (18 %), lymphoma (8 %) and neuroblastoma (8 %). Most survivors had received chemotherapy (81 %), 59 % had surgery, 17 % had radiotherapy (6 % including cranial irradiation), and 4 % had bone marrow transplantation. Mean age at diagnosis was 3.3 years (SD = 2.3); mean duration of treatment was 465 days (SD = 450); and mean time since diagnosis was 10.5 years (SD = 2.5). Survivors were diagnosed between the years 1995 and 2005. We found that 11 % of patients had had a relapse.

Table 1 Characteristics of study participants

Survivors ($N = 425$)	n (%[a])
Socio-demographic characteristics	
Gender	
Male	241 (57)
Female	184 (43)
Age at survey (years)	
8–10	59 (14)
>10–12	91 (21)
>12–14	120 (28)
>14–16	155 (36)
Migration background	
No	393 (92)
Yes	32 (8)
Language region	
German	293 (69)
French	114 (27)
Italian	18 (4)
Parental education	
Primary education	36 (9)
Secondary education	264 (67)
Tertiary education	97 (24)
Child lives with	
Both parents	332 (81)
One parent and partner	20 (5)
One parent	54 (13)
Institution	3 (1)
Siblings	
No siblings	65 (15)
Has sibling(s)	360 (85)
Clinical characteristics	
Diagnosis (ICCC-3)	
Leukemia	162 (38)
Lymphoma	32 (8)
CNS	76 (18)
Neuroblastoma	32 (8)
Retinoblastoma	29 (7)
Renal tumor	31 (7)
Hepatic tumor	9 (2)
Bone tumor	8 (2)
Soft tissue sarcoma	22 (5)
Germ cell tumor	10 (2)
Langerhans cell histiocytosis	11 (3)
Other tumors[b]	3 (1)
Chemotherapy	
No	81 (19)
Yes	344 (81)
Surgery	
No	173 (41)
Yes	252 (59)

Table 1 continued

Survivors ($N = 425$)	n (%[a])
Radiotherapy	
No	351 (83)
Yes, excluding cranial	47 (11)
Yes, including cranial	27 (6)
Bone marrow transplantation	
No	407 (96)
Yes	18 (4)
Age at diagnosis (years)	
>1	73 (17)
1–5	248 (58)
>5–10	104 (24)
Duration of treatment (days)	
≤500	208 (49)
>500–1000	127 (30)
>1000	90 (21)
Time since diagnosis (years)	
5–10	235 (55)
>10–16	190 (45)
Relapse	
No	377 (89)
Yes	48 (11)

Percentages are based upon available data for each variable

CNS Central Nervous System, *ICCC-3* International Classification of Childhood Cancer—third Edition, *n* number

[a] Column percentages are given

[b] Other malignant epithelial neoplasms, malignant melanomas and other or unspecified malignant neoplasms

Health-related quality of life (HRQoL)

Self-reported HRQoL was similar to norms for *physical well-being*, and slightly higher for *psychological well-being* ($p = 0.030$), *autonomy and parents* ($p = 0.034$), *peers and social support* ($p = 0.042$) and highest for *school environment* ($p < 0.001$; Fig. 2). Parent-reported HRQoL was lower than norms for *physical well-being* ($p < 0.001$), similar for *psychological well-being*, *autonomy and parents*, *peers and social support* and slightly higher for *school environment* ($p = 0.035$). Survivors rated their HRQoL higher than their parents for *physical well-being* ($p < 0.001$); *psychological well-being* ($p = 0.005$); *autonomy and parents* ($p = 0.035$); and *peers and social support* (0.002). HRQoL scores ≤ 45 were self-reported by 24–32 % of survivors and parent-reported by 27–45 %, with the highest proportion for physical well-being (32 % self-reported, 45 % parent-reported, Fig. 3).

Socio-demographic factors associated with HRQoL

We here present the results from the multivariable linear regression analyses for parent-reported HRQoL. (Details of the univariable analyses can be found in Supplemental Tables 2 and 3, and multivariable linear regression analyses for self-reported HRQoL in Supplemental Table 4). In summary, survivors from the Italian- or French-speaking region of Switzerland had lower HRQoL than survivors from the German-speaking region, except for the psychological dimension; and survivors with migration background reported higher HRQoL than those without migration background. Survivors from the French- and Italian-speaking regions had lower HRQoL for *physical well-being* ($\beta = -5.84$, $p < 0.001$; Table 2), *autonomy and parents* ($\beta = -8.01$, $p < 0.001$), *peers and social support* ($\beta = -6.77$, $p < 0.001$) and *school environment* ($\beta = -4.99$, $p < 0.001$). Survivors with migration background had higher HRQoL than survivors without migration background for *autonomy and parents* ($\beta = 5.65$, $p = 0.010$) and *peers and social support* ($\beta = 4.88$, $p = 0.045$). After using Bonferroni correction living in the French or Italian language region remained significantly associated with a lower HRQoL for all dimensions, except for the psychological dimension. In the univariable models (Supplemental Tables 2 and 3), living situation and parental education were not significantly associated with HRQoL and thus were not included in the multivariable models.

