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Original Research

Health-related quality of life in Dutch adult survivors of childhood cancer: A nation-wide cohort study

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Abstract ***Aim:*** To investigate the health-related quality of life (HRQOL) of Dutch adult childhood cancer survivors (CCS) and to identify risk factors of impaired HRQOL.
Methods: Adult CCS (age >18, diagnosed <18, ≥5 years since diagnosis) from the Dutch LATER registry completed the Medical Outcome Study Short Form 36 (SF-36) to measure HRQOL and provided sociodemographic characteristics. Age-adjusted mean SF-36 scale scores of CCS were compared to the Dutch general population for men and women separately using t-tests, with effect size *d*. Multivariate logistic regression models were built to identify

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sociodemographic and cancer-related risk factors for impaired physical and mental HRQOL.
Results: Both male and female CCS (N = 2301, mean age = 35.4 years, 49.6% female) reported significantly ($p \leq .005$) worse HRQOL than the general population on almost all scales of the SF-36 ($-.11 \leq d \leq -.56$). Largest differences were found on vitality and general health perceptions. Significant risk factors ($p \leq .05$) for impaired physical HRQOL were female sex, older age at diagnosis, not having a partner, low educational attainment, disease recurrence and exposure to radiotherapy, specifically to lower extremity radiation. Odds ratios (ORs) ranged from 1.6 to 3.7. Significant risk factors for impaired mental HRQOL were age 26–35 years, male sex, not having a partner and low educational attainment. ORs ranged from 1.3 to 2.0.
Conclusion: Adult CCS had worse HRQOL than the general population. CCS most at risk were those with low educational attainment and without a partner. Adult CCS could benefit from routine surveillance of their HRQOL. Special attention for CCS' vitality and health perceptions and beliefs is warranted.

1. Introduction

With the rising number of childhood cancer survivors (CCS) reaching adulthood because of improved survival, understanding late effects of treatment and their health-related quality of life (HRQOL) has become crucial. In spite of advanced treatments, survival comes at the cost of late effects for many [1,2]. Late effects can influence all areas of adult life [1–3], so understanding late effects requires a multidimensional approach. Engel's biopsychosocial model, which proposes that behaviour and social circumstances can influence physical health and vice versa, provides a suitable framework for this [4]. It is crucial to consider more than the physical component of HRQOL in CCS by paying attention to the mental component of HRQOL and including social factors, such as employment or relationship status.

Many studies previously examined HRQOL of adult CCS with varying instruments, with contradictory results [5]. Focusing on studies using the Medical Outcome Study Short Form 36 (SF-36), some studies report HRQOL of CCS to be comparable to that of general population controls [6–9] while others report mental health, as a component of HRQOL, to be better than that of the general population [6,10,11]. Yet, other studies suggest worse HRQOL in CCS compared to general population or siblings [9,12–17]. In these studies, differences are mostly found in physical HRQOL domains [13,15–18] and less often in mental HRQOL domains [13,17].

The most commonly described cancer-related characteristics related to poor HRQOL are a very young age or in adolescence at diagnosis, longer time since diagnosis and the presence of late effects or another major medical condition [11,14,15,19,20]. Central nervous system (CNS) and bone tumour survivors as well as those who received cranial irradiation are often found to carry the highest risk, especially in physical domains [10,14,15]. Worse HRQOL of CCS is further influenced by sociodemographic factors, such as female sex, having no partner, being unemployed, lower household income and lower educational attainment [11,14,20].

To deliver optimal care for CCS, it is crucial to expand our understanding of HRQOL of CCS in our population. Over the years, several smaller studies were performed in the Netherlands, but a nationwide cohort study has never been conducted.

The main aim of this nationwide cohort study is to compare HRQOL of Dutch adult CCS to that of the general population, using the SF-36. Furthermore, we aimed to identify risk factors for impaired HRQOL to target and tailor survivorship care.

2. Methods

2.1. Design and population

This is a nationwide cohort study on the HRQOL of Dutch CCS. CCS were prospectively recruited from the Dutch LATER registry, which contains information on CCS from seven Dutch pediatric oncology centers (N = 6165, diagnosed between 1963 and 2001 at the age of <18 years and ≥5 years since diagnosis) [21]. Of these CCS, 5480 were alive at the time of sending out the questionnaire. After excluding those who were too young at the time of survey (aged <18 years), lost to follow-up, or ineligible otherwise (N = 39), a total of 4531 Dutch CCS were invited to participate in the study. Between 2016 and 2018, all eligible CCS received an information letter, informed consent form and paper-pencil questionnaire by mail from the hospital that

provided them with survivorship care. A few weeks after the initial invitation, non-responders were sent a reminder.

