Loes van Erp

PSYCHOSOCIAL CHALLENGES OF CHILDHOOD CANCER SURVIVORSHIP

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Colofon
Psychosocial challenges of childhood cancer survivorship

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PSYCHOSOCIAL CHALLENGES OF CHILDHOOD CANCER SURVIVORSHIP

Psychosociale uitdagingen van het overleven van kinderkanker
(met een samenvatting in het Nederlands)

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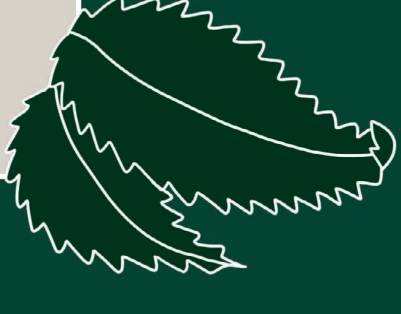

CHAPTER 1

GENERAL INTRODUCTION

Childhood cancer survivors (CCS) are a growing population in need of specialized care. Thanks to the advancement of childhood cancer treatments, average overall five-year survival rates have increased to approximately 80%[1]. Because of improved survival outcomes, there are currently more than 500.000 CCS in Europe[2,3] and an increasing number of them reaches adulthood. With this improvement of survival, comes a responsibility for researchers and clinicians to accumulate a solid base of evidence on the long-term outcomes of CCS' physical and mental health, to which this thesis aims to contribute.

A lot of research focuses on the physical health outcomes of CCS, including late effects that may occur years after treatment. Over the years, generic psychosocial outcomes and the incidence of psychopathology have gotten more attention. It is important to note that generic psychosocial outcomes and psychopathology outcomes do not paint a full picture of the functioning and experiences of CCS. Generic outcomes are broadly applicable to many populations, both healthy and diseased or disabled, and aim to describe general constructs of psychosocial functioning or psychopathology. Because every disease or disability comes with its own unique challenges, it is crucial to investigate illness-specific, and in this case survivor-specific, outcomes as well. Besides this, survivors' self-reported needs should be assessed in research, so that survivorship care can be improved to better meet these needs.

The introduction of this thesis provides a global overview of pediatric oncology and pediatric oncology care in The Netherlands, late effects of treatment on physical and mental health as well as Health-Related Quality of Life (HRQOL). Besides, current survivorship care, and the well-being of young adult childhood cancer survivors (YACCS) will be described, focusing on survivor-specific outcomes and psychosocial interventions in particular. Furthermore the aims of this thesis are outlined.

Diagnosis and treatment of childhood cancer

In the Netherlands, approximately 600 children (0-18 years old) are diagnosed with cancer each year[4]. Each of these childhood cancer diagnoses fall into one of more than 100 subtypes, making each disease a rare occurrence. Despite this rarity, and despite children making up only a small percentage of cancer diagnoses in the Netherlands each year, cancer remains the leading cause of death by disease in children[5].

Diagnosis

Cancer is the uncontrolled growth of abnormal cells anywhere in the body. There are many types of cancer, that can roughly be divided into three groups:

- Hematologic cancers are cancers that begin in the blood forming tissue or the immune system (e.g. leukemias and lymphomas)[6];
- Central nervous system (CNS) tumors mostly refer to tumors in the brain (e.g. medulloblastoma, craniopharyngioma)7;
- Solid tumors cover a wide range of malignancies of organs (e.g. Wilm's tumor in the kidney), bone and soft tissue (e.g. Ewing sarcoma or osteosarcoma)[8].

Hematologic cancers form the most common cancer diagnoses in children, accounting for about 45% of all diagnoses. Children are most commonly diagnosed with leukemia, and acute lymphoblastic leukemia (ALL) specifically accounts for about 20% of childhood cancer diagnoses [9,10]. This translates to approximately 110 children in the Netherlands each year[9,10].

CNS tumors, as a group, account for almost a third of childhood cancer diagnoses[4]. The most common type of CNS tumor is the pilocytic astrocytoma, a type of low grade glioma that occurs in 19-24% of children with a brain tumor[11].

Solid tumors account for 30-35% of childhood cancer diagnoses[12]. The most common solid tumor in children is neuroblastoma, which occurs mostly in the abdominal or chest cavity. In approximately half of all neuroblastoma cases, metastases are already present at first diagnosis, resulting in a poor prognosis[13].

The incidence of specific diagnoses varies across age groups. While ALL or various blastomas are more common in children under 8, Hodgkin's lymphoma and bone tumors are more common in older children and adolescents[12].

Treatment

Before 2018, children with cancer were treated in seven pediatric oncology centers in The Netherlands, housed within academic children's hospitals. Since 2018, all Dutch children with a suspected cancer are referred to the Princess Máxima Center for pediatric oncology in Utrecht. Pediatric oncologists in the Princess Máxima Center take the lead in treatments, but sometimes children can undergo relatively simple treatments (e.g. administering chemotherapy) in a shared care hospital closer to their home. The number of shared care hospitals is limited, to ensure that each center has sufficient expertise to care for children with cancer. Treatment of childhood cancer generally follows protocols, which are continually adapted and studied for optimization purposes. Often children are included in a study that aims to evaluate the effectiveness of a new or altered protocol.

Childhood cancer treatment consists of three main treatment modalities that can be combined: chemotherapy, radiotherapy, and surgery. Besides these three, allogeneic or autologous stem cell transplants can be applied. A relatively new development in pediatric oncology is the use of immunotherapy.

During treatment, children are subjected to medical procedures that can be stressful, painful, and fear inducing for them. Besides, some children have to spend a significant amount of time in the hospital. These experiences can cause medical traumatic stress, to which most are resilient but which can cause long term distress for some[14,15].

Furthermore, with all treatment modalities, there is a risk of acute side effects. Chemotherapy suppresses the bone marrow, which causes anemia, low platelet and leukocyte counts. Fatigue, bleeding propensity, and proneness to infection are the result of these changes. Chemotherapy can lead to nausea, hair loss, and damage to the mucus membranes (mucositis). Radiotherapy can cause fatigue, irritation of the skin and mucus membranes, local hair loss, and inflammation of the gastrointestinal system. Proton therapy, a relatively novel form of radiotherapy, can be used for children with cancer in The Netherlands since 2018. All proton therapy treatments are performed in the proton therapy center of the University Medical Center Groningen. Proton therapy is potentially less damaging to tissues, and therefore may lead to fewer late effects. For surgery, there is a risk of complications, such as bleeding or infections. And apart from these unforeseen side effects, surgery leaves a child with scars or permanent mutilations such as amputation. Besides acute side effects, toxic childhood cancer treatments can cause side effects that emerge months to years after treatment completion, also called late effects. These will be discussed at greater detail later.

Supportive and psychosocial care

Because childhood cancer treatment is so intensive, families of a child with cancer are offered supportive and psychosocial care in order to achieve and maintain optimal quality of life. Supportive care can help reduce pain or other discomforts, which can be caused by treatment or the disease itself. Psychosocial care aims to prevent and reduce distress, emotional problems, and developmental delay. Besides the child with cancer, psychosocial care can focus on parents or siblings in order to support the system around the child.

In the Princess Máxima Center, every family has access to a child life specialist, psychologist, social worker, and, during treatment, teachers (educational services), in accordance with the standards of care[16]. Child life specialists aim to stimulate children's development to prevent developmental delays as much as possible. To reach this goal, they use various techniques, such as psycho-education, distraction or exposure to prepare children for medical procedures or guide them through such procedures. Social workers provide support for parents, both emotionally and practically (e.g. financial, work, and relationship support). Psychologists diagnose and treat emotional or behavioral problems in children with cancer and, in some occasions, their parents.

As part of the standard of care, pediatric oncologists in the Princess Máxima Center are encouraged to monitor their patients' quality of life with the use of Patient Reported Outcome Measures (PROMS) via the online KLIK-PROM-portal[17]. With KLIK, children with cancer who are 8 years or older fill out questionnaires about their HRQOL every three months[18]. Under the age of 8 parents fill in questionnaires about their child. Besides this, all parents fill in questionnaires about themselves. The pediatric oncologist can use the portal as guidance to discuss certain potentially problematic domains of HRQOL or as an alert for psychosocial problems in need of referral to psychosocial care. The use of the KLIK PROM portal was shown to be beneficial as it resulted in increased discussion of patient outcomes, enhanced patient-clinician communication, higher patient satisfaction, and better HRQOL[19,20].

After diagnosis, the treatment phase can last up to two years or even more. After treatment completion, children receive follow-up care. The frequency of follow-up is based on the risk of late effects associated with the child's diagnosis and treatment. Follow-up care focusses on monitoring health after treatment. An important part of this monitoring is early detection of recidivism. The risk of recidivism varies widely between childhood cancer types. On top of that, psychosocial health is monitored using the KLIK PROM portal.

Survivorship care in the Netherlands

Survivorship care is aimed at surveillance for physical functioning and late effects and optimizing survivors' quality of life.

In the Netherlands, the first outpatient clinic for survivorship care started in 1995 at the Amsterdam Medical Center. In the period thereafter, each of the other six pediatric oncology centers in the Netherlands all organized their own survivorship care outpatient clinics. After centralizing pediatric oncology care to the Princess Máxima Center in Utrecht in 2018, most survivorship care was also centralized there, although some separate survivorship outpatient clinics remained.

Survivorship care in the Netherlands is offered to survivors life long. The surveillance offered is based on a survivor's risk for late effects, including second malignancies, which is described in the Dutch guideline for follow-up in survivors of childhood cancer[21]. The guideline specifies which diagnostic tests or screening procedures are indicated based on the treatment a survivor has had[21]. Recently, the survivorship care clinic in the Princess Máxima Center started using the KLIK-PROM portal to monitor the HRQOL of survivors between 18-30 years of age.

Consequences of childhood cancer survival

Generally, a patient who was treated for cancer is considered to have survived if they are still alive five years after their initial diagnosis. Overall survival of childhood cancers has risen considerably over the past decades. Nowadays, around 80% of children diagnosed with cancer survives for at least five years[1].

Unfortunately, due to the toxicity of treatment, surviving childhood cancer comes at the cost of late effects of childhood cancer treatment for many CCS. This puts them at an increased risk for (chronic) health problems at an earlier age compared to peers with no history of childhood cancer[22,23]. Besides physical late effects, and risk of second malignancies, survivors of childhood cancer face psychosocial challenges. Below, the physical outcomes and psychosocial outcomes (HRQOL and mental health) after childhood cancer will be discussed, as well as survivor-specific challenges and survivors' participation in society.

Consequences for physical health

Physical morbidity after childhood cancer is high. In a retrospective cohort study of Dutch survivors of childhood cancer with a median time after diagnosis of 17 years, 75% of survivors had at least one adverse event, and 40% of survivors had at least one severe or life-threathening or disabling adverse event[24]. A US cohort study showed survivors of childhood cancer to be at a substantially higher risk for poor health outcomes than siblings[22].

Late effects of childhood cancer treatment can affect a multitude of organ systems. The most frequently occurring medical late effects are second malignancies, cardiovascular disease, dysfunction of various organs, endocrine and metabolic disorders[22,24-27]. A Dutch study of burden of disease after childhood cancer showed that survivors are twice as likely to be hospitalized than reference groups, especially for endocrine conditions, new cancers, and symptoms without a diagnosis[28].

Health-Related Quality of Life

In addition to survival, attaining and maintaining optimal HRQOL is an important goal in pediatric oncology, both before and after treatment[29], and one of the core missions of the Princess Máxima Center.

Quality of Life (QOL) is a broad concept that incorporates all aspects of an individual's existence. The World Health Organization (WHO) defines Quality of Life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns[30]. HRQOL is a component of QOL relating only to the health domain[31]. It is generally accepted that the construct of HRQOL incorporates at least three broad domains: physical, psychological and social functioning. Physical functioning refers to activities of daily living, as well as to physical symptoms resulting from disease or treatment. Psychological functioning ranges from severe psychological distress to a positive sense of well-being, and it may encompass cognitive functioning. Social functioning refers to social relationships and interactions, and to societal integration. Beyond this core set of HRQOL domains, additional issues may be relevant for specific groups of patients, depending on the functional domains affected by the disease or treatment.

HRQOL of adult CCS has been investigated many times in multiple studies, using varying instruments[32]. Some studies find HRQOL of survivors to be comparable to that of the general population[33-36], while others studies suggest it to be worse compared to general population or siblings[26, 36-41]. In the latter case, differences are mostly found in physical HRQOL domains[38-42] and less often in mental HRQOL domains[38, 41]. Some studies even find that CCS' mental HRQOL is better than that of the general population[33, 43, 44].

Medical characteristics most commonly found to be related to poor HRQOL are a diagnosis at a very young age or in adolescence[50], longer time since diagnosis and the presence of late effects or another major medical condition[26, 39, 44-46]. CNS and bone tumor survivors, as well as those who received cranial irradiation, are clearly defined risk groups, especially for impaired physical HRQOL[26, 39, 43]. Apart from medical characteristics, sociodemographic factors, such as female sex, not having a partner, being unemployed, lower household income, and lower educational attainment, and coping are related to HRQOL of CCS[26, 44, 46, 73,74].

In order to improve survivorship care, understanding of HRQOL is crucial. Many studies in the Netherlands and the rest of Europe have added to the evidence base, but large nation-wide cohort studies from the Netherlands are still lacking.

Consequences for mental health

Generally speaking, survivors are resilient in face of the consequences of childhood cancer. Psychopathology is the exception rather than the rule. However, compared to the general population, survivors as a group can be at an increased risk of experiencing psychosocial difficulties (e.g., distress, symtoms of anxiety or depression, PTSD)[26, 47-49]. Most survivors seem to be doing well, but a subset is vulnerable[44, 50]. The most clearly identified risk groups with regard to mental health in pediatric oncology are survivors of CNS or bone tumors, female survivors, those diagnosed either at a very young age or during adolescence, and those treated with cranial radiotherapy[26, 39, 43, 46, 51].

Participation and inclusion in society

Late effects can make it difficult for CCS to participate in society. The literature shows that CCS may reach a lower educational attainment, and are less likely to be employed or married than peers without a history of childhood cancer[52-54]. Furthermore, CCS face discrimination when trying to obtain a mortgage or life or health insurance. The latter issue has gotten more attention in recent years, with cancer survivors moving the European Union to implement the ‘right to be forgotten’, in order to ensure equal treatment of survivors who wish to obtain mortgage or insurance[55]. Starting in 2021, legislation was implemented in the Netherlands to prevent life insurance and funeral insurance companies from asking about a prior cancer diagnosis when a person no longer has detectable cancer and has survived without remission for 10 years or 5 years, in the case of cancer diagnosed before the age of 21[56].

Survivor-specific challenges

The previously described outcomes are mostly based on research with generic psychosocial measurements, which has gained the attention of researchers over the past decade. In order to better understand survivors’ experiences, investigation of survivor-specific outcomes, such as the perceived impact of cancer or survivors’ coping with late effects is crucial. The sparse literature on these outcomes shows that perceived impact of cancer is related to quality of life[57]. This is in line with other findings and theories, for example the relationship between perceived health and psychosocial outcomes in adolescent and young adult CCS[58], as well as the integrative model of pediatric medical traumatic stress, proposing that subjective experience of stress is the most indicative of eventual problems[15].

As most previous studies have used generic measurements, it is of great importance for future studies to take survival specific psychosocial factors, such as the impact of cancer which can be
measured using the Impact of Cancer – Childhood Survivors questionnaire, into account to get a broad perspective on CCS functioning.

A developmental view of childhood cancer survivorship: focus on young adults

The experience of childhood cancer survivorship and the support needs of survivors can evolve and vary when survivors age and develop. With more and more survivors reaching adulthood, we need scientific insight into the experiences and challenges of childhood cancer survivorship after childhood and throughout the lifespan. Hence it is important to research CCS at all life stages, including YACCS as a distinct age group.

During young adulthood, defined in this thesis as the period from the age of 18 to 30, people are faced with many developmental challenges that are aimed at connecting the period between childhood and adolescence to adulthood, in the first place by developing identity and establishing independence[59]. YACCS’ relationship with their parents, HCPs (health care providers) and other adults may be more dependent because of cancer, treatment, or late-effects. This can have potential delaying or disruptive effects on YACCS’ autonomy development. Parents of a child who is or was ill during childhood may experience more challenges in the process of allowing their children to become independent. A portion of children has lasting disabilities, making it more difficult for both the child and the parents to develop independence. Furthermore, childhood cancer, its treatment, and late effects often decrease participation in peer-based and school-based activities[60, 61]. Cognitive problems resulting from treatment, and non-attendance at school can result in lower educational achievement[62-64]. Previous research from the Netherlands showed that Dutch YACCS reach fewer milestones than their peers, especially in the domains of autonomy and psycho-sexual development, and that this may influence their quality of life[65, 66].

While YACCS are often included in psychosocial survivorship research, they are generally not studied as a separate age group with outcomes that are specifically relevant in young adulthood. YACCS, however, may have needs that are different from their peers without a history of childhood cancer but also from other cancer survivors, such as those who were first diagnosed with cancer in adolescence or young adulthood (AYAs). For YACCS, the potential disruption to their development takes place earlier in their life than for AYAs. At the young adult age, when AYAs are in the acute phase of the disease, YACCS have mostly finished their treatment and may already be dealing with (chronic) late effects.

Survivor-specific outcomes may help us to understand the distinctness and needs of YACCS, as YACCS themselves reported generic measurements to be missing content that is particularly relevant to them[67]. Topics described as especially relevant by YACCS include, but are not limited to: identity formation, faster maturation, survivor guilt, overprotective parents, worry about fertility, and relationships[67, 68].

The current standards of care recommend screening and psychosocial care for survivors[69]. Because YACCS are faced with unique challenges, their needs may differ from those of peers without a history of childhood cancer and both younger and older CCS. Little is known about YACCS' support needs during survivorship care, and psychosocial interventions for YACCS' are lacking. Both are important if we want to further improve survivorship care in the years to come.

Psychosocial interventions

There are few existing interventions in psychosocial pediatric oncology. Described below are examples of interventions that target younger CCS, or survivors of cancer during adolescence or young adulthood (AYA).

An example of an intervention for cancer survivors is Recapture Life AYA, a video conferencing intervention that is based on Cognitive Behavior Therapy (CBT). The recent evaluation of Recapture Life in a multicenter randomized controlled trial (RCT) showed that those who received the intervention reported using more CBT skills at the six-week follow-up[70]. While quality of life did not improve at the 12-monht follow-up, and perceived negative impact of cancer, anxiety, and depression had increased (but still remained in the normal range), the RCT showed that AYAs closer to the end of their treatment experienced the greatest benefit from peer-support while AYAs who were treated longer ago experienced better results with Recapture Life[70].

For younger CCS in the Netherlands, an existing evidence-based group intervention called 'Op Koers Oncologie' is already available. Op Koers Oncologie is an adapted version of the original 'Op Koers' course which was developed for children with chronic illnesses[71]. Op Koers was evaluated in a study, showing that participants significantly improved their disease-related skills[71]. The intervention includes psycho-education and basic principles from CBT, relaxation and social competence training[72]. This intervention could potentially be appropriate for YACCS.

Survivorship research in the Netherlands

Over the past years, through the collaboration of researchers from many different disciplines in pediatric oncology, a large registry of diagnosis, treatment, and late-effects data of Dutch CCS was established and a nation-wide cohort study of late-effects after childhood cancer treatment was conducted: the Dutch Childhood Cancer Survivor LATER Study (DCCSS LATER study).

The cohort under investigation of the DCCSS LATER study includes all Dutch CCS diagnosed with cancer in the period between 1963 and 2001 in one of the seven pediatric oncology centers, before the age of 18 years, and who survived at least 5 years after their diagnosis. This resulted in a cohort of 6165 survivors, from whom data on the diagnosis and treatment of their primary cancer and all recurrences was collected from medical files. After establishing this database, the LATER registry, the DCCSS LATER-study was conducted in two separate parts.

DCCSS LATER part 1

The DCCSS study part 1 (2010-2017) aimed to create an overview of the health and well-being of survivors in the DCCSS LATER cohort. Survivors filled out questionnaires about their sociodemographic characteristics, physical health, risk behaviors, burden of disease, and a few psychosocial outcomes. No results from this study are described in this thesis.

DCCSS LATER part 2

In the DCCS LATER study part 2 (2014-2020), survivors from the DCCSS LATER cohort were invited to visit the late effects outpatient clinic for physical examination and further, more specific, examinations to determine the presence of late effects. A multitude of late effects was investigated, all in separate sub studies. Survivors were invited to participate in the sub studies that were most relevant to their diagnosis and treatment history based on the literature. Besides the visit to the outpatient clinic, survivors filled out questionnaires on a multitude of topics, including their psychosocial well-being in the DCCSS LATER 2 Psycho-oncology study. The DCCSS LATER 2 Psycho-oncology study included various generic and survivor-specific psychosocial outcomes; HRQOL as assessed with the TNO-AZL Questionnaire for Adult Health-Related Quality of Life (TAAQOL), and the psychosocial developmental trajectory as assessed with the Course of Life Questionnaire (CoLQ), described in this thesis.

Other research projects

Not all survivorship research in the Netherlands is a part of the DCCSS LATER study, but the diagnosis and treatment data from the LATER registry are widely used in survivorship research, because of the high fidelity of the available data.

Separate projects that were conducted in recent years and included in this thesis are the SF-36 project and the YACCS project, which are further described in the outline of the thesis. Figure 2 gives an overview of (psychosocial) survivorship research conducted in the Netherlands in recent years, as well as research projects that are ongoing. The projects presented in gray were not included in this thesis.

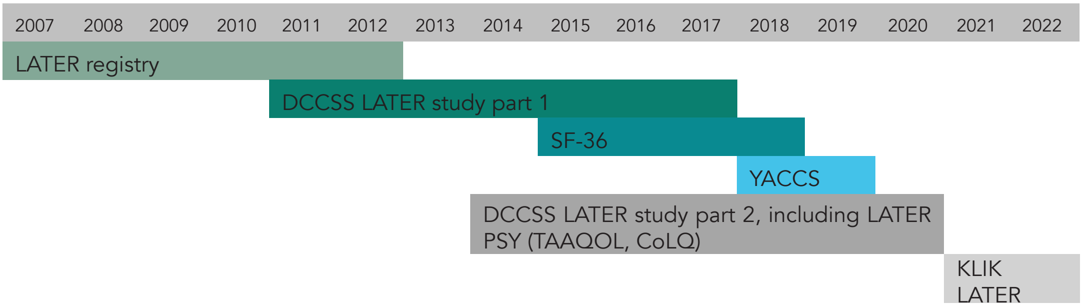

Figure 2. Overview of survivorship research in the DCCSS LATER cohort and the YACCS project (2007-2022).

Outline of this thesis

The work described in this thesis was aimed at increasing the understanding of psychosocial challenges of childhood cancer survivorship. Specifically, the research described in this thesis focuses on HRQOL of adult survivors of childhood cancer in part I and focusses on psychosocial challenges of young adult survivors in part II.

Part I: Health-Related Quality of Life of adult survivors of childhood cancer

The first part of this thesis aims to provide an overview of HRQOL in Dutch adult CCS (see table 1). It describes two nation-wide cohort studies, the SF-36 project and the TAAQOL project from the DCCSS LATER study part 2. Nation-wide cohort studies can help us understand the HRQOL of CCS as a group, while the large numbers allow us to identify potential risk factors for poor HRQOL. In both studies, we made use of a large number of detailed diagnosis and treatment characteristics from the LATER registry.