Cancer-related factors associated with HRQoL

Survivors of CNS tumors, neuroblastoma or those with a relapse had lower parent-reported HRQoL for several domains compared to survivors of other diagnoses or those who did not experience a relapse. Survivors of CNS tumors had lower HRQoL for *physical well-being* ($\beta = -5.27$, $p = 0.007$, Table 2), *psychological well-being* ($\beta = -4.39$, $p = 0.044$) and *peers and social support* ($\beta = -5.17$, $p = 0.028$). Survivors of neuroblastoma had lower HRQoL for *psychological well-being* ($\beta = -5.20$, $p = 0.047$). Survivors of renal or hepatic tumors had higher HRQoL for the dimensions *autonomy and parents* ($\beta = 5.27$, $p = 0.011$) and *school environment* ($\beta = 5.66$, $p = 0.044$). Survivors who had had a relapse had lower HRQoL for physical well-being ($\beta = -5.41$, $p = 0.005$). After using Bonferroni correction, survivors of CNS tumors and those who had had a relapse remained significantly associated with a lower HRQoL for *physical well-being*, and survivors of a renal or hepatic tumor remained to be significantly associated with higher HRQoL for *school environment*.

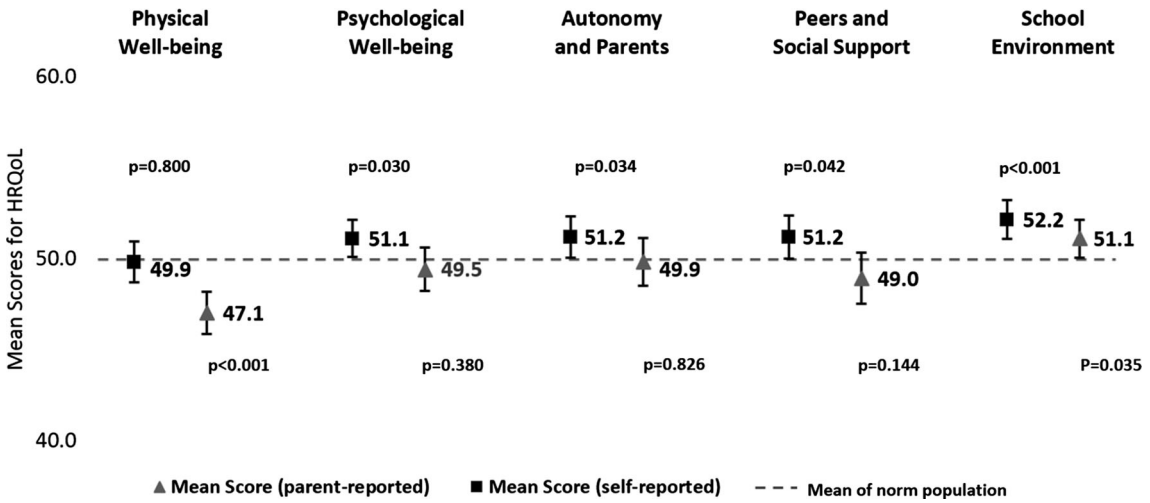
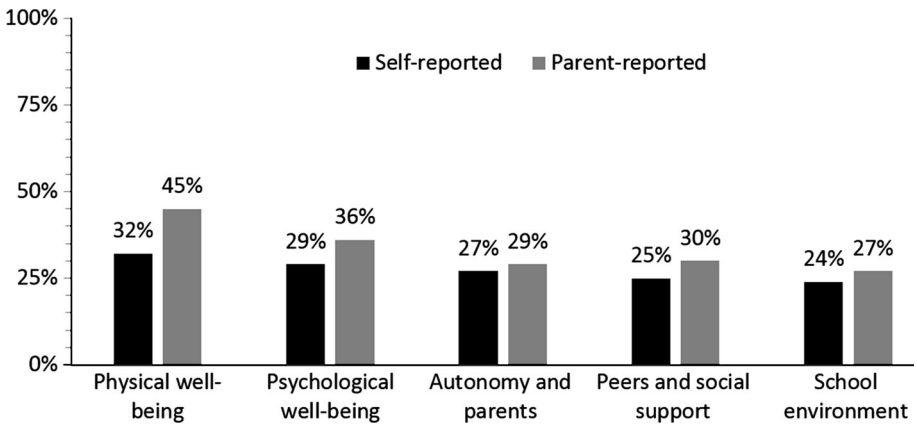