This study was approved by the Medical Ethical Committee of the Amsterdam University Medical Center/location VUmc (2011.405).

2.2. Measures

HRQOL: The SF-36 is a well-known self-reported questionnaire that assesses HRQOL over the last four weeks, intended for both research and clinical practice [22]. The SF-36 consists of eight scales: 1) limitations in physical activities due to health problems (physical functioning, PF); 2) limitations in social activities due to physical or emotional problems (social functioning, SF); 3) limitations in usual role activities due to physical health problems (role limitation physical, RP; 4) bodily pain (BP); 5) general mental health (MH); 6) limitations in usual role activities due to emotional problems (role limitation emotional, RE); 7) vitality (VIT); and 8) general health perceptions (GH) [22]. Scale scores are transformed to a 0–100 scale. Higher scores indicate better HRQOL. Furthermore, one can calculate an overall physical and mental component score (PCS and MCS, respectively) based on the mean ± standard deviation of 50 ± 10 in the general population [23].

Validity and internal reliability of the Dutch version of the SF-36 were previously shown to be good [24]. In the present study, internal consistency for the eight scales was good to excellent (Cronbach's α = .83-.92). Reference values (mean and standard deviation) from the Dutch general population are available for men and women in various age groups. These reference data were collected by Aaronson et al. in a random nationwide sample of Dutch adults [24].

2.2.1. Cancer-related characteristics

Data on diagnosis according to the third edition of the International Classicication of Chilhood Cancer (ICCC-3) [41] and treatment of the initial cancer and recurrences from medical records were obtained from the Dutch LATER registry: cancer type; age at diagnosis; disease recurrence; treatment with groups of chemotherapy, radiotherapy and/or surgery; treatment with bone marrow or stem cell transplantation (BMT/SCT); locations of radiotherapy exposure.

2.2.2. Sociodemographic characteristics

Data on sex, having a partner (yes/no) and highest completed education (low = primary education, lower vocational education, lower and middle general secondary education; middle = middle vocational education, higher general secondary education, preuniversity education; high = higher vocational education, university) were obtained by questionnaire. Age and place of birth (within or outside of the Netherlands) were derived from the Dutch LATER registry.

2.3. Statistical analyses

Using one-sample t-tests and Chi–Square tests (with Cohen's d and Cremer's V as effect sizes), we compared responders to non-responders to the invitation for the study on available cancer-related and sociodemographic characteristics.

Mean SF-36 scale scores of CCS were compared to those of the Dutch general population [24], for men and women separately weighted by age group. Within sex, age group–specific weight factors were assigned to the scale scores of the general population. The weight factors were based on the distribution (proportion) of age groups in the CCS. A Bonferroni correction was applied for the number of comparisons per sex group (α = .05/10 = .005).

Impaired HRQOL was defined for PCS and MCS as a score below 2 standard deviations from the age and sex appropriate score in the general population. Multivariate logistic regression analysis was used to identify sociodemographic (age, sex, having a partner, educational attainment, born in or outside of the Netherlands) and cancer-related risk factors (age at diagnosis; diagnosis; disease recurrence; treatment with various groups of chemotherapy, radiotherapy and/or surgery; treatment with BMT/SCT and locations of radiotherapy exposure) for impaired PCS or MCS. Characteristics that were significant in univariate analyses at $\alpha \leq .1$ were selected for multivariate logistic regression models predicting PCS and MCS. Because of dependencies between cancer-related characteristics, separate models were constructed for 1) sociodemographic characteristics and diagnosis, 2) sociodemographic characteristics and basic treatment, 3) sociodemographic characteristics and BMT/SCT treatment and 4) sociodemographic characteristics and treatment details. Age and sex were included in every model.

Statistical analyses were performed using IBM SPSS Statistics version 25. All tests were two-sided.

3. Results

3.1. Sample

After receiving questionnaires from 2316 CCS (response rate = 51%), 15 responders were excluded from the analyses (proxy report, Down syndrome, terminally ill, no medical record available). Finally, questionnaires of 2301 CCS (49.6% female, mean age = 35.4 ± 9.6 years, mean time since diagnosis = 28.4 ± 8.7 years) could be used for analyses. Significant but small differences between responders and non-responders were found on several cancer-related characteristics (Table 1).