The main difference between the two cohort studies lies in the measurements used; the SF-36 in Chapter 2 and the TAAQOL in Chapter 3. The Short Form-36 (SF-36) is a well-known and internationally widely used measurement of both the physical and mental components of HRQOL. Like most HRQOL measurements, the TAAQOL aims to measure the level of impairment experienced by an individual. The unique attribute of the TAAQOL is that besides impairment, it asks responders to quantify the burden they experience because of the impairments. This allows us to paint a more complete picture of how an individual experiences their HRQOL.

	Aims	Sample characteristics	Outcome measures
Part I: Health-Related Quality of Life of adult survivors of childhood cancer			
Chapter 2	To investigate the HRQOL of adult CCS and to identify risk factors of impaired HRQOL.	2301 adult CCS, all diagnoses, aged ≥18, diagnosed <18, diagnosed between 1963-2001, ≥ 5 years since diagnosis	HRQOL: SF-36
Chapter 3	To compare HRQoL of adult male and female CCS to the general population and study medical determinants.	1766 adult CCS, all diagnoses, aged ≥18, diagnosed <18, diagnosed between 1963-2001, ≥ 5 years since diagnosis	HRQOL: TAAQOL

Table 1. The aims of part I of this thesis

Part II: Age-specific psychosocial challenges of young adult childhood cancer survivors

The second part of this thesis starts with describing the urgent need for research into YACCS as a distinct group, separately from both older and younger CCS, but especially, separately from young adult survivors who were diagnosed with cancer during adolescence or young adulthood (AYACS) (Chapter 4).

YACCS are potentially a vulnerable subgroup of CCS because of the combination of normal developmental tasks in young adulthood and the experience of childhood cancer survivorship. Survivors may have missed milestones in their psychosocial development both during and after childhood cancer. Chapter 5 presents the achievement of psychosocial developmental milestones while growing up with a history of cancer in young adults of the DCCSS LATER cohort.

Even though attention for generic psychosocial outcomes has increased, the literature about survivor-specific outcomes, outcomes directly related to childhood cancer and survivorship experiences, is sparse. Besides, we know little about what survivors want or need in terms of support during survivorship care. Especially quantitative research on this topic is limited. Furthermore, there are no interventions that were designed specifically for YACCS. For this reason, the YACCS-project is a trifold study that focussed specifically on the well-being (Chapter 6) and needs of YACCS (Chapter 7) as well as Op Koers Online for YACCS (Chapter 8) as a potential intervention for YACCS. For an overview of the aims, see table 2.

	Aims	Sample characteristics	Outcome measures
Part II Age-specific psychosocial challenges of young adult childhood cancer survivors			
Chapter 4	To explore and describe differences between the cancer and survivorship experiences of YACCS and AYACS.	NA	NA
Chapter 5	To compare the psychosocial developmental trajectory of YACCS with young adults from the general population.	558 YACCS, all diagnoses, aged 18-30, diagnosed <18, diagnosed between 1963-2001, ≥ 5 years since diagnosis	Psychosocial developmental milestones: CoLQ
Chapter 6	To increase our understanding of the psychosocial well-being of YACCS as well as the positive and negative impacts of cancer	151 YACCS, all diagnoses, aged 18-30, diagnosed ≤18, ≥ 5 years since diagnosis	Impact of cancer: IOC-CS HRQOL: PedsQL 4.0 YA Depression and anxiety: HADS Fatigue: CIS-20R
Chapter 7	To assess support needs and its determinants (sociodemographic, medical and psychosocial functioning) in YACCS	151 YACCS, all diagnoses, aged 18-30, diagnosed ≤18, ≥ 5 years since diagnosis	Need for support questionnaire HRQOL: PedsQL 4.0 YA Depression and anxiety: HADS Fatigue: CIS-20R
Chapter 8	To examine feasibility and preliminary effectiveness of an online group intervention Op Koers Online for YACCS.	10 YACCS, all diagnoses, aged 18-30, diagnosed ≤18, ≥ 5 years since diagnosis	Distress: Distress Thermometer Sense of control/Self-efficacy: Mastery Scale Illness cognitions: ICQ Impact of cancer: IOC-CS HRQOL: PedsQL 4.0 YA

Table 2. The aims of part II of this thesis

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PART I

HEALTH-RELATED QUALITY OF LIFE OF ADULT SURVIVORS OF CHILDHOOD CANCER

2

CHAPTER 2

HEALTH-RELATED QUALITY OF LIFE IN DUTCH ADULT SURVIVORS OF CHILDHOOD CANCER: A NATION-WIDE COHORT STUDY

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Highlights

- The first nationwide cohort study of health-related quality of life (HRQOL) in Dutch adult childhood cancer survivors (CCS) (N = 2301).
- Dutch adult CCS reports worse HRQOL than the general population.
- Cancer-related risk factors are associated with impaired physical, not mental HRQOL
- Risk factors for impaired physical/mental HRQOL are low education and having no partner.

Abstract

Aim

To investigate the Health-Related Quality of Life (HRQOL) of Dutch adult childhood cancer survivors (CCS) and to identify risk factors of impaired HRQOL.

Methods

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

Results

Both male and female CCS (N=2301, mean age=35.4 years, 49.6% female) reported significantly ($p \leq .005$) worse HRQOL than the general population on almost all scales of the SF-36 ($-.11 \leq d \leq -.56$). Largest differences were found on vitality and general health perceptions. Significant risk factors ($p \leq .05$) for impaired physical HRQOL were: female sex, older age at diagnosis, not having a partner, low educational attainment, disease recurrence, exposure to radiotherapy, specifically to lower extremity radiation. Odds ratios (ORs) ranged from 1.6 to 3.7. Significant risk factors for impaired mental HRQOL were: age 26-35 years, male sex, not having a partner and low educational attainment. ORs ranged from 1.3 to 2.0.

Conclusion

Adult CCS had worse HRQOL than the general population. CCS most at risk were those with low educational attainment and without a partner. Adult CCS could benefit from routine surveillance of their HRQOL. Special attention for CCS’ vitality and health perceptions and beliefs is warranted.

Introduction

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

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

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

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

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

Methods

Design and population

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

questionnaire by mail from the hospital that provided them with survivorship care. A few weeks after the initial invitation, non-responders were sent a reminder.
This study was approved by the Medical Ethical Committee of the Amsterdam University Medical Center/location VUmc (2011.405).

Measures

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

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

Cancer-related characteristics

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

Sociodemographic characteristics

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

Statistical analyses

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

Mean SF-36 scale scores of CCS were compared to those of the Dutch general population[24], for men and women separately weighted by age group. Within sex, age-group-specific weight factors were assigned to the scale scores of the general population. The weight factors were based on the distribution (proportion) of age-

groups in the CCS. A Bonferroni correction was applied for the number of comparisons per sex group (α=.05/10=.005).

Impaired HRQOL was defined for PCS and MCS as a score below 2 standard deviations from the age and sex appropriate score in the general population. Multivariate logistic regression analysis was used to identify sociodemographic (age, sex, having a partner, educational attainment, born in or outside of the Netherlands) and cancer-related risk factors (age at diagnosis; diagnosis; disease recurrence; treatment with various groups of chemotherapy, radiotherapy, and/or surgery; treatment with BMT/SCT and locations of radiotherapy exposure) for impaired PCS or MCS.

Characteristics that were significant in univariate analyses at α≤.1 were selected for multivariate logistic regression models predicting PCS and MCS. Because of dependencies between cancer-related characteristics, separate models were constructed for 1) sociodemographic characteristics and diagnosis, 2) sociodemographic characteristics and basic treatment, 3) sociodemographic characteristics and BMT/SCT treatment and 4) sociodemographic characteristics and treatment details. Age and sex were included in every model.

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

Results

Sample

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

HRQOL of CCS versus the general population

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

Association of sociodemographic and cancer-related characteristics with impaired HRQOL

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

In all four multivariate models predicting impaired PCS (Table 3), female CCS (OR=1.8, *p*≤.001) and those diagnosed at an older age compared to 0-5 years (6-11:1.8≤OR≤1.9,

$p \leq .001$; 12-17:1.6≤OR≤1.7, $.014 \leq p \leq .028$) were at a significantly higher risk of impaired PCS. Furthermore, CCS with a partner (OR=.6, $.001 \leq p \leq .003$) and those with a middle or high educational attainment compared to low educational attainment (OR=.5, $.001 \leq p \leq .002$ and OR=.3, $p \leq .001$ respectively,) were significantly less likely to report impaired PCS.

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

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

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

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

Discussion

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

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

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

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

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

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

Strengths & limitations

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

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

Finally, CCS in the study were diagnosed before 2002. While the frequency and intensity in which certain treatments are used may have changed to improve survival and reduce late-effects since then, we can assume that currently identified risk factors are also relevant for children treated with cancer in more recent time periods.

Clinical implications

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

Conclusion

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

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

	Responders		Non-responders			
	(N=2301)		(N=2214)[a]			
	Mean ± SD (range)	% (N)	Mean ± SD (range)	% (N)	T / χ^2	ES[b]
Socio-demographic						
Age (years)	35.4 ± 9.6 (18.3-69.0)				c	
18-25		19.2 (441)				
26-35		36.1 (830)				
36-45		29.3 (675)				
46-55		13.4 (309)				
55-65		1.8 (41)				
66-75		.2 (5)				
Sex (female)		49.6 (1142)		38.7 (856)	55.0	.11
Partner status						
No partner		34.0 (744)				
Partner		66.0 (1445)				
Educational attainment[d]						
Low		10.6 (232)				
Middle		51.2 (1119)				
High		38.2 (836)				
Born outside of The Netherlands		1.9 (33)			c	
Medical characteristics						
Age at diagnosis (years)	7.0 ± 4.8 (0-17.9)		6.6 ± 4.6 (0-17.9)**			.08
0-5		50.5 (1163)				
06-11		28.9 (666)				
12-17		20.5 (472)				
Time since diagnosis (years)	28.4 ± 8.7 (15.3-54.3)				c	
05-10		0.0 (0)				
11-15		2.0 (46)				
16-20		23.1 (530)				
20-25		20.1 (461)				
26-30		17.7 (407)				
31-35		14.7 (338)				
35-55		22.3 (512)				
Recurrence (yes)		13.3 (305)				
Diagnosis						
Leukaemias		35.1 (808)		34.0 (752)	.6	.01
Lymphomas		17.6 (404)		19.2 (425)	2.1	.02
CNS tumours		11.4 (262)		12.9 (285)	2.4	.02
Neuroblastoma		5.3 (122)		5.0 (110)	.2	.01
Retinoblastoma		.4 (10)		.7 (16)	1.7	.02
Renal tumours		10.6 (243)		10.5 (232)	≤.1	≤.01
Hepatic tumours		.7 (16)		.9 (20)	.6	.01
Bone tumours		6.0 (139)		4.7 (104)	3.9	.03

Soft tissue sarcomas	7.6 (174)	6.6 (145)	1.7	.02
Germ cell tumours	3.9 (89)	3.7 (82)	.1	≤.01
Epithelial neoplasms & melanomas	1.3 (31)	1.7 (37)	.8	.01
Other malignant neoplasms	.1 (3)	.0 (1)	.9	.01
Treatment for primary and recurrences				
Surgery (S) only	8.4 (193)	12.9 (284)	23.8***	.07
Radiotherapy (RT) only	.4 (10)	.3 (7)	.4	.01
Chemotherapy (CT) only	20.9 (481)	23.2 (512)	3.4	.03
S + RT	6.7 (155)	6.1 (134)	.8	.01
S + CT	31.2 (717)	31.0 (685)	.01	≤.01
RT + CT	12.1 (278)	9.9 (219)	5.4*	.04
S + RT + CT	20.1 (463)	15.8 (348)	14.6***	.06
No S, RT, or CT	.2 (4)	.9 (20)	11.4**	.05
BMT/SCT	5.7 (132)	5.3 (118)	.3	.01
Radiotherapy regions				
Cranio-spinal	21.0 (481)	17.6 (388)	8.1**	.04
TBI	3.4 (78)	2.9 (65)	.7	.01
Thorax	6.3 (144)	4.9 (107)	4.3*	.03
Abdominal pelvic area	7.8 (180)	6.3 (139)	4.0*	.03
Testes	.3 (8)	.4 (9)	.1	.01
Neck	3.8 (87)	3.3 (72)	.9	.01
Upper extremities	.7 (16)	.8 (17)	.1	≤.01
Lower extremities	1.3 (31)	1.0 (22)	1.2	.02
Unknown location	.3 (8)	.2 (4)	1.2	.02
Radioisotopes	.8 (19)	.6 (13)	.9	.01
Chemotherapy medications				
Alkylating agents	52.9 (1218)	47.6 (1051)	13.1***	.05
Anthracyclines	45.9 (1057)	43.9 (970)	1.9	.02
Epipodophyllotoxin	19.1 (439)	19.2 (423)	≤.1	≤.01
Vinca alkaloids	75.1 (1728)	71.6 (1581)	7.2**	.04
Platinum compounds	11.6 (266)	11.6 (257)	≤.1	≤.01
Antimetabolites	48.1 (1106)	47.1 (1040)	.4	.01
Asparaginase	30.7 (706)	31.2 (688)	.1	≤.01

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

** significant at α=.05*

*** significant at α=.01*

**** significant at α=.001*

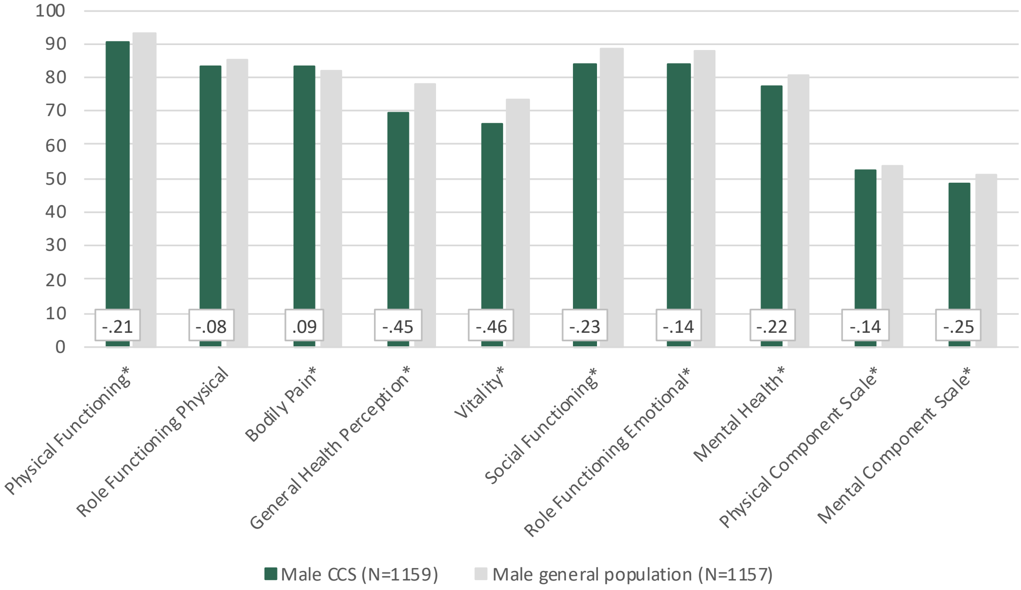
a Non-responders: those who were invited to participate but did not return a questionnaire (N=2214). N slightly varies across variables.

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

c Data was available for too few non-responders to allow a comparison.

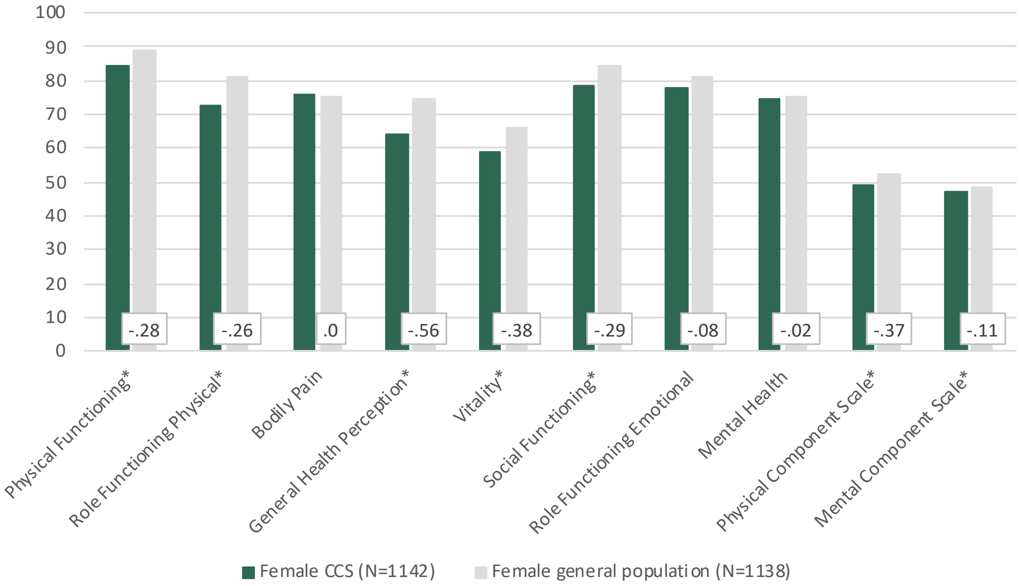
d low = primary education, lower vocational education, lower and middle general secondary education;
middle = middle vocational education, higher general secondary education, pre-university education;
high = higher vocational education, university

Fig. 1.A. Health-related quality of life (HRQOL) of male childhood cancer survivors (CCS) versus male general population, including effect sizes (Cohen's d)



* significant at α .005 (.05/10)

Fig. 1.B Health-related quality of life (HRQOL) of female childhood cancer survivors (CCS) versus female general population, including effect sizes (Cohen's d)



* significant at α .005 (.05/10)

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

	Impaired PCS		Impaired MCS	
	OR	90% CI	OR	90% CI
Sociodemographic				
Age (years, ref = 18-25)				
26-35	1.4*	[1.0;2.0]	1.1	n.s.
36-45	1.0	n.s.	.7	n.s.
46-55	0.7	n.s.	.9	n.s.
55-75	1.0	n.s.	.7	n.s.
Sex (ref = male)	1.5***	[1.2;1.9]	.6***	.003
Partner	.6***	[.4;.7]	.6***	[.4;.7]
Education (ref = low)[a]				
Middle	.5***	[.4;.7]	-	n.s.
High	.3***	[.2;.5]	.4***	[.7;1.5]
Born outside of The Netherlands	-	n.s.	-	n.s.
Medical characteristics				
Age at diagnosis (years)	1.0*	[1.0;1.0]	-	n.s.
Time since diagnosis (years)	1.0**	[1.0;1.0]	-	n.s.
Recurrence (yes)	1.7***	[1.3;2.3]	-	n.s.
Diagnosis				
Leukemia	-	n.s.	-	n.s.
Lymphoma	.6**	[.4;.9]	-	n.s.
CNS tumor	1.8***	[1.3;2.5]	-	n.s.
Neuroblastoma	-	n.s.	-	n.s.
Retinoblastoma	-	n.s.	4.1**	[1.3;12.9]
Renal tumor	.5**	[.3;.8]	.7*	.110
Hepatic tumor	-	n.s.	-	n.s.
Bone tumor	-	n.s.	-	n.s.
Soft tissue sarcoma	-	n.s.	-	n.s.
Germ cell tumor	-	n.s.	-	n.s.
Other tumor	-	n.s.	-	n.s.
Unspecified tumor	-	n.s.	-	n.s.
Treatment				
Surgery	-	n.s.	-	n.s.
Radiotherapy	1.8***	[1.4;2.2]	-	n.s.
Cranio-spinal	1.6***	[1.2;2.0]	-	n.s.
TBI	2.0**	[1.2;3.3]	-	n.s.
Thorax	-	n.s.	-	n.s.
Pelvic area	-	n.s.	-	n.s.
Testes	-	n.s.	-	n.s.
Neck	-	n.s.	-	n.s.
Upper extremities	-	n.s.	-	n.s.
Lower extremities	2.7**	[1.3;5.6]	-	n.s.
Radioisotopes	2.4*	[.9;6.0]	-	n.s.
Chemotherapy	.8*	[.6;1.0]	-	n.s.
Alkylating agents	-	n.s.	-	n.s.
Anthracyclines	-	n.s.	-	n.s.
Epipodophyllotoxin	-	n.s.	-	n.s.
Vinca alkaloids	.7**	[.6;.9]	-	n.s.
Platinum compounds	1.7***	[1.3;2.3]	1.4*	[1.0;2.0]
Antimetabolites	-	n.s.	-	n.s.

Asparaginase	.8	[.6;1.0]	-	n.s.
BMT/SCT	1.8**	[1.1;2.6]	-	n.s.

HRQOL, health-related quality of life; PCS, physical component score; MCS, mental component score; OR, odds ratio; CI, confidence interval; n.s., not significant; CNS, central nervous system; BMT, bone marrow transplantation; SCT, stem cell transplantation; TBI, total body irradiation.
* significant at α=.10, **significant at α=.05, *** significant at α=.01
[a] low = primary education, lower vocational education, lower and middle general secondary education; middle = middle vocational education, higher general secondary education, pre-university education; high = higher vocational education, university

Table 3: Multivariate logistic regression analyses explaining impaired physical HRQOL (PCS) by sociodemographic and medical characteristics (N=2154)^{a}

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

Radioisotopes[b]	1.5	[.4;5.5]
Chemotherapy[b]		
Vinca alkaloids[b]	.9	[.6;1.2]
Platinum compounds[b]	1.2	[.8;1.8]
Asparaginase[a]	.9	[.6;1.3]

HRQOL, health-related quality of life; PCS, physical component score; OR, odds ratio; CI, confidence interval; BMT, bone marrow transplantation; SCT, stem cell transplantation; CNS, central nervous system; TBI, total body irradiation.

* significant at α=.05, **significant at α=.01, *** significant at α=.001

[a] Separate models for diagnosis, basic treatment, BSC/SCT, and specific treatment are shown.

[b] ref = no

[c] low = primary education, lower vocational education, lower and middle general secondary education; middle = middle vocational education, higher general secondary education, pre-university education; high = higher vocational education, university

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

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

HRQOL, health-related quality of life; MCS, physical component score; OR, odds ratio; CI, confidence interval.

* significant at α=.05, **significant at α=.01, *** significant at α=.001

[a] Separate models for diagnosis and specific treatment are shown.

[b] ref = no

[c] low = primary education, lower vocational education, lower and middle general secondary education;

middle = middle vocational education, higher general secondary education, pre-university education;

high = higher vocational education, university

3

CHAPTER 3:

INCREASED HEALTH-RELATED QUALITY OF LIFE IMPAIRMENTS OF MALE AND FEMALE SURVIVORS OF CHILDHOOD CANCER: DCCSS-LATER 2 PSYCHO-ONCOLOGY STUDY

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Abstract

Background

The objective of this study was to compare the health-related quality of life (HRQOL) of Dutch adult male and female childhood cancer survivors (CCSs) to general population references and to study medical determinants.

Methods

CCSs from the Dutch Childhood Cancer Survivor Study LATER cohort (1963-2001) part 2, who were 18 years old or older (time since diagnosis ≥ 5 years), were invited to complete the TNO-AZL Questionnaire for Adult Health-Related Quality of Life. Domain scores and proportions of CCSs with impaired HRQOL (score < 25th percentile of the reference scores) were compared with references via Mann-Whitney U tests and logistic regression analyses corrected for age and sex ($P < .004$). Interactions of group with sex were included if they were significant ($P < .05$). Moreover, medical determinants were analyzed with multivariable logistic regression analyses.

Results

HRQOL scores for 1766 CCSs (mean age, 35.9 years [standard deviation, 9.4 years]; male, 51%; response rate, 71%) differed from references on most domains with small effect sizes. Both male and female CCSs were more often impaired in gross and fine motor functioning, cognitive functioning, sleep, and vitality with odds ratios (ORs) > 1.4. In addition, female CCSs were more often impaired in daily activities, pain, and sexuality (ORs, 1.4-1.9) and were less often aggressive (OR, 0.6). CCCs of central nervous system (CNS) tumors, bone tumors, and retinoblastoma and those with cranial, abdominopelvic, or lower extremity radiotherapy were at increased risk of impairment in 1 or more domains.