Fig. 2 The mean scores for parent- and self-reported HRQoL with 95 % confidence intervals and *p* values from *t* tests comparing parent- and self-reported HRQoL to the norm (mean = 50, SD = 10)

Fig. 3 The proportion of survivors with a HRQoL score ≤ 45



In the univariable models (Supplemental Tables 2 and 3), treatment duration and age at diagnosis were not associated with HRQoL and thus were not included in the multivariable models.

Discussion

In this study, we found that the overall HRQoL in young survivors of childhood cancer was comparable to population norms for most parent-reported dimensions and higher for most self-reported dimensions. Overall physical well-being was rated lowest, with self-reported HRQoL being comparable to norms and parent-reported HRQoL being lower than norms. Survivors rated their HRQoL higher than it was reported by their parents for four out of the five dimensions. Survivors of CNS tumors and those who had had a relapse had lower parent- and self-reported HRQoL in several dimensions. Survivors of neuroblastoma had lower parent-reported HRQoL for selected dimensions.

Comparison with other studies and interpretation of results

Like in our study, other studies also found that the overall HRQoL in survivors was comparable to population norms [18, 19, 21]. Further we found that HRQoL was lowest for physical well-being (self-reported: mean = 49.9, parent-reported: mean = 47.1) which is consistent with other studies that found physical well-being to be the most impaired dimension of HRQoL [11, 16]. A recent study from the SCCSS showed that more survivors than siblings report they are limited in sports (9.5 vs. 1.1 %), mainly due to musculoskeletal and neurological problems [43], which might in return affect their physical well-being.

Table 2 Association of socio-demographic and cancer-related factors with parent-reported HRQOL from multivariable linear regression models

	Physical well-being			Psychological well-being			Autonomy and parents			Peers and social support			School environment		
	β^a	95 % CI[b]	p^c	β^a	95 % CI[b]	p^c	β^a	95 % CI[b]	p^c	β^a	95 % CI[b]	p^c	β^a	95 % CI[b]	p^c
Female	0.72	−1.52; 2.96	0.525	1.26	−1.22; 3.74	0.320	2.29	−0.14; 4.71	0.064	1.77	−0.88; 4.42	0.189	1.41	−0.70; 3.52	0.190
Adolescent[d]	0.11	−2.45; 2.68	0.930	1.18	−1.67; 4.03	0.415	0.55	−2.23; 3.34	0.697	1.23	−1.82; 4.28	0.428	1.16	−1.26; 3.58	0.346
French/Italian language region	−5.84	−8.22; −3.46	<0.001	−1.42	−1.67; 4.03	0.292	−8.01	−10.59; −5.42	<0.001	−6.77	−9.59; −3.95	<0.001	−4.99	−7.24; 2.74	<0.001
Migration background	1.03	−3.01; 5.06	0.617	2.56	−1.90; 7.03	0.259	5.65	1.37; 9.93	0.010	4.88	0.11; 9.64	0.045	2.50	−1.31; 6.31	0.198
Diagnosis[e]															
Lymphoma	1.01	−3.30; 5.32	0.645	−0.33	−5.09; 4.44	0.892	2.01	−2.69; 6.71	0.401	−2.09	−7.18; 2.99	0.419	−1.12	−5.24; 2.99	0.592
CNS	−5.27	−9.10; −1.43	0.007	−4.39	−8.66; −0.12	0.044	−2.21	−6.32; 1.91	0.293	−5.17	−9.77; −0.57	0.028	−1.97	−5.54; 1.60	0.279
Neuroblastoma	−2.33	−6.93; 2.27	0.320	−5.20	−10.34; −0.07	0.047	−3.95	−8.95; 1.06	0.122	−1.56	−6.96; 3.84	0.571	−1.89	−6.20; 2.41	0.388
Retinoblastoma	−0.72	−5.45; 4.02	0.766	−2.80	−8.17; 2.57	0.306	1.49	−3.69; 6.66	0.572	−4.33	−9.92; 1.26	0.129	3.53	−0.93; 8.00	0.121
Renal/hepatic tumor	0.37	−3.60; 4.34	0.855	1.73	−2.66; 6.12	0.440	5.72	1.30; 10.13	0.011	4.03	−9.92; 1.26	0.092	5.66	1.83; 9.48	0.004
Bone tumor/Soft tissue sarcoma	−2.94	−7.43; 1.56	0.200	−1.39	−6.37; 3.59	0.583	−1.97	−6.81; 2.88	0.426	−0.69	−5.99; 4.62	0.799	0.86	−3.38; 5.11	0.689
Other tumor	4.09	−1.14; 9.31	0.125	2.03	−3.75; 7.80	0.491	1.78	−4.02; 7.59	0.546	2.00	−4.18; 8.17	0.525	4.79	−0.14; 9.72	0.057
Treatment[f]															
Chemotherapy	−2.24	−5.79; 1.31	0.216	−2.15	−6.12; 1.81	0.287	−2.22	−6.05; 1.60	0.254	−0.33	−4.54; 3.88	0.878	−1.22	−4.54; 2.11	0.472
Radiotherapy	−0.94	−4.00; 2.11	0.544	1.87	−1.62; 5.37	0.293	−1.07	−4.44; 2.30	0.532	1.31	−2.33; 4.96	0.478	0.36	−2.55; 3.27	0.806
Bone marrow transplantation	−0.20	−5.72; 5.32	0.944	−4.97	−11.26; 1.32	0.121	−0.70	−6.56; 5.16	0.814	4.11	−2.41; 10.62	0.216	−1.44	−6.65; 3.76	0.587
>10 years since diagnosis	−0.12	−2.67; 2.42	0.924	−1.11	−3.92; 1.70	0.437	−1.89	−4.61; 0.83	0.172	−1.01	−4.01; 2.00	0.511	−0.34	−2.72; 2.05	0.781
Relapse	−5.41	−9.17; −1.64	0.005	−3.05	−7.25; 1.15	0.155	0.28	−3.80; 4.37	0.892	1.51	−3.02; 6.03	0.513	−0.49	−4.05; 3.08	0.788

