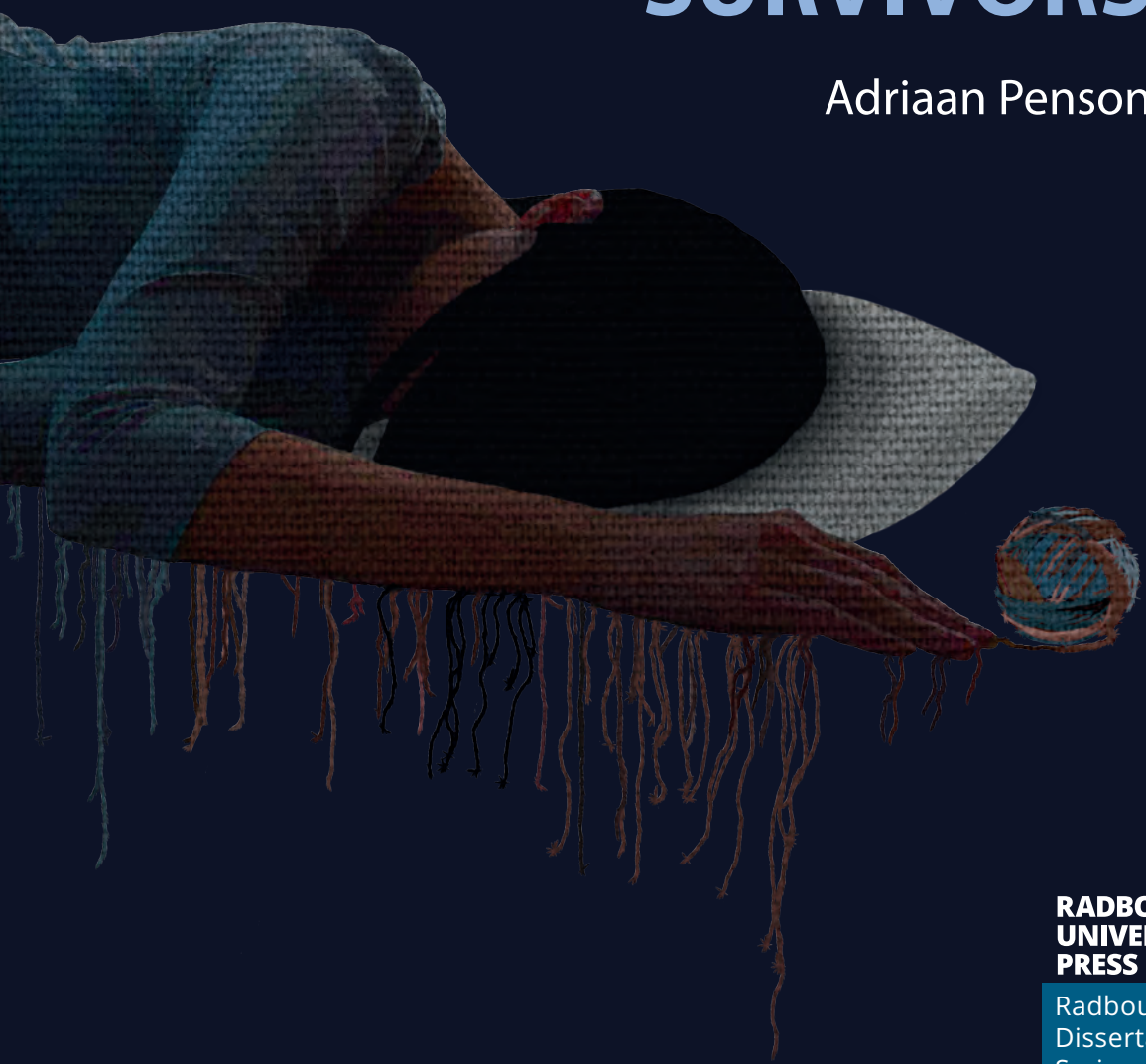
UNRAVELING CHRONIC FATIGUE IN CHILDHOOD CANCER SURVIVORS

Adriaan Penson



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Unraveling chronic fatigue in childhood cancer survivors

Adriaan Penson

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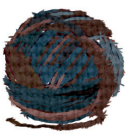
Chapter 1

General introduction



Childhood cancer and survivorship

Every year, more than 500 children are diagnosed with cancer in the Netherlands [1]. Of these patients, more than 80% survive the disease, compared to only 40% 60 years ago [2, 3]. This increasing survival rate has led to a growing number of childhood cancer survivors (CCS) [4]. Successful cancer treatment increases the risks for long term health issues, for example cardiovascular disease or secondary malignancies [5-8]. These health issues are so called late effects of treatment, as they are known to be directly related to the cancer treatment. Awareness of potential late effects is underscored in risk-based guidelines for childhood cancer survivorship [9, 10]. In the Netherlands, children who survive cancer for more than 5 years are referred to a LATER outpatient clinic, a clinic specialized in the care for late-effects of cancer treatment. During a regular check-up, survivors are screened for late effects so that health issues are detected timely and can be treated adequately. The survivors are seen by a specialized doctor and, depending on the cancer diagnosis and treatment that the survivors received, several assessments are done, according to international guidelines, to screen for high risk late effects. Based on the results of this screening, a personalized care-plan is formulated with advise on treatment or measures to prevent late effects. This care-plan is formulated in close collaboration with the survivor to meet his or her needs.

Fatigue as a late effect following treatment

Fatigue, described as a feeling of tiredness or exhaustion, is an often reported side-effect during childhood cancer treatment. Next to feelings of nausea and pain, fatigue is one of the most prevalent symptoms during treatment [11]. Even years after treatment, feelings of fatigue might still be present and affect a person's ability to work, do household chores or engage in sports and social activities [12-14]. Nevertheless, fatigue symptoms are not frequently discussed, as survivors may sometimes feel (social) barriers to do so or do not feel understood when they discuss their fatigue with family, friends or healthcare professionals [15, 16]. Not recognizing fatigue as a late effect of treatment that might affect a person's daily life was shown to be a barrier to seek proper medical help [16, 17]. Since it is difficult to adequately recognize problematic fatigue, it might not be discussed during a clinic visit and is easily missed. If it is recognized, little is known about how to effectively treat fatigue in CCS. It is important to better understand fatigue as a late effect, recognize it timely, assess the effects it has on the person's daily life and develop effective treatment strategies that suit the survivor's needs.

Definition of fatigue

It is difficult to define fatigue. When fatigue is reported during or following cancer treatment, it is often referred to as cancer-related fatigue (CRF). The definition of CRF differs widely across studies [18]. An often used definition was proposed by the National Comprehensive Cancer Network (NCCN), defining CRF as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning [19]. Using this definition, several key aspects can be identified:

1. It is a *subjective* feeling that can be physical, emotional and/or cognitive, meaning it can be experienced differently by individuals. This is important to keep in mind when assessing fatigue symptoms.
2. It is *persistent*, meaning that fatigue symptoms are experienced for a substantial period of time. This excludes fatigue symptoms that are proportional to recent physical, or other fatigue-inducing, activities which might explain acute fatigue that often subsides rapidly.
3. Fatigue symptoms have to be *related to cancer and/or cancer treatment*.
4. Fatigue *interferes* with usual functioning.

When aiming to research fatigue quantitatively, it is important to assess this subjective feeling reliable and systematically. This can be done using a questionnaire, as it reflects the subjective feelings of fatigue and a total score reflecting the severity of fatigue. The persistence of fatigue can be assessed by determining the duration of fatigue symptoms. A duration of six months was proposed to indicate chronic fatigue [20]. Key aspect 3 is more complicated as CCS are several years past diagnosis (in the Netherlands survivorship starts at 5 years post-diagnosis, but this can differ between countries and between diagnoses), which means that we often cannot directly link the fatigue to the childhood cancer treatment simply because we cannot exclude that other factors than the cancer and/or cancer treatment have induced the fatigue. For the current thesis, we focus on the first two key aspects and use the definition of chronic fatigue (CF): a subjective feeling of severe fatigue that persists for at least six months. Lastly, key aspect 4 shows that it is important to know what the consequences of having fatigue are on daily functioning.

Definition of chronic fatigue that is used throughout this thesis:
Chronic fatigue (CF) = a subjective feeling of severe fatigue, assessed with a validated questionnaire, that persists for ≥6 months.

What is already known and what are the aims of this thesis?

Prevalence of CF in CCS

A systematic review by van Deuren et al. [21] showed that, dependent on the methodology used to study fatigue, the prevalence of fatigue in CCS ranges widely from 0% to 61.7%. Differences in study populations (e.g. subgroups of CCS based on childhood cancer diagnosis, time since diagnosis or age), sample sizes and definitions used to study fatigue made it difficult to compare prevalence rates. One of the main aims of her thesis was to study the prevalence of fatigue in CCS [22]. Using the definition of CF as stated above, a prevalence of 26.1% was found in a nationwide cohort of CCS in the Netherlands [23]. This was significantly higher than the control group of siblings where a prevalence rate of 14.1% was found.

Screening and assessment

In the guideline of the International Guideline Harmonization Group (IGHG) it is recommend to regularly screen for fatigue during follow-up [24]. However, no short and easy to use screening instrument has yet been validated in CCS.

In **Chapter 2**, the Short Fatigue Questionnaire (SFQ) is presented as a potential screening instrument for severe fatigue. It is a short version of the Checklist Individual Strength (CIS), a questionnaire often used to assess fatigue severity, and has the potential to more swiftly and easily screen for severe fatigue. However, its psychometric properties and a validated cut-off score to indicate severe fatigue have not yet been determined.

In **Chapter 3**, we determine whether psychometric properties of the SFQ and the CIS are satisfying when applied in the CCS population. Psychometric properties of questionnaires might differ between populations, therefore it is important to know the population-specific psychometric properties of these fatigue measures.

Association and putative causation of chronic fatigue in CCS

With one in four CCS presenting with CF [23], it is a prevalent symptom that needs attention. One of the important questions to ask is “why do these CCS experience fatigue?” or in other words, what factors are related to CF in CCS and might play a role in triggering and/or maintaining the fatigue? In previous studies, several parameters have been associated with fatigue in CCS, varying from cancer related factors (e.g. cancer diagnosis or cancer treatment), demographics (e.g. age and sex), social factors (e.g. employment status and educational level), bio-physical factors (e.g. somatic health issues and inflammatory markers), lifestyle factors (e.g. body-mass index and

physical activity) and psychological factors (e.g. anxiety and depression) [21, 24, 25]. However, never have these factors been studied together, which is important as factors might influence each other's relation with fatigue.

In **Chapter 4,** we propose a model, including factors that have previously been associated with fatigue in CCS. This hypothesized model is analyzed in **Chapter 5** where the assumed triggering, maintaining and moderating factors of CF are presented.

A next step would be to determine how these factors are causally related. In **Chapter 6**, results of a structural equation modeling (SEM) are presented with the aim to show possible causal relationships of the associated factors found in **Chapter 5** and CF. SEM is an approach that can be used to asses potentially causal relationships between factors using cross-sectional data.

Fatigue is a multidimensional symptom. It would be valuable to determine whether subgroups of CCS can be identified who experience different types of CF. If so, it would be interesting to investigate if subgroups differ on fatigue-related factors and characteristics to determine whether specific treatment strategies might be more suitable for a certain subgroup. In **Chapter 7** we zoom in on the group of CCS with CF and determine whether subtypes can be identified. The CIS dimensions *concentration*, *motivation,* and *physical activity* are used to indicate different dimensions of fatigue. If we find subgroups, we will determine their characteristics.

Consequences of chronic fatigue in CCS

In cancer survivorship care, the management of late effects and reducing their impact on a person's well-being has become a key goal [26]. To refer to a person's well-being, the term health-related quality of life (HRQOL) is often used [27]. HRQOL is the multidimensional assessment of a patient's perception on overall function and wellbeing and it covers a broad spectrum including the physical, cognitive, emotional and social functioning of a person. Childhood cancer and treatment negatively impact the HRQOL of patients and even years after treatment the HRQOL of CCS remains impaired compared to the general population [28-30]. Previous studies have suggested that fatigue might play a role in this decreased HRQOL in CCS [31-34]. However, only subgroups of CCS were studied (focusing on specific diagnoses or age groups) or the definition of CF was not met, making it difficult to distinguish between acute and chronic fatigue. Also, to know the impact of CF, it is important to adjust for other factors that might impact HRQOL, like age, sex, educational level, employment status and other health issues [29, 35].

Although we know that CF is a debilitating symptoms that might negatively impact the daily lives of survivors, the relation between CF and various aspect of HRQOL remains unknown. **Chapter 8** describes the impact CF has on HRQOL domains.

Finally, **Chapter 9** provides a summary of all chapters and in **Chapter 10** we discuss the findings reported on in this thesis, relate them to the literature and consider the clinical implications the findings might have. Also, directions regarding future research are discussed.

Dutch Childhood Cancer Survivor Study

The studies reported on in this thesis use data from the Dutch Childhood Cancer Survivor Study (DCCSS) LATER part 2 [36]. This cross-sectional clinical study was a nationwide collaboration of seven pediatric oncology centers in the Netherlands, of which the Radboudumc Nijmegen was one, with the aim to study late effects after treatment for childhood cancer. This fatigue study was one of the studies that were part of the project that was conducted between 2017 and 2020.

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Chapter 2

Short Fatigue Questionnaire: Screening for severe fatigue

Adriaan Penson, Sylvia van Deuren, Margreet Worm-Smeitink, Ewald Bronkhorst, Frank H. J. van den Hoogen, Baziel G. M. van Engelen, Marlies Peters, Gijs Bleijenberg, Jan H. Vercoulen, Nicole Blijlevens, Eline van Dulmen-den Broeder, Jacqueline Loonen, Hans Knoop

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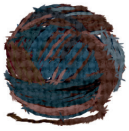

Abstract

Objective: To determine psychometric properties, a cut-off score for severe fatigue and normative data for the 4-item Short Fatigue Questionnaire (SFQ) derived from the multi-dimensional fatigue questionnaire Checklist Individual Strength (CIS).

Methods: Data of previous studies investigating the prevalence of fatigue in ten chronic conditions (n=2985) and the general population (n=2288) was used to determine the internal consistency (Cronbach's alpha) of the SFQ, its relation with other fatigue measures (EORTC QLQ-30 fatigue subscale and digital fatigue diary), a cut-off score for severe fatigue (ROC analysis) and to examine whether the four SFQ items truly measure the same construct. Norms were calculated for ten patient groups and the Dutch general population.

Results: Cronbach's alpha of the SFQ were excellent in almost all groups. Pearson's correlations between the SFQ and the EORTC-QLQ-C30 fatigue subscale and a fatigue diary were respectively 0.76 and 0.68. ROC analysis showed an area under the curve of 0.982 (95% CI: 0.979 – 0.985) and cut-off score of 18 was suggested which showed a good sensitivity (0.984) and specificity (0.826) as well as excellent values for the positive and negative prediction values within all groups using the CIS as golden standard. Factor analysis showed a one factor solution (Eigenvalue: 3.095) with factor loadings of all items on the factor being greater than 0.87.

Conclusion: The SFQ is an easy to use, reliable and valid instrument to screen for severe fatigue in clinical routine and research.

Introduction

Fatigue, defined as a sense of tiredness, lack of energy or feeling of exhaustion, is a common symptom in several clinical conditions [1]. Persistent severely fatigued persons, indicated as such by a cut-off score on a validated fatigue questionnaire, are limited in their daily functioning, visit their physician more often and have an increased risk for developing other diagnoses [2, 3]. It is important to identify and monitor the severity of fatigue and provide proper care to patients who are affected by it. Being a multidimensional, subjective experience, fatigue is best measured by the use of a questionnaire consisting of several subscales with multiple dimensions. The Checklist Individual Strength (CIS) [4] is an example of a reliable fatigue questionnaire containing multiple subscales assessing different dimensions of fatigue. This 20-item instrument is well validated and used in various patient groups [4-7]. However, the CIS, but also other instruments like the Multidimensional Fatigue Instrument (MFI) [8] or the Chalder Fatigue Scale (CFQ) [9], are relatively long. In clinical routine it is desirable to have a screening instrument that measures fatigue swiftly and is easy to administer. The Shortened Fatigue Questionnaire (SFQ), a 4-item version of the CIS, is such a questionnaire [10, 11]. The four items of the SFQ have, being part of the CIS, been translated into English, German, Spanish, Swedish, French, Portuguese, Turkish, Italian, Polish, and Japanese. For its use in clinical routing, it is essential to have a validated cut-off score to indicate the presence of severe fatigue. Most fatigue scales lack such a cut-off score making them less suitable for the management of fatigue in clinical practice. An example of a short fatigue questionnaire with a validated cut-off score is the Fatigue Severity Scale (FSS) [12]. However, next to having more than twice as much items compared to the SFQ, to calculate a total score of the 9 FFS items several calculations need to be carried out which make its use as a screening instrument less optimal. The availability of a short, easy to administer fatigue questionnaire with a validated cut-off score can aid assessment of clinical relevant levels of fatigue. The aim of the current study is to determine psychometric properties of the SFQ, a cut-off score indicating severe fatigue and to present normative data of a wide range of chronic conditions and the general population.

Methods

Participants

SFQ data were derived from the CIS, gathered in previous studies for the following participants: A sample of the general Dutch population (n=2288), derived from CentERdata [13], a research institute at Tilburg University in the Netherlands with

access to data of a large panel reflecting the distribution of the Dutch population in age, sex, education level, and social and economic status; Patients with chronic fatigue syndrome (CFS, n=1407) [14] meeting the revised 2003 US Centers for Disease Control and Prevention criteria for CFS [15, 16]; Patients with Diabetes type 1 (n=214) [17], Rheumatoid Arthritis (RA, n=228) [18], advanced cancer (n= 135) [19], Facioscapulohumeral Muscular Dystrophy (FSHD, n=137) [20], Myotonic Dystrophy (MD, n=320) [20], Hereditary Motor and Sensory Neuropathy type 1 (HMSN, n=136) [20], Chronic Obstructive Pulmonary Disease (COPD, n=160) [21], breast cancer survivors (n= 150) [22] and cancer survivors treated with stem cell transplantation (SCT, n=98) [23].

Additional participants

Extracting SFQ from CIS: Although identical, the four items of the SFQ may be answered differently when being part of a more extensive questionnaire (CIS). To investigate this possible difference, the SFQ and CIS were completed by patients who were consecutively referred to a tertiary treatment center for chronic fatigue (Fatigued group 1 (FG1), n=127).

Cut-off score: People referred to a tertiary treatment center for chronic fatigue between 2000 and 2016 were included. This group consisted of patients with medically unexplained fatigue, possibly meeting CDC criteria for CFS, as well as patients with a chronic medical condition and patients who were successfully treated for cancer but reported fatigue (Fatigued group 2 (FG2), n=4854). SFQ total scores were derived from the CIS which they completed as part of their assessment.

A description of all participants is given in Table 1 in appendix A.

SFQ

The Shortened Fatigue Questionnaire (SFQ) [10] consists of four items ('I feel tired', 'I tire easily', 'I feel fit' and 'I feel physically exhausted'; see appendix B). Each item is scored on a 7-point Likert Scale, ranging from 1 'yes, that is true' to 7 'no, that is not true'. Scores of items 1, 2 and 4 are reversed and then all item scores are added up which results in a total score varying from 4-28. Higher scores reflect a higher level of fatigue.

Other fatigue measures

The EORTC-QLQ-C30 [24], a questionnaire to assess quality of life containing 15 subscales (one assessing fatigue), was completed by the participating cancer survivors (n=247, one participant had missing data) [22, 23].

An electronic fatigue diary (EFD) was completed to assess fatigue in 68 of the Diabetes type 1 participants [17]. At the day of assessment, these participants were asked to indicate their fatigue status at that particular moment on a visual analog scale. They scored their level of fatigue six times during that day with the mean score representing their fatigue severity.

Statistical analyses

IBM SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) was used for all statistical analyses.

Extracting SFQ from CIS: Total mean scores of the SFQ and corresponding CIS items completed by FG1 were compared using a paired samples t-test.

Factor analysis: To investigate if the items of the SFQ indeed measure one underlying variable, we conducted a confirmatory factor analysis (CFA) in the general Dutch population cohort (n=2288) by means of a principal component analysis including all four items. We expected to find one factor, representing fatigue severity. Item correlation matrix, Kaiser-Meyer-Oklin (KMO) test and Bartlett's test of sphericity were calculated to test adequacy of the data for CFA. Model fit was examined using the Root Mean Square Error of Approximation (RMSEA), with a value < 0.06 as a cut-off value to indicate good model fit [25]. A Scree plot was calculated to examine the possibility of a 2- or more factor solution.

Psychometric properties: Cronbach's alpha was calculated for all groups to determine the internal consistency. To gain insight in the construct validity, Pearson's correlations were calculated between the SFQ and the EORTC-QLQ-C30 fatigue subscale and between the SFQ and the EFD.

Cut-off score: Receiver Operating Characteristic (ROC) analysis was performed. FG2 was labeled severely fatigued. A healthy subgroup of the general Dutch population who reported no sick days in the past month (n=1906) was thought to not experience clinically relevant levels of fatigue (mean total SFQ score: 11.4, SD: 5.8) and was labeled not severely fatigued. In addition, for all plausible cut-off scores (determined by the ROC analyses) the positive prediction value (PPV; probability that a person is truly severely fatigued when indicated so by the total SFQ score) and negative prediction value (NPV; probability that a person is truly not severely fatigued when indicated so by the total SFQ score) were calculated using the validated cut-off score (≥ 35) of the CIS fatigue subscale (CIS-fatigue) [50] to indicate true 'cases' and 'non-cases'.

Normative data: Mean total scores and quartile scores of the SFQ were calculated for all groups.

An overview of the analyses that were conducted in each participant group is given in Table 1 in appendix A.

Results

Extracting SFQ from CIS

Mean total score of the SFQ and of the same four items being part of the CIS showed no significant difference (-0.19; 95% CI -0.52-0.15; p-value = 0.27).

Factor analysis

The data was adequate to perform CFA: Item correlation matrix showed all coefficients ≥ 0.75, KMO value was 0.85 and Bartlett's test of sphericity was significant (p<0.001). CFA showed a one factor solution (Eigenvalue: 3.095) explaining 77.4% of the variance with factor loadings of all items on the factor greater than 0.87. A two-, three- or four factor solution resulted in Eigenvalues smaller than 1, confirming a one-factor solution (Figure 1). RMSEA had a value of 0.0012 which supports a good model fit.

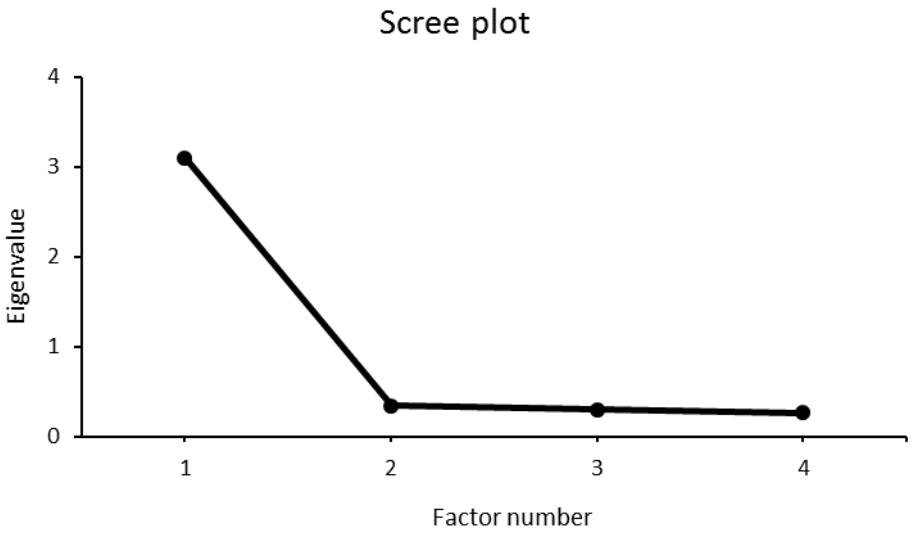

Figure 1. Scree plot showing the Eigenvalues of different factor solutions

Psychometric properties of the SFQ

Cronbach's alpha is presented for all groups in Table 3 in appendix A and, except for the CFS patients (0.57), showed acceptable to excellent values (0.72 – 0.92). Pearson's correlation between SFQ total score and the EORTC-QLQ-C30 subscale fatigue score was 0.76 and between the SFQ and the EFD 0.68.

Cut-off score

ROC analysis showed an area under the curve of 0.983 (95% CI: 0.980 – 0.986). Table 1 shows the sensitivity and specificity of several possible cut-off points for the SFQ. A cut-ff score of 22 resulted in the highest combined sensitivity and specificity. A cut-off score of 18 showed a high sensitivity (0.986) and specificity (0.826) and resulted in an excellent combined PPV and NPV for all groups. Table 2 in appendix A shows the PPV and NPV of these two plausible cut-off scores for all groups.

Normative data

Population norms of all groups are presented in Table 3 in appendix A.

Table 1. Sensitivity and Specificity for best fitting cut-off points of the SFQ

Cut-off point (equal or higher = Severe Fatigue)*	Sensitivity (%)	Specificity (%)
17	99.1	78.4
18	98.6	82.6
19	98.1	86.0
20	97.1	88.3
21	96.0	91.9
22	94.1	94.3
23	89.6	95.5
24	85.6	97.3

*A range of possible cut-off points is shown.

Discussion

Psychometric characteristics of the SFQ were shown to be adequate. Cronbach's alpha was high for almost all study populations, except for the CFS population. A plausible explanation for the latter could be the fact that the CFS group scored extremely high on the SFQ decreasing the variance of the item- and total scores. The reason

why this group scored this high on the SFQ is explained by the fact that one of the criteria to meet the case definition of CFS is scoring above the cut-off score of 35 on the CIS fatigue severity subscale. As the SFQ is derived from the CIS, this will lead to a restricted range of scores. This suggests that the internal consistency itself was not necessarily lower in the CFS population. The relation between the SFQ and other fatigue measures showed the construct validity to be satisfying.

A cut-off score to indicate the presence of severe fatigue was presented. From a clinical perspective we believe a cut-off score of 18 to best match the purpose of the SFQ as a screening tool. Next to a good sensitivity and specificity, it shows an excellent NPV, a value which was stressed to be of great importance for screening tools [26], for all groups. The higher the NPV, the higher the chance that a person is truly not fatigued when indicated as such by the SFQ. A high NPV is essential since it ensures that persons who are truly severe fatigued will not be overlooked. Severely fatigued persons as indicated by the SFQ will undergo more extensive fatigue assessment, including clinical history-taking and a multidimensional fatigue questionnaire. Persons wrongly identified as severely fatigued (a low PPV increases the chance of doing so) are thus filtered out. Therefore, we suggest a cut-off score of 18 (with excellent NPV's and good PPV's for all groups) to screen for severe fatigue. Screening needs to be followed by a more detailed assessment including a multi-dimensional fatigue questionnaire. In this way, the persistence, the person's functional impairment and other somatic or psychological factors which might be related to the fatigue symptoms can be determined.

To conclude, with good psychometric properties, a cut-off score for severe fatigue and population norms presented, the SFQ can be used as screening instrument to identify severe fatigue in the clinic as well as for medical research purposes.

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Supplementary material

APPENDIX A

Table 1. Description studypopulations

Group	N*	Recruitment	Definition	Mean age (SD)	% Female	Analyses applied**
General Dutch population	2288	Representative cohort of Dutch population (CentERdata)	Reflects the distribution of the Dutch population in age, sex, education level, and social and economic status	51.6 (17.1)	44	a,b,d
CFS	1407	**Consecutively referred patients from a tertiary treatment center for chronic fatigue**	All met the, in 2003 revised, CDC criteria for CFS and were referred for assessment and treatment **between 2007 and 2013**	37.5 (11.8)	74	a,b
Diabetes type 1	214	**Random sample of patients who visited a university outpatient clinic for diabetes**	Type 1 diabetes mellitus patients	47.9 (13.0)	53	a,b,c
RA	228	**Consecutively referred patients from a university outpatient clinic for rheumatology**	Diagnosed with RA by a rheumatologist according to the 1987 ACR classification criteria for RA. No history of malignancies or comorbidities that could cause fatigue	55.9 (10.8)	63	a,b
Advanced solid tumors	135	**Recruited from the Departments of Medical Oncology of a university medical center and a general hospital**	Diagnosis of advanced incurable solid tumors and receiving active treatment aimed at prolonging life	59	61	a,b
Breast cancer survivors	150	**Recruited from a university medical center and six regional hospitals**	**Breast cancer survivors who were off-treatment for at least 6 months and for maximal 5 years and who were younger than 50 years of age**	45.9 (6.3)	100	a,b,c

Table 1. Continued

Group	N*	Recruitment	Definition	Mean age (SD)	% Female	Analyses applied**
Survivors treated with SCT	98	**Recruited from the Department of Hematology at a university medical center**	Treated with SCT for leukemia or non-Hodgkin's lymphoma. Patients with graft-versus-host disease or anemia were excluded	44.8 (10.9)	42	a,b,c
FSHD	137	**Recruited from the Neuromuscular Center of a university hospital and the Dutch Neuromuscular Diseases Association**	Patients diagnosed with Facioscapulohumeral Muscular Dystrophy	43.7 (10.2)	50	a,b
MD	320	**Recruited from the Neuromuscular Center of a university hospital and the Dutch Neuromuscular Diseases Association**	**Patients diagnosed with adult onset Myotonic Dystrophy**	42.9 (10.0)	53	a,b
HMSN	136	**Recruited from the Neuromuscular Center of a university hospital and the Dutch Neuromuscular Diseases Association**	**Patients diagnosed with Hereditary Motor and Sensory Neuropathy type I**	42.5 (10.8)	60	a,b
COPD	160	**Recruited from three different pulmonary outpatient clinics in the Netherlands between 2002 and 2005**	**Patients diagnosed with COPD (GOLD stage 2-3) with no primary co-morbidity**	64.2 (9.1)	23	a,b
FG1	127	**Consecutively referred patients from a tertiary treatment center for chronic fatigue**	Persons referred to a tertiary treatment center for assessment of fatigue.	36.9 (13.5)	72	e
FG2	4854	**Recruited from a tertiary treatment center for chronic fatigue**	Persons referred to a tertiary treatment center for assessment of fatigue between 2000 and 2016	38.9 (13.0)	69	d

*Total number of included participants for data analysis is given. Participants of whom no SFQ score could be derived from the CIS were excluded from our study.

**Not all groups were used for all analyses. The following labels show which groups were used for which analysis: a= SFQ norm values b= internal consistency SFQ, c= construct validity SFQ, d=ROC analysis, e=validation of SFQ data collection (SFQ items extracted from completed CIS).

Table 2. PPV and NPV for SFQ cut-off scores 18 and 22

Group	Cut-off score 18		Cut-off score 22	
	PPV (%)	NPV (%)	PPV (%)	NPV (%)
General Dutch population	89.7	97.3	100	84.5
CFS*	n/a	n/a	n/a	n/a
Diabetes type 1	91.5	92.5	98.3	76.1
RA	90.0	94.5	100	78.9
Advanced solid tumors	87.1	95.4	100	71.7
Breast cancer survivors	92.9	94.7	100	80.9
Survivors treated with SCT	96.9	95.5	100	81.0
FSHD	96.3	87.7	100	60.2
MD	94.9	82.4	99.4	51.6
HMSN	95.2	86.5	100	63.6
COPD	76.9	95.0	100	87.3

CIS-fatigue was used as a "gold standard" with a cut-off score of 35 to indicate cases and non-cases.*CFS participants were included based on a CIS-fatigue score of 35 or higher and therefore no PPV and NPV scores could be calculated for this study group.

Table 3. Population norms SFQ

Group	N	Mean (SD)	25th	50th	75th	α
General Dutch population	2288	12.51 (6.32)	7	12	17	0.90
CFS	1407	25.97 (2.44)	25	27	28	0.57
Diabetes type 1	214	15.42 (7.77)	8	16	22	0.92
RA	228	16.14 (6.98)	11	16	22	0.88
Advanced solid tumors	135	16.26 (7.08)	10	18	22	0.89
Breast cancer survivors	150	14.77 (7.64)	8	15	21	0.90
Survivors treated with SCT	98	13.76 (7.16)	7	14	19	0.92
FSHD	137	18.20 (6.14)	14	19	23	0.85
MD	320	20.48 (6.08)	17	22	25	0.85
HMSN	136	19.12 (6.13)	15	20	24	0.86
COPD	160	13.64 (6.28)	9	13	17	0.72

Mean – and quartile scores are presented for the total score of the SFQ. Cronbach's alpha (α) is also presented.

APPENDIX B

Shortened Fatigue Questionnaire (SFQ)

◢ Amsterdam University Medical Centers

Expert Center for Chronic Fatigue

Name: ..... Gender : male/female

Date of birth: .....

Date of assessment: .....

This page contains four statements. Please indicate to what extent these statements apply to you by ticking one of the seven boxes next to the statement. Each box reflects how much the statement applied to you during **the past two weeks.**

For example, if you feel that the statement is entirely true, tick the left box as follows:

yes, that is true | X | | | | | | no, that is not true

If you feel that the answer is neither 'yes, that is true', nor 'no, that is not true' , tick the box that best matches how you felt.
For example:

yes, that is true | | | | X | | | | no, that is not true

Please reply to all four statements and tick only one box per statement.

1. I feel tired — yes, that is true | | | | | | | | no, that is not true
2. I tire easily — yes, that is true | | | | | | | | no, that is not true
3. I feel fit — yes, that is true | | | | | | | | no, that is not true
4. Physically, I feel exhausted — yes, that is true | | | | | | | | no, that is not true

Scoring SFQ

Amsterdam University Medical Centers

Expert Center for Chronic Fatigue

1.	I feel tired	Yes, that is true	7	6	5	4	3	2	1	no, that is not true
2.	I tire easily	yes, that is true	7	6	5	4	3	2	1	no, that is not true
3.	I feel fit	yes, that is true	1	2	3	4	5	6	7	no, that is not true
4.	Physically, I feel exhausted	yes, that is true	7	6	5	4	3	2	1	no, that is not true

Total score SFQ: .....

Chapter 3

Assessing fatigue in childhood cancer survivors: Psychometric properties of the Checklist Individual Strength and the Short Fatigue Questionnaire

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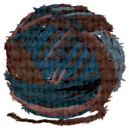

Abstract

Background: Fatigue is often reported by patients with childhood cancer both during and after cancer treatment. Several instruments to measure fatigue exist, although none are specifically validated for use in childhood cancer survivors (CCS). The aim of the current study was to present norm values and psychometric properties of the Checklist Individual Strength (CIS) and Short Fatigue Questionnaire (SFQ) in a nationwide cohort of CCS.

Methods: 2073 participants were included from the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort. Normative data, construct validity, structural validity and internal consistency were calculated for the CIS and SFQ. In addition, reliability, and a cut-off score to indicate severe fatigue were determined for the SFQ.

Results: Correlations between CIS/SFQ and vitality measures asking about fatigue were high (>0.8). Correlations between CIS/SFQ and measures of different constructs (sleep, depressive emotions, role functioning emotional) were moderate (0.4-0.6). Confirmatory factor analysis resulted in a four-factor solution for the CIS and a one-factor solution for the SFQ with Cronbach's alpha for each (sub)scale showing good to excellent values (>0.8). Test-retest reliability of the SFQ was adequate (Pearson's correlation = 0.88; ICC = 0.946; weighted Cohen's kappa item scores ranged 0.31-0.50) and a cut-off score of 18 showed good sensitivity and specificity scores (92.6% and 91.3% respectively).

Conclusion: The current study shows that the SFQ is a good instrument to screen for severe fatigue in CCS. The CIS can be used as a tool to assess the multiple fatigue dimensions in CCS.

Introduction

Cancer-related fatigue, defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning [1], is often reported by patients with childhood cancer both during and after (successful) cancer treatment. It was shown to be a debilitating late effect even years after treatment, limiting a person's daily functioning and affecting quality of life [2-4]. The National Comprehensive Cancer Network (NCCN) recommends to screen all cancer patients for fatigue regularly during and after treatment [1]. Fatigue is a subjective multi-dimensional phenomenon best assessed with a questionnaire [5]. Several instruments to measure fatigue exist, although none are specifically validated for use in adult childhood cancer survivors (CCS).

A frequently used multi-dimensional questionnaire to measure fatigue is the Checklist Individual Strength (CIS) [6]. It has a total of 20 items using four subscales to distinguish between fatigue severity, concentration problems, reduced motivation, and activity level. The CIS was validated in patients and survivors of adult-onset cancer [7], but not in CCS specifically .

The CIS can be a good instrument to assess the multiple dimensions of fatigue, but to screen for fatigue it is desirable to have a shorter instrument. Guidelines for survivors of adult cancer recommend screening for fatigue using a numerical rating scale (NRS) [1, 8], but this may not be a reliable screening technique in CCS as a single-item screening instrument was found to not be accurate for identifying cases of clinically significant fatigue in survivors of pediatric brain tumors [9]. With the current lack of an available adequate screening instrument, the international late effects of childhood cancer guideline harmonization group (IGHG) recommends screening for fatigue performing a short medical history asking about the survivor's feelings of tiredness and exhaustion [10]. Nonetheless, a systematic measure to indicate whether a person experiences severe fatigue would be preferable. A validated questionnaire with a cut-off score to indicate severe fatigue could be that measure.

A recent study showed that the Short Fatigue Questionnaire (SFQ) [11], a short version of the CIS, is an excellent instrument to screen for severe fatigue in the general population and several patient populations, among which survivors of breast cancer and adult hematologic cancer survivors [12]. With a cut-off score to indicate severe fatigue [12], the SFQ could be an objective screening instrument in CCS.

The SFQ and the CIS are questionnaires that are potentially useful in CCS care. The SFQ as short screening instrument and the CIS as multidimensional fatigue questionnaire have already shown to be valid in multiple patient populations, including cancer patients and survivors of adult-onset cancer [7, 12]. To test whether previously shown questionnaire properties are also applicable to CCS, validation of both instruments in this patient population is needed. The current study aim was to investigate psychometric properties of the CIS and the SFQ in a nationwide cohort of CCS. Additionally, to indicate how CCS score the CIS and SFQ compared to other populations, norm values are presented.

Methods

Participants

Participants were included from the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort [13]. This nationwide cohort CCS, diagnosed before the age of 18 between January 1st 1963 and December 31st 2001 in the Netherlands, was started for a multidisciplinary DCCSS LATER program for CCS late effect care and research. During a clinic visit, which took place in the period 2017 - 2020, data was collected for the study (details can be found elsewhere [14]). Among other questionnaires (described in detail below), the CIS and SFQ were completed by the participants. A subgroup of the participants completed the SFQ twice within one week, one during the clinic visit and a second one digitally at home (second version was part of a questionnaire survey for the whole study cohort which most participants already completed in 2013 except for a small subgroup who weren't able to participate in the original survey and were therefore asked to complete it for the current study). All participants gave written informed consent (if aged <16 (n=3), parents gave additional written consent). The study was approved by the Medical Research Ethics Committee of the Amsterdam University Medical Center (registered at toetsingonline.nl, NL34983.018.10).

Fatigue measures

CIS: The Checklist Individual Strength (CIS) [6] has 20 items (supplemental Table 1) and was designed to measure four fatigue dimensions, namely *fatigue severity* (CIS-fatigue; 8 items), *concentration* (5 items), *motivation* (4 items) and *physical activity level* (3 items). Some items are reversed before scores are added up (supplemental Table 1) to calculate the total score, which can range from 20-140 with a higher score corresponding to more problematic fatigue. A score of 35 or higher on the subscale *fatigue severity* indicates severe fatigue which was validated in the general Dutch population [7].

SFQ: The Short Fatigue Questionnaire (SFQ) [11] consists of four items (identical to four items of the CIS-fatigue; supplemental Table 1) measuring fatigue severity. Three item scores are reversed and then all item scores are added up, resulting in a total score that varies from 4-28 with a higher score reflecting more fatigue. The SFQ was validated in the general Dutch population and a cut-off score of 18 or higher was suggested to indicate severe fatigue [12].

Other measures

To determine the relationship between the CIS/SFQ and other (fatigue-related) measures, two health-related quality of life questionnaires that include aspects of fatigue (e.g. *vitality*) were completed:

TAAQOL: The TNO and AZL Questionnaire for Adult's Quality of Life (TAAQOL) [15] has 45 items assessing health-related quality of life (HRQOL) in twelve domains (*Gross motor function, Fine motor function, Cognitive function, Sleep, Pain, Social functioning, Daily activities, Sexuality, Vitality, Positive emotions, Aggressiveness, Depressive emotions*). The subscale *Vitality* contains four items which measure the occurrence of feelings of vitality. (supplemental Table 1). Scale scores were calculated following instructions described elsewhere [16] with higher scores indicating good HRQOL. The TAAQOL has been validated in both the general population and in patients with chronic diseases [15, 17].

SF-36: The Short-Form 36 (SF-36) assesses eight health concepts (*Vitality, Physical functioning, Bodily pain, General health perceptions, Role functioning physical, Role functioning emotional, Social functioning, Mental health*) [18]. The subscale Vitality consists of four items (supplemental Table 1), covering feelings of energy and fatigue. Scale scores were calculated following instructions described elsewhere [19], so that higher scores indicate better HRQOL. The SF-36 has been validated in several patient populations, among which cancer patients [20] and CCS [21].

The questionnaires were digitally completed during the clinic visit (participants who were not able to visit the clinic or who were not able to complete the questionnaires during the visit were asked to complete a digital or paper versions at home).

Statistical analysis

IBM SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) and *R* [22] were used to conduct the analyses (all tests with α=0.05). To examine possible selection bias between study participants and non-participants (eligible CCS that did not return informed consent or did not complete study questionnaires), groups were compared on sex, decade of birth, childhood cancer

diagnosis, decade of diagnosis, treatment with chemotherapy and /or radiotherapy (yes/no). Cramér's V were calculated to examine effects sizes of potential differences between the groups. 744 persons explicitly refused to participate (see flowchart in supplemental Figure 1) and were therefore excluded from this analysis.

