




# Psychosocial functioning of adult siblings of Dutch very long-term survivors of childhood cancer: DCCSS-LATER 2 psycho-oncology study

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## Abstract

**Objective:** To describe psychosocial outcomes among adult siblings of very long-term childhood cancer survivors (CCS), to compare these outcomes to reference populations and to identify factors associated with siblings' psychosocial outcomes.

**Methods:** Siblings of survivors (diagnosed <18 years old, between 1963 and 2001, >5 years since diagnosis) of the Dutch Childhood Cancer Survivor Study DCCSS-LATER cohort were invited to complete questionnaires on HRQoL (TNO-AZL Questionnaire for Adult's HRQoL), anxiety/depression (Hospital Anxiety and Depression Scale), post-traumatic stress (Self-Rating Scale for Post-traumatic Stress Disorder), self-esteem (Rosenberg Self-Esteem Scale) and benefit and burden (Benefit and Burden Scale for Children). Outcomes were compared to a reference group if available, using Mann-Whitney U and chi-Square tests. Associations of siblings' sociodemographic and CCS' cancer-related characteristics with the outcomes were assessed with mixed model analysis.

**Results:** Five hundred five siblings (response rate 34%, 64% female, mean age 37.5, mean time since diagnosis 29.5) of 412 CCS participated. Siblings had comparable HRQoL, anxiety and self-esteem to references with no or small differences ( $r = 0.08 - 0.15$ ,  $p < 0.05$ ) and less depression. Proportions of symptomatic PTSD were very small (0.4%–0.6%). Effect sizes of associations of siblings' sociodemographic and CCS cancer-related characteristics were mostly small to medium ( $\beta = 0.19 - 0.67$ ,  $p < 0.05$ ) and no clear trend was found in the studied associated factors for worse outcomes.

A list of non-author study group members appears in the acknowledgments.

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**Conclusions:** On the very long-term, siblings do not have impaired psychosocial functioning compared to references. Cancer-related factors seem not to impact siblings' psychosocial functioning. Early support and education remain essential to prevent long-term consequences.

**KEYWORDS**

benefit and burden, health-related quality of life, pediatric oncology, post-traumatic stress, psycho-oncology, psychosocial outcomes, siblings, survivors of childhood cancer

## 1 | INTRODUCTION

Siblings of children with cancer are impacted by their brother or sister's disease. During treatment, siblings may experience disruptions of daily and academic life, changes in family relations and feelings of worry, loneliness and neglect.<sup>1-4</sup> During this period and even after treatment, siblings may need psychosocial support.<sup>5</sup> The Integrative Trajectory Model of Pediatric Medical Traumatic Stress describes that although most families recover over time after the diagnosis of a pediatric illness, a small proportion continues to experience problems, even after months or years.<sup>6</sup> Most literature on siblings' wellbeing focuses on children below the age of 18. A systematic review shows that emotional and behavioral functioning of adult siblings was similar to references and states that methodological limitations hamper conclusions about health related quality of life (HRQoL).<sup>7</sup> A more recent study shows lower mental HRQoL in adult siblings than in peers.<sup>8</sup> Regarding post-traumatic stress, adult siblings do not experience more symptoms than controls.<sup>9</sup> Besides generic outcomes such as HRQoL, disease-specific outcomes such as benefits and burden of having a brother or sister with cancer may be relevant. Literature on siblings' burden of and positive experiences with cancer is scarce,<sup>10</sup> but post-traumatic growth seems to be higher in young-adult siblings than in controls that were asked about a major stressful event.<sup>9</sup> Minor siblings report higher self-esteem as a positive effect.<sup>11</sup>

Previous research into factors associated with psychosocial functioning of adult siblings points out that females and older siblings are at risk,<sup>9</sup> as well as adult siblings who were older at diagnosis and older than the childhood cancer survivor (CCS).<sup>12</sup> Further risk factors are lower income, lower education, nonwhite race, lower perceived social support and health problems, whereas cancer-related factors typically are not associated with wellbeing of siblings.<sup>7</sup>

It is especially relevant to study the wellbeing of adult siblings of very long-term CCS since knowledge on very long-term psychosocial functioning in siblings is limited and it was found that siblings' risk for mental health problems starts to diverge from controls from approximately 15 years after diagnosis,<sup>12</sup> while the follow-up period of most studies is shorter. The aim of the current study is to describe HRQoL, anxiety, depression, post-traumatic stress, benefit and burden and self-esteem among adult siblings of very long-term CCS and to compare these outcomes to reference populations. Furthermore, we aimed to determine factors associated with siblings' psychosocial outcomes.