Table 1
Sample characteristics of CCS (N = 2301).

Characteristics	Responders (N = 2301) Mean ± SD (range)	% (N)	Non-responders (N = 2214)[a] Mean ± SD (range)	% (N)	T/χ^2	ES[b]
Socio-demographic						
Age (years)	35.4 ± 9.6 (18.3–69.0)				[c]	
18–25		19.2 (441)				
26–35		36.1 (830)				
36–45		29.3 (675)				
46–55		13.4 (309)				
55–65		1.8 (41)				
66–75		.2 (5)				
Sex (female)		49.6 (1142)		38.7 (856)	55.0	.11
Partner status						
No partner		34.0 (744)				
Partner		66.0 (1445)				
Educational attainment[d]						
Low		10.6 (232)				
Middle		51.2 (1119)				
High		38.2 (836)				
Born outside of the Netherlands		1.9 (33)			[c]	
Medical characteristics						
Age at diagnosis (years)	7.0 ± 4.8 (0–17.9)		6.6 ± 4.6 (0–17.9)**			.08
0–5		50.5 (1163)				
6–11		28.9 (666)				
12–17		20.5 (472)				
Time since diagnosis (years)	28.4 ± 8.7 (15.3–54.3)				[c]	
5–10		0.0 (0)				
11–15		2.0 (46)				
16–20		23.1 (530)				
20–25		20.1 (461)				
26–30		17.7 (407)				
31–35		14.7 (338)				
35–55		22.3 (512)				
Recurrence (yes)		13.3 (305)				
Diagnosis						
Leukaemias		35.1 (808)		34.0 (752)	.6	.01
Lymphomas		17.6 (404)		19.2 (425)	2.1	.02
CNS tumours		11.4 (262)		12.9 (285)	2.4	.02
Neuroblastoma		5.3 (122)		5.0 (110)	.2	.01
Retinoblastoma		.4 (10)		.7 (16)	1.7	.02
Renal tumours		10.6 (243)		10.5 (232)	≤.1	≤.01
Hepatic tumours		.7 (16)		.9 (20)	.6	.01
Bone tumours		6.0 (139)		4.7 (104)	3.9	.03
Soft tissue sarcomas		7.6 (174)		6.6 (145)	1.7	.02
Germ cell tumours		3.9 (89)		3.7 (82)	.1	≤.01
Epithelial neoplasms and melanomas		1.3 (31)		1.7 (37)	.8	.01
Other malignant neoplasms		.1 (3)		.0 (1)	.9	.01
Treatment for primary and recurrences						
Surgery (S) only		8.4 (193)		12.9 (284)	23.8***	.07
Radiotherapy (RT) only		.4 (10)		.3 (7)	.4	.01
Chemotherapy (CT) only		20.9 (481)		23.2 (512)	3.4	.03
S + RT		6.7 (155)		6.1 (134)	.8	.01
S + CT		31.2 (717)		31.0 (685)	.01	≤.01
RT + CT		12.1 (278)		9.9 (219)	5.4*	.04
S + RT + CT		20.1 (463)		15.8 (348)	14.6***	.06
No S, RT, or CT		.2 (4)		.9 (20)	11.4**	.05
BMT/SCT		5.7 (132)		5.3 (118)	.3	.01
Radiotherapy regions						
Cranio-spinal		21.0 (481)		17.6 (388)	8.1**	.04
TBI		3.4 (78)		2.9 (65)	.7	.01
Thorax		6.3 (144)		4.9 (107)	4.3*	.03
Abdominal pelvic area		7.8 (180)		6.3 (139)	4.0*	.03
Testes		.3 (8)		.4 (9)	.1	.01
Neck		3.8 (87)		3.3 (72)	.9	.01
Upper extremities		.7 (16)		.8 (17)	.1	≤.01

(continued on next page)

Table 1 (*continued*)

Characteristics	Responders (N = 2301) Mean ± SD (range)	% (N)	Non-responders (N = 2214)[a] Mean ± SD (range)	% (N)	T/χ^2	ES[b]
Lower extremities		1.3 (31)		1.0 (22)	1.2	.02
Unknown location		.3 (8)		.2 (4)	1.2	.02
Radioisotopes		.8 (19)		.6 (13)	.9	.01
Chemotherapy medications						
Alkylating agents		52.9 (1218)		47.6 (1051)	13.1***	.05
Anthracyclines		45.9 (1057)		43.9 (970)	1.9	.02
Epipodophyllotoxin		19.1 (439)		19.2 (423)	≤.1	≤.01
Vinca alkaloids		75.1 (1728)		71.6 (1581)	7.2**	.04
Platinum compounds		11.6 (266)		11.6 (257)	≤.1	≤.01
Antimetabolites		48.1 (1106)		47.1 (1040)	.4	.01
Asparginase		30.7 (706)		31.2 (688)	.1	≤.01