Normative data: Mean total scores and percentile scores of the SFQ and CIS (total and subscale scores) were calculated.

Construct validity: Pearson's correlation between the CIS/SFQ and the vitality subscale of the TAAQOL and the SF-36 was calculated (convergent validity). As both vitality subscales assess symptoms of fatigue, strong correlations ($r \geq 0.7$) were expected. Pearson's correlation between the CIS/SFQ and the sleep and depressive emotions subscales of the TAAQOL and the role functioning emotional subscale of the SF-36 were also calculated (discriminant validity). We assume fatigue to be moderately related with the HRQOL concepts sleep, depressive emotions and emotional functioning (r between 0.4 and 0.7) because it concerns concepts that have certain overlap, but differ from fatigue as was pointed out by previous studies [23, 24].

Structural validity: Confirmatory factor analysis (CFA) was done to determine a single factor structure for the SFQ (fatigue severity) and a four-factor structure for the CIS (fatigue severity, concentration, motivation, physical activity). The structure of both instruments had already been validated in the general (Dutch) population [7, 12], however has yet to be confirmed in CCS specifically. Maximum likelihood estimation [25] with direct Oblimin rotation [26] was performed. Eigenvalues ≥ 1 were used to identify factors and then factor loadings for each item were calculated (>0.4 was considered good factor loading). Item correlation matrix, Kaiser-Meyer-Oklin (KMO) test and Bartlett's test of sphericity were calculated to test adequacy of the data to perform a factor analysis. Model fit was examined using the Root Mean Square Error of Approximation (RMSEA), with a value < 0.06 as a cut-off value to indicate good model fit [27].

Internal consistency: To indicate whether the items of the instruments measure the same underlying constructs, Cronbach's alpha was calculated for the SFQ and the four subscales of the CIS. It is a measure between 0 and 1 indicating how items hold together in a scale where >0.9 is seen as excellent, >0.8 as good, >0.7 as acceptable and <0.6 as poor internal consistency.

Reliability: To determine test-retest reliability of the SFQ, data from a subgroup of the participants (n=90) who completed the SFQ twice within one week, were analyzed in three ways (following Bruton, Conway & Holgate who proposed that a combination

of approaches is more likely to give a true picture of the instrument's reliability [28]). Pearson's correlation and Intraclass Correlation Coefficient (ICC) [29] between the two measurement moments were calculated for total scores and weighted Cohen's Kappa (Kw) [30] for all individual items of the SFQ. To calculate the ICC, a two-way random effects, absolute agreement, single measurement model was used [31]. The CIS was only completed once, therefore its test-retest reliability could not be investigated.

Cut-off score SFQ: To confirm whether the suggested cut-off score of 18 for the SFQ to determine severe fatigue can also be used in the CCS population, an ROC analysis was done. True 'severe fatigue cases' were determined using the cut-off score of 35 on the *CIS-fatigue*. Sensitivity (proportion of truly identified severe fatigue cases) and specificity (proportion of truly identified non-cases) were calculated for a range of possible cut-off scores for the SFQ (18 ± 2). Youden's index was calculated, a value between 0 and 1 with a higher value suggesting a better cut-off point [32, 33]. In addition, the positive prediction value (PPV; proportion of severe fatigue cases identified by the SFQ that are true cases) and negative prediction value (NPV; proportion of non-cases identified by the SFQ that are truly non-cases) were calculated.

If a participant had one or more missing values for the CIS/SFQ items and therefore no subscale score could be determined, the participant was excluded from the analyses of that particular subscale. Supplemental Table 1 shows the number of participants for each subscale.

Results

In total, 2073 participants (43.8% of eligible persons) were included in the current study (flowchart in supplemental Figure 1). A comparison with non-participants is shown in supplemental Table 3. There are no large differences between the groups (small effect sizes), suggesting no selection bias in the study cohort. Table 1 shows the participant characteristics.

Mean total- and subscale scores for the CIS and SFQ are shown in Table 2. Also, percentile scores (25^{th}, 50^{th} and 75^{th}) are presented.

Table 1. Participant characteristics (n=2073)

Characteristic	No.	%
Sex		
Male	1055	50.9
Female	1018	49.1
Age at participation (years)		
<20	67	3.2
20-29	593	28.7
30-39	770	37.1
≥40	643	31.0
Age at diagnosis (years)		
0-5	972	46.9
5-10	554	26.7
10-15	431	20.8
15-18	116	5.6
Primary childhood cancer diagnosis [a]		
Leukemia	736	35.5
Non-Hodgkin lymphoma [b]	243	11.7
Hodgkin lymphoma	141	6.8
CNS	192	9.3
Neuroblastoma	124	6.0
Retinoblastoma	11	0.5
Renal tumors	237	11.4
Hepatic tumors	18	0.9
Bone tumors	121	5.8
Soft tissue tumors	146	7.1
Germ cell tumors	72	3.5
Other and unspecified [c]	32	1.5
Period of childhood cancer diagnosis		
1960-1969	31	1.5
1970-1979	284	13.7
1980-1989	640	30.9
> 1990	1118	53.9
Childhood cancer treatment [d]		
Surgery only	143	6.9
Chemotherapy, no radiotherapy	1112	53.6
Radiotherapy, no chemotherapy	106	5.1
Radiotherapy and chemotherapy	700	33.8
No treatment or treatment unknown	12	0.6

[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3).

[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas.

[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

[d] Treatment data included primary treatment and all recurrences.

Normative data

Table 2. Norm values for the CIS and SFQ

	N*	Mean (SD)	25th	50th	75th
CIS					
Fatigue severity (range 8-56)	2059	25.89 (13.14)	14.0	24.0	36.0
Concentration (range 5-35)	2055	14.98 (7.82)	9.0	13.0	21.0
Motivation (range 4-28)	2061	10.36 (5.38)	6.0	9.0	14.0
Activity (range 3-21)	2060	9.24 (5.23)	5.0	8.0	13.0
Total score (range 20-140)	2038	60.44 (26.85)	38.0	57.0	80.0
SFQ					
Total score (range 4-28)	1998	13.36 (7.32)	7.0	13.0	19.0

*Sum scores were calculated when all items for that particular scale were completed by the participant.

Construct validity

Pearson's correlations between the total score of the CIS/SFQ and the vitality, sleep and depressive emotions subscales of the TAAQOL and the vitality and emotional role functioning subscales of the SF-36 are shown in Table 3. Correlations between CIS/SFQ and the vitality subscales were high (>0.8), indicating good convergent validity. Correlations between CIS/SFQ and the HRQOL domains sleep, depressive emotions and role functioning emotional were moderate (between 0.4 and 0.6), indicating good discriminant validity.

Table 3. Pearson's Correlations between total scores of the CIS and SFQ and subscales of the TAAQOL and SF-36

	CIS	SFQ
TAAQOL		
Vitality	-0.857	-0.889
Sleep	-0.471	-0.451
Depressive emotions	-0.574	-0.507
SF-36		
Vitality	-0.841	-0.844
Emotional role functioning	-0.522	-0.461

All correlations were statistically significant ($p<0.01$)

Structural validity

CIS: Item correlations for items of the same subscale ranged 0.51-0.82 and for items of different subscales 0.28-0.78. KMO test showed a value of 0.96, Bartlett's test of sphericity was significant (p<0.001) and the RMSEA was 0.07. CFA resulted in a four-factor solution with each factor explaining 53.7%, 11.0%, 6.4% and 5.0% of the variance respectively (76.1% total variance explained). In supplemental Figure 2A the Scree plot is shown, confirming a four-factor solution. The Eigenvalues for the four factors and factor loadings of all items (range 0.443 – 0.925) are shown in supplemental Table 2. All items loaded good (>0.4) on their original subscale, with items 14 and 20 loading good on 2 subscales (*fatigue severity* and *activity* subscale).

SFQ: Item correlations were all >0.7, KMO test showed a value of 0.84, Bartlett's test of sphericity was significant (p<0.001) and the RMSEA was 0.13. CFA resulted in a one-factor solution explaining 81.1% of the variance. In supplemental Figure 2B the Scree plot is shown with an Eigenvalue of 3.245 confirming a one-factor solution. Supplemental Table 2 presents the factor loadings of the items, which were all good (range 0.785 – 0.939).

Internal consistency

Cronbach's alpha for the subscales *fatigue severity, concentration*, *motivation* and *physical activity level* of the CIS were 0.95, 0.91, 0.85 and 0.91 respectively (alpha for all 20 items was 0.95), indicating good to excellent internal consistency. Cronbach's alpha for the SFQ was 0.92 indicating excellent internal consistency.

Reliability

A total of 90 participants completed the SFQ twice within one week. 39 participants completed both SFQ questionnaires on the same day, 51 participants completed the second SFQ within a week of the first one (mean number of days between both measurements was 4 days; n=90). Pearson's correlation between total scores of the two SFQ measurements was high (0.88; p<0.001) and the ICC was excellent (0.946; 95%CI: 0.907-0.967). Kw scores for item 1-4 were 0.50, 0.43, 0.31 and 0.34 respectively (all p<0.01) reflecting fair to moderate item agreement.

Cut-off score SFQ

ROC analysis showed an area under the curve of 0.974 (95% CI: 0.969 – 0.980). Sensitivity and specificity of the suggested cut-off score of 18 (± 2) are presented in Table 4. This table also shows the PPV and NPV. The suggested cut-off score of 18 had the highest value for the Youden's index (highest combined sensitivity and specificity) and showed good PPV and NPV.

Table 4. Sensitivity, specificity, positive prediction value (PPV) and negative prediction value (NPV) of several SFQ cut-off scores

SFQ total score	Sensitivity %	Specificity %	PPV %	NPV %
16	97.0	81.8	68.1	98.6
17	95.4	87.0	74.7	97.9
18	92.6	91.3	81.0	96.9
19	86.1	94.6	86.5	94.4
20	75.9	97.2	91.5	90.9

Discussion

The aim of the current study was to present norm-values and psychometric properties of the SFQ, a four-item screening instrument for severe fatigue, and the CIS, a multidimensional fatigue questionnaire, in a nationwide cohort of CCS. Results show psychometric properties of the SFQ and CIS to be good in CCS and therefore the SFQ can be used to screen for severe fatigue in this population and the CIS can be used to evaluate the multiple fatigue dimensions.

The IGHG guideline [10] suggests to screen regularly for severe fatigue, however no screening instrument had yet been validated in CCS. Single-item screening (with the Fatigue Thermometer) was shown to not be reliable to indicate clinically significant fatigue in survivors of adolescent brain tumors [9] suggesting a multiple-item instrument to be more optimal for screening in CCS. With the lack of a validated screening instrument, it is currently suggested to screen for fatigue by performing a medical history focused on the survivors feelings of tiredness and exhaustion (at every long-term follow-up visit). Recommended questions to ask are “do you get tired easily” or “are you too tired or exhausted to enjoy the things you like to do” [10]. The first of these questions is asked in the SFQ, accompanied by questions asking about exhaustion and fitness level. Looking at the suggestions made in the guideline, the SFQ meets the requirements to screen for fatigue in CCS. The current study showed psychometric properties of the SFQ in CCS to be adequate plus the suggested cut-off score of 18 to indicate severe fatigue showed the highest combined sensitivity and specificity, in addition to a good PPV and NPV in CCS and can therefore be perfectly used for fatigue surveillance.

The guideline further suggests additional testing with a validated fatigue measure for survivors with an indication for severe fatigue [10]. The *PedsQL Multidimensional*

Fatigue Scale or the *PROMIS Pediatric Fatigue measure* are suggested as both have been validated in CCS [34, 35]. However, psychometric properties presented in those studies are limited. Psychometric properties presented of the *PedsQL* by Robert et al. [34] are good (Cronbach's Alpha of total score and three subscales all ≥0.88), but other psychometric properties remained to be determined. Also, the cohort in which the study was conducted was relatively small (n=64) and did not include all childhood malignancies (only CNS, hematological, lymphoma and solid tumor cancer diagnoses were included). The study by Hinds et al. [35] showed the *PROMIS Pediatric Fatigue measure* to be a valid instrument to distinguish different levels of fatigue and that it is feasible for cancer patients and survivor populations to properly complete the questionnaire. However, no psychometric properties of the PROMIS in CCS were presented and the studied cohort only included survivors of leukemia, lymphoma, brain tumors or solid tumors. The current study was the first to validate the CIS in a nationwide cohort CSS including all childhood malignancies and showed the CIS to be a good instrument to investigate multiple dimensions of fatigue. The structural validity we found in CCS (four-factor solution) is comparable to what has been reported in the general Dutch population [7], a Japanese working population [36], a healthy Portuguese population [37] and a population of patients with Rheumatoid Arthritis [38]. Item 14 (Physically I am in bad shape) and 20 (Physically I feel I am in good shape) had good factor loadings (≥0.4) for both the *fatigue severity* subscale and the *physical activity* subscale meaning these items could be used for both subscales. However, to ensure optimal comparison of subscale scores between different populations, we suggest using the original structure of the CIS (item 14 and 20 in *fatigue severity* subscale). Correlations with the vitality subscales of the SF-36 and TAAQOL was good (Table 3). A high correlation with these subscales that ask about (life) energy, tiredness and exhaustion mean that these issues and symptoms of fatigue are reflected in the total score of the CIS and SFQ as well. On the other hand, moderate correlations with the sleep, depressive emotions and role functioning emotional subscales show that the CIS and SFQ can discriminate well between fatigue and these, often with fatigue interfering, symptoms.

Norm values can help interpreting results. Subscale- and total norm scores of the CIS were comparable to norm scores of adult-onset breast cancer and hematological cancer survivors [7]. Compared to norms of the general Dutch population, CCS score higher on all subscales and the total score of the CIS. As previous literature showed symptoms of fatigue to be more prevalent in CCS compared to controls [4, 39, 40], it was expected that CCS would show higher norm values. Since no large differences in diagnosis and treatment related variables between participants and non-participants were found, we assume norm values of the current CCS study cohort to be generalizable.

A limitation of the current study was the lack of a gold standard for confirming the cut-off score of 18 for severe fatigue of the SFQ. No validated cut-off instrument to indicate severe fatigue was yet available in CCS and therefore we used the cut-off score of the CIS (≥35) as a gold standard in the current study. The current study showed the structure and internal consistency of the items and subscales of the CIS to be good and comparable to populations it is already been widely used in (general population, survivors of adult cancer) [7] and we therefore believe that the cut-off score of 35 can be safely used in CCS as well.

To conclude, with a growing population of cancer survivors worldwide and fatigue as a frequently reported late effect, structural screening for clinically significant fatigue will become more and more important. The current study shows the SFQ to be a good instrument to screen for severe fatigue in CCS. Would the SFQ indicate a person to be severely fatigued (total score ≥ 18), it is suggested to do additional testing and the CIS can then be used as a tool to assess the multiple fatigue dimensions.

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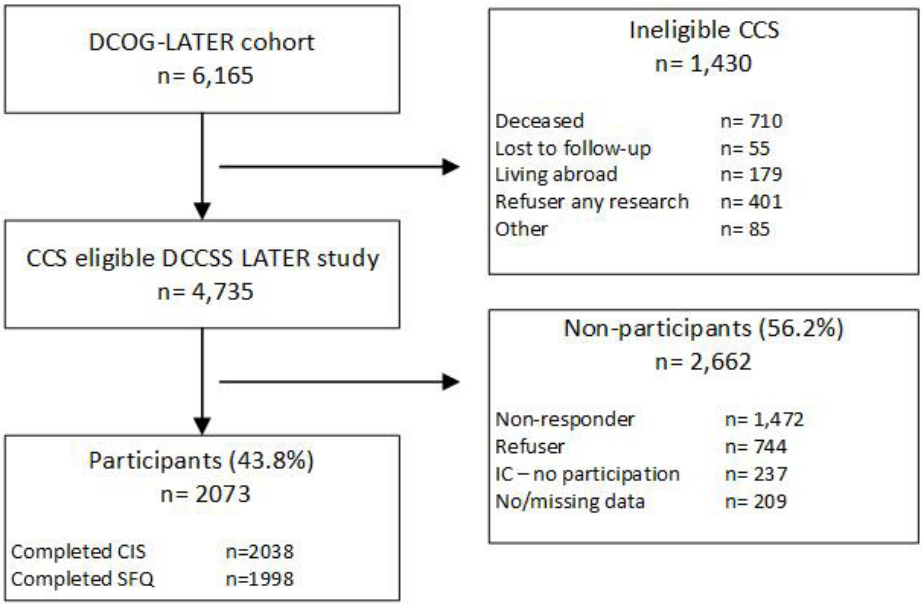
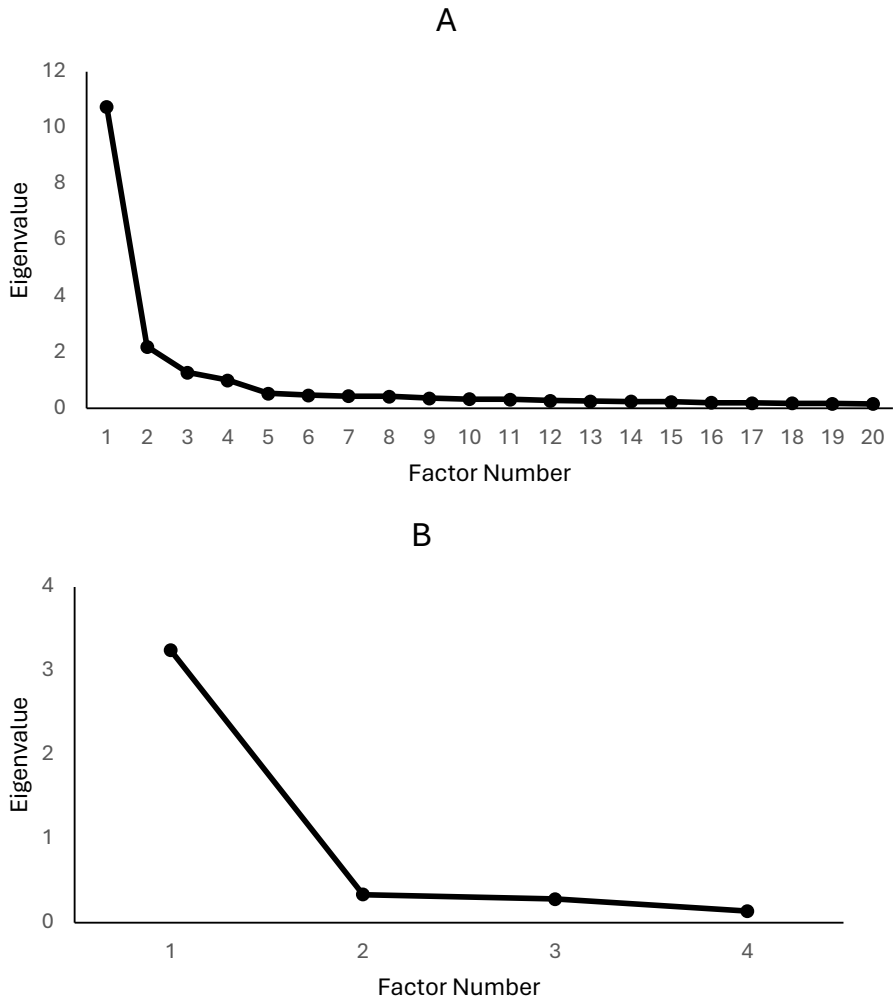
Supplementary material



Supplemental Figure 1. Flowchart of participant inclusion.



Supplemental Figure 2. Scree plots of the CIS (A) and SFQ (B).

Supplemental Table 1. Items of the fatigue measures

Item	Answer options	No. (%) [a]
CIS		2038 (98.3)
Please indicate to what extend the following statements applied to you during the past two weeks		
Subscale fatigue severity		2059 (99.3)
- I feel tired [c]	Yes, that is true ▫ ▫ ▫ ▫ ▫ ▫ ▫ No, that is not true	
- Physically, I feel exhausted [c]	"	
- I feel fit [b]	"	
- I feel weak [c]	"	
- I feel rested [b]	"	
- Physically I am in bad shape [c]	"	
- I tire easily [c]	"	
- Physically I am in good shape [b]	"	
Subscale concentration		2055 (99.1)
- Thinking requires effort [c]	Yes, that is true ▫ ▫ ▫ ▫ ▫ ▫ ▫ No, that is not true	
- When I am doing something, I can keep my thoughts on it [b]	"	
- I find it easy to concentrate [b]	"	
- It takes a lot of effort to concentrate on things [c]	"	
- My thoughts easily wander [c]	"	

Supplemental Table 1. Continued

Item	Answer options	No. (%) [a]
Subscale motivation		2061 (99.4)
- I feel very active [b]	Yes, that is true ▫ ▫ ▫ ▫ ▫ ▫ ▫ No, that is not true	
- I feel like doing all kinds of nice things [b]	"	
- I have a lot of plans [b]	"	
- I don't feel like doing anything [c]	"	
Subscale physical activity level		2060 (99.4)
- Physically I am very active [b]	Yes, that is true ▫ ▫ ▫ ▫ ▫ ▫ ▫ No, that is not true	
- Physically I am little active [c]	"	
- My physical activity level is low [c]	"	
SFQ		1998 (96.4)
Please indicate to what extend the following statements applied to you during the past two weeks		
- I feel tired [c]	Yes, that is true ▫ ▫ ▫ ▫ ▫ ▫ ▫ No, that is not true	
- I tire easily [c]	"	
- I feel fit [b]	"	
- Physically, I feel exhausted [c]	"	
TAAQOL subscale vitality		1758 (84.8)
During the past four weeks, did you feel		
- energetic?	▫ no ▫ a little ▫ some ▫ a lot	

Supplemental Table 1. Continued

Item	Answer options	No. (%) [a]
TAAQOL subscale vitality		1758 (84.8)
- tired?	"	
- fit?	"	
- exhausted quickly?	"	
SF-36 subscale vitality		1716 (82.8)
During the past four weeks, did you		
- feel full of life?	▫ always ▫ most of the time ▫ often ▫ sometimes ▫ rarely ▫ never	
- have a lot of energy?	"	
- feel worn out?	"	
- feel tired?	"	

[a] Number of participants that a subscale score could be calculated for.[b] Normal items scoring (yes, that is true =1, no, that is not true=7)[c] Reversed items scoring (yes, that is true =7, no, that is not true=1)

Supplemental Table 2. Factor loadings of items

CIS					
Items	**Factor 1 Fatigue severity**	**Factor 2 Concentration**	**Factor 3 Motivation**	**Factor 4 Activity**	**Communality**
Fatigue severity items					
1 I feel tired	0.925	0.038	0.023	0.073	0.838
4 Physically I feel exhausted	0.771	0.020	0.062	0.062	0.737
6 I feel fit	0.464	0.019	0.221	0.317	0.762
9 I feel weak	0.443	0.155	0.114	0.166	0.545
12 I feel rested	0.768	0.113	0.058	0.026	0.732
14 Physically I am in bad shape	0.453	0.011	0.043	0.551	0.698
16 I tire easily	0.799	0.045	0.002	0.072	0.761
20 Physically I feel I am in good shape	0.445	0.010	0.035	0.490	0.738
Concentration items					
3 Thinking requires effort	0.236	0.563	0.069	0.033	0.560
8 When I am doing something, I can keep my thoughts on it	0.063	0.881	0.008	0.013	0.732
11 I find it easy to concentrate	0.007	0.898	0.025	0.008	0.817
13 It takes a lot of effort to concentrate	0.004	0.864	0.021	0.015	0.734
19 My thoughts easily wander	0.011	0.775	0.014	0.020	0.611
Motivation items					
2 I feel very active	0.263	0.001	0.444	0.240	0.655
5 I feel like doing all kinds of nice things	0.080	0.042	0.838	0.033	0.710
15 I have a lot of plans	0.106	0.022	0.735	0.026	0.501
18 I don't feel like doing anything	0.112	0.140	0.623	0.010	0.617
Activity items					
7 I think I do a lot in a day	0.028	0.009	0.159	0.799	0.773
10 I think I do very little in a day	0.089	0.055	0.006	0.908	0.763
17 My physical activity level is low	0.065	0.072	0.015	0.794	0.768
Initial Eigenvalue	10.748	2.194	1.281	1.006	
Explained variance (total: 76.1%)	53.7%	11.0%	6.4%	5.0%	

Supplemental Table 2. Continued

SFQ		
Items	**Factor 1 Fatigue severity**	**Communality**
1 I feel tired	0.939	0.882
2 I tire easily	0.906	0.821
3 I feel fit	0.822	0.676
4 Physically I feel exhausted	0.785	0.617
Initial Eigenvalue	3.245	
Explained variance	81.1%	

Supplemental Table 3. Comparison participants vs. non-participants

Characteristic	Participants (n=2073)N (%)	Non-participants (n=1918)*N (%)	ES [e]
Female sex	1018 (49.1)	736 (38.4)	0.11
Decade of birth <1960	22 (1.1)	20 (1.0)	0.02
1960-1969	166 (8.0)	137 (7.1)	
1970-1979	539 (26.0)	479 (25.0)	
1980-1989	784 (37.8)	745 (38.8)	
≥1990	562 (27.1)	537 (28.0)	
Age at diagnosis 0-5	972 (46.9)	891 (46.5)	0.02
5-10	554 (26.7)	529 (27.6)	
10-15	431 (20.8)	376 (19.6)	
15-18	116 (5.6)	122 (6.3)	
Primary childhood cancer diagnosis [a]			
Leukemia	736 (35.5)	626 (32.6)	0.06
Non-Hodgkin lymphoma [b]	243 (11.7)	228 (11.9)	
Hodgkin lymphoma	141 (6.8)	142 (7.4)	
CNS	192 (9.3)	229 (11.9)	
Neuroblastoma	124 (6.0)	95 (5.0)	
Retinoblastoma	11 (0.5)	13 (0.7)	
Renal tumors	237 (11.4)	207 (10.8)	
Hepatic tumors	18 (0.9)	24 (1.3)	
Bone tumors	121 (5.8)	100 (5.2)	
Soft tissue tumors	146 (7.0)	147 (7.7)	
Germ cell tumors	72 (3.5)	79 (4.1)	
Other and unspecified [c]	32 (1.5)	28 (1.5)	
Childhood cancer treatment [d]			
Surgery only	143 (6.9)	232 (12.1)	0.14
Chemotherapy, no radiotherapy	1112 (53.6)	1098 (57.2)	
Radiotherapy, no chemotherapy	106 (5.1)	119 (6.2)	
Radiotherapy and chemotherapy	700 (33.8)	443 (23.1)	
No treatment/treatment unknown	12 (0.6)	26 (1.4)	
Recurrence			
No	1797 (86.7)	1699 (88.6)	0.03
Yes	276 (13.3)	219 (11.4)	

*Refusers (n=744) were excluded from the analysis.

[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3).

[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas.

[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

[d] Treatment data included primary treatment and all recurrences.

[e] Effect size, calculated as Cramér's V (<0.1=little, 0.1=low, 0.3=medium, 0.5=high).

Chapter 4

Methodology of the DCCSS LATER fatigue study: A model to investigate Chronic Fatigue in long-term survivors of Childhood Cancer

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Abstract

Background: A debilitating late effect for childhood cancer survivors (CCS) is cancer-related fatigue (CRF). Little is known about the prevalence and risk factors of fatigue in this population. Here we describe the methodology of the Dutch Childhood Cancer Survivor Late Effect Study on fatigue (DCCSS LATER fatigue study). The aim of the DCCSS LATER fatigue study is to examine the prevalence of and factors associated with CRF, proposing a model which discerns predisposing, triggering, maintaining and moderating factors. Triggering factors are related to the cancer diagnosis and treatment during childhood and are thought to trigger fatigue symptoms. Maintaining factors are daily life- and psychosocial factors which may perpetuate fatigue once triggered. Moderating factors might influence the way fatigue symptoms express in individuals. Predisposing factors already existed before the diagnosis, such as genetic factors, and are thought to increase the vulnerability to develop fatigue. Methodology of the participant inclusion, data collection and planned analyses of the DCCSS LATER fatigue study are presented.

Results: Data of 1955 CCS and 455 siblings was collected. Analysis of the data is planned and we aim to start reporting the first results in 2022.

Conclusion.: The DCCSS LATER fatigue study will provide information on the epidemiology of CRF and investigate the role of a broad range of associated factors in CCS. Insight in associated factors for fatigue in survivors experiencing severe and persistent fatigue may help identify individuals at risk for developing CRF and may aid in the development of interventions.

Background

Childhood cancer survival rate has improved significantly over the last few decades, with currently an expected 5-year survival rate of more than 80 percent [1-3]. Unfortunately, survival does not come without consequences of cancer treatment. Almost three quarters of Childhood Cancer Survivors (CCS) suffers from late effects following cancer treatment which can occur years or even decades after treatment [4]. A debilitating late effect is Cancer-Related Fatigue (CRF)[5]. The National Comprehensive Cancer Network (NCCN) has defined CRF as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning [6]. It differs from fatigue experienced by healthy individuals; CRF is more severe, more distressing, leads to disability and is less likely to be relieved by rest [7]. In addition, CRF most likely has a negative impact on quality of life (QoL) but thus far this has only been investigated in subgroups of CCS [8, 9].

Previous literature did not establish consensus about the prevalence and risk factors of CRF in CCS. A systematic review investigating CRF in CCS showed a wide range in prevalence rates (0% - 61.7%, n=18,682) [10]. In addition, a recently published guideline for the surveillance of CRF in childhood, adolescent, and young adult cancer survivors also showed a wide range of prevalence rates (10% - 85%, n=11,628) [11]. Both studies stated that clinical and statistical heterogeneity of previous literature made it difficult to compare the results and draw conclusions regarding CRF prevalence and risk factors. To gain knowledge on the prevalence and associated factors of CRF, a sufficiently large, systematic and comprehensive multicenter collaborative project was suggested [11].

Fatigue is a subjective, multifactorial symptom. Diverse factors such as age, sex, mental status and health status have, among others, been shown to influence fatigue [12]. As these factors are closely related, it is desirable to evaluate their relationship with fatigue following cancer in a multivariable model. In this way, possible associations between factors are taken into account and confounding is corrected for. An example of such a model was presented by Bower et al. [13], including diagnosis and treatment related factors and predisposing and maintaining factors to investigate the role of neuro-immune reactions on CRF in survivors of adult-onset cancer (ACS). Another multivariable model was presented by Koornstra et al. [14] to investigate CRF in cancer patients and included a vast array of associated factors among which were comorbidities, medication use and tumor related factors. Both models emphasize the importance of a multicausal and multidisciplinary approach to investigate CRF.

Studies using such models to investigate associated factors of CRF have focused on patients and survivors of adult-onset cancer [13, 14]. In the current study we will focus on CRF in CCS using a model which distinguishes between predisposing, triggering, maintaining and moderating factors (Figure 1).

Here, we describe the methodology of the Dutch Childhood Cancer Survivor Late Effect Study on fatigue (DCCSS LATER fatigue study). The aim of the DCCSS LATER fatigue study is to examine the prevalence of and factors associated with CRF in CCS, based on the presented model. Also, the impact of CRF on QoL in CCS will be investigated. This is the first study to use a nationwide (Dutch) cohort including all tumor types to investigate the role of a broad range of associated factors of CRF in CCS. Combining these factors in one study will hopefully increase the knowledge of CRF in CCS and enable adequate identification of risk groups.

Methods

2.1. Study design

The DCCSS LATER fatigue study is a cross-sectional study in a nationwide cohort of Dutch CCS. It is part of the DCCSS LATER study which is a comprehensive, multidisciplinary program for patient care and research into various late effects in CCS. Where the DCCSS LATER fatigue study focuses on fatigue as a late effect in CCS, other DCCSS LATER sub-studies focus on second primary malignancies, thyroid function, hormone deficiency, metabolic syndrome, reproductive potential, bone mineral density, sexuality and psychosexual development, cardiovascular toxicity, renal effects, pulmonary dysfunction, psychosocial consequences, splenic function, hyposalivation and benign sequalae. In all pediatric oncology centers in the Netherlands data was collected from patient files, questionnaires and during a visit at the expert clinic for late effects following cancer (LATER outpatient clinic). During the visit, which took place between 2017 and 2020, participants received regular medical care and simultaneously data was collected for the DCCSS LATER study. The DCCSS LATER fatigue study was approved by the Medical Research Ethics Committee of the Amsterdam University Medical Center (registered at toetsingonline.nl, NL34983.018.10). The study was carried out in accordance with the declaration of Helsinki [15].

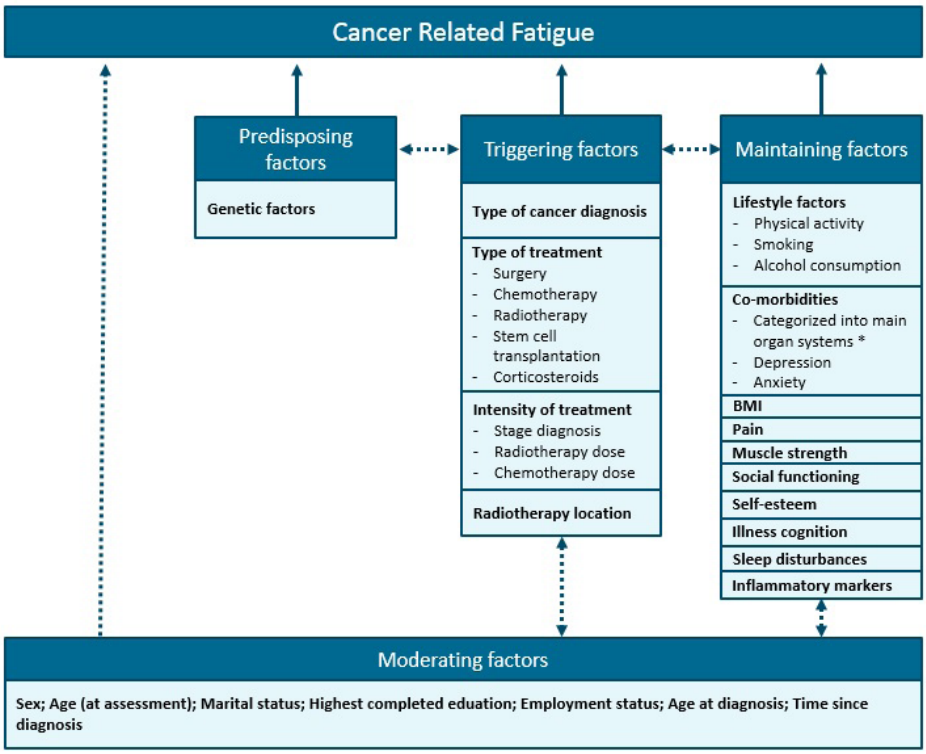

Figure 1. Hypothesized multivariable CRF model in CCS.

Model showing associated factors of CRF divided into predisposing- (genetic factors and blood biomarkers which are thought to impact the vulnerability to fatigue), triggering- (factors related to the cancer diagnosis and treatment during childhood and are thought to trigger fatigue symptoms), maintaining- (daily life- and psychosocial factors which may perpetuate fatigue once triggered) and moderating factors (factors which might influence the way fatigue symptoms express in individuals). Continuous lines: factors that are hypothesized to be directly related to CRF. Dashed lines: factors that are hypothesized to possibly act as moderator or confounder for other factors, but might also directly be related to CRF.BMI: Body Mass Index.* Included comorbidities are categorized into the following main organ systems: Neoplasms, Cardiac-, vascular-, respiratory-, gastro-intestinal-, hepatobiliary-, renal and urinary tract-, endocrine-, musculoskeletal-, ear-, eye-, nervous system-, and other conditions.

2.2. Objectives

The objectives of the DCCSS LATER fatigue study are to 1) investigate the prevalence of CRF in a cohort of CCS including all cancer types and 2) determine factors which might be associated with CRF in CCS. This study will provide an estimate of overall- and treatment specific risks for CRF in CCS. This knowledge should enable identification of groups at risk for developing fatigue following cancer treatment.

2.3. Current status of the study

At the moment of writing, data collection has already finished. Currently, the data is being cleaned by data-managers. The aim is to start with the analyses of the data in 2021.

2.4. The study population

Participants of the DCCSS LATER fatigue study were included from the DCCSS LATER cohort (n=6165). This is a nationwide cohort of five-year CCS diagnosed with histologically confirmed malignancies [16] or Langerhans cell histiocytosis before the age of 18 between January 1st 1963 and December 31st 2001 in the Netherlands. From this cohort, CCS living in the Netherlands who were alive on January 1, 2017, when the invitation process started, were invited to participate (Figure 2A). Participants gave written informed consent (or their parents when aged < 16 years, n=3).

2.4.1 Controls

Siblings: A control group consisting of siblings of CCS were included which enables matching on many unmeasured factors such as ethnicity, genetic background, culture, community, socioeconomic status and family environment. Survivors who participated in the study were asked to provide contact details of their siblings which were used to invite them to participate. Siblings, who have not had cancer and who can read and speak Dutch, and who gave written informed consent, were approached to participate in the sibling control group (Figure 2B).

Population controls: Data of Dutch population controls participating in the *Lifelines project* will be used as a second control group, since siblings may be affected by the disease history of their brother or sister in some way. These participants broadly represent the general Dutch population. *Lifelines* is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of approximately 167,000 persons living in the North East of The Netherlands [17]. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to health and disease of the general population. When we start data analysis for the DCCSS LATER fatigue study, *Lifelines* data of approximately 90.000 participants will be made available and will then be matched on age and sex with the survivors. The Lifelines control group will be substantially larger than the CCS study group, ensuring sufficient power to analyze differences in prevalence rates. Participants with a (self-reported) history of cancer will not be included in this control group.

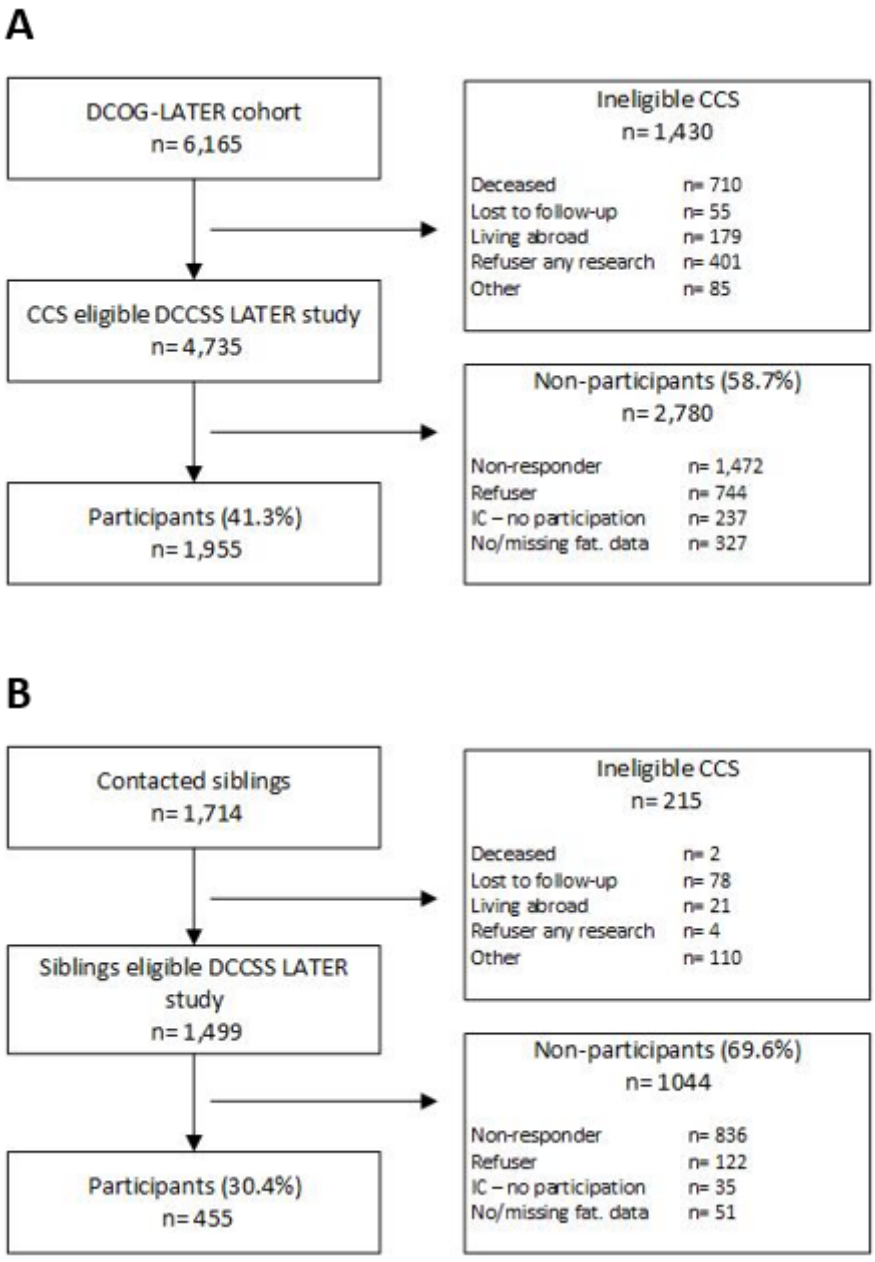

Figure 2. Flowchart.

A: Flowchart of the CCS participants. **B:** Flowchart of the sibling participants. IC – no participation: Gave consent, however did not participate. No/missing fat. data: Did not complete the Checklist Individual Strength subscale fatigue (CIS-fatigue), or duration fatigue symptoms was unknown. When only one item of the CIS-fatigue was missing, the missing value was imputed with the mean score of the other seven items (n=5 survivors and n=3 siblings). Participants with two or more missing values on the CIS-fatigue were excluded.