[a] Regression coefficients resulting from multivariable linear regression

[b] 95 % confidence interval

[c] p value

[d] Adolescents are participants aged 13–16 years at survey with the reference category being participants aged 8–12 years

[e] Leukemia is the reference category, the category "other tumor" includes all diagnoses with $n < 20$ (10 germ cell tumors, 11 Langerhans cell histiocytosis, three other rare tumors)

[f] Each survivor could have had more than one treatment, having had surgery only is the reference category

In general, survivors ranked their HRQoL higher than their parents did. This is in accord with other studies of survivors of retinoblastoma [19] or craniopharyngioma [18] and in studies that used the PedsQL 4.0 instrument of survivors in all diagnostic groups [44], but also with studies assessing HRQoL in children or adolescents suffering from chronic diseases such as renal transplant patients [45], children with congenital lower limb deficiencies [36], or children with mental health problems [34]. A qualitative study of 15 healthy children and their parents used the KIDSCREEN instrument to examine the underlying reasons for discrepancies in self- and parent-reported HRQoL [46]. They found that children and parents interpreted the items similarly, but children tended to base their response on a single experience and give more extreme answers. We found something similar in our study, where more survivors than parents provided the highest score for all questions within a HRQoL dimension, raising the ceiling effect in survivors over that in parents (Supplemental Table 1). We recommend to always integrate self- and parent-reported data in HRQoL in order to assess a child's HRQoL comprehensively.

Some socio-demographic factors were associated with HRQoL in our study. Survivors and parents from the French- and Italian-speaking regions of Switzerland reported lower HRQoL for most dimensions than survivors from the German-speaking region. One reason for discrepancies between the language regions might be that norm data was retrieved from children of the German-speaking region in Switzerland and did not include children from the French- or Italian-speaking region [41]. To test this, we would need norm scores for children in the French- and Italian-speaking regions. It is interesting that survivors with migration background had higher parent-reported HRQoL than survivors without migration background for the domains of *autonomy and parents* and *peers and social support*. We know of no other studies that analyze the effect of migration background on HRQoL in young survivors, but in an earlier SCCSS study, which used SF-36 to measure HRQoL, migration background was not associated with higher HRQoL [6]. A study from Germany found that migrants of kindergarten age thought their health was better than their native German peers did [47]. The authors conclude this might result from changing migration patterns in Europe, and an increase in migrants with healthy profiles. Further research will need to illuminate the role of migration background for HRQoL.