Conclusions

Dutch adult CCSs, especially females, have impaired HRQOL in several domains; this is most pronounced in cognitive functioning. The vulnerabilities of subgroups at risk, such as CCSs of CNS tumors, were confirmed. Surveillance of HRQOL and multidisciplinary survivor care are recommended.

Lay Summary

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

Introduction

With improved survival for patients with childhood cancer, the number of childhood cancer survivors (CCSs) has increased. Long-term CCSs often experience long-term health problems[1] and sometimes impaired psychosocial well-being.[2] Optimal health-related quality of life (HRQOL) is considered a main treatment outcome in pediatric oncology in addition to survival.[3] Individuals' subjective experience of their health problems and limitations in functioning represents an important aspect of HRQOL. Although most self-reported HRQOL measurements inherently rely on subjective experiences, previous population-based studies have used HRQOL instruments that lack specific questioning of this aspect or that describe the health status of CCSs instead.[4-7] Comprehensive insight into the HRQOL of CCSs is thus lacking in the current literature, and this is relevant to study to determine the long-term impact of childhood cancer.

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

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

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

Material and methods

Study design

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

Participants

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

Measures

TNO-AZL Questionnaire for Adult's HRQoL

HRQOL was assessed with the TNO-AZL Questionnaire for Adult Health-Related Quality of Life (TAAQOL), which was developed by TNO and Leiden University Medical Center (AZL).[12] The 45 items of the TAAQOL measure health status problems weighted by their impact on well-being in 12 multi-item domains: gross motor functioning, fine motor functioning, cognitive functioning, sleep, pain, social functioning, daily activities, sexuality, vitality, positive emotions, depressive emotions, and aggressive emotions. Items consist of 2 parts: the first part assesses the prevalence of a health problem or limitation in the past month, and the second part assesses the emotional response to the health problem or limitation if present. An example of an item in the pain domain is as follows: "In the last month, how often did you have a backache?" (part 1) and "How much did that bother you?" (part 2). Both parts are answered on a 4-point Likert scale. A single score (0-4) is attributed to each combination: a score of 4 is given when there is no limitation (indicated on part 1 of the item), a score of 3 is given when there is a limitation (ie, a little, some, or a lot) but the person is not bothered by the limitation (indicated on part 2 of the item), a score of 2 is given when there is a limitation and the person is a "a little" bothered, a score of 1 is given when there is a limitation and the person is "quite a lot" bothered, and a score of 0 is given when there is a limitation and the person is "very much" bothered. Domain sum scores are calculated and linearly transformed to a 0 to 100 scale. Higher scores indicate better HRQOL. The domains vitality, positive emotions, depressive emotions, and aggressiveness assess the occurrence of these feelings only in the past month. The conceptual, convergent, and criterion validity and reliability of the TAAQOL are satisfactory.[12] The TAAQOL has been validated in people with chronic illness, including patients with cancer, and it has previously been used to measure HRQOL in youth with pediatric bone tumors.[12, 13] The internal consistency of the domain scores in the current study was acceptable to good (Cronbach α range, 0.74-0.92). Dutch general population reference data that were collected by the TAAQOL authors in 2004 from a random selection from the national telephone registry are available.[12] To obtain a reference sample with a mean age similar to that of the CCSs, reference data from adults aged 18 to 50 years were selected (n = 2476; female, 42%; mean age, 35.4 years [standard deviation, 8.1 years]).

Determinants

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

Statistical analyses

Demographic and medical characteristics of participants and nonparticipants were described. Differences between participants and nonparticipants were tested with χ2 tests and Cramer's V. Means, standard deviations, medians, and interquartile ranges of TAAQOL scores were computed for male and female CCSs. Sex-stratified TAAQOL scores were compared with the reference group via Mann-Whitney U tests with effect size r. Logistic regression analyses, corrected for sex and age, were used to determine differences between CCSs and references in proportions of impaired HRQOL in each domain. Scores below the 25th percentile of the reference group were considered impaired HRQOL in accordance with Rose et al.[15] Interaction terms of group (CCSs vs references) with sex were tested and included in the final models if significant. Where applicable, odds ratios (ORs) of impaired HRQOL for male and female CCSs were obtained from 2 separate models. Effect sizes V and r of up to .2 were considered small, effect sizes of .2 to .5 were considered small to medium, effect sizes of .5 to .8 were considered medium to large, and effect sizes of >.8 were considered large.16 ORs of 1.40/0.71, 2.27/0.44, and 3.66/0.27 were considered equivalent to effect sizes of .2, .5, and .8, and they accounted for 25% of individuals with impairment in the reference group (Henian Chen, personal written communication, July 16, 2020).[17]

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

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

Results

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

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

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

Discussion

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

Compared with male CCSs, female CCSs experienced impairment in HRQOL more often and in more domains. The difference between male and female CCSs exceeds general population differences between men and women. Thus, the long-term HRQOL of women seems to be affected more by childhood cancer and its treatment. This may be explained by female CCSs being more inclined to report or discuss problems than male CCSs.[10] Nevertheless, future studies should consider sex-specific long-term risks of childhood cancer treatment.[11] Survivor care professionals need to be aware of these sex differences in the impact of childhood cancer diagnosis and treatment and be especially sensitive to impairments in females in motor and cognitive functioning and additionally in pain, sexuality, and daily activities.

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

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

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

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

Limitations

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

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

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Figure 1: Flowchart of participants from the LATER cohort to the DCCSS LATER 2 psycho oncology study.

DCCSS LATER 2 indicates Dutch Childhood Cancer Survivor LATER Study 2; TAAQOL, TNO-AZL Questionnaire for Adult Health-Related Quality of Life.

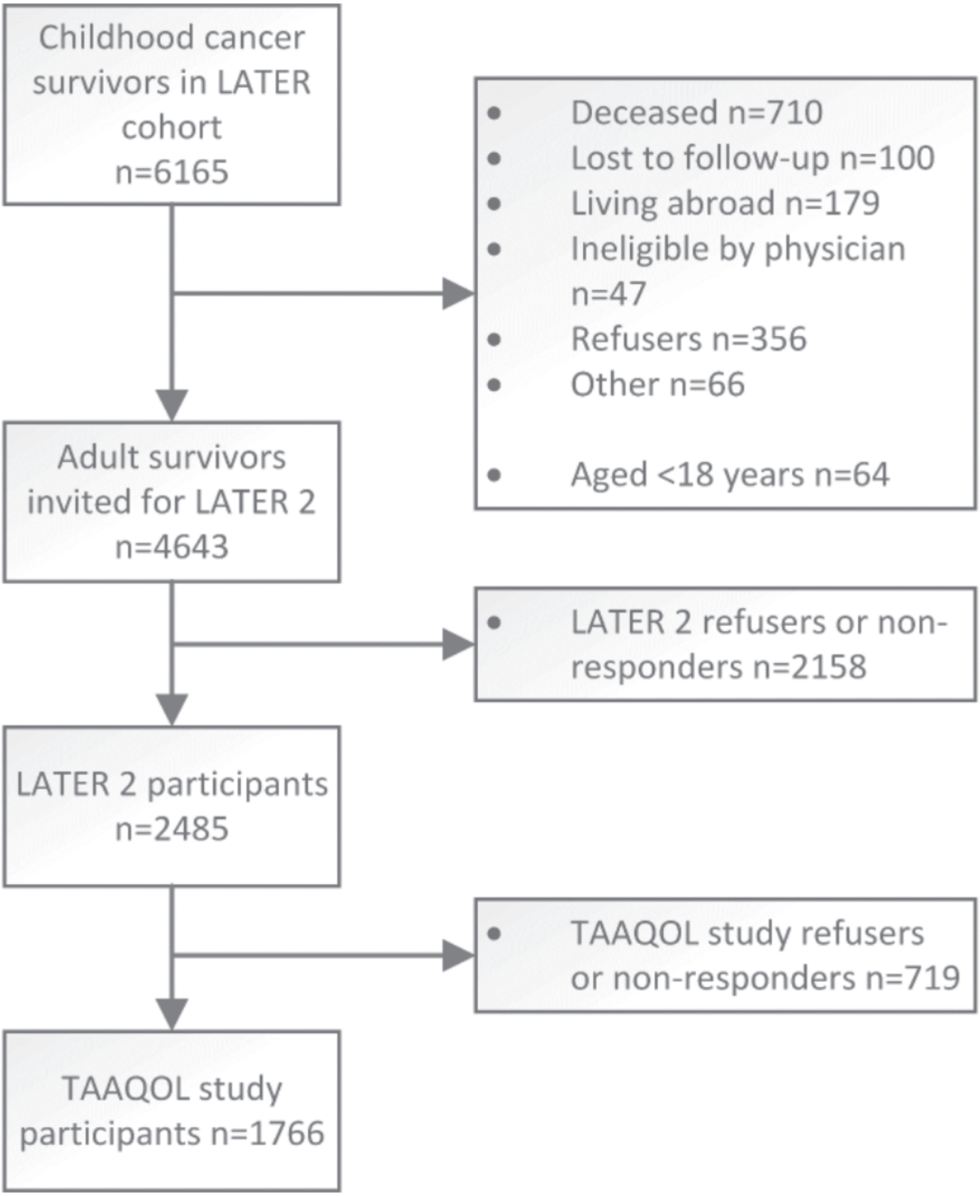

Table 1. Demographic and medical characteristics of participants and non-participants

Characteristics	Participants (n=1766), %	Non-participants (n= 2877), %[a]	Cramer's V of difference between participants and non-participants[b]
Demographic			
Age at invitation [b]			.02
<18 y	0	0	
18-30 y	33	34	
30-40 y	38	39	
>40 y	30	28	
Sex			.09[c]
Male	51	59	
Female	49	41	
Transgender	0	0	
Medical			
Age at diagnosis			.03
0-4 y	45	46	
5-9 y	27	27	
10-14 y	22	20	
15-17 y	6	6	
Follow-up time since childhood cancer diagnosis			.05
5-10 y	0	0	
10-20 y	20	19	
20-30 y	40	41	
30-40 y	30	29	
40-50 y	10	10	
50-60 y	1	1	
Primary childhood cancer diagnosis (ICCC)			
Leukemias, myeloprofiferative diseases and myelodysplastic diseases	34	34	.01
Lymphomas and reticulo endothelial neoplasms	19	18	.002
CNS and miscellaneous intracranial and intraspinal neoplasms	9	13	.04[e]
Neuroblastoma and other peripheral nervous cell tumors	6	4	.02
Retinoblastoma	1	1	.01
Renal tumors	11	10	.01
Hepatic tumors	1	1	.01
Bone tumors	6	5	.02
Soft tissue and other extraosseous sarcomas	7	7	.01
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	3	4	.02
Other and unspecified malignant neoplasms	2	2	.01

Treatment period			.05[e]
1963-1969	2	1	
1970-1979	14	13	
1980-1989	32	31	
1990-1999	43	45	
2000-2001	10	10	
Surgery [f]	50	51	.03
Radiotherapy [f]	40	34	.10[c]
Radiotherapy region [b,f,g]			
Head Cranium	19	16	.03[e]
Spinal	5	4	.02
TBI	4	2	.05 [c]
Thorax	7	5	.04[e]
Abdominopelvic area	9	7	.03[e]
Testes	1	<1	.01
Neck	4	3	.03
Upper extremities	1	1	.004
Lower extremities	1	1	.01
Radioisotopes	1	1	.03
Chemotherapy[f]	88	80	.09[c]
Hematopoietic cell transplantation[f]			.06[d]
No	93	95	
Autologous transplant	3	2	
Allogenic transplant	4	3	

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

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

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

[c] significant at α=.001.

[d] significant at α=.01.

[e] significant at α=.05.

[f] For primary cancer and recurrences.

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

Figure 2: Proportions of individuals with impaired health-related quality of life among CCSs and references and odds ratios (with 99.6% CIs) of the differences between groups corrected for age and sex.

The results are shown for males and females separately if the interaction term of sex with group was significant. Effects of at least small to medium size are in bolded.
CCS indicates childhood cancer survivor.

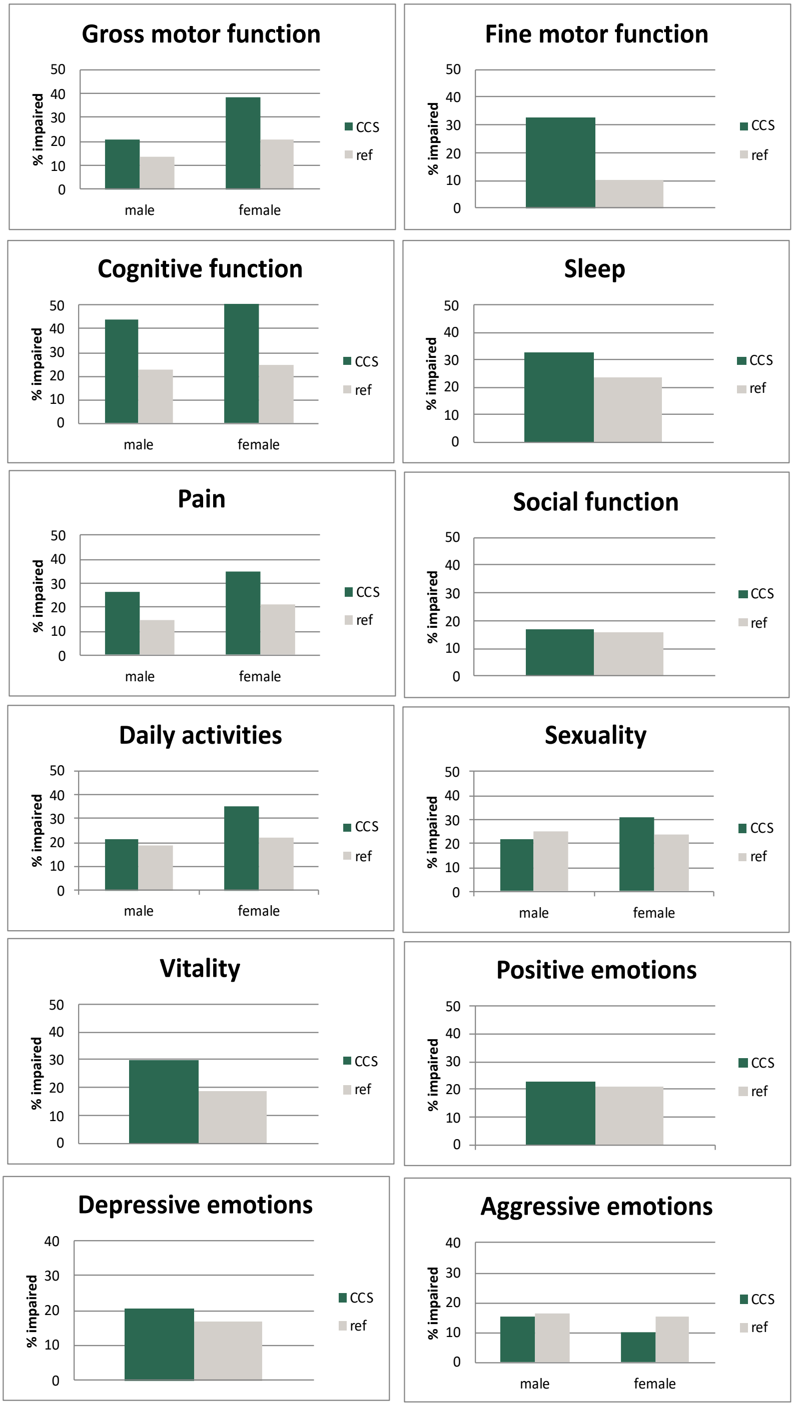

Table 2: Description of TAAQOL domains among male and female CCSs and effect size of difference with the reference group

	Male CCSs (n=904)					r[a]
TAAQOL	mean	SD	median	IQR	missing	
Gross motor functioning	90.9	16.7	100	87.5-100	1	.12[b]
Fine motor functioning	98.6	6.4	100	100-100	2	.08[b]
Cognitive functioning	76.0	25.2	87.5	56.3-100	2	.25[b]
Sleep	75.6	25.1	81.3	62.5-100	1	.08[b]
Pain	77.9	20.4	81.3	62.5-93.8	1	.07[b]
Social functioning	87.2	18.2	93.8	81.3-100	2	.03
Daily activities	85.1	23.7	100	75.0-100	3	.02
Sexuality	89.2	21.9	100	87.5-100	19	.05[c]
Vitality	66.1	25.9	75.0	50.0-83.3	4	.06[b]
Positive emotions	69.2	23.7	66.7	58.3-91.7	7	.06[c]
Depressive emotions	80.8	19.9	83.3	75.0-100	5	.03
Aggressive emotions	87.9	17.3	100	77.8-100	12	.02

	Female CCSs (n=862)					r[a]
TAAQOL	mean	SD	median	IQR	missing	
Gross motor functioning	82.8	22.7	93.8	68.8-100	0	.19[b]
Fine motor functioning	94.8	12.0	100	93.8-100	0	.15[b]
Cognitive functioning	67.8	28.1	75.0	43.8-93.8	1	.34[b]
Sleep	64.6	29.0	68.8	43.8-87.5	2	.15[b]
Pain	66.7	24.3	68.8	50.0-87.5	2	.17[b]
Social functioning	86.1	19.4	93.8	75.0-100	5	.01
Daily activities	76.3	28.9	87.5	56.3-100	3	.11[b]
Sexuality	84.0	26.2	100	75.0-100	33	.07[b]
Vitality	53.8	28.4	58.3	33.3-75.0	2	.15[b]
Positive emotions	69.4	23.4	66.7	58.3-91.7	4	.04
Depressive emotions	75.1	21.4	83.3	66.7-91.7	3	.05[b]
Aggressive emotions	90.3	14.2	100	88.9-100	14	.10[c]

*T*able 3: Multivariable analyses of determinants of impaired health-related quality of life

	Gross motor functioning 515 impaired (29%), OR (95% CI)		Fine motor functioning 299 impaired (17%), OR (95% CI)		Cognitive functioning 874 impaired (50%), OR (95% CI)		Sleep 574 impaired (33%), OR (95% CI)		Pain 467 impaired (27%), OR (95% CI)		Social functioning 301 impaired (17%), OR (95% CI)	
	Block 1+2	Block 1+3	Block 1+2	Block 1+3	Block 1+2	Block 1+3	Block 1+2	Block 1+3	Block 1+2	Block 1+3	Block 1+2	Block 1+3
Block 1 Demographics												
Age at invitation (reference 18-30 y)												
30-40 y	1.3 (1.0;1.7)	1.2 (0.9;1.6)	1.2 (0.8;1.6)	1.1 (0.8;1.5)	1.1 (0.9;1.4)	1.0 (0.8;1.3)	1.1 (0.9;1.4)	1.1 (0.9;1.5)	1.2 (0.9;1.5)	1.2 (0.9;1.6)	1.1 (0.8;1.6)	1.0 (0.7;1.4)
40 y and over	2.7^a (2.0;3.6)	2.0^a (1.4;2.7)	1.5^c (1.1;2.2)	1.3 (0.9;1.8)	1.0 (0.8;1.3)	0.9 (0.7;1.1)	1.1 (0.9;1.5)	1.1 (0.9;1.5)	1.8^a (1.4;2.4)	1.7^a (1.3;2.3)	1.3 (0.9;1.8)	1.0 (0.7;1.4)
Female sex (reference male)	2.5^a (2.0;3.1)	2.5^a (2.0;3.1)	4.3^a (3.2;5.8)	4.4^a (3.3;5.8)	1.6^a (1.3;1.9)	1.7^a (1.4;2.0)	2.1^a (1.7;2.6)	2.1^a (1.7;2.5)	2.3^a (1.8;2.9)	2.3^a (1.9;2.9)	1.3^c (1.0;1.6)	1.3 (1.0;1.6)
Medical												
Age at diagnosis (reference 0-5 y)												
5-10 y	1.0 (0.8;1.3)	1.1 (0.8;1.4)	1.1 (0.8;1.6)	1.2 (0.8;1.6)							1.0 (0.7;1.4)	1.1 (0.8;1.5)
10-15 y	1.2 (0.9;1.6)	1.4^c (1.1;1.9)	1.3 (0.9;1.9)	1.4 (1.0;1.9)							1.0 (0.7;1.4)	1.2 (0.9;1.7)
15-18 y	0.9 (0.6;1.5)	1.3 (0.8;2.2)	0.8 (0.5;1.5)	0.9 (0.5;1.7)							1.2 (0.7;2.0)	1.6 (0.9;2.7)
Recurrence (any vs none)	1.5^b (1.1;2.0)	1.3 (0.9;1.7)										
Block 2: Primary cancer diagnosis												
Leukemia	0.8 (0,6;1.1)						0.8^c (0.6;1.0)					
Lymphoma	0.7 (0.5;1.0)		0.9 (0.6;1.3)		0.9 (0.7;1.1)				0.8 (0.6;1.1)			
CNS tumor	1.5^c (1.0;2.2)		1.9^b (1.3;2.8)		1.6^b (1.1;2.2)						2.1^a (1.5;3.0)	
Neuroblastoma											0.4^c (0.2;0.8)	
Retinoblastoma									10.3^b (2.1;51.4)			
Renal tumor											0.7 (0.5;1.1)	
Hepatic tumor									0.2 (0.0;1.5)			
Bone tumor	3.2^a (2.0;5.2)								1.4 (0.9;2.1)			
Germ cell tumor			1.5 (0.8;2.8)						1.4 (0.8;2.4)			
Block 3: Cancer treatment^d												
Surgery		1.2 (0.9;1.5)		1.1 (0.8;1.5)				1.1 (0.9;1.4)				
Radiotherapy regions^e												

Head Cranium	1.7[a] (1.3;2.3)	1.5[c] (1.1;2.1)	1.7[a] (1.3;2.3)			2.0[a] (1.5;2.8)
Spinal			1.1 (0.7;1.8)			1.0 (0.6;1.8)
TBI				0.7 (0.4;1.2)		
Thorax	1.1 (0.7;1.7)					
Abdominopelvic area	1.9[b] (1.3;2.8)			1.4 (0.9;2.0)	1.4 (1.0;2.1)	
Lower extremities	6.5[a] (2.3;18.2)				2.4[c] (1.1;5.6)	
Radioisotopes				1.9 (0.7;4.8)		
Chemotherapy	0.8 (0.6;1.1)	0.9 (0.6;1.3)		0.7[c] (0.5;1.0)	0.8 (0.6;1.0)	