2.5. Data collection

Fatigue

The Checklist Individual Strength (CIS) [18], a 20-item questionnaire, scored on a 7-point Likert Scale, was used to assess fatigue severity. The CIS measures several aspects of fatigue using the subscales *fatigue severity* (CIS-fatigue; 8 items), *concentration* (5 items), *motivation* (4 items) and *physical activity level* (3 items). The total score ranges from 20-140 where a higher score corresponds with more problems in this area. The CIS is a reliable and valid instrument for the assessment of fatigue, with a score of 35 or higher on the *CIS-fatigue severity subscale* (range 8 – 56) indicating severe fatigue, which was validated in currently treated cancer patients and ACS [19].

Triggering factors

Factors related to the cancer diagnosis and treatment during childhood are thought to trigger fatigue. Information about the diagnosis and cancer treatment was collected by data-managers using a uniform and standardized protocol [20]. Details comprise information on treatment start and end dates, treatment type i.e. surgery, chemotherapy (CT), radiotherapy (RT) and stem cell transplantation (SCT), treatment dose of CT and RT and RT location. All treatment data cover treatments for the initial tumor and all recurrences plus RT boosts when applicable. Survivors who received radiotherapy will be categorized in groups dependent on the body part which was irradiated. We will distinguish between patients who received RT to the head, total body, spine, thorax, abdomen/pelvic region, neck, upper extremities and lower extremities (see Figure 1 in appendix A). Radiation-exposed volume to the head will be categorized into three groups (full-cranial-, partial-cranial- and no-cranial irradiation) following previously described methodology [21] and all irradiated regions will additionally be categorized according to dose tertiles. Survivors who received chemotherapy will be categorized in groups dependent on the specific agent they were given. We will distinguish between patients who received anthracyclines, platinum derivates, alkylating agents, vinca alkaloids and antimetabolites. Agents will additionally be categorized according to dose tertiles.

Moderating factors

Moderating factors might influence the way fatigue expresses in individuals. For example, females who received cancer treatment might experience different consequences compared to men who received the same cancer treatment. In that case, sex acts as a moderator leading to the development of fatigue symptoms in individuals who received cancer treatment. We believe that several demographic- and cancer treatment related factors (see Figure 1, moderating factors) may act as a moderator for

other included factors and are therefore presented as such in the hypothesized model (dashed lines from moderating factors to other factors). However, these factors may also directly influence CRF (dashed line from moderating factors directly to CRF). The exact role of these variables is yet to be determined and will be investigated by means of the planned analyses (see below). During the clinic visit, a questionnaire asking about the participant's demographic data (see Table 1 in appendix A) was completed. Age at diagnosis was collected and time since diagnosis was calculated.

Predisposing factors

Of the possible predisposing factors of fatigue, here the role of genetic factors will be studied. Genetic factors are thought to increase the vulnerability to develop fatigue. Venous blood samples were collected from survivors (n=1874) during the clinic visit after overnight fastening and stored at -80 degrees Celsius for future evaluation. From participants of whom we were not able to collect a blood sample and from survivors after allogeneic SCT, saliva samples were collected. A genome-wide association study (GWAS) will be carried out to identify genetic variants associated with fatigue.

Maintaining factors

Maintaining factors are daily life- and psychosocial factors which may perpetuate fatigue once triggered. During the clinic visit, height and weight of the participants was measured to calculate their body mass index (BMI). BMI will be categorized as follows: Underweight (BMI <18.5), normal weight (18,5≤BMI<25), overweight (25≤BMI<30), obesity (BMI≥30). Grip strength was measured using an analogue hand dynamometer. Grip strength was shown to be a good reflection of a person's muscle strength in general [22, 23]. Grip strength was measured four times (two times left arm, two times right arm) and the mean score will be used as an indication for muscle strength. Additionally, a general health questionnaire containing items about the participant's medical history and current medical state was completed on paper prior to the clinic visit (see Table 1 in appendix A for details). During the clinic visit, completeness of this questionnaire was checked by one of the research nurses and discussed with the participant when a question needed clarification. Self-reported health problems and comorbidities were validated by the physician. Comorbidities will be categorized according to previous published methodology [111] into main organ system categories: Neoplasms, Cardiac-, vascular-, respiratory-, gastro-intestinal-, hepatobiliary-, renal and urinary tract-, endocrine-, musculoskeletal-, ear-, eye-, nervous system-, and other conditions. Inflammatory markers (interleukin-1, interleukin-6, CRP) will be measured in the venous blood samples which were collected during the clinic visit. In addition, the following questionnaires were completed digitally on a laptop during the clinic visit:

TAAQOL

To assess QoL, the TNO (Netherlands Organisation for Applied Scientific Research) and AZL (Leiden University Medical Centre) Questionnaire for Adult's Quality of Life (TAAQOL) was completed [25]. The TAAQOL contains twelve subscales (Gross motor function, Fine motor function, Cognitive function, Sleep, Pain, Social functioning, Daily activities, Vitality, Happiness, Aggressiveness, Depressive moods) with a total of 45 items, each scored on a 4-point Likert scale. Crude scale scores are linearly transformed to a 0-100 scale with higher scores indicating better functioning. The questionnaire has been validated in both the general population as well as in patients with chronic diseases [25, 26]. The impact of fatigue on the health related domains of QoL in CCS will be reported on in a separate study.

HADS

The Hospital Anxiety and Depression Scale (HADS) [27] was used to assess the level of psychological distress. It asks the participant about anxious and depressive feelings in the past four weeks, each containing seven items on a 4-point Likert scale. The HADS was found to be able to assess symptom severity and caseness of anxiety disorders and depression in both somatic, psychiatric and primary care patients, and in the general population [28]. A cutoff score of ≥ 8 for both the anxiety subscale and the depression subscale can be used to identify possible cases [28]. The HADS was validated in different age groups of the Dutch population [29].

RSES

The Rosenburg Self-Esteem Scale (RSES) [30] was used as a measure for self-esteem. It contains ten items, each asking the participant about global self-worth on a 4-point Likert scale. The total score ranges from 10-40, where a higher score corresponds with a higher self-esteem. The RSES shows satisfying psychometric properties [31].

PSQI

The Pittsburgh Sleep Quality Index (PSQI) [32] was used to assess sleep quality. It assesses seven components (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction) which are scored 0 (no difficulty) to 3 (severe difficulty), making the total score range from 0-21. Psychometric properties are good and have been validated in several patient populations, including breast cancer patients [33, 34]. The PSQI can be used to screen participants for the presence of significant sleep disturbance with a cut-off score greater than 5 discriminating between good and poor sleepers [32].

SQUASH

The Short Questionnaire to assess health- enhancing physical activity (SQUASH) [35] was used to assess the participant's physical activity level. It measures how frequent, how intense and how long a participant carried out a certain type of activity (physical activity from and to work, physical activity at work, physical activity during spare time and physical activity doing household activities). The SQUASH is a valid instrument for categorizing adults according to the Dutch physical activity guideline [36].

ICQ

The Illness Cognition Questionnaire (ICQ) was used as an instrument to assess the participant's illness beliefs. It has 3 subscales (helplessness, acceptance and perceived benefits) each consisting of six items measured on a 4-point Likert scale, with a total score ranging from 18-72. Its psychometric properties were shown to be sufficient in patients with chronic diseases such as rheumatoid arthritis and multiple sclerosis [37] and in parents of a child with cancer [38].

An overview of the data we have collected and how the measures will be used to create the model parameters is shown in Table 2 in appendix A. This table also shows which parameters will be available for each group of participants, i.e. CCS, sibling controls and/or Lifelines controls. Survivors who were willing to be involved in research, but who declined a visit to the LATER outpatient clinic or who were not able to come in, were invited to participate in the questionnaire-part only which could be completed digitally at home.

To examine possible selection bias in the group of survivors that agreed to participate in the DCCSS LATER fatigue study, the following, anonymized, data of the survivors who declined to participate will be retained in the central database: sex, decade of birth, childhood cancer diagnosis, decade of diagnosis, treatment with chemotherapy and /or radiotherapy (yes/no).

2.6. Definition of fatigue

CRF, is thought to be related in time to the cancer diagnosis and treatment. However, to make the comparison with fatigue in the control groups who have not had cancer, the term CRF is not applicable. To enable a comparison between CCS and controls, we will use the term Chronic Fatigue (CF). For a reliable distinction between cases and non-cases, it is important to use a fatigue questionnaire with a validated cut-off score to indicate severe fatigue. It is also important to take into account the minimal duration of symptoms of at least six months which was proposed to define chronic fatigue [39] and has been used in other populations as well [8, 10, 40, 41].

We define CF as severe fatigue, indicated with a score of 35 or higher on the *CIS fatigue severity subscale* [19], which persists for at least six months. A question on symptom duration is part of the general health questionnaire, see Table 1 in appendix A.

2.7. Statistical analyses

To examine possible selection bias between study participants and persons who declined to participate, independent t-tests will be conducted to compare the groups on sex, decade of birth, childhood cancer diagnosis, decade of diagnosis, treatment with chemotherapy and /or radiotherapy (yes/no).

Prevalence rates of CF within the survivors and the two control populations will be presented descriptively. Logistic regression analysis will be done with CF (yes/no) as dependent variable and group (CCS, siblings, population controls) as independent variable to determine whether prevalence rates differ between groups.

To determine factors which might be associated with CF in CCS, a multivariable logistic regression analysis will be performed with CF as dependent variable and the triggering, maintaining and moderating factors as independent variables. The predisposing genetic factors will be analyzed in a separate sub-study. Multivariable logistic regression will produce an Odds Ratio (OR) for each possible risk factor (OR with 95% CI will be presented). Each group of factors will be entered as separate block of independent variables in the analysis. Each block will be analyzed both separately as well as in combination with the other blocks to examine the association of all factors with each other. In addition, structural equation modeling (SEM) will be applied [42]. To analyze structural relationships between factors we will apply both confirmatory analyses, by assuming a particular structure between variables and testing whether this structure is supported by the available data, and more exploratory analyses that search over different structures in an attempt to detect potential causal relationships [43, 44]. The analyses will be carried out in all three study groups (with the factors available for each specific group; CCS, sibling controls and population controls) to examine if associated factors differ between groups. We will test for multicollinearity.

IBM SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) and *R* [45] will be used for the statistical analyses.

Results

3.1 Study population

Characteristics of the total DCCSS LATER cohort (n=6165) can be found elsewhere [46]. Of this cohort, 4735 eligible CCS participants were invited to participate in the DCCSS LATER study. Data of 1955 CCS and 455 siblings was collected. In the following months, data will be checked on correctness and cleaned. Analysis of the data is planned for 2021 and we aim to start reporting the first results in 2022.

3.2 Expected results

We will report the prevalence of CF for CCS and two control populations. Factors associated with CF in CCS will be determined, distinguishing between predisposing, triggering, maintaining and moderating factors as presented in our model. Furthermore, we aim to create certain profiles which will help identify CCS at-risk for the development of CF.

Discussion

We presented the methodology of the DCCSS LATER fatigue study which will investigate CF in a nationwide cohort of CCS. The study presents a model discerning predisposing, triggering, maintaining and moderating factors of CF in CCS. Investigating a broad range of possible associated factors in a single study using clearly defined methods is expected to give insight into the prevalence and associated factors of CF in CCS and will enable comparison with other studies. We hypothesize the prevalence rate of CF in CCS to be around 25%. This number is based on the combined prevalence rates of severe fatigue seen in the included studies in the previous mentioned systematic review [10] with CCS aged 16-71 years at assessment. A pilot study conducted in a partly overlapping cohort of Dutch CCS (*unpublished data, Sylvia van Deuren et al.)* found a similar prevalence rate of CF using the Short Fatigue Questionnaire [47, 48] to indicate CF.

In our study, the predisposing factors studied are genetic factors that might be related to how sensitive a person is to develop CF following cancer and its treatment and might also influence the persistence of fatigue. Because of the massive scope of the GWAS in which we will analyze these genetic factors, this will be done in a separate study. It is assumed that triggering factors are related to the cancer diagnosis and treatment during childhood, starting CF. Maintaining factors are daily life-, psychosocial- and inflammatory factors that may perpetuate the fatigue once triggered. Moderating

factors might influence the way CF expresses in individuals. In the current study we included several demographic- and treatment related factors which might possibly act as moderators. An overview of all factors is shown in Figure 1, wherein all variables are shown that are believed to be related to fatigue. This relation can be direct (direct lines from factors to fatigue in Figure 1) or indirect (dashed lines between the factors in Figure 1), for example as a confounder, moderator or mediator to other variables. Using the presented model, we aim to investigate the precise contribution of all these variables to CF in CCS. Below, we hypothesize on the potential associated factors described in the model.

Fatigue model

The fatigue model presented is hypothetical and based on findings in the literature and on clinical experience in the LATER outpatient clinic. We hypothesize that the presented factors all play a role in the development and/or persistence of fatigue symptoms in CCS. We categorized the factors in a way we think to be appropriate and plausible. The precise role of each factor is yet to be examined. The model as presented in the current paper is meant as a starting point to create an overview of all possible associated factors. We aim, when the DCCSS LATER fatigue study is finished, to present a directed acyclic graph (DAG), a tool to help interpreting relationships in research [49], including only those variables that are directly related to CRF or act as a confounder, moderator or mediator.

Predisposing factors

It is suggested that genetic mechanisms are involved in subjective experiences such as fatigue in cancer survivors [50]. For example, breast cancer survivors with fatigue show higher expression of genes of the pro-inflammatory system that are under control of the transcriptions factor NF-κB, compared to non-fatigued survivors [51]. Identification of genetic factors associated with CF in CCS will aid to adapt treatment based on risk models predicting susceptibility to specific late effects. Such approaches are likely to get a more prominent role in survivor care in the future [52]. In a follow up study we will investigate in detail the relation between genetics and CF in CCS. Based on the above mentioned prevalence rate, we will be able to detect Odds Ratios of 1.6 or higher per allele (allele frequency of 0.3), however with the exploratory approach of the study we believe outcomes to still be interesting. In addition, this dataset can be used for validation of previous findings in literature and can be the basis for meta-GWAS with other similar cohorts.

Moderating factors

Several studies showed female sex to be associated with fatigue [53-56], making it likely that such an association will be present in CCS. Furthermore, age at diagnosis can influence the occurrence and severity of late effects [57, 58]. However, it is unknown whether age at diagnosis could influence the development of CF in particular. A systematic review conducted in CCS suggests age at diagnosis to not play a role in CF, however no pooled conclusion could be made [10]. Also, little is known about the relation between CF and age at assessment in CCS. It is hypothesized that a higher age at assessment is associated with CF as two studies showed higher prevalence of fatigue in older age groups of survivors compared to survivors of younger age [8, 59].

A meta-analysis in breast cancer survivors showed that having a partner decreased the risk of fatigue [60]. A questionnaire study focusing on demographic-, lifestyle- and treatment factors conducted in the DCCSS cohort showed marital status not to be related to CF (*unpublished data, Sylvia van Deuren et al.)*. We expect to find similar results. All these variables can directly act on the prevalence of CF or indirectly, via other variables such as type of treatment or diagnosis, in which case they act as moderator or confounder.

Triggering factors

Type and intensity of cancer treatment have been associated with an increased risk for the development of several late adverse effects [61, 62]. A systematic review by van Deuren et al. [10] included multiple studies investigating triggering factors for fatigue in CCS and concluded that due to differences in study methodology, no conclusion could be drawn. Previous mentioned questionnaire study (*unpublished data, Sylvia van Deuren et al.*) focusing on demographic-, lifestyle- and treatment factors conducted in the DCCSS cohort showed CCS with CNS tumors to have higher odds for reporting CF compared to other childhood diagnoses. In the current study, we will investigate the association of diagnosis- and treatment-related factors with CF in CCS in more detail including all factors described in the CRF model. We will not only examine the type of treatment (surgery, RT, CT, SCT) but also the relation of treatment intensity and RT location on fatigue. Using the proposed model, we will be able to correct for multiple possible confounding factors and by doing so, we will be able to elaborate on the precise role of diagnosis- and treatment-related factors in the development of CF in CCS.

Maintaining factors

Gielissen et al. [63] proposed maintaining factors to be responsible for the persistence of fatigue, based on a cognitive behavioral model of CRF in which it is assumed that cognitions and behavior can maintain fatigue. Factors such as, social functioning, illness cognitions and sleep disturbances are topics addressed during cognitive behavior therapy (CBT) which was shown to be an effective therapy to reduce fatigue in ACS [63]. A pilot study investigating CBT in CCS showed promising results [64] and another study showed a substantial overlap in cognitive behavioral factors that can maintain fatigue between CCS and patients with chronic fatigue syndrome or ACS [65]. This suggests that these factors also might play an important role in maintaining CF in CCS.

Physical and psychological comorbidities have also been associated with fatigue. For example, Mulrooney et al. [54] described that CCS with heart failure, pulmonary fibrosis, depression or obesity reported more fatigue and sleep disorders. Ho and colleagues [66] showed fatigue to be related to depression in survivors of both childhood- and adult onset cancer and Karimi et al. [67] investigated the relation between depression and fatigue in CCS specifically and also showed a significant association. In contrast to Goërtz et al. (*unpublished data, Yvonne MJ Goërtz et al.*), who showed that factors associated with fatigue in several chronic conditions are not disease specific, but generic. They suggest a trans-diagnostic approach for understanding fatigue in patients with chronic health conditions. Contributing to these results, Nap-van der Vlist et al. [68] suggest a trans-diagnostic approach in children with chronic conditions as well. By including several comorbidity categories in the presented multi-factorial fatigue model, we aim to determine the precise role of these health conditions in perpetuating fatigue symptoms in CCS.

Physical activity levels were shown to be associated with fatigue levels during a one-year follow-up in a mixed cohort of childhood cancer patients and survivors [69]. Muscle strength was suggested to be related to fatigue in patients with advanced cancer [70]. In the current study hand grip strength will be used as an indication for muscle strength [22]. We hypothesize physical activity and muscle strength to be negatively correlated with CF in CCS. Information about smoking and alcohol consumption was not collected from the participants in the current study and this is considered a limitation.

Previous studies suggest Inflammatory markers to play a role in the experience of fatigue symptoms in (adult) cancer patients [13, 71, 72]. However it remains unknown whether these markers might still be related to fatigue in CCS. Therefore inflammatory

markers (interleuking-6, interleukin-6 and CRP) are included in our fatigue model to investigate their association with chronic fatigue in CCS.

Above, we discussed multiple factors possibly associated with CRF in CCS and included them in a model. We aimed to create a complete model but we acknowledge that there are other factors not included in the model that also might be associated with CRF and interesting to investigate. Examples are traumatic events or past history of mood disorders. Future studies might consider including these factors.

Conclusion

Using the model as presented, the DCCSS LATER fatigue study will provide information on the epidemiology and associated factors of CF in CCS. With person-centered care getting a more prominent role in the health-care system, insight in possible risk factors for survivors experiencing CF is of great interest to identify individuals at risk for developing CF. Ultimately, this study will hopefully contribute to the improvement of current treatment protocols decreasing CF and improving quality of life in CSS.

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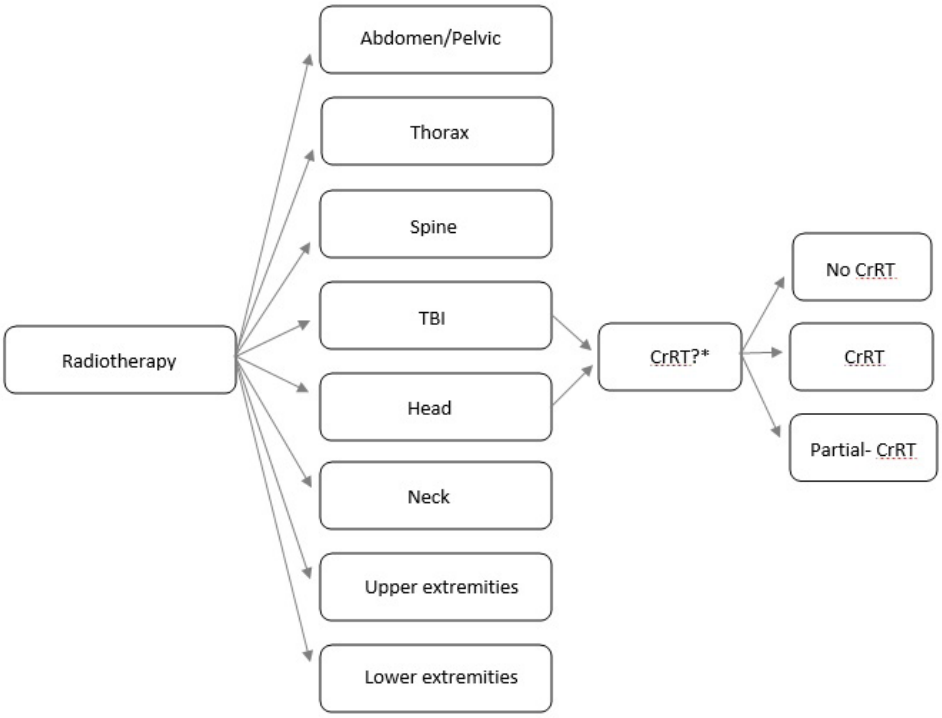
Supplementary material



Supplementary Figure 1. Flowchart of the categorization process of survivors who received Radiotherapy. *Survivors who received radiotherapy directed to the head – including those who received total body irradiation (TBI) – will be assigned to one of three subgroups: full-cranial volume (full-cranial radiotherapy (CrRT); defined as 100% of the cranium in field), partial-cranial volume (partial-CrRT; defined as any CrRT with less than 100% of the cranium in field), and radiotherapy to the head without cranial involvement (no brain tissue in the field; not considered CrRT).

Supplementary Table 1. Items in the questionnaires regarding the participant's demographic data, medical history and current medical state

Subject	Item in the general health questionnaire
General Health	
Medical status	Could you please indicate if you currently or ever did suffer any of the the conditions stated below. If so, could you please state in what year you got the diagnosis and if you are currently using medication for it (and if so, which medication). The following conditions were listed: heart attack, angina pectoris, heart valve defect, pericarditis, cardiomyopathy, heart failure, cardiac arrhythmia, heart defect since birth ….*, other heart disease…*, stroke, vascular abnormality ….*, condition with increased risk for thrombosis (protein C deficiency, protein S deficiency, factor V Leiden mutation, other ….*), hypertension, high cholesterol, stomach or intestine problems, lung disease ….*, kidney problems (for example kidney stones, too much protein in your urine, cysts) ….*, adrenal glands problems ….*, liver problems ….*, musculoskeletal problems (for example arm/leg/elbow/knee) ….*, diabetes, epilepsy, cataract, tinnitus, reduced height growth, hypothyroidism, hyperthyroidism, thyroid nodule, other thyroid conditions ….*, other condition related to hormone regulation ….*, other condition ….*
Medical status	Do you, more than 3 times a year, experience problems with your respiratory system?
Medical status	Have you ever had an infection of the urinary tract (including a fever)? If so, how many times? 1 time, 2-5 times or more than 5 times?
Medical status	Do you use hearing aid?
Fatigue status	Do you experience fatigue problems and if so, for how long do these fatigue problems exist (number of weeks/months/years)?
Medication use	Do you use medication, other than for a condition you may experience as described above, more than once a week (for example aspirin, ibuprofen)? If so, please list them here.
Demographic data	
Age	What is your date of birth?
Age	At what date did you fill in this questionnaire?
Sex	Are you a male or a female?
Education status	What is your highest completed level of education? (answer options vary from primary school to university)
Employment status	Are you currently employed? If so, what work do you do?
Marital status	Are you currently in a relationship?

This table shows the items of the general health questionnaire in detail. *Participants could, if applicable, write the name of a condition at the dashed line.

Supplementary Table 2. Model parameters and how they were measured in the DCCSS LATER fatigue study

Parameter	Measure	Available for
Fatigue		
Fatigue severity	CIS	CCS, Sibling controls, Lifelines controls
Fatigue duration	General health questionnaire	CCS, Sibling controls, Lifelines controls
Predisposing factors		
Genetic factors	Blood sample	CCS (subgroup)
Triggering factors		
Cancer diagnosis	Patient record	CCS
Cancer treatment	Patient record	CCS
Maintaining factors		
Physical activity [c]	SQUASH	CCS, Lifelines controls
Somatic comorbidities	General health questionnaire	CCS, Sibling controls [b]
Depression [c]	HADS	CCS, Sibling controls [b]
Anxiety [c]	HADS	CCS, Sibling controls [b]
BMI	Height and weight measured during visit [a]	CCS, Sibling controls, Lifelines controls
Muscle strength [c]	Hand dynamometer	CCS
Pain [c]	TAAQOL, subscale pain	CCS, Sibling controls [b]
Self-esteem [c]	RSES	CCS, Sibling controls [b]
Social functioning [c]	TAAQOL, subscale social functioning	CCS, Sibling controls
Sleep disturbances [c]	PSQI	CCS, Sibling controls [b]
Illness cognition [c]	ICQ	CCS, Sibling controls
Pro-inflammatory markers [c, d]	Blood sample	CCS
Moderating factors		
Sex (male/female)	Patient record / General health questionnaire	CCS, Sibling controls, Lifelines controls
Age at assessment	Patient record / General health questionnaire	CCS, Sibling controls, Lifelines controls
Age at diagnosis	Patient record	CCS
Time since diagnosis	Patient record / General health questionnaire	CCS
Marital status	General health questionnaire	CCS, Lifelines controls

Supplementary Table 2. Continued

Parameter	Measure	Available for
Moderating factors		
Education status	General health questionnaire	CCS, Lifelines controls
Employment status	General health questionnaire	CCS, Lifelines controls

CCS: Long term survivors of childhood cancer, CIS: Checklist Individual Strength, SQUASH: Short Questionnaire to assess health- enhancing physical activity, HADS: Hospital Anxiety and Depression Scale, TAAQOL: TNO and AZL Questionnaire for Adult's Quality of Life, RSES: Rosenberg Self-Esteem Scale, PSQI: Pittsburgh Sleep Quality Index, ICQ: Illness Cognition Questionnaire.

[a] For CCS participants who will not visit the clinic, height and weight will be asked in a questionnaire. For the Lifelines participants, height and weight is measured during a visit at the Lifelines clinic.

[b] Parameters were measured in the Lifelines controls as well, however using a different questionnaire.

[c] Parameters will be used as a predictor for CF in the DCCSS LATER fatigue study, however will be described as primary outcome in other DCCSS LATER substudies.

[d] Interleukin-1, Interleukin-6, C-reactive protein (CRP)

Chapter 5

Chronic fatigue in childhood cancer survivors is associated with lifestyle and psychosocial factors

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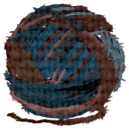

Abstract

Purpose: To determine factors associated with chronic fatigue (CF) in childhood cancer survivors (CCS).

Methods: Participants were included from the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort, a nationwide cohort of CCS (≥5 years post-diagnosis) and siblings as controls. Fatigue severity was assessed with the *fatigue severity subscale* of the Checklist Individual Strength (*CIS-fatigue*). CF was defined as scoring ≥35 on the *CIS-fatigue* and having fatigue symptoms for ≥6 months. Twenty-four parameters were assessed, categorized into assumed fatigue triggering, maintaining and moderating factors. Multivariable logistic regression analyses were performed to investigate the association of these factors with CF.

Results: 1927 CCS participated in the study (40.7% of invited cohort), of whom 23.6% reported CF (compared to 15.6% in sibling controls, p<0.001). The following factors were associated with CF: Obesity (vs. healthy weight, OR 1.93; 95% CI 1.30-2.87), moderate physical inactivity (vs. physical active, OR 2.36; 95% CI 1.67-3.34), poor sleep (yes vs. no, OR 2.03; 95% CI 1.54-2.68), (sub)clinical anxiety (yes vs. no, OR 1.55; 95% CI 1.10-2.19), (sub)clinical depression (yes vs. no, OR 2.07; 95% CI 1.20-3.59), pain (continuous, OR 1.49; 95% CI 1.33-1.66), self-esteem (continuous, OR 0.95; 95% CI 0.92-0.98), helplessness (continuous, OR 1.13; 95% CI 1.08-1.19), social functioning (continuous, OR 0.98; 95% CI 0.97-0.99) and female sex (vs. male sex, OR 1.79; 95% CI 1.36-2.37).

Conclusion: CF is a prevalent symptom in CCS that is associated with several assumed maintaining factors, with lifestyle and psychosocial factors being the most prominent. These are modifiable factors and may therefore be beneficial to prevent or reduce CF in CCS.

Introduction

Chronic fatigue (CF), defined as severe fatigue that persists for at least six months, is a common late effect following childhood cancer treatment leading to an impaired quality of life [1, 2]. Few studies have investigated which factors are associated with CF in CCS [3-6], but these studies focused on a specific group of factors, e.g. treatment related factors or demographic factors only, or included small subgroups of CCS participants, limited to certain diagnoses or age groups. Various variables have been associated with fatigue in CCS, including factors related to the childhood cancer (e.g. type of diagnosis or treatment), demographics (e.g. age and sex), and lifestyle and psychosocial aspects (e.g. depression, sleeping disorders, physical (in)activity), [7-9]. However, due to methodological differences between the studies, it is difficult to draw conclusions regarding the strength of the association of these factors with CF in CCS. To investigate the relative relations with CF in CCS, these factors should be studied together in a large cohort CCS, including all childhood cancer diagnoses.

We have proposed a model to arrange factors in one comprehensive multivariable model in order to determine associated factors for CF in CCS [10]. In the model, factors are categorized based on their assumed relation with CF (Figure 1): Triggering factors (thought to play a role at the onset of CF), maintaining factors (thought to perpetuate fatigue once triggered) and moderating factors (might influence the way fatigue expresses in individuals). In a previous questionnaire based study, where the prevalence of CF was determined in CCS and sibling controls, parts of the proposed model were tested and female sex, being unemployed, having comorbidities and CNS as a childhood cancer diagnosis were associated with CF [1]. However, based on the model performance, it was concluded that additional factors need to be considered to explain CF in CCS [1]. In the current study we collected and analyzed all factors of the proposed model in a large nationwide cohort of CCS, which allowed us to determine the relative association of the factors with CF, in an attempt to address the current knowledge gap. Secondary aim of the study was to confirm previous found prevalence rates of CF in a Dutch nationwide cohort of CCS and sibling controls [1].

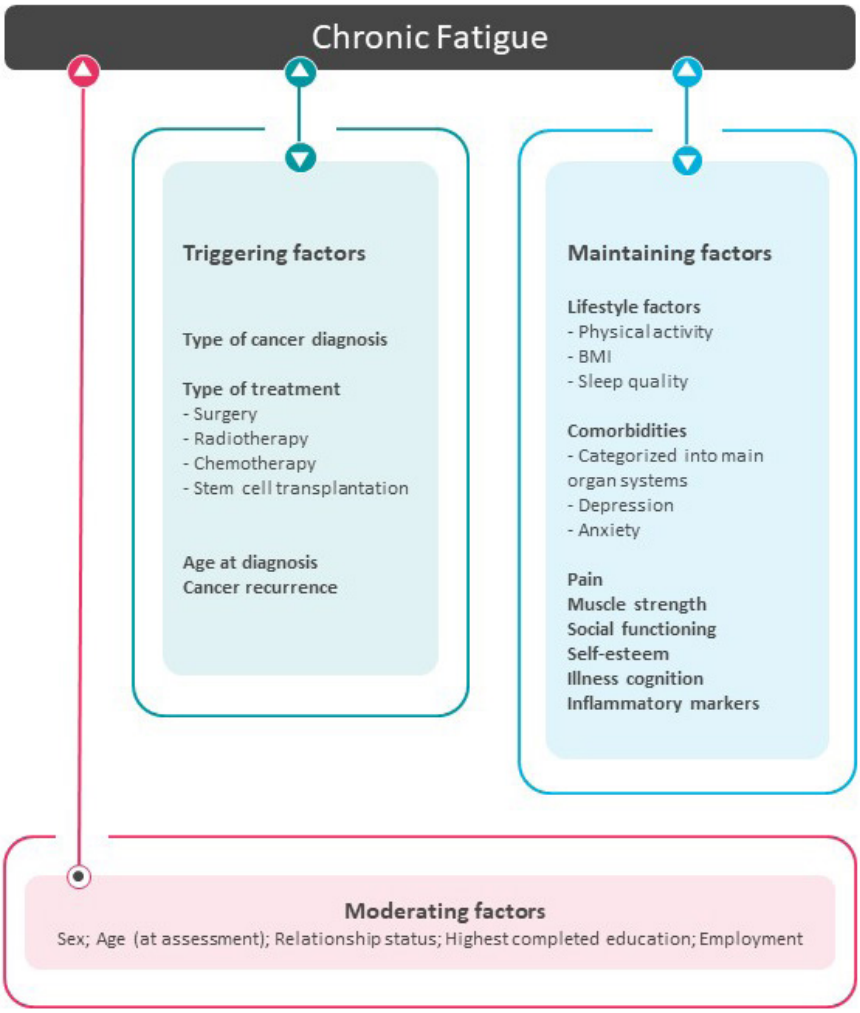

Figure 1. Proposed model showing assumed relations between factors and CF in CCS.
Figure shows assumed relations of study parameters that have previously been found to be associated with CF [10]. Triggering factors are assumed to play a role at the onset of fatigue. Maintaining factors are assumed to perpetuate fatigue once triggered. Moderating factors are assumed to have an effect on the strength of fatigue symptoms in individuals. The following change has been made compared to the model presented in [10]: Age at diagnosis is considered a triggering factors ensuring all treatment/diagnosis related factors are categorized in one group of factors as we assume childhood cancer and its treatment to be a triggering factor for fatigue. Also, we believe age at diagnosis to play a part at the onset of fatigue, which is the definition of the assumed triggering factors, and not so much a moderating factor many years after diagnosis. Comorbidities are categorized following previously published main organ system categories [11].

Methods

Study design and participants

This study was part of the Dutch Childhood Cancer Survivor Study Late Effect (DCCSS LATER) study part 2 [12]. Participants were included from the DCCSS LATER cohort, a nationwide cohort including all five-year cancer survivors who were diagnosed before the age of 18 between January 1st 1963 and December 31st 2001 in the Netherlands (n=6165, baseline characteristics described elsewhere [13]). Of this cohort, CCS who were still alive and living in The Netherlands and who were not lost to follow-up or had previously declined to participate in any research were eligible to participate in the study (n=4735).

In addition, siblings of the CCS participants were asked to participate as a control group to compare CF prevalence rates. Contact information was provided by the CCS participants and siblings who had not had cancer, were approached to participate (n=1499).

All participants for the current study were 18 years or older, were able to read and speak Dutch and gave written informed consent to participate. The DCCSS LATER fatigue study was approved by the Medical Research Ethics Committee of the Amsterdam University Medical Centers (registered at toetsingonline.nl, NL34983.018.10).

Data collection

A detailed description of the methodology and data collection was previously published [10]. In short, data were collected during a visit at the LATER outpatient clinic, which took place between 2017 and 2020 in one of the seven pediatric oncology centers in the Netherlands. Fatigue severity was assessed with the *fatigue severity subscale* of the Checklist Individual Strength (CIS) [14], a questionnaire shown to have satisfying psychometric properties in CCS [15]. CF was defined as a score of 35 or higher on the *CIS fatigue severity* subscale, indicating severe fatigue [16], which persists for 6 months or longer (duration of fatigue symptoms was assessed in a separate item next to the CIS). Participants were included if they had sufficient data to determine their fatigue status: at least 7 of the 8 CIS fatigue severity items completed (with one missing value, the mean of the remaining completed items was imputed) and the duration of fatigue symptoms known (if fatigue severity subscale score ≥35).

Additionally, the following measures were completed as previous research indicated these factors to be related to fatigue [7-10]: Height and weight to calculate body mass index (BMI); social outcomes, e.g., level of education, employment status and relationship status, were assessed using a questionnaire (see Supplementary Table 1

for specific items); somatic comorbidities were assessed using a questionnaire (see Supplementary Table 1 for details) and categorized as having 0, 1-2 or >2 of previously defined physical outcomes [11]; pain was assessed using a 6-point Likert scale; physical activity was assessed using the European Prospective Investigation into Cancer and Nutrition (EPIC) physical activity questionnaire and categorized following the four-point physical activity index as being active, moderately active, moderately inactive or inactive [17, 18]; sleep quality was assessed using the Pittsburg Sleep Quality Index (PSQI) with a score of >5 to indicate poor sleep [19, 20]; anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) with subscale score of ≥8 indicating (sub)clinical anxiety and depression [21, 22]; grip strength was measured with a hand dynamometer to reflect muscle strength [23]; social functioning was assessed using the TNO (Netherlands Organisation for Applied Scientific Research) and AZL (Leiden University Medical Centre) Questionnaire for Adult's Quality of Life (TAAQOL) social functioning domain [24]; self-esteem was assessed using the Rosenberg Self-Esteem Scale (RSES) [25, 26]; feelings of helplessness, acceptance and perceived benefits were assessed using the Illness Cognition Questionnaire (ICQ) [27, 28]; as an inflammatory marker, C-reactive protein (CRP) levels were analyzed from venous blood samples. Treatment and diagnosis data of primary diagnoses and all recurrences of the CCS participants were collected from medical records by data managers using a uniform protocol [29]. Details about data collection, categorization and availability for each of these measures are given in Supplementary Table 1. If participants were not able to visit the outpatient clinic, questionnaires could be completed from home digitally.

Statistical analyses

Differences in baseline characteristics between study participants and non-participants, i.e. non-responders and excluded participants because of missing/insufficient fatigue data or age<18 years, were compared using chi-square tests (with Cramér's V effect size).

Prevalence rates of CF of CCS and sibling controls were compared using a chi-square analysis and an additional regression analysis to adjust for age and sex differences. To determine which factors were associated with CF in CCS, multivariable logistic regression analyses with CF (yes/no) as dependent variable and the assumed triggering factors (primary childhood cancer diagnosis and treatment, hematopoietic stem cell transplantation, cancer recurrence, age at diagnosis), maintaining factors (BMI, physical activity index, (sub)clinical anxiety, (sub)clinical depression, pain, self-esteem, illness cognition, muscle strength, inflammatory markers, social functioning, sleep problems, comorbidities), and moderating factors (sex, age at assessment, educational level, employment status, relationship status) as independent variables were conducted.

Due to power restrictions we used a forward selection procedure to come to a final model including the most strongly related factors. Firstly, each group of factors -the assumed triggering, maintaining and moderating factors- was analyzed separately in a multivariable model, which ensured the relative associations to be determined, as each analyzed variable was adjusted for the other variables of the same group. Variables that were significantly associated with CF ($p<0.05$) in the separate models were included in one final multivariable model. Area under the curve (AUC) was calculated for the final model as an indication of model performance, with >0.7 considered acceptable [30]. Variance inflation factors (VIF) were calculated for all independent variables with a threshold of >5 to test for problematic multicollinearity [31].

IBM SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) was used for the analyses. Missing data of the independent variables, assumed to be missing at random (no pattern observed), were imputed with Multiple Imputation, using the Markov chain Monte Carlo method to create twenty imputed datasets and using Rubin's rules to pool the analyses [32-34]. Number of missing values per study variable are shown in Supplementary Table 1. All study variables were included in the Multiple Imputation process, including the diagnosis and treatment related variables which had no missing values. Complete case analysis was done as a sensitivity analysis.

Results

Participant characteristics

A total of 2282 CCS and 506 siblings participated in the DCCSS LATER fatigue study part 2 (48.2% and 33.8% of eligible persons respectively). Of these participants, 1927 CCS and 449 siblings completed the fatigue questionnaire for the current study (*CIS fatigue severity* subscale score and duration fatigue). The flowcharts are depicted in Supplementary Figure 1. Participant characteristics are shown in Table 1.

Compared to non-participants (non-responders, lacking/missing fatigue questionnaire data or age <18 years), participants were more often female (48.3% vs. 39.9%, $p<0.001$), more often treated with a combination of chemotherapy and radiotherapy (33.2% vs. 24.4%, $p<0.001$) and more often received hematopoietic stem cell transplantation (6.8% vs. 3,9%, $p=0.001$), however effect sizes for these differences were small (0.09, 0.13 and 0.07 respectively). An overview of participant and non-participant characteristics is shown in Supplementary Table 2.

Prevalence and associated factors

Prevalence of CF was 23.6% in CCS compared to 15.6% in siblings (p<0.001, also after correction for age and sex). Table 2 shows the results of the multivariable logistic regression analyses. Analyses of the separate multivariable models showed no association with the triggering factors, but several maintaining and moderating factors to be associated with CF. The latter were included in the final multivariable model in which obesity (vs. healthy weight, OR 1.93; 95% CI 1.30-2.87), moderate physical inactivity (vs. physical active, OR 2.36; 95% CI 1.67-3.34), poor sleep (yes vs. no, OR 2.03; 95% CI 1.54-2.68), (sub)clinical anxiety (yes vs. no, OR 1.55; 95% CI 1.10-2.19), (sub)clinical depression (yes vs. no, OR 2.07; 95% CI 1.20-3.59), pain (continuous, OR 1.49; 95% CI 1.33-1.66), self-esteem (continuous, OR 0.95; 95% CI 0.92-0.98), helplessness (continuous, OR 1.13; 95% CI 1.08-1.19), social functioning (continuous, OR 0.98; 95% CI 0.97-0.99) and female sex (vs. male sex, OR 1.79; 95% CI 1.36-2.37) were found to be associated with CF.

AUC of this model was >0.86 for each imputed dataset (20 imputations, pooled AUC could not be generated), indicating excellent model performance. VIF were <2.0 for all factors included in the analyses, suggesting no problematic multicollinearity to be present. Based on the found associations, the proposed model that was presented in Figure 1 was adjusted and now only includes the factors that were found to be statistically significant associated with CF (Figure 2). Results of a post-hoc analysis, investigating in more detail the relation between CF and number of comorbidities, is shown in Supplementary Table 3.