SD, standard deviation; ES, effect size; TBI, total body irradiation; CNS, central nervous system; BMT, bone marrow transplantation; SCT, stem cell transplantation,

*Significant at $\alpha = .05$.

**Significant at $\alpha = .01$.

***Significant at $\alpha = .001$.

[a] Non-responders: those who were invited to participate but did not return a questionnaire (N = 2214). N slightly varies across variables.

[b] Cohen's d (.2 = small effect, .5 = medium effect, .8 = large effect) used for continuous variables, Cremers V (≤.1 = little if any association, .1 = low association, .3 = medium association, .5 = high association) used for proportions.

[c] Data were available for too few non-responders to allow a comparison.

[d] Low = primary education, lower vocational education, lower and middle general secondary education; middle = middle vocational education, higher general secondary education, pre-university education; high = higher vocational education, university.

3.2. HRQOL of CCS versus the general population

Male CCS scored significantly worse than the male general population on all scales, including PCS and MCS ($-.14 \leq d \leq -.46$), except for RP (Fig. 1A). Female CCS scored significantly lower than the female general population on all scales, including PCS and MCS ($-.11 \leq d \leq -.56$), except on BP, RE and MH. Largest differences ($d \geq .45$) were found for VIT and GH (Fig. 1B).

3.3. Association of sociodemographic and cancer-related characteristics with impaired HRQOL

On PCS and MCS, respectively, 10.2% (N = 231) and 9.5% (N = 216) of CCS scored 2 standard deviations below the general population. For the results of the preselection, see Table 2.

In all four multivariate models predicting impaired PCS (Table 3), female CCS (odds ratio [OR] = 1.8, $p \leq .001$) and those diagnosed at an older age compared to 0–5 years (6–11: $1.8 \leq OR \leq 1.9$, $p \leq .001$; 12–17: $1.6 \leq OR \leq 1.7$, $.014 \leq p \leq .028$) were at a significantly higher risk of impaired PCS. Furthermore, CCS with a partner (OR = .6, $.001 \leq p \leq .003$) and those with a middle or high educational attainment compared to low educational attainment (OR = .5, $.001 \leq p \leq .002$ and OR = .3, $p \leq .001$, respectively) were significantly less likely to report impaired PCS.

In one of the models, CCS aged 26–35 years were at a higher risk, while in two models, CCS aged 46–55 years were at a lower risk of impaired PCS than CCS aged 18–25 years (26–35: OR = 1.6, $p = .042$; 46–55: $.4 \leq OR \leq .6$, $.008 \leq p \leq .039$).

In two models, disease recurrence predicted a higher risk of impaired PCS (OR = 1.6, $.012 \leq p \leq .020$).

Regarding treatment, those exposed to radiotherapy (OR = 1.8, $p \leq .001$), specifically to the lower extremities (OR = 3.5, $p = .010$), were at a significantly higher risk to experience impaired PCS.

For impaired MCS, only two multivariate models were built (Table 4), as neither BMT/SCT nor basic treatment characteristics were significant in the preselection. In both models, women (OR = .7, $.029 \leq p \leq .037$), those with a partner (OR = .6, $p = .005$) and those with a high educational attainment compared with low educational attainment (OR = .5, $p = .004$) were at lower risk of impaired MCS. The age group 26–35 years was at a higher risk of impaired MCS than those aged 18–25 years, in the second model (OR = 1.5, $p = .040$).