## 2 | METHODS

### 2.1 | Participants

This study is part of the Dutch Childhood Cancer Survivor Study DCCSS-LATER study part 2; clinical visit & questionnaire study in which data was collected between 2016 and 2020.<sup>13</sup>

In the DCCSS-LATER 2 psycho-oncology study, siblings ( $\geq 18$  years old,  $n = 1479$ ) of adolescent and adult CCS (diagnosed  $< 18$  years old and between 1963 and 2001,  $> 5$  years since diagnosis) were invited to participate in a psychosocial questionnaire study via mail or online if the CCS gave consent. If siblings did not respond, a reminder was sent or they were contacted by phone. The medical ethics board of Amsterdam University Medical Centers, location AMC (ref: 2010/332) approved the study protocol.

### 2.2 | Measures

HRQoL was measured with the TNO-AZL Questionnaire for Adult's HRQoL (TAAQoL) that assesses health status problems weighted by their impact. It consists of 45 items covering 12 domains, from which we used 10: cognitive functioning, sleep, pain, social functioning, daily activities, sexuality, vitality, positive-, depressive- and aggressive emotions. Item scores (4-point Likert scale) are added up and transformed to scale scores of 0–100, higher scores indicating better HRQoL. Psychometric properties are satisfactory.<sup>14</sup> Cronbach's  $\alpha$  of the scale scores in the current sample was 0.63–0.92. Reference data from the general Dutch population are available,<sup>14</sup> to obtain a reference sample with a mean age similar to that of our sample, reference data from adults aged 18–59 years were selected.

*Anxiety and depression* were measured with the Hospital Anxiety and Depression Scale (HADS), that consists of 14 items (4-point Likert scale). Items are divided over two scales measuring anxiety and depression (range 0–21). Higher scores indicate more symptoms. The cut-off point for (sub)clinical anxiety and depression was eight.<sup>15,16</sup> Psychometric properties are good.<sup>17</sup> Cronbach's  $\alpha$  of the scale scores in the current sample was 0.79–0.81. Reference data from the general Dutch population are available.<sup>18</sup>

*Post-traumatic stress symptoms* related to childhood cancer were measured with the Self-Rating Scale for Post-Traumatic Stress Disorder (SRS-PTSD). The SRS-PTSD consists of 17 items (3-point Likert scale) that correspond to the diagnostic DSM-IV symptoms of PTSD

and result in a total scale and three subscales: re-experiencing, avoidance and hyper arousal. Presence of at least one symptom in all three scales is considered subclinical PTSD<sup>19</sup> and presence of at least one re-experiencing, three avoidance and two hyper arousal symptoms is considered symptomatic PTSD.<sup>20,21</sup> Psychometric properties are adequate.<sup>20</sup> Cronbach's  $\alpha$  for the total scale in the current study was 0.70.

*Self-esteem* was measured with the Rosenberg self-esteem questionnaire, which consists of 10 items (4-point Likert scale). A higher score indicates higher self-esteem (range 10–40). Psychometric properties are good.<sup>22</sup> Cronbach's  $\alpha$  in the current study was 0.90. Reference data from the general Dutch population are available.<sup>23</sup>

*Benefit finding and disease-related burden* of having a sibling CCS were measured with the Benefit and Burden Scale for Children (BBSC<sup>24</sup>), minimally adapted for the use in adults with approval of the original author. The questionnaire consists of two scales with 10 items (see Table 1) on a Likert scale ([1] 'Not at all true for me', [2] 'a little bit', [3] 'somewhat', [4] 'quite a bit', [5] 'Very much true for me'): benefit finding (Cronbach's  $\alpha$  0.90) and disease-related burden (Cronbach's  $\alpha$  0.77) of childhood cancer. Mean item scale scores were

TABLE 1 Items of the Benefit and Burden Scale for Children.

n-range	316–320 Mean $\pm$ SD
<b>Benefit finding</b>	
Learned what is important in life	3.2 $\pm$ 1.4
Learned to be happy and enjoy life	3.0 $\pm$ 1.5
Have become a stronger person	2.7 $\pm$ 1.3
Family has grown closer	2.7 $\pm$ 1.3
Know how much I am loved	2.6 $\pm$ 1.5
Learned to be nicer to others	2.1 $\pm$ 1.1
Learned to better cope with problems	2.0 $\pm$ 1.2
Know my real friends	2.0 $\pm$ 1.4
Learned to be more patient	2.0 $\pm$ 1.1
Made new friends	1.4 $\pm$ 0.8
<b>Disease-related burden</b>	
Afraid to upset others	1.5 $\pm$ 0.9
Cannot enjoy life the way I used to	1.3 $\pm$ 0.9
Less hopeful about life	1.2 $\pm$ 0.7
Afraid to be a burden to my family	1.3 $\pm$ 0.8
Less self-confident	1.3 $\pm$ 0.7
Moodier and more irritable	1.2 $\pm$ 0.5
Less happy with my life	1.2 $\pm$ 0.5
Less time to spend with friends	1.1 $\pm$ 0.4
Less time to do fun things	1.1 $\pm$ 0.4
Feel embarrassed when seen in public	1.1 $\pm$ 0.4

calculated. Scores of siblings <4 years old at the time of diagnosis of the CCS were not used.