Table 3 (Cont.): Multivariable analyses of determinants of impaired HRQoL

	Daily activities 494 impaired (28%), OR (95% CI)		Sexuality 454 impaired (27%), OR (95% CI)		Vitality 530 impaired (30%), OR (95% CI)		Positive emotions 395 impaired (23%), OR (95% CI)		Depressive emotions 361 impaired (21%), OR (95% CI)		Aggressive emotions 223 impaired (13%), OR (95% CI)	
	Block 1+2	Block 1+3	Block 1+2	Block 1+3	Block 1+2	Block 1+3	Block 1+2	Block 1+3	Block 1+2	Block 1+3	Block 1+2	Block 1+3
Block 1: Demographics												
Age at invitation (reference 18-30 y)												
30-40 y	1.2 (0.9;1.5)	1.1 (0.9;1.5)	1.0 (0.7;1.2)	1.0 (0.8;1.3)	1.1 (0.8;1.4)	1.0 (0.8;1.3)	0.9 (0.7;1.2)	0.9 (0.7;1.2)	0.8 (0.6;1.1)	0.8 (0.6;1.1)		0.9 (0.6;1.2)
40 y and over	1.3 (1.0;1.7)	1.1 (0.8;1.5)	1.2 (0.8;1.5)	1.2 (0.9;1.6)	1.4^c (1.1;1.8)	1.1 (0.8;1.4)	1.2 (0.9;1.6)	1.0 (0.8;1.4)	0.8 (0.6;1.1)	0.8 (0.6;1.0)		0.8 (0.6;1.2)
Female sex (reference male)	2.0^a (1.6;2.5)	2.0^a (1.6;2.5)	1.6^a (1.3;2.0)	1.5^a (1.2;1.9)	2.2^a (1.8;2.8)	2.3^a (1.9;2.9)	1.0 (0.8;1.2)	1.0 (0.8;1.2)	1.7^a (1.3;2.1)	1.7^a (1.3;2.2)		0.6^a (0.4;0.8)
Block 2: Cancer diagnosis												
Leukemia	0.9 (0.7;1.1)											
Lymphoma					0.8 (0.6;1.1)				0.8 (0.6;1.1)			
CNS tumor	1.8^a (1.2;2.5)				1.7^b (1.2;2.4)		1.6^b (1.1;2.3)					
Bone tumor			1.4 (0.9; 2.2)									
Block 3: Cancer treatment^d												
Surgery		1.1 (0.8;1.3)										
Radiotherapy regions^e												
Head Cranium		1.3 (1.0;1.8)		0.8 (0.6;1.0)		1.7^a (1.2;2.2)		1.5^b (1.1;2.1)				
Spinal		1.4 (0.8;2.3)				1.2 (0.7;1.9)		1.2 (0.7;2.0)		1.8^c (1.1;2.9)		
TBI				0.6 (0.3;1.2)				0.6 (0.3;1.2)		0.4^c (0.2;0.9)		
Abdominopelvic area		1.3 (0.9 1.9)		1.5^c (1.0;2.2)		1.7^b (1.2;2.4)						
Testes												2.8 (0.7;11.3)
Lower extremities		2.2 (1.0;5.3)				1.9 (0.8;4.5)						
Radioisotopes		2.6^c (1.0;6.6)										
Chemotherapy		0.7^c (0.5;1.0)										

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

Supplemental information

SI Table 1: Odds of CCS at risk of impaired health-related quality of life compared to references using logistic regression analyses[1] including interactions of group with sex (male is reference category)

	CCS vs references			Sex*group		
	OR	99.6% CI	*p*-value	OR	95% CI	*p*-value
Gross motor functioning	1.65	1.16; 2.36	<0.001	1.36	1.00; 1.85	0.049
Fine motor functioning	2.10	1.17; 3.78	<0.001	1.01	0.64; 1.59	0.966
Cognitive functioning	2.66	2.00; 3.55	<0.001	1.44	1.10; 1.88	0.007
Sleep	1.47	1.06; 2.03	0.001	1.21	0.91; 1.61	0.187
Pain	1.34	1.06; 1.71	0.016	1.40	1.03; 1.91	0.031
Social functioning	1.10	0.76; 1.58	0.476	1.01	0.72; 1.41	0.946
Daily activities	1.15	0.83; 1.60	0.208	1.68	1.25; 2.25	0.001
Sexuality	0.86	0.69; 1.06	0.162	1.67	1.25; 2.23	<0.001
Vitality	1.84	1.29; 2.62	<0.001	1.19	0.88; 1.61	0.267
Positive emotions	1.13	0.82; 1.55	0.280	0.93	0.69; 1.25	0.611
Depressive emotions	1.26	0.87; 1.82	0.076	1.10	0.80; 1.52	0.553
Aggressive emotions	0.93	0.65; 1.33	0.560	0.66	0.49; 0.90	0.025

[1] Analyses were corrected for age and sex

SI Table 2: Univariate logistic regression analyses of determinants with impaired HRQoL.

Impaired HRQoL in:	Gross motor functioning OR (90% CI)	Fine motor functioning OR (90% CI)	Cognitive functioning OR (90% CI)	Sleep OR (90% CI)	Pain OR (90% CI)	Social functioning OR (90% CI)
Sociodemographic						
Age (years, ref = 18-30)						
30-39	1.3 ** (1.1; 1.7)	1.1 (0.9, 1.5)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)
40 and over	2.8*** (2.2; 3.5)	1.4 ** (1.1, 1.9)	1.0 (0.8, 1.2)	1.2 (1.0, 1.5)	1.8 *** (1.5, 2.3)	1.3 (1.0, 1.6)
Sex (ref = male)	2.4*** (2.0; 2.8)	4.3 *** (3.4, 5.5)	1.6*** (1.4, 1.9)	2.1*** (1.8, 2.5)	2.3*** (1.9, 2.8)	1.2 (1.0, 1.5)
Medical characteristics						
Age at diagnosis (years, ref 0-5)						
5-10	1.2 (0.9; 1.4)	1.2 (0.9, 1.5)	1.2 (1.0, 1.4)	0.9 (0.8, 1.2)	1.1(0.9, 1.4)	1.2 (1.0, 1.6)
10-15	1.6*** (1.3; 2.0)	1.4 * (1.0, 1.8)	1.2 (1.0, 1.4)	1.2 (0.9, 1.4)	1.2 (0.9, 1.5)	1.3 (1.0, 1.7)
15-18	1.8** (1.2; 2.5)	1.0 (0.6, 1.7)	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)	1.2 (0.8, 1.8)	1.5 * (1.0, 2.4)
Recurrence (yes)	1.4*** (1.1; 1.8)	1.1 (0.8, 1.5)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	1.1 (0.9, 1.4)	1.2 (0.9, 1.6)
Diagnosis						
Leukemia	0.7*** (0.6; 0.8)	0.9 (0.7, 1.1)	1.0 (0.9, 1.2)	0.8** (0.6, 0.9)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)
Lymphoma	0.7** (0.6; 0.9)	0.7* (0.5, 1.0)	0.8** (0.6, 0.9)	0.8 (0.7, 1.0)	0.7** (0.6, 0.9)	0.9 (0.7, 1.2)
CNS tumor	1.5** (1.1; 1.9)	1.8 *** (1.4, 2.5)	1.6*** (1.2, 2.2)	1.3 (1.0, 1.7)	1.2 (0.9, 1.6)	2.3*** (1.7, 3.0)
Neuroblastoma	1.0 (0.7; 1.4)	1.1 (0.7, 1.7)	0.7 (0.5, 1.0)	1.1 (0.8, 1.6)	1.2 (0.9, 1.8)	0.4** (0.2, 0.7)
Retinoblastoma	1.2 (0.4; 3.9)	0.6 (0.1, 3.5)	1.3 (0.4, 3.9)	1.0 (0.3, 3.3)	9.8*** (2.6, 36.8)	2.4 (0.8, 7.8)
Renal tumor	1.0 (0.8; 1.3)	0.8 (0.6, 1,1)	0.9 (0.7, 1.1)	1.0 (0.8, 1.4)	0.9 (0.7, 1.2)	0.7* (0.5, 1.0)
Hepatic tumor	xxx	0.3 (0.1, 1.7)	0.7 (0.3, 1.6)	1.9 (0.8, 4.1)	0.2* (0.0. 0.9)	1.0 (0.4, 3.0)
Bone tumor	4.1*** (3.0; 5.8)	1.0 (0.6, 1.5)	0.9 (0.6, 1.2)	1.3 (0.9, 1.8)	1.7** (1.2, 2.3)	1.2 (0.8, 1.9)
Soft tissue sarcoma	1.3 (1.0; 1.8)	1.4 (1.0, 2.1)	1.2 (0.9, 1.7)	1.3 (1.0, 1.8)	1.0 (0.7, 1.4)	1.2 (0.8, 1.8)
Germ cell tumor	1.2 (0.8; 2.0)	1.8 * (1.1, 3.0)	1.2 (0.8, 1.9)	1.2 (0.8, 1.9)	1.6* (1.0. 2.6)	0.7 (0.3, 1.3)
Treatment						
Surgery	1.4*** (1.2; 1.7)	1.3 * (1.0, 1.5)	1.1 (0.9, 1.2)	1.4***(1.2, 1.6)	1.2 (1.0, 1.4)	1.1 (0.9, 1.4)

Radiotherapy	2.2*** (1.8; 2.6)	1.4 ** (1.2, 1.8)	1.3*** (1.1, 1.6)	1.2 (1.0, 1.4)	1.4*** (1.2, 1.7)	1.5*** (1.2, 1.8)
Head Cranium	1.7*** (1.4; 2.1)	1.4 ** (1.1, 1.8)	1.7*** (1.4, 2.1)	1.0 (0.8, 1.3)	1.2 (1.0, 1.5)	2.0*** (1.6, 2.6)
Spinal	1.3 (0.9; 2.0)	1.0 (0.6, 1.6)	1.6** (1.1, 2.3)	0.8 (0.6, 1.3)	0.8 (0.5, 1.3)	1.7** (1.1, 2.6)
TBI	1.0 (0.7; 1.6)	0.8 (0.4, 1.4)	0.7 (0.5, 1.1)	0.5** (0.3, 0.9)	0.7 (0.4, 1.1)	0.8 (0.4, 1.4)
Thorax	1.6** (1.2; 2.2)	0.9 (0.6, 1.3)	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)	1.2 (0.8, 1.8)
Abdominopelvic area	2.2*** (1.7; 3.0)	1.4 (1.0, 1.9)	1.1 (0.8, 1.5)	1.6*** (1.2, 2.1)	1.8*** (1.3, 2.4)	0.8 (0.6, 1.2)
Testes	0.6 (0.2; 2.6)	xxx	0.8 (0.3, 2.5)	0.3 (0.0, 1.5)	0.3 (0.1, 2.0)	0.6 (0.1, 3.5)
Neck	0.9 (0.6; 1.4)	0.8 (0.4, 1.3)	1.0 (0.7, 1.4)	1.2 (0.8, 1.8)	1.0 (0.6, 1.5)	0.8 (0.4, 1.4)
Upper extremities	2.5 (0.9; 6.4)	1.6 (0.5, 4.9)	2.1 (0.7, 5.6)	1.5 (0.6, 3.9)	2.0 (0.8, 5.2)	1.6 (0.5, 4.9)
Lower extremities	9.6*** (4.2; 22.0)	2.0 (1.0, 4.3)	0.5 (0.2, 1.0)	1.5 (0.8, 3.0)	3.3*** (1.7, 6.6)	2.0 (1.0, 4.3)
Radioisotopes	1.8 (0.8; 3.8)	1.8 (0.7, 4.2)	1.8 (0.8, 3.9)	2.3* (1.1, 5.0)	1.0 (0.4, 2.3)	0.6 (0.2, 1.9)
Chemotherapy	0.7*** (0.5; 0.8)	0.7** (0.5, 0.9)	0.8 (0.6, 1.0)	0.6*** (0.5, 0.8)	0.7** (0.6, 0.9)	0.8 (0.6, 1.1)
BMT/SCT	0.9 (0.7; 1.3)	0.9 (0.6, 1.4)	0.8 (0.6, 1.1)	0.7* (0.5, 0.9)	0.5 ** (0.4, 0.8)	0.8 (0.5, 1.2)

SI Table 2 (cont.): Preselections for multivariable models: univariate logistic regression analyses of determinants with impaired health in domains of HRQoL.

Impaired HRQoL in:	Daily Activities OR (90% CI)	Sexuality OR (90% CI)	Vitality OR (90% CI)	Positive emotions OR (90% CI)	Depressive emotions OR (90% CI)	Aggressive emotions OR (90% CI)
Sociodemographic						
Age (years, ref = 18-30)						
30-39	1.1 (0.9; 1.4)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)	0.8* (0.6, 1.0)	0.9 (0.7, 1.1)
40 and over	1.3* (1.0; 1.6)	1.2 (1.0, 1.5)	1.3** (1.0, 1.6)	1.1 (0.9, 1.4)	0.8* (0.6, 1.0)	0.8 (0.6, 1.1)
Sex (ref = male)	2.0*** (1.7, 2.4)	1.6*** (1.3, 1.9)	2.3*** (1.9, 2.7)	1.0 (0.8, 1.2)	1.7*** (1.4, 2.1)	0.6*** (0.5, 0.8)
Medical characteristics						
Age at diagnosis (years, ref 0-5)						
5-10	1.1 (0.9, 1.4)	1.0 (0.8, 1.2)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)
10-15	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	0.9 (0.7, 1.2)	1.0 (0.8, 1.4)
15-18	1.3 (0.9, 1.8)	1.3 (0.9, 1.9)	1.0 (0.7, 1.5)	1.1 (0.7, 1.6)	0.8 (0.5, 1.2)	0.9 (0.6, 1.6)

Recurrence (yes)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.0 (0.7, 1.4)
Diagnosis						
Leukemia	0.8** (0.7, 0.9)	0.8 (0.7, 1.0)	0.9 (0.8, 1.1)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)
Lymphoma	0.8 (0.7, 1.0)	0.9 (0.7, 1.2)	0.7** (0.6, 0.9)	1.0 (0.8, 1.3)	0.7** (0.6, 0.9)	0.8 (0.6, 1.1)
CNS tumor	1.8*** (1.4, 2.4)	1.0 (0.8, 1.4)	1.7*** (1.3, 2.3)	1.6** (1.2, 2.1)	1.3 (1.0, 1.8)	1.0 (0.7, 1.5)
Neuroblastoma	1.2 (0.8, 1.7)	0.8 (0.5, 1.2)	0.9 (0.6, 1.3)	0.6 (0.4, 1.0)	1.0 (0.7, 1.5)	0.9 (0.5, 1.5)
Retinoblastoma	0.7 (0.2, 2.7)	0.3 (0.1, 2.0)	1.2 (0.4, 3.7)	0.4 (0.1, 2.5)	1.9 (0.6, 6.2)	0.9 (0.1, 4.9)
Renal tumor	0.8 (0.6, 1.0)	1.1 (0.8, 1.4)	0.8 (0.6, 1.1)	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)	1.2 (0.9, 1.7)
Hepatic tumor	1.8 (0.8, 4.1)	1.5 (0.7, 3.5)	1.3 (0.5, 2.9)	0.7 (0.3, 2.1)	1.2 (0.5, 3.1)	xxx
Bone tumor	1.1 (0.8, 1.6)	1.5* (1.1, 2.1)	1.3 (0.9, 1.8)	0.9 (0.6, 1.4)	1.0 (0.7, 1.5)	1.0 (0.6, 1.7)
Soft tissue sarcoma	1.1 (0.8, 1.5)	1.3 (0.9, 1.8)	1.3 (0.9, 1.7)	1.3 (0.9, 1.8)	1.2 (0.8, 1.7)	1.2 (0.7, 1.8)
Germ cell tumor	0.9 (0.6, 1.5)	1.2 (0.7, 1.9)	1.1 (0.7, 1.7)	0.9 (0.5, 1.6)	0.9 (0.5, 1.6)	1.3 (0.7, 2.4)
Treatment						
Surgery	1.3** (1.1, 1.5)	1.2 (1.0, 1.4)	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)	1.2 (1.0, 1.5)	0.9 (0.7, 1.1)
Radiotherapy	1.3** (1.1, 1.6)	1.0 (0.8, 1.2)	1.5*** (1.3, 1.8)	1.3** (1.1, 1.6)	1.0 (0.8, 1.2)	1.1 (0.9, 1.4)
Head Cranium	1.4** (1.1, 1.7)	0.8* (0.6, 1.0)	1.5***(1.2, 1.9)	1.6*** (1.3, 2.1)	1.2 (1.0, 1.6)	1.1(0.8, 1.5)
Spinal	1.7** (1.1, 2.4)	0.7 (0.5, 1.1)	1.5* (1.1, 2.2)	1.7** (1.1, 2.5)	1.8** (1.2, 2.6)	1.4 (0.8, 2.2)
TBI	0.6 (0.4, 1.0)	0.6* (0.3, 1.0)	0.7 (0.4, 1.1)	0.6* (0.3, 1.0)	0.3** (0.2, 0.7)	1.3 (0.7, 2.2)
Thorax	1.4 (1.0, 1.9)	1.2 (0.9, 1.7)	1.1 (0.8, 1.5)	1.3 (0.9, 1.9)	0.9 (0.6, 1.3)	1.1 (0.7, 1.7)
Pelvic area	1.4* (1.0, 1.8)	1.8*** (1.3, 2.4)	1.7*** (1.3, 2.2)	1.0 (0.7, 1.4)	0.9 (0.7, 1.3)	1.1 (0.8, 1.7)
Testes	0.3 (0.1, 1.8)	0.3 (0.1, 2.0)	0.3 (0.1, 1.7)	0.4(0.1, 2.5)	1.9 (0.6, 6.2)	3.4* (1.1, 11.0)
Neck	1.0(0.6, 1.5)	1.0 (0.7, 1.6)	0.7 (0.4, 1.1)	1.1 (0.7, 1.8)	0.8 (0.4, 1.3)	0.5 (0.2, 1.1)
Upper extremities	0.9 (0.3, 2.6)	2.3 (0.9, 6.3)	2.3 (0.9, 6.1)	0.3 (0.1, 1.7)	0.8 (0.2, 2.8)	1.4 (0.4, 4.9)
Lower extremities	2.2* (1.1, 4.3)	0.8 (0.3, 1.8)	2.0* (1.0, 3.9)	0.9 (0.4, 2.1)	1.6 (0.8, 3.4)	1.9 (0.8, 4.4)
Radioisotopes	2.9** (1.3, 6.2)	1.1 (0.4, 2.5)	1.4 (0.6, 3.0)	0.9 (0.4, 2.3)	1.0 (0.4, 2.6)	0.8 (0.2, 2.7)
Chemotherapy	0.6*** (0.5, 0.8)	0.9 (0.7, 1.1)	0.8 (0.6, 1.0)	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)	0.9 (0.7, 1.3)
BMT/SCT	0.6 ** (0.4, 0.8)	0.6 ** (0.4, 0.9)	0.6 * (0.4, 0.9)	0.6 * (0.4, 1.0)	0.4** (0.3, 0.7)	1.2 (0.7, 1.8)

** significant at α=.10, **significant at α=.05, *** significant at α=.01 xxx: too few cases for analysis*

PART II

AGE-SPECIFIC PSYCHOSOCIAL CHALLENGES OF YOUNG ADULT CHILDHOOD CANCER SURVIVORS

4

CHAPTER 4

PSYCHOSOCIAL CONSEQUENCES OF SURVIVING CANCER IN CHILDHOOD VERSUS IN ADOLESCENCE/YOUNG ADULTHOOD: A CALL FOR CLEARER DELINEATION BETWEEN GROUPS

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The number of young people who have survived cancer continues to grow worldwide.[1] Alongside this welcome medical achievement, there is now increasing recognition of the importance of evaluating and supporting the psychosocial needs of these young cancer survivors.[2] Significant progress has been made in improving understanding of the needs of young cancer survivors and in developing interventions to meet these needs.[3] One aspect that warrants more attention and discussion is the impact of the young person's stage of development at the time of their diagnosis and treatment on longer term psychosocial outcomes.

Currently, in the literature, the distinction between young survivors of cancers diagnosed in childhood, adolescence, and young adulthood is often not clear. Often, the needs of young people who have survived childhood cancer are merged with the needs of young people who have survived adolescent or young adult cancer.[4-6] Lack of clarity around the defined age range for adolescents and young adults in the field adds additional challenges. In other instances, there is a lack of clarity as to which group of young survivors is being described.[7, 8]

In this commentary, we hypothesise that developmental stage at cancer diagnosis, and the interruptions experienced in achieving developmental milestones, is central to the experience of having and surviving cancer, and can influence subsequent outcomes as a survivor. We posit the need for assessment of the potential psychosocial differences between survivors of cancer diagnosed during childhood ['Childhood Cancer Survivors' or 'CCS'] and survivors of cancer diagnosed during adolescence and young adulthood ['Adolescent and Young Adult Cancer Survivors' or 'AYACS)']. There is wide variability in the age ranges used to delineate children from adolescents and young adults in the literature,[9] however the focus of this manuscript will be on the experiences of childhood cancer survivors who were diagnosed before the age of 16 (CCS), and comparing their experiences with those diagnosed during adolescence and young adulthood, i.e. from age 16 to 25 years (AYACS). We define survivors as those who are at least five years since their cancer diagnosis. In this commentary, we draw attention to the challenges in appropriately meeting the psychosocial needs of these two groups when definitions and terminology used are unclear. We conclude by calling for each group to receive separate research and clinical attention.

CCS and AYACS experience different developmental interruptions

It is unlikely that the experience of receiving a cancer diagnosis and undergoing cancer treatment in children and adolescents/young adults can be the same in light of rapid developmental changes young people experience during these years. It is crucial to place the experience of having cancer in the context of this development.

Infancy is dominated by emotional development, dependence, trust and parental relationships. The pre-school period is influenced by cognitive development and characterized by egocentric and magical thinking, and associative logic, as well as development of self-regulation.(16) The school-age period is then dominated by the development of logical thinking, increased awareness of self, and the increasing importance of social interactions. Receiving a cancer diagnosis during early childhood therefore potentially disrupts early social skills development, identity formation, early childhood education (e.g. pre-school and early school years),[3] and family functioning.[10]

CCS may not always remember their lives 'before cancer' and potentially have limited understanding of their illness and treatment.[11] Their parents may not have shared all details regarding their cancer experience with them and likely took responsibility for making medical decisions on behalf of their child.[11] This may mean that CCS are heavily dependent on their family's narrative of their cancer experience. A key challenge for CCS then can be to "catch up" on key early developmental milestones, especially during the transition from adolescence to young adulthood. They need to adjust earlier in life than AYACS to living with the consequences of the treatment of their cancer.

Adolescence features the development of abstract thinking, identity formation and the search for independence, which begin to be realized in early adulthood.[12] Having cancer as an adolescent or young adult therefore disrupts critical, but different, developmental milestones to having cancer as a child. AYACS have a lived (and remembered) experience of their life before their cancer, as well as potentially more awareness or understanding of the implications of their cancer diagnosis and treatment. They may be less likely than CCS to rely on their parents to "fill in the gaps". However, a diagnosis during adolescence and young adulthood may significantly disrupt autonomy and identity development for young people.[13, 14] In some instances, young adults who have recently moved out of their family home return, due to their medical treatment and support needs, impacting their development and family and social relations. Concrete milestones for AYACS after their cancer experience then include progressing or completing formal education, pursuing and keeping employment, moving out of home, earning an income, developing romantic and sexual relationships, and having children.