Complete case analysis showed the same variables to be associated with CF (see Supplementary Table 4), except for depression. However, the complete case analysis lacks statistical power, therefore reliability of these results is questionable.

Discussion

In the current study we present the prevalence rate and associated factors of CF in a nationwide cohort of CCS. Results showed various assumed maintaining factors to be associated with CF: Lifestyle factors -e.g., physical inactivity, obesity and poor sleep-, psychosocial factors -e.g., anxiety, depression, self-esteem, social functioning and feelings of helplessness- and pain showed the most strong associations with CF.

CF in CCS

We showed that approximately one in four CCS have CF, emphasizing its magnitude in this population and replicating previous findings [1]. The increased prevalence of CF in CSS compared to sibling controls (23.6% vs. 15.6%) suggests the experience of having had cancer during childhood to increase the likelihood of becoming chronically fatigued. It could be that symptoms of fatigue persist from the period of childhood diagnosis, where fatigue is an often seen side-effect of cancer and its treatment [35, 36], but fatigue might also manifest at a later stage in life. In the latter case, it may be due to the cancer and its treatment that CCS are more prone to develop CF over time. However, only prospective studies can inform us on how CF develops over time.

No association between CF and diagnosis and treatment related factors was found. This suggests that not a particular type of diagnosis or treatment triggers CF, but a history of cancer in general (thus explaining the increased prevalence in CCS compared to sibling controls). In previous studies, relations between CF and specific diagnosis-related factors have been found, with an association of CF with CNS as childhood cancer diagnosis being the most illustrative [1, 37]. It was hypothesized that, as a result of treatment to the head/cranium, these CCS are at increased risk for developing fatigue, similar as they are at risk for neurocognitive impairment [4, 38]. However, results showed no such association to be present when assessed in a large cohort including all childhood diagnoses. Also no significant association was found between CF and RT locations involving the head/cranium, i.e. head/cranium, spinal or total body irradiation (univariable analyses, data not shown). Results are in line with literature showing CNS tumor patients treated with cranial/spinal irradiation to have normalized levels of fatigue after treatment completion compared to pre-treatment [39].

Lifestyle and psychosocial factors were found to be associated with CF. Lifestyle and psychosocial factors are potentially modifiable factors, in contrast to disease and treatment related factors. Therefore, focusing on these modifiable factors for prevention or tailored interventions, might be beneficial to reduce CF. The recommendation guideline for the surveillance of fatigue in childhood, adolescent and young adult (CAYA) survivors, proposed by the International Guideline Harmonization Group (IGHG), stated that potential risk factors for fatigue are clinical, e.g. psychological distress, health issues or pain, and demographical factors, e.g. age, sex, employment and education, not diagnosis or treatment related factors [9]. However, evidence to support these findings was low to moderate, mainly because of the lack of studies using a validated fatigue measure [9]. The current study, using a validated fatigue measure [15], confirms that not diagnosis and treatment related factors, but lifestyle and psychosocial factors are associated with CF in CCS. Our

results are in concordance with studies in other patient populations suggesting that CF-related factors are not disease specific, i.e. diagnosis or treatment related, but are trans-diagnostic, i.e. are similar for different long term medical conditions, such as lifestyle and psychosocial related factors [40-42]. These studies found that factors such as female sex, physical inactivity, sleep disturbances, depression and pain, which were found to be associated with CF in our study as well, were associated with fatigue across different (chronic) diseases and to a same extent in healthy subjects. This suggests that fatigue is a generic symptom which expresses similarly over different (patient) populations, and presumably asks for a generic approach.

Clinical implications

We found that several assumed maintaining factors, i.e. psychosocial and lifestyle factors, were associated with CF. Therefore, when CCS present with fatigue symptoms, it might be good to screen for these associated factors or discuss it during consultation. Symptoms tend to cluster, as was shown in cancer patients and survivors of adult-onset cancer [43-45], therefore it is likely for CSS to present with multiple symptoms simultaneously as well.

In addition, psychosocial and lifestyle factors are assumed modifiable variables and are therefore potentially interesting to target when aiming to reduce CF. For example, previous studies have shown psychological interventions, e.g. cognitive behavioral therapy (CBT), to be effective interventions to reduce fatigue levels in survivors of adult-onset cancer and also a pilot study with CBT in CCS showed promising results [46-49]. Also, physical activity interventions, e.g. lifestyle and exercise counseling and exercise or yoga programs, show promising results [50, 51]. Both psychological and physical activity interventions are recommended by the American Society of Clinical Oncology guideline to treat fatigue in survivors of adult-onset cancer [52] and the IGHG recommendations for fatigue-surveillance in CAYA survivors [9]. The current results show that targeting psychological and/or lifestyle factors might indeed be beneficial to reduce fatigue in CCS, thus encouraging a similar recommendation to treat CF in CCS as well. However, to determine the effect of CBT and physical activity interventions in CCS, studies in larger sample sizes and regional/cultural specific populations are needed to confirm and validate these results before vast recommendations can be made. Next to possible interventions that tackle CF-related issues, prevention strategies might benefit from focusing on CF-associated factors, such as lifestyle factors, as they might reduce the risk of developing CF.

The role of comorbidities

Previous literature showed that having one or more comorbidities was associated with fatigue in cancer survivors [1, 53, 54]. In the current study, having (multiple) comorbidities was not associated with CF. However, post-hoc analysis did show a univariable relation between having comorbidities and CF, suggesting other factors to mediate this relation. Reduced physical activity, sleep problems, pain, lower self-esteem, helplessness and problems with social functioning were found as possible mediators (Supplementary Table 3). A plausible pathway explaining the relation between number of comorbidities and CF could therefore be that having one or multiple comorbidities negatively influences other factors such as pain, helplessness, self-esteem, social functioning, physical activity and sleep quality, which causes these patients to experience more fatigue. As CCS are at increased risk for various health issues [55, 56], this hypothesis might also partly explain the increased prevalence of CF in CCS.

Strengths and limitations

This study is part of a nationwide collaboration and includes a large nationwide cohort consisting of all five-year survivors who were diagnosed between 1963 and 2002 including all childhood malignancies, which contributes to the generalizability of the results. Being one of sixteen sub-studies of the DCCSS LATER study [12] ensured a lot of topics to be studied at the same time in the same cohort. This unique study design made it possible to include many factors that were hypothesized to be associated with CF in CCS [10], which ensured these factors to be analyzed relative to each other, resulting in a more complete picture of CF and its associated factors. The high AUC of the model (>0.86 in all imputed datasets), which can be interpreted as a proxy for the completeness of the model, also reflects this as it shows excellent performance of the final model [30]. Compared to the previously conducted questionnaire based study where only part of the proposed model was tested [1], the current model shows improved model performance (0.86 vs. 0.71 in previous study), suggesting the current model to be more complete.

No information was available on current smoking habits or alcohol consumption which is considered a limitation. Although current literature shows smoking is not associated with fatigue [1, 9], and therefore including it in the model would probably not have affected the results, information on alcohol consumption could have been of added value to the model. Another limitation is that we cannot discard the possibility of selection bias as small differences between participants and non-participants were seen. Therefore it is possible that certain subgroups of CCS were less/more inclined to participate in the current study. However, effect sizes for differences between

participants and non-participants were small, therefore it is unlikely for these differences to have impacted the results of the study.

Lastly, we elaborated on assumed triggering, maintaining and moderating factors of CF. However, as data were cross-sectional, no causal inferences can be made based on these findings. The exact relation between factors needs to be confirmed in a longitudinal study.

Conclusion

CF is a prevalent symptom in CCS that is associated with several assumed maintaining factors, with lifestyle and psychosocial factors being the most prominent. These are modifiable factors and may therefore be beneficial to prevent or reduce CF in CCS.

Table 1. Demographic characteristics of CCS & sibling participants and childhood cancer diagnostic and treatment characteristics of the CCS participants

Characteristic	CCS (n=1927)	Sibs (n=449)	P-value
	N (%)	N (%)	
Sex			
Male	996 (51.7)	165 (36.7)	<0.001 [e]
Female	931 (48.3)	284 (63.3)	
Age at assessment (years)			
Mean (SD)	35.1 (9.3)	36.8 (10.2)	0.001 [f]
18-29	599 (31.1)	118 (26.3)	0.023 [e]
30-39	737 (38.2)	165 (36.7)	
≥40	591 (30.7)	166 (37.0)	
CF			
Yes	454 (23.6)	70 (15.6)	<0.001 [g]
No	1473 (76.4)	379 (84.4)	
Age at diagnosis (years)			
Mean (SD)	6.7 (4.7)		
0-5	886 (46.0)		
>5-10	519 (26.9)		
>10-15	414 (21.5)		
>15-18	108 (5.6)		

Table 1. Continued

Characteristic	CCS (n=1927)	Sibs (n=449)	P-value
	N (%)	N (%)	
Primary childhood cancer diagnosis [a]			
Leukemia	678 (35.3)		
Non-Hodgkin lymphoma [b]	234 (12.1)		
Hodgkin lymphoma	135 (7.0)		
CNS	177 (9.2)		
Neuroblastoma	111 (5.8)		
Retinoblastoma	10 (0.5)		
Renal tumors	220 (11.4)		
Hepatic tumors	17 (0.9)		
Bone tumors	109 (5.7)		
Soft tissue tumors	141 (7.3)		
Germ cell tumors	65 (3.4)		
Other and unspecified [c]	30 (1.6)		
Period of childhood cancer diagnosis			
1963-1969	29 (1.5)		
1970-1979	255 (13.2)		
1980-1989	607 (31.5)		
>1990	1036 (53.6)		
Childhood cancer treatment [d]			
Surgery only	131 (6.8)		
Chemotherapy, no radiotherapy	1047 (54.3)		
Radiotherapy, no chemotherapy	100 (5.2)		
Radiotherapy and chemotherapy	640 (33.2)		
No treatment/treatment unknown	9 (0.5)		
Stem cell transplantation			
Yes	131 (6.8)		
No	1783 (92.5)		
Unknown	13 (0.7)		
Cancer recurrence			
No	1675 (86.9)		
Yes	252 (13.1)		

Abbreviations: CCS=Childhood Cancer Survivors; CF=Chronic fatigue; CNS=Central Nervous System.

[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

[d] Treatment data included primary treatment and all recurrences.

[e] Chi-Square test [f] Independent t-test

[g] Chi square test & logistic regression analysis to correct for age and sex.

Table 2. Results of logistic regression analyses showing lifestyle & psychosocial and demographic factors to be associated with CF.

Factor	% non CF participants*	% CF participants*	Separate models [e]		Final model [f]	
	(n=1473)	(n=454)	OR	95% CI	OR	95% CI
Triggering factors						
Age at diagnosis (years)						
0-5	47.1	42.3	ref	ref		
>5-10	26.6	28.0	1.15	0.88 – 1.52		
>10-15	20.6	24.4	1.34	0.99 – 1.83		
>15-18	5.7	5.3	1.02	0.61 – 1.72		
Primary childhood cancer diagnosis [a]						
Leukemia	36.3	31.5	ref	ref		
Non-Hodgkin lymphoma [b]	12.3	11.7	1.04	0.72 – 1.51		
Hodgkin lymphoma	7.3	6.2	0.76	0.47 – 1.24		
CNS	8.7	10.8	1.23	0.77 – 1.96		
Neuroblastoma	5.5	6.6	1.37	0.83 – 2.28		
Retinoblastoma	0.5	0.7	1.60	0.39 – 6.66		
Renal tumors	11.3	11.9	1.16	0.80 – 1.69		
Hepatic tumors	1.1	0.2	0.26	0.03 – 2.00		
Bone tumors	5.4	6.6	1.25	0.77 – 2.03		
Soft tissue tumors	6.8	9.0	1.37	0.90 – 2.10		
Germ cell tumors	3.5	2.9	0.87	0.45 – 1.68		
Other and unspecified [c]	1.4	2.0	1.38	0.59 – 3.23		
Childhood cancer treatment [d]						
Surgery only	6.5	7.7	ref	ref		
Chemotherapy, no radiotherapy	56.2	48.2	0.88	0.54 – 1.46		
Radiotherapy, no chemotherapy	4.9	6.2	1.12	0.62 – 2.05		
Radiotherapy and chemotherapy	31.8	37.7	1.25	0.76 – 2.05		
No treatment/ treatment unknown	0.5	0.2	0.37	0.05 – 3.12		
Hematopoietic stem cell transplantation						
No	92.0	94.3	ref	ref		
Autologous	2.4	2.6	1.14	0.57 – 2.28		
Allogeneic	4.8	2.9	0.57	0.30 – 1.08		
Unknown	0.8	0.2	0.23	0.03 – 1.81		
Recurrence						
No	86.6	87.9	ref	ref		
Yes	13.4	12.1	0.81	0.57 – 1.14		

Table 2. Continued

Factor	% non CF participants*	% CF participants*	Separate models [e]		Final model [f]	
	(n=1473)	(n=454)	OR	95% CI	OR	95% CI
Maintaining factors						
BMI						
Healthy weight	55.2	44.7	ref	ref	ref	ref
Underweight	2.7	4.0	1.26	0.56 – 2.85	1.36	0.61 – 3.04
Overweight	31.9	31.4	1.30	0.95 – 1.77	1.30	0.95 – 1.78
Obese	10.2	19.9	**2.03**	**1.37 – 3.02**	**1.93**	**1.30 – 2.87**
Physical activity index						
Inactive	4.6	10.1	1.30	0.71 – 2.38	1.15	0.62 – 2.15
Moderately inactive	20.3	31.7	**2.42**	**1.72 – 3.40**	**2.36**	**1.67 – 3.34**
Moderately active	23.8	21.9	1.42	0.98 – 2.06	1.36	0.94 – 1.97
Active	51.3	36.3	ref	ref	ref	ref
HADS						
(Sub)clinical Anxiety (no = ref)	13.4	43.3	**1.53**	**1.09 – 2.15**	**1.55**	**1.10 – 2.19**
(Sub)clinical Depression (no=ref)	3.2	22.4	**2.01**	**1.15 – 3.51**	**2.07**	**1.20 – 3.59**
Pain						
Total score, 1-6 Likert scale	1.74	2.74	**1.51**	**1.35 – 1.69**	**1.49**	**1.33 – 1.66**
Self-esteem						
RSES total score (continuous)	33.6	28.7	**0.94**	**0.90 – 0.97**	**0.95**	**0.92 – 0.98**
Illness Cognition (continuous)						
Helplessness total score	7.4	10.3	**1.11**	**1.05 – 1.17**	**1.13**	**1.08 – 1.19**
Acceptance total score	20.3	17.9	0.98	0.94 – 1.02		
Disease benefits total score	16.9	16.1	1.02	0.99 – 1.06		
Muscle strength (continuous)						
Handgrip strength in kg	40.7	36.1	0.99	0.98 – 1.00		
Inflammatory markers						
CRP in mg/L (continuous)	4.4	5.4	1.01	0.99 – 1.03		
Social functioning (continuous)						
TAAQOL subscale score	89.6	74.4	**0.98**	**0.97 – 0.99**	**0.98**	**0.97 – 0.99**
PSQI						
Poor sleeper (no = ref)	28.3	64.0	**2.06**	**1.56 – 2.72**	**2.03**	**1.54 – 2.68**

Table 2. Continued

Factor	% non CF participants*	% CF participants*	Separate models [e]		Final model [f]	
	(n=1473)	(n=454)	OR	95% CI	OR	95% CI
Comorbidities						
0	48.0	33.7	ref	0.81 – 1.45		
1-2	44.1	47.0	1.09	0.83 – 2.08		
>2	7.9	19.3	1.31			
Moderating factors						
Sex						
Male	56.5	36.1	ref	ref	ref	ref
Female	43.5	63.9	**2.29**	**1.83 – 2.87**	**1.79**	**1.36 – 2.37**
Age at assessment (years)						
18-29	32.9	25.1	ref	ref	ref	ref
30-39	38.1	38.8	**1.67**	**1.26 – 2.22**	1.25	0.89 – 1.76
≥40	29.0	36.1	**1.91**	**1.42 – 2.56**	1.23	0.86 – 1.77
Educational level						
Low	12.4	16.4	ref	ref		
Middle	41.9	46.7	0.93	0.66 – 1.31		
High	45.7	36.9	0.74	0.52 – 1.04		
Employment status						
Employed	88.8	72.3	ref	ref	ref	ref
Not employed	11.2	27.7	**2.79**	**2.10 – 3.72**	1.34	0.92 – 1.95
Relationship status						
In a relationship	77.8	73.0	**0.72**	**0.54 – 0.97**	0.95	0.67 – 1.34
Not in a relationship	22.2	27.0	ref	ref	ref	ref

Abbreviations: CF=Chronic fatigue; CNS=Central Nervous System; BMI=Boddy Mass Index; HADS= Hospital Anxiety and Depression Scale; RSES=Rosenberg Self-Esteem Scale; CRP=C-Reactive Protein; TAAQOL= TNO (Netherlands Organisation for Applied Scientific Research) and AZL (Leiden University Medical Centre) Questionnaire for Adult's Quality of Life; PSQI= Pittsburg Sleep Quality Index; 95% CI=95% Confidence Interval.

*Mean scores are shown for continues variables

[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

[d] Treatment data included primary treatment and all recurrences.

[e] Three separate multivariable logistic regression models with Chronic fatigue as dependent variable and the assumed triggering, maintaining and moderating factors as independent variables. Each variable was adjusted for the other variables of the same group.

[f] Chronic fatigue as dependent variable and the statistically significant ($p<0.05$) factors from the separate models [e] as independent variables in one "final model". Each variable was adjusted for the other variables included in this final model.

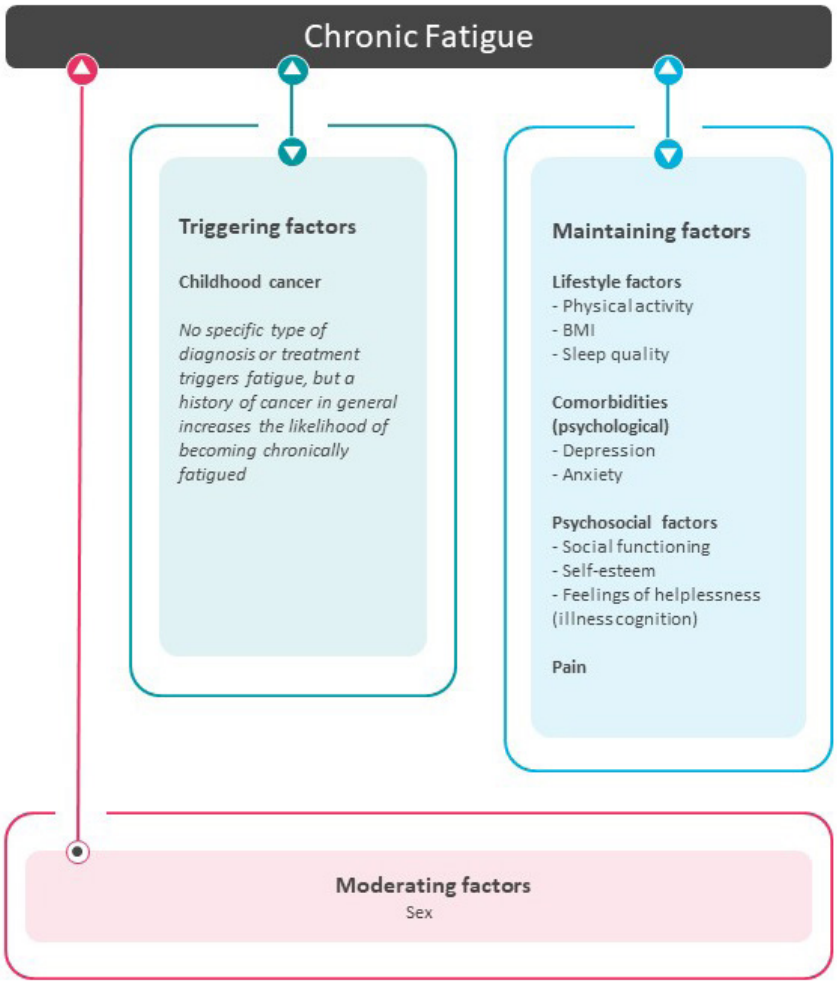

Figure 2. Adjusted model showing CF-associated factors in CCS.

Figure shows the factors that were statistically significant associated with CF in the final model. Triggering factors are assumed to play a role at the onset of fatigue. No specific diagnosis or treatment was found to be associated with CF, still the prevalence of CF in CCS was increased compared to sibling controls (23.6% vs. 15.6%), suggesting that a history of cancer in general plays a role in triggering symptoms of fatigue. Maintaining factors are assumed to perpetuate fatigue once triggered. Moderating factors are assumed to have an effect on the strength of fatigue symptoms in individuals.

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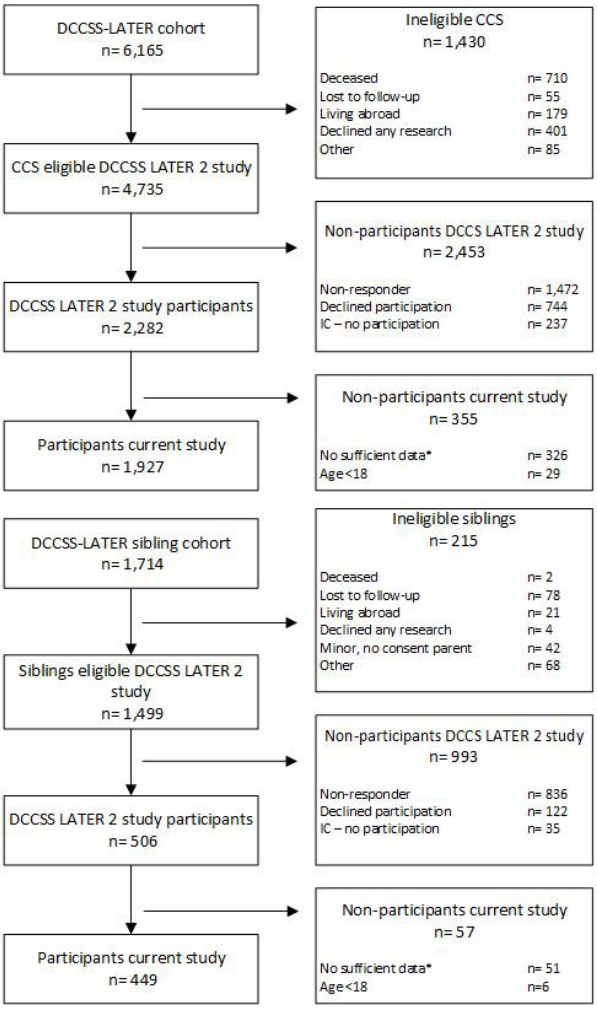
Supplementary material



Supplementary Figure 1. Flowcharts of CCS and sibling study participants.

*Sufficient data to determine fatigue status: at least 7 of the 8 CIS fatigue severity items completed (with one missing value, the mean of the remaining completed items was imputed) + duration of fatigue symptoms completed (if fatigue severity subscale score ≥35).

Supplementary Table 1. Overview of data collection, -categories and -availability CCS participants (n=1927)

Variable of interest	Type of questionnaire or questionnaire item (when applicable)	Categories	Data availability
Age at assessment	Date of assessment – date of birth	In years (continuous)	n=1927
BMI	Length (cm) and weight (kg) measured during clinic visit	Underweight: BMI <18.5 Healthy weight: BMI between 18.5 and 25 Overweight: BMI between 25 and 30 Obesity: BMI ≥30	n=1865
Employment status	Do you currently have work? Yes/no	Employed: Currently employed Unemployed: Currently unemployed	n=1807
Educational level	What is the highest level of education you have completed? Answer options: primary education, vocational education, preparatory secondary vocational education, secondary vocational education, school of higher general secondary education, pre-university education, higher vocational education, university, special school.	Low: Primary education, vocational education, special school Middle: Preparatory secondary vocational education, secondary vocational education, school of higher general secondary education, pre-university education High: Higher vocational education, university	n=1809
Relationship status	Are you currently in a relationship? Yes/no	Partner: Currently in relationship No partner: Currently not in a relationship	n=1610

Supplementary Table 1. Continued

Variable of interest	Type of questionnaire or questionnaire item (when applicable)	Categories	Data availability
Somatic comorbidities	Could you please indicate if you currently or ever did suffer any of the conditions stated below. If so, could you please state in what year you got the diagnosis and if you are currently using medication for it (and if so, which medication). The following conditions were listed: heart attack, angina pectoris, heart valve defect, pericarditis, cardiomyopathy, heart failure, cardiac arrhythmia, heart defect since birth ….*, other heart disease…*, stroke, vascular abnormality ….*, condition with increased risk for thrombosis (protein C deficiency, protein S deficiency, factor V Leiden mutation, other ….*), hypertension, high cholesterol, stomach or intestine problems, lung disease ….*, kidney problems (for example kidney stones, too much protein in your urine, cysts) ….*, adrenal glands problems ….*, liver problems ….*, musculoskeletal problems (for example arm/leg/elbow/knee) ….*, diabetes, epilepsy, cataract, tinnitus, reduced height growth, hypothyroidism, hyperthyroidism, thyroid nodule, other thyroid conditions ….*, other condition related to hormone regulation ….*, other condition ….* Additional items assessing problems with the respiratory system and hearing loss were completed.	Participants were categorized as having 0, 1-2 or >2 of the following comorbidities, as described by Streefkerk et al. [11] [a]: Neoplasms, Cardiac-, Vascular-, Respiratory-, Gastro-intestinal-, Hepatobiliary-, Renal and urinary tract-, Endocrine-, Musculoskeletal-, Ear-, Eye-, Nervous system-, Other conditions.	 n=1912 n=1902 n=1896 n=1902 n=1758 n=1904 n=1902 n=1888 n-1905 n=1909 n=1903 n=1907 n=1908
Pain	How much pain did you experience in the past four weeks? Answer options: none (1), very mild, mild, some, much, very much (6).	Total pain score (range 1-6)	n=1883

Supplementary Table 1. Continued

Variable of interest	Type of questionnaire or questionnaire item (when applicable)	Categories	Data availability
Physical activity	EPIC physical activity questionnaire items were used to categorize participants using the four-point physical activity index as proposed by Wareham et al. [17]	Inactive: sedentary job and no recreational activity Moderately inactive: sedentary job with <0.5h recreational activity per day or standing job with no recreational activity Moderately active: sedentary job with 0.5-1h recreational activity per day or physical job with no recreational activity Active: sedentary job with >1h recreational activity per day or standing job with >0.5h recreational activity per day or physical job with at least some recreational activity or heavy manual job	n=1744
Anxiety	The outcomes of the seven items of the HADS anxiety subscale were added up and the total score was used to indicate person's as having anxiety yes/no.	No anxiety: HADS anxiety subscale score <8 Anxiety: HADS anxiety subscale score ≥8	n=1624
Depression	The outcomes of the seven items of the HADS depression subscale were added up and the total score was used to indicate person's as having depression yes/no.	No depression: HADS depression subscale score <8 Depression: HADS depression subscale score ≥8	n=1622
Muscle strength	Grip strength was measured four times (two times left arm, two times right arm). The mean score was used to indicate muscle strength. Measurements were done in seated position, with the upper arm next to the body and the elbow flexed 90 degrees.	Mean grip strength (kg)	n=1543
Social functioning	TAAQOL social functioning domain items were added up and linearly transformed to a 0-100 scale following instructions described elsewhere [23] (higher scores reflecting better social functioning)	TAAQOL social functioning domain score (continuous)	n=1679
Self-esteem	Ten items of the RSES were added up (total score ranging 10-40), with a higher score reflecting higher self-esteem	RSES total score (continuous)	n=1633

Supplementary Table 1. Continued

Variable of interest	Type of questionnaire or questionnaire item (when applicable)	Categories	Data availability
Illness cognition	The three subscales of the ICQ (helplessness, acceptance and perceived benefits) were calculated by adding up the six items of each subscale (subscale scores ranging 6-24). Higher scores indicate more helplessness, acceptance and perceived benefits respectively.	ICQ subscale helplessness (continuous) ICQ subscale acceptance (continuous) ICQ subscale perceived benefits (continuous)	n=1601 n=1593 n=1597
Sleep quality	Seven PSQI component scores and total scores were calculated using scoring instructions described elsewhere Buysse et al.[18]. To compute the global score, the 7 component scores were added up. If at least 5 of the 7 component scores were present, a mean of the non-missing components was used to impute the missing value(s), as proposed by Beck et al. [19]	Good sleeper: PSQI total score ≤5 Poor sleeper: PSQI total score >5	n=1831
Inflammatory marker	CRP levels were measured in venous blood samples that were drawn after overnight fasting and stored at -80 °C. CRP levels <0.6 mg/L were listed as missing.	CRP level (mg/L)	n=1420

*Participants could, if applicable, write the name of a condition at the dashed line. Abbreviations: BMI=Body Mass Index; EPIC=European Prospective Investigation into Cancer and Nutrition; HADS=Hospital Anxiety and Depression Scale; TAAQOL= TNO (Netherlands Organisation for Applied Scientific Research) and AZL (Leiden University Medical Centre) Questionnaire for Adult's Quality of Life; RSES= Rosenburg Self-Esteem Scale; ICQ= Illness Cognition Questionnaire; PSQI=Pittsburg Sleep Quality Index; CRP= C-Reactive Protein. [a] Compared to the conditions listed by Streefkerk et al. [11], the following conditions differ slightly: Eye conditions include only cataract and eye removal and for ear conditions only hearing loss was assessed. The following conditions were not included: urinary tract obstruction, underweight, obesity, headache, hydrocephalus, other neurological conditions, decreased pulmonary functioning, dermatological conditions.

Supplementary Table 2. Comparison CCS participants vs. non-participants

Characteristic	Participants (n=1927)	Non participants (n=2064) *	P-value [e]	ES [f]
	N (%)	N (%)		
Sex				
Male	996 (51.7)	1241 (60.1)	<0.001	0.09
Female	931 (48.3)	823 (39.9)		
Year of birth				
<1960	21 (1.1)	21 (1.0)		
1960 – 1969	152 (7.9)	151 (7.3)	0.11	0.05
1970 – 1979	502 (26.1)	516 (25.0)		
1980 – 1989	740 (38.4)	789 (38.2)		
≥1990	512 (26.5)	587 (28.5)		
Age at diagnosis (years)				
0-5	886 (46.0)	977 (47.3)		
5-10	519 (26.9)	564 (27.3)	0.24	0.03
10-15	414 (21.5)	393 (19.1)		
15-18	108 (5.6)	130 (6.3)		
Primary childhood cancer diagnosis [a]				
Leukemia	678 (35.2)	684 (33.1)		
Non-Hodgkin lymphoma [b]	234 (12.1)	237 (11.5)		
Hodgkin lymphoma	135 (7.0)	148 (7.2)		
CNS	177 (9.2)	244 (11.8)		
Neuroblastoma	111 (5.8)	108 (5.2)	0.35	0.06
Retinoblastoma	10 (0.5)	14 (0.7)		
Renal tumors	220 (11.4)	224 (10.9)		
Hepatic tumors	17 (0.9)	25 (1.2)		
Bone tumors	109 (5.7)	112 (5.4)		
Soft tissue tumors	141 (7.3)	152 (7.4)		
Germ cell tumors	65 (3.4)	86 (4.2)		
Other and unspecified [c]	30 (1.6)	30 (1.5)		
Period of childhood cancer diagnosis				
1963-1969	29 (1.5)	18 (0.9)	0.15	0.04
1970-1979	255 (13.2)	255 (12.4)		
1980-1989	607 (31.5)	631 (30.6)		
>1990	1036 (53.8)	1160 (53.1)		
Childhood cancer treatment [d]				
Surgery only	131 (6.8)	244 (11.8)		
Chemotherapy, no radiotherapy	1047 (54.3)	1163 (56.3)		
Radiotherapy, no chemotherapy	100 (5.2)	125 (6.1)	<0.001	0.13
Radiotherapy and chemotherapy	640 (33.2)	503 (24.4)		
No treatment/ treatment unknown	9 (0.5)	23 (1.1)		

Supplementary Table 2. Continued

Characteristic	Participants (n=1927)	Non participants (n=2064) *	P-value [e]	ES [f]
	N (%)	N (%)		
Hematopoietic stem cell transplantation				
Yes	131 (6.8)	81 (3.9)	0.001	0.07
No	1783 (92.5)	1974 (95.6)		
Missing	13 (0.7)	9 (0.5)		
Cancer recurrence				
No	1675 (86.9)	1821 (88.2)	0.21	0.02
Yes	252 (13.1)	243 (11.8)		

*Non-participants were invited to participate but did not return or complete the fatigue questionnaire (non-responders + lacking/missing complete or fatigue specific questionnaire data). In flowchart in Supplementary Figure 1, non-participants DCCSS LATER 2 (n=2.453) and non-participants current study (n=355) are added up, minus 744 CCS who declined participation and who were therefore not analyzed.

[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

[d] Treatment data included primary treatment and all recurrences.

[e] Chi-Square test

[f] Cramér's V effect size (<0.1=little, 0.1=low, 0.3=medium, 0.5=high).

Supplementary Table 3. Post-hoc analyses showing relation between number of comorbidities and chronic fatigue, before and after adding other factors to the model

	Starting model	+physical activity	+pain	+anxiety	+depression	+BMI	+sleep problems
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Number of Comorbidities							
0	ref	ref	ref	ref	ref	ref	ref
1-2	1.32 (1.03 – 1.68)	1.28 (1.00 – 1.64)	1.20 (0.93 – 1.55)	1.31 (1.02 – 1.70)	1.29 (0.99 – 1.66)	1.31 (1.02 – 1.67)	1.34 (1.04 – 1.73)
>2	2.82 (1.98 – 4.00)	2.54 (1.78 – 3.65)	2.27 (1.55 – 3.30)	2.58 (1.79 – 3.74)	2.65 (1.81 – 3.86)	2.78 (1.94 – 3.96)	2.54 (1.75 – 3.68)
	+muscle strength	**+social functioning**	**+self-esteem**	**+helplessness**	**+acceptance**	**+disease benefits**	**+CRP**
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Number of Comorbidities							
0	ref	ref	ref	ref	ref	ref	ref
1-2	1.29 (1.01 – 1.65)	1.29 (0.99 – 1.68)	1.27 (0.97 – 1.65)	1.06 (0.82 – 1.38)	1.34 (1.04 – 1.73)	1.37 (1.07 – 1.75)	1.31 (1.03 – 1.68)
>2	2.68 (1.88 – 3.81)	2.37 (1.62 – 3.47)	2.45 (1.67 – 3.60)	1.46 (0.97 – 2.21)	2.62 (1.82 – 3.78)	2.97 (2.08 – 4.23)	2.75 (1.93 – 3.92)

Results of logistic regression analyses are shown with chronic fatigue as dependent variable and number of comorbidities (combined with each hypothesized mediating factor) as independent variables. Starting model is univariable logistic regression model with CF as dependent variable and number of comorbidities as independent variable (adjusted for age and sex). Every hypothesized mediating factor is added to the starting model to determine the change in OR. A change of >10% in OR compared to the starting model indicates that particular factor to be a possible mediator/confounder for the association between number of comorbidities and chronic fatigue (this was the case for the factors physical activity, pain, sleep problems, social functioning, self-esteem and helplessness). All models were adjusted for age and sex.

Chapter 6

Structural Equation Modeling to determine putative causal factors for chronic fatigue in childhood cancer survivors

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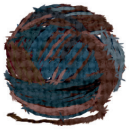
Under review Cancer Medicine



Abstract

Objective: To investigate putative causal relations for Chronic Fatigue (CF) using structural equation modeling (SEM).

Methods: The current study is part of the Dutch Childhood Cancer Survivor Study, including childhood cancer survivors who were ≥5 years post diagnosis. CF was defined as scoring ≥35 on the *fatigue severity subscale* of the Checklist Individual Strength combined with a duration of fatigue of ≥6 months. Interrelationships between factors that were previously associated with CF and their causal relation with CF were investigated using SEM and causal discovery methodology, while the results were presented in a path diagram. A bootstrap method was used to ascertain how robust each finding was, presenting the percentage of times that each discovered edge was found in 1000 bootstrap samples as a measure of confidence (with >50% to be confident in a found edge).

Results: 1927 CCS participated in the study (23.6% reported CF). Results indicated that sex and pain had a putative causal effect on CF (bootstrap confidence 78% and 100% respectively), while CF was causally linked to physical activity and helplessness (bootstrap confidence 72% and 55% respectively). The relation between CF and depression was found to be two-way (bootstrap confidence 67%), indicating a reciprocal relation or the presence of a latent confounder. The same applied to the relations between CF and anxiety, sleep problems, BMI, self-esteem and social functioning, but this could not be confirmed with high confidence (bootstrap confidence <50%).

Conclusion: This study provides some insight into the complex etiology of CF and could give guidance in the development of appropriate prevention and/or intervention strategies for CF in CCS.

Background

One in four long-term Childhood Cancer Survivors (CCS) suffers from chronic fatigue (CF) [1]. CF is a debilitating symptom that affects quality of life [2]. Previous studies have shown multiple variables to be related to CF in CCS, for example childhood cancer diagnosis and treatment related variables, demographics and various lifestyle and psychological variables [3-5]. However, due to methodological differences between previous studies, it remains unknown what the precise relation of these variables with CF is.

In a recent publication we determined the relationship of CF with aforementioned variables in one model and showed that lifestyle and psychosocial factors were most strongly associated with CF in CCS [6]. However, as we used cross-sectional data and multiple regression analysis, we could only determine the associations between CF and the other variables. To better understand the etiology of CF in CCS, a next step would be to indicate how these factors might possibly be causally related to CF. In the current study, we employed data-driven causal discovery methods to ascertain putative causal relationships.

A variety of data-driven computational methods for causal discovery have been developed in the past decades, aiming to find underlying causal relations from (cross-sectional) observational data [7]. Claassen and Heskes [8] have proposed a Bayesian approach for constraint-based causal discovery (BCCD) in which Bayesian scoring is used to constrain the set of possible causal models that could have generated the data, while conflict resolution is used for cases where different edges seem equally likely. In other words, all possible causal pathways are tested, but only the most likely ones, based on the observed data probability distribution, are retained. This approach works in the presence of latent confounders and can be used to infer both causal, i.e. a cause-effect relation between variables is present, and two-way relations, i.e. a cyclical relation between variables or a latent confounder is present (see Box 1 for definitions of causal and two-way relations used in the current study). In the same vein, Structural Equation Modeling (SEM) is an approach that can be used to assess potentially causal relationships between factors using cross-sectional data [9, 10]. We used the SEM approach to investigate hypothesized relations based on background knowledge and expert opinion and to analyze possible causal relations for CF in CCS using the causal structure output of BCCD.

The aim of the current study was to determine causal relations between CF and factors that were previously shown to be associated with CF. Understanding relations between

factors and how they are causally related to CF in CCS could lead to new insights which can help develop strategies to prevent or treat CF.

Methods

Study design and participants

This cross-sectional study, which was part of the Dutch Childhood Cancer Survivor Study on Late Effects (DCCSS LATER) part 2 [11], extends on previously published methodology and results [6]. In short, study participants were included from the DCCSS LATER cohort, a Dutch nationwide cohort including five-year cancer survivors [12]. Participants, who were still alive and living in The Netherlands at time of data collection (2017-2020) and who were not lost to follow-up or had previously declined to participate in any research, were invited to participate in the study (N=4735). Participants for the current study were 18 years of age or older and gave written informed consent to participate. The DCCSS LATER fatigue study was approved by the Medical Research Ethics Committee of the Amsterdam UMC (registered at toetsingonline.nl, NL34983.018.10).

Data collection

Fatigue severity was assessed with the *fatigue severity subscale* of the Checklist Individual Strength (CIS) [13]. The CIS has satisfying psychometric properties in CCS [158]. CF was defined as reporting severe fatigue (a score of 35 or higher on the *CIS fatigue severity* subscale [15]) with a duration of at least 6 months. The duration of fatigue symptoms, when applicable, was assessed in a separate item next to the CIS.

In a previous study we found that out of a large pool of possible CF-related variables, the following factors to be associated with CF: BMI, physical activity, anxiety, depression, pain, self-esteem, feelings of helplessness, social functioning and sleep problems [6]. We focused on these factors in the current study. In the period 2017-2020, data were collected during a clinic visit (or by digital questionnaires when a visit was not possible) as follows:

- To calculate Body Mass Index (BMI), height and weight were measured manually during the clinic visit (or self-reported when a clinic visit was not possible).
- The European Prospective Investigation into Cancer and Nutrition (EPIC) physical activity questionnaire [16] was used to assess weekly physical activities. EPIC items were used to categorize participants using the four-point physical activity index

as proposed by Wareham et al. [16] into being A) physically active, B) moderately physically active, C) moderately physically inactive or D) physically inactive.
- The Hospital Anxiety and Depression Scale (HADS) [17, 18] was used to assess feelings of anxiety and depression. Participants were indicated as having (sub) clinical anxiety or depression based on HADS scale scores (subscale score ≥8).
- Pain was measured on a 6-point Likert scale, ranging from having no pain (score of 1) to very much pain (score of 6).
- The Rosenburg Self-Esteem Scale (RSES) [19, 20] was used to assess self-esteem. Items were added up (total score ranging 10-40), with a higher score reflecting higher self-esteem.
- The Illness Cognition Questionnaire (ICQ) [21, 22] helplessness subscale was used as an indication of feelings of helplessness. Six items of the subscale were added up (range 6-24), with higher scores reflecting more feelings of helplessness, related to the childhood cancer.
- The TNO (Netherlands Organisation for Applied Scientific Research) and AZL (Leiden University Medical Centre) Questionnaire for Adult's Quality of Life (TAAQOL) social functioning domain [23] was used as an indication of the participant's social functioning. Subscale scores were transformed to a 0-100 scale following instructions described elsewhere [23], with higher scores reflecting better social functioning.
- The Pittsburg Sleep Quality Index (PSQI) [24, 25] was used to assess sleep quality. A global score that reflects overall sleep quality was computed following instructions described elsewhere [24, 25]. Participants with a global score ≤ 5 were indicated as 'poor sleepers'.