*Associated factors* consisted of demographic characteristics (siblings' age at participation and at diagnosis of CCS, sex, level of education, number of siblings, survivor's age) and cancer-related characteristics of the CCS (primary childhood cancer diagnosis, metastasis and recurrence of primary tumor). Demographic factors were obtained from the DCCSS-LATER 1 or 2 study.<sup>25</sup> Cancer-related factors were obtained from the DCCSS-LATER registry.<sup>25</sup>

## 2.3 | Statistical analyses

Differences between characteristics of participants and non-participants/LATER cohort were tested with independent *t*-tests and chi-square tests, having Cohen's *d* and Cramer's *V* as effect sizes. Outcomes were analyzed descriptively. In addition, HRQoL, anxiety, depression and self-esteem were compared with references of comparable age for males and females separately, using Mann Whitney-U tests with effect size *r*, and chi-square tests.

Mixed model analyses were conducted to determine factors associated with psychosocial outcomes, controlled for age and sex. Random intercepts were included to account for dependency of outcomes of siblings of the same CCS.

*p*-values  $\leq 0.05$  were considered statistically significant, except for comparisons between siblings and references, where a Bonferroni correction was applied for the number of scales within the outcomes. Effect size *V*, effect size *r* and standard regression coefficients (categorical variables) of 0.2, 0.5 and 0.8 and standard regression coefficients (continuous variables) of 0.1, 0.3 and 0.5 are considered small, medium and large respectively.<sup>26</sup>

## 3 | RESULTS

### 3.1 | Participants

In total, 505 of 1479 siblings (34% of siblings invited through their CCS, 64% female, mean age 37.5 years, mean time since diagnosis 29.5 years) of 412 CCS gave informed consent and completed at least one questionnaire. Participants and non-participants differed in sex and age, but not in education (Table 2). CCS' diagnosis differed from the LATER cohort.<sup>25</sup> All effect sizes are small to moderate.

### 3.2 | Outcomes

Several small differences ( $r = 0.08$ – $0.18$ ) between siblings and references were found on psychosocial outcomes (Table 3). Regarding HRQoL, females had lower cognitive functioning and higher social functioning and positive and depressive emotions and aggressiveness than references. Males had lower cognitive functioning and sleep than references. Both female and male siblings had less depression

TABLE 2 Sociodemographic characteristics of siblings and CCS cancer-related characteristics.

	Participants		Non-participants <sup>a</sup>		Cohen's <i>d</i> or Cramer's <i>V</i>
	<i>n</i>	Mean ± SD or %	<i>n</i>	Mean ± SD or %	
Sibling characteristics					
Age	505	37.5 ± 10.1 range 17.8–64.6	871	35.3 ± 9.7 range 16.6–76.6	Cohen's <i>d</i> 0.22**
Sex	505		871		Cramer's <i>V</i> 0.17**
Male		36.0		53.7	
Female		64.0		46.3	
Attained level of education <sup>b</sup>	410		427		0.08
Low		6.3		9.4	
Middle		42.7		46.1	
High		51.0		44.5	
Number of siblings	422				
1		33.4			
>1		66.6			
Follow-up time since diagnosis (years)	465	29.5 ± 8.4			
Sibling age at diagnosis					
<4		37.0			
4–12		43.7			
12+		19.4			
Age difference	465				
Sibling >2 years younger		50.1			
Difference <2 years		11.8			
Sibling >2 years older		38.1			
CCS cancer-related characteristics			Total CCS cohort		
Primary childhood cancer diagnosis	465		6159		0.12*
Hematologic cancers		55.7		51.2	
CNS tumor		7.7		13.7	
Solid tumor		36.6		35.1	
Metastasis of primary tumor	454	14.6			
Recurrence of primary tumor	465	9.7			

Abbreviation: CCS, childhood cancer survivors.

<sup>a</sup>Non-participants are siblings of CCS that were approached for our study after consent by their CCS but did not participate.