CCS and AYACS may experience different psychosocial challenges, but the data is unclear

Evidence suggests that subgroups of both CCS and AYACS experience psychosocial challenges in survivorship.[3] Data are however lacking that clearly distinguish the outcomes and needs of these two groups, despite experiencing different developmental interruptions. We posit that CCS and AYACS are likely to have:

1) <u>Some similar psychosocial outcomes caused by similar experiences</u>.
For example, a subset of CCS and AYACS experience mental health challenges after completion of their cancer treatment, possibly due to a similar need to process their cancer experience, feeling 'different' from their peers, experiencing changes in their relationships, and worrying about cancer recurrence;[10]

2) <u>Some similar psychosocial outcomes, with different experiences driving these outcomes</u>.
For example, while CCS and AYACS can both experience concerns regarding sexual functioning and fertility, it is unlikely that CCS were sexually active or had made concrete family planning decisions before their cancer diagnosis. AYACS in contrast, may need to adjust to new sexual functioning post-cancer and contemplate the impact of cancer on their previous expectations about starting a family; and

3) <u>Some different psychosocial outcomes because they experienced different developmental interruptions</u>.
For example, while data directly comparing cognitive outcomes for CCS versus

AYACS are sparse, cognitive difficulties may be more pronounced for CCS, for whom the achievement of early, yet foundational, cognitive milestones (e.g. literacy and numeracy) may have been significantly disrupted. In contrast, AYACS may have had their attendance and engagement during the final years of high school/university disrupted, compromizing development of higher order cognitive skills.[15-17]

A call for clearer delineation when assessing the needs of CCS and AYACS

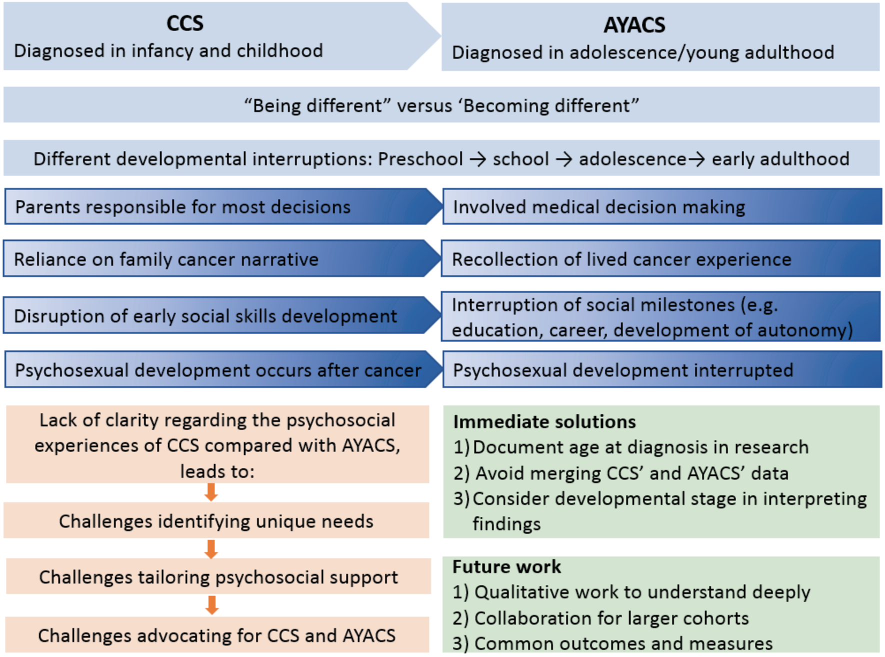
While it is clear that CCS and AYACS experience differing developmental trajectories, the lack of clear delineation between these two groups in the literature makes it difficult to understand, and therefore meet, the psychosocial needs of these two growing populations. As summarized by Figure 1, the lack of delineation between groups in current research has the potential to reduce researchers' and clinicians' ability to understand the specific needs of each group of young people. There is a need for a clear theoretical underpinning of research in this area, based on our understanding of child, adolescent and young adult development.

Blurring CCS with AYACS impairs our ability to differentiate their age-specific needs and develop evidence-based interventions for each group. Without accurate understanding of CCS' and AYACS' needs, it is difficult to provide tailored psychosocial care for young cancer survivors. It is also difficult to raise awareness and advocate for the needs of young people who have survived cancer. It is time to move beyond generic studies which merge CCS and AYACS together, and beyond studies that do not clearly define their cohorts. By identifying the similarities and differences between CCS and AYACS more clearly, future research and care will be able to provide more targeted and appropriate supports for all young people after surviving cancer.

Our immediate recommendations to survivorship researchers across the field are to: 1) always document both age at cancer diagnosis/treatment and current age in all types of survivorship research, 2) avoid merging the outcomes and needs of CCS and AYACS within the one study and where possible, conducting subgroup analyses to explore any differences, and 3) consider survivors' developmental stage at cancer diagnosis/treatment when interpreting research findings.

Our pragmatic vision for future work focuses on 1) additional qualitative research to provide deeper, nuanced understanding of young people's survivorship experiences, and to highlight differences and similarities between CCS and AYACS across psychosocial domains (including, but not limited to, mental health, social and sexual development and cognitive development), 2) Encouraging collaboration across sites and countries to build larger research cohorts that allow examination of differences in outcomes and needs between CCS and AYACS. This approach may address some of the challenges in our field in recruiting and gathering robust data and 3) Working towards agreement on the use of common patient-reported outcomes and on which outcomes/needs to measure, which would support building the evidence base from a quantitative perspective. Our hope is that these developments will, in time, enable us to truly understand the shared, and distinct, experiences of two growing groups of cancer survivors: CCS and AYACS.

Figure 1: Distinguishing between CCS and AYACS and consequences of lack of clarity



Abbreviations: CCS: Childhood cancer survivors; AYACS: Adolescent and young adult cancer survivors.

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5

CHAPTER 5

PSYCHOSOCIAL DEVELOPMENTAL MILESTONES OF YOUNG ADULT SURVIVORS OF CHILDHOOD

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Submitted for publication.

Abstract

Purpose

The study aimed to compare the psychosocial development of young adult survivors of childhood cancer (YACCS) with a norm group of young adults from the general population.

Methods

From 2017 to 2020, 558 YACCS (18-30 years, 51% female, 10.9% CNS cancer) who participated in the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort (diagnosed 1963-2001) part 2, completed the Course of Life Questionnaire (CoLQ), that assesses achievement of milestones in Autonomy, Psychosexual and Social development.

Differences between YACCS and norm group were examined with ANOVA and Cohen's d (CoLQ-scales) and with logistic regression analysis and Odds Ratio (OR) (CoLQ-items); for the total group and YACCS of CNS cancer.

Results

The total group of YACCS did not report a less favorable psychosocial development than the norm group. YACCS of CNS cancer scored lower than norm (p 0.000) on the scales Autonomy (d -0.36) and Psychosexual (d -0.46). Additionally, on half of the items of Autonomy (OR 0.25-0.34), Psychosexual (OR 0.30-0.48) and Social (OR 0.23-0.47) development, YACCS of CNS cancer were less likely ($p<0.01$) than the norm group to have achieved the milestones.

Conclusion

Overall, psychosocial development of YACCS was as favorable as the norm, but YACCS of CNS cancer were at risk of an unfavorable psychosocial development in all domains. Monitoring psychosocial development should be included in the standards of psychosocial care, especially for CNS cancer patients and survivors, to be able to trace delay. Personalized interventions should be offered to improve the psychosocial development in an early stage.

Background

Childhood cancer may have psychosocial consequences in the short and long term. To attain the goals in a typical psychosocial development, survivors of childhood cancer face extra challenges due to their disease history. Childhood cancer and its treatment often increase parental dependence and decrease participation in peer-based and school-based activities [1, 2]. Cognitive problems and non-attendance at school as a result of the disease and treatment can result in lowered educational achievement [3-5]. As a result, growing up with or after childhood cancer may have consequences for the psychosocial development of children, adolescents and young adults.

The attainment of social and academic competence, peer relationships, independence from parents and identity are generally recognized as important milestones in the development of a child into young adulthood [6-8]. The achievement of these psychosocial milestones is of importance to the adjustment in adult life [9-11]. Functioning of young adult childhood cancer survivors (YACCS) may be affected due to earlier missed experiences and delays in the achievement of psychosocial developmental milestones. Previous research in 2000/2001 among YACCS from the long-term follow-up clinic at the Academic Medical Center Amsterdam, The Netherlands [12], revealed that YACCS were at risk of a hampered psychosocial development. On group level, the differences with the general population were rather small [12], which indicated that the majority of YACCS were likely to have a favorable psychosocial developmental trajectory. However, YACCS of cancer in the central nervous system (CNS) and/or treated with radiotherapy appeared to be at risk of delays in the achievement of psychosocial developmental milestones, especially in the social and psychosexual domain [13]. Furthermore, YACCS who had achieved fewer psychosocial milestones while growing up, were more likely to apply for disability benefits [14] and to experience worse health-related quality of life in young adulthood [13].

Care should not be limited to the physical and cognitive aspects of the disease but should also focus on the most optimal psychosocial functioning of the patient such as autonomy and social contacts with peers [15]. Knowledge about possible delay in the psychosocial development enables health care providers to aim for the most favorable psychosocial functioning of patients and survivors and to provide timely and relevant interventions. Literature about the achievement of psychosocial developmental milestones in survivors of childhood cancer is rather scarce. Since the first Dutch study twenty years ago [12], as far as we know, only a few, mostly small studies about the psychosocial development of YACCS were published. Nies et al. [16] found no differences in psychosocial development between Dutch YACCS of childhood differentiated thyroid carcinoma and non-affected YACCS, while Lehmann et al. [17], Van Dijk et al. [18] and Dieluweit et al. [19] demonstrated delay in psychosexual development in survivors of childhood cancer.

To expand the limited knowledge about the achievement of psychosocial developmental milestones while growing up with childhood cancer, the present study aimed to compare the psychosocial development of a nationwide cohort of YACCS with a norm group of young adults from the general population. We hypothesized that especially YACCS of CNS cancer achieved fewer psychosocial developmental milestones than the norm group.

Methods

Procedures and participants

YACCS from the Dutch Childhood Cancer Survivors (DCCSS) LATER 2 Psycho-oncology study

Psycho-oncology data were collected between 2017 and 2020 as part of a nationwide cross-sectional cohort study: the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort (diagnosed between 1/1/1963 and 31/12/2001) part 2; clinical visit & questionnaire study. It concerned all patients diagnosed before the age of 18, and at least 5 years after diagnosis at time of study [20]. Survivors were included if they were living in the Netherlands at time of the childhood cancer diagnosis and treated in one of the seven former pediatric oncology/hematology centers in the Netherlands; Amsterdam University Medical Center (VU University Medical Center and Academic Medical Center Amsterdam), Leiden University Medical Center, Erasmus Medical Center Rotterdam, University Medical Center Groningen, Radboud University Medical Center Nijmegen and University Medical Center Utrecht.

YACCS, aged 18-30 years, who gave informed consent for the DCCSS LATER 2 Psycho-oncology study, as part of the DCCSS LATER 2 study, received a questionnaire about psychosocial developmental milestones (Course of Life Questionnaire; CoLQ) at the end of their visit to the outpatient clinic for the DCCSS LATER 2 study or by mail. YACCS had the opportunity to complete the questionnaire online or paper-pencil. Informed consent was obtained from all individual participants included in the study. The medical ethics boards of all participating centers approved the study (MEC2010_332).

Norm group of young adults

In 2012, 655 young adults from the general Dutch population, aged 18-30 years, completed the CoLQ to update previous normative data of the CoLQ that were collected in the context of research among YACCS in 2000/2001 [12]. Data were collected online in cooperation with TNS NIPO (operating under the name of ‘Kantar Public’), a Dutch market research agency. A stratified sample was drawn from a panel of TNS NIPO, based on Dutch population figures regarding key demographics (age, sex, marital status and education) [21].

Measures

The Course of life questionnaire (CoLQ) was used to assess the achievement of psychosocial developmental milestones [12]. The CoLQ was developed, validated and normed in 2000-2001 [12, 22] and updated in 2012 (see Procedures and participants). In the meantime the CoLQ was used in almost 2000 young adults grown up with 18 different pediatric diseases [23]. The CoLQ asks retrospectively whether, or at what age, the respondent had achieved certain milestones. The items are divided into five domains; three psychosocial developmental domains and two risk behavior domains. In the present study, the items of the three psychosocial domains were used: Autonomy development (6 items about autonomy at home and outside home; range 6-12), Psychosexual development (4 items about love and sexual relations; range 4-8), Social development (12 items about social contacts with peers at school and in leisure time; range 12-24). A higher score indicates the accomplishment of more psychosocial developmental milestones.

Validity, test-retest reliability and internal consistency of the CoLQ were satisfactory in previous studies, though the internal consistency of Autonomy was moderate [12, 13, 22]. The Cronbach's alphas in the present study were for Autonomy, Psychosexual and Social development respectively: norm group 0.49, 0.77, 0.74; YACCS 0.54, 0.79, 0.76.

Socio-demographic and medical characteristics

Data on age, sex and medical characteristics (see Table 1) of the participants and non-participants were obtained from the Dutch LATER registry.

Statistical analyses

Differences between participants and non-participants/norm group were tested with independent t-tests and Chi-Square tests. Analysis of variance (ANOVA) by group, age and sex was performed to test differences between YACCS and the norm group on the mean scale scores of the CoLQ. Effect sizes d were calculated by dividing the difference in mean scores between YACCS and norm group by the standard deviation in the norm group. After Cohen [24], effect sizes up to 0.2 were considered to be small, effect sizes about 0.5 to be medium and effect sizes of about 0.8 to be large. Because the distribution of the scale scores of Psychosexual development and Social development was left skewed, we checked the results with non-parametric tests (Mann-Whitney U-tests).

In order to gain more detailed insight into the psychosocial development, differences between YACCS and the norm group on item level, indicating the achievement of individual milestones, were explored additionally. Logistic regression analysis by group, age and sex was carried out, including Odds Ratios (ORs) for YACCS versus the norm group.

The analyses were conducted for the total group of YACCS and for YACCS of CNS cancer. A significance level of 0.013 was used for the analyses on scale level; 0.05 divided by the number of three scales. For the explorative analyses on item level, a significance level of 0.01 was used.

Results

Participants

Of the 1,416 eligible YACCS in the age range 18-30 years, a total of 828 (58.5%) participated in the DCSS LATER 2 study, of whom 558 (67.4%) completed the CoLQ. The percentages female sex and hematopoietic transplant were significantly higher in participants from the present study (CoLQ) than in YACCS who did not participate in the present study or other parts of the DCCSS-LATER 2 study (51.1% versus 38.2% and 8.3% versus 5.4%, respectively).

The total group of YACCS was older than the norm group (Mean 25.78, SD 3.33 versus Mean 24.75, SD 3.79; p 0.00) but they did not differ on sex (51.1% versus 51.0% female). YACCS of CNS cancer (Mean 26.78, SD 3.35; *p* 0.00) were also older than the norm group and the proportion of female was higher in YACCS than in the norm group (68.9% vs 51.0%, *p* 0.01).

Psychosocial developmental milestones on scale level

YACCS total group versus the norm group

No significant differences ($p < 0.013$) were found between the CoLQ mean scale scores of the total group of YACCS and the norm group according to ANOVA by group, age and sex (Table 2). Mann-Whitney U-tests yielded similar results.

YACCS of CNS cancer versus the norm group

CNS YACCS had significantly lower mean CoLQ scales scores than the norm group on Autonomy development (d -0.36; p<0.001) and Psychosexual development (d -0.46; p<0.001). YACCS of CNS cancer did not differ significantly from the norm group on Social development (d -0.26; p 0.035) (Table 2). Mann-Whitney U-tests yielded similar results.

Psychosocial developmental milestones on item level

YACCS total group versus the norm group

The total group of YACCS did not differ significantly (p<0.01) from the norm group on the items of Autonomy and Psychosexual development (Table 3). In the Social development domain, the total group of YACCS was significantly more likely to have been member of a sports club, in the period of secondary school (OR 1.80, p<0.001) and after secondary school (OR 1.72, p<0.001).

YACCS of CNS cancer versus the norm group

In the Autonomy development domain, YACCS of CNS cancer were significantly less likely than the norm group to have achieved three out of the six milestones (Table 3). It concerned: having a paid job in the period of secondary school (OR 0.27, p<0.001), going on holiday without adults before the age of 18 (OR 0.34, p 0.001), leaving their parents' place (OR 0.25, p<0.001).

With regard to Psychosexual development, YACCS of CNS cancer were significantly less likely than the norm group to have achieved three out of the four milestones: first girlfriend or boyfriend before the age of 18 (OR 0.44, p 0.003), for the first time sexual intimacy before the age of 19 (OR 0.48, p 0.009), for the first time sexual intercourse before the age of 19 (OR 0.30, p<0.001).

In the Social development domain, YACCS of CNS cancer were significantly less likely than the norm group to have achieved the following four milestones out of twelve: having more than four friends (OR 0.46, p 0.005), belonging to a group of friends (OR 0.37, p<0.001), spending leisure time with friends (OR 0.23, p<0.001) and going out to a bar or disco (OR 0.47, p 0.009), in the period of secondary school. They were significantly more likely to have been member of a sports club; in the period of secondary school (OR 2.81, p 0.003) and after secondary school (OR 2.22, p 0.004).

Discussion

Overall, the psychosocial development of the total group of YACCS was as favorable as the psychosocial development of peers from the general Dutch population, while YACCS of CNS cancer appeared to be at risk of an unfavorable psychosocial development. YACCS of CNS cancer achieved half as many milestones as their peers in all three psychosocial developmental domains with differences on scale scores of small to moderate size. On the positive side, they were more likely to have been member of a sports club, which is in favor of their social contacts with peers, apart from the physical health advances. This positive result was also found in the total group of YACCS.

On the one hand, the results were not surprising because it is generally known from previous research that, overall, survivors of childhood cancer function well psychosocially, while problems were seen in subgroups of survivors [25], especially in survivors of CNS cancer [13, 26-28]. The cognitive problems many survivors of CNS cancer face, could increase dependence of parents and complicate contacts with peers, which in turn could result in delay of the achievement of psychosocial developmental milestones.

On the other hand, the favorable psychosocial development of the total group of YACCS was not expected because the psychosocial development of YACCS appeared to be hampered in a previous study, twenty years ago [12]. The explanation of these conflicting results is probably twofold. First, improvements in treatment, efforts to reduce toxicity of treatment in particular, and improvements in (psychosocial) care over the past fifteen to twenty years may have helped prevent adverse consequences for psychosocial development. Overall, YACCS in the present study tend to have higher scores on the scales and items of the CoLQ than the YACCS twenty years ago, which indicates that the psychosocial development of YACCS improved between 2000 and 2020. A second explanation may lie in the normative data that reflect developments in Dutch society. In the current normative data, several milestones were achieved by a lower proportion of young adults than in the normative data from 2000/2001 [12], for example membership of sports clubs and age at first sexual intercourse. This is in line with developments in the Dutch society [29, 30] but these developments were not seen in survivors. Maybe this kind of societal developments had less impact on children and adolescents whose life was all about surviving and dealing with the consequences of childhood cancer and its treatment. Regarding the result that survivors were more likely to have been member of a sports club than their peers, it could also be that patients and survivors of childhood cancer were more strongly stimulated to participate in sport clubs than healthy children and adolescents. It is likely that health care providers and parents more and more focus on improving quality of life and wellbeing and consider participation in a sports club an effective way to improve physical and social wellbeing. The explanations discussed above contribute to smaller differences between the psychosocial development of YACCS and peers, in favor of the YACCS as total group.

Study limitations

These results yield insight into the psychosocial development of a large nationwide cohort of YACCS but the results do not paint the complete picture. The psychosocial development is more comprehensive than the milestones assessed retrospectively with the CoLQ. To prevent recall bias, the milestones were strictly factual and do not go further back than the period of primary school. Another limitation of the CoLQ concerns the moderate internal consistency of the Autonomy development scale. It is acceptable to use scales with moderate internal consistency for group comparisons because internal consistency gives an indication of random error; it has nothing to do with systematic error. However, larger random errors make it more difficult to detect differences between groups [31]. This limitation was partly overcome by the analysis of the individual milestones within the scales.

Although more than two-thirds of the YACCS who participated in the DCCSS LATER

2 study completed the CoLQ, the overall response rate was moderate. Probably this did not affect the representativeness of the sample because the medical history of the participants and non-participants was very similar. It is unlikely that the difference in hematopoietic transplant between participants and non-participants biased the results because the number of YACCS who received hematopoietic transplant was small. Finally, the representativeness of the Dutch norm group was not optimal. Our norm sample was more often born in the Netherlands than the general Dutch population (97% versus 91%), more often highly educated (30% versus 25%), more often employed (69% versus 59%) and more often married or living together with a partner (36% versus 31%) [32]. However, we can only speculate about the possible confounding effect on the results of our study because three out of these demographics (educational level, employment and marital status) can be considered a possibly affected outcome of being a survivor of childhood cancer [12, 33, 34].

Clinical implications

Since most of the children and adolescents with cancer reach adulthood today, health care providers need to understand the psychosocial consequences of growing up with or after childhood cancer. Knowledge about possible delay in the psychosocial development of patients and survivors could help optimizing their development to adulthood and achieving a sustainably good quality of life in adulthood. Though overall survivors in this study showed no delay in psychosocial development, survivors of CNS cancer appeared to be at risk of a suboptimal psychosocial development. Further research should reveal whether other subgroups at risk could be designated.

Attention to the achievement of psychosocial milestones is warranted to detect and support those at risk at an early stage. It is recommended to include monitoring of psychosocial developmental milestones in the standards of psychosocial care for patients and survivors [35, 36], especially for patients and survivors of CNS cancer, and especially at important transition moments such as the transition from primary to secondary school or the transition from school to work. Monitoring should not stop after transition from pediatric to adult health care because survivors who were delayed in their psychosocial development deserve attention and support into adulthood. Follow-up of survivors is also important because 'growing into deficit' is a known phenomenon, especially in survivors with cognitive late effects of diagnosis and treatment. Monitoring can be

facilitated by electronic systems that assesses patient-reported outcomes, for example the Dutch KLIK-PROM system [37].

Interventions to optimize psychosocial development should focus on changeable, psychosocial factors, such as coping with the consequences of childhood cancer by patients, survivors and parents. Parents and other caregivers should be encouraged to stimulate autonomy by treating patients and survivors as normally as possible and avoid overprotection. In addition to stimulating autonomy in daily life, it is important to empower survivors to take control of their own health. Stimulating patients and survivors to join in activities with peers is important for their psychosocial functioning. Group programs based on Cognitive behavioral-based therapy (CBT) [38] or Acceptance and Commitment Therapy (ACT)[39] could be helpful in stimulating coping with the consequences of childhood cancer and could prevent and diminish psychosocial problems in patients, survivors and parents [40, 41]].

We found that especially survivors of CNS cancer were less likely to have a paid job during adolescence while jobs during adolescence increase the likelihood of job participation in adulthood [14], offers the possibility to gain work experience and to earn own money, and it improves self-esteem. Therefore, it is recommended to support adolescents in finding (paid) jobs. Last but not least, a personalized approach is of utmost importance, especially in case of CNS cancer because of the complex and individual consequences of CNS cancer. It is important to find out which psychosocial milestones are feasible within the capabilities of the patient or survivor.

Conclusions

Overall, the psychosocial development of survivors was as favorable as in the norm group, but survivors of CNS cancer appeared to be at risk of an unfavorable development in all three developmental domains. Monitoring of the achievement of psychosocial development should be included in the standards of psychosocial care especially for CNS cancer patients and survivors in order to be able to trace and minimize delay in the psychosocial development at an early stage. Considering the complex and individual consequences of CNS cancer, especially CNS cancer survivors need a personalized approach.