4. Discussion

In this first Dutch nationwide HRQOL cohort study including CCS of the LATER cohort (diagnosed between 1963 and 2001), both male and female CCS were found to experience worse HRQOL than the general population on almost all domains. Effect sizes ranged from small to moderate. This finding is in line with the majority of existing research with the SF-36 in CCS [9,12–17]. However, other previous studies with the SF-36 have found HRQOL of CCS to be comparable to that of the general population [6–9]. These conflicting results can be explained by differences in the survivor groups that were included, such as differences in

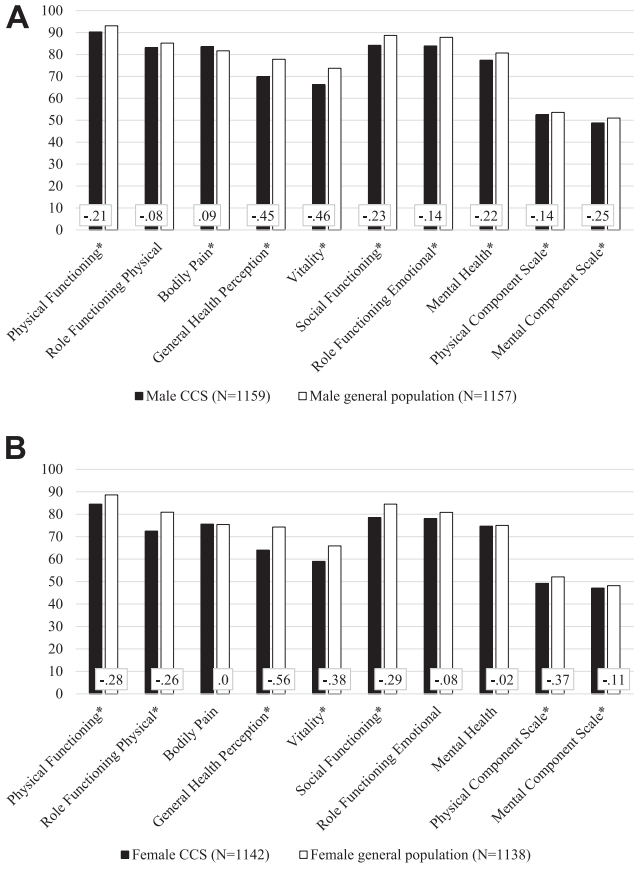

Fig. 1. A. Health-related quality of life (HRQOL) of male childhood cancer survivors (CCS) versus male general population, including effect sizes (Cohen's d). *Significant at $\alpha = .005$ (.5/10). B. HRQOL of female CCS versus female general population, including effect sizes (Cohen's d). *Significant at $\alpha = .005$ (0.5/10).

diagnosis or follow-up time, as well as the use of different reference groups (siblings, healthy peers, or the general population).

Three domains stood out when comparing CCS to the general population: vitality, general health perceptions and pain. Vitality and general health perceptions showed the largest differences to the general population, indicating that these are the areas that are most problematic for CCS. Problems with vitality, or rather, fatigue, are commonly reported in CCS, and an international guideline was recently published [25], stressing the need to address fatigue in survivorship care. CCS did not report more pain than the general population. While pain in CCS is understudied [26], based on some previous literature, we expected pain to be a problem among CCS [27].

CCS with impaired HRQOL are at risk for experiencing functional limitations in daily life, due to problems with their physical or mental health. In line with previous literature on HRQOL of CCS, low educational attainment and not having a partner were identified as sociodemographic risk factors for impaired physical and mental HRQOL [11,14,20]. We recognise that educational attainment is widely assumed to be a risk factor of worse or impaired HRQOL in the general population, but evidence on this topic is lacking in the literature. Similar to our study, the cancer-related risk factors for impaired physical HRQOL, older age at diagnosis [11] and disease recurrence [7], were also identified in previous studies with the SF-36 components as risk factors.

We did not find bone tumours to be a risk factor for impaired HRQOL, while some earlier studies did [10,14,15]. However, we found a strong impact of radiation on the lower extremities. It could be that the effect of the treatment is stronger than the effect of the diagnosis on its own. Similarly, CNS-tumour diagnosis, a common risk factor in previous studies [9,10,15,28], was not associated with impaired HRQOL in our multivariate models. However, we did find a significant association in the univariate analysis. In the multivariate models, this effect was partially explained by lower educational attainment and not having a partner (results not shown) as has been demonstrated before [29,30].

The results indicated that CCS between 26 and 35 might be at a higher risk for impaired mental and physical HRQOL than the CCS aged 18–25 years. Those aged between 18 and 25 years, in turn, seemed to have a higher risk than older adults for impaired physical HRQOL, identifying young adult CCS as a potentially vulnerable group [31].