<sup>b</sup>Low: primary education, lower vocational education, lower and middle secondary education; middle: middle vocational education, higher secondary education, pre-university education; high: higher vocational education, university.

\*\**p*-value <0.01, \*\**p*-value <0.001, significant differences (*p* < 0.05).

and (sub)clinical depression than references, while no differences were found on anxiety. Self-esteem was higher for females compared to references, but not for males. The percentage of siblings reporting subclinical and symptomatic PTSD because of the CCS's disease was respectively 4.4% and 0.4% for females and 4.3% and 0.6% for males. Mean scale scores for benefit and burden were 2.3 (“a little bit” to

“somewhat”) and 1.1 (“none at all” to “a little bit”) respectively, indicating less burden than benefit (Table 1). For benefit, the items with the highest score were “I have learned what is really important in life” (mean 3.2), “I have learned to be happy and to enjoy good things” (mean 3.0) and “I became a stronger person” (mean 2.7). For burden the items with the highest score were “I am afraid to make other

TABLE 3 Psychosocial outcomes in siblings of CCS.

	Total group Median (percentile 25; 75)	Female siblings Median (percentile 25; 75) or %	Female references Median (percentile 25; 75) or %	r <sup>a</sup> /OR	Male siblings Median (percentile 25; 75) or %	Male references Median (percentile 25; 75) or %	r <sup>a</sup> /OR
HRQoL, n-range	490-495	311-315	1678-1806		177-180	1362-1399	
Cognitive functioning	87.5 (62.5; 100)	87.5 (62.5; 100.0)	93.7 (75.0; 100.0)	-0.15 <sup>ab</sup>	87.5 (56.3; 100.0)	93.8 (81.3; 100.0)	-0.15 <sup>ab</sup>
Sleep	75.0 (50.0; 93.8)	68.8 (50.0; 93.8)	75.0 (56.3; 93.8)	0.05*	75.0 (56.3; 98.4)	87.5 (68.8; 100.0)	-0.10 <sup>ab</sup>
Pain	81.3 (62.5; 87.5)	75.0 (62.5; 87.5)	75.0 (62.5; 87.5)	0.01*	81.3 (68.8; 93.8)	87.5 (68.8; 100.0)	0.01*
Social functioning	100.0 (87.5; 100)	100.0 (87.5; 100.0)	93.8 (75.0; 100.0)	0.14 <sup>ab</sup>	96.9 (81.3; 100.0)	93.8 (75.0; 100.0)	0.06*
Daily activities	100.0 (75.0; 100)	100.0 (75.0; 100.0)	96.9 (75.0; 100.0)	0.01*	100.0 (76.6; 100.0)	100.0 (81.3; 100.0)	0.01*
Sexuality	100.0 (75.0; 100)	100.0 (75.0; 100.0)	100.0 (75.0; 100.0)	0.00*	100.0 (75.0; 100.0)	100.0 (75.0; 100.0)	0.00*
Vitality	75.0 (50.0; 83.3)	66.7 (50.0; 83.3)	66.7 (50.0; 75.0)	0.03*	75.0 (58.3; 83.3)	75.0 (58.3; 83.3)	0.02*
Positive emotions	66.7 (58.3; 91.7)	66.7 (66.7; 91.7)	66.7 (58.3; 75.0)	0.09 <sup>ab</sup>	66.7 (58.3; 91.7)	66.7 (58.3; 75.0)	0.05*
Depressive emotions	83.3 (75.0; 100)	83.3 (66.7; 91.7)	83.3 (66.7; 91.7)	0.09 <sup>ab</sup>	91.7 (75.0; 100.0)	88.9 (75.0; 91.7)	0.02*
Aggressive emotions	100.0 (88.9; 100)	100.0 (88.9; 100.0)	88.9 (77.8; 100.0)	0.08 <sup>ab</sup>	100.0 (77.8; 100.0)	88.9 (77.8; 100.0)	0.02*
Anxiety and depression, n	485	307	785		178	811	
Anxiety	4.0 (2.0; 6.0)	4.0 (2.0; 6.0)	4.0 (2.0; 7.0)	0.04*	4.0 (2.0; 6.0)	3.0 (1.0; 6.0)	-0.05*
(Sub)clinical anxiety	17.5%	18.2%	21.9%	0.80*	16.3%	16.2%	1.01*
Depression	1.0 (0.0; 3.0)	1.0 (0.0; 3.0)	2.0 (1.0; 5.0)	-0.18 <sup>ac</sup>	2.0 (0.0; 4.0)	2.0 (1.0; 5.0)	-0.10 <sup>ac</sup>
(Sub)clinical depression	7.4%	7.2%	14.1%	0.47 <sup>ac</sup>	7.9%	14.3%	0.51 <sup>ac</sup>
Posttraumatic stress, n(-range)	453	282-305			171-177		
Total score	1 (1; 2)	1.0 (1.0; 2.0)			1.0 (1.0; 1.0)		
Symptomatic post-traumatic stress		0.4%			0.6%		
Subclinical post-traumatic stress		4.4%			4.3%		
Symptomatic re-experience		35%			22%		
Symptomatic avoidance		1%			1%		
Symptomatic hyperactivity		1%			4%		
Self-esteem, n	494	315	584		179	494	