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Table 1. Demographic and medical characteristics of YACCS: participants versus non-participants/normgroup

	Participants (N = 558)			Non-participants (N = 858)[a]				Norm group (N = 655)[b]			
	M	SD	Range	M	SD	Range	*p*	M	SD	Range	*p*
Age at study (years)	25.78	3.33	18.10-30.97	25.48	3.45	18.01-31.00	0.10	24.75	3.79	18.0130.99	<0.001
Age at first diagnosis (years)	4.25	3.12	0.00-14.67	4.31	2.99	0.00-14.62	0.73				
Time since first diagnosis (years)	20.92	3.31	15.02-29.17	21.18	3.42	14.81-30.93	0.16				
	N		%	N		%	*p*	N		%	*p*
Sex							<0.001				0.977
Male	273		48.9	530		61.8		321		49.0	
Female	285		51.1	328		38.2		334		51.0	
Age at first diagnosis (years)							0.86				
0-5	418		74.9	644		75.1					
06-11	128		22.9	199		23.2					
12-15	12		2.2	15		1.7					
Time since first diagnosis (years)							0.19				
10-19	258		46.2	375		43.7					
20-29	300		53.8	479		55.8					
30-39	0		0.0	4		0.5					
Diagnosis [c]							0.76				
Leukemia/lymphoma	299		53.6	453		52.8					
Solid tumor	198		35.5	300		35.0					
CNS cancer[d]	61		10.9	105		12.2					
Treatment[e]							0.10				

Chemotherapy only (with/without surgery)	394	70.6	585	68.3	
Radiotherapy only (with/without surgery)	14	2.5	33	3.9	
Surgery alone	48	8.6	96	11.2	
Combination therapy (chemo + radiotherapy, with/without surgery)	98	17.6	129	15.1	
No treatment	4	0.7	14	1.6	
Hematopoietic transplant					0.03
Yes	46	8.3	46	5.4	
No	511	91.7	811	94.6	
Relapse					0.63
Yes	61	10.9	101	11.8	
No	497	89.1	757	88.2	

Significant differences between participants and non-participants and between participants and norm group were presented in bold.
[a] YACCS who did not participate in the present study or any other part of the DCCS-LATER study part 2.
[b] The Norm group consist of young adults from the general Dutch population.
[c] first, primary diagnosis
[d] central nervous system and miscellaneous intracranial and intraspinal neoplasm
[e] for primary cancers and recurrences

Table 2. Psychosocial developmental milestones YACCS (total group and CNS cancer) versus the norm group; CoLQ scale scoresa.

	YACCS total group			YACCS CNS cancer			Norm group			YACCS	CNS
	Males	Females	Total	Males	Females	Total	Males	Females	Total	total vs norm effect size *d*	Cancer vs norm effect size *d*
Autonomy Mean	9.17	9.17	9.17	8.63	8.52	8.56 [b]*	8.95	9.22	9.09	0.05	-0.36
SD	1.52	1.55	1.53	1.64	1.55	1.57	1.44	1.46	1.46		
N	272	282	554	19	42	61	321	334	655		
Psychosexual Mean	6.87	6.90	6.88	6.33	6.10	6.17 [b]*	6.64	6.94	6.80	0.06	-0.46
SD	1.35	1.39	1.37	1.57	1.38	1.43	1.38	1.35	1.37		
N	267	280	547	18	42	60	321	334	655		
Social Mean	20.92	20.35	20.63	20.47	19.12	19.51	20.12	20.33	20.23	0.15	-0.26
SD	2.67	2.83	2.76	2.58	2.81	2.79	2.89	2.59	2.74		
N	264	279	543	17	42	59	321	334	655		

CNS: Central Nervous System and miscellaneous intracranial and intraspinal neoplasm
Cohen's d: mean score of YACCS total group or YACCS CNS cancer minus the mean score of the norm group divided by the standard deviation of the norm group (according to Cohen [27]). After Cohen [27], effect sizes up to 0.2 were considered to be small, effect sizes about 0.5 to be medium and effect sizes of about 0.8 to be large.
*p<0.001
Significant differences (p <0.013) between YACCS and the norm group are presented in bold.
[a] A higher scale score indicates that more milestones were achieved.
[b] YACCS of CNS cancer scored significantly lower than the norm group, according to ANOVA corrected for age and sex.

Table 3. Psychosocial developmental milestones YACCS (total group and CNS cancer) versus the norm group; CoLQ item scores.

	YACCS total group		YACCS CNS cancer		Norm group		total vs Norm	CNS cancer vs Norm
	%	N	%	N	%	N	OR [99%-CI]	OR [99%-CI]
(a) Frequencies of the (dichotomised) items of Autonomy development								
Regular job in your family, primary school							0.74 [0.54;1.01]	0.57 [0.27;1.22]
yes	33.4	186	29.5	18	39.5	259		
no	66.6	371	70.5	43	60.5	396		
Paid jobs, primary school							1.39 [0.99;1.94]	0.81 [0.35;1.86]
yes	31.7	177	23.0	14	23.8	156		
no	68.3	381	77.0	47	76.2	499		
Regular job in your family, secondary school							1.14 [0.84;1.54]	1.03 [0.51;2.08]
yes	55.3	308	54.1	33	52.2	342		
no	44.7	249	45.9	28	47.8	313		
Paid jobs, secondary school							0.76 [0.51;1.14]	0.27 ^{a**} [0.13;0.57]
at the age of 18 or younger	81.5	455	62.3	38	85.0	557		
at the age of 19 or older / never	18.5	103	37.7	23	15.0	98		
For the first time being on holiday without adults							1.05 [0.78;1.42]	0.34 ^{a*} [0.15;0.78]
at the age of 17 or younger	44.4	247	21.3	13	42.6	279		
at the age of 18 or older / never	55.6	309	78.7	48	57.4	376		
Leaving your parents' place							0.70 [0.47;1.06]	0.25 ^{a**} [0.09;0.65]
not living with your parents	69.7	388	65.6	40	65.8	431		
still living with your parents	30.3	169	34.4	21	34.2	224		
(b) Frequencies of the (dichotomised) items of Psycho-sexual development								
First girlfriend / boyfriend							1.00 [0.73;1.37]	0.44 ^{a*} [0.22;0.89]
at the age of 17 or younger	64.5	359	45.9	28	63.4	415		
at the age of 18 or older / never	35.5	198	54.1	33	36.6	240		
For the first time falling in love							1.16 [0.73;1.83]	0.51 [0.21;1.23]
at the age of 18 or younger	88.8	492	78.7	48	86.6	567		
at the age of 19 or older / never	11.2	62	21.3	13	13.4	88		

For the first time sexual intimacy							1.10 [.78;1.55]	0.48^{a*} [0.23;0.99]
at the age of 18 or younger	75.3	417	60.0	36	72.4	474		
at the age of 19 or older / never	24.7	137	40.0	24	27.6	181		
For the first time sexual intercourse							1.04 [0.77;1.42]	0.30^{a**} [0.14;0.63]
at the age of 18 or younger	59.5	328	32.8	20	57.4	376		
at the age of 19 or older / never	40.5	223	67.2	41	42.6	279		

CNS Central Nervous System and miscellaneous intracranial and intraspinal neoplasm; OR odds ratio / exponent B; CI Confidence Interval

*p<0.01; **p<0.001; Significant differences (p<0.01) between YACCS and the norm group are presented in bold.

[a] The proportion of YACCS CNS cancer that achieved the milestone was significantly lower than the proportion in the norm group, according to logistic regression analyses corrected for age and sex.

[b] The proportion of YACCS CNS cancer that achieved the milestone was significantly higher than the proportion in the norm group, according to logistic regression analyses corrected for age and sex

Table 3 continued

	YACCS total group		YACCS CNS cancer		Norm group		total vs Norm	CNS cancer vs Norm
	%	N	%	N	%	N	OR [99%-CI]	OR [99%-CI]
(c) Frequencies of the (dichotomised) items of Social development								
At least one year of membership in a sports club, primary school							1.37 [0.92;2.04]	2.83 [0.82;9.75]
yes	84.5	469	91.7	55	80.3	526		
no	15.5	86	8.3	5	19.7	129		
Number of friends in first-third grade, primary school							1.04 [0.76;1.41]	0.67 [0.33;1.34]
4 or more	61.0	340	50.8	31	60.0	393		
less than 4	39.0	217	49.2	30	40.0	262		
Number of friends in fourth-sixth grade, primary school							1.14 [0.84;1.56]	0.68 [0.34;1.38]
4 or more	63.4	352	50.8	31	60.3	395		
less than 4	36.6	203	49.2	30	39.7	260		
Best friend, primary school							1.39 [0.97;1.97]	0.81 [0.37;1.75]
yes	78.7	437	70.5	43	71.9	471		
no	21.3	118	29.5	18	28.1	184		
Most of the time playing with….., primary school							0.83 [0.56;1.23]	0.46 [0.21;1.02]
friends	81.5	455	72.1	44	84.0	550		
brothers and/or sisters, parents, on your own	18.5	103	27.9	17	16.0	105		
At least one year of membership in a sports club, secondary school							1.80^{b}** [1.29;2.50]	2.81 ^{b}* [1.15;6.85]
yes	74.5	415	81.7	49	62.4	409		
no	25.5	142	18.3	11	37.6	246		
Number of friends, secondary school							1.15 [0.84;1.57]	0.46 ^{a}* [0.23;0.94]
4 or more						406		
less than 4	64.5	360	42.6	26	62.0	249		
	35.5	198	57.4	35	38.0			

Best friend, secondary school							1.22 [0.88;1.69]	0.79 [0.38;1.66]
yes	70.6	393	63.9	39	66.1	433		
no	29.4	164	36.1	22	33.9	222		
Belonging to a group of friends, secondary school							1.14 [0.79;1.66]	0.37^{a}** [0.18;0.76]
yes	80.1	444	57.4	35	78.6	515		
no	19.9	110	42.6	26	21.4	140		
Leisure time, mainly with ….., secondary school							0.74 [0.50;1.10]	0.23^{a}** [0.11;0.48]
friends	79.9	446	57.4	35	83.5	547		
brothers and/or sisters, parents, on your own	20.1	112	42.6	26	16.5	108		
Going out to a bar or disco, secondary school							0.93 [0.66;1.32]	0.47 ^{a}* [0.23;0.99]
sometimes / often	74.4	415	60.7	37	74.0	485		
never	25.6	143	39.3	24	26.0	170		
At least one year of membership in a sports club, after secondary school							1.72 ^{b}** [1.27;2.34]	2.22 ^{b}* [1.09;4.52]
yes	53.0	296	57.4	35	39.4	258		
no	47.0	262	42.6	26	60.6	397		

CNS Central Nervous System and miscellaneous intracranial and intraspinal neoplasm; OR odds ratio / exponent B; CI Confidence Interval

*p<0.01; **p<0.001; Significant differences (p<0.01) between YACCS and the norm group are presented in bold.

[a]The proportion of YACCS CNS cancer that achieved the milestone was significantly lower than the proportion in the norm group, according to logistic regression analyses corrected for age and sex.

[b]The proportion of YACCS CNS cancer that achieved the milestone was significantly higher than the proportion in the norm group, according to logistic regression analyses corrected for age and sex.

6

CHAPTER 6

A VULNERABLE AGE GROUP: THE IMPACT OF CANCER ON THE PSYCHOSOCIAL WELL-BEING OF YOUNG ADULT CHILDHOOD CANCER SURVIVORS

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Abstract

Purpose

This study aimed to increase our understanding of the psychosocial well-being of young adult childhood cancer survivors (YACCS) as well as the positive and negative impacts of cancer.

Methods

YACCS (aged 18-30, diagnosed ≤18, time since diagnosis ≥5 years) cross-sectionally filled out the "Pediatric Quality of Life Inventory Young Adults" (PedsQL-YA), "Hospital Anxiety and Depression Scale" (HADS), "Checklist Individual Strengths" (CIS-20R) to measure fatigue and survivor-specific "Impact of Cancer – Childhood Survivors" (IOC-CS), which measures the long-term impact of childhood cancer in several domains. Descriptive statistics (IOC-CS), logistic regression (HADS, CIS-20R), and ANOVA (PedsQL-YA, HADS, CIS-20R) were performed. Associations between positive and negative impacts of childhood cancer and psychosocial outcomes were examined with linear regression analyses.

Results

YACCS (N=151, 61.6% female, mean age 24.1±3.6, mean time since diagnosis 13.6±3.8) reported lower HRQOL ($-.4 \leq d \leq -.5$, $p \leq .001$) and more anxiety ($d=.4$, $p \leq .001$), depression ($d=.4$, $p \leq .01$), and fatigue ($.3 \leq d \leq .5$, $p \leq .001$) than young adults from the general Dutch population. They were at an increased risk of experiencing (sub)clinical anxiety (OR=1.8, $p=.017$). YACCS reported more impact on scales representing a positive rather than negative impact of CC. Various domains of impact of childhood cancer were related to psychosocial outcomes, especially "Life Challenges" (HRQOL β=-.18, anxiety β=.36, depression β=.29) and "Body & Health" (HRQOL β=.27, anxiety β=-.25, depression β=-.26, fatigue β=-.47).

Conclusion

YACCS are vulnerable to psychosocial difficulties, but they also experience positive long-term impacts of childhood cancer. Positive and negative impacts of childhood cancer were associated with psychosocial outcomes in YACCS. Screening of psychosocial outcomes and offering targeted interventions are necessary to optimize psychosocial long-term follow-up care for YACCS.

Background

With the survival rate of childhood cancer rising, researchers and clinicians have an increased interest in the late effects of treatment. Long-term physical morbidity is high for childhood cancer survivors (CCS) [1, 2], as well as difficulty with psychological well-being [3-5].

Looking at the well-being of a patient population within the framework of a biopsychosocial model can be beneficial when studying the role of physical, psychological, and social factors [6]. In the biopsychosocial model, behavioral and social circumstances can influence the emergence, course and experience of a disease, while the disease in itself influences psychological well-being and social relationships [6]. In accordance with the biopsychosocial model, knowledge of psychosocial late effects is crucial for improving life beyond childhood cancer. Attention to psychosocial late effects may be especially important for young adult childhood cancer survivors (YACCS) as young adulthood is a crucial life phase with many developmental challenges to overcome, e.g., relationships, sexuality, cognition, education, employment and developing autonomy. A life-threatening disease such as cancer can disrupt this crucial development. This seems to be confirmed by research, as overall, YACCS reach fewer developmental milestones than young adults without a history of childhood cancer, which negatively affects their quality of life [7, 8]. Both age-specific challenges and their potential disruption due to cancer can be seen within biological, psychological and social domains, and can often present in multiple domains.

Contradicting findings have been reported on Health-Related Quality of Life (HRQOL) and well-being of CCS [3, 9-17]. Most (young) adult CCS did not report psychopathology, but survivors of central nervous system (CNS) tumors, those treated with cranial irradiation, and those with chronic health conditions had worse outcomes (distress, anxiety, depression, somatization, HRQOL, mental health dysfunction, fatigue, PTSD, unemployment, educational attainment) compared to reference groups [3, 4, 12, 13, 17-23]. While some studies indicate that fatigue is a problem among (YA)CCS [18, 20], other studies show that fatigue levels among CCS do not differ from reference groups or that clinical significance is questionable [24, 25]. A recent review concluded that the prevalence of severe fatigue among CCS remains unclear, due in part to the heterogeneity of studies regarding inclusion criteria and samples as well as the questionnaires used to assess fatigue [26]. As fatigue has previously been linked to poor (HR)QOL [5, 18, 27], it is crucial to investigate the incidence of fatigue in the Dutch population of YACCS and explore underlying mechanisms.

While almost all CCS studies include YACCS, most research among CCS does not differentiate between children, young adults and older adults. Researching YACCS separately from older and younger CCS is crucial in order to understand the specific vulnerabilities and needs of young adults, which is necessary to provide CCS with targeted interventions that may help them bridge the gap between themselves and healthy peers early in their lives.

Besides the distinction of YACCS from both younger and older CCS, it is important to study YACCS separately from patients with and survivors of adolescent and young adult (AYA(-S)) cancer. While YACCS and AYA(-S) may be the same age, YACCS distinguish themselves regarding their diagnosis and treatment, a longer time since diagnosis, the presence of late-effects of treatment, and a possible lack of knowledge about both their medical history and risk of late effects because of missed information during childhood. AYA cancer patients and YACCS are sometimes studied as one group, while results for the one group are not generalizable to the other [28, 29]. Survivors of cancer in the AYA age report challenges (i.e., financial independence and protecting parents, cognitive decline in case of a brain tumor). These challenges differ from those reported by YACCS: identity formation, social isolation, health care transitions, and for those diagnosed with a brain tumor: cognitive deficits, limited career options, poor social skills. However, the two groups also express common challenges, such as physical appearance, fertility, late effects, social relationships, and changing priorities [30].

In order to increase our understanding of the experiences of and challenges for YACCS (aged 18-30, diagnosis at age <18), it is of great importance to look further than generic psychosocial constructs. Taking survivor-specific psychosocial factors into account can yield a broader perspective on the functioning of YACCS, which may help us tailor interventions to their needs. To gain broad insight into this functioning, the present study focused on generic psychosocial well-being, psychopathology, and survivor-specific constructs. First, to align with the previous literature, this study aimed to describe generic HRQOL, depression, anxiety, and fatigue in Dutch YACCS in comparison with reference groups. Secondly, the study aimed to describe the perceived impact of CC, both positive and negative. By examining this survivor-specific construct, the authors aimed to deepen our insight into the experiences of YACCS. Finally, the study aimed to investigate the role of the survivor-specific construct of perceived impact in explaining generic psychosocial outcomes and psychopathology (HRQOL, depression, anxiety, and fatigue) in Dutch YACCS controlled for sociodemographic and medical characteristics.

Methods

A total of 400 YACCS were selected by a data manager of the Dutch LATER registry from 946 YACCS who met the eligibility criteria for the study (aged 18-30, diagnosed at age <18, ≥5 years since diagnosis, treated at one of the four participating Dutch pediatric oncology centers, and no participation in the Dutch LATER study in the past 4 months) in the pseudonymized Dutch LATER registry. The selection was stratified in order to have an equal representation of men and women between the ages of 18 to 24 and 25 to 30, as well as various groups based on age at diagnosis.

A total of 22 YACCS were excluded from the invitation for being recently deceased, having no known address, or living abroad. In 2018, the 378 remaining eligible YACCS were invited to fill out questionnaires on paper or online. Participants provided written informed consent and the Medical Ethical Committee of the University Hospital Utrecht reviewed this study (case number 18/256).

Measures

Medical characteristics. Diagnosis and treatment data on the initial childhood cancer and recurrences, as well as aggregated data for non-participants, was collected from the Dutch LATER registry.

Sociodemographic characteristics. Date of birth, gender, marital status, number of children, employment, and educational level (attained and current) were acquired.

HRQOL. The Pediatric Quality of Life Inventory Young Adults (PedsQL-YA) measures HRQOL in four scales (Physical Functioning: 8 items, Cronbach's α=.86; Emotional Functioning: 5 items, Cronbach's α=.84; Social Functioning: 5 items, Cronbach's α=.85; and Work/School Functioning: 5 items, Cronbach's α=.80), a total scale (all 23 items, Cronbach's α=.92), and a Psychosocial Summary Scale (PSY) combining emotional, social, and work/school functioning (15 items, Cronbach's α=.90). Higher scores (range 0-100) indicate better HRQOL. The PedsQL-YA has good psychometric properties and a reference group of Dutch young adults is available [31].

Anxiety and depression. The Hospital Anxiety and Depression Scale (HADS) measures anxiety and depression in separate scales and a total scale [32]. Participants are asked to respond to 14 statements, seven about anxiety (Cronbach's α=.88) and seven about depression (Cronbach's α=.85) by selecting one of four reactions specific to that statement. Higher scores on the HADS signal higher levels of anxiety and depression. Scale scores ≥8 for anxiety and depression are considered (sub)clinical. The HADS has good psychometric properties [33] and a reference group of Dutch young adults is available [34].

Fatigue The Checklist Individual Strength (CIS-20R) is a valid measure of fatigue, consisting of four scales: Fatigue Severity (8 items, Cronbach's α=.79), Concentration (5 items, Cronbach's α=.91), Motivation (4 items, Cronbach's α=.82), and Activity (3 items, Cronbach's α=.90) . In this study the total score was not used, as its meaning is unclear [35]. Higher scores reflect more fatigue and fatigue-related impairment. The CIS-20R has good psychometric properties and a reference group of Dutch young adults is available [35].

Impact of cancer The IOC-CS is a survivor-specific questionnaire that measures perceived negative and positive impacts of CC [36]. It includes five positive impact scales (Socializing: 3 items, Cronbach's α=.59; Talking with parents: 4 items, Cronbach's α=.92; Body & Health: 8 items, Cronbach's α=.80; Health Literacy: 5 items, Cronbach's α=.71; Personal Growth: 5 items, Cronbach's α=.71) and six negative impact scales (Thinking & Memory problems: 5 items, Cronbach's α=.76; Sibling Concerns: 2 items, Cronbach's α=.69; Life Challenges: 12 items, Cronbach's α=.86; Relationship Concerns: 7 items, Cronbach's α=.65 for partnered YACCS and .63 for non-partnered YACCS; Financial Problems: 3 items, Cronbach's α=.77). Higher scores indicate more positive or negative impact. The IOC-CS has been translated and back-translated into Dutch by Grootenhuis and Maurice-Stam in cooperation with the author of the original IOC-CS. The original version has good psychometric properties [36].

Statistical analyses

To compare characteristics of participants and non-participants, one sample t-tests and binominal tests were used.

Differences between YACCS and the reference group were tested, controlled for age and sex, using logistic regression with odds ratio (HADS, CIS-20R) and ANOVA (PedsQL-YA, HADS, CIS-20R) with Cohen's *d* (.2 small, .5 medium, .8 large effect size) [37]. The IOC-CS scales were analyzed descriptively, using item scores and mean item scale scores.

Associations between positive and negative impacts of cancer (IOC-CS) and psychosocial outcomes were examined with multiple linear regression analyses. Separate models were estimated for PedsQL-YA total HRQOL, HADS anxiety, HADS depression and CIS-20R Fatigue Severity, with positive and negative impacts of cancer (the IOC-CS mean item scale scores) as independent variables, while controlling for sociodemographic (sex and education) and medical (age at diagnosis, time since diagnosis, tumor type, recurrences, treatment) characteristics. All independent variables were entered in one step in all models. A significance level of .05 was used for all analyses based on two-sided tests. To adjust for multiple comparisons, a Bonferroni correction was applied per questionnaire for the PedsQL-YA (.05/6=.008), HADS (.05/3=.017), and CIS-20R (.05/4=.013).

Results

Sample Characteristics

A total of 151 YACCS (61.6% female, mean age 24.1±3.6, mean time since diagnosis 13.6±3.8) completed the questionnaire (response rate=40%). Participants were more often female and less likely to have received a bone marrow transplantation (BMT) than non-participants (Table 1).

Psychosocial well-being of YACCS compared to the reference group

YACCS reported lower HRQOL than the reference group on all PedsQL-YA scales ($-.4 \le d \le -.5$) as well as higher levels of anxiety ($d=.4$, $p \le .001$) and depression ($d=.4$, $p=.019$). YACCS were more likely to experience (sub)clinical anxiety than the reference group (29.8% vs. 18.8%, OR=1.8). On the CIS-20R, YACCS reported increased Fatigue Severity ($d=.5$) and worse Concentration ($d=.3$) and were more likely to experience severe fatigue than the reference group (36.2% vs. 20.8%, OR=2.4, Table 2).

Positive and negative impacts of childhood cancer

On scale level, most positive impact was reported on Socializing and least on Personal Growth. On item level, least positive impact was reported on “I have a special bond with others with cancer,” “I have all the information I need,” and “I know where to find information about cancer” (Table 3).

On scale level, most negative impact was reported on Thinking/Memory and least on Financial Problems. On item level, highest negative impact was reported on “It’s hard to make decisions,” “I worry about how my cancer affects my sibling,” and “I feel like I missed out on life” (Table 3).

Associations of impact of childhood cancer with psychosocial outcomes

Two positive and two negative survivor-specific impact scales were associated with more than one psychosocial outcome (Table 4). More positive perception of Socializing was associated with better HRQOL ($\beta=.24$) and less depression ($\beta=-.24$). More positive perception of one’s Body & Health was related to better HRQOL ($\beta=.27$) and less anxiety ($\beta=-.25$), depression ($\beta=-.26$), and fatigue ($\beta=-.47$).

Regarding the negative impact scales, experiencing more Life Challenges was associated with lower HRQOL ($\beta=-.18$), more anxiety ($\beta=.36$), and more depression ($\beta=.29$). More Relationship Concerns were associated with lower HRQOL ($\beta=-.16$) and more depression (β=.19).