Regarding female and male sex as risk factors for impaired physical and mental HRQOL, respectively, it is important to note that the definition of impaired physical HRQOL in this study was based on general population norm values adjusted for sex and age [24]. Therefore, it seems that childhood cancer survivorship puts women at an additional risk, besides the higher risk for women that has been demonstrated in the general population [24,32]. The larger risk of impaired mental HRQOL for male CCS than for female CCS contrasts what is often found in the general population and in previous CCS studies [6,11,14,20,24,32]. Differences in impact of childhood cancer between the sexes should be explored in future research [33].

4.1. Strengths and limitations

This study made use of detailed and reliable diagnosis and treatment data of CCS diagnosed before 2002 from the Dutch LATER registry. The large number of participating CCS resulted in high power for the analyses. The few significant differences between responders and non-responders were so small that the sample can be considered representative of Dutch adult CCS. Even with a large sample, some subgroups were small causing low power to detect specific risk factors. For example, a diagnosis of retinoblastoma showed a high OR which indicated that survivors of rare tumours (such as retinoblastoma) or rarely used therapies (such as

Table 2
Preselection: univariate logistic regression analysis explaining impaired HRQOL by each sociodemographic and medical characteristic separately (N = 2271).

Characteristics	Impaired PCS		Impaired MCS	
	OR	90% CI	OR	90% CI
Sociodemographic				
Age (years, ref = 18–25)				
26-35	1.4*	1.0; 2.0	1.1	n.s.
36-45	1.0	n.s.	.7	n.s.
46-55	0.7	n.s.	.9	n.s.
55-75	1.0	n.s.	.7	n.s.
Sex (ref = male)	1.5***	1.2; 1.9	.6***	.4;1.0
Partner	.6***	.4 .7	.6***	.4 .7
Education (ref = low)[a]				
Middle	.5***	.4; .7	–	n.s.
High	.3***	.2; .5	.4***	.7; 1.5
Born outside of the Netherlands	–	n.s.	–	n.s.
Medical characteristics				
Age at diagnosis (years)	1.0*	1.0; 1.0	–	n.s.
Time since diagnosis (years)	1.0**	1.0; 1.0	–	n.s.
Recurrence (yes)	1.7***	1.3; 2.3	–	n.s.
Diagnosis				
Leukaemia	–	n.s.	–	n.s.
Lymphoma	.6**	.4; .9	–	n.s.
CNS-tumour	1.8***	1.3; 2.5	–	n.s.
Neuroblastoma	–	n.s.	–	n.s.
Retinoblastoma	–	n.s.	4.1**	1.3; 12.9
Renal tumour	.5**	.3; .8	.7*	.5;.8
Hepatic tumour	–	n.s.	–	n.s.
Bone tumour	–	n.s.	–	n.s.
Soft-tissue sarcoma	–	n.s.	–	n.s.
Germ cell tumour	–	n.s.	–	n.s.
Other tumour	–	n.s.	–	n.s.
Unspecified tumour	–	n.s.	–	n.s.
Treatment				
Surgery	–	n.s.	–	n.s.
Radiotherapy	1.8***	1.4; 2.2	–	n.s.
Cranio-spinal	1.6***	1.2; 2.0	–	n.s.
TBI	2.0**	1.2; 3.3	–	n.s.
Thorax	–	n.s.	–	n.s.
Pelvic area	–	n.s.	–	n.s.
Testes	–	n.s.	–	n.s.
Neck	–	n.s.	–	n.s.
Upper extremities	–	n.s.	–	n.s.
Lower extremities	2.7**	1.3; 5.6	–	n.s.
Radioisotopes	2.4*	.9; 6.0	–	n.s.
Chemotherapy	.8*	.6; 1.0	–	n.s.
Alkylating agents	–	n.s.	–	n.s.
Anthracyclines	–	n.s.	–	n.s.
Epipodophyllotoxin	–	n.s.	–	n.s.
Vinca alkaloids	.7**	.6; .9	–	n.s.
Platinum compounds	1.7***	1.3; 2.3	1.4*	1.0; 2.0
Antimetabolites	–	n.s.	–	n.s.
Asperginase	.8	.6; 1.0	–	n.s.
BMT/SCT	1.8**	1.1; 2.6	–	n.s.

HRQOL, health-related quality of life; PCS, physical component score; MCS, mental component score; OR, odds ratio; CI, confidence interval; n.s., not significant; CNS, central nervous system; BMT, bone marrow transplantation; SCT, stem cell transplantation; TBI, total body irradiation. *Significant at $\alpha = .10$, **Significant at $\alpha = .05$, ***Significant at $\alpha = .01$.