Cancer-related factors were associated with some HRQoL outcomes. Survivors of CNS tumors had lower parent- and self-reported HRQoL for the domains of *physical and psychological well-being* and lower parent-reported HRQoL for the dimension of *peers and social support*. Other studies also found that survivors of CNS tumors had reduced HRQoL than healthy controls [17], ALL survivors [16], or siblings [21]. The intense treatment for CNS tumors (radiotherapy, cranial surgery and chemotherapy) may affect *physical* and *psychological well-being*, both diminished in survivors of CNS tumors in our study. Studies on survivors of CNS tumors showed that their overall quality of life was lower than in siblings [21]; and their HRQoL measured by the PedsQL 4.0 was lower for psychosocial, physical, emotional, social and school dimensions than in healthy children [17]. Survivors of CNS tumors frequently suffer from reduced neurocognitive functioning and sometimes have to repeat a year in school [48], which might affect the HRQoL dimension *peers and social support*. We also found that survivors of neuroblastoma had lower parent-reported HRQoL for the dimension of *psychological well-being*. However, those findings warrant to be investigated in an independent study, including large numbers of neuroblastoma survivors. Most probably, the intensive treatment, especially for high-risk neuroblastoma, affects HRQoL. Some researchers found that neuroblastoma survivors with hearing loss had more problems with reading, mathematics and attention in general at school than those who had normal hearing [49]. However, in our study, HRQoL for *school environment* was not significantly diminished in neuroblastoma survivors. Survivors of renal or hepatic tumors had higher parent-reported HRQoL for *autonomy and parents* and *school environment*, which might be explained by the fact that those diagnostic groups undergo less intensive treatment and survivors may be more independent from their parents. Another study found that adult survivors of childhood Wilms' tumor were similar to population norms on most HRQoL measures assessed by SF-36 [14].

Survivors who had experienced a relapse had lower parent- and self-reported HRQoL for *physical well-being*. The extended period of illness and treatment, and the distress caused by the uncertainty of cure, most probably reduces HRQoL. Another study from the SCCSS that used the SF-36 showed that adult survivors of childhood ALL who had had a relapse reported poorer general health than those who had not had a relapse [13].

Implication for practice

Assessing HRQoL in survivors during clinical follow-up, with a special focus to survivors of CNS tumors, neuroblastoma, and those who have had a relapse, might help to identify problems. The follow-up specialist should inform the survivor about specific support. This could be, e.g., psychological support, or in other cases a physiotherapist helping with physical limitations. We found that for each HRQoL dimension at least one-fourth of survivors had a score $\leq$45. According to a recent qualitative study, a

threshold of ≤45 might be clinically relevant, since those survivors feel different compared to peers due to their cancer and might benefit from specific support [40]. Further studies are needed to determine whether the KIDCREEN-27 questionnaire can be used as a screening tool to identify survivors with low HRQoL, whether it can be applied during clinical follow-up, and which thresholds would be suitable to identify survivors at risk for low HRQoL.

Limitations and strengths

Some limitations must be taken into account when interpreting our results. The KIDSCREEN-27 instrument measures HRQoL only in the week previous to the survey. Our results are cross-sectional, and we cannot determine whether or how HRQoL in survivors changes over time. The norm data we used were retrieved from the German-speaking region of Switzerland, but 27 % of our study participants were from the French-speaking region and 4 % from the Italian-speaking region of Switzerland, which might bias our results. We also have to take into account that after using Bonferroni corrections, only survivors with a CNS tumor or a relapse had still a significantly lower HRQoL for physical *well-being* than other survivors. So further research needs to validate whether young survivors of CNS tumors also have a lower HRQoL for the dimensions *autonomy and parents*, and *peers and social support*, and whether HRQoL is really lower in survivors of neuroblastoma.

Our study was strengthened by its large population-based sample of survivors diagnosed recently, according to the latest treatment protocols. By using the KIDSCREEN-27 instrument, we were able to assess five different dimensions of HRQoL in a short questionnaire. We were also able to compare our data to recent national normative data, which made our results comparable to population norms. By analyzing both self- and parent-reported HRQoL, we were able to gather a more complete picture of HRQoL in our study population.

Conclusion

In this study, we could show that overall HRQoL in young survivors is comparable to healthy norms, and even slightly better than norms for self-reported HRQoL. HRQoL was mostly affected by a previous diagnosis of CNS tumor, or by the occurrence of relapse. Assessing self- and parent-reported HRQoL during follow-up care in young survivors could help clinicians identify problems early so that they can provide effective support and prevent HRQoL from declining.

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Conflict of interest The authors declare that they have no conflict of interest.

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