Discussion

This is one of the first studies to investigate survivor-specific psychosocial well-being in a large sample of YACCS specifically, and the first to do so in the Netherlands. This study shows that YACCS appear to be vulnerable to psychosocial difficulties. They reported worse HRQOL and more anxiety, depression, and fatigue than the reference group. Effect sizes ranged from small (depression) to large (fatigue severity). This is in accordance with findings of some earlier studies in CCS cohorts, which include YACCS but do not focus specifically on them [3, 5, 13, 15, 38-40]. Psychosocial well-being similar to that of the general population has also been reported [9-12, 16, 19, 41, 42].

Our study illuminates the experiences of YACCS regarding impact of childhood cancer. The IOC-CS scale scores in this study found more impact on concepts representing positive impact (Socializing, Talking with parents, Body & Health) than on concepts representing negative impact (Thinking & Memory problems, Life Challenges). This finding is in line with a study among CCS in the USA [36]. Survivors may have a tendency to minimize the effect of the negative aspects of their cancer experience on their current lives while maximizing the positive aspects [43, 44].

Clinical implications

Based on our findings that YACCS report worse HRQOL and more anxiety, depression, and fatigue, the authors recommend routine psychosocial screening during long-term follow-up (LTFU). LTFU clinics need to have mechanisms, e.g., in-house psychologists or adequate referral options, in place to follow-up when screening results call for psychosocial support for a YACCS. These recommendations are in line with the existing standards of care [45]. Fatigue warrants special attention as a known late effect of treatment. In a large cohort, fatigue, as well as poor sleep and vitality, was shown to be associated with survivors' neurocognitive functioning independent of other well-known risk factors (e.g., cranial radiation and female gender) [46], making it an important topic to be addressed by physicians, nurses, and psychosocial care providers during LTFU.

YACCS' scores on some specific items of the IOC-CS yield important insights for psychosocial care. Item scores on Health Literacy of the IOC-CS showed that YACCS perceived a lack of information about the long-term effects of childhood cancer as well as a lack of the skills required to obtain such information. Information provision and supporting YACCS' health literacy skills are important tasks for health care providers during LTFU. YACCS have previously reported problems with autonomy development [7] and gaining independence from their parents [47, 48], as well as with lacking information [49]. This disruption in crucial developmental areas during young adulthood could have consequences for their psychosocial well-being as well as their self-management in adulthood. YACCS may therefore benefit from a focus on patient-empowerment during their LTFU.

Positive and negative impacts of childhood cancer were more strongly associated with psychosocial well-being than sociodemographic and medical characteristics (see Table 4), which Zebrack [44] also found. These findings align with earlier studies that showed the role of self-reported functional limitations and health beliefs in relation to HRQOL of CCS [42, 50] as well as a strong association between fatigue and emotional distress and functional limitations in survivors of childhood Hodgkin's lymphoma [51]. YACCS' perception of their Body & Health, Life Challenges, Socializing, and Relationships need special attention during LTFU based on their associations with psychosocial outcomes found in this study. While Thinking and Memory problems had the highest perceived negative impact, they were not associated with the psychosocial outcomes in our sample of YACCS. This finding is worth further exploration, because previous literature suggests that neuropsychological late effects of childhood cancer are common and can be severe [52, 53]. Furthermore, previous results showed that neuropsychological late effects can potentially influence psychosocial outcomes such as HRQOL [54-56] and fatigue [46].

Regarding the high percentages of explained variance in our models, it is arguable that perceived impact of childhood cancer and generic psychosocial outcomes are overlapping constructs. Furthermore, it is plausible to assume that the associations between impact of childhood cancer and psychosocial well-being are bidirectional. Accordingly, interventions directed at the perceived impact of cancer, e.g. cognitive behavioral therapy (CBT), could also improve psychosocial well-being, and vice versa. The value of understanding perceived impact of childhood cancer is that it may help us tailor interventions specifically to YACCS by focusing on maladaptive cognitions related to the impact of childhood cancer in young adulthood. In line with this understanding, the psychosocial department at the Princess Máxima Center has recently added an e-health module for YACCS to our CBT-based program “Op Koers” [57], and conducted a pilot. The initial results were promising. The authors’ next research efforts will focus on evaluating the intervention in order to provide this vulnerable group with an evidence-based psychosocial program.

Study limitations

This study has some limitations that need to be taken into account. First, there was a 40% response rate, though non-participants hardly differed from participants. Compared to other studies from the Dutch LATER cohort, survivors of CNS tumors seem to be underrepresented in our study [58].This may complicate the generalization of our study’s findings to all Dutch YACCS. Our within-group models are probably unaffected by the response rate. Second, because of the cross-sectional nature of this study, it was impossible to distinguish between cause and effect within the relationships found in our sample. Third, educational attainment was included as a predictor in our regression models because this variable was most indicative of socioeconomic status (SES) out of the data available. However, educational attainment has previously been found to be an outcome of childhood cancer history in the literature [23, 47]. Fourth, the presence of chronic health problems due to the disease were not taken into account in the regression models because we did not have access to data on disease burden.

Lastly, a limited number of independent variables were entered into our linear regression model. The aim of this study was to investigate the role of the positive and negative impact of cancer as opposed to creating the most fitting model to explain psychosocial outcomes in YACCS.

Conclusion

YACCS are a vulnerable group. That said, they reported more positive than negative impacts of CC. The perceived impact of CC, positive as well as negative, was more strongly associated with psychosocial well-being than sociodemographic and medical characteristics. Addressing perceived impact of childhood cancer may be the gateway for targeting psychosocial interventions in pediatric oncology. Routine psychosocial screening of YACCS for HRQOL, anxiety, depression, and fatigue is recommended. Psychosocial interventions should be offered to YACCS proactively and focus primarily on perceived impact of cancer.

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Table 1. Characteristics of participants and non-participants

	Participants (N ≈ 151)		Non-participants (N = 223)		
	Mean ± SD (range)	%(N)	Mean ± SD (range)	%(N)	*p* value
Socio-demographic	24.1 ± 3.6		24.0 ± 3.4		
Age (years)	(18-30)		(18-30)		.659
Sex (female)		61.6 (93)		40.8 (90)	.000**
Marital/Relationship status					
Yes		51.0 (75)			
No		49.0 (72)			
Employment status					
Paid occupation		70.9 (105)			
No paid occupation		29.1 (43)			
Educational attainment					
Low		19.3 (28)			
Middle		48.3 (70)			
High		32.4 (47)			
Current education					
Low		3.1 (2)			
Middle		27.7 (18)			
High		69.2 (45)			
Medical characteristics					
Age at diagnosis	10.5 ± 4.5 (.4 – 17)		10.6 ± 4.5 (0-18)		.756
Time since diagnosis	13.6 ± 3.8 (6 – 27)		13.5 ± 3.7 (6-28)		.652
Diagnosis					
Hematologic cancers		66.9 (101)		61.7 (142)	.119
CNS tumors		8.6 (13)		9.9 (22)	.358
Solid tumors		24.5 (37)		28.3 (63)	.173
Recurrence		13.9 (21)			
Treatment[a, b]					
Surgery (S)		61.6 (93)		63.7 (142)	.323
Chemotherapy (CT)		95.4 (144)		95.5 (213)	.522
Radiotherapy (RT)		37.1 (56)		35.0 (78)	.323
SCT/BMT		7.3 (11)		13.5 (30)	.012*
Treatment combinations[b]					
CT only		32.5 (49)			
CT+RT		6.0 (9)			
RT+S		4.6 (7)			
CT+S		30.5 (46)			
CT+S+RT		26.5 (40)			

* p<0.05; ** p<0.01 (two-sided)

[a] More than one category possible

[b] Treatments for primary tumor and (if applicable) recurrence(s)

Table 2. Psychosocial well-being of YACCS (N ≈ 151) versus reference groups.

	YACCS				Reference group[a]				
	M	SD	95%CI	%(N)	M	SD	%(N)	Cohen's*d*	OR
PedsQL-YA (total score)	77.7*	16.3	[75.0;80.3]		83.9	13.1		-.5	
Physical	80.2*	19.7	[77.0;83.3]		87.1	16.0		-.4	
Emotional	70.2*	21.2	[66.8;73.6]		77.2	18.0		-.4	
Social	82.1*	20.0	[78.9;85.3]		87.2	14.5		-.4	
Work/school	76.8*	19.1	[73.7;79.8]		82.3	15.7		-.4	
Psychosocial	76.3*	16.9	[73.6;79.0]		82.2	13.7		-.4	
HADS (total score)	9.4*	6.9	[8.3;10.5]		7.0	5.7		.4	
Anxiety	5.9*	4.3	[5.3;6.6]		4.4	3.5		.4	
Depression	3.5*	3.5	[2.9;4.1]		2.6	2.8		.3	
(Sub)clinical anxiety (≥8)			[.2;.4]	30.2 (45)			18.8 (42)		1.8*
(Sub)clinical depression (≥8)			[.1;.2]	12.8(19)			7.6 (17)		1.7
CIS-20R									
Fatigue Severity	30.6*	9.9	[29.0;32.2]		25.2	10.4		.5	
Concentration	15.8*	7.8	[14.6;17.1]		13.8	6.3		.3	
Motivation	10.6	5.1	[9.8;11.5]		11.1	4.7		-.1	
Activity	9.9	5.1	[9.1;10.7]		9.7	4.6		.1	
Severe fatigue (≥35)			[.3;.4]	36.2 (54)			20.8 (55)		2.4***

M mean; SD standard deviation; OR odds ratio

PedsQL-YA: *p<.008 (two-sided)

HADS: *p<.017 (two-sided)

CIS-20R: *p<.013 (two-sided)

[a] PedsQL-YA N=649; HADS N=224; CIS-20-R N=264

Table 3: Perceived impact of cancer according to the IOC-CS

Positive impact scales	N	M^{a}	SD
Socializing	149	4.0	.91
Do not feel left out of friends' lives	149	4.3	1.1
Do not avoid social activities	147	4.2	1.1
Make friends easily	149	3.4	1.1
Talking with Parents	150	3.5	1.2
Mom comfortable talking about cancer	148	3.5	1.3
Can talk with dad about cancer	147	3.5	1.3
Can talk with mom about cancer	148	3.5	1.4
Dad comfortable talking about cancer	146	3.4	1.3
Body & Health	151	3.5	.7
Eat healthy diet	151	3.9	.7
Lead healthy life	151	3.9	.8
Self-confident	151	3.6	.9
Feel in control	151	3.5	1.1
Healthy as those w/o cancer	151	3.4	1.3
Believe I'm attractive	151	3.2	1.0
Like my body	151	3.2	1.0
Exercise	151	3.1	1.2
Health Literacy	151	3.3	.8
Easy to talk to doctor about cancer	151	4.1	1.0
Know who to see for med problems	151	4.0	.8
Feel doctor knows cancer effects	150	3.1	1.3
Know where to find cancer info	151	2.8	1.3
Have all cancer info I need	150	2.6	1.1
Personal Growth	150	2.8	.9
More mature than those without cancer	151	3.2	1.4
Cancer part of self	150	3.1	1.3
Learned about self	150	3.1	1.3
Good things came from cancer	150	2.9	1.3
Special bond with others with cancer	145	1.9	1.1
Negative impact scales			
Thinking / Memory	150	2.5	.9
Hard to make decisions	150	3.1	1.2
Hard time thinking	150	2.6	1.4
Trouble w/long-term memory	150	2.5	1.4
Hard to learn	150	2.3	.9
Trouble w/short-term memory	150	2.2	1.3
Sibling Concerns	141	2.3	1.1
Worry how cancer affected siblings	142	2.8	1.4
Sibling had problems related to my cancer	141	1.8	1.2
Life Challenges	151	2.1	.8
Missed out on life	149	2.8	1.5
Wonder why I got cancer	151	2.5	1.4
Worry about health	150	2.4	1.3
Wonder why I survived	151	2.4	1.5
Want to forget cancer	150	2.2	1.4
Afraid to die	150	2.1	1.4
Unsure about future	150	2.1	1.3
Worry I will die at young age	150	2.0	1.3
Cancer controls my life	148	2.0	1.2
Angry about cancer	151	1.9	1.2
Time is running out	149	1.5	1.0
Something I did caused cancer	151	1.5	1.1

Relationship Concerns total	150	1.8	.8
Partnered	77	1.7	.7
Hard to talk to partner about health problem	77	2.1	.9
Worry partner will leave if cancer returns	77	1.7	1.2
Worry about having sex with partner	77	1.4	.7
Non-partnered	73	1.9	.8
Worry about telling potential partner about fertility	73	2.2	1.3
Worry about having no relationship	73	2.2	1.2
Worry about having sex	73	1.8	1.2
Worry about telling potential partner about cancer	73	1.6	.9
Financial Problems	147	1.3	.5
Trouble getting assistance/services	147	1.5	1.0
Parents financial problems from cancer	147	1.2	.6
Financial problems from cancer	147	1.1	.6

[a] Mean item scores: 1 = “none at all”, 2 = “a little bit” 3 = “somewhat”, 4 = “quite a bit” 5 = “very much

Table 4: Linear regression models for HRQOL (PedsQL-YA total score), anxiety, depression (HADS), and fatigue (CIS-20R), with positive and negative impacts of cancer (IOC-CS) as independent variables and controlling for sociodemographic and medical characteristics; N = 133.

	HRQOL			Anxiety			Depression			Fatigue Severity		
	β	B	95%CI	β	B	95%CI	β	B	95%CI	β	B	95%CI
Sex (ref=male) Education (ref=low)	ns			.17*	1.40	[.19;2.62]	-.16*	-1.12	[-2.05;-.19]	ns		
Middle	ns			ns			ns			ns		
High	ns			ns			ns			ns		
Age at diagnosis	ns			ns			ns			ns		
Time since diagnosis	ns			ns			ns			ns		
Diagnosis (ref = hematological)												
CNS tumor	ns			-.24*	-3.86	[-7.05;-.67]	ns			ns		
Solid tumor	ns			ns			ns			ns		
Recurrence	ns			ns			ns			ns		
Treatment (ref = chemotherapy only)												
Chemotherapy and radiotherapy	ns			ns			ns			ns		
Chemotherapy and surgery	ns			ns			ns			ns		
Radiotherapy and surgery	ns			ns			ns			ns		
Surgery, chemo-, and radiotherapy	ns			ns			ns			ns		
BMT (ref= no)	ns			ns			ns			ns		
Positive impact of cancer												
Socializing	.24**	4.22	[1.55; 6.89]	ns			-.24**	-.94	[-1.60;-.29]	ns		
Talking with parents	ns			ns			ns			ns		
Body & Health	.27**	6.73	[2.65; 10.81]	-.25*	-1.61	[-2.91;-.30]	-.26**	-1.40	[-2.40;-.40]	-.47***	-7.37	[-10.68;-4.06]
Health Literacy	ns			ns			.20*	.91	[.14;.69]	ns		
Personal Growth	ns			ns			ns			ns		

Negative impact of cancer	ns			ns			ns			ns
Thinking/Memory	ns			ns			ns			ns
Sibling Concerns	.14*	1.92	[.01; 3.82]	ns			ns			ns
Life Challenges	-.18*	-3.45	[-6.79;-.11]	.36**	1.86	[.79;2.93]	.29**	1.24	[.43;2.06]	ns
Relationship Concerns	-.16*	-3.26	[-6.43;-.08]	ns			.19*	.85	[.07;1.63]	ns
Financial Concerns	ns			-.26**	-2.19	[-3.58;-.80]	ns			ns
R^2	.662***			.513***			.572***			.458***

ns non-significant, but still included in the model
* $p<.05$ ** $p<.01$ *** $p<.001$ (two-sided).


7

CHAPTER 7

SUPPORT NEEDS OF DUTCH YOUNG ADULT CHILDHOOD CANCER SURVIVORS

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Abstract

Background

Studies about support needs of young adult childhood cancer survivors (YACCS) previously focused mainly on information needs. This study assessed support needs and associated factors (socio-demographic, medical, and psychosocial functioning) in Dutch YACCS.

Methods

YACCS (aged 18-30, diagnosed ≤18 years, time since diagnosis ≥5 years) cross-sectionally filled out a questionnaire regarding their need for various types of support (concrete information, personal counseling, and peer contact) in eight domains (physical consequences of childhood cancer, social-emotional consequences, relationships and sexuality, fertility, lifestyle, school and work, future perspective, insurance and mortgage), and questionnaires assessing health-related quality of life (PedsQL-YA), anxiety and depression (HADS), and fatigue (CIS-20R). Descriptive statistics were used to describe support needs. Linear regression was used to identify characteristics associated with support needs.

Results

151 YACCS participated (response = 40%). Most YACCS reported a need for support in one or more domains (88.0%, N=133). More than half of the participants reported a need for concrete information in the domains lifestyle, fertility, and physical consequences of childhood cancer and 25-50% in the domains insurance and mortgages, future perspective, and social-emotional consequences of childhood cancer. In the domains lifestyle, physical as well as emotional consequences of childhood cancer, 25-50% reported a need for counseling. Overall need for support was positively associated with middle ($\beta=.26$, $p=.024$) and high ($\beta=.35$, $p=.014$) compared to low educational attainment and subclinical anxiety ($\beta=.22$, $p=.017$), and negatively associated with social functioning ($\beta=-.37$, $p=.002$) in multivariate analyses.

Conclusion

YACCS report the strongest need for support, for concrete information, in the domains lifestyle, fertility, and physical consequences of childhood cancer. Associated factors were mostly socioeconomic and psychosocial in nature. Psychosocial care should be an integral part of survivorship care for YACCS, with screening for psychosocial problems, information provision including associated emotional consequences and support if necessary (psycho-education) and tailored interventions, and adequate referrals to more specialized care if necessary.

Introduction

In 2020, the number of childhood cancer survivors (CCS) in Europe reached 500,000 [1, 2]. Due to childhood cancer treatment, many CCS experience late-effects, (chronic) health problems that may manifest up until many years after the end of treatment [3, 4]. Besides physical late-effects, CCS may experience psychosocial problems and impaired quality of life [5, 6]. Therefore, survivorship care aiming at both their physical and psychosocial health is crucial in keeping CCS as healthy as possible after treatment. Current standards of care recommend that survivorship care should contain routine screening and provision of psychosocial interventions in order to optimize early detection and treatment of psychosocial problems [7]. However, limited data is available about what CCS themselves report to need in terms of psychosocial support during survivorship care.

Previous studies on needs in adult CCS and survivors of adolescent and young adult (AYA) cancer focused on need for information, showing that these populations reported unmet needs, especially information regarding their illness, late effects, lifestyle, and sexual issues [8-13]. Unmet information needs in CCS and AYA cancer survivors were found to be associated with psychosocial problems such as anxiety, depression, distress, and a lower quality of life [10, 11, 14]. Furthermore, unmet information needs can negatively impact survivorship care attendance [10, 12]. Knowing the needs of CCS could help tailor the content of psychosocial survivorship care to the needs of CCS, which may foster engagement with survivorship care in this population.

Psychosocial support during survivorship care can include psycho-education (concrete information, associated emotional consequences and support aimed at improving coping and self-management) about the diagnosis, treatment and late effects, counseling (psychological interventions or therapy), and peer contact (e.g., group meetings). A few studies have explored needs in a broader context than information needs. One large study found needs related to psycho-emotional problems, coping, care and support as well as a need for cancer and treatment related information in CCS [15]. A recent qualitative study from Switzerland also provided insight into the needs of adult CCS beyond need for information, showing that survivors have unmet needs for psychosocial support [16].

Insight in the needs of young adult CCS in survivorship care (YACCS, 18-30 years old) may be especially impactful to long-term health and well-being of CCS. Young adulthood is an important developmental stage with many challenges. This life phase is marked by the development of autonomy and identity [17]. The experience of childhood cancer and late effects was found to hinder YACCS' development in terms of achieved milestones regarding autonomy development, psycho-sexual development, and social development [18]. This delay in development may influence their quality of life [19]. Thus, young adulthood may be the prime time to empower YACCS to take control of their own health. In addition, various studies have shown that YACCS are vulnerable to psychosocial problems, such as reduced (health-related) quality of life and higher levels of distress, anxiety, depression, post-traumatic stress disorder (PTSD), and fatigue [5, 6, 20-24]. One of our recent studies on Dutch YACCS showed that their psychosocial well-being is worse than that of Dutch peers, and that the impact of cancer played an important role in explaining psychosocial well-being [25]. Therefore, YACCS could benefit from psychosocial surveillance and support as a part of their survivorship care.

Insight in the needs of YACCS may improve the attendance of survivorship care of this vulnerable population in the middle of crucial development, so their psychosocial well-being can be surveilled and supported. However, evidence on the specific needs of YACCS is scarce. YACCS are often researched in combination with adolescent and young adult cancer patients, or survivors of cancer during young adulthood. A qualitative study found that YACCS and survivors of AYA cancer describe similar resource needs: age-appropriate information, peer support, and proactive attention for salient issues by health care professionals [26]. Besides common challenges (physical appearance, fertility late effects, social relationships, and changing priorities), difficulty with identity formation, social isolation, and complex health care transitions were identified as issues specifically important to YACCS [26].

Insight into the needs of YACCS can be used to tailor psychosocial support during survivorship care to YACCS needs. Therefore, the aims of the present study are to assess Dutch YACCS' support needs in various domains and to examine whether need for support is associated with sociodemographic and medical characteristics of YACCS as well as with their psychosocial well-being.

Methods

The Dutch LAnge TERmijn (LATER, translation: long term) registry contained 946 eligible YACCS, aged 18-30, diagnosed at age 0-18, ≥5 years since diagnosis, and treated at one of four participating Dutch pediatric oncology centers (located in Amsterdam, Rotterdam, Utrecht, and Groningen). A total of 400 YACCS were randomly selected by a data manager from the pseudonymized Dutch LATER registry. The selection was stratified in order to have an equal representation of men and women, and of age groups (18-25 and 26-30 years) and diagnosis age groups (0-7, 7-13 and 13-18 years) to account for differences in developmental stage.

After excluding 22 YACCS who had no known address, were living abroad, or were recently deceased, 378 eligible YACCS were invited by the researchers with an information letter in the mail in June of 2018. YACCS could fill out questionnaires on paper or online. Participants provided written informed consent and the Medical Ethical Committee of the University Hospital Utrecht reviewed this study (case number 18/256). Patient information letters were presented to members of the survivor committee of the Dutch Childhood Cancer Association in order to assure appropriate use of understandable language.

Measures

Sociodemographic characteristics: In a short list of sociodemographic questions, date of birth, sex, partner status, number of children, employment status and attained and current education (low = primary education, lower vocational education, lower and middle general secondary education; middle = middle vocational education, higher general secondary education, pre-university education; high = higher vocational education, university) were asked.

Medical characteristics: The Dutch LATER registry provided data on the initial cancer diagnosis and treatment as well as recurrences and aggregated data about non-participants.

Need for support: Support needs were assessed using a questionnaire made specifically for the purpose of this study focusing on different domains of support and types of support, based on literature and clinical experience of hospital psychologists and survivorship care doctors (Appendix A). YACCS were asked to indicate need for support in the following eight predefined domains: physical consequences of childhood cancer, social and emotional consequences of childhood cancer, relationships and/or sexuality, fertility, lifestyle and health risks after childhood cancer, choices relating to school and work, future perspectives, and insurance and mortgages. YACCS could also indicate any other areas where they need support. For each domain, YACCS could indicate whether they felt a need for one or multiple support types by ticking one or multiple boxes: concrete information, personal counseling, peer support, other support, or no support needed. A total needs score was calculated as a sum score (range: 0-9) indicating in how many domains YACCS reported need for at least one support type.
Health-related quality of life (HRQOL): The Pediatric Quality of Life Inventory Young Adults (PedsQL-YA) measures generic HRQOL. The PedsQL-YA has four scales (Physical, Emotional, Social, and Work/School Functioning), a total scale and a Psychosocial Summary Scale combining emotional, social, and work/school functioning. Higher scores (range 0-100) represent better HRQOL. The PedsQL-YA has good psychometric properties and a reference group of Dutch young adults is available [27]. This study made use of the scales Physical, Social, and Work/School Functioning. The Emotional Functioning scale, total scale and Psychosocial Summary Scale of the PedsQL-YA were not used because of correlation with the scores on the anxiety and depression measurement.