[a] Low = primary education, lower vocational education, lower and middle general secondary education; middle = middle vocational education, higher general secondary education, pre-university education; high = higher vocational education, university.

Table 3
Multivariate logistic regression analyses explaining impaired physical HRQOL (PCS) by sociodemographic and medical characteristics (N = 2154)[a].

Characteristics	Impaired PCS—diagnosis		Impaired PCS—basic treatment		Impaired PCS—BMT/SCT		Impaired PCS—specific treatment	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sociodemographic								
Age (years, ref = 18–25)								
26–35	1.5	1.0; 2.4	1.4	.9; 2.2	1.6*	1.0; 2.4	1.5	1.0; 2.3
36–45	.9	.6; 1.5	.8	.5; 1.2	.9	.6; 1.5	.9	.5; 1.4
46–55	.6	.3; 1.1	.4**	.2; .8	.6	.3; 1.1	.5*	.3; 1.0
55–75	.6	.2; 2.1	.5	.1; 1.6	.7	.2; 2.3	.5	.1; 1.7
Sex (ref = male)	1.8***	1.3; 2.4	1.8***	1.4; 2.5	1.8***	1.4; 2.5	1.8***	1.4; 2.5
Partner[b]	.6**	.4; .8	.6**	.5; .8	.6***	.4; .8	.6**	.5; .8
Education (ref = low)[c]								
Middle	.5**	.3; .8	.5**	.3; .8	.5**	.3; .7	.5**	.3; .8
High	.3***	.2; .5	.3***	.2; .5	.3***	.2; .5	.3***	.2; .5
Medical								
Age at diagnosis (years, ref = 0–5)								
6–11	1.9***	1.3; 2.6	1.8**	1.3; 2.6	1.9***	1.3; 2.7	1.8**	1.3; 2.5
12–17	1.7*	1.1; 2.6	1.7*	1.1; 2.5	1.7*	1.1; 2.5	1.6*	1.1; 2.4
Recurrence (yes)	1.6*	1.1; 2.3	1.3	.9; 2.0	1.6*	1.1; 2.3	1.4	.9; 2.0
Diagnosis								
Lymphoma[b]	.7	.5; 1.1						
CNS-tumour[b]	1.1	.7; 1.6						
Renal tumour[a]	.7	.4; 1.2						
Basic treatment								
Radiotherapy[b]			1.8***	1.3; 2.4				
Chemotherapy[b]			.9	.6; 1.3				
BMT/SCT[b]					1.3	.8; 2.3		
Specific treatment								
Radiotherapy								
Cranio-spinal[b]							1.4	1.0; 2.0
TBI[b]							1.9	1.0; 3.6
Lower extremities[b]							3.5**	1.3; 9.1
Radioisotopes[b]							1.5	.4; 5.5
Chemotherapy[b]								
Vinca alkaloids[b]							.9	.6; 1.2
Platinum compounds[b]							1.2	.8; 1.8
Asperginase[a]							.9	.6; 1.3

HRQOL, health-related quality of life; PCS, physical component score; OR, odds ratio; CI, confidence interval; n.s., not significant; BMT, bone marrow transplantation; SCT, stem cell transplantation; CNS, central nervous system; TBI, total body irradiation.
*Significant at $\alpha = .05$, **significant at $\alpha = .01$, ***significant at $\alpha = .001$.
[a] Separate models for diagnosis, basic treatment, BMT/SCT and specific treatment are shown.
[b] ref = no.
[c] Low = primary education, lower vocational education, lower and middle general secondary education; middle = middle vocational education, higher general secondary education, pre-university education; high = higher vocational education, university.

radiotherapy on testes) could be at risk for impaired HRQOL, but we were unable to demonstrate this statistically.

Both mental and physical HRQOL were investigated, and this study incorporated sociodemographic and cancer-related characteristics, in accordance with the biopsychosocial model described by Engel (4). Because of biopsychosocial interconnectedness, sociodemographic factors that were identified as risk factors, such as low educational attainment and not having a partner, are also known consequences of a childhood cancer history [29,30,34]. While this makes it difficult to distinguish cause and effect, these factors were included, as they may help clinicians identify CCS who could be at risk for impaired HRQOL. Previous research has additionally shown the importance of unemployment as a risk factor for worse HRQOL in CCS [11,14], but we were unable to replicate this because information about employment was not available. Similarly, we could not include disease burden of physical late effects [12,19] and psychological factors such as coping [35,36], self-esteem [37], or perceived impact of cancer [38] that have been shown to be associated with HRQOL.