(Continues)

TABLE 3 (Continued)

	Total group		Female siblings		Female references		Male siblings		Male references	
	Median (percentile 25; 75)	or %	Median (percentile 25; 75)	or %	Median (percentile 25; 75)	or %	Median (percentile 25; 75)	or %	Median (percentile 25; 75)	or %
	33.0 (29.0; 37.0)		32.0 (29.0; 36.0)		31.0 (29.0; 35.0)		34.0 (30.0; 37.0)		33.0 (30.0; 37.0)	
Benefit and burden <sup>d</sup> , n-range	319–320		206–207				113			
Benefit	23.0 (16.0; 31.0)		23.0 (16.5; 31.0)				23.3 (15.0; 31.5)			
Burden	11.0 (10.0; 13.0)		11.0 (10.0; 13.0)				11.0 (10.0; 13.0)			
										0.03
										0.08*
										r <sup>2</sup> /OR

Abbreviation: CCS, childhood cancer survivors.

\*Siblings differ significantly from references according to Mann-Whitney-U tests or Chi-Square tests;

<sup>a</sup>Effect size for differences between siblings and references; calculated with  $r = Z\text{-score of the difference}/\sqrt{N}$ .

<sup>b</sup> $p < 0.005$  after Bonferroni correction;

<sup>c</sup> $p < 0.025$  after Bonferroni correction.

<sup>d</sup>Only age group >4 years old was used.

people sad or upset" (mean 1.5), "I can't enjoy like I used to anymore" (mean 1.3) and "I am less hopeful about life" (mean 1.3).

### 3.3 | Associated factors

Tables 4 and 5 show the associations of sociodemographic and cancer-related factors with psychosocial outcomes. Age group 12+ at diagnosis had better sleep (compared to 0–4 years) and more perceived benefit (compared to 4–12 years). Having >1 sibling was associated with less pain compared to having 1 sibling. Being >2 years younger or older than the CCS was related to more problems in cognitive functioning and sleep than having a similar age, respectively. Regarding the cancer-related factors, only one significant association was found. Siblings of CCS with CNS tumors reported less pain than other diagnoses. All associations were of small to medium size ( $\beta = -0.27\text{--}0.41$ ,  $p < 0.05$ ), except the association between age at diagnosis and benefit ( $\beta = 0.67$ ,  $p < 0.001$ ).

## 4 | DISCUSSION

This study of siblings of the first Dutch nationwide cohort of CCS aimed to gain insight into very long-term psychosocial functioning of adult siblings of CCS and to determine associated factors. Siblings in our sample had comparable outcomes to references. Proportions of symptomatic PTSD were very small and siblings experienced some benefits but hardly any burden of having a brother or sister with childhood cancer. No clear pattern of risk or protective factors for worse psychosocial outcomes could be determined. These results demonstrate that most siblings in our sample seem to have integrated this past experience in their current lives and that they are resilient >17 years after the diagnosis of the CCS. This supports previous results that most families achieve normal wellbeing over time, after a diagnosis of childhood cancer.<sup>6</sup>

### 4.1 | Outcomes

Overall, HRQoL in our sample was comparable to references. The few differences in the HRQoL domains had different directions and small effect sizes, there was no clear trend. This substantiates existing literature on adult siblings that described similar or better HRQoL in siblings compared to references, but the studies either have methodological limitations such as using unvalidated measures or poorly defined samples<sup>7,27,28</sup> or were less long-term after diagnosis.<sup>29,30</sup> Our outcomes do differ from a recent study that shows lower mental QoL in siblings compared to the general population.<sup>8</sup> However, the population is not comparable since siblings in their sample were different in terms of age, CCS diagnosis and time since diagnosis. Siblings had similar anxiety and less depression compared to references, which is consistent with literature.<sup>9,30</sup> To our knowledge, no studies have been done into PTSD symptoms of adult siblings on the long-term,

TABLE 4 Standardized coefficients ( $\beta$ ) of associations of sociodemographic variables and cancer-related variables with HRQoL (TAAQoL).