Diagnosis and treatment data of primary diagnoses and all recurrences of the CCS participants were collected from medical records by data managers using a uniform protocol [26]. More details regarding data collection can be found elsewhere [11, 27].

Statistical analyses

Descriptive statistics were calculated using the diagnosis and treatment related variables to describe the group of participants. Chi-square analyses were performed to analyze differences between participants and non-participants, with Cramér's V effect sizes used to indicate little (<0.1), low (0.1), medium (0.3) and high (0.5) differences between groups.

A combination of both expert opinions (of authors AP, IW, HK and JL) and the BCCD algorithm [8] was used to determine the potential causal relations between CF and its associated factors. An SEM analysis was performed to evaluate novel causal

and two-way relations suggested by BCCD. More specifically, the following steps were conducted:

1. Using available literature [28-31] and expert opinions of the authors we have outlined possible causal and two-way relationships between CF and all factors. All pathways between the study variables were indicated as being A) causal, B) two-way or C) not (directly) related. The hypothesized causal and two-way relations are presented in Table 2 (focusing on CF) and Supplementary Table 2 (all possible relations) and represent the initial SEM.
2. We ran the BCCD algorithm [8] on the data, incorporating information from the initial SEM from step 1. This was done to limit the number of putative causal relations to be tested, ensuring the algorithm to focus on these relations with sufficient statistical power. Any pathway hypothesized as "not related" was enforced missing when running BCCD. Pathways hypothesized as causal were given as input to BCCD as background knowledge. These could be overruled and turned into two-way relations when BCCD found inconsistencies with the data. Along the same lines, BCCD could turn hypothesized two-way relations in the initial SEM into causal relations. This resulted in a new, partially data-driven, model.
3. To ascertain how robust each finding was, we used the bootstrap method [32] to resample our data 1000 times and reran step 2 on each bootstrap sample. We reported the percentage of times that each relation was found in the bootstrap samples as a confidence measure, with >50% as a majority decision threshold assumed to indicate adequate confidence in the relation. Any relations turned by BCCD in >50% of the bootstrap samples were adjusted in the initial SEM. We will refer to the adjusted model as the final SEM. Overall model fit (Bayesian information criterion (BIC) score) [33] was used to indicate whether the model improved compared to the hypothesized causal model from step 1, taking into account both goodness-of-fit and model complexity (lower BIC score indicates improvement). The Bayes factor (K) was derived from the BIC and indicates the strength of this improvement (a Bayes factor of 100 would mean that the proposed model is approximately 100 times more likely than the initial model, given the data) [34].

R [129] (lavaan and RUcausal packages [36, 37]) was used for the analyses. Missing data (no pattern observed) were imputed using multiple imputation (Markov chain Monte Carlo method, twenty imputed datasets) [38-40]. The imputed datasets were pooled to get an estimate of the covariance matrix and then corrected for correlation inflation by using the equivalent size of a single imputed dataset for the analyses.

Box 1. Definitions of causal and two-way relations used in the current study.

Causal relation: Factor A is a plausible cause for factor B

Two-way relation: Factor A and factor B are dependent; one or both of the following could be true.
- Factor A and factor B have a cyclical relationship (A causes B and B causes A);
- A latent confounder is present between factor A and factor B

Results

Participant characteristics (n=1927) are presented in Table 1. A flowchart with the participants inclusion process and a comparison with non-participants is shown in Supplementary Figure 1 and Supplementary Table 1 respectively.

SEM output of the hypothesized model and the final, BCCD adjusted, model are presented in Supplementary Table 3, including bootstrap confidence percentages of all analyzed relations. Edge orientations that changed after incorporating the BCCD output are shown in Table 2 (focusing on CF) and Supplementary Table 4 (all possible relations). The BIC score of the BCCD-adjusted model improved significantly, corresponding to a Bayes factor (K) of 2.4×10^5, which indicates decisive strength of evidence in favor of this final SEM model compared to the initial SEM. Sex and pain were found to be putative causal factors of CF, with a bootstrap confidence of 78% and 100% respectively, while CF was found to be a putative causal factor for both physical activity (lower physical activity index) and helplessness (higher score), with a bootstrap confidence of 72% and 55% respectively. The relation between CF and depression was found to be two-way (with a bootstrap confidence of 67%). The results also suggest that the relations between CF and anxiety, sleep problems, BMI, self-esteem and social functioning are two-way, but this could not be confirmed with high confidence from the data (all relations <50% bootstrap confidence). A simplified graphical version of the results is presented in Figure 1, where a path diagram shows the interrelationships between CF and the studied associated factors.

Discussion

In the current study, we presented plausible causal relations for CF in CCS, with which we aimed to gain more insight into the etiology of CF.

Clinical implications

Several causal relations were found to be present in the data using BCCD. Pain was found to be a causal factor for CF and, with a bootstrap confidence of 100%, this was the most confident edge found. This is in agreement with studies conducted in other patient populations that suggested pain to predict or cause fatigue [29, 41]. This is an interesting finding as it makes pain reduction a potential intervention strategy to tackle CF. In the current study, 32.4 % of the participants with CF reported to have rather much (24.7%) or (very) serious pain (7.7%), compared to 8.7% in the non-CF participants. This means that almost one-third of the CCS with CF experience some form of pain and might therefore benefit from interventions aimed at reducing pain symptoms. However, details regarding the pain's nature, i.e. acute or chronic pain, or the duration of the pain symptoms remains unknown, which makes the interpretation of the exact relation between pain and CF difficult. In addition, the results show that it is plausible that there is a causal relation between pain and CF, however we cannot determine the strength of this relation relative to other contributing factors using the SEM approach. Whether a reduction of pain symptoms also leads to a clinically relevant decrease in the level of fatigue symptoms remains to be determined, e.g., by conducting an intervention study aimed at pain management in CCS and assess its effect on CF. Studies in other patient populations have suggested a reduction in pain to possibly reduce symptoms of fatigue [42, 43]. Future studies might explore this causal pathway in CCS in more detail.

Sex was also found to be a causal factor for CF. Although sex does not actively cause symptoms of fatigue, we believe sex to act as an indirect causal factor. The precise nature of this causal relation remains a question, but females tend to more often experience fatigue compared to males, which might be related hormonal/biological differences between the sexes [44, 45]. Also, sex differences have been associated with (risk factors for) other outcomes as well, e.g., neurological and cardiovascular [46, 47]. This emphasizes the need to provide care that is tailored to the person's situation and needs, which might be different for men and women.

CF was found to be a causal factor for reduced physical activity. Concordantly, in patients with osteoarthritis fatigue was shown to be a strong predictor for reduced physical activity, while among the elderly, fatigue was suggested to be the cause for reduced physical activity [48, 49]. The causality seems plausible as people who experience severe fatigue symptoms might have little energy or less motivation to actively engage in sports activities or perform energy consuming daily activities. On the other hand, previous studies showed that interventions aimed at increasing physical activity also decreased fatigue symptoms [50]. This suggests that, although

CF might cause one to be less physically active as was found in the current study, a reversed causal relation is also plausible, such that increasing physical activity might decrease CF symptoms.

CF was also found to be a causal factor for feelings of helplessness. Here, helplessness is an indication of the disease-related feelings of helplessness, referring to the childhood cancer diagnosis. Items to assess feelings of helplessness were, among others, "*because of the childhood cancer I miss the things I like to do the most*", "*the childhood cancer controls my life*" and "*the childhood cancer impairs me to do things that are important to me*". Thus, CCS scoring high on these items experience difficulties in their current daily lives because of the childhood cancer. One of the reasons could be because of symptoms of CF, which was shown to impair HRQOL of CCS [2]. As CF could be a result of the childhood cancer diagnosis and treatment or perceived as caused by the childhood cancer by the CCS, CF might increase feelings of helplessness in relation to childhood cancer. Although this pathway seems plausible, it must be taken into account that the bootstrap confidence of 55.4% for the causal relation between CF and helplessness is not as high as the confidence levels for the causal relations between CF and pain, sex and physical activity (100%, 77.8% and 72.3% respectively). Future research might investigate the causal relation between illness cognition and CF in more detail.

A two-way relation of CF with depression was found. This is in concordance with literature in other patient populations where studies found that interventions aimed to reduce symptoms of depression also reduced symptoms of fatigue, and vice versa [51-53]. This shows that there is an overlap in symptoms between fatigue and depression and raises the question whether particular subgroups might exist: a subgroup of people with predominant fatigue who present with depressive symptoms as a consequence and a subgroup of people with a predominant depression who have fatigue symptoms as part of the depressive symptomatology. Identifying such subgroups is relevant as treatment strategies might differ between groups.

The relations of CF with anxiety, BMI, self-esteem, sleep problems and social functioning were hypothesized to be two-way, however this could not be confirmed with high confidence (<50% bootstrap confidence). Nevertheless, regardless of the precise causal pathways producing these associations, it is known that these symptoms are related to CF in CCS [6]. A study in patients with chronic fatigue syndrome showed that insufficient social support plays an important role in perpetuating symptoms of fatigue [54]. In addition, some studies have shown cognitive behavioral therapy (CBT), an intervention that includes topics such as social functioning, anxiety and sleep problems, to be an effective intervention to reduce fatigue in survivors of adult-

onset cancer, as did a pilot study in CCS [55-57]. This suggests that a causal relation between abovementioned factors and CF may be present, but longitudinal studies in CCS are needed to confirm whether reducing any of these symptoms might reduce symptoms of fatigue (or the other way around).

Several plausible causal and two-way relations for CF were shown in the current study. These results can help to understand the complex phenomenon that is CF and provide guidance in finding a suitable prevention or intervention strategy.

Study limitations

The following needs to be taken into account when interpreting the results. Although SEM is an adequate technique for analyzing causal structure in a large network of variables and helps to investigate possible causalities using cross-sectional data, findings should be confirmed in experimental settings wherever possible, using longitudinal data. We used expert knowledge to limit the number of possible relations to be tested. This ensured the algorithm to focus on the relations of interest with sufficient statistical power. However, some relations that were not defined by the experts might be present that were not tested in the current study.

We chose >50% for the bootstrap confidence percentages as a threshold to keep or turn edges in the BCCD adjusted SEM. We believe this majority decision threshold to adequately indicate a confident relation. Had we chosen a rather stricter threshold (for example 75%), some edges would not be present in the final SEM, but the remaining edges would have stronger support in the data. Also, whenever a causal or two-relation was found, it remains to be determined whether the relation is clinically relevant. Nevertheless, the aim of the current study was to determine the direction of putative causal relations in an exploratory fashion, and we believe the current methodology suits that purpose well.

Another limitation regards the differences between participants and non-participants. Participants were more often female, more often treated with a combination of radiotherapy and chemotherapy and more often treated with hematopoietic stem cell transplantation compared to non-participants. Therefore, there is a possibility of selection bias, although effect sizes were small (Cramér's V effect sizes ≤ 0.13).

Conclusion

The current study presents plausible causal and two-way relations for CF in CCS. The results give more insight in the complex etiology of CF, which could offer some guidance in the development of prevention or intervention strategies.

Table 1. Characteristics of participants

Characteristic	Participants (n=1927)	
	n	%
Sex		
Male	996	51.7
Female	931	48.3
Age at assessment (years)		
Mean (SD)	35.1 (9.3)	
18-29	599	31.1
30-39	737	38.2
≥40	591	30.7
CF		
Yes	454	23.6
No	1473	76.4
Age at diagnosis (years)		
Mean (SD)	6.7 (4.7)	
0-4	886	46.0
5-9	519	26.9
10-14	414	21.5
15-17	108	5.6
Primary childhood cancer diagnosis [a]		
Leukemia	678	35.3
Non-Hodgkin lymphoma [b]	234	12.1
Hodgkin lymphoma	135	7.0
CNS	177	9.2
Neuroblastoma	111	5.8
Retinoblastoma	10	0.5
Renal tumors	220	11.4
Hepatic tumors	17	0.9
Bone tumors	109	5.7
Soft tissue tumors	141	7.3
Germ cell tumors	65	3.4
Other and unspecified [c]	30	1.6
Period of childhood cancer diagnosis		
1963-1969	29	1.5
1970-1979	255	13.2
1980-1989	607	31.5
>1990	1036	53.6
Childhood cancer treatment [d]		
Surgery only	131	6.8
Chemotherapy, no radiotherapy	1047	54.3
Radiotherapy, no chemotherapy	100	5.2
Radiotherapy and chemotherapy	640	33.2
No treatment/treatment unknown	9	0.5
Hematopoietic Stem cell transplantation		
Yes	131	6.8
No	1783	92.5
Unknown	13	0.7

Table 1. Continued

Characteristic	Participants (n=1927)	
	n	%
Recurrence		
No	1675	86.9
Yes	252	13.1
Sex		
Male	996	51.7
Female	931	48.3
Age at assessment		
18-29	599	31.1
30-39	737	38.2
≥40	591	30.7
Educational level		
Low	240	13.3
Middle	774	42.8
High	795	43.9
Missing	118	-
Employment status		
Employed	1538	85.1
Not employed	269	14.9
Missing	120	-
Relationship status		
In a relationship	1266	78.6
Not in a relationship	344	21.4
Missing	317	-
BMI		
Healthy weight	993	53.2
Underweight	54	2.9
Overweight	588	31.5
Obesity	230	12.3
Missing	62	-
Physical activity index		
Inactive	93	5.3
Moderately inactive	402	23.1
Moderately active	413	23.7
Active	836	47.9
Missing	183	-
(sub)clinical Anxiety		
No	1304	80.3
Yes	320	19.7
Missing	303	-
(sub)clinical Depression		
No	1492	92.0
Yes	130	8.0
Missing	305	-

Table 1. Continued

Characteristic	Participants (n=1927)	
	n	%
Poor sleeper		
No	1176	64.2
Yes	655	35.8
Missing	96	-
Pain total score (range 1-6)		
Mean (SD)	2.0 (1.2)	
Missing	44	
Self-esteem total score (range 10-40)		
Mean (SD)	32,8 (5.6)	
Missing	294	
Helplessness total score (range 6-24)		
Mean (SD)	7.8 (3.1)	
Missing	326	
Social functioning total score (range 0-100)		
Mean (SD)	87.2 (18.4)	
Missing	248	

Abbreviations: BMI=Body mass index; CF=Chronic fatigue; SD=Standard deviation.[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.[d] Treatment data included primary treatment and all recurrences.

Table 2. Hypothesized causal and two-way relations for CF and associated factors & adjusted relations after BCCD output

Hypothesized relations	Relations after incorporating BCCD output
CF ← sex	CF ← sex
CF ← pain	CF ← pain
CF ↔ BMI	CF ↔ BMI
CF ↔ physical activity	CF → physical activity
CF ↔ sleep problems	CF ↔ sleep problems
CF ↔ social functioning	CF ↔ social functioning
CF ↔ self-esteem	CF ↔ self-esteem
CF ↔ depression	CF ↔ depression
CF ↔ anxiety	CF ↔ anxiety
CF ↔ helplessness	CF → helplessness

Abbreviations: BCCD=Bayesian constraint-based causal discovery; BMI=Body mass index; CF=Chronic fatigue.Hypothesized relations are based on expert opinions of authors AP, IW, HK and JL in combination with available literature [28-31]. Direction of arrow shows direction of (hypothesized) causality:
A → B = A hypothesized to cause B
A ← B = B hypothesized to cause A
A ↔ B = hypothesized two-way relation

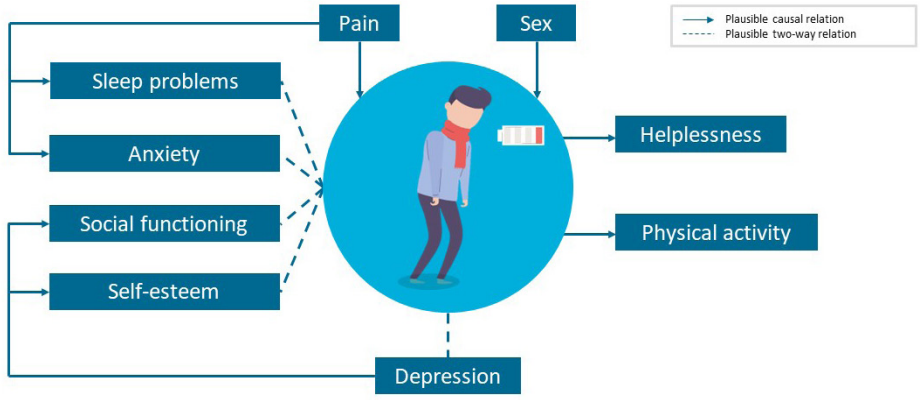


Figure 1. Path diagram showing (causal) relations between Chronic Fatigue and associated factors after incorporating BCCD output.
Diagram shows plausible causal and two-way relations of Chronic Fatigue. Directed edge indicates plausible causal relationship (confirmed or adjusted by BCCD with > 50% confidence), dotted edge indicates a potential two-way relation between variables (the two-way relation of CF and depression was confirmed by BCCD with >50% confidence, the other two-way relations were hypothesized by the experts and not confirmed or adjusted by BCCD with >50% confidence). Note: Diagram is a simplified version of the found relations in the final SEM, not all relations between associated factors are shown (see Supplementary Table 2 for more details about all found relations).

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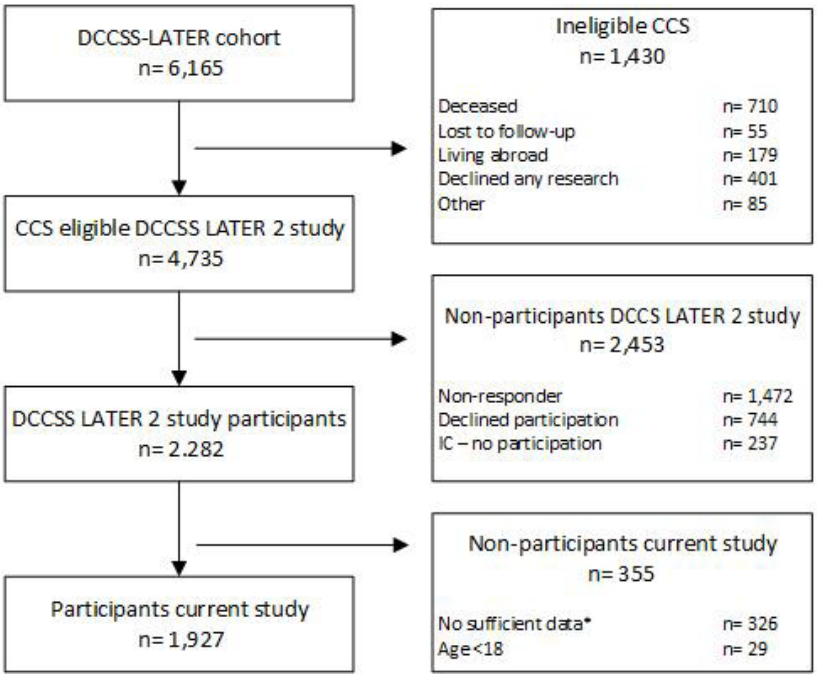
Supplementary material



Supplementary Figure 1. Flowcharts of CCS and sibling study participants.
*Sufficient data to determine fatigue status: at least 7 of the 8 CIS fatigue severity items completed (with one missing value, the mean of the remaining completed items was imputed) + duration of fatigue symptoms completed (if fatigue severity subscale score ≥35).

Supplementary Table 1. Comparison CCS participants vs. non-participants

Characteristic	Participants (n=1927)	Non participants (n=2064) *	P-value [e]	ES [f]
	N (%)	N (%)		
Sex				
Male	996 (51.7)	1241 (60.1)	<0.001	0.09
Female	931 (48.3)	823 (39.9)		
Year of birth				
<1960	21 (1.1)	21 (1.0)		
1960 – 1969	152 (7.9)	151 (7.3)	0.11	0.05
1970 – 1979	502 (26.1)	516 (25.0)		
1980 – 1989	740 (38.4)	789 (38.2)		
≥1990	512 (26.5)	587 (28.5)		
Age at diagnosis (years)				
0-5	886 (46.0)	977 (47.3)		
5-10	519 (26.9)	564 (27.3)	0.24	0.03
10-15	414 (21.5)	393 (19.1)		
15-18	108 (5.6)	130 (6.3)		
Primary childhood cancer diagnosis [a]				
Leukemia	678 (35.2)	684 (33.1)		
Non-Hodgkin lymphoma [b]	234 (12.1)	237 (11.5)		
Hodgkin lymphoma	135 (7.0)	148 (7.2)		
CNS	177 (9.2)	244 (11.8)		
Neuroblastoma	111 (5.8)	108 (5.2)		
Retinoblastoma	10 (0.5)	14 (0.7)	0.35	0.06
Renal tumors	220 (11.4)	224 (10.9)		
Hepatic tumors	17 (0.9)	25 (1.2)		
Bone tumors	109 (5.7)	112 (5.4)		
Soft tissue tumors	141 (7.3)	152 (7.4)		
Germ cell tumors	65 (3.4)	86 (4.2)		
Other and unspecified [c]	30 (1.6)	30 (1.5)		
Period of childhood cancer diagnosis				
1963-1969	29 (1.5)	18 (0.9)		
1970-1979	255 (13.2)	255 (12.4)	0.15	0.04
1980-1989	607 (31.5)	631 (30.6)		
>1990	1036 (53.8)	1160 (53.1)		
Childhood cancer treatment [d]				
Surgery only	131 (6.8)	244 (11.8)		
Chemotherapy, no radiotherapy	1047 (54.3)	1163 (56.3)	<0.001	0.13
Radiotherapy, no chemotherapy	100 (5.2)	125 (6.1)		
Radiotherapy and chemotherapy	640 (33.2)	503 (24.4)		
No treatment/treatment unknown	9 (0.5)	23 (1.1)		
Hematopoietic stem cell transplantation				
Yes	131 (6.8)	81 (3.9)	0.001	0.07
No	1783 (92.5)	1974 (95.6)		
Missing	13 (0.7)	9 (0.5)		

Supplementary Table 1. Continued

Characteristic	Participants (n=1927)	Non participants (n=2064) *	P-value [e]	ES [f]
	N (%)	N (%)		
Cancer recurrence				
No	1675 (86.9)	1821 (88.2)	0.21	0.02
Yes	252 (13.1)	243 (11.8)		

*Non-participants were invited to participate but did not return or complete the fatigue questionnaire (non-responders or missing fatigue questionnaire data). In flowchart in Supplementary Figure 1, non-participants DCCSS LATER 2 (n=2.453) and non-participants current study (n=355) are added up, minus 744 CCS who declined participation and who were therefore not analyzed.

[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

[d] Treatment data included primary treatment and all recurrences.

[e] Chi-Square test

[f] Cramér's V effect size (<0.1=little, 0.1=low, 0.3=medium, 0.5=high).

Supplementary Table 2. Hypothesized causal and two-way relations for CF and associated factors.

Study variable	Hypothesized causal relations	Hypothesized two-way relations
CF	CF ← sex CF ← pain	CF ↔ BMI CF ↔ physical activity CF ↔ sleep problems CF ↔ social functioning CF ↔ self-esteem CF ↔ depression CF ↔ anxiety CF ↔ helplessness
Sex	Sex → CF Sex → sleep problems Sex → self-esteem Sex → depression Sex → anxiety Sex → helplessness Sex → pain Sex → BMI	n/a
BMI	BMI ← sex BMI → self-esteem	BMI ↔ CF BMI ↔ physical activity BMI ↔ sleep problems BMI ↔ depression
Anxiety	Anxiety ← pain Anxiety ← sex Anxiety → social functioning Anxiety → sleep problems	Anxiety ↔ CF Anxiety ↔ helplessness Anxiety ↔ self-esteem Anxiety ↔ depression
Depression	Depression ← sex	Depression ↔ CF Depression ↔ anxiety Depression ↔ helplessness Depression ↔ pain Depression ↔ physical activity Depression ↔ sleep problems Depression ↔ social functioning Depression ↔ self-esteem Depression ↔ BMI
Pain	Pain → CF Pain → sleep problems Pain → social functioning Pain → self-esteem Pain → anxiety Pain → helplessness Pain ← sex	Pain ↔ physical activity Pain ↔ depression
Physical activity	Physical activity → self-esteem Physical activity → helplessness Physical activity ← social functioning Physical activity ← sleep problems	Physical activity ↔ CF Physical activity ↔ depression Physical activity ↔ pain Physical activity ↔ BMI

Supplementary Table 2. Continued

Study variable	Hypothesized causal relations	Hypothesized two-way relations
Sleep problems	Sleep problems → physical activity Sleep problems → social functioning Sleep problems ← sex Sleep problems ← self-esteem Sleep problems ← anxiety Sleep problems ← pain	Sleep problems ↔ CF Sleep problems ↔ depression Sleep problems ↔ helplessness Sleep problems ↔ BMI
Self-esteem	Self-esteem → sleep problems Self-esteem → social functioning Self-esteem ← pain Self-esteem ← BMI Self-esteem ← physical activity Self-esteem ← sex	Self-esteem ↔ CF Self-esteem ↔ helplessness Self-esteem ↔ depression Self-esteem ↔ anxiety
Social functioning	Social functioning → physical activity Social functioning ← sleep problems Social functioning ← self-esteem Social functioning ← anxiety Social functioning ← pain	Social functioning ↔ CF Social functioning ↔ helplessness Social functioning ↔ depression
Helplessness	Helplessness ← pain Helplessness ← physical activity Helplessness ← sex	Helplessness ↔ CF Helplessness ↔ self-esteem Helplessness ↔ depression Helplessness ↔ social functioning Helplessness ↔ anxiety Helplessness ↔ sleep problems

Abbreviations: CF=Chronic Fatigue, BMI=Body Mass Index. Hypothesized relations are based on expert opinions of authors AP, IW, HK and JL in combination with available literature [191-194]. Direction of arrow shows direction of hypothesized causality:

A → B = A hypothesized to cause B

A ← B = B hypothesized to cause A

A ↔ B = hypothesized two-way relation

If no edge was present between parameters, no (unmediated) relation was hypothesized.

Supplementary Table 3. Output SEM analyses

	Initial SEM [a]			Final SEM [b]			
BIC	**88442.9**			**88422.7**			
Causal relations (regressions)	**Estimate**	**SE**	**p-value**	**Estimate**	**SE**	**p-value**	**Confidence in edge**
Chronic fatigue ~							
Female sex	0.107	0.018	<0.001	0.101	0.018	<0.001	77.8%
Pain	0.116	0.008	<0.001	0.116	0.008	<0.001	100%
Anxiety ~							<50%
Female sex	0.565	0.158	<0.001	0.565	0.158	<0.001	82.0%
Pain	0.865	0.066	<0.001	0.865	0.066	<0.001	
Depression ~							
Female sex	0.201	0.133	0.132	0.107	0.137	0.435	<50%
Sleep problems ~							
Female sex	0.313	0.126	0.013	0.460	0.132	0.001	<50%
Pain	0.571	0.054	<0.001	0.792	0.057	<0.001	99.8%
Anxiety	0.251	0.021	<0.001	-	-	-	-
Self-esteem	-0.091	0.014	<0.001	-0.087	0.014	<0.001	87.9%
Pain ~							
Female sex	0.400	0.054	<0.001	0.405	0.054	<0.001	90.4%
Self-esteem ~							
Female sex	-1.384	0.254	<0.001	-1.587	0.196	<0.001	83.2%
Pain	-1.068	0.103	<0.001	-0.389	0.086	<0.001	<50%
Physical activity	0.138	0.111	0.217	-0.047	0.100	0.639	<50%
BMI	-0.018	0.021	0.406	0.011	0.021	0.585	<50%
Depression	-	-	-	-1.071	0.034	<0.001	59.0%
Social functioning ~							
Pain	-0.571	0.323	0.078	-0.650	0.313	0.038	<50%
Anxiety	-0.859	0.128	<0.001	-0.612	0.126	<0.001	<50%
Self-esteem	1.057	0.080	<0.001	-	-	-	-
Sleep problems	-0.545	0.132	<0.001	-0.234	-0.128	0.069	<50%
Depression	-	-	-	-2.613	-0.146	<0.001	64.2%
Physical activity ~							
Sleep problems	0.003	0.008	0.680	0.013	0.008	0.094	<50%
Social functioning	0.003	0.001	0.011	0.001	0.001	0.620	<50%
Chronic fatigue	-	-	-	-0.356	0.059	<0.001	72.3%
Helplessness ~							
Female sex	0.170	0.130	0.191	0.042	0.127	0.742	<50%
Pain	0.737	0.056	<0.001	-	-	-	-
Physical activity	-0.280	0.063	<0.001	-0.262	0.064	<0.001	<50%
Chronic fatigue	-	-	-	2.331	0.159	<0.001	55.4%
BMI ~							
Female sex	0.331	0.206	0.108	0.175	0.208	0.403	<50%

Supplementary Table 3. Continued

	Initial SEM [a]			Final SEM [b]			
BIC	**88442.9**			**88422.7**			
Two-way relations (covariances)	**Estimate**	**SE**	**p-value**	**Estimate**	**SE**	**p-value**	**Confidence in edge**
Chronic fatigue ~~							
Anxiety	0.424	0.032	<0.001	0.426	0.032	<0.001	<50%
Depression	0.487	0.028	<0.001	0.493	0.028	<0.001	67.4%
Sleep problems	0.161	0.023	<0.001	0.272	0.027	<0.001	<50%
Self-esteem	-0.627	0.049	<0.001	-0.121	0.035	0.001	<50%
Social functioning	-0.942	0.131	<0.001	-0.580	0.122	<0.001	<50%
Physical activity	-0.046	0.008	<0.001	-	-	-	-
Helplessness	0.354	0.027	<0.001	-	-	-	-
BMI	0.162	0.037	<0.001	0.190	0.038	<0.001	<50%
Anxiety ~~	5.601	0.258	<0.001	5.636	0.259	<0.001	<50%
Depression	-9.699	0.467	<0.001	-8.013	0.415	<0.001	60.6%
Self-esteem	3.191	0.234	<0.001	0.373	0.168	0.026	<50%
Helplessness	-	-	-	2.956	0.240	<0.001	52.2%
Sleep-problems							
Depression ~~	0.931	0.136	<0.001	2.389	0.234	<0.001	<50%
Sleep problems	0.888	0.083	<0.001	0.895	0.083	<0.001	<50%
Pain	-8.935	0.404	<0.001	-	-	-	-
Self-esteem	-9.815	0.802	<0.001	-	-	-	-
Social functioning	-0.247	0.054	<0.001	-0.174	0.056	0.002	<50%
Physical activity	3.709	0.207	<0.001	3.033	0.187	<0.001	66.1%
Helplessness	0.628	0.228	0.006	0.810	0.241	0.001	<50%
BMI							
Sleep problems ~~	0.535	0.158	0.001	0.750	0.173	<0.001	<50%
Helplessness	0.215	0.277	0.438	0.251	0.278	0.366	<50%
BMI							
Pain ~~	-0.099	0.028	<0.001	-0.066	0.028	0.018	<50%
Physical activity	-	-	-	0.651	0.080	<0.001	62.3%
Helplessness							
Self-esteem ~~	-6.423	0.376	<0.001	-2.200	0.257	<0.001	59.1%
Helplessness	-	-	-	11.195	1.447	<0.001	83.9%
Social functioning							
Social functioning ~~	-9.281	0.941	<0.001	-6.583	0.897	<0.001	77.2%
Helplessness							
Physical activity ~~	-0.352	0.099	<0.001	-0.298	0.097	0.002	<50%
BMI							

CF=Chronic Fatigue, BMI=Body Mass Index. Significant edge: p<0.05. Hyphens (-) denote that a type of relation is missing in one of the SEMs (because the other type of relation was present).

[a] Hypothesized relations based on literature and expert opinion of authors AP, IW, HK and JL

[b] We ran BCCD causal discovery algorithm using the initial SEM as input. Any missing edge in the initial SEM was also enforced missing for running BCCD. Hypothesized causal relations in the initial SEM were given as input to BCCD as background knowledge. These can be overruled and turned into two-way relations when BCCD finds inconsistencies with the data. Along the same lines, BCCD can turn hypothesized two-way

relations in the initial SEM into causal relations. A bootstrap resampling method was conducted to determine confidence levels of all edges in the model (percentage of times an edge was discovered in the 1000 bootstrap samples) and to determine possible new edges based on these confidence levels (new edges with a confidence of >50% were included in the final model). This resulted in a BCCD adjusted model with an improved model fit: the final SEM.

Supplementary Table 4. Changes made to the hypothesized model after incorporating BCCD output

Edge orientation in hypothesized model	Edge orientation after incorporating BCCD output	Bootstrap confidence in edge
CF ↔ physical activity	CF → physical activity	72.3%
CF ↔ helplessness	CF → helplessness	55.4%
Depression ↔ social functioning	Depression → social functioning	64.2%
Self-esteem → social functioning	Self-esteem ↔ social functioning	83.9%
Pain → helplessness	Pain ↔ helplessness	62.3%
Depression ↔ self-esteem	Depression → self-esteem	59.0%
Anxiety → sleep problems	Anxiety ↔ sleep problems	52.2%

CF=Chronic Fatigue. After incorporating the BCCD output, the BIC score improved significantly from 88442.86 to 88422.69 (lower is better), corresponding to a Bayes factor of approximately 2.4×10^5. The table shows the edge orientations that were changed after BCCD output incorporation. Direction of arrow shows direction of (hypothesized) causality:
→ = causal relation
↔ = two-way relation

Chapter 7

Different subtypes of chronic fatigue in childhood cancer survivors

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Abstract

Introduction: The aim of the current study was to investigate whether subtypes of chronic fatigue (CF) can be identified in childhood cancer survivors (CCS) and if so, to determine the characteristics of participants with a specific subtype.

Methods: Participants were included from the nationwide DCCSS LATER cohort. The Checklist Individual Strength (CIS) was completed to assess fatigue. Participants with CF (scored ≥ 35 on the *fatigue severity* subscale and indicated to suffer from fatigue for ≥ 6 months) were divided into subgroups using two-step cluster analysis based on the CIS *concentration*, *motivation* and *physical activity* subscales. Differences between groups on demographics, psychosocial, lifestyle and treatment related variables were determined using ANOVA and chi-square analyses (univariable) and multinomial regression analysis (multivariable).

Results: A total of 1910 participants participated in the current study (n=450 with CF; n=1460 without CF). Three CF subgroups were identified: Subgroup 1 (n=133, 29% of participants) had *CF with problems in physical activity*, subgroup 2 (n=111, 25% of participants) had *CF with difficulty concentrating* and subgroup 3 (n=206, 46% of participants) had *multi-dimensional CF*. Compared to subgroup 1, subgroup 2 more often report sleep problems, limitations in social functioning and less often have >2 comorbidities. Subgroup 3 more often report depression, sleep problems, a lower self-esteem and limitations in social functioning and a lower educational level compared to subgroup 1.

Conclusion: Different subgroups of CCS with CF can be identified based on fatigue dimensions physical activity, motivation and concentration. Results suggests that different intervention strategies, tailored for each subgroup, might be beneficial.

Introduction

Chronic fatigue (CF) is often reported by childhood cancer survivors (CCS) [1]. It is a persistent, subjective feeling of severe fatigue that can reduce quality of life [2]. Symptoms of fatigue can differ widely between subjects, varying from feeling too tired to participate in daily life activities to experiencing difficulties concentrating. Fatigue is multi-dimensional and can be measured in individuals using validated instruments [3]. A variation of questionnaires is available to capture the different aspects of fatigue. In research, CF is often used as a comprehensive term to describe all fatigue dimensions, but little is known about the heterogeneity in the appearance of CF. Identifying subgroups who experience different types of CF and characterize these different fatigue dimensions might help to tackle symptoms on a more personalized level. It is plausible that persons who experience physically related fatigue symptoms, i.e. physical exhaustion or reduced physical activity, prefer interventions focused on this physical aspect opposed to persons who experience fatigue symptoms related to mental activities, i.e. concentration or motivational problems. The aim of the current study was to investigate whether subtypes of CF could be identified in CCS and if so, determine demographic, psychosocial and/or diagnosis and treatment related characteristics of participants with different fatigue subtypes.

Methods

Study design and participants

This study is part of the Dutch Childhood Cancer Survivor Study on Late Effects (DCCSS LATER) part 2 [4], a cross-sectional study including participants from the nationwide DCCSS LATER cohort (n=6,165, baseline characteristics described elsewhere [5]). In total, 4,735 eligible CCS were invited to participate (for flowchart of invitation process, see [4]). Participants were included if fatigue status could be determined (CF; yes or no): at least 7 of the 8 CIS fatigue severity items completed (with one missing value, the mean of the remaining completed items was imputed). If participants had severe fatigue (fatigue severity subscale score ≥35), the item assessing the duration of fatigue symptoms had to be completed. Participants who did not have sufficient data to determine fatigue status (n=326) or participants who had missing data on one of the other CIS subscales (n=4) were excluded. All participants were 18 years or older, were able to read and speak Dutch and gave written informed consent to participate. The DCCSS LATER fatigue study was approved by the Medical Research Ethics Committee of the Amsterdam University Medical Centers (registered at toetsingonline.nl, NL34983.018.10).

Data collection

The CIS [6] was completed to assess fatigue and measures four fatigue dimensions, i.e. *fatigue severity* (8 items), *concentration problems* (5 items), *reduced motivation* (4 items) and *problems with physical activity* (3 items) on a 7-point Likert scale. Subscale items and information on how to score each item is presented in Supplementary Table 1. A score of ≥35 on the *fatigue severity* dimension indicates the presence of severe fatigue. This cut-off score was validated in the general Dutch population [7] and the DCCSS LATER cohort [8]. To indicate whether participants scored elevated or problematic on the CIS fatigue dimensions *concentration problems*, *reduced motivation* and *problems with physical activity* we used the mean subscale values of the general Dutch population, presented by Worm-Smeitink et al. [7], plus 1 or 2 standard deviations respectively as a threshold (≥18, ≥16 and ≥12 to indicate elevated subscale scores and ≥24, ≥20 and ≥16 to indicate problematic subscale scores on the respective subscales). Subsequently, an item assessing the duration of fatigue symptoms ("for how many weeks/months/years have you been fatigued?"), when applicable, was completed. CCS who reported severe fatigue and a duration of fatigue symptoms of six months or longer were indicated as having CF.

In addition to fatigue, other constructs were assessed through questionnaires completed at home or during a clinic visit between 2017-2022.

- The European Prospective Investigation into Cancer and Nutrition (EPIC) physical activity questionnaire was used as an indication for the participants' physical activity level (participants were categorized following the physical activity index as being active, moderately active, moderately inactive or inactive) [9].
- The Hospital Anxiety and Depression Scale (HADS) to assess symptoms of anxiety and depression, with subscale scores ≥8 to indicate (sub)clinical symptoms [10, 11].
- The Pittsburg Sleep Quality Index (PSQI) to determine if participants had sleep problems (PSQI total score ≥5) [12, 13].
- The TNO (Netherlands Organisation for Applied Scientific Research) and AZL (Leiden University Medical Centre) Questionnaire for Adult's Quality of Life (TAAQOL) social functioning dimension (scored 0-100 after linear transformation) with higher scores reflecting better social functioning [14].
- The Rosenburg Self-Esteem Scale (RSES) to assess self-esteem (scored 10-40, with higher score reflecting higher self-esteem) [15, 16].
- The Illness Cognition Questionnaire (ICQ) helplessness subscale to reflect feelings of helplessness (scored 6-24 with higher scores reflecting more feelings of helplessness), related to the childhood cancer diagnosis [17, 18].

– A general questionnaire assessing level of education, employment status, relationship status, somatic comorbidities (categorized as having 0, 1-2 or >2 health issues of pre-defined organ systems [19]) and pain (6-point Likert scale, with higher scores reflecting more pain).
– Height and weight of the participant were manually assessed during the clinic visit and used to calculate Body Mass Index (BMI)

Treatment and diagnosis data of primary cancer diagnoses and all recurrences of the participants were collected from medical records by data managers prior to the study [218]. A detailed description about participant inclusion and data collection has been previously published [21].

Statistical analyses

Participants who reported CF (severe fatigue for ≥ 6 months) were included in the two-step cluster analysis. Two-step cluster analysis [22] was conducted to group participants based on the total scores of the CIS fatigue *concentration*, *motivation* and *physical activity* subscales. Silhouette measure of cohesion was used as an indication of the goodness-of-fit of the found clusters, with a score of >0.2 considered fair [23].

To compare subgroup characteristics (subgroups indicated by two-step cluster analysis), ANOVA (to compare means) and Pearson's chi-square (to compare category distributions) analyses were done. When applicable, i.e. if overall Bonferroni adjusted p-value (p=0.05/number of comparisons) for subgroup comparison was statistical significant, post hoc analyses, i.e. Bonferroni tests for continuous variables and Bonferroni adjusted z-tests for categorical variables, were done to indicate which subgroups differed from each other.

To compare subgroup characteristics and CIS subscale scores with non-fatigued CCS (control group), ANOVA (to compare means) and Pearson's chi-square (to compare category distributions) analyses were done. Mean subgroup CIS subscale scores were compared with dimension scores reported by a healthy subgroup of the general Dutch population who reported no sick days in the past month (n=1,923), previously presented by Worm-Smeitink et al.[7], using independent t-tests.

To determine whether subgroup characteristics remained different after mutual adjustment, multinomial regression analysis was done with the CF subgroups as dependent variable and age, sex, BMI, relationship status, employment status, educational level, anxiety, depression, sleep problems, physical activity index,

pain, self-esteem, helplessness, social functioning and number of comorbidities as independent variables.

Analyses were performed in participants with complete data, but sensitivity analyses were done using imputed data. Missing data (no pattern observed) were imputed using multiple imputation (Markov chain Monte Carlo method, twenty imputed datasets, using Rubin's rules to pool the analyses) [24-26]. IBM SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) was used for the analyses.

