Original Article

Increased health-related quality of life impairments of male and female survivors of childhood cancer: DCCSS LATER 2 psycho-oncology study

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BACKGROUND: The objective of this study was to compare the health-related quality of life (HRQOL) of Dutch adult male and female childhood cancer survivors (CCSs) to general population references and to study medical determinants. **METHODS:** CCSs from the Dutch Childhood Cancer Survivor Study LATER cohort (1963-2001) part 2, who were 18 years old or older (time since diagnosis ≥ 5 years), were invited to complete the TNO-AZL Questionnaire for Adult Health-Related Quality of Life. Domain scores and proportions of CCSs with impaired HRQOL (score < 25th percentile of the reference scores) were compared with references via Mann-Whitney *U* tests and logistic regression analyses corrected for age and sex ($P < .004$). Interactions of group with sex were included if they were significant ($P < .05$). Moreover, medical determinants were analyzed with multivariable logistic regression analyses. **RESULTS:** HRQOL scores for 1766 CCSs (mean age, 35.9 years [standard deviation, 9.4 years]; male, 51%; response rate, 71%) differed from references on most domains with small effect sizes. Both male and female CCSs were more often impaired in gross and fine motor functioning, cognitive functioning, sleep, and vitality with odds ratios (ORs) > 1.4. In addition, female CCSs were more often impaired in daily activities, pain, and sexuality (ORs, 1.4-1.9) and were less often aggressive (OR, 0.6). CCCs of central nervous system (CNS) tumors, bone tumors, and retinoblastoma and those with cranial, abdominopelvic, or lower extremity radiotherapy were at increased risk of impairment in 1 or more domains. **CONCLUSIONS:** Dutch adult CCSs, especially females, have impaired HRQOL in several domains; this is most pronounced in cognitive functioning. The vulnerabilities of subgroups at risk, such as CCSs of CNS tumors, were confirmed. Surveillance of HRQOL and multidisciplinary survivor care is recommended. ***Cancer* 2022;128:1074-1084**.

LAY SUMMARY:

- The health-related quality of life in a Dutch nationwide cohort of 1766 survivors of childhood cancer was studied.
- Survivors of childhood cancer were found to have lower health-related quality of life in several domains (eg, motor functioning and vitality) in comparison with the general population.
- They most often reported low cognitive functioning (eg, memory and attention).
- Females had low health-related quality of life in more domains than males.
- Survivors of brain tumors had low health-related quality of life in most domains.
- Monitoring health-related quality of life regularly and collaborating between disciplines in survivor care is recommended.

KEYWORDS: childhood cancer survivors, cognitive functioning, cohort study, health-related quality of life, population at risk.

INTRODUCTION

With improved survival for patients with childhood cancer, the number of childhood cancer survivors (CCSs) has increased. Long-term CCSs often experience long-term health problems[1] and sometimes impaired psychosocial well-being.[2] Optimal health-related quality of life (HRQOL) is considered a main treatment outcome in pediatric oncology in addition to survival.[3] Individuals' subjective experience of their health problems and limitations in functioning represents an important aspect of HRQOL. Although most self-reported HRQOL measurements inherently rely on subjective

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experiences, previous population-based studies have used HRQOL instruments that lack specific questioning of this aspect or that describe the health status of CCSs instead.[4-7] Comprehensive insight into the HRQOL of CCSs is thus lacking in the current literature, and this is relevant to study to determine the long-term impact of childhood cancer.

A HRQOL instrument including the perceived impact of health problems, rather than the impairments in functioning itself, has not been used in a large cohort of CCSs. As for health status and other HRQOL instruments, previous cohort studies have found small differences between CCS and reference groups, both positive and negative. As for domains of HRQOL, physical functioning has most frequently been found to be impaired in CCSs.[4,5] As for subgroups at risk, CCSs of central nervous system (CNS) or bone tumors and those who have received radiotherapy have been found to report poorer health according to large cohort studies.[4-7]

Female sex has often been identified as a risk factor for lower health status in CCSs,[8] and some studies have found larger effect sizes for impaired health status in women compared with men.[9,10] However, studies have generally drawn conclusions on overall group differences from reference samples rather than by sex, and some authors have argued that the established sex differences in CCSs are comparable to sex differences found in the general population.[9,10] We recently found female CCSs to be at additional risk for impaired physical HRQOL in comparison with male CCSs in excess of the higher risk for women versus men in the general population.[6] Also, Armstrong et al[11] found that physical and cognitive health may be affected more in female CCSs than male CCSs. Therefore, it is interesting to investigate sex differences in the impact of childhood cancer on long-term HRQOL.

In this study, we aimed to compare the HRQOL of Dutch male and female CCSs and a reference group from the general population. Also, we aimed to study medical predictors of impaired HRQOL in Dutch CCSs.

MATERIALS AND METHODS

Study Design

This report is part of the psycho-oncology study of the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort part 2; clinical visit and questionnaire study. The DCCSS LATER 2 study is a cross-sectional study executed in the LATER cohort; it originally included 6165 survivors who were diagnosed between 1963 and 2001 in the 7 pediatric oncology centers in the Netherlands at that time (Amsterdam University Medical Center [VU Medical Center and Academic Medical Center], Leiden University Medical Center, Erasmus Medical Center Rotterdam, University Medical Center Groningen, Radboudumc Nijmegen, and University Medical Center Utrecht).The DCCSS LATER 2 study protocol was approved by all medical ethics boards of all participating centers. Details of the methodology of the DCCSS LATER 1 and 2 studies were described elsewhere (C. Teepen, J. L. Kok, E. A. M. Feijen, et al, unpublished data and E. A. M. Feijen, J. C. Teepen, and J. J. Loonen, et al, unpublished data, October 29, 2021).