<i>n</i>	Cognitive functioning 403	Sleep 405	Pain <sup>a</sup> 405	Social functioning 405	Daily activities 405 $\beta$ (95% CI)	Sexuality 401	Vitality 405	Positive emotions 405	Depressive emotions 405	Aggressive emotions 403
Sibling sociodemographic factors										
Sex (ref: male)	0.01 (-0.19; 0.21)	-0.15 (-0.36; 0.05)	<b>-0.37***</b> (-0.57; 0.17)	<b>0.27*</b> (0.05; 0.48)	-0.17 (-0.38; 0.04)	-0.01 (-0.22; 0.20)	<b>-0.36***</b> (-0.57; -0.16)	0.06 (-0.15; 0.27)	-0.14 (-0.35; 0.06)	<b>0.23*</b> (0.03; 0.43)
Age	0.02 (-0.11; 0.15)	0.04 (-0.09; 0.17)	-0.04 (-0.16; 0.09)	-0.11 (-0.24; -0.01)	-0.01 (-0.11; 0.14)	-0.07 (-0.20; 0.06)	-0.01 (-0.14; 0.11)	<b>-0.20**</b> (-0.33; -0.07)	-0.06 (-0.19; 0.07)	-0.01 (-0.14; 0.11)
Age at diagnosis (years, ref <4)										
4-12	0.01 (-0.23; 0.26)	0.23 (-0.02; 0.48)	-0.07 (-0.31; 0.17)	-0.03 (-0.28; 0.22)	-0.08 (-0.33; 0.17)	-0.01 (-0.26; 0.24)	-0.06 (-0.30; 0.18)	-0.02 (-0.27; 0.23)	-0.003 (-0.25; 0.24)	-0.09 (-0.33; 0.15)
12+	-0.08 (-0.43; 0.26)	<b>0.39*</b> (0.04; 0.074)	0.17 (-0.16; 0.50)	-0.07 (-0.42; 0.28)	-0.03 (-0.31; 0.37)	0.04 (-0.31; 0.38)	0.31 (-0.03; 0.65)	0.10 (-0.25; 0.45)	0.26 (-0.09; 0.61)	-0.03 (-0.36; 0.31)
>1 sibling (ref: 1 sibling)	0.02 (-0.20; 0.23)	-0.02 (-0.24; 0.19)	<b>0.28**</b> (0.08; 0.48)	-0.03 (-0.25; 0.18)	0.04 (-0.17; 0.25)	0.11 (-0.10; 0.33)	0.03 (-0.18; 0.24)	-0.08 (-0.29; 0.14)	0.08 (-0.14; 0.30)	0.13 (-0.07; 0.34)
Age difference between sibling and CCS (ref: <2 years difference)										
Sibling >2 years younger	<b>-0.39*</b> (-0.71; -0.06)	-0.19 (-0.53; 0.14)	-0.19 (-0.51; 0.13)	-0.11 (-0.45; 0.23)	-0.14 (-0.47; 0.19)	-0.23 (-0.57; 0.11)	-0.19 (-0.51; 0.14)	-0.27 (-0.60; 0.07)	-0.23 (-0.56; 0.10)	-0.01 (-0.31; 0.33)
Sibling >2 years older	-0.28 (-0.61; 0.05)	<b>-0.41*</b> (-0.74; -0.07)	-0.28 (-0.60; 0.04)	-0.10 (-0.45; 0.24)	-0.15 (-0.49; 0.18)	-0.34 (-0.68; 0.01)	-0.11 (-0.44; 0.21)	0.19 (-0.53; 0.15)	-0.33 (-0.66; 0.01)	-0.0003 (-0.32; 0.32)
CCS cancer-related factors										
CNS (ref: other diagnoses)	-0.18 (-0.55; 0.20)	-0.17 (-0.54; 0.20)	<b>0.38*</b> (0.03; 0.72)	-0.04 (-0.42; 0.32)	0.04 (-0.33; 0.40)	-0.14 (-0.51; 0.23)	-0.07 (-0.44; 0.30)	-0.03 (-0.40; 0.34)	-0.24 (-0.61; 0.14)	0.08 (-0.28; 0.43)
Metastasis (ref: no)	0.05 (-0.24; 0.35)	0.02 (-0.27; 0.32)	-0.02 (-0.30; 0.25)	0.09 (-0.20; 0.39)	0.21 (-0.07; 0.50)	-0.14 (-0.15; 0.43)	0.19 (-0.10; 0.48)	-0.08 (-0.21; 0.37)	-0.09 (-0.39; 0.20)	-0.07 (-0.36; 0.21)
Recurrence (ref: no)	-0.05 (-0.39; 0.29)	-0.04 (-0.38; 0.30)	-0.13 (-0.45; 0.19)	0.16 (-0.18; 0.50)	-0.0002 (-0.33; 0.33)	0.03 (-0.31; 0.36)	-0.05 (-0.38; 0.29)	-0.03 (-0.37; 0.31)	-0.04 (-0.38; 0.31)	0.10 (-0.22; 0.42)

Note: Significant ( $p < 0.05$ ) associations are presented in bold.