Results

Prevalence CF subgroups

In total, 450 CCS with CF and 1460 CCS without CF (control group) participated in the current study (see Flowchart in Supplementary Figure 1). Two-step cluster analysis in the participants with CF identified three distinct CF subgroups. A Silhouette measure of cohesion of 0.4 indicated that subgroups could adequately be identified based on the CIS subscale scores. The following three subgroups were identified: Subgroup 1 contained 133 participants (29%), subgroup 2 had 111 participants (25%) and subgroup 3 was the largest with 206 participants (46%).

Subgroup 1 experiences the least difficulties, with no problematic CIS concentration scores and <1% problematic CIS motivation scores. This group also has the lowest prevalence of anxiety, depression and sleeping problems and scores best on self-esteem and social functioning. Still, half of this group has elevated CIS physical activity scores and one in four scores problematic on this dimension. Compared to the non-CF CCS, this subgroup scores worst on the CIS motivation and physical activity dimension. Compared to the general population this subgroup scores worse on the CIS physical activity dimension. Hence, we labeled this CF subgroup as having "*fatigue with problems in physical activity*".

Subgroup 2 is characterized by a high score on the CIS concentration dimension, with every participant in this group having an elevated CIS concentration score and more than half scoring problematic on the concentration dimension. In addition, a high prevalence of anxiety and sleeping problems and, to a lesser extent, depression was seen in this group. This group had elevated scores on the physical activity dimension as well, when compared to non-CF CCS and the general population, however compared to the other CF-subgroups, this subgroup seems to be scoring less problematic on the

physical activity dimension. Hence, we labeled this CF subgroup as having "*fatigue with difficulty concentrating*".

Subgroup 3 was characterized by high scores on all CIS dimensions, the highest fatigue severity score, a high prevalence of anxiety, depression and sleeping problems, feeling helpless and scoring low on self-esteem and this subgroup was also characterized by a lower educational level compared to the other subgroups and, although not statistically significant, a higher percentage of unemployment. Almost everyone in this group had elevated scores on all CIS dimensions and about half of this group scored problematic on all CIS dimensions, i.e. 50.0%, 43.7% and 57.8% for the dimensions concentration, motivation and physical activity respectively. As scores on all fatigue dimensions were elevated and/or problematic and worse compared to non-CF CCS and the general population, we labeled this CF subgroup as having "*multi-dimensional fatigue*".

Subgroups did not differ on diagnosis and treatment related factors, except that *CF subgroup multi-dimensional fatigue* less often received chemotherapy only compared to the non-CF group and the *CF subgroup with problems in physical activity*.

A comparison between the subgroups on CIS subscale scores is shown in Table 1. A comparison between subscale scores of the subgroups and the general population is shown in Table 2. A comparison between the subgroup characteristics and diagnosis and treatment related factors is shown in Supplementary Table 2. Differences between the groups remained when analyzed in a multivariable model (Table 3). A comparison with non-participants is shown in Supplementary Table 3.

Table 1. CIS dimension scores of the non-CF control group and the CF subgroups

CIS dimension	Non-CF group (n=1460)	CF with problems in physical activity (n=133)	CF with difficulty concentrating (n=111)	Multi-dimensional fatigue (n=206)
CIS fatigue severity				
Mean dimension score (SD)	19.4 (8.5)[1,2,3]	41.2 (4.8)[3]	42.1 (5.0)[3]	44.7 (6.3)[1,2]
CIS concentration				
Mean dimension score (SD)	12.6 (6.6)[2,3]	12.0 (4.1)[2,3]	25.6 (3.9)[1,3]	23.6 (5.8)[1,2]
Proportion scoring elevated[$]	23.3%[1,2,3]	11.3%[2,3]	100%[1,3]	87.4%[1,2]
Proportion scoring problematic[£]	7.9%[1,2,3]	0%[2,3]	60.4%[1]	50.0%[1]
Number of missing values	-	-	-	-
CIS motivation				
Mean dimension score (SD)	8.5 (4.1)[1,2,3]	11.8 (3.7)[3]	11.0 (2.9)[3]	19.4 (3.6)[1,2]
Proportion scoring elevated[$]	7.1%[1,3]	18.0%[2,3]	5.4%[1,3]	87.9%[1,2]
Proportion scoring problematic[£]	1.9%[3]	0.8%[3]	0%[3]	43.7%[1,2]
Number of missing values	-	-	-	-
CIS physical activity				
Mean dimension score (SD)	5.0 (2.9)[1,2,3]	12.3 (4.2)[3]	11.5 (4.5)[3]	16.1 (3.6)[1,2]
Proportion scoring elevated[$]	3.8%[1,2,3]	54.9%[3]	48.6%[3]	91.7%[1,2]
Proportion scoring problematic[£]	0%[1,2,3]	24.1%[3]	21.6%[3]	57.8%[1,2]
Number of missing values	-	-	-	-

CIS = Checklist Individual Strength. Non-CF group=CCS participants without CF.

[$] To indicate whether participants scored elevated on the CIS fatigue dimensions concentration, motivation and physical activity we used the mean subscale values of the general Dutch population + 1 standard deviation (presented by Worm-Smeitink et al. [7]) as a threshold (≥18, ≥16 and ≥12 respectively).

[£] To indicate whether participants scored problematic on the CIS fatigue dimensions concentration, motivation and physical activity we used the mean subscale values of the general Dutch population + 2 standard deviations (presented by Worm-Smeitink et al. [7]) as a threshold (≥24, ≥20 and ≥16 respectively). Differences between the groups are shown as follows (using Bonferroni post hoc test for continuous variables and Bonferroni adjusted z-tests for categorical variables):

[1] significant difference with CF subgroup with problems in physical activity (subgroup 1);

[2] significant difference with CF subgroup with difficulty concentrating (subgroup 2);

[3] significant difference with CF subgroup multi-dimensional fatigue (subgroup 3). Between group differences did not change after multiple imputation (significant difference remained in majority of 20 imputed datasets).

Table 2. CIS dimension scores of CF subgroups compared to population controls

CIS dimension	General population [a]	CF with problems in PA (n=133)	CF with difficulty concentrating(n=111)	Multi-dimensional fatigue (n=206)
CIS concentration				
Mean scale score (SD)	12.44 (5.96) [2,3]	12.0 (4.1)	25.6 (3.9)	23.6 (5.8)
CIS motivation				
Mean scale score (SD)	11.14 (4.74) [3]	11.8 (3.7)	11.0 (2.9)	19.4 (3.6)
CIS physical activity				
Mean scale score (SD)	8.28 (4.29) [1,2,3]	12.3 (4.2)	11.5 (4.5)	16.1 (3.6)

PA=physical activity.

[a] General Dutch population controls, i.e., group of healthy population controls who reported no sick days in past month (n=1,923), previously presented by Worm-Smeitink et al.[7]

[1] Significant difference between general population and CF subgroup with problems in physical activity (subgroup 1);

[2] significant difference between general population and CF subgroup with difficulty concentrating (subgroup 2);

[3] significant difference between general population and CF subgroup multi-dimensional fatigue (subgroup 3).

Significant difference: p-value <0.05 calculated with independent t-test

Table 3. Results of the Multinomial regression analyses to compare CF subgroup characteristics

	CF with difficulty concentrating (n=111)	Multi-dimensional fatigue (n=206)
Characteristic	***OR (95% CI)***	***OR (95% CI)***
Mean age in years	1.01 (0.97 – 1.05)	1.02 (0.98 – 1.05)
Sex (ref=female)	1.24 (0.68 – 2.26)	1.20 (0.68 – 2.13)
BMI		
Underweight	0.52 (0.12 – 2.22)	0.28 (0.06 – 1.23)
Healthy weight	ref	ref
Overweight	1.01 (0.53 –1.94)	1.15 (0.60 – 2.18)
Obesity	0.92 (0.40 – 2.08)	1.76 (0.82 – 3.77)
In a relationship (ref=not in a relationship)	0.93 (0.46 – 1.91)	1.06 (0.53 – 2.12)
Not employed (ref=employed)	0.59 (0.28 – 1.23)	0.79 (0.40 – 1.57)
Educational level		
Low	1.38 (0.51 – 3.70)	**2.46 (1.01 – 5.98)**
Middle	1.68 (0.89 – 3.19)	1.55 (0.84 – 2.85)
High	ref	ref
Clinically relevant Anxiety (ref =no)	1.62 (0.83 – 3.17)	1.33 (0.71 – 2.48)
Clinically relevant Depression (ref =no)	2.60 (0.72 – 9.38)	**5.53 (1.88 – 16.3)**
Sleeping problems (ref =no)	**2.23 (1.21 – 4.11)**	**2.38 (1.43 – 4.25)**

Table 3. Continued

	CF with difficulty concentrating (n=111)	Multi-dimensional fatigue (n=206)
Characteristic	***OR (95% CI)***	***OR (95% CI)***
Physical activity index		
Inactive	0.69 (0.18 – 2.62)	1.00 (0.28 – 3.54)
Moderately inactive	1.13 (0.54 – 2.37)	1.68 (0.84 – 3.38)
Moderately active	1.75 (0.79 – 3.86)	1.59 (0.73 – 3.48)
Active	ref	ref
Pain (continuous)	1.04 (0.83 – 1.30)	0.97 (0.78 – 1.20)
Self-esteem (continuous)	0.97 (0.90 – 1.03)	**0.90 (0.84 – 0.97)**
Helplessness (continuous)	1.08 (0.97 – 1.20)	1.11 (1.00 – 1.22)
Social functioning (continuous)	**0.98 (0.97 – 0.99)**	**0.98 (0.97 – 0.99)**
Number of comorbidities		
0	ref	ref
1-2	1.00 (0.54 – 1.86)	1.31 (0.70 – 2.44)
>2	**0.37 (0.14 – 0.96)**	0.55 (0.23 – 1.33)

Table shows results of multinomial regression analysis with CF subgroup 1 (problems with physical activity; n=133) as reference group. Bold odds ratio's show statistically significant difference with the reference group.

Discussion

The aim of the current study was to investigate whether subgroups of CF could be identified in CCS. Using two-step cluster analysis, three CF subgroup were identified based on the CIS dimensions *concentration, motivation* and *physical activity*: 1) *Fatigue with problems in physical activity*, 2) *fatigue with difficulty concentrating* and 3) *multi-dimensional fatigue*.

Comparison with existing literature

Previous studies mostly aimed at identifying subgroups in cancer survivors focusing on the severity of fatigue, including both fatigued and non-fatigued participants [27, 28]. Although this approach is interesting, the current study aimed to identify subgroups based on the different dimensions of fatigue rather than the severity of symptoms. Some studies did focus on dimensions of fatigue, for example in the review of de Raaf, de Klerk & van der Rijt, physical and mental fatigue were suggested to be separate concepts in cancer patients [29]. Also in people with chronic diseases, physical and mental fatigue are frequently present, where they often occur simultaneously, but they can also occur separately [30]. This suggests that different fatigue subtypes exist, however these

subtypes had not been identified in CCS yet. Identifying subgroups based on fatigue dimensions could be of particular interest when choosing an optimal intervention strategy. Several fatigue interventions exist, all aimed at different fatigue-related factors. Determining whether subgroups can be identified that are characterized by specific fatigue-related factors might help to choose a matching intervention.

Based on the current results, i.e. differences in CIS dimension scores and subgroup characteristics between the three identified subgroups, we can conclude that subtypes of chronic fatigue are present in CCS. It should be emphasized that all subgroups reported CF, and thus all subgroups experience severe fatigue symptoms, however CF is characterized differently across the three subgroups. All subgroups showed fatigue symptoms regarding physical activity, but the *subgroup with difficulty concentrating* and the *multi-dimensional fatigue* subgroup also showed fatigue regarding concentration and/or motivation. In the latter groups, psychosocial outcomes were present, suggesting there is a relation between the fatigue dimensions concentration and motivation and psychosocial outcomes. This makes us believe that the dimensions concentration and motivation represent a psychological or mental fatigue.

Results showed that all subgroups experience problems with physical activity (elevated physical activity dimension scores compared to non-CF CCS and the general population), but differ on concentration/motivation dimensions (mental fatigue). With subgroup 1 showing the least problems on the psychosocial characteristics, we believe this group to predominantly experience fatigue problems regarding physical activity. Compared to subgroup 2, who predominantly experience concentration problems, subgroup 1 more often has >2 comorbidities, which might be related to the fatigue symptoms these CCS experience regarding physical activity.

One explanation for the differences in symptoms experienced by the subgroups, might be the therapy received during childhood cancer. In a previous study we found that type of childhood cancer treatment was not associated with CF [31], however the current results indicate that whenever CCS have CF, type of treatment might be associated with the type of fatigue that CCS experience. The *multi-dimensional fatigue* subgroup less often received chemotherapy only compared to the non-CF group and the *CF subgroup with problems in physical activity,* indicating that the *multi-dimensional* subgroup more often received radiotherapy (with or without chemotherapy). Radiotherapy has been associated with a higher risk for various comorbidities, e.g., cardiovascular, neurocognitive and fertility problems [32-35], and might therefore be a plausible cause for the multi-faceted problems that CCS in this group experience.

Clinical implications

Exploring how to distinctly tackle CF in different subgroups might result in more effective intervention strategies. Several studies in various patient populations have shown that fatigue can be experienced on different dimensions, whether or not simultaneously [29, 30, 36]. It might therefore be plausible that tailored interventions focusing on different fatigue dimensions might be beneficial in reducing fatigue symptoms. For example, the *CF subgroup with problems in physical activity* (subgroup 1) might benefit most from interventions focusing on the physical activity dimension, such as exercise therapy, a promising intervention to tackle fatigue in CCS [37]. CCS who experience *fatigue with difficulty concentrating* (subgroup 2) might benefit most from interventions addressing psychological aspects that were related to this subgroup, such as cognitive behavioral therapy (CBT) or mindfulness. A pilot study in CCS showed CBT to be a promising intervention to reduce fatigue and psychological distress [38]. However, compared to CCS without CF, both subgroups score worse on all characteristics, therefore all these aspects need to be taken into account when determining the best interventions strategy. Still, it might be beneficial to focus on the fatigue dimension that is predominantly affected. Future intervention studies should investigate whether using different strategies based on fatigue dimensions could indeed be helpful in decreasing symptoms on specific dimensions of fatigue.

Subgroup 3 shows *multi-dimensional fatigue*, therefore tackling one specific fatigue dimension might not be the preferred strategy. This group also shows high prevalence rates of anxiety, depression and sleeping problems and scores low on psychosocial outcomes such as self-esteem and social functioning. In addition, this subgroup was lower educated compared to the non-CF group and the other subgroups and also seemed to be more often unemployed (although the latter was not statistically significant), which suggests that this group might experience difficulties regarding educational and/or employment related demands. Therefore, as there seems to be multi-factorial issues to be present in this group, a multidimensional approach might be most beneficial here.

Strengths and limitations

The current study is part of a nationwide collaboration, including a cohort that includes CCS with all childhood cancer diagnoses and treatments, contributing to the generalizability of the results. A limitation of the current study is that data are cross-sectional. Therefore, we can determine associations between subgroups and certain characteristics, however we cannot determine causality. For example, we assume that the *muti-dimensional fatigue* subgroup are experiencing difficulties regarding educational and/or employment related demands, which might be a consequence of the multi-dimensional problems that they experience. However due to the cross-sectional nature of the data, we can only speculate. A longitudinal study where CCS are

followed from the end of cancer therapy into survivorship might provide information regarding the origin and the course of the symptoms and wat the consequences are. In addition, it would be interesting to compare subgroups on characteristics that were not included in the current study, for example social determinants or genetic factors. Future studies might include these factors.

Conclusion

To conclude, three different CF subtypes were identified in CCS. A subgroup presenting with *CF and problems with physical activity*, a second group with *CF and difficulty concentrating* and a third group presenting with *multi-dimensional fatigue*. This indicates that different intervention strategies, focused at the fatigue dimension most affected in each subgroup, might be beneficial.

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Supplementary material

Supplementary Table 1. CIS subscale items and scoring

CIS items	*Answer options and scoring*
Please indicate to what extend the following statements applied to you during the past two weeks	Yes, that is true ▫ ▫ ▫ ▫ ▫ ▫ ▫ No, that is not true
Subscale fatigue severity	
- I feel tired	7 6 5 4 3 2 1
- Physically, I feel exhausted	7 6 5 4 3 2 1
- I feel fit	1 2 3 4 5 6 7
- I feel weak	7 6 5 4 3 2 1
- I feel rested	1 2 3 4 5 6 7
- Physically I am in bad shape	7 6 5 4 3 2 1
- I tire easily	7 6 5 4 3 2 1
- Physically I am in good shape	1 2 3 4 5 6 7
Subscale concentration	
- Thinking requires effort	7 6 5 4 3 2 1
- When I am doing something, I can keep my thoughts on it	1 2 3 4 5 6 7
- I find it easy to concentrate	1 2 3 4 5 6 7
- It takes a lot of effort to concentrate on things	7 6 5 4 3 2 1
- My thoughts easily wander	7 6 5 4 3 2 1

CIS items	*Answer options and scoring*
Subscale motivation	
- I feel very active	1 2 3 4 5 6 7
- I feel like doing all kinds of nice things	1 2 3 4 5 6 7
- I have a lot of plans	1 2 3 4 5 6 7
- I don't feel like doing anything	7 6 5 4 3 2 1
Subscale physical activity level	
- Physically I am very active	1 2 3 4 5 6 7
- Physically I am little active	7 6 5 4 3 2 1
- My physical activity level is low	7 6 5 4 3 2 1

Supplementary Table 2. Characteristics of the non-CF control group and CF subgroups

Characteristic	Non-CF group (n=1460)	CF with problems in physical activity (n=133)	CF with difficulty concentrating (n=111)	Multi-dimensional fatigue (n=206)
Mean age in years (SD)	34.7 (9.3)[3]	36.2 (9.3)	35.6 (9.5)	36.9 (9.0)
Number of missing values	-	-	-	-
Sex				
Male	826 (56.6%)	52 (39.1%)	37 (33.3%)	72 (35.0%)
Female	634 (43.3%)[1,2,3]	81 (60.9%)	74 (66.7%)	134 (65.0%)
Number of missing values	-	-	-	-
BMI				
Underweight	36 (2.6%)	7 (5.4%)	5 (4.5%)	6 (3.0%)
Healthy weight	786 (55.7%)[3]	59 (45.4%)	54 (49.1%)	84 (42.4%)
Overweight	446 (31.6)	42 (32.3%)	34 (30.9%)	61 (30.8%)
Obesity	142 (10.1%)[3]	22 (16.9%)	17 (15.5%)	47 (23.7%)
Number of missing values	50	3	1	8
Relationship status				
In a relationship	247 (20.2%)	27 (23.9%)	24 (25.3%)	45 (27.1%)
Not in a relationship	973 (79.8%)	86 (76.1%)	71 (74.7%)	121 (72.9%)
Number of missing values	240	20	16	40
Employment status				
Employed	1215 (89.0%)	96 (76.2%)	83 (79.0%)	129 (66.5%)
Not employed	150 (11.0%)[1,2,3]	30 (23.8%)	22 (21.0%)	65 (33.5%)
Number of missing values	95	7	6	12
Educational level				
Low	168 (12.3%)[3]	13 (10.3%)[3]	12 (11.4%)[3]	45 (23.2%)[1,2]
Middle	568 (41.6%)	55 (43.7%)	55 (52.4%)	89 (45.9%)
High	631 (46.2%)[3]	58 (46.0%)[3]	38 (36.2%)	60 (30.9%)[1]
Number of missing values	93	7	6	12
Clinically relevant Anxiety				
No	1086 (87.6%)	86 (76.8%)	47 (52.8%)	78 (45.6%)
Yes	154 (12.4%)[1,2,3]	26 (23.2%)[2,3]	42 (47.2%)[1]	93 (54.4%)[1]
Number of missing values	220	21	22	35
Clinically relevant depression				
No	1198 (96.8%)	109 (97.3%)	73 (82.0%)	102 (59.6%)
Yes	40 (3.2%)[2,3]	3 (2.7%)[2,3]	16 (18.0%)[1,3]	69 (40.4%)[1,2]
Number of missing values	222	21	22	35
Sleeping problems				
No	1012 (72.9%)	72 (55.4%)	33 (32.0%)	52 (26.8%)
Yes	377 (27.1%)[1,2,3]	58 (44.6%)[2,3]	70 (68.0%)[1]	142 (73.2%)[1]
Number of missing values	71	3	8	12

Supplementary Table 2. Continued

Characteristic	Non-CF group (n=1460)	CF with problems in physical activity (n=133)	CF with difficulty concentrating (n=111)	Multi-dimensional fatigue (n=206)
Physical activity index				
Inactive	55 (4.2%)[3]	9 (7.9%)	6 (5.8%)	23 (12.0%)
Moderately inactive	267 (20.2%)[1,3]	40 (35.1%)	29 (27.9%)	62 (32.5%)
Moderately active	317 (24.0%)	22 (19.3%)	28 (26.9%)	41 (21.5%)
Active	683 (51.7%)[1,3]	43 (37.7%)	41 (39.4%)	65 (34.0%)
Number of missing values	138	19	7	15
Pain mean score (SD)	1.7 (1.1)[1,2,3]	2.6 (1.3)	2.8 (1.2)	2.9 (1.3)
Number of missing values	43	-	-	-
Self-esteem mean score (SD)	34.0 (4.9)[1,2,3]	31.9 (4.5)[2,3]	29.6 (5.3)[1,3]	26.4 (6.0)[1,2]
Number of missing values	212	21	23	34
Helplessness mean score (SD)	7.1 (2.2)[1,2,3]	8.5 (3.2)[3]	9.8 (3.9)[3]	11.5 (4.6)[1,2]
Number of missing values	232	26	22	41
Social funct. mean score (SD)	90.9 (14.6)[1,2,3]	85.5 (19.3)[2,3]	73.9 (24.7)[1]	68.2 (23.3)[1]
Number of missing values	179	18	16	31
Number of comorbidities				
0	705 (48.8%)[1,3]	49 (36.8)	43 (38.7)	63 (30.6)
1-2	633 (43.8%)	58 (43.6)	54 (48.6)	101 (49.0)
>2	107 (7.4%)[1,3]	26 (19.5)	14 (12.6)	42 (20.4)
Number of missing values	15	-	-	-
Childhood cancer diagnosis [§]				
Leukemia	528 (36.2%)	46 (34.6%)	39 (35.1%)	58 (28.2%)
NHL [¥]	180 (12.3%)	16 (12.0%)	11 (9.9%)	25 (12.1%)
HL	106 (7.3%)	8 (6.0%)	4 (3.6%)	15 (7.3%)
CNS	128 (8.8%)	8 (6.0%)	10 (9.0%)	30 (14.6%)
Neuroblastoma	81 (5.5%)	11 (8.3%)	4 (3.6%)	15 (7.3%)
Retinoblastoma	7 (0.5%)	1 (0.8%)	0 (0%)	2 (1.0%)
Renal tumors	165 (11.3%)	16 (12.0%)	18 (16.2%)	20 (9.7%)
Hepatic tumors	16 (1.1%)	0 (0%)	0 (0%)	1 (0.5%)
Bone tumors	77 (5.3%)	10 (7.5%)	8 (7.2%)	11 (5.3%)
Soft tissue tumors	99 (6.8%)	11 (8.3%)	11 (9.9%)	19 (9.2%)
Germ cell tumors	52 (3.6%)	4 (3.0%)	3 (2.7%)	6 (2.9%)
Other and unspecified [¶]	21 (1.4%)	2 (1.5%)	3 (2.7%)	4 (1.9%)
Number of missing values	-	-	-	-
Childhood cancer treatment	96 (6.6%)	7 (5.3%)	9 (8.1%)	19 (9.2%)
Surgery only	819 (56.1%)[3]	75 (56.4%)[3]	55 (49.5%)	85 (41.3%)[1]
CT (no RT)	72 (4.9%)	6 (4.5%)	5 (4.5%)	17 (8.3%)
RT (no CT)	465 (31.8%)	45 (33.8%)	42 (37.8%)	84 (40.8%)
RT + CT	8 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)
No treatment/unknown				
Number of missing values	-	-	-	-

Supplementary Table 2. Continued

Characteristic	Non-CF group (n=1460)	CF with problems in physical activity (n=133)	CF with difficulty concentrating (n=111)	Multi-dimensional fatigue (n=206)
Hematopoietic stem cell transplantation				
No	1342 (91.9%)	124 (93.2%)	106 (95.5%)	194 (94.2%)
Autologous	35 (2.4%)	4 (3.0%)	2 (1.8%)	6 (2.9%)
Allogeneic	71 (4.9%)	5 (3.8%)	2 (1.8%)	6 (2.9%)
Unknown	12 (0.8%)	0 (0%)	1 (0.9%)	0 (0%)
Age at diagnosis (years)				
0-5	688 (47.1%)	56 (42.1%)	51 (45.9%)	85 (41.3%)
5-10	389 (26.6%)	34 (25.6%)	29 (26.1%)	64 (31.1%)
10-15	299 (20.5%)	38 (28.6%)	23 (20.7%)	48 (23.3%)
15-18	84 (5.8%)	5 (3.8%)	8 (7.2%)	9 (4.4%)
Number of missing values	-	-	-	-
Cancer recurrence				
No	1264 (86.6%)	117 (88.0%)	97 (87.4%)	181 (87.9%)
Yes	196 (13.4%)	16 (12.0%)	14 (12.6%)	25 (12.1%)
Number of missing values	-	-	-	-

Abbreviations: HL=Hodgkin Lymphoma, NHL=Non-Hodgkin lymphoma, CNS=Central Nervous System tumors, CT=Chemotherapy, RT=Radiotherapy. Non-CF group=participants without CF. BMI categories (Underweight: BMI<18.5, Healthy weight: BMI between 18.5 and 25, Overweight: BMI between 25 and 30, Obesity: BMI ≥30). Educational level categories (Low: Primary education, vocational education, special school, Middle: Preparatory secondary vocational education, secondary vocational education, school of higher general secondary education, pre-university education, High: Higher vocational education, university). Treatment data included primary treatment and all recurrences.

[$] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[¥] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[¶] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

Differences between the groups are shown as follows (using Bonferroni post hoc test for continuous variables and Bonferroni adjusted z-tests for categorical variables): [1] significant difference with CF subgroup with problems in physical activity (subgroup 1); [2] significant difference with CF subgroup with difficulty concentrating (subgroup 2); [3] significant difference with CF subgroup multi-dimensional fatigue (subgroup 3). Between group differences did not change after multiple imputation (significant difference remained in majority of 20 imputed datasets).

Supplementary Table 3. Comparison CCS participants vs. non-participants

Characteristic	Participants CF(n=450)	Participants without CF (n=1,460) [e]	Non participants because non-responder or insufficient data (n=2,081) [f]
	N (%)	N (%)	N (%)
Sex			
Male	161 (35.8)*	826 (56.6)*	1250 (60.1)
Female	289 (64.2)	634 (43.5)	831 (39.9)
Year of birth			
<1960	3 (0.7)	18 (1.2)	21 (1.0)
1960 – 1969	53 (11.8)*	97 (6.6)	153 (7.4)
1970 – 1979	130 (28.9)	369 (25.3)	519 (24.9)
1980 – 1989	168 (37.3)	565 (38.7)	796 (38.3)
≥1990	96 (21.3)*	411 (28.2)	592 (28.4)
Age at diagnosis (years)			
0-5	192 (42.7)	688 (47.1)	983 (47.2)
5-10	127 (28.2)	389 (26.6)	567 (27.2)
10-15	109 (24.2)*	299 (20.5)	399 (19.2)
15-18	22 (4.9)	84 (5.8)	132 (6.3)
Primary childhood cancer diagnosis [a]			
Leukemia	143 (31.8)	528 (36.2)	691 (33.2)
Non-Hodgkin lymphoma [b]	52 (11.6)	180 (12.3)	239 (11.5)
Hodgkin lymphoma	27 (6.0)	106 (7.3)	150 (7.2)
CNS	48 (10.7)	128 (8.8)	245 (11.8)
Neuroblastoma	30 (6.7)	81 (5.5)	108 (5.2)
Retinoblastoma	3 (0.7)	7 (0.5)	14 (0.7)
Renal tumors	54 (12.0)	165 (11.3)	225 (10.8)
Hepatic tumors	1 (0.2)	16 (1.1)	25 (1.2)
Bone tumors	29 (6.4)	77 (5.3)	115 (5.5)
Soft tissue tumors	41 (9.1)	99 (6.8)	153 (7.4)
Germ cell tumors	13 (2.9)	52 (3.6)	86 (4.1)
Other and unspecified [c]	9 (2.0)	21 (1.4)	30 (1.4)
Period of childhood cancer diagnosis			
1963-1969	8 (1.8)	21 (1.4)	18 (0.9)
1970-1979	86 (19.1)*	168 (11.5)	256 (12.3)
1980-1989	140 (31.1)	461 (31.6)	637 (30.6)
>1990	216 (48.0)*	810 (55.5)	1170 (56.2)
Childhood cancer treatment [d]			
Surgery only			
Chemotherapy, no radiotherapy	35 (7.8)*	96 (6.6)*	244 (11.7)
Radiotherapy, no chemotherapy	215 (47.8)*	819 (56.1)	1176 (56.5)
Radiotherapy and chemotherapy	28 (6.2)	72 (4.9)	125 (6.0)
No treatment/ treatment unknown	171 (38.0)*	465 (31.8)*	507 (24.4)
	1 (0.2)	8 (0.5)	29 (1.4)

Supplementary Table 3. Continued

Characteristic	Participants CF(n=450)	Participants without CF (n=1,460) [e]	Non participants because non-responder or insufficient data (n=2,081) [f]
Hematopoietic stem cell transplantation			
Yes	25 (5.6)	106 (7.3)*	81 (3.9)
No	424 (94.4)	1342 (91.9)*	1991 (95.7)
Missing	1 (0.2)	12 (0.8)	9 (0.4)
Cancer recurrence			
No	395 (87.7)	1264 (86.6)	1837 (88.3)
Yes	55 (12.2)	196 (13.4)	244 (11.7)

*significant difference (p<0.05, chi square test) with non-participants.

[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

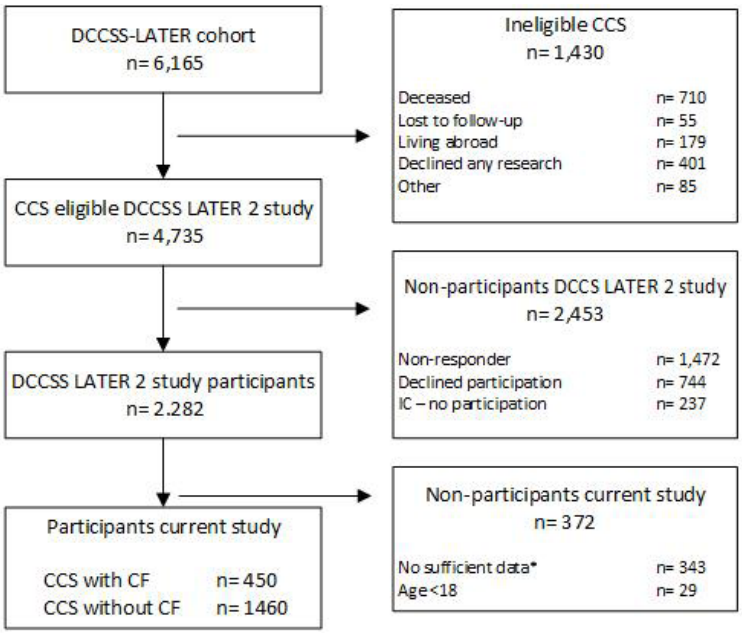
[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

[d] Treatment data included primary treatment and all recurrences.

[e] Participants without CF (controls)

[f] Non-participants DCCSS LATER fatigue study were invited to participate but did not return or complete the fatigue questionnaire (non-responders + lacking/missing complete or fatigue specific questionnaire data). In flowchart in Supplementary Figure 1, non-participants DCCSS LATER 2 (n=2,453) and non-participants current study because of no sufficient data or age <18 (n=372) are added up, minus 744 CCS who declined participation and who were therefore not analyzed.



Supplementary Figure 1. Flowchart of participants.
*Sufficient data to determine fatigue status: at least 7 of the 8 CIS fatigue severity items completed (with one missing value, the mean of the remaining completed items was imputed) + duration of fatigue symptoms completed (if fatigue severity subscale score ≥35). Participants who did not have sufficient data (n=343), either to determine fatigue status (n=326) or who had missing data on one of the other CIS subscales (n=17), were excluded. A total of n=450 participants with CF were included in the study and n=1460 participants without CF as a control group.

Chapter 8

The impact of cancer-related fatigue on HRQOL in survivors of childhood cancer

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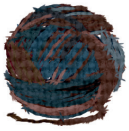

Abstract

Background: Early detection and management of late effects of treatment and their impact on health-related quality of life (HRQOL) has become a key goal of childhood cancer survivorship care. One of the most prevalent late effects is chronic fatigue (CF). The current study aimed to investigate the association between CF and HRQOL in a nationwide cohort of CCS.

Methods: Participants were included from the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort, a nationwide cohort of CCS. Participants completed the Checklist Individual Strength (CIS) to indicate CF (*CIS fatigue severity subscale* ≥35 and duration of symptoms ≥6 months) and the Short Form-36 (SF-36) and TNO (Netherlands Organization for Applied Scientific Research) and AZL (Leiden University Medical Centre) adult's health-related quality of life questionnaire (TAAQOL) as measures for HRQOL. Differences in mean HRQOL domain scores between CF and non-CF participants were investigated using independent samples t-tests and ANCOVA to adjust for age and sex. The association between CF and impaired HRQOL (scoring ≥2 SD below population norm) was investigated using logistic regression analyses, adjusting for confounders.

Results: A total of 1695 participants were included in the study. Mean HRQOL domain scores were significantly lower in participants with CF. In addition, CF was associated with impaired HRQOL on all domains (except physical functioning) with adjusted odds ratio's ranging from 2.1 (95%CI 1.3-3.4; sexuality domain) to 30.4 (95%CI 16.4 – 56.2; vitality domain).

Conclusion.: CF is associated with impaired HRQOL, urging screening and regular monitoring of fatigue, and developing possible preventive programs and interventions.

Introduction

With a growing population of childhood cancer survivors (CCS) [1-3], early detection and management of late effects of treatment and their impact on daily life has become a key goal of survivorship care [4]. Personalized cancer survivorship care [5], aimed at empowering survivors and supporting self-management, using Patient Reported Outcomes (PROs) to evaluate late effects, will become more and more important. PROs capture issues affecting quality of life that matter to the patient, for example the ability to work, participate in social activities, practice sports and perform household activities or chores. Investigating PROs and what affects them is relevant when aiming to improve quality of life in CCS. A core concept of PROs are Health-Related Quality of Life (HRQOL) outcomes, reflecting the subjective perception of health [6, 7].

Here we use the term HRQOL, referring to a person's subjective appraisal of physical, mental, and social well-being, matching the 1947 World Health Organization's (WHO) definition of 'health' [8]. Previous studies showed CCS to have impaired HRQOL compared to the general population [9, 10]. Several childhood diagnosis and sociodemographic factors were associated with impaired HRQOL in CCS [9-11]. Also, late effects such as cardiovascular or pulmonary dysfunction were associated with poor HRQOL [12, 13].

A late effect often reported by CCS is chronic fatigue (CF) [214], indicating severe fatigue which persists for 6 months or longer. Previous studies showed fatigue to negatively affect HRQOL in CCS [15-18] but only included subgroups of CCS or did not take into account the severity and/or persistence of fatigue symptoms. Also, other possible confounding factors that have been related to poor HRQOL (for example depression or having a medical condition [19, 20]) were not taken into account. Therefore the association of CF (indicated with a validated cut-off point and including duration of symptoms) with HRQOL remains unclear. In the current study we aim to overcome these limitations and determine the association between CF and HRQOL in CCS after correcting for confounders.

Thus, the aim of the current study was to investigate the independent association of CF and HRQOL in a nationwide cohort of adult CCS including all childhood malignancies. We believe it is important to assess the association between CF and HRQOL as such new evidence will improve our understanding of the role of CF in decreasing HRQOL in CCS and determine whether CF could potentially be a feasible factor to target when aiming to improve HRQOL.

Methods

Design & participants

Cross-sectional data were collected for the Dutch Childhood Cancer Survivor Study (DCCSS) LATER Fatigue Study [21] as part of the DCCSS LATER 2 study (Feijen, Teepen, Loonen et al. under review). Participants aged ≥18 years were included from the DCCSS LATER cohort, a nationwide cohort of CCS diagnosed before the age of 18 between January 1st 1963 and December 31st 2001 in the Netherlands [22] and who are at least five years post diagnosis. All participants who were able to read and speak Dutch and who gave written informed consent to participate received an invitation by mail to visit the outpatient clinic for care and participation in clinical research between 2017 and 2020 (details described elsewhere [21]). If eligible survivors did not respond within a few weeks, a reminder was sent via mail. Data on childhood cancer diagnosis and treatment were collected by data managers using a uniform and standardized protocol [23]. Data on fatigue status was collected with questionnaires during the clinic visit and questionnaires assessing HRQOL were completed at home (on paper or digitally). The DCCSS LATER fatigue study was approved by the Medical Research Ethics Committee of the Amsterdam University Medical Centers (registered at toetsingonline.nl, NL34983.018.10).

Measures

Fatigue

The Checklist Individual Strength (CIS) [24], a 20-item questionnaire, scored on a 7-point Likert Scale, was used to assess fatigue severity. The CIS was designed to measure several aspects of fatigue with the subscales *fatigue severity* (8 items), *concentration* (5 items), *motivation* (4 items) and *physical activity level* (3 items). The CIS is a reliable and valid instrument for the assessment of fatigue, with a score of 35 or higher on the *CIS fatigue severity* subscale (range 8 – 56) indicating severe fatigue [25]. Psychometric properties of the CIS were shown to be good in CCS (high correlation with other fatigue measures and four-factor structure confirmed with all factors having high internal consistency) [26]. Symptom duration was asked in a separate item. To identify participants experiencing CF, we define CF as severe fatigue, indicated with a score of 35 or higher on the *CIS fatigue severity* subscale [25], which persist for at least six months [27].

HRQOL

The 36-item Short Form Health Survey (SF-36) [28, 29] was used to determine eight HRQOL domains (see Supplementary Table 1). For each domain, item scores are coded,

summed, and transformed to a scale from 0 (worst) to 100 (best) following instructions described elsewhere [28, 30]. The survey was constructed for self-administration by persons 14 years of age and older. The Dutch version of the SF-36 was shown to be valid and reliable (item internal consistency and -discriminant validity as well as known groups comparisons met criterium values) [31].

The TNO (Netherlands Organisation for Applied Scientific Research) and AZL (Leiden University Medical Centre) Questionnaire for Adult's Quality of Life (TAAQOL) [32] subscales sleep (SL), sexuality (SE) and cognitive functioning (CO) were used in the current study. Scale scores were calculated and linearly transformed to a 0-100 scale (following instructions described elsewhere [33]) with higher scores indicating better functioning. The questionnaire has been validated in both the general population as well as in patients with chronic diseases, confirming the assumed questionnaire structure, with all subscales having high reliability [32, 34].

The HRQOL domains physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), mental health (MH) of the SF-36 and the domains sleep (SL), sexuality (SE) and cognitive functioning (CO) of the TAAQOL were investigated in the current study (see Supplementary Table 1 for details). Participants who scored ≥ 2 standard deviations from the general population mean [31, 33] on a HRQOL subscale were identified as "impaired" for this domain.

Other measures

The following questionnaires were completed as measures for possible confounders, i.e. depression, anxiety, sleep quality, somatic comorbidities and sociodemographic factors, based on their relation with fatigue and HRQOL in previous literature [10, 12-14, 20, 35-37].

The Hospital Anxiety and Depression Scale (HADS) [38] was used to assess symptoms of anxiety and depression. The HADS assesses anxious and depressive feelings over the past four weeks, with both subscales containing seven items on a 4-point Likert scale. A cutoff score of ≥ 8 for both the anxiety subscale and the depression subscale was used to identify (sub)clinical cases [39].

The Pittsburg Sleep Quality Index (PSQI) [40] was used to assess overall sleep quality. The PSQI, with a total of 18 items (four free response items and fourteen 4-point Likert scale items), generates a total of seven component scores, namely subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use

of sleeping medication and daytime function. The components are scored 0-3, with a total score ranging from 0-21 and higher scores indicating poorer sleep. A total score >5 was used to indicate poor sleep [40].

A general health questionnaire, containing items to assess demographic characteristics (age, sex, employment status and education level) was completed. Details about this questionnaire were described elsewhere [21]. In addition, almost all participants in the current study participated in the 2013 LATER questionnaire study (DCCS LATER 1 study; Teepen, Kok, Feijen et al. under review) assessing physical health issues (n=1367). These self-reported health issues were validated based on self-reported medication use and medical files when needed and were used to categorize participants as having 0, 1-2, or >2 clinically relevant somatic comorbidities based on a previously published outcomes set [41].

Statistical analysis

To examine possible selection bias between study participants and non-participants (eligible CCS that did not return informed consent or did not complete study questionnaires), Chi-Square tests (with Cramér's V as effect size) were calculated to compare the groups on sex, decade of birth, childhood cancer diagnosis, decade of diagnosis, treatment with chemotherapy and /or radiotherapy (yes/no).

Participants were assigned to one of the following groups: a) CCS without CF (NCF group), b) CCS with CF (CF group). If one *CIS fatigue severity* subscale item was missing, this was imputed with the mean value of the remaining seven *CIS fatigue severity* subscale items. To identify significant differences in mean total scores of the HRQOL domains between the CF group and NCF group, independent samples t-tests were calculated (with Cohen's d effect size) and an ANCOVA was done with age and sex as covariates to correct for differences between the groups. Mean total score differences between the CF group and population norms [31, 33] were tested with independent samples t-tests.