Participants

For the current study, adult CCSs (18 years old or older at the time of the invitation) were eligible. Thus, 4643 adult CCSs were invited for DCCSS LATER 2 and were eligible for this study. CCSs who gave informed consent for the psycho-oncology study received an HRQOL questionnaire between February 2016 and March 2020 at the end of their visit to the outpatient clinic for the DCCSS LATER 2 study or by mail.

Measures

TNO-AZL Questionnaire for Adult Health-Related Quality of Life

HRQOL was assessed with the TNO-AZL Questionnaire for Adult Health-Related Quality of Life (TAAQOL), which was developed by TNO and Leiden University Medical Center (AZL).[12] The 45 items of the TAAQOL measure health status problems weighted by their impact on well-being in 12 multi-item domains: gross motor functioning, fine motor functioning, cognitive functioning, sleep, pain, social functioning, daily activities, sexuality, vitality, positive emotions, depressive emotions, and aggressive emotions. Items consist of 2 parts: the first part assesses the prevalence of a health problem or limitation in the past month, and the second part assesses the emotional response to the health problem or limitation if present. An example of an item in the pain domain is as follows: "In the last month, how often did you have a backache?" (part 1) and "How much did that bother you?" (part 2). Both parts are answered on a 4-point Likert scale. A single score (0-4) is attributed to each combination: a score of 4 is given when there is no limitation (indicated on part 1 of the item), a score of 3 is given when there is a limitation (ie, a little, some, or a lot) but the person is not bothered by the limitation (indicated on part 2 of the item), a score of 2 is given when there is a limitation and the person is a "a little" bothered, a score of 1 is given when there is a limitation and the person is "quite a lot" bothered, and a score of 0 is given when there is a limitation and the person

is "very much" bothered. Domain sum scores are calculated and linearly transformed to a 0 to 100 scale. Higher scores indicate better HRQOL. The domains vitality, positive emotions, depressive emotions, and aggressiveness assess the occurrence of these feelings only in the past month. The conceptual, convergent, and criterion validity and reliability of the TAAQOL are satisfactory.[12] The TAAQOL has been validated in people with chronic illness, including patients with cancer, and it has previously been used to measure HRQOL in youth with pediatric bone tumors.[12,13] The internal consistency of the domain scores in the current study was acceptable to good (Cronbach α range, 0.74-0.92). Dutch general population reference data that were collected by the TAAQOL authors in 2004 from a random selection from the national telephone registry are available.[12] To obtain a reference sample with a mean age similar to that of the CCSs, reference data from adults aged 18 to 50 years were selected (n = 2476; female, 42%; mean age, 35.4 years [standard deviation, 8.1 years]).

Determinants

Demographics (age at invitation [called "age"] and sex) and medical characteristics were obtained from the DCCSS LATER registry. The included medical characteristics described the diagnosis (International Classification for Childhood Cancer, third edition) and treatment of the initial cancer and recurrences: age at diagnosis, diagnosis, disease recurrence, surgery, radiotherapy, chemotherapy, and hematopoietic cell transplantation. Because radiotherapy has previously been found to be a risk factor for HRQOL,[4,5] we studied radiotherapy in more detail by including several regions of exposure that were assigned as described previously (see yes/no variables in Table 1; survivors could have multiple regions of exposure).[14]

Statistical Analyses

Demographic and medical characteristics of participants and nonparticipants were described. Differences between participants and nonparticipants were tested with χ^2 tests and Cramer's V. Means, standard deviations, medians, and interquartile ranges of TAAQOL scores were computed for male and female CCSs. Sex-stratified TAAQOL scores were compared with the reference group via Mann-Whitney *U* tests with effect size *r*. Logistic regression analyses, corrected for sex and age, were used to determine differences between CCSs and references in proportions of impaired HRQOL in each domain. Scores below the 25th percentile of the reference group were considered impaired HRQOL in accordance with Rose et al.[15] Interaction terms of group (CCSs vs references) with sex were tested and included in the final models if significant. Where applicable, odds ratios (ORs) of impaired HRQOL for male and female CCSs were obtained from 2 separate models. Effect sizes V and *r* of up to .2 were considered small, effect sizes of .2 to .5 were considered small to medium, effect sizes of .5 to .8 were considered medium to large, and effect sizes of >.8 were considered large.[16] ORs of 1.40/0.71, 2.27/0.44, and 3.66/0.27 were considered equivalent to effect sizes of .2, .5, and .8, and they accounted for 25% of individuals with impairment in the reference group (Henian Chen, personal written communication, July 16, 2020).[17]

Medical determinants of impaired HRQOL in CCSs were studied with multivariable logistic regression analyses for each domain. Medical characteristics that showed a univariate association with HRQOL for a specific domain with a *P* value ≤ .1 were selected for multivariable modeling of that domain of HRQOL. Because of dependencies between medical characteristics, hematopoietic cell transplantation was not included in the multivariable models, and 2 separate models were created for each domain: one including diagnosis characteristics and another including treatment characteristics. Multivariable models were adjusted for sex and age.