<sup>a</sup>Model without random intercept, as it was redundant.

\* $p$ -value <0.05, \*\* $p$ -value <0.01, \*\*\* $p$ -value <0.001.

TABLE 5 Standardized coefficients ( $\beta$ ) of associations of sociodemographic variables and cancer-related variables with anxiety, depression (HADS), PTSD (PTSD-SRS), self-esteem (RSES), benefit and burden (BBSC).

<i>n</i>	Anxiety 398	Depression 398	PTSD 371 $\beta$ (95% CI)	Self-esteem 404	Benefit 400	Burden 400
Sibling sociodemographic factors						
Sex (ref: male)	0.17 (-0.03; 0.37)	-0.12 (-0.32; 0.09)	0.17 (-0.02; 0.37)	<b>-0.30*</b> (-0.50; -0.10)	<b>0.20*</b> (0.002; 0.39)	0.14 (-0.07; 0.35)
Age	-0.11 (-0.23; 0.02)	0.04 (-0.09; 0.18)	<b>-0.19**</b> (-0.31; -0.07)	0.05 (-0.07; 0.18)	<b>-0.19**</b> (-0.31; -0.07)	-0.10 (-0.24; 0.03)
Age at diagnosis (years; ref <4) <sup>a</sup>						
4–12	0.01 (-0.23; 0.25)	-0.004 (-0.26; 0.25)	-0.04 (-0.28; 0.19)	0.23 (-0.01; 0.47)	NA	NA
12+	-0.08 (-0.42; 0.25)	-0.12 (-0.47; 0.24)	0.11 (-0.22; 0.43)	0.27 (-0.06; 0.61)	<b>0.67***</b> (0.35; 0.99)	0.19 (-0.16; 0.54)
>1 sibling (ref: 1 sibling)	-0.19 (-0.39; -0.02)	-0.03 (-0.25; 0.19)	-0.04 (-0.24; 0.15)	-0.06 (-0.27; 0.14)	-0.09 (-0.28; 0.11)	-0.04 (-0.26; 0.17)
Age difference between sibling and CCS (ref: <2 years difference)						
Sibling >2 years younger	0.26 (-0.05; 0.58)	0.24 (-0.09; 0.58)	-0.22 (0.53; 0.10)	-0.30 (-0.62; 0.02)	-0.11 (-0.42; 0.19)	-0.16 (-0.50; 0.17)
Sibling >2 years older	0.27 (-0.05; 0.59)	0.12 (-0.21; 0.46)	0.08 (-0.24; 0.40)	-0.21 (-0.53; 0.11)	0.13 (-0.18; 0.44)	-0.10 (-0.43; 0.24)
CCS cancer-related factors						
CNS (ref: other diagnoses)	-0.06 (-0.43; 0.31)	0.13 (-0.26; 0.52)	0.04 (-0.30; 0.38)	-0.04 (-0.40; 0.32)	0.14 (-0.20; 0.49)	0.21 (-0.17; 0.59)
Metastasis (ref: no)	0.05 (-0.34; 0.24)	0.08 (-0.22; 0.39)	0.05 (-0.32; 0.23)	-0.01 (-0.30; 0.35)	-0.14 (-0.42; 0.14)	-0.25 (-0.56; 0.05)
Recurrence (ref: no)	-0.13 (-0.46; 0.20)	0.12 (-0.23; 0.47)	0.01 (-0.30; 0.32)	0.02 (-0.30; 0.35)	0.20 (-0.11; 0.51)	0.33 (-0.02; 0.67)

Note: Significant ( $p < 0.05$ ) associations are presented in bold.

Abbreviation: CCS, childhood cancer survivors.

<sup>a</sup>Age at diagnosis reference category for the Benefit and burden scales is 4–12.