To investigate the association of CF with HRQOL, univariate and multivariable logistic regression was performed, allowing to adjust for potential confounders. Univariate logistic regression was done with the HRQOL domains as dependent variable (impaired yes/no) and CF (yes/no) as independent variable. Multivariable logistic regression was done to determine whether a possible association would remain after adjustment for confounders (age, sex, BMI, employment status, educational level, sleep quality, depression, anxiety, number of somatic comorbidities, childhood diagnosis and treatment; see Supplementary Table 2). Missing data of the independent variables

(Supplementary Table 3; Little's MCAR test p=0.34) were imputed using multiple imputation (five imputed datasets, using Rubin's rules to pool the analyses) [42-44]. Variance inflation factors (VIF) were calculated for all independent variables with a threshold of >10 to test for multicollinearity [45]. IBM SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) was used for the statistical analyses.

Results

Participants

A total of 2282 CCS participated in the DCCSS LATER 2 study (48.2% of eligible persons) of whom 1695 completed the fatigue and HRQOL questionnaires for the current study as such that fatigue status (*CIS fatigue severity* subscale score and fatigue duration) and at least one of the eleven HRQOL subscale scores could be calculated (74.3%; flowchart in Figure 1).

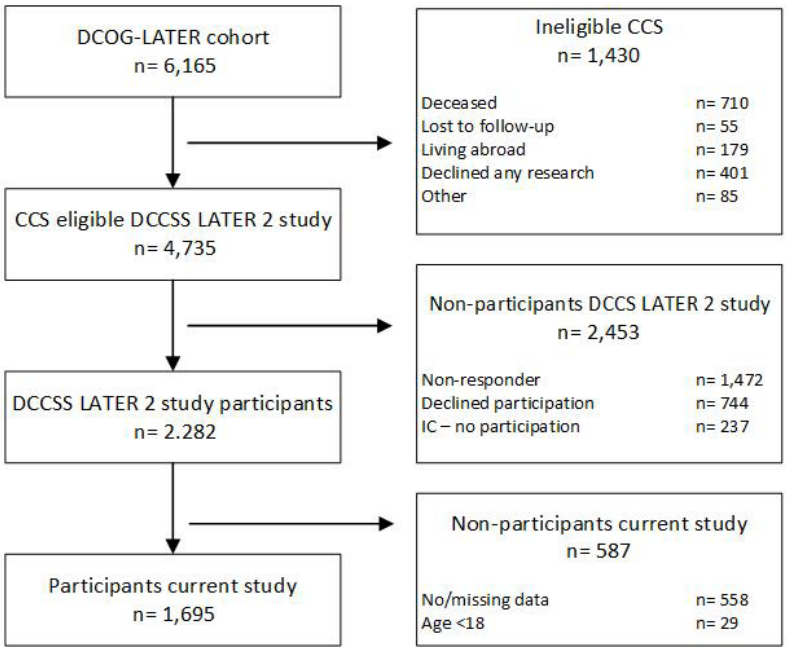

Figure 1. Flowchart of CCS participants.
IC – no participation: Did return informed consent wanting to participate but did not participate (due to logistic reasons or lack of time for example). No/missing data: no or incomplete data for the CIS fatigue severity subscale, duration of fatigue symptoms or all HRQOL subscales

Participants differed from non-participants on sex and received childhood cancer treatment, however effect sizes were small (Cramér's V ranged 0.03-0.12; Supplementary Table 4). 744 persons declined participation and were therefore excluded from all analyses.

Participant characteristics are shown in Table 1. Compared to CCS without CF, CCS with CF were more often female (63.4% vs. 43.6%), aged ≥40 years (35.0% vs. 29.7%), less often diagnosed after 1990 (48.6% vs. 54.4%) and received less often only chemotherapy (47.5% vs. 56.1%), but more often a combination of radiotherapy and chemotherapy (38.6% vs. 32.0%).

Chronic fatigue and HRQOL scale scores

CCS with CF scored significantly lower on all HRQOL domains compared to CCS without CF (Figure 2). Independent t-tests resulted in p-values <0.001 for all domains, also after adjustment for age and sex (ANCOVA p-values <0.001), with large Cohen's d effect sizes (>0.8) for all domains except SE (0.59). Mean differences ranged from 14.0 (SE) to 41.6 (RP) with the largest differences seen on the domains RP, RE and VT (mean difference >30). CCS with CF scored below population norm values on all domains as well (p<0.001).

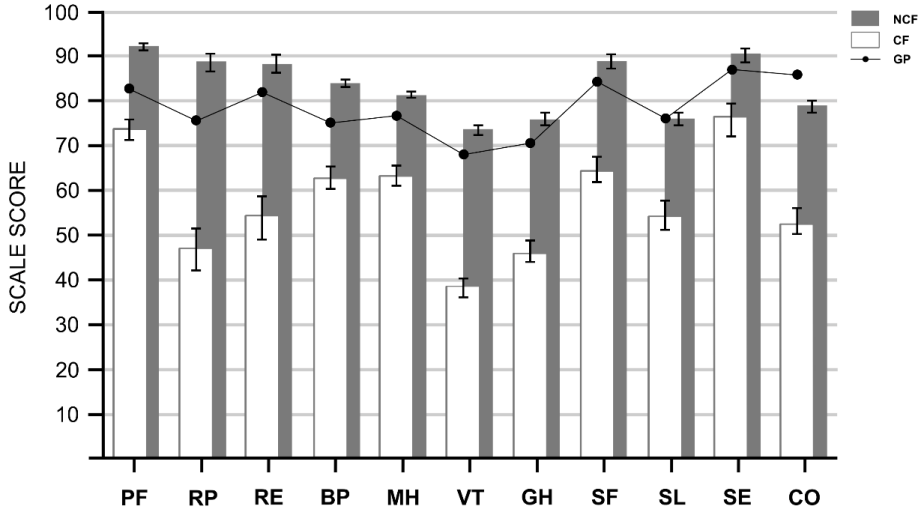

Figure 2. Mean total scores for HRQOL domains for CCS with and without chronic fatigue.
Mean Health Related Quality of Life (HRQOL) subscale scores of Childhood Cancer Survivors (CCS) with chronic fatigue (CF) and CCS without chronic fatigue (NCF). Error bars show 95% Confidence Interval. Black line represents mean subscale scores of the General Population (GP)[31, 33]. Subscales of SF-36: PF=Physical Functioning, RP=Role physical, RE=Role Emotional, BP=Bodily Pain, MH=Mental Health, VT=Vitality, GH=General Health. Subscales of TAAQOL: SL=Sleep, SE=Sexuality, CO=Cognitive Functioning.

Table 1. Participant Characteristics for total cohort and by chronic fatigue status

Characteristic	Total cohort CCS (n=1695)	CCS NCF (n=1304)	CCS CF (n=391)	P-value [e]
	N (%)	N (%)	N (%)	
Sex				
Male	878 (51.8)	735 (56.4)	143 (36.6)	<0.001
Female	817 (48.2)	569 (43.6)	248 (63.4)	
Age at assessment (years)				
<20	30 (1.8)	26 (2.0)	4 (1.0)	
20-29	485 (28.6)	390 (29.9)	95 (24.3)	0.050
30-39	656 (38.7)	501 (38.4)	155 (39.6)	
≥40	525 (30.9)	387 (29.7)	137 (35.0)	
Age at diagnosis (years)				
0-5	770 (45.4)	605 (46.4)	165 (42.2)	
5-10	458 (27.0)	350 (26.8)	108 (27.6)	0.262
10-15	370 (21.8)	272 (20.9)	98 (25.1)	
15-18	97 (5.7)	77 (5.9)	20 (5.1)	
Primary childhood cancer diagnosis [a]				
Leukemia	581 (34.3)	459 (35.2)	122 (31.2)	
Non-Hodgkin lymphoma [b]	210 (12.4)	165 (12.7)	45 (11.5)	
Hodgkin lymphoma	121 (7.1)	95 (7.3)	26 (6.6)	
CNS	158 (9.3)	114 (8.7)	44 (11.3)	
Neuroblastoma	97 (5.7)	70 (5.4)	27 (6.9)	0.259
Retinoblastoma	8 (0.5)	5 (0.4)	3 (0.8)	
Renal tumors	193 (11.4)	150 (11.5)	43 (11.0)	
Hepatic tumors	17 (1.0)	16 (1.2)	1 (0.3)	
Bone tumors	101 (6.0)	76 (5.8)	25 (6.4)	
Soft tissue tumors	124 (7.3)	88 (6.7)	36 (9.2)	
Germ cell tumors	56 (3.3)	46 (3.5)	10 (2.6)	
Other and unspecified [c]	29 (1.7)	20 (1.5)	9 (2.3)	
Period of childhood cancer diagnosis				
1963-1969	28 (1.7)	21 (1.6)	7 (1.8)	0.002
1970-1979	226 (13.3)	151 (11.6)	75 (19.2)	
1980-1989	542 (32.0)	423 (32.4)	119 (30.4)	
>1990	899 (53.0)	709 (54.4)	190 (48.6)	
Childhood cancer treatment [d]				
Surgery only	109 (6.4)	81 (6.2)	28 (7.2)	
Chemotherapy, no radiotherapy	917 (54.1)	731 (56.1)	186 (47.6)	
Radiotherapy, no chemotherapy	93 (5.5)	68 (5.2)	25 (6.4)	0.047
Radiotherapy and chemotherapy	568 (33.5)	417 (32.0)	151 (38.6)	
No treatment/ treatment unknown	8 (0.5)	7 (0.5)	1 (0.3)	

Table 1. Continued

Characteristic	Total cohort CCS (n=1695)	CCS NCF (n=1304)	CCS CF (n=391)	P-value [e]
	N (%)	N (%)	N (%)	
Recurrence				
No	1468 (86.6)	1125 (86.3)	343 (87.7)	0.460
Yes	227 (13.4)	179 (13.7)	48 (12.3)	

Abbreviations: CCS= Childhood Cancer Survivors, NCF=group without chronic fatigue, CF= group with chronic fatigue, CNS= Central Nervous System.

[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

[d] Treatment data included primary treatment and all recurrences.

[e] Chi square test for differences between NCF and CF group.

Table 2. Association of CF with impaired HRQOL

HRQOL subscale	Unadjusted OR	95% CI	Adjusted OR [a]	95% CI	Adjusted OR [b]	95% CI
SF-36						
PF	4.24	3.34 – 7.66	3.68	2.01 – 6.72	2.01	0.95 – 4.26
RP	11.47	7.99 – 16.46	10.16	7.05 – 14.66	6.34	4.19 – 9.56
RE	9.13	6.58 – 12.67	8.81	6.30 – 12.30	4.01	2.67 – 6.04
BP	10.42	5.34 – 20.33	8.52	4.33 – 16.76	5.72	2.64 – 12.39
MH	12.58	6.53 – 24.26	14.92	7.58 – 29.34	2.47	1.04 – 5.84
VT	49.66	28.63 – 86.13	52.69	30.03 – 92.44	30.35	16.41 –56.16
GH	13.06	8.11 – 21.03	12.05	7.43 – 19.55	6.88	3.94 – 12.01
SF	10.84	6.94 – 16.93	10.59	6.72 – 16.71	3.87	2.26 – 6.63
TAAQOL						
SL	5.02	3.58 – 7.03	4.56	3.23 – 6.43	n/a *	n/a *
SE	4.44	2.99 – 6.59	4.14	2.77 – 6.19	2.08	1.28 – 3.38
CO	6.29	4.84 – 8.19	6.07	4.63 – 7.94	3.06	2.21 – 4.23

Results of multivariable logistic regression analyses with HRQOL domains as dependent outcome variable and CF as independent variable.

[a] Adjusted for age and sex.

[b] Adjusted for age, sex, BMI, employment status, educational level, poor sleep quality, anxiety, depression, number of somatic comorbidities, childhood cancer diagnosis, childhood cancer treatment.

*The HRQOL domain sleep was excluded from this analysis as sleep quality was considered a confounder and both factors show too much overlap to include in the same model. Abbreviations: HRQOL=Health related quality of life, CF=chronic fatigue, OR=Odds ratio, 95%CI=95% confidence interval, PF=Physical Functioning, RP=Role physical, RE=Role Emotional, BP=Bodily Pain, MH=Mental Health, VT=Vitality, GH=General Health, SL=Sleep, SE=Sexuality, CO=Cognitive Functioning

Association chronic fatigue with impaired HRQOL

Univariate logistic regression showed CF to be associated with impaired HRQOL domains (Table 2). OR's for CF were significantly increased for all HRQOL domains, with OR's for RP, BP, MH, VT GH and SF >10. After adjustment for confounders, CF remained significantly associated with impaired HRQOL (Table 2), except for the PF domain (p=0.069). The largest OR was seen for VT, but also the domains RP, BP and GH showed OR's exceeding five-fold risks for CCS with CF compared to CCS without CF.

Discussion

The aim of the current study was to investigate the association of CF with HRQOL in a nationwide cohort of CCS. Compared to CCS without CF and the general population, CCS with CF scored markedly lower on almost all studied HRQOL domains, independent of other potentially influential factors, demonstrating CF to be associated with worse HRQOL in CCS. These results emphasize the importance of including CF screening and monitoring in survivorship care aiming to improve quality of life as it was shown to affect the daily lives of CCS on multiple aspects.

Recent studies conducted in the DCCSS LATER cohort already showed CCS to more often have impaired HRQOL than the general population on several domains [9, 10]. The current study focused on the role of CF on impaired HRQOL in CCS. Except for PF, all HRQOL domains showed a clear and independent association with CF after adjustment for many known characteristics. The domain PF illustrates a person's ability to perform physically demanding (household) tasks such as walking the stairs or doing groceries. In the unadjusted analysis, the association between PF and CF was less strong than for the other domains, suggesting that PF is less affected by CF in CCS. Also, other factors than fatigue might be more associated with this HRQOL domain. Having other health issues and poor sleep have previously been related to decreased physical functioning in other patient populations, for example survivors of breast cancer [46, 47], and therefore it is possible that these factors in particular might have caused the effect of CF to flatten in the current study. The strongest association was seen between CF and the VT domain (OR 30.352). This strong association could be expected as feelings of vitality are no doubt affected by fatigue. However, the *CIS fatigue severity* subscale and SF-36 VT subscale had a moderate correlation (data not shown) indicating both scales to reflect different concepts.

Previous studies show CF to have a negative impact on HRQOL in multiple patient populations [48-51], and also in subgroups of CCS it was already suggested that (chronic)

fatigue affects HRQOL [15, 17]. The current study confirms this, showing the impact of CF on a broad range of HRQOL subscales in a generalizable cohort of CCS. Studies including CCS of all childhood diagnoses (except CNS tumors in Frederick et al.)[16, 18] also showed fatigued CCS to have decreased HRQOL domains compared to non-fatigued CCS, however the questionnaires they used to assess fatigue symptoms did not have validated cut-off scores to indicate severe fatigue and the duration of symptoms was not taken into account. In addition, 44% of the participants in the study by Frederick et al. [18] were aged 12-19 years and >52% of the participants in the study by Mulrooney et al. [16] were Hodgkin lymphoma survivors, whilst the current study focused on long-term adult CCS (aged >18 years) of all childhood malignancies. The current study combined the strengths of previous studies (cohort including all childhood diagnoses, questionnaire with validated cut-off score to indicate severe fatigue, take into account symptom duration) and showed CF to negatively impact HRQOL domains in a generalizable cohort CCS. Our results show CF to play an important role in decreasing multiple HRQOL aspects in CCS, emphasizing that it should be addressed in CCS care when aiming to improve HRQOL.

Owing to the cross-sectional design of the study, we do not know if CF causes HRQOL to decrease. It is also plausible that HRQOL is causally related to the occurrence and/or duration of CF. Therefore, although our study shows a strong association between CF and HRQOL, the causal relation between CF and impaired HRQOL remains to be studied, preferably in a longitudinal study. Also, differences in mean HRQOL scores between the CF group and the general population were not adjusted for age and sex as we did not have sufficient data of the general population to do so. This should be taken into account when interpreting the HRQOL domain differences between these groups. Another limitation of the current study was the comparatively low number of participants with domain specific HRQOL scores defined as 'impaired' for the purpose of the analyses (ranging from 46 (PF and BP) to 321 (CO)). Including multiple independent variables in the multivariable logistic regression analyses with few 'cases' could have affected the power to detect associations. However, independent variables were included one-by-one until the final model was analyzed so that power issues concerning the models (large OR confidence intervals for example) that may occur would have been noticed (which was not the case). Furthermore, data on self-reported somatic comorbidities, here used as a summary frequency score, were collected in 2013 (Teepen, Kok, Feijen et al. under review) which is slightly earlier than the parameters studied here (2016-2020). Although it is possible that new conditions might have affected some survivors (e.g. false negatives or too low counts in the current data), false-positives are unlikely since the questionnaire focused on chronic conditions, likely still present at the time of the current study.

An international guideline for childhood, adolescent and young adult cancer survivors that was published in 2020 already stressed the importance to screen for fatigue regularly and to treat it adequately [52]. The current study adds to this call as it indicates CF as a late effect clearly impairing HRQOL on various domains. Early detection of severe fatigue symptoms and providing a (personalized) intervention could prevent symptoms to become worse and affect HRQOL. Using a screening instrument, for example the Short Fatigue Questionnaire (SFQ) [53], could help to detect severe fatigue early. The SFQ is a 4-item questionnaire and is fast and easy to administer with a validated cut-off score to indicate severe fatigue [26, 54]. To get a more complete assessment of fatigue and its impact, a multidimensional fatigue questionnaire such as the CIS and a HRQOL questionnaire such as the SF-36 or TAAQOL could be used. Completing these questionnaires would probably take less than 20 minutes and scoring could be automated using online assessment. Psychosocial therapies such as cognitive behavioral therapy or exercise therapy could be possible interventions to think off, as previous studies have shown it to be adequate for treating CF in survivors of adult cancer and its potential was shown in CCS as well, although more studies are needed to confirm these results [52, 55-58].

To conclude, early detection and management of late effects of treatment and their impact on quality of life have become a key goal of CCS health care. Understanding the impact of specific late effects on HRQOL is crucial when aiming to improve the quality of CCS daily lives. The current study shows CF to have a negative impact on multiple HRQOL domains, indicating the urge for structural screening and, when needed, adequate treatment of fatigue symptoms in CCS care.

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Supplementary material

Supplementary Table 1. Health-related quality of life concepts measured by the SF-36 and TAAQOL

Dimension	Abbreviation	Definition	Number of items
SF-36			
Physical functioning	PF	Limitations in physical activities because of health problems	10
Social functioning	SF	Limitations in social activities because of physical or emotional problems	2
Bodily pain	BP	Experience of physical pain in daily life	2
General mental health	MH	Psychological distress and well-being	5
Role limitations (physical)	RP	Limitations in usual role/ work-related activities because of physical health problems	4
Role limitations (emotional)	RE	Limitations in usual role/ work-related activities because of emotional problems	3
Vitality	VT	Feelings of energy and fatigue	4
General health perceptions	GH	Perception of current and future health including resistance to illness	5
TAAQOL			
Sleep	SL	Problems/limitations concerning sleeping (lying awake, sleeping restlessly)	4
Sexuality	SE	Problems/limitations concerning sex (frequency, satisfaction)	2
Cognitive functioning	CO	Problems/limitations concerning cognitive functioning (concentrating, remembering)	4

Supplementary Table 2. Confounder variables included in multivariable analysis and their categories

Variable of interest	Questionnaire item (when applicable)	Categories
Age at assessment	Date of assessment – date of birth	In years continuous
BMI	Length (cm) and weight (kg) measured during clinic visit	Underweight: BMI <18.5 Healthy weight: BMI between 18.5 and 25 Overweight: BMI between 25 and 30 Obesity: BMI ≥30
Employment status	Do you currently have work? Yes/no	Employed: Currently employed Unemployed: Currently unemployed
Educational level	What is the highest level of education you have completed? Answer options: primary education, vocational education, preparatory secondary vocational education, secondary vocational education, school of higher general secondary education, pre-university education, higher vocational education, university, special school.	Low: Primary education, vocational education, special school Middle: Preparatory secondary vocational education, secondary vocational education, school of higher general secondary education, pre-university education High: Higher vocational education, university
Sleep quality	Seven PSQI component scores and total scores were calculated using scoring instructions described elsewhere [40]	Good sleeper: PSQI total score ≤5 Poor sleeper: PSQI total score >5
Anxiety	The outcomes of the seven items of the HADS anxiety subscale were added up and the total score was used to indicate person's as having anxiety yes/no.	No anxiety: HADS anxiety subscale score <8 Anxiety: HADS anxiety subscale score ≥8
Depression	The outcomes of the seven items of the HADS depression subscale were added up and the total score was used to indicate person's as having depression yes/no.	No depression: HADS depression subscale score <8 Depression: HADS depression subscale score ≥8
Number of somatic comorbidities	In 2013 a questionnaire about health issues was completed and used to indicate whether a participant suffered one or more health issues as classified by Streefkerk et al. [41]	0: Zero comorbidities 1-2: One or two comorbidities >2: More than two comorbidities

Abbreviations: BMI=Body Mass Index; PSQI=Pittsburg Sleep Quality Index; HADS=Hospital Anxiety and Depression Scale

Supplementary Table 3. Overview missing values

Variable	Number of missing values (%)
SF-36	
PF	40 (2.4)
RP	41 (2.4)
RE	49 (2.9)
BP	45 (2.7)
MH	53 (3.1)
VT	53 (3.1)
GH	53 (3.1)
SF	44 (2.6)
TAAQOL	
SL	12 (0.7)
SE	60 (3.5)
CO	10 (0.6)
PSQI poor sleeper (yes/no)	53 (3.1)
HADS anxiety (yes/no)	79 (4.7)
HADS depression (yes/no)	81 (4.8)
BMI	48 (2.8)
Employment status	18 (1.1)
Educational level	17 (1.0)
Number of somatic comorbidities	328 (19.4)

Abbreviations: PF=Physical Functioning, RP=Role Physical, RE=Role Emotional, BP=Bodily Pain, MH=Mental Health, VT=Vitality, GH=General Health, SL=Sleep, SE=Sexuality, CO=Cognitive Functioning. The variables sex, age at assessment, primary childhood diagnosis, treatment, and chronic fatigue were not included in the table as no missing values were present.

Supplementary Table 4. Comparison participants vs. non-participants

Characteristic	Participants (n=1695)N (%)	Non-participants (n=2296)*N (%)	p-value [e]	ES [f]
Female sex	817 (48.2)	937 (40.8)	<0.001	0.07
Decade of birth				
<1960	20 (1.2)	22 (0.9)		
1960-1969	143 (8.4)	160 (7.0)	0.230	0.04
1970-1979	436 (25.7)	582 (25.3)		
1980-1989	654 (38.6)	875 (38.1)		
≥1990	442 (26.1)	658 (28.6)		
Age at diagnosis				
0-5	770 (45.4)	1093 (47.6)		
5-10	458 (27.0)	625 (27.2)	0.167	0.04
10-15	370 (21.8)	437 (19.0)		
15-18	97 (5.7)	141 (6.1)		
Primary childhood cancer diagnosis [a]				
Leukemia	581 (34.3)	781 (34.0)		
Non-Hodgkin lymphoma [b]	210 (12.4)	261 (11.4)		
Hodgkin lymphoma	121 (7.1)	162 (7.1)		
CNS	158 (9.3)	263 (11.5)		
Neuroblastoma	97 (5.7)	122 (5.3)		
Retinoblastoma	8 (0.5)	16 (0.7)	0.526	0.05
Renal tumors	193 (11.4)	251 (10.9)		
Hepatic tumors	17 (1.0)	25 (1.1)		
Bone tumors	101 (6.0)	120 (5.2)		
Soft tissue tumors	124 (7.3)	169 (7.4)		
Germ cell tumors	56 (3.3)	95 (4.1)		
Other and unspecified [c]	29 (1.7)	31 (1.4)		
Childhood cancer treatment[d]				
Surgery only	109 (6.4)	266 (11.6)		
Chemotherapy, no radiotherapy	917 (54.1)	1293 (56.3)	<0.001	0.12
Radiotherapy, no chemotherapy	93 (5.5)	132 (5.7)		
Radiotherapy and chemotherapy	568 (33.5)	575 (25.0)		
No treatment/treatment unknown	8 (0.5)	30 (1.3)		
Recurrence				
No	1468 (86.6)	2028 (88.3)	0.103	0.03
Yes	227 (13.4)	268 (11.7)		

*Non-participants were invited to participate but did not return or complete the fatigue and HRQOL questionnaires

[a] Diagnostic groups included all malignancies covered by the third edition of the International Classification of Childhood Cancer (ICCC-3) as well as multifocal Langerhans cell histiocytosis.

[b] Includes all morphology codes specified in the ICCC-3 under lymphomas and reticuloendothelial neoplasms, except for Hodgkin lymphomas. Also includes multifocal Langerhans cell histiocytosis.

[c] Includes all morphology codes specified in the ICC-3 under other malignant epithelial neoplasms and malignant melanomas and other and unspecified malignant neoplasms.

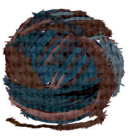
[d] Treatment data included primary treatment and all recurrences.

[e] Chi-Square test

[f] Effect size, calculated as Cramér's V (<0.1=little, 0.1=low, 0.3=medium, 0.5=high).

Chapter 9

Summary of findings



The aim of this thesis was to better understand Chronic Fatigue (CF) in Childhood Cancer Survivors (CCS) and its consequences, i.e., **to unravel chronic fatigue in childhood cancer survivors.** We determined the suitability of a fatigue instrument for the **screening** for severe fatigue, investigated which factors are associated with fatigue and elaborated on plausible causal relations between these factors (**associations and putative causation**). Lastly, we determined how fatigue impacts the lives of survivors (**consequences**).

Screening

In **Chapter 2**, we investigated the psychometric properties of the Short Fatigue Questionnaire (SFQ), a short and easy to use screening instrument, in the general Dutch population and ten patient groups. It was found that the SFQ is a reliable instrument and a cut-off score of ≥18 was determined to be optimal to identify severe fatigue. In **Chapter 3**, we determined the psychometric properties of the SFQ and the Checklist Individual Strength (CIS), a multi-dimensional fatigue questionnaire, in CCS and validated the proposed cut-off score. It was concluded that the psychometric properties of the SFQ and CIS in CCS are adequate.

Associations and putative causation

To study CF in CCS, we proposed a model (**Chapter 4**) and categorized variables based on their assumed relation with CF in CCS, being 1) *Triggering factors*, i.e. childhood cancer diagnosis and treatment related factors thought to play a role at the onset of fatigue; 2) *maintaining factors*, i.e. factors thought to perpetuate fatigue once triggered; 3) *moderating factors*, i.e. factors thought to influence the way fatigue expresses in individuals. In **Chapter 5** we investigated the association of CF with of each of these groups of factors in CCS using logistic regression analyses. Based on the results, we concluded that the assumed maintaining factors have the strongest association with CF in CCS. The following outcomes were independently associated with CF: Obesity, physical inactivity, poor sleep, (sub)clinical anxiety, depression, pain, self-esteem, feelings of helplessness, social functioning and female sex. Even after adjustment for other fatigue-related factors and confounders, these factors, related to lifestyle and psychosocial well-being, remained associated with CF.

Using Structural Equation Modeling (SEM) we assessed these associated factors in more detail and determined putative causal relations between these factors and CF (**Chapter 6**). Two factors were shown to be plausible causal factors for CF, namely female sex

and pain. CF was found to be a putative causal factor for reduced physical activity and feelings of helplessness. In addition, next to causal relations, some two-way relations were hypothesized, which means that factors are dependent, but that the direction of the causality could be A) both ways, meaning that there is a reciprocal relationship between factors, or B) a latent confounder could be present. A two-way relation between CF and depression could be confirmed with high confidence using SEM.

In **Chapter 7** we showed that different subtypes of CF exist in CCS. One subgroup reported fatigue with problems in physical activity (29% of CCS with CF), a second group reported fatigue with difficulty concentrating (25% of CCS with CF) and a third group reported problems on multiple dimensions (46% of CCS with CF). The latter subgroup consists of almost half of all CCS with CF and they reported elevated scores on all CIS fatigue domains. This subgroup is further characterized by symptoms of anxiety, depression, sleep problems, low scores on self-esteem and feelings of helplessness. This group is also lower educated, seems to be more often unemployed, and reported lower scores on social functioning.

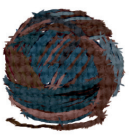
Consequences

In **Chapter 8** we concluded that CF is associated with a decreased health-related quality of life (HRQOL) in CCS. We assessed a total of 11 HRQOL domains of CCS with CF and CCS without CF and compared domain scores to scores in the general population. CCS with CF reported lower HRQOL compared to CCS without CF and the general population. CF was associated with impaired HRQOL in CCS, even after adjustment for other symptoms known to affect HRQOL, which implicates that CF is independently associated with an impaired HRQOL in CCS.

In **Chapter 10** the findings of this thesis are discussed.

Chapter 10

General discussion



In this chapter, we discuss how the results of this thesis contribute to a better understanding of CF in CCS.

Interpretation of results and clinical implications

Screening

Guidelines for the surveillance of fatigue in survivors of childhood, adolescent and adult-onset cancer (CAYA) all recommend to regularly screen for fatigue [1-3]. However, there is no consensus on how to best conduct this screening. Many fatigue questionnaires exist, but none had been validated in CCS. We aimed to determine the potential of the Short Fatigue Questionnaire (SFQ) as a screening instrument for severe fatigue and to determine whether its psychometric properties are satisfying when used in CCS.

The current thesis indicates the SFQ to be a valid and reliable instrument to screen for severe fatigue in CCS. The SFQ is a short version of the Checklist Individual Strength (CIS), which is a multi-dimensional fatigue instrument that is already widely used to measure fatigue severity [4-6]. The presented cut-off score of ≥18 has a high sensitivity and in addition, a good negative predictive value, a value that was stressed to be of great importance for screening tools [7]. Combined with a good specificity and positive predictive value, the SFQ is an excellent instrument to screen for severe fatigue. The latter two indicate the chance that someone without severe fatigue is truly identified as such. Although both scores are high, there is still a small chance that people are falsely identified as severely fatigued. The consequences of being falsely identified are minimal, as a positive screening does not lead to costly and burdensome follow-up procedures, as is often the case in the surveillance for other long-term effects such as cardiomyopathy or secondary tumors [8-10]. Further in-depth analyses of the fatigue symptoms, for example using the multidimensional CIS and discuss the symptoms during the anamnesis, could indicate in more detail whether someone is truly affected by severe fatigue.

Next to an adequate validity and reliability, the IGHG surveillance recommendations present several considerations before using a fatigue screening instrument in clinical practice [1]: It should not be too extensive and readily available for health care providers (HCP) and preferably be available in multiple different languages. The SFQ complies with all these considerations. Lastly, to be a useful instrument along the total cancer survivorship trajectory of CCS, the screening instrument should have versions for different age groups. The SFQ is now validated in adult CCS, however not yet in a

<18 years of age CCS cohort. When assessed in other childhood cohorts, i.e., healthy children, children with chronic fatigue syndrome and children with a chronic disease, psychometric properties of the SFQ were good, although a cut-off score of ≥21 might be preferable to indicate severe fatigue in adolescents compared to a cut-off score of ≥18 in adults [11].

Associations and putative causation of chronic fatigue in CCS

We aimed to determine what factors are related to CF in CCS and might play a role in triggering and/or maintaining fatigue. We found a significantly higher prevalence rate of CF in CCS compared to a sibling control group and the general Dutch population [12], suggesting that a history of cancer plays a role in developing CF in later life. Going through an often traumatic and life-threatening phase during childhood that includes cancer treatment might have induced the fatigue symptoms. However, CCS participants of studies reported on in this thesis were several years past diagnosis (28 years on average), and we do not know when the CF began or its course during these years.

During childhood cancer treatment, fatigue is a frequently reported side-effect [13], therefore it might be possible that fatigue symptoms originating from treatment are perpetuated over time. In survivors of young adult cancers, 60% of those with CF reported to have fatigue symptoms since cancer treatment [14]. A recent study investigating the longitudinal development of fatigue in children in the first five years after treatment reported that symptoms of fatigue improve in the first years after treatment, but seem to worsen again five years after treatment [15]. In concordance, a meta-analysis in breast cancer survivors suggests the prevalence of severe fatigue to decrease in the first half year after treatment completion, possibly to increases again in the years thereafter [16]. However, more longitudinal studies are needed to investigate fatigue patterns following childhood cancer.

An increase in fatigue scores several years past treatment might be related to social obligations that come with entering adulthood. An increase in demands can be seen throughout young adulthood, where a person becomes more and more independent which comes with various responsibilities and the need to find a balance regarding work, family and social activities. These socio-cultural demands could potentially be accompanied by an increase in fatigue. CCS might be more prone to develop fatigue as a result of increased demands as they might be affected by the treatment they received on multiple levels, for example cognitively or socially.

Now, many years into survivorship, lifestyle and psychosocial factors were found to be associated with CF in CCS (**Chapter 5**). This echoes findings in other populations [17-20]. These factors do not seem to be diagnosis or treatment specific, but are similar for different patient populations and could therefore be referred to as trans-diagnostic. A trans-diagnostic approach for fatigue has been proposed in recent studies [21-23]. Not only were associated factors found to be similar for multiple chronic diseases, but also compared to healthy subjects, indicating that fatigue might be a generic symptom [21]. Thus, regardless of how fatigue was triggered in CCS, when CF is present multiple years past treatment, it seems associated with trans-diagnostic/generic factors.

Putative Causation

We aimed to determine how fatigue-associated factors might be causally related. Of the lifestyle and psychosocial factors that were found to be associated with CF, sex and pain seemed to be causal factors for CF (**Chapter 6**). We assume sex to not actively cause symptoms of fatigue, but factors that are related to the female sex might [24, 25]. Females might have a higher interoceptive sensibility, i.e. the perception of the body's internal state [26]. With possibly hormonal or other biological differences underlying the difference in fatigue levels, the nature of the fatigue symptoms might be different for men and women, demanding different treatment strategies. More research is needed to determine these sex differences in more detail.

Pain was found to be a putative causal factor for CF. A causal relation between pain and fatigue was already suggested in studies investigating chronic pain [27, 28], and also in breast cancer survivors bodily pain was shown to be a predictor of fatigue over time [29]. This makes it plausible that a similar causal pathway exists in CCS as well. On the other hand, there are authors who argue that the relation between pain and fatigue could also be bidirectional and that more, longitudinal and experimental, research is needed to draw more definite conclusions [30]. Details regarding the nature of pain in CCS, i.e. is it related to specific comorbidities or local inflammation, or its duration, i.e. is it acute or chronic, remained unknown in our study and that makes the interpretation of the relation between pain and CF in CCS difficult. A systematic review investigating pain in CCS showed that the prevalence of chronic pain (pain that is prevalent ≥3 months) varies between 11-44%, and the prevalence of any pain reported varies between 4-74% [31]. In the current thesis, almost one-third of CCS with CF reported to have had severe or very severe pain (score of ≥4 on 6-point Likert scale) over the past four weeks, which is almost 4 times higher compared to CCS without CF. So, regardless of the precise location, nature or duration of the pain symptoms, these results indicate that fatigue and pain co-occur in one-third of the CCS with CF and should therefore be taken into account when investigating CF in CCS. For example by

including pain as a topic of interest during the anamnesis in CCS who report CF or by using a pain screening instrument such as a Numerical Rating Scale (NRS) [32] or Visual Analogue Scale (VAS) [33].

Several two-way relations were hypothesized, of which a two-way relation between CF and depression could be confirmed with high confidence using SEM. This two-way pathway is in concordance with previous research investigating the relation between depression and fatigue, where it was suggested that fatigue may be the result of a depression, but that a person who continuously perceives his or her energy as insufficient may also become depressed [34]. In the current thesis, one in four CCS reported to have CF and the prevalence of depression was 9%, which is even lower compared to Dutch reference norms [35]. The prevalence of depression is much higher in CCS with CF, namely 22%. This higher prevalence rate was also found in fatigued survivors of breast cancer [36]. A study by Müller et al. [37] showed a reduction in fatigue to act as a mediator for the effect of cognitive behavioral therapy (CBT) on depressive symptoms. This suggests that interventions aimed at reducing fatigue symptoms, might also reduce depressive symptoms.

Some hypothesized causal or two-way pathways have been confirmed using SEM, others have not. Regardless of the precise causality, it is likely that these factors are strongly related. Several studies have found (chronic) fatigue and many of these factors, namely anxiety, depression, sleeping problems, pain and reduced physical activity, often cluster or co-occur in survivors of (childhood) cancer [38, 39]. Clinicians should be aware of this and not just focus on one of these symptoms, but take into account this whole pallet of different factors that might all impair the CCS' well-being.

Different types of CF

We aimed to determine whether subgroups of CCS could be identified who experience different types of CF. We found that 29% of the CCS with CF report predominantly problems with physical activity, another 25% report predominantly concentration problems and the remaining group (46%) report problems on multiple dimensions (**Chapter 7**). That fatigue is a multidimensional construct, including a physical and mental aspect, was already known [40], and fatigue subgroups based on these dimensions have also been found in other patient populations [41, 42]. Here, also a majority of patients reported to experience a combination of problems with physical activity and concentration [41], concordant with our results.

Other studies, in different populations, found subtypes of fatigue based on fatigue severity rather than based on dimensions of fatigue [43-45]. However, studies used

different methodology or included both fatigued and non-fatigued participants in their analyses [44, 45], where we focused on CCS who were identified with CF, and determined subtypes of fatigue based on fatigue dimensions within this group of fatigued participants, rather than fatigue severity.

It has been suggested that different dimensions of fatigue should be taken into account when measuring fatigue in non-oncology populations [46]. The current results opt for a similar recommendation when assessing fatigue in CCS. Therefore, after positive screening for CF, we recommend specifying the symptoms of the survivor by using a multidimensional instrument to capture both the mental and physical factors associated with fatigue.

Consequences

We aimed to determine the impact of CF on Health-related Quality of Life (HRQOL). After adjustment for factors that were previously shown to be related to lower HRQOL domain scores in the DCCSS LATER cohort [47, 48], CF was independently associated with an impaired HRQOL in CCS (**Chapter 8**). CF was associated with impaired scores on various HRQOL domains, among which the *role physical* and *role emotional* domains. These two domains refer to usual role limitations, reflected in work-related activities or other daily activities. Both the physical aspect, e.g., difficulty with performing physical activities, and mental aspect, e.g., not able to perform activities as careful as usual, are assessed. In addition, in **Chapter 5** we found that CCS with CF were more often unemployed compared to CCS without CF (28% vs. 11%). HRQOL and social outcomes might be closely related, as was shown in patients with chronic fatigue syndrome, where participants who perceived their work as physically demanding were more likely to be unemployed [49]. Combining increased role limitations and unemployment in CCS with CF, a pathway could be hypothesized where chronic fatigue might cause people perceiving their work as highly demanding which could lead to difficulties in maintaining one's job which could lead to unemployment. To adequately support these CCS, it is important to know when the fatigue symptoms started and whether fatigue is indeed a limiting factor regarding one's employment or whether other factors are in play.

Limitations in a range of HRQOL domains and social outcomes such as employment status, suggests that there is a subgroup of CCS who have substantial problems participating in society. Trying to characterize this group even further, using the different subgroups defined in **Chapter 7**, the multiple-dimensions subgroup seems to

be the subgroup that is affected most. This group seems to be more often unemployed and is also lowest educated compared to the other subgroups and the non-CF CCS. Perhaps, this subgroup suffers from multiple symptoms/late effects since their childhood cancer diagnosis, impairing them to fully participate in school/study, work and social activities. Future studies should focus on this particular group of interest trying to better understand these CCS and their needs.

Previous studies showed that CCS are more likely to have undesirable social outcomes compared to both siblings and population controls [50-52]. Results of the current thesis suggest that a multi-problem subgroup can be defined. It is important to recognize this group early and support them adequately with the aim to prevent worsening of social outcomes and optimize quality of life. A multi-disciplinary approach might be preferable, where all symptoms are identified and managed, rather than focusing on solely one symptom. It is important to identify these apparently vulnerable CCS as early as possible so that proper support can hopefully prevent them from any disadvantages later in life. It remains unknown how this vulnerability is precisely related to the childhood cancer, but it is probably a complex interplay between multiple factors, that might vary between individuals.

Recently, a guideline was published for the short-term surveillance of health problems, which starts at the end of treatment and continues for up to five years [53]. We encourage such guidelines, covering the early stages of survivorship and defining survivors at risk for certain outcomes, as CCS at risk could be supported in trying to prevent certain late-effects or societal difficulties, rather than intervene when late-effects have already occurred.

Possible interventions

Guidelines for CAYA and adult-onset cancer survivors (IGHG and ASCO guidelines) recommend both physical activity and psychosocial interventions to treat fatigue [1, 3]. In **Chapter 5** we showed several factors to be associated with CF. These factors might provide some guidance in choosing a treatment strategy.

Cognitive behavioral therapy (CBT)

CBT is a psychological treatment and addresses topics such as anxiety, depressive feelings, sleep disturbances, physical activity regulation and social support, all factors that were shown to be associated with CF in CCS. CBT was shown to be an effective intervention to reduce levels of fatigue in both cancer patients receiving active

treatment and survivors of adult-onset cancer [54-56]. The effect of CBT on levels of fatigue in CCS should be investigated further. A pilot study in CCS already showed promising results [57], however results need to be replicated in a larger controlled intervention study.