P values ≤ .05 were considered statistically significant except for comparisons between CCSs and the reference group, where a Bonferroni correction was applied to the level of significance for the 12 domains (.05/12 = .004).

RESULTS

Of the eligible participants, 54% (n = 2485) participated in DCCSS LATER 2. The TAAQOL was completed and returned by 1766 of these CCSs (71% response rate). Figure 1 shows a flowchart of the participants. CCSs had a mean age of 35.9 years (standard deviation, 9.4 years; range, 18-71 years), and 51% were male. The primary tumor had recurred in 14% of the CCSs. Table 1 describes the demographic and medical characteristics of participants and nonparticipants and the results of comparisons between participants and nonparticipants. Significant differences were below V = .1 except for radiotherapy; 40% of participants and 34% of nonparticipants had received radiotherapy (V = .10; *P* < .001).

Table 2 describes the TAAQOL domains for male CCSs and female CCSs and the results of analyses comparing them with the reference group. Although many of the domain scores of CCSs differed statistically significantly from those of the reference population, the effects were small. The only small to medium differences were

TABLE 1. Demographic and Medical Characteristics of Participants and Nonparticipants

Characteristics	Participants (n = 1766), %	Nonparticipants (n = 2877), %[a]	Cramer's V of Difference Between Participants and Nonparticipants[b]
Demographics			
Age at invitation[b]			.02
<18 y	0	0	
18-30 y	33	34	
30-40 y	38	39	
40 y and over	30	28	
Sex			.09[c]
Male	51	59	
Female	49	41	
Transgender	0	0	
Medical characteristics			
Age at diagnosis			.03
0-5 y	45	46	
5-10 y	27	27	
10-15 y	22	20	
15-18 y	6	6	
Follow-up time since childhood cancer diagnosis			.05
5-10 y	0	0	
10-20 y	20	19	
20-30 y	40	41	
30-40 y	30	29	
40-50 y	10	10	
50-60 y	1	1	
Primary childhood cancer diagnosis (ICCC)			
Leukemias, myeloproliferative diseases, and myelodysplastic diseases	34	34	.01
Lymphomas and reticuloendothelial neoplasms	19	18	.002
CNS and miscellaneous intracranial and intraspinal neoplasms	9	13	.04[e]
Neuroblastoma and other peripheral nervous cell tumors	6	4	.02
Retinoblastoma	1	1	.01
Renal tumors	11	10	.01
Hepatic tumors	1	1	.01
Bone tumors	6	5	.02
Soft tissue and other extraosseous sarcomas	7	7	.01
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	3	4	.02
Other and unspecified malignant neoplasms	2	2	.01
Treatment period			.05[e]
1963-1969	2	1	
1970-1979	14	13	
1980-1989	32	31	
1990-1999	43	45	
2000-2001	10	10	
Surgery[f]	50	51	.03
Radiotherapy[f]	40	34	.10[c]
Radiotherapy region[b,f,g]			
Head cranium	19	16	.03[e]
Spinal	5	4	.02
TBI	4	2	.05[c]
Thorax	7	5	.04[e]
Abdominopelvic area	9	7	03[e]
Testes	1	<1	.01
Neck	4	3	.03
Upper extremities	1	1	.004
Lower extremities	1	1	.01
Radioisotopes	1	1	.03
Chemotherapy[f]	88	80	.09[c]
Hematopoietic cell transplantation[f]			.06[d]
No	93	95	
Autologous transplant	3	2	
Allogeneic transplant	4	3	

Abbreviations: CNS, central nervous system; DCCSS LATER, Dutch Childhood Cancer Survivor LATER Study; ICCC, International Classification for Childhood Cancer; TAAQOL, TNO-AZL Questionnaire for Adult Health-Related Quality of Life; TBI, total body irradiation.

[a]Nonparticipants were those who were invited to participate but did not return a TAAQOL questionnaire; n varies slightly across variables because of missing values.

[b]Data were missing for survivors who declined the use of their data in the DCCSS LATER registry (n = 745).

[c]Significant at α = .001.

[d]Significant at α = .01.

[e]Significant at α = .05.

[f]For primary cancer and recurrences.

[g]Survivors could have multiple regions of radiotherapy exposure.