\* $p$ -value <0.05, \*\* $p$ -value <0.01, \*\*\* $p$ -value <0.001.



but <1% seems very low compared to minor siblings shorter after diagnosis, of whom 22% had PTSD symptoms related to the childhood cancer of their brother or sister.<sup>31</sup> These percentages are based on the DSM-IV criteria, since no measurement based on the DSM V criteria was available at the time of inclusion. Self-esteem was comparable to references for males and slightly higher for females. Higher self-esteem of siblings was also found in minor siblings around 9 years after diagnosis.<sup>11</sup>

Siblings reported more benefit than burden of their CCS disease. Items that had the highest means correspond with previously identified themes in growth in family members of CCS (e.g. item "learned what's important in life" to theme 'new values and life priorities').<sup>10</sup> It suggests that having a brother or sister with cancer leads to positive changes on the very long-term. None of the burden items got a mean higher than 1.5 out of 5. The low specific burden scores are in line with the other generally positive psychosocial outcomes. The generally positive results could be explained by psychosocial care that was widely available in the Netherlands, preventing siblings from developing psychosocial problems. Another factor might be that siblings are resilient, which is supported by the model of medical traumatic stress.<sup>6</sup>

#### 4.2 | Associated factors

No clear trend is visible in the studied associated factors. Effect sizes are small to moderate and no factor impacts more than one outcome, other than being 12+ years old at diagnosis, which is related to better sleep and more perceived benefit. In previous research, being older at diagnosis was only associated with worse health behaviors such as use of tobacco.<sup>32</sup> Furthermore, we found only small effects of birth order, in worse cognitive functioning for younger siblings and worse sleep for older siblings. Previous studies into birth order found that having an older CCS is a risk factor for higher rates of reaching out for mental health support<sup>12</sup> and in siblings of children with a chronic disease, the older siblings seem to be more impacted.<sup>33</sup> Literature about adult siblings is lacking. Concerning cancer-related factors, we expected higher risk for siblings of CCS with CNS tumors, because of worse outcomes for CCS with CNS themselves. However, having a child with a CNS tumor was also not related to psychosocial functioning in parents of long-term CCS.<sup>34</sup> Apart from an association of small to medium size between siblings of CNS CCS and pain, we found no associations between the outcomes and cancer-related factors, which is substantiated in literature.<sup>8,11,35</sup>

Following these results, factors that impact long-term psychosocial functioning of siblings of CCS might not differ from factors that impact the functioning of the general population.

#### 4.3 | Clinical implications

Literature suggests siblings are at risk for problems in psychosocial functioning closer to diagnosis and the need for sibling support is

stressed in the standards of care.<sup>5</sup> The PAT could be used for psychosocial risk screening, which may help providing early intervention to prevent long-term consequences for families at risk.<sup>36</sup> Besides, age adequate information about the diagnosis and treatment is recommended and it is now commonly part of psychosocial support which will further empower the siblings of now diagnosed patients who will be the CCS in the future. Nonetheless, the current findings are reassuring and can be used in psycho educating families and potentially in comforting families.

#### 4.4 | Limitations

This study is one of the first to report on very long-term psychosocial functioning of siblings of CCS in a nationwide cohort. Besides generic outcomes such as HRQoL we looked into benefit and related burden of siblings. Our sample is large, which is of added value to the shortage of research on big samples.<sup>7</sup> To date, research on long-term functioning has been limited to approximately 20 years after diagnosis, whereas our sample's mean time since diagnosis is 29.5 years. Some limitations of the study should be taken into account in the interpretation of the results. Information on CCS health impairment, family functioning or psychosocial support that siblings received was not collected, where it could have impacted the current well-being.<sup>11,35,37</sup> Further research could investigate these factors to identify siblings at-risk. Another limitation is that siblings were compared to the norm populations, so that siblings' functioning might not be accurately contextualized and which makes comparison of results between studies difficult. Concerning methodology, one of the multivariate models could not be adjusted for dependency of siblings of the same CCS, but because the intra-class coefficient was not significant, a non-adjusted model could be used instead.<sup>38</sup> The internal consistency of two HRQoL scale scores were questionable (0.63 for aggressive emotions and 0.68 for pain), which means results should be interpreted with caution. Siblings were only eligible after the CCS gave consent, which may have caused selection bias. Besides, bereaved siblings were outside the scope of the current research question. Findings are mixed in terms of vulnerability of that specific group.<sup>12,36</sup> The reported response rate (34%) is a reflection of the invited siblings after the CCS gave consent and not of the entire sibling cohort. The exact response rate of the entire sibling cohort is unknown but will be lower than 34%, which may have decreased the generalizability of the results, even though the differences between participants and non-participants are small.

#### 5 | CONCLUSION

On the very long-term, siblings in our sample do not have impaired psychosocial functioning compared to references. Factors related to the disease of their brother or sister seem not to impact siblings' psychosocial functioning.

## AUTHOR CONTRIBUTIONS

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

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## CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflicts of interest to disclose.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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