Lifestyle interventions

Physical activity and BMI were found to be associated with CF in CCS. This suggests that interventions aimed at improving these factors, such as exercise therapy or lifestyle behavioral interventions, might potentially decrease symptoms of fatigue. The focus of these interventions lies on reducing fatigue by improving the physical condition and/or lifestyle of a person. Studies have shown that interventions aimed at increasing the physical activity of participants, e.g., exercise or physical therapy, might reduce fatigue [58-60]. These interventions often consist of specific physical exercises, once or twice a week, most of the time supervised, where persons are actively encouraged to exercise with the focus to reduce fatigue. Lifestyle behavior interventions on the other hand not only takes the physical condition of people into account, but broader lifestyle goals that might be related to daily tasks, a healthier dietary intake or losing weight. Such lifestyle interventions might be effective to reduce fatigue [61], however more studies are needed to investigate the effect of lifestyle interventions on the levels of fatigue in CCS.

Pain management

Whenever CCS with CF also report severe pain symptoms, pain reduction might be a treatment option to consider. Pain reduction as a treatment to reduce fatigue symptoms has not yet been studied broadly, but some studies suggest that pain reduction could be beneficial to reduce fatigue. For example, a study by Yamada et al. in patients with musculoskeletal issues showed reductions in pain severity to possibly contribute to reductions in fatigue severity [62]. A promising intervention to do so could be educating a person about his/her pain symptoms and pain mechanisms as a study by Oosterwijck et al. showed pain physiology education to improve both pain scores and SF-36 vitality scores [63]. The effect of specific pharmaceutical interventions (pain medication) to reduce fatigue symptoms has not yet been studied thoroughly.

eHealth

Digital interventions, or eHealth, are easily accessible and limit the time burden and traveling expenses. This might be beneficial for CCS who are severely fatigued and because of that feel a barrier to travel for treatment. An interesting option might be an eHealth CBT intervention, as CBT was shown to be effective in reducing fatigue symptoms when it was internet based, in survivors of breast cancer [56]. Also, an eHealth

intervention where both psychosocial and lifestyle aspects can be addressed (separately or combined), could be an option, as a meta-analysis showed eHealth interventions combining both aspects to be effective in reducing fatigue levels in adult-onset cancer survivors [64]. Therapist guided eHealth interventions are preferred over self-guided interventions as these seem to be more effective in managing fatigue symptoms [64]. Studies in CCS investigating the feasibility of eHealth tools -that are based on the CBT principles and include digital, therapist guided, lifestyle coaching- in CCS, are currently being conducted and results of these (pilot) studies are expected soon [65, 66].

Choosing the right intervention

Above, several options for the treatment of CF in CCS were proposed. Every intervention focuses on specific CF-related factors, therefore might fit best to a specific fatigue profile that is most affected by these factors. However, it is unknown whether choosing an intervention based on CF-associated factors would be beneficial to reduce fatigue levels as no studies have been conducted to investigate this. The CF subgroups could help to identify CCS who are expected to have the most benefit from one intervention or another. More research is needed to determine whether personalizing CF interventions based on CF subtypes is associated with reduced fatigue levels. Next to choosing an intervention based on CF subtype and its related factors, preferences of the CCS should always be taken into account. With multiple options that could all be potentially useful in treating fatigue, the intervention that suits the lifestyle and beliefs of the CCS are important to take into account.

Person centered survivorship care

The aim of cancer survivorship care is to prevent and early detect late effects of treatment to assure fast and adequate follow-up, to improve health and health-related quality of life of CCS. Survivorship care can play an important role in providing guidance to reduce the impact that late effects have on the quality of life of survivors and their families. To provide high quality care, a person centered care (PCC) approach is encouraged, which includes compassion and partnership with the patient, or survivor in this case, taking into account the survivor's values, preferences and needs [67]. To secure these values, a model was presented that demonstrates the optimal structure of comprehensive cancer survivorship care [68]. The survivor's personal believes, life situation and health condition are taken into account.

The PCC approach is of particular interest for the subgroup of CCS who are affected by multiple symptoms. Using the PCC approach, a detailed symptom profile of the

survivor is made including all symptoms of interest, ensuring appropriate follow-up care that fits the needs of the survivor. Having problems on various dimensions, it might be difficult to fully retain autonomy. With a multi-disciplinary team that can provide support for the CCS on various levels, i.e. physically and mentally, but also regarding social problems that they face such as educational or employment related issues, personal support can be provided that is needed to function optimally. Applying the PCC approach to CF in late-effect care would mean that if, after screening, CF turns out to be clinically relevant, a detailed evaluation and appropriate follow-up care including in depth discussion of the applicable consequences and treatment options are discussed with the CCS.

Methodological considerations

Sibling controls vs. population controls

For the Dutch Childhood Cancer Survivor Study (DCCSS) LATER part 2 [69], siblings of the CCS were invited to participate in the study as a control group. By including the siblings as a control group, we believe both groups to be similar regarding unmeasured social and cultural outcomes. However, it might be that someone who has experienced their brother or sister to go through a life-threatening disease such as cancer during childhood, could potentially be affected by this traumatic experience as well [70]. Therefore, results of the sibling control group might not represent the general population. It might thus be good to, in future research, compare results with a population based cohort as well. We planned to include data from the Lifelines cohort [71], a population based cohort in the Netherlands, for the current thesis to determine the prevalence and associated factors for CF in the general population. However, methodological differences between the study cohorts made it difficult to compare results with the CCS cohort. Therefore, for the current thesis, we decided to focus on the associated factors and putative causalities for CF in CCS.

Associations vs. prediction model

Associations indicate whether or not two or more variables are related to each other. Often, both dependent and independent variables are measured at the same timepoint. Risk prediction indicates whether one variable might predict the outcome of a second variable. Often, the dependent variable is measured later in time compared to the independent variable. Both types of analyses make us of a similar technique, namely regression analyses, however statistical methodology might differ and the output is interpreted and used differently.

For the current thesis we decided to focus on associated factors for CF in CCS. Due to methodological differences between previous studies that investigated associated factors for fatigue in CCS, no consensus could be made [72]. Therefore, it remained unknown which factors actually play a role in possibly triggering, maintaining and moderating fatigue. Fatigue is a very complex, multidimensional problem, with various factors that might play a role. Ideally, longitudinal data should be used to determine causality between factors. However, data for the current study are cross-sectional, meaning that only associations can be made for the timepoint that CF is already present. Still, to provide some structure in choosing an optimal intervention strategy, and to provide a rationale for future research investigating treatment options for CF in CCS, it was important to investigate which factors are associated with CF in CCS.

A risk-prediction model would also have been interesting and informative, however the following considerations were made. Firstly, data used for this thesis are cross-sectional and collected multiple years after childhood cancer treatment. For a prediction model it would have been more interesting to have assessed data regarding possible risk factors during or right after treatment so that a risk profile can be made based on these parameters. Secondly, risk prediction can be helpful to indicate which survivors are at increased risk for certain (life-threatening) health outcomes and should therefore be regularly screened during follow-up. For example, identifying groups of CCS who are at increased risk for secondary malignancies such as colorectal or breast cancers [73, 74]. Screening for these secondary malignancies is often costly and might come with potential harms for the survivor [9]. Therefore, prediction models that identify CCS who might benefit most from screening are very welcome. This way, not all CCS have to be screened. For CF however, screening is much more easy, so the need to identify certain subgroups of CCS who might benefit most from screening, is not particularly urgent. Still, it would be very interesting to, immediately after treatment completion, identify CCS who are at risk for CF and come up with a prevention strategy so that less CCS struggle with CF later in life. To do this adequately, the course of fatigue and its associated factors should be investigated from the start of cancer treatment to determine when and how such a prevention strategy could be most beneficial.

Future directions

Longitudinal studies

Due the lack of longitudinal studies in CCS, little is known about the course of fatigue over time. Therefore, we can only speculate about the origin of the fatigue symptoms.

Symptoms could be triggered during treatment and perpetuated over time, symptoms could start later - without the cancer diagnosis or treatment to play a role- or the overall experience of having had cancer might have caused an individual to be more prone to develop CF. One hypothesis of why CCS are more prone to develop CF is as follows: The childhood cancer treatment might have caused subtle damage, which might be somatic and/or cognitive, causing one's physical and/or mental resilience to decrease and with that increase the likelihood of experiencing fatigue. However, little is known about the cause of fatigue and its course over time in CCS.

A longitudinal study could provide insight in the course of fatigue over time and its associated factors. Also, the assumed maintaining factors for CF in CCS and putative causal relations between these factors, could be validated in a longitudinal study. A longitudinal study design consisting of repeated measures might be preferable as such a study would make it possible to capture change over time within subjects [75]. However, such a study in a large nationwide cohort would require a lot of time, considerable funding and a structured and dedicated participant follow-up.

The Childhood Cancer Survivor Study (CCSS) [76] or the St. Jude LIFE cohort [77] are examples of cohort studies in North America that include assessments over various timepoints. With the DCCSS LATER cohort, a similar design could be possible in the Netherlands. With the questionnaire based study between 2012-2014 [78] and the clinical study between 2016-2020 [69], fatigue is already measured at two timepoints, and plans for a third study are already in the making. However, as these cohorts are multiple years past diagnosis, it would not provide insight into the origin of fatigue and its course in the first years after treatment. To study the onset of fatigue, it is preferable to study participants from the start of treatment until many years past treatment.

Intervention studies

Only few studies have investigated the effect of interventions on fatigue levels in CCS. Adequately powered studies in CCS, preferable randomized and controlled, are needed to validate whether these are effective to reduce fatigue in CCS.

A randomized controlled trial (RCT) to investigate the efficacy of CBT, exercise therapy and lifestyle coaching on reducing levels of fatigue in CCS would be interesting. Since we found that subtypes of CF exist in CCS, we hypothesize that each subgroup would benefit most from an intervention strategy that focuses on the characteristics of that specific subgroup. To investigate this hypothesis, participants could be stratified into subgroups, based on their CF subtype, to determine whether some subgroups respond

better to certain interventions. Additionally, it might be interesting to investigate whether adding an intervention focused on pain management, when applicable, would lead to a significant additional reduction in fatigue levels compared to only exercise therapy, lifestyle coaching or CBT. The optimal treatment strategy for each subgroup could be analyzed in an adequately powered RCT, for instance by using an umbrella trial design, where multiple interventions are investigated in a single patient population [79]. Interventions are then allocated to subgroups within this patient population based on pre-defined characteristics that are hypothesized to best fit a specific intervention. By using an umbrella design, multiple different treatment strategies are investigated simultaneously in one single trial.

Genetic factors

The genetics of CF might be another interesting topic to investigate. In a future study, we aim to do a genome-wide association study (GWAS) to identify genetic variants that might be related to CF in CCS. A GWAS to determine whether CF is related to specific single-nucleotide polymorphisms (SNPs) would be interesting as it might provide additional information regarding the etiology of CF. It might help to categorize subgroups even further, based on different genotypes. In addition, it could indicate biological processes that might be related to CF, that could potentially lead to new treatment strategies or additional interventions.

Conclusion

With this thesis we aimed to address currently existing knowledge gaps by investigating factors that are associated with CF and to determine the consequences of CF. We showed that CF is a symptom that deserves attention and that it needs to be recognized as a debilitating symptom that frequently occurs in survivors of childhood cancer and therefore should be screened for regularly. Together with the survivor, factors that might be related to the CF and could play a role in maintaining the symptoms should be discussed, with a focus on lifestyle and psychosocial factors. Future studies should investigate which interventions are effective to reduce fatigue in CCS and how interventions can be personalized to specific CF subgroups.

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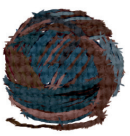
Appendices



Nederlandse samenvatting

Elk jaar krijgen in Nederland meer dan 500 kinderen de diagnose kanker. De afgelopen jaren is de overlevingskans toegenomen en nu overleeft meer dan 80% van de kinderen de ziekte. Wanneer je kanker hebt gehad, kan dit echter grote gevolgen hebben voor de rest van je leven. Zo kan het zijn dat de behandeling, welke vaak bestaat uit chemotherapie en/of radiotherapie, klachten geeft welke tot lang na de afloop van de behandeling kunnen blijven bestaan. Voorbeelden hiervan zijn hartklachten, een verminderd gehoor of verminderde vruchtbaarheid. Ook is er, na bepaalde behandelingen, een verhoogde kans om een tweede keer kanker te krijgen. Deze negatieve gevolgen worden "*lange-termijn effecten*" van de kankerbehandeling genoemd. Om ervoor te zorgen dat deze *lange-termijn effecten* tijdig worden herkend, krijgen personen die kanker hebben overleefd (ook wel *survivors* genoemd, naar de Engelse term voor overlevende) regelmatig een uitnodiging voor een gezondheidscheck in het ziekenhuis. In Nederland zijn er gespecialiseerde centra, de zogenaamde Late-Effecten na Kanker poliklinieken (LATER poli), die deze zorg verlenen. Tijdens een bezoek aan de LATER poli komen eventuele gezondheidsklachten aan bod. Aanvullend worden een aantal specifieke tests gedaan, op basis van de behandelgeschiedenis van de persoon, om eventuele lange-termijn effecten vroegtijdig op te sporen. Op deze manier kan er tijdig een passende behandeling gestart worden mocht dat nodig zijn.

Ernstige vermoeidheid behoort ook tot de lange termijn effecten van kanker op kinderleeftijd. Tijdens de behandeling wordt vermoeidheid vaak gezien als bijwerking van de behandeling. Naast misselijkheid en pijnklachten is vermoeidheid een van de meest gerapporteerde bijwerkingen tijdens de behandeling. De gevolgen van vermoeidheid zijn nog niet goed beschreven, maar zelfs jaren na de behandeling kan het de levens van survivors enorm beïnvloeden omdat het personen bemoeilijkt om bijvoorbeeld te werken, huishoudelijke taken uit te voeren of te sporten. Ook op vragen als "waarom ben ik vermoeid?" of "wat kan ik doen om mijn klachten te verminderen?" is nog geen duidelijk antwoord. Daarom was het doel van dit proefschrift om vermoeidheidsklachten bij survivors van kinderkanker te onderzoeken met als doel om meer inzicht te krijgen in dit symptoom.

Wat is vermoeidheid?

Vermoeidheid is subjectief, wat betekent dat het door iedereen anders kan worden ervaren. Anders dan bij hartklachten of gehoorbeschadiging, bestaat er geen fysieke test die gedaan kan worden om te bepalen of iemand vermoeidheidsklachten heeft of niet. Om het toch meetbaar te maken, wordt het vaak in kaart gebracht met behulp van een vragenlijst. Een dergelijke vragenlijst bevat meerdere vragen of stellingen die

de survivor beantwoordt door aan te geven in hoeverre hij of zij het eens is met de betreffende vraag of stelling. Enkele voorbeelden van stellingen zijn "ik voel me fit", "lichamelijk voel ik me uitgeput" of "het kost me moeite om ergens mijn aandacht bij te houden". Aan het eind van de vragenlijst worden de antwoorden gescoord en bij elkaar opgeteld en wordt er een totaalscore berekend. Deze score weerspiegelt dan de ernst van de vermoeidheidsklachten. Ook voor het huidige proefschrift hebben we vermoeidheid op deze manier in kaart gebracht. Hiervoor gebruikten we de vermoeidheidsvragenlijst "*Checklist Individuele Spankracht*" of "*CIS*" in het kort. In totaal bevat deze vragenlijst 20 stellingen, verdeeld over 4 subschalen:

1. Ernst van de vermoeidheidsklachten
2. Problemen met concentratie
3. Problemen met motivatie
4. Problemen met fysieke activiteit

De eerste subschaal "ernst van de vermoeidheidsklachten" werd gebruikt om te bepalen of iemand ernstige vermoeidheidsklachten had. Als dit het geval was, en de survivor aangaf dat de klachten tenminste 6 maanden bestonden, werd ervan uit gegaan dat de persoon last had van "*chronische vermoeidheid*". Voor dit proefschrift hebben we de focus gelegd op deze *chronische vermoeidheid*.

Wat was het doel van dit proefschrift?

– Screenen op vermoeidheid

We noemden al dat vermoeidheid het beste gemeten kan worden met een vragenlijst. Vaak bestaan deze vragenlijsten uit meerdere vragen die verschillende onderwerpen omvatten. Om snel in kaart te brengen of iemand vermoeidheidsklachten heeft, zou het makkelijker zijn om niet de hele vragenlijst direct in te vullen, maar een aantal korte items om te bepalen of vermoeidheid überhaupt een rol van betekenis speelt. Om dit te doen kan gebruikt gemaakt worden van een zogenaamd "*screeningsinstrument*". Echter, een *screeningsinstrument* om ernstige vermoeidheid in kaart te brengen bij survivors van kinderkanker bestond nog niet. Daarom was het onderzoeken van een dergelijk *screeningsinstrument* een belangrijk doel van dit proefschrift.

– Factoren die een rol spelen bij vermoeidheid

Chronische vermoeidheid komt bij ongeveer 1 op de 4 survivors voor. Het is echter nog niet duidelijk hoe het kan dat de ene persoon wel vermoeidheidsklachten krijgt, maar de ander niet. Verschillende factoren lijken hierbij een rol te spelen. Zo

zijn er studies die laten zien dat een bepaalde kanker diagnose of behandeling op kinderleeftijd het risico verhoogt op vermoeidheidsklachten. Andere studies laten zien dat demografische of sociale factoren een rol spelen, bijvoorbeeld leeftijd, geslacht of het opleidingsniveau van een persoon. Ook zouden lichamelijke of psychische klachten, zoals het hebben van een bepaalde lichamelijke aandoening of ontsteking, of juist mentale klachten zoals een depressie, mogelijk een rol kunnen spelen. Als laatste lijkt ook leefstijl van invloed op vermoeidheid. Zo zouden lichamelijke activiteit of het lichaamsgewicht van een persoon van invloed kunnen zijn op vermoeidheidsklachten. Al deze factoren werden in aparte studies onderzocht, maar nog niet eerder werden al deze factoren samen in één studie bestudeerd. Dit is belangrijk om te doen omdat de factoren elkaar ook onderling kunnen beïnvloeden, waardoor de precieze relatie is van een factor met vermoeidheid moeilijk te bepalen is.

– Gevolgen van vermoeidheid

Eén van de belangrijkste doelen van de LATER poli is om ervoor te zorgen dat de kwaliteit van leven van survivors zo optimaal mogelijk is. Door survivors te ondersteunen en te begeleiden bij moeilijkheden die ze ervaren als gevolg van mogelijke lange-termijn effecten na de behandeling, wordt gestreefd naar een zo goed mogelijk welzijn in het vervolg van hun leven. Het lijkt erop dat vermoeidheidsklachten het leven van survivors negatief beïnvloedt, echter is dit nog niet onderzocht in een grootschalige studie. Ook is het niet duidelijk welke aspecten van het dagelijkse leven van survivors precies beïnvloed worden. Daarom was een doel van dit proefschrift om de impact van vermoeidheid op verschillende aspecten van de kwaliteit van leven bij survivors te bepalen.

De LATER studie

Voor dit proefschrift is data gebruikt van de SKION LATER studie. Dit was een landelijke studie waarvoor alle kinderkanker survivors die zijn behandeld tussen 1963 en 2001 werden uitgenodigd om deel te nemen. Zij kregen een uitnodiging om tussen 2016 en 2020 een bezoek te brengen aan één van de 7 toenmalige LATER poli's in Nederland voor een reguliere gezondheidscheck, waarbij, bij survivors die schriftelijk daarvoor toestemming hadden gegeven, aanvullend data werd verzameld voor de studie. Naast vermoeidheid werden er verschillende andere lange-termijn effecten onderzocht, waaronder hartproblematiek, vruchtbaarheid en leefstijl.

Resultaten

In **Hoofdstuk 2** werd de Verkorte Vermoeidheidsvragenlijst (VVV) gepresenteerd als screeningsinstrument voor ernstige vermoeidheid. De VVV bestaat uit 4 stellingen en is een verkorte versie van de CIS. Met de VVV kan snel en eenvoudig bepaald worden of iemand ernstig vermoeid is en op die manier kan als het ware een voorselectie gemaakt worden van personen waarbij vermoeidheid op de voorgrond staat en bij wie dus, tijdens een consult, aandacht aan vermoeidheid besteed moet worden. Elk antwoord op een van de vier stellingen van de VVV geeft een bepaalde score. Al deze scores worden bij elkaar opgeteld, wat uiteindelijk een totaalscore geeft die kan variëren tussen de 4 en 28. Een score van 18 of hoger wijst erop dat een survivor ernstig vermoeid is. Met deze meting zie je niemand over het hoofd en kunnen deze personen de juiste zorg krijgen. Het is belangrijk om de bruikbaarheid van een vragenlijst te toetsen in een specifieke populatie, bijvoorbeeld kinderkanker survivors, omdat de eigenschappen van een bepaalde groep de resultaten van een vragenlijst kunnen beïnvloeden. In **Hoofdstuk 3** werd dit gedaan en toonden we aan dat de VVV ook in kinderkanker survivors gebruikt kan worden als screeningsinstrument. Het belang van screenen op vermoeidheid was al duidelijk, maar het ontbrak aan het juiste instrument om dit goed te doen. De resultaten van dit proefschrift laten zien dat de VVV een uitstekende vragenlijst is om te screenen op ernstige vermoeidheid bij kinderkanker survivors.

In **Hoofdstuk 4** presenteerden we een model met factoren die vermoedelijk samenhangen met chronische vermoeidheid:

- *Triggers.* Dit zijn factoren die een rol spelen bij het tot stand komen van de vermoeidheid
- *In-stand-houdende factoren* spelen een rol bij het aanhouden van de klachten
- *Modererende factoren* beïnvloeden in welke mate iemand de vermoeidheidsklachten als ernstig en bepalend ervaart

Factoren die in eerdere studies werden gelinkt aan vermoeidheid, werden op basis van hun vermoedelijke relatie met vermoeidheid ingedeeld in één van deze categorieën. In **Hoofdstuk 5** werd dit model gebruikt als basis om de daadwerkelijke relaties tussen deze factoren en chronische vermoeidheid te bepalen. De resultaten van die analyses lieten zien dat met name leefstijl factoren (bijvoorbeeld ernstig overgewicht, lage fysieke activiteit en slaapproblemen) en psychosociale factoren (bijvoorbeeld angst- en depressieve klachten, weinig zelfvertrouwen en sociale contacten) gerelateerd zijn aan vermoeidheid. Dit is interessant aangezien deze factoren mogelijk beïnvloedbaar zijn, en daarmee zouden de vermoeidheidsklachten wellicht behandeld kunnen worden. Factoren die te maken hebben met de behandeling voor kanker op kinderleeftijd (type

diagnose of type behandeling bijvoorbeeld) lieten geen relatie zien met chronische vermoeidheid. Dit doet vermoeden dat niet een specifieke diagnose of behandeling het risico op vermoeidheidsklachten vergroot, maar dat vermoedelijk de algemene impact van het doormaken van een ernstige ziekte op kinderleeftijd een rol speelt bij het tot stand komen van de vermoeidheidsklachten.

In **Hoofdstuk 6** lieten we zien hoe de factoren die in hoofdstuk 5 aan vermoeidheid werden gekoppeld met elkaar samenhangen. Allereerst hebben we geschetst hoe deze factoren mogelijk gerelateerd zouden zijn aan elkaar en aan de vermoeidheidsklachten. Hierbij zijn de volgende opties onderzocht:

1. Er is een oorzaak-gevolg relatie. Dit betekent dat een stijging of daling van de ene factor, een stijging of daling van de andere factor tot gevolg heeft.
2. Er is een tweezijdige relatie. Dit betekent dat beide factoren elkaar beïnvloeden. Een stijging van de ene factor, betekent een stijging van de andere factor en andersom. Ook kan het zijn dat er een derde factor in het spel is die niet is gemeten, maar die beide gemeten factoren beïnvloedt waardoor het lijkt alsof er een relatie is tussen beiden.

Deze geschetste relaties zijn daarna getoetst met de daadwerkelijke data met behulp van een computer algoritme. De resultaten lieten zien dat het aannemelijk is dat pijnklachten en geslacht (meer vrouwen dan mannen rapporteren vermoeidheidsklachten) mogelijk vermoeidheid beïnvloeden en dat vermoeidheid zelf mogelijk de oorzaak is van een verminderde fysieke activiteit en gevoelens van hulpeloosheid. Vermoeidheid en depressie hebben mogelijk een tweezijdige relatie, waarbij het zowel aannemelijk is dat vermoeidheid depressieve gevoelens tot gevolg heeft, maar ook dat het ervaren van depressieve gevoelens vermoeidheid tot gevolg kan hebben. Voor de overige factoren (angstklachten, overgewicht, slaapproblemen, zelfvertrouwen en het sociaal functioneren) werd een dergelijke relatie wel verwacht, maar niet overtuigend teruggevonden.

In **Hoofdstuk 7** werd onderzocht of er subtypen van chronische vermoeidheid zijn bij kinderkanker survivors. Studies in andere patiëntengroepen doen vermoeden dat vermoeidheid meerdere aspecten heeft. Denk hierbij aan lichamelijke of mentale aspecten. Met behulp van de verschillende onderwerpen die uitgevraagd worden met de CIS (problemen met concentratie, motivatie en/of fysieke activiteit) werd onderzocht of subgroepen van vermoeide kinderkanker survivors anders scoren op deze onderwerpen. Uit de resultaten blijkt dat er drie groepen te onderscheiden zijn binnen de survivors met chronische vermoeidheid: Een groep heeft met

name problemen met lichamelijke activiteit (29%), een groep heeft met name concentratieproblemen (25%) en een groep heeft klachten op alle dimensies (46%). Deze laatste groep heeft, naast vermoeidheid, ook meerdere andere problemen zoals angstklachten, depressie, slaapproblemen en een verminderd zelfvertrouwen. Ook is deze groep lager opgeleid en scoren ze lager wat betreft sociaal functioneren vergeleken met de andere twee groepen. Dit doet vermoeden dat de problematiek bij deze groep complex is en deze survivors wellicht baat hebben bij een multidisciplinaire aanpak om deze problemen te verminderen. Het feit dat er verschillende groepen te onderscheiden zijn, kan betekenen dat elke groep een andere aanpak vergt wat betreft de vermoeidheidsklachten.

In **Hoofdstuk 8** zagen we dat survivors met chronische vermoeidheid een lagere kwaliteit van leven hadden vergeleken met survivors zonder chronische vermoeidheid. Verschillende aspecten werden meegenomen, waaronder 'algemene gezondheid', 'fysieke/sociale taken uitvoeren op werk' en 'cognitief functioneren'. Op basis van eerdere studies werd een dergelijke relatie tussen vermoeidheid en kwaliteit van leven verwacht, maar de resultaten lieten ook zien dat de relatie stand hield wanneer rekening gehouden werd met verschillen in andere factoren die de kwaliteit van leven beïnvloeden. Deze resultaten laten zien dat chronische vermoeidheid een negatieve invloed heeft op meerdere aspecten van kwaliteit van leven.

Conclusie

Met dit proefschrift laten we zien dat chronische vermoeidheid vaak voorkomt bij survivors van kinderkanker, en daarmee de kwaliteit van leven van vele survivors negatief beïnvloed. Het is daarom van belang om ernstige vermoeidheid tijdig op te merken zodat een passende behandeling geadviseerd kan worden. De VVV werd gepresenteerd als een screeningsinstrument dat gebruikt kan worden om snel en eenvoudig te bepalen of iemand ernstig vermoeid is of niet. Met behulp van de CIS kan eventueel vervolgonderzoek gedaan worden om de precieze aard van de klachten in kaart te brengen. Wanneer iemand chronische vermoeidheidsklachten heeft, is het belangrijk om de volgende factoren uit te vragen:

- Leefstijl factoren, zoals ernstig overgewicht, fysieke activiteit en slaapproblemen.
- Psychosociale factoren, zoals angst- en depressieve klachten, zelfvertrouwen en omvang en kwaliteit van sociale contacten.
- Pijnklachten.

Mogelijk spelen deze factoren een rol bij het in stand houden van de vermoeidheidsklachten en kan beïnvloeding van deze factoren leiden tot minder

moeheid. Bij het zoeken naar een passende behandeling, kunnen deze factoren uitkomst bieden. Mogelijk hebben verschillende subtypen vermoeidheid baat bij verschillende interventies. Er is echter meer onderzoek nodig om te bepalen welke behandelingen het best ingezet kunnen worden om vermoeidheidsklachten te verminderen bij survivors van kinderkanker.

Data management plan

Data collection

Data was already collected as part of the DCCSS LATER study. Participants for this study were included from the DCCSS LATER cohort (n=6165). This is a nationwide cohort of five-year CCS diagnosed with histologically confirmed malignancies or Langerhans cell histiocytosis before the age of 18 between January 1st 1963 and December 31st 2001 in the Netherlands. From this cohort, CCS living in the Netherlands who were alive on January 1, 2017, when the invitation process started, were invited to participate. Participants gave written informed consent (or their parents when aged < 16 years, n=3).

Survivors who participated in the study were asked to provide contact details of their siblings which were used to invite them to participate as control group. Siblings, who have not had cancer and who can read and speak Dutch, and who gave written informed consent, were approached to participate in the sibling control group.

During a clinic visit, which took place between 2017 and 2020, a broad range of data was collected, mostly through the use of questionnaires. But also some physical measurements were done, for example a blood, saliva and urine sample were collected, height and weight were measured, and muscle strength was measured using a hand dynamometer.

Questionnaires that were completed were the following:

- Checklist Individual Strength (+item about symptom duration)
- A questionnaire asking about the participant's demographic factors (sex, relationship status, employment status, educational level) and health status
- TAAQOL
- SF36
- Hospital Anxiety and Depression Scale (HADS)
- Rosenburg Self-esteem Scale (RSES)
- Pittsburg Sleep Quality Index (PSQI)
- Short Questionnaire to assess health-enhancing physical activity (SQUASH)
- Illness cognition questionnaire (ICQ)

Factors related to the cancer diagnosis and treatment during childhood were collected from medical files by data-managers using a uniform and standardized protocol.

For one of the studies of the thesis (short fatigue questionnaire: screening for severe fatigue), data of previous conducted studies was made available to us for analyses. We collaborated with Margreet Worm-Smeitink from Amsterdam University Medical centers, and Marlies Peters and Gijs Bleijenberg from the Radboudumc to receive a dataset containing data of fatigue scores of 10 chronic conditions and the general Dutch population. These data are considered their property and therefore data requests should be done in collaboration with them.

Data storage

Most data was collected using questionnaires. Some physical measurement were done during a clinic visit (blood, urine, saliva sample; height and weight; muscle strength).

Data was stored and managed in Utrecht by the LATER consortium and the data needed to answer our particular research question(s) was transferred to us. Data was stored in .sav format (SPSS).

Data was structured in SPSS files, using pseudonymized ID numbers (key to link pseudonyms to participants is held by the LATER consortium data managers department). Data cleaning and analyses were documented in SPSS syntaxes. Data files consist of raw data files that were stored in original form, plus files that also contain edited data. SPSS syntaxes were made to clean and analyze the data, these syntax files were the "work-files". Every time changes were made, a new version of the syntax was saved with the date of that day in the filename to ensure the most recent file to be used the next time again. Same accounts for the SPSS datafiles.

Documentation of the data

Documentation of data computing, data cleaning and data analyses were done in SPSS syntaxes, accompanied with a logbook in MS Word, explaining every step of the way.

Ethics

All participants gave written informed consent to participate in the study. Data were stored using a pseudonym, making sure outcomes cannot be tracked to a specific person. Transferring of data was done using the safe tool 'Surfdrive'. The study was carried out in accordance with the declaration of Helsinki, ensuring all ethical questions were taken care of.

A web-based central database architecture, the DCCSS LATER database, has been designed. The web-based architecture allows data entry from all participating centres and not only supports an efficient process of data entry but also provides validation

of data through a central software program. The web-based central database contains no personal identifiers. Data including a LATER identification number, diagnosis and cancer treatment of all CCS are stored in this central database. The local participating centres are holding the patient identifying data of the CCS.

The DCCSS LATER fatigue study was approved by the Medical Research Ethics Committee of the Amsterdam University Medical Centers (registered at toetsingonline.nl, NL34983.018.10).

Copyright and Intellectual Property Rights

Data is owned by the LATER study consortium. Data sharing is a topic currently assessed within the consortium. Multiple studies are done with the data, and therefore strict agreements were made on how to handle study specific data.

Access and security

Data is saved locally on a location known by the PhD student (Adriaan Penson). This location is only accessible by research employees of the expert center late effects after cancer. Sharing data with colleagues only happens using "Surfdrive", a safe and cloud-based service. Study specific data will be kept on the local server after study completion. DCCSS LATER study data will be stored and overlooked centrally by well-trained data-managers in Utrecht. Reusage of the data will be decided upon by the DCCSS LATER consortium. Long-term preservation of the data will be done centrally by well-trained data-managers in Utrecht (DCCSS LATER consortium). Data-sharing will be done centrally by the DCCSS LATER consortium. It is currently discussed how and when the data will become widely available/shared.

Responsible data manager

The DCCSS LATER consortium is responsible for the data management. Study specific data management is the responsibility of the PhD student (Adriaan Penson), e.g., data storage, data cleaning, data analyses, data archiving. Name of the data-manager responsible for the data at the DCCSS LATER consortium is Margriet van der Heiden-van der Loo

PhD portfolio

Department: Hematology
PhD period: **01/01/2020 – 31/03/2024**
PhD Supervisor(s): **Prof. dr. N.M.A. Blijlevens, Prof. dr. J.A. Knoop**
PhD Co-supervisor(s): **dr. J.J. Loonen, dr. I. Walraven**

Training activities	Hours
Courses	
RIHS - Introduction course for PhD candidates (2020)	15.00
RU - Statistics for PhD's by using SPSS (2020)	56.00
Radboudumc - eBROK course (for Radboudumc researchers working with human subjects) (2020)	26.00
RU - Scientific Writing for PhD candidates (2021)	84.00
Course Module MED-BMS17 hands on: GWAS (2022)	80.00
RU - Design and Illustration (2022)	28.00
Radboudumc - Scientific integrity (2022)	20.00
RU - Academic English Conversation and Pronunciation (2022)	42.00
Course module MED-BMS61 Statistical modelling in medical research (2022)	80.00
Course module MED-BMS16 Causal inference in observational research (2022)	80.00
RIHS PhD council workshop: prepare your defence (2022)	1.00
Radboudumc – Re-registration eBROK (2023)	5.00
Seminars	
Dutch Cancer Society fatigue meeting (oral presentation, 2020)	5.00
Amalia Children's Hospital research meeting (oral presentation, 2020)	5.00
Dutch Cancer Society fatigue meeting (organisation and oral presentation, 2021)	8.00
Research meetings LATER Princess Máxima Centre (oral presentation, 2021)	5.00
Dutch Cancer Society fatigue meeting (oral presentation, 2022)	5.00
Research meetings LATER Princess Máxima Centre (oral presentation, 2023)	5.00
Amalia Children's Hospital research meeting (oral presentation, 2023)	5.00
Conferences	
PanCare meeting, Utrecht (2021)	20.00
CaRe days (2021)	8.00
KiKa Tom Voûte Young investigator event (2021)	4.00
PhD retreat (oral presentation, 2022)	20.00
Care days (2022)	8.00
International Cancer Survivorship Symposium, Bern (oral presentation, 2022)	16.00
KiKa Tom Voûte Young investigator event (2022)	4.00
International Symposium on Late Complications after Childhood Cancer (ISLCCC), Utrecht (poster presentation, 2022)	20.00
International Society of Paediatric Oncology (SIOP) annual congress, Barcelona (two poster presentations, 2022)	26.00
International Symposium on Late Complications after Childhood Cancer (ISLCCC), Atlanta (poster presentation & pitch, 2023)	26.00
Symposium Leven na Kinderkanker, Utrecht (oral presentation & workshop, 2023)	16.00
PanCare meeting, Ghent (oral presentation, 2023)	26.00

Training activities	Hours
Other	
Workshops supervising students (2020)	6.00
Research integrity round: sex and gender and research integrity (2020)	2.00
Online webinar science & communication: social media for scientists (2020)	1.00
Research meetings LATER Princess Máxima Centre (2020)	12.00
Webinars Lifelines data catalogue and genetics (2021)	3.00
Workshop how to write a rebuttal (2021)	2.00
Workshop how to search for research grants (2021)	2.00
Webinar Planetree: Stepped care (2021)	2.00
Research meetings LATER Princess Máxima Centre (2021)	12.00
Research meetings expertisecentrum LATER (2021)	10.00
Workshop Person Centred Care expertisecentrum LATER (2022)	4.00
Research meetings LATER Princess Máxima Centre (2022)	12.00
Research meetings expertisecentrum LATER (2022)	10.00
Research meetings LATER Princess Máxima Centre (2023)	12.00
Teaching activities	
Lecturing	
Workshops 'working with MS Excel'	10.00
Supervision of internships / other	
Supervision bachelor students course 'research proposal'	40.00
Co-supervision master student biomedical sciences Princess Máxima Centre	15.00
Total	**902.00**

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Publications

Adriaan Penson, Sylvia van Deuren, Margreet Worm-Smeitink, et al. (2020) Short Fatigue Questionnaire: Screening for severe fatigue. *Journal of Psychosomatic Research*
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DOI: 10.1002/cncr.33993

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DOI: 10.1111/bjh.18031

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DOI: 10.3390/cancers14122851

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DOI: 10.1016/j.esmoop.2023.102044

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DOI: 10.1002/cncr.35119

Adriaan Penson, Iris Walraven, Ewald Bronkhorst et al. (2024) Different subtypes of chronic fatigue in childhood cancer survivors; A DCCSS LATER study. *Pediatric Blood & Cancer*
DOI: 10.1002/pbc.30951

Eline Bouwman, **Adriaan Penson**, Selina van den Oever et al. Unhealthy lifestyle behaviors, overweight, and obesity among childhood cancer survivors in the Netherlands; A DCCSS LATER study. *Cancer*
DOI: 10.1002/cncr.35338

Submitted papers

Adriaan Penson, Ioan Gabriel Bucur, Iris Walraven et al. Structural Equation Modeling to determine putative causal factors for chronic fatigue in childhood cancer survivors; a DCCSS LATER study. *Under review, Cancer Medicine*

Oral presentations

Impact of cancer-related fatigue on HRQOL in childhood cancer survivors. International Cancer survivorship symposium, Bern, February 2022, online

Cancer-related fatigue in childhood cancer survivors. RIHS PhD Retreat, Nijmegen, April 2022

Impact of cancer-related fatigue on HRQOL in childhood cancer survivors. KWF fatigue meeting, May 2022, online

Triggering, maintaining and moderating factors for cancer-related fatigue in childhood cancer survivors. Association for researchers in Psychology and Health congress, Enschede, March 2023

Leefstijl en vermoeidheid, de regie in eigen handen nemen. Symposium Leven na Kinderkanker, Utrecht, June, 2023

Associated factors for chronic fatigue in childhood cancer survivors. Pancare Meeting, Ghent, September 2023

Vermoeidheid na kinderkanker: onderzoek naar risicofactoren opent de weg naar behandeling. Afscheidssymposium Jacqueline Loonen, de Vereeniging Nijmegen, November 2023

Poster presentations

How to screen for severe fatigue? International Symposium in Late Effects after childhood cancer, Utrecht, July 2022

Chronic fatigue is associated with impaired Health-Related Quality of Life in Childhood Cancer Survivors. International Society of Pediatric Oncology annual congress, Barcelona, October 2022

Chronic Fatigue in Childhood Cancer Survivors, associated factors and plausible causality. International Symposium in Late Effects after childhood cancer, Atlanta (USA), June 2023

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Dit proefschrift had niet tot stand kunnen komen zonder de bijdrage en support van een heleboel mensen. Bij deze wil ik graag mijn dank tonen.

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Curriculum vitae

Adriaan Penson is geboren op 27 juni 1991 te Geleen. Het grootse gedeelte van zijn jeugd woont hij in Urmond, in de provincie Limburg. Nadat hij in 2010 zijn VWO diploma behaald heeft op de middelbare school (Trevianum te Sittard, een plek waar hij met veel plezier aan terugdenkt), verhuist hij naar Nijmegen om Fysiotherapie te gaan studeren aan de Hogeschool van Arnhem en Nijmegen. In het laatste jaar van deze vier jaar durende HBO opleiding merkt hij dat hij, in tegenstelling tot alle andere studenten in zijn jaar, het schrijven van de wetenschappelijke scriptie enorm leuk vindt om te doen. Dit zet hem aan het denken en doet hem uiteindelijk besluiten om de wetenschappelijke kant van het vak op te gaan in de vorm van een premaster biomedische wetenschappen aan de Radboud Universiteit van Nijmegen, gevolgd door een tweejarige master. Na kort als fysiotherapeut werkzaam te zijn geweest, besluit hij om na het afronden van zijn master het wetenschappelijk onderzoek in te gaan. Zo belandt hij in 2018 bij het Expertisecentrum Late Effecten na Kanker, oftewel de LATER poli, in het Radboudumc. Eerst in een functie als datamanager, waarbij zijn voorliefde voor cijfertjes en statistische analyses samenkomen. Naast het verwerken van proefpersoon data voor wetenschappelijke studies ondersteunt hij collega onderzoekers op de afdeling bij het doen van statistische analyses in SPSS (een computerprogramma waar menig onderzoeker de kriebels van krijgt, maar waar Adriaan's hart sneller van gaat kloppen). Als er in 2020 de mogelijkheid ontstaat om zelf een promotietraject te gaan doen, vallen alle puzzelstukjes op z'n plek. Ook al is er lichte twijfel in het begin, omdat de rol als datamanager hem zo goed past en er als promovendus toch meer van je verwacht wordt dan alleen maar mooie databestanden onderhouden en statistische analyses uitvoeren, zegt hij uiteindelijk volmondig 'JA!' tegen deze unieke kans. Hierop terugkijkend heeft hij daar geen seconde spijt van gehad en is hij enorm dankbaar voor die geboden kans, daar hij met ontzettend veel plezier en voldoening terugblikt op de afgelopen 4 jaar die dit mooie project hebben mogen zijn, met dit proefschrift als resultaat.

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