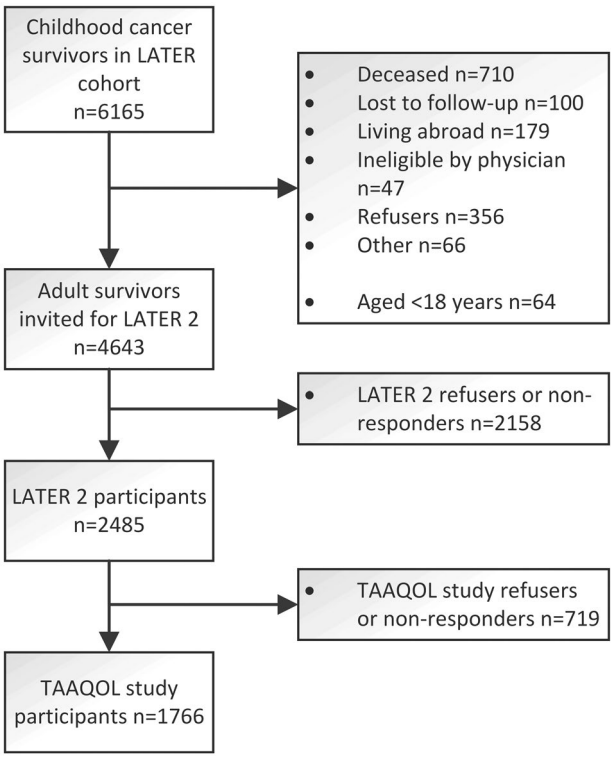

Figure 1. Flowchart of participants from the LATER cohort of the DCCSS LATER 2 psycho-oncology study. DCCSS LATER 2 indicates Dutch Childhood Cancer Survivor LATER Study 2; TAAQOL, TNO-AZL Questionnaire for Adult Health-Related Quality of Life.

observed in cognitive functioning, which was lower in CCSs than references. Figure 2 displays the proportions of individuals with impaired HRQOL in the domains and ORs of the differences between CCSs and references. Supporting Table 1 shows the models including the interaction between group and sex to determine whether ORs differed significantly between male and female CCSs. For both sexes, the odds of impairment were higher in CCSs with at least small to medium effect sizes in cognitive functioning (OR for males, 2.7; 99.6% CI, 2.0-3.6; OR for females, 3.8; 99.6% CI, 2.9-5.0), gross motor functioning (OR for males, 1.7; 99.6% CI, 1.2-2.4; OR for females, 2.3; 99.6% CI, 1.7-3.0), fine motor functioning (OR, 2.1; 99.6% CI, 1.6-2.8), vitality (OR, 2.1; 99.6% CI, 1.7-2.5), and sleep (OR, 1.6; 99.6% CI, 1.3-2.0). In addition, female CCSs had higher odds of impairment than female references with small to medium effect sizes in daily activities (OR, 1.9; 99.6% CI, 1.5-2.6), pain (OR, 1.9; 99.6% CI, 1.4-2.5), and sexuality (OR, 1.4; 99.6% CI, 1.1-1.9). Finally, CCSs were not at increased risk of impaired social functioning, reduced positive emotions, or increased aggressive emotions. Moreover, female CCSs less often had increased aggressive emotions than female references (OR, 0.6; 99.6% CI, 0.4-0.9).

Univariate associations of demographic and medical variables with impaired HRQOL are described in Supporting Table 2. Table 3 shows the results of the multivariable models. CCSs older than 40 years were at risk for impaired HRQOL in several domains (gross and fine motor functioning, pain, and vitality). Those with a diagnosis of a CNS tumor (vs all other childhood cancer types) and—from a separate model—CCSs who had received radiotherapy to the head or cranial region (vs all other CCSs) had higher odds of impaired HRQOL in the majority of the domains. CCSs with certain diagnoses had higher odds of impaired HRQOL in a specific domain, namely retinoblastoma CCSs in pain (OR, 10.3; 95% CI, 2.1-51.4) and bone tumor CCSs in gross motor functioning (OR, 3.2; 95% CI, 2.0-5.2). Radiotherapy in 1 or more regions affected HRQOL in all domains except sleep and aggressive emotions, whereas surgery and chemotherapy were not significant risk factors in the multivariable models. Apart from the head and cranial region, those who had received radiotherapy in the abdominopelvic area or the lower extremities had impaired HRQOL in multiple domains.

DISCUSSION

This study of 12 domains of HRQOL in a national cohort of CCSs provides a comprehensive overview of impairments and medical determinants in Dutch CCSs that can guide survivor monitoring and care. Dutch adult CCSs more often had impaired HRQOL than the general population reference group in several domains; this was most pronounced in cognitive functioning and in physical domains such as gross and fine motor functioning, vitality, and pain. Notably, effect sizes in comparison with references were larger for the proportion at risk than the domain scores. This underlines that although most CCSs are resilient, they are at increased risk for HRQOL problems.[2] Also, it shows the importance of looking beyond group scores and study subgroups of CCSs who are impaired or have problems. It should be recognized that the prospect of children currently treated for cancer may be more positive because changes have been made to childhood cancer treatment to reduce long-term effects in recent decades.[18]

Compared with male CCSs, female CCSs experienced impairment in HRQOL more often and in more domains. The difference between male and female CCSs exceeds general population differences between men and women. Thus, the long-term HRQOL of women seems to be affected more by childhood cancer and its

TABLE 2. Description of TAAQOL Domains Among Male and Female CCSs and Effect Sizes of Difference With the Reference Group