Finally, CCS in the study were diagnosed before 2002. While the frequency and intensity in which certain treatments are used may have changed to improve

Table 4
Multivariate logistic regression analysis explaining impaired mental HRQOL (MCS) by sociodemographic and medical characteristics (N = 2154)[a].

Characteristics	Impaired MCS—diagnosis		Impaired MCS—specific treatment	
	OR	95% CI	OR	95% CI
Sociodemographic				
Age (years, ref = 18–25)				
26–35	1.5	1.0; 2.3	1.5*	1.0; 2.3
36–45	1.0	.6; 1.6	1.1	.7; 1.7
46–55	1.1	.6; 1.8	1.1	.7; 1.9
55–75	1.0	.3; 3.4	1.1	.3; 3.7
Sex (ref = male)	.8*	.5; 1.0	.7*	.5; 1.0
Partner[b]	.6*	.5 .9	.6**	.5 .9
Education (ref = low)[c]				
Middle	1.1	.7; 1.8	1.1	.7; 1.8
High	.5**	.3; .8	.5**	.3; .8
Medical				
Diagnosis				
Retinoblastoma[b]	3.4	.7; 17.5		
Renal tumour	.7	.4; 1.3		
Specific treatment				
Chemotherapy[b]				
Platinum compounds[b]			1.2	.8; 1.9

HRQOL, health-related quality of life; PCS, physical component score; OR, odds ratio; CI, confidence interval.
*Significant at $\alpha = .05$, **significant at $\alpha = .01$, ***significant at $\alpha = .001$.
[a] Separate models for diagnosis and specific treatment are shown.
[b] ref = no.
[c] Low = primary education, lower vocational education, lower and middle general secondary education; middle = middle vocational education, higher general secondary education, pre-university education; high = higher vocational education, university.

survival and reduce late effects since then, we can assume that currently identified risk factors are also relevant for children treated with cancer in more recent time periods.

4.2. Clinical implications

The results of this study stress the importance of surveilling HRQOL in CCS during survivorship care, especially for those with one or multiple risk factors for impairment, in line with the current standard of care in survivorship care [39]. As both men and women had the biggest impairments in vitality and general health perceptions compared with the general population, this should be addressed in survivorship care. It is crucial to note that identified risk factors were both sociodemographic and cancer-related in nature, and that for impaired mental HRQOL, no cancer-related risk factors were identified. Therefore, the decision to surveil CCS for impaired HRQOL should include consideration of sociodemographic factors. To implement surveillance of HRQOL and other psychosocial outcomes during survivorship care, digital tools for patient-reported outcomes, such as the Dutch KLIK-PROM system [40], can be used. Furthermore, survivorship care units should employ psychologists and/or adequately refer to psychologists, preferably psychologists with background knowledge about (pediatric) oncology. Finally, talking about HRQOL and psychosocial well-being should be an integral part of the training of all health-care providers in survivorship care. In all efforts, special attention for vitality is necessary.

5. Conclusion

Dutch CCS report lower HRQOL than the general population. Risk factors for impaired HRQOL were both sociodemographic and medical in nature. CCS most at risk were those with low educational attainment and without a partner. Systematic attention for HRQOL is necessary during survivorship care and should include special consideration of vitality and general health perceptions, especially for CCS who display one or more risk factors for impairment.

Authors' contributions

Loes van Erp carried out the investigation and wrote the article. Loes van Erp and Heleen Maurice-Stam contributed to formal analysis, validation and framing study methodology. Loes van Erp and Anne-Lotte van der Kooi contributed to data curation and project administration. Heleen Maurice-Stam, Martha Grootenhuis and Eline van Dulmen-den Broeder contributed to conceptualization and supervision. Leontien Kremer, Marloes van Gorp, Martha Grootenhuis, Eline van Dulmen-den Broeder and Margriet van der Heiden-van der Loo also contributed to framing the study methodology. Wim Tissing, Heleen van der Pal, Andrica de Vries, Marry van den Heuvel-Eibrink, Birgitta Versluys, Jaqcueline Loonen, Dorine Bresters, Marlous Louwerens, Marleen van den Berg, Cécile Ronckers, Leontien Kremer and Margriet van der Heiden-van der Loo contributed identifying and obtaining resources. Marloes van Gorp also contributed to supervision. Eline van Dulmen-den Broeder contributed to funding acquisition. All the authors contributed to reviewing and editing the article.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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