	Male CCSs (n = 904)						Female CCSs (n = 862)					
TAAQOL	Mean	SD	Median	IQR	Missing	r^a	Mean	SD	Median	IQR	Missing	r^a
Gross motor functioning	90.9	16.7	100	87.5-100	1	.12[b]	82.8	22.7	93.8	68.8-100	0	.19[b]
Fine motor functioning	98.6	6.4	100	100-100	2	.08[b]	94.8	12.0	100	93.8-100	0	.15[b]
Cognitive functioning	76.0	25.2	87.5	56.3-100	2	**.25**[b]	67.8	28.1	75.0	43.8-93.8	1	**.34**[b]
Sleep	75.6	25.1	81.3	62.5-100	1	.08[b]	64.6	29.0	68.8	43.8-87.5	2	.15[b]
Pain	77.9	20.4	81.3	62.5-93.8	1	.07[b]	66.7	24.3	68.8	50.0-87.5	2	.17[b]
Social functioning	87.2	18.2	93.8	81.3-100	2	.03	86.1	19.4	93.8	75.0-100	5	.01
Daily activities	85.1	23.7	100	75.0-100	3	.02	76.3	28.9	87.5	56.3-100	3	.11[b]
Sexuality	89.2	21.9	100	87.5-100	19	.05[c]	84.0	26.2	100	75.0-100	33	.07[b]
Vitality	66.1	25.9	75.0	50.0-83.3	4	.06[b]	53.8	28.4	58.3	33.3-75.0	2	.15[b]
Positive emotions	69.2	23.7	66.7	58.3-91.7	7	.06[c]	69.4	23.4	66.7	58.3-91.7	4	.04
Depressive emotions	80.8	19.9	83.3	75.0-100	5	.03	75.1	21.4	83.3	66.7-91.7	3	.05[b]
Aggressive emotions	87.9	17.3	100	77.8-100	12	.02	90.3	14.2	100	88.9-100	14	.10[c]

Abbreviations: CCS, childhood cancer survivor; IQR, interquartile range; SD, standard deviation; TAAQOL, TNO-AZL Questionnaire for Adult Health-Related Quality of Life; TBI, total body irradiation.

[a]Effect sizes were calculated with $r = Z$-score of the difference/($\sqrt{n}$). Effects of at least small to medium size are bolded.

[b]Mann-Whitney $P < .004$ for difference from the general population sample: CCSs lower.

[c]Mann-Whitney $P < .004$ for difference from the general population sample: CCSs higher.

treatment. This may be explained by female CCSs being more inclined to report or discuss problems than male CCSs.[10] Nevertheless, future studies should consider sex-specific long-term risks of childhood cancer treatment.[11] Survivor care professionals need to be aware of these sex differences in the impact of childhood cancer diagnosis and treatment and be especially sensitive to impairments in females in motor and cognitive functioning and additionally in pain, sexuality, and daily activities.

Because of our large sample and extensive LATER registry, we were able to study the risk of impaired HRQOL for diagnosis subgroups and radiotherapy regions in detail. Because childhood cancer treatment often consists of several modalities, results for radiotherapy regions are to be considered exploratory and may in some cases also be explained by a type of surgery (eg, amputation). Nevertheless, the results relate therapy in different body regions to impairments in specific HRQOL domains. In line with previous findings, CCSs who had CNS tumors or had received cranial radiotherapy were at increased risk for impaired HRQOL in several domains.[4-6] In addition, we found that those who had received abdominopelvic radiotherapy were at increased risk in several domains of HRQOL. Bone tumor CCSs and those who had received radiotherapy to the lower extremities had an increased risk of impaired gross motor functioning and pain.[4-6] Retinoblastoma CCSs had an increased risk of impairment in the pain domain, which in the TAAQOL includes items on pain in the muscles, joints, neck, or back. Although this is a very small subgroup of CCSs, we found a very high OR, which was similar to previous results of an Italian cohort study.[19] Older CCSs had an increased risk of impaired gross motor functioning and pain, but the effect of age in our sample of CCSs was not different from the general population (results not shown). In conclusion, our study supports previous results for vulnerabilities in certain subgroups such as CNS and bone tumor CCSs and additionally suggests increased HRQOL impairments in other subgroups such as those who have received abdominopelvic radiotherapy.

The high proportion (50%) of CCSs with impaired self-perceived cognitive functioning (<25th percentile of the reference population) warrants attention for this domain. Apparently, many long-term CCSs and also those who have not received cranial irradiation experience some limitations in concentration, memory, or attention, and this is consistent with previous reports and similar to survivors from cancer in adulthood.[20,21] Our results thus provide further evidence that screening for cognitive deficits should be recommended for the entire population of CCSs. A recent review also recommended such screening to take place at regular intervals with different levels of detail depending on risk or previous impairment[22] in line with the psychosocial standards of care.[23] If needed, a referral or intervention should take place early.[24] Because HRQOL includes the subjective burden of health problems, impairments may additionally be reduced by interventions in response to cognitive deficits; eg, using acceptance and commitment therapy for long-term CCSs who have persisting problems.[25]

Survivors were impaired in the vitality domain, which includes items that indicate feeling energetic or

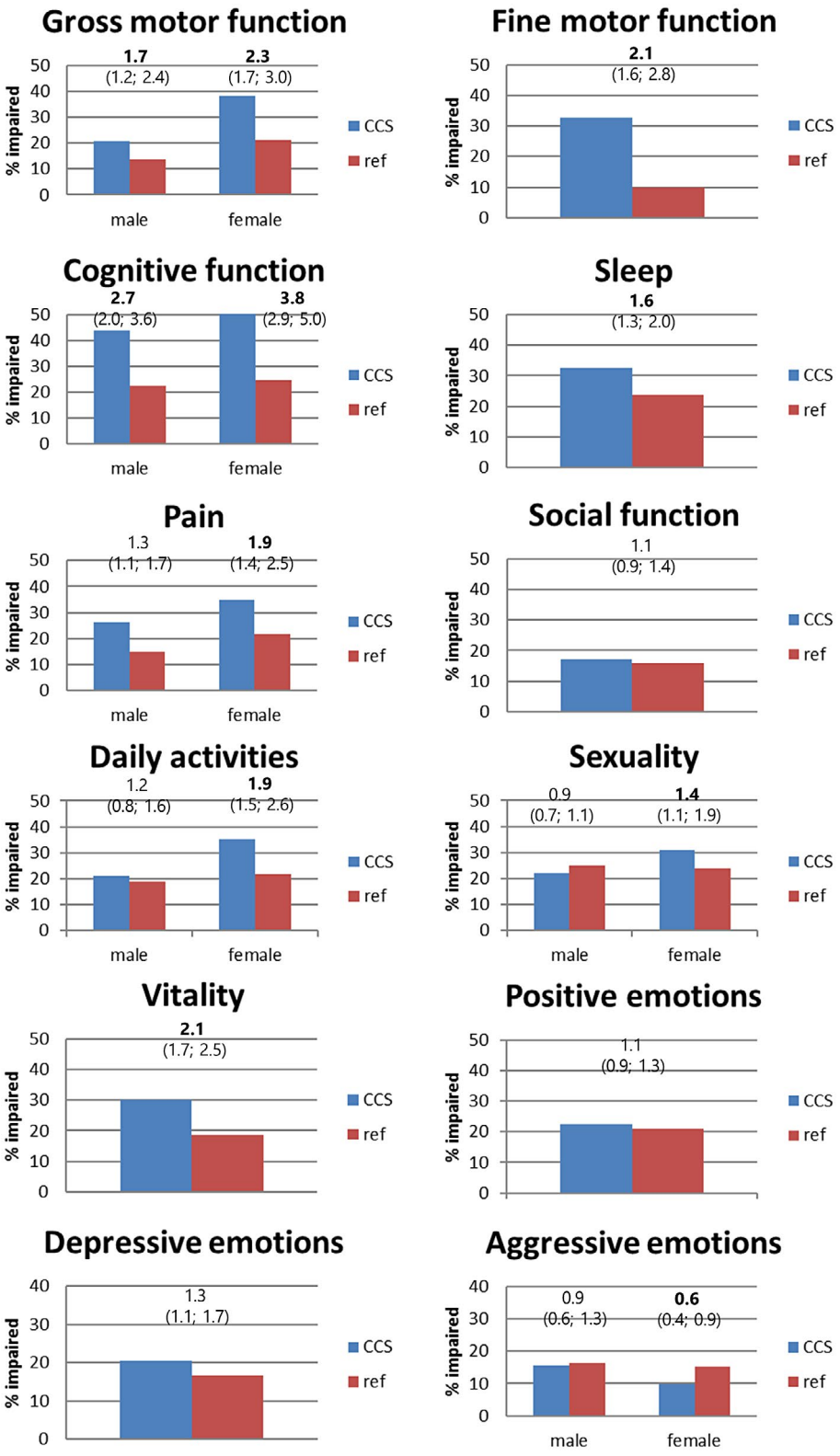

Figure 2. Proportions of individuals with impaired health-related quality of life among CCSs and references and odds ratios (with 99.6% CIs) of the differences between groups corrected for age and sex. The results are shown for males and females separately if the interaction term of sex with group is significant. Effects of at least small to medium size are bolded. CCS indicates childhood cancer survivor.

TABLE 3. Multivariable Analyses of Determinants of Impaired Health-Related Quality of Life

	Gross Motor Functioning: 515 Impaired (29%), OR (95% CI)		Fine Motor Functioning: 299 Impaired (17%), OR (95% CI)		Cognitive Functioning: 874 Impaired (50%), OR (95% CI)		Sleep: 574 Impaired (33%), OR (95% CI)		Pain: 467 Impaired (27%), OR (95% CI)		Social Functioning: 301 Impaired (17%), OR (95% CI)	
	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3
Block 1												
Demographics												
Age at invitation (reference 18-30 y)												
30-40 y	1.3 (1.0-1.7)	1.2 (0.9-1.6)	1.2 (0.8-1.6)	1.1 (0.8-1.5)	1.1 (0.9-1.4)	1.0 (0.8-1.3)	1.1 (0.9-1.4)	1.1 (0.9-1.5)	1.2 (0.9-1.5)	1.2 (0.9-1.6)	1.1 (0.8-1.6)	1.0 (0.7-1.4)
40 y and over	**2.7[a] (2.0-3.6)**	**2.0[a] (1.4-2.7)**	**1.5[b] (1.1-2.2)**	1.3 (0.9-1.8)	1.0 (0.8-1.3)	0.9 (0.7-1.1)	1.1 (0.9-1.5)	1.1 (0.9-1.5)	**1.8[a] (1.4-2.4)**	**1.7[a] (1.3-2.3)**	1.3 (0.9-1.8)	1.0 (0.7-1.4)
Female sex (reference male)	**2.5[a] (2.0-3.1)**	**2.5[a] (2.0-3.1)**	**4.3[a] (3.2-5.8)**	**4.4[a] (3.3-5.8)**	**1.6[a] (1.3-1.9)**	**1.7[a] (1.4-2.0)**	**2.1[a] (1.7-2.6)**	**2.1[a] (1.7-2.5)**	**2.3[a] (1.8-2.9)**	**2.3[a] (1.9-2.9)**	1.3[b] (1.0-1.6)	1.3 (1.0-1.6)
Medical												
Age at diagnosis (reference 0-5 y)												
5-10 y	1.0 (0.8-1.3)	1.1 (0.8-1.4)	1.1 (0.8-1.6)	1.2 (0.8-1.6)							1.0 (0.7-1.4)	1.1 (0.8-1.5)
10-15 y	1.2 (0.9-1.6)	**1.4[b] (1.1-1.9)**	1.3 (0.9-1.9)	**1.4 (1.0-1.9)**							1.0 (0.7-1.4)	1.2 (0.9-1.7)
15-18 y	0.9 (0.6-1.5)	1.3 (0.8-2.2)	0.8 (0.5-1.5)	0.9 (0.5-1.7)							1.2 (0.7-2.0)	**1.6 (0.9-2.7)**
Recurrence (any vs none)	**1.5[c] (1.1-2.0)**	1.3 (0.9-1.7)										
Block 2: primary cancer diagnosis												
Leukemia	0.8 (0,6-1.1)						0.8[b] (0.6-1.0)					
Lymphoma	**0.7 (0.5-1.0)**		0.9 (0.6-1.3)		0.9 (0.7-1.1)				0.8 (0.6-1.1)			
CNS tumor	**1.5[b] (1.0-2.2)**		**1.9[c] (1.3-2.8)**		**1.6[c] (1.1-2.2)**						**2.1[a] (1.5-3.0)**	
Neuroblastoma											**0.4[b] (0.2-0.8)**	
Retinoblastoma									**10.3[c] (2.1-51.4)**			
Renal tumor											**0.7 (0.5-1.1)**	
Hepatic tumor									0.2 (0.0-1.5)			
Bone tumor	**3.2[a] (2.0-5.2)**								**1.4 (0.9-2.1)**			
Germ cell tumor			**1.5 (0.8-2.8)**						**1.4 (0.8-2.4)**			
Block 3: cancer treatment[d]												
Surgery		1.2 (0.9-1.5)		1.1 (0.8-1.5)				1.1 (0.9-1.4)				
Radiotherapy regions[e]												
Head cranium		**1.7[a] (1.3-2.3)**		**1.5[b] (1.1-2.1)**		**1.7[a] (1.3-2.3)**						**2.0[a] (1.5-2.8)**
Spinal						1.1 (0.7-1.8)						1.0 (0.6-1.8)
TBI								0.7 (0.4-1.2)				
Thorax		1.1 (0.7-1.7)										
Abdominopelvic area		**1.9[c] (1.3-2.8)**						**1.4 (0.9-2.0)**		**1.4 (1.0-2.1)**		
Lower extremities		**6.5[a] (2.3-18.2)**								**2.4[b] (1.1-5.6)**		
Radioisotopes								**1.9 (0.7-4.8)**				
Chemotherapy		0.8 (0.6-1.1)		0.9 (0.6-1.3)				**0.7[b] (0.5-1.0)**		0.8 (0.6-1.0)		

	Daily Activities: 494 Impaired (28%), OR (95% CI)		Sexuality: 454 Impaired (27%), OR (95% CI)		Vitality: 530 Impaired (30%), OR (95% CI)		Positive Emotions: 395 Impaired (23%), OR (95% CI)		Depressive Emotions: 361 Impaired (21%), OR (95% CI)		Aggressive Emotions: 223 Impaired (13%), OR (95% CI)	
	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3
Block 1: demographics												
Age (reference 18-30 y)												
30-39 y	1.2 (0.9-1.5)	1.1 (0.9-1.5)	1.0 (0.7-1.2)	1.0 (0.8-1.3)	1.1 (0.8-1.4)	1.0 (0.8-1.3)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.8 (0.6-1.1)	0.8 (0.6-1.1)		0.9 (0.6-1.2)
≥40 y	1.3 (1.0-1.7)	1.1 (0.8-1.5)	1.2 (0.8-1.5)	1.2 (0.9-1.6)	**1.4[c] (1.1-1.8)**	1.1 (0.8-1.4)	1.2 (0.9-1.6)	1.0 (0.8-1.4)	0.8 (0.6-1.1)	0.8 (0.6-1.0)		0.8 (0.6-1.2)
Female sex (reference male)	**2.0[a] (1.6-2.5)**	**2.0[a] (1.6-2.5)**	**1.6[a] (1.3-2.0)**	**1.5[a] (1.2-1.9)**	**2.2[a] (1.8-2.8)**	**2.3[a] (1.9-2.9)**	1.0 (0.8-1.2)	1.0 (0.8-1.2)	**1.7[a] (1.3-2.1)**	**1.7[a] (1.3-2.2)**		**0.6[a] (0.4-0.8)**

TABLE 3. *Continued*

	Daily Activities: 494 Impaired (28%), OR (95% CI)		Sexuality: 454 Impaired (27%), OR (95% CI)		Vitality: 530 Impaired (30%), OR (95% CI)		Positive Emotions: 395 Impaired (23%), OR (95% CI)		Depressive Emotions: 361 Impaired (21%), OR (95% CI)		Aggressive Emotions: 223 Impaired (13%), OR (95% CI)	
	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3	Blocks 1 + 2	Blocks 1 + 3
Block 2: cancer diagnosis												
Leukemia	0.9 (0.7-1.1)											
Lymphoma					0.8 (0.6-1.1)				0.8 (0.6-1.1)			
CNS tumor	**1.8[a] (1.2-2.5)**				**1.7[b] (1.2-2.4)**		**1.6[b] (1.1-2.3)**					
Bone tumor			**1.4 (0.9-2.2)**									
Block 3: cancer treatment[d]												
Surgery		1.1 (0.8-1.3)										
Radiotherapy regions[e]												
Head cranium		1.3 (1.0-1.8)		0.8 (0.6-1.0)		**1.7[a] (1.2-2.2)**		**1.5[b] (1.1-2.1)**				
Spinal		**1.4 (0.8-2.3)**				1.2 (0.7-1.9)		1.2 (0.7-2.0)		**1.8[c] (1.1-2.9)**		
TBI				**0.6 (0.3-1.2)**				**0.6 (0.3-1.2)**		**0.4[c] (0.2-0.9)**		
Abdominopelvic area		1.3 (0.9 1.9)		**1.5[c] (1.0-2.2)**		**1.7[b] (1.2-2.4)**						
Testes												**2.8 (0.7-11.3)**
Lower extremities		**2.2 (1.0-5.3)**				**1.9 (0.8-4.5)**						
Radioisotopes		**2.6[c] (1.0-6.6)**										
Chemotherapy		**0.7[c] (0.5-1.0)**										

Abbreviations: CNS, central nervous system; OR, odds ratio; TBI, total body irradiation.
Effects of at least small to medium size are bolded.
[a]Significant at α = .001.
[b]Significant at α = .01.
[c]Significant at α = .05.
[d]For primary cancer and recurrences.
[e]Survivors could have multiple regions of radiotherapy exposure.

fatigued. Fatigue is one of the most common side effects of childhood cancer treatment and is known to persist in a subgroup of CCSs. In accordance with recent recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group, lifelong screening for fatigue using validated fatigue measures should be implemented.[26] Also, interventions are needed especially in light of the established association with cognitive functioning and because Dutch CCSs were previously found to have impaired mental or cognitive fatigue in particular.[27,28] Interventions should consider the biopsychosocial nature of fatigue[29] and take sleep problems into account.[30] Also, because associations were found between lifestyle behaviors and HRQOL in CCSs, early information on healthy behaviors may prevent or reduce fatigue.[31]

CCSs were not often impaired in psychosocial domains such as social functioning and positive, depressive, and aggressive emotions, and this is in line with previous literature and also shows their psychosocial resilience.[4,5] Nonetheless, the TAAQOL explicitly includes "experienced bother" in the other domains of HRQOL as well. As such, the results of impairments in other domains, including gross and fine motor functioning, are not to be regarded as purely physical problems, and the long-term follow-up of CCSs requires a multidisciplinary approach to prevention and treatment that includes psychosocial care.[32]

Limitations

To study the representativeness of our cohort, we compared participants with nonparticipants. We found some differences between them in the distributions of demographic and medical characteristics, but these were all small. There was a difference in the periods in which data were collected between CCSs and references. Thus, our results may have been affected by periodic trends, but we expect this periodic effect to be small because HRQOL has been stable over time in the Netherlands.[33] Also, the reference group had a high proportion of women,[12] but because sex was accounted for in all analyses, this did not affect our results. In this article, we have considered only medical determinants. Future research may additionally determine the indirect influence of childhood cancer on long-term HRQOL outcomes in Dutch CCSs through social factors (eg, educational level or relationship status) and late effects.[34,35] In addition, psychosocial factors such as coping styles contribute to HRQOL in CCSs and thus may provide opportunities for the prevention of or interventions for HRQOL impairments in CCSs.[36]

In conclusion, Dutch adult CCSs more often had impaired HRQOL than the general population in several domains; this was most pronounced in cognitive functioning. Compared with male CCSs, female CCSs had impaired HRQOL more often and in more domains and accordingly may need more attention. Dutch CCSs with CNS tumors and those who received cranial radiotherapy were at higher risk for long-term impaired HRQOL in multiple domains. HRQOL surveillance is recommended in CCSs, especially for cognitive functioning and fatigue, as is a multidisciplinary approach to the prevention and treatment of impairments in HRQOL.

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AUTHOR CONTRIBUTIONS

Marloes van Gorp: Formal analysis and writing–original draft. **Loes M. E. van Erp:** Writing–review and editing. **Anne Maas:** Writing–review and editing. **Leontien C. M. Kremer:** Conceptualization, funding acquisition, and writing–review and editing. **Eline van Dulmen-den Broeder:** Project administration and writing–review and editing. **Wim J. E. Tissing:** Project administration and writing–review and editing. **Jacqueline J. Loonen:** Project administration and writing–review and editing. **Helena J. H. van der Pal:** Project administration and writing–review and editing. **Andrica C. H. de Vries:** Project administration and writing–review and editing. **Marry M. van den Heuvel-Eibrink:** Project administration and writing–review and editing. **Cécile M. Ronckers:** Project administration and writing–review and editing. **Dorine Bresters:** Project administration and writing–review and editing. **Marloes Louwerens:** Project administration and writing–review and editing. **Margriet van der Heiden-van der Loo:** Data curation and writing–review and editing. **Gea A. Huizinga:** Project administration and writing–review and editing. **Heleen Maurice-Stam:** Conceptualization, funding acquisition, and writing–review and editing. **Martha A. Grootenhuis:** Conceptualization, funding acquisition, and writing–review and editing.

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