Anxiety and depression: The Hospital Anxiety and Depression Scale (HADS) aims to measure levels of anxiety and depression in separate scales [28]. Scale scores ≥8 for anxiety and depression are considered (sub)clinical. The HADS has good psychometric properties [29] and a reference group of Dutch young adults is available [30].

Fatigue: The Checklist Individual Strength Revised (CIS-20R) measures fatigue, and consists of four scales: Fatigue Severity, Concentration, Motivation, and Activity [31]. Higher scores indicate higher levels of fatigue and fatigue-related impairment. Fatigue severity was used in the current study, with a score of 35 or more classified as severe fatigue [31]. The CIS-20R has good psychometric properties and a reference group of Dutch young adults is available [31].

Statistics

Statistical tests were performed using IBM SPSS version 25. All tests were two-sided. Before conducting the main analyses, several preparatory analyses were conducted. First, missing data were imputed on the basis of the guidelines of the questionnaires used. Second, the internal consistency of each scale used in the analyses was calculated, yielding satisfactory Cronbach's α: PedsQL-YA .80≤α≤.84; HADS .79≤α≤.88; CIS-20R fatigue severity scale α=.78.

Differences between participants and non-participants on available sociodemographic and medical characteristics were tested using one-sample t-tests and binominal tests.

To characterize the sample, psychosocial functioning of the YACCS, as measured with the PedsQL-YA, HADS, and CIS-20R, was compared to reference groups of Dutch young adults with ANOVA or logistic regression, as reported in a previous study [25]. To answer our first research question about the assessment of YACCS' support needs, an overview of support needs was created by calculating frequencies for each support type per domain. Then, to describe need for support, two scores were calculated: (1) a dichotomous domain score indicating whether or not a YACCS reported need for at least one support type in a domain and (2) a needs sum score (range: 0-9) indicating in how many domains YACCS reported need for at least one support type.

To study associations of support needs with sociodemographic (sex, attained education, partner status), medical (age at diagnosis, time since diagnosis, diagnosis, treatment, recurrence) characteristics as well as psychosocial outcomes (PedsQL-YA physical and social functioning scales, dichotomous HADS anxiety ≥8, dichotomous HADS depression ≥8, dichotomous CIS-20R fatigue severity ≥35), multivariate linear regression analysis for the needs sum score was performed with the aforementioned characteristics as independent variables. To gain more detailed insight, separate multivariate logistic regression analyses were performed exploratively for each of the eight dichotomous domain scores. To reduce the number of independent variables in the multivariate logistic regression analyses, independent variables were selected if they were univariately associated with the dichotomous domain score at α=.05. For each dichotomous domain score, the selected independent variables were entered into the multivariate models at once (Table 3).

Results

Sample Characteristics

A total of 151 YACCS (61.6% female, mean age 24.1 SD 3.6, mean time since diagnosis 13.6 SD3.8) participated by returning a completed questionnaire (response rate=40%). Participants were significantly more often female (*p*≤.001) and had less often received a bone marrow transplantation (BMT) (*p*=.012) than non-participants (Table 1). YACCS' scores on the HRQOL scales were lower than those of the general population, and YACCS were more likely to experience anxiety and severe fatigue than the general population (study reported elsewhere [25]).

Support needs

Most YACCS reported a need for support in one or more domains (88.0%). On average, YACCS reported any need of support in 4.4 domains (SD=2.6, range=0-9). The percentage of YACCS reporting any need for support in the various domains was: 76.2% for lifestyle and health risks after childhood cancer, 69.5% for physical consequences of childhood cancer, 68.2% for fertility, 54.3% on insurances and mortgages, 53.6% for social-emotional consequences of childhood cancer, 49.0% on future perspective, 34.4% for relationships and sexuality, 29.8% on school and work, and 4.6% on other domains.

Figure 1 shows the percentage of YACCS indicating a need for information, counseling, and peer contact in each domain. On all domains except for school and work, concrete information was the support type most mentioned. More than half of the participating YACCS reported a need for concrete information in the domains lifestyle and health risks after childhood cancer, fertility, and physical consequences of childhood cancer. Between 25 and 50% of YACCS reported a need for concrete information about insurances or mortgages, future perspective, and social emotional consequences of childhood cancer. Also 25 to 50% of YACCS reported a need for personal counseling on lifestyle and health, and physical as well as social emotional consequences of childhood cancer. Need for peer support was reported in all domains ranging from 1.3% in fertility and insurance/mortgage to 11.9% in social emotional consequences. Very few YACCS reported a need for types of support other than concrete information, personal counseling or peer support, so the corresponding percentages were not shown in the figure.

Associations between need for support and sociodemographic and medical characteristics as well as psychosocial-well-being.

In multivariate linear regression analysis, the needs sum score was significantly positively associated with middle (β=.26, p=.024) and high (β=.35 p=.014) compared to low educational attainment, as well as with (sub)clinical anxiety (β=.22, p=.017), and negatively associated with social functioning (β=-.37, p=.002). The full model explained 58.7% of variance in needs (Table 2).

Need for support in the various domains was explored in more detail using multivariate logistic regression analyses, the results of which are displayed in Table 3.

Discussion

This study found that a large majority of YACCS report a need for support, in particular for information. This study added to the literature by specifically investigating the young adult subgroup of CCS and studying need for support in various domains and various support types. YACCS reported needs beyond information, with around one in 6 to one in 3 YACCS reporting a need for counseling across the domains.

Many YACCS reported a need for information, which was also demonstrated in previous studies [8, 11-13]. Information needs were the highest in the domains of physical consequences of childhood cancer and fertility which is in line with the results of previous studies [13, 32], and in the domain lifestyle and health risks. With information being reported as most needed on almost all domains, it seems that providing YACCS with age-appropriate information as early as possible should be a very high priority in survivorship care. In addition, from clinical practice, we know that medical information could impact survivors psychologically. Health care providers should be aware of this and be prepared to refer survivors for psychosocial support if necessary.

The psychosocial factors (sub)clinical anxiety, and lower social functioning were identified as associates of higher overall need for support. More anxiety and poorer overall HRQOL were previously identified as predictors of more support needs [11, 14]. Through examining the various subdomains of HRQOL to gain a deeper understanding of which parts of HRQOL would influence support needs, we identified social function as the most relevant subdomain of overall HRQOL for needs. No medical characteristics were associated with the overall support needs.

We found different associated factors for support needs in specific domains. Support needs in certain domains (physical and social-emotional consequences of childhood cancer, relationships and sexuality, school and work, and future perspective) were mostly predicted by psychosocial factors, specifically lower social functioning and reporting (sub)clinical anxiety. Support needs in other domains (fertility, lifestyle and health after childhood cancer) were mostly predicted by sociodemographic characteristics such as female sex and higher educational attainment. The latter was not in line with previous studies. A study among survivors of AYA cancer found that those with lower educational attainment had more unmet needs [9] and a study of information needs in CCS found no effect of educational attainment [11]. The difference with earlier literature may be explained by the investigation of specific topics, like fertility and lifestyle and health after childhood cancer. While medical characteristics were not associated with needs in most domains in the present study, higher age at diagnosis and cancer recurrence were associated with need for support related to insurance and mortgages and relationships and sexuality.

Some specific results stood out. First of all, a need for support regarding fertility was strongly related to female sex and higher education, but not to any variables related to treatment that could cause infertility or any psychosocial variables. Need for support regarding sexuality, however, was significantly associated with lower social functioning and marginally associated with (sub)clinical anxiety. These results indicate that sexuality and fertility are subjects that are of interest to different subgroups of CCS and should both be discussed during survivorship care including the possibilities for support. Furthermore, looking at earlier literature about work and school performance of (YA) CCS [33, 34], it seems surprising that the need for support in this domain in the current study was the lowest among all domains (29.8%). It could be the case that problems relating to work and school are only pronounced in a small subset of the YACCS in this study. For example, central nervous system (CNS) tumor survivors were previously reported to be at an increased risk to experience problems related to school and work [33, 34].

Implications

As young adulthood centers around the development of autonomy and identity [17], YACCS in particular should be empowered to take control of their own health. Currently, YACCS attendance of survivorship care is not optimal [8, 35], while there is evidence to suggest that they are vulnerable on both the physical and psychosocial levels [3, 5, 6, 20, 23, 25]. The suboptimal attendance is worrisome, because survivorship care is crucial to keep CCS as healthy as possible. CCS not attending survivorship care in (young) adulthood may be a result of a suboptimal transition from pediatric to adult care [36]. Making psychosocial survivorship care more tailored to the needs of CCS at all life stages, and during the vulnerable phase of young adulthood in particular, could help improve attendance. Insight into the needs of YACCS who did not attend survivorship care would be helpful. Unfortunately, the present study could not provide this insight because attendance of survivorship care was not assessed. Knowing what YACCS need is a first step to tailoring psychosocial survivorship care to their needs. Monitoring using patient reported outcomes in clinical practice could be useful to assess unmet needs and to monitor HRQOL as an indication of needs for which psychosocial support can be offered [37, 38].

This study stresses the need for adequate provision of information and information sources to YACCS during survivorship care. Having an accessible and age-appropriate information program could improve the participation of YACCS in their survivorship care [39, 40]. Looking at the results of the present study, information for YACCS should go beyond the physical consequences of childhood cancer and specific late-effects, but also focus on emotional and social consequences. Besides providing information, health care providers should be encouraged to routinely discuss the possibilities for support, such as counseling, with YACCS in survivorship care [7]. YACCS in need of such psychosocial support have previously reported difficulties finding it [16]. Therefore, survivorship care centers should offer psychosocial support in addition to information provision directly to YACCS, or provide adequate referrals, usually to clinics in the network of care. To be of the best service to survivors, medical and psychosocial health care professionals need to work together multidisciplinary [16]. While doctors are responsible to provide patients with accurate medical information and advice, psychosocial care providers may help survivors attach a meaning to that information and cope with the impact this information has on them (e.g., counseling after news about infertility or a higher risk for subsequent tumors, or implementing lifestyle advice in daily life). YACCS could benefit from age-appropriate psychosocial interventions. Survivorship care clinics could specifically consider developing and offering interventions that can be delivered online, as the current events of the coronavirus disease 2019 (COVID-19) pandemic have forced us to consider more innovative ways to deliver psychosocial care away from hospitals or health care facilities. Online psychosocial care is especially compatible with survivorship care, because of the often low frequency of survivorship care clinic visits. Existing online interventions that could be used or adapted for YACCS include cognitive behavioral therapy based group interventions such as Recapture Life-AYA and Op Koers Online [41, 42].

Strengths and limitations

This study provides valuable insights into the specific needs of YACCS as a separate group from older CCS and survivors of AYA cancer. Looking at the few differences between responders and non-responders, we believe that stratifying the selection of YACCS was successful in obtaining a diverse sample.

Many previous studies on support needs in (YA)CCS were qualitative [16, 26], since needs are hard to quantify. Using a newly developed questionnaire provides the added value of quantification of YACCS' needs in a novel way, specifically centering around the multiple types of support in domains that are relevant to YACCS and on several support types, including psychosocial needs and support. We studied needs in general rather than unmet needs, to reduce the influence of care that the YACCS receive at our institute and improve generalizability of our results to other institutes and countries.

Unfortunately, our analyses of associations in the specific support need domains were limited by the number of participants, so the results of the multivariate logistic regression analyses should be interpreted in an explorative way. Larger study samples are necessary to further investigate associations between support needs and sociodemographic and medical characteristics, as well as YACCS' well-being. Larger studies could include variables that were not included in the present study, such as the presence and nature of late effects, or psychosocial factors such as coping.

Conclusions

Most YACCS reported a need for support, in particular for information, especially regarding lifestyle and health risks after childhood cancer, physical consequences of childhood cancer, and fertility. Information provision including associated emotional consequences and support if necessary (psycho-education) should be at the base of survivorship care for YACCS, in order to meet their need for information as well as empower them to take control over their health during the crucial life phase of young adulthood. Health care providers should routinely discuss psychosocial well-being and consider possibilities for psychosocial support with YACCS and provide adequate referral when necessary.

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Table 1 Characteristics of participants and non-participants

	Participants (N ≈ 151)[a]	Non-participants (N = 223)[b]	*p*
Socio-demographic			
Age (years, mean ± SD (range))	24.1 ± 3.6 (18-30)	24.0 ± 3.4 (18-30)	.659
Sex (female, N(%))	61.6 (93)	40.8 (90)	≤.001
Partner status N(%)			
Yes	51.0 (75)		
No	49.0 (72)		
Employment status N(%)			
Paid occupation	70.9 (105)		
Without paid occupation	29.1 (43)		
Attained Education[c] N(%)			
Low	19.3 (28)		
Middle	48.3 (70)		
High	32.4 (47)		
Current education[c] N(%)			
Low	3.1 (2)		
Middle	27.7 (18)		
High	69.2 (45)		
Medical characteristics			
Age at diagnosis (years, mean ± SD (range))	10.5 ± 4.5 (.4 – 17)	10.6 ± 4.5 (0-18)	.756
Time since diagnosis (years, mean ± SD (range))	13.6 ± 3.8 (6 – 27)	13.5 ± 3.7 (6-28)	.652
Diagnosis N(%)			
Hematologic cancers	66.9 (101)	61.7 (142)	.119
CNS tumors	8.6 (13)	9.9 (22)	.358
Solid tumors	24.5 (37)	28.3 (63)	.173
Recurrence N(%)	13.9 (21)		
Treatment[d] N(%)			
Surgery (S)	61.6 (93)	63.7 (142)	.323
Chemotherapy (CT)	95.4 (144)	95.5 (213)	.522
Radiotherapy (RT)	37.1 (56)	35.0 (78)	.323
SCT/BMT	7.3 (11)	13.5 (30)	.012
Treatment combinations[e] N(%)			
CT only	32.5 (49)		
CT+RT	6.0 (9)		
RT+S	4.6 (7)		
CT+S	30.5 (46)		
CT+S+RT	26.5 (40)		
	Participants (N ≈ 151)	General population[f,g]	
Psychosocial well-being mean ± SD (range) / % (N)			
PedsQL-YA physical	80.2 ± 19.7 (21.9-100)	87.1 ± 16.0	≤.001
PedsQL-YA social	82.1 ± 20.0 (10.0-100)	87.2 ± 14.5	.001
PedsQL-YA school/work	76.8 ± 19.1 (5.0-100)	82.3 ± 15.7	≤.001
HADS anxiety (≥8)	30.2 (45)	18.8 (42)	.017
HADS depression (≥8)	12.8 (19)	7.6 (17)	.134
CIS-20R fatigue severity (≥35)	36.2 (54)	20.8 (55)	≤.001

[a] Data incomplete for some participants. The numbers in the table are based on the records with complete data per variable.

[b] No medical information available from 4 non-participants

[c] low = primary education, lower vocational education, lower and middle general secondary education; middle = middle vocational education, higher general secondary education, pre-

university education; high = higher vocational education, university

[d] More than one category possible

[e] Treatments for primary tumor and (if applicable) recurrence(s)

[f] PedsQL-YA N=649; HADS N=224; CIS-20-R N=264

[g] Study reported elsewhere [25]

Abbreviations: PedsQL-YA: Pediatric Quality of Life – Young Adults; HADS: Hospital Anxiety and Depression Scale; CIS-20R: Checklist Individual Strength Revised

Fig. 1: Needs of YACCS in eight domains by support type

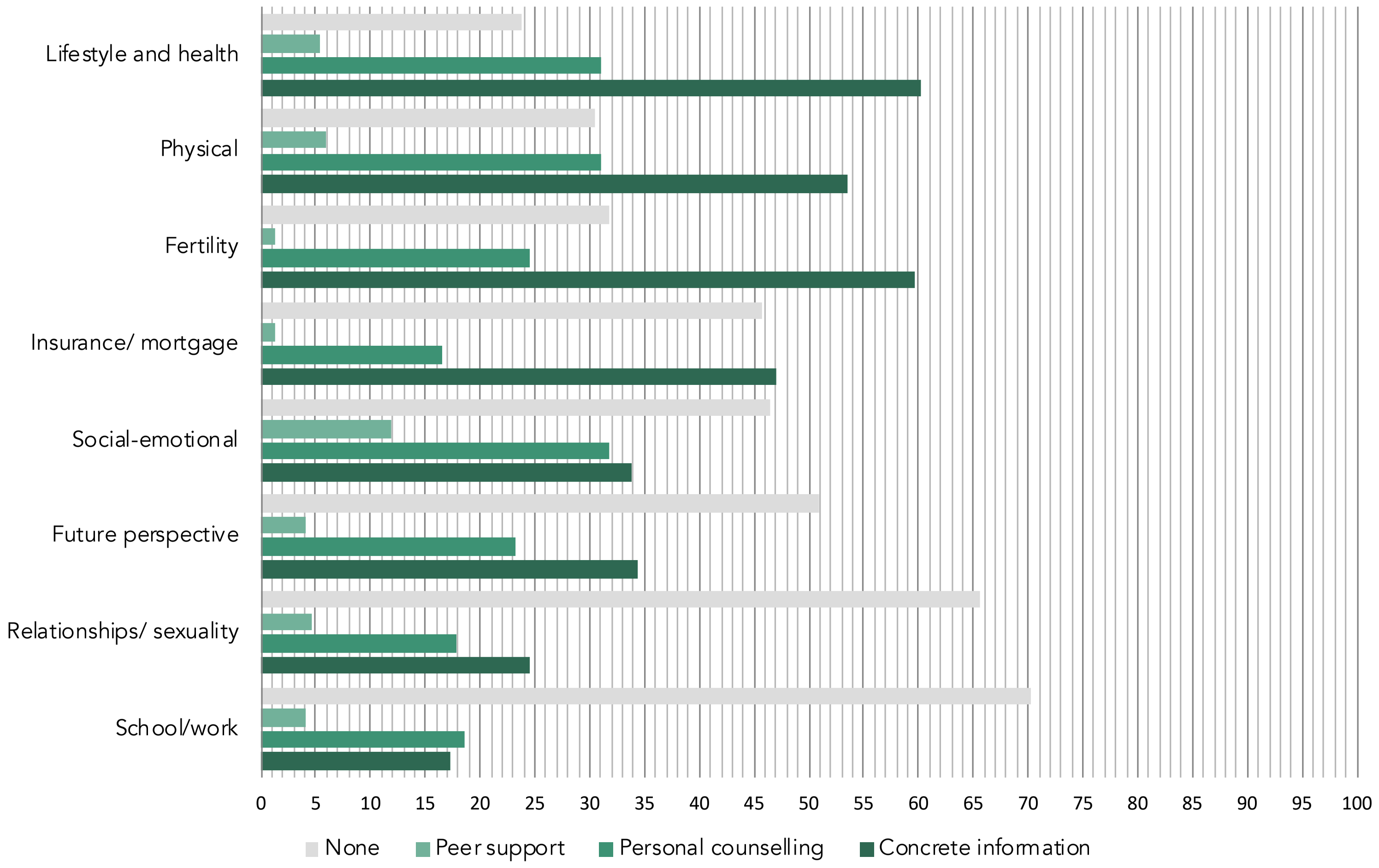

Table 2 Multivariate linear regression model for support needs with sociodemographic and medical characteristics as well as psychosocial well-being as independent variables; N = 143a.

	Total needs score			
	β	*B*	95%CI	*p*
Sociodemographic				
Sex (ref=male)	.14	.74	[-.09;1.57]	.080
Attained Education (ref=low)				
Middle	.26	1.29	[.18;2.41]	.024
High	.35	1.85	[.39;3.31]	.014
Medical				
Age at diagnosis	-.06	-.03	[-.17;.11]	.652
Time since diagnosis	-.10	-.07	[-.21;.08]	.359
Diagnosis (ref = hematological)				
CNS tumor	-.12	-1.15	[-3.20;90]	.268
Solid tumor	-.001	.01	[-1.12;1.11]	.991
Recurrence	.12	.86	[-.31;2.02]	.147
Surgery (yes/no)	-.03	-.17	[-1.18;.84]	.740
Chemotherapy (yes/no)	-.18	-2.04	[-4.15;.08]	.059
Radiotherapy (yes/no)	-.09	-.47	[-1.46;.52]	.352
Psychosocial				
PedsQL-YA Physical Functioning	.03	.003	[-.02;.03]	.820
PedsQL-YA Social Functioning	-.37	-.05	[-.08;-.02]	.002
PedsQL-YA Work/School Functioning	-.05	-.01	[-.03;.02]	.653
HADS (sub)clinical anxiety (≥8)	.22	1.22	[.22;2.21]	.017
HADS (sub)clinical depression (≥8)	-.10	-.77	[-2.14;.61]	.273
CIS-20R severe fatigue (≥35)	.09	.47	[-.46;1.40]	.316
R^2	.587			

[a] Number of respondents who completed all questionnaires.

Abbreviations: CNS Central Nervous System; PedsQL-YA Pediatric Quality of Life – Young Adults; HADS Hospital Anxiety and Depression Scale; CIS-20R Checklist Individual Strength Revised

Table 3 Multivariate logistic regression models for any support needs on the eight domains with sociodemographic and medical characteristics as well as psychosocial well-being as independent variables.

	Physical			Social-emotional			Relationships/ Sexuality			Fertility		
	(69.5%, N=105)[a]			(53.6%, N=81)[a]			(34.4%, N=52)[a]			(68.2%, N=103)[a]		
	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*
Socioeconomic												
Sex (ref=male)	1.58	[.73; 3.42]	.249	-	-	-	1.74	[.76; 3.98]	.189	4.26	[1.94; 9.38]	≤.001
Attained Education (ref=low)												
Middle	-	-	-	-	-	-	-	-	-	2.42	[.93; 6.28]	.070
High	-	-	-	-	-	-	-	-	-	8.43	[2.55; 27.82]	≤.001
Medical												
Age at diagnosis	-	-	-	-	-	-	-	-	-	-	-	-
Time since diagnosis	-	-	-	-	-	-	-	-	-	-	-	-
Diagnosis (ref = hematological)												
CNS tumor	-	-	-	-	-	-	-	-	-	-	-	-
Solid tumor	-	-	-	-	-	-	-	-	-	-	-	-
Recurrence	-	-	-	-	-	-	2.62	[.94; 7.32]	.067	-	-	-
Surgery (yes/no)	-	-	-	-	-	-	-	-	-	-	-	-
Chemotherapy (yes/no)	-	-	-	-	-	-	-	-	-	-	-	-
Radiotherapy (yes/no)	-	-	-	-	-	-	-	-	-	-	-	-
Psychosocial												
PedsQL-YA Physical Functioning (0-100)	-	-	-	1.03	[1.0; 1.06]	.065	-	-	-	-	-	-
PedsQL-YA Social Functioning (0-100)	.98	[.96; 1.01]	.135	.91	[.88;.95]	≤.001	.98	[.96; 1.0]	.021	-	-	-
PedsQL-YA Work/School Functioning (0-100)	-	-	-	.99	[.96; 1.02]	.574	-	-	-	-	-	-
HADS (sub)clinical anxiety ≥8)	4.29	[1.36; 13.53]	.013	5.66	[2.05; 15.65]	.001	2.24	[.92; 5.44]	.075	-	-	-
HADS (sub)clinical depression (≥8)	-	-	-	.44	[.08; 2.26]	.322	1.04	[.30; 3.64]	.954	-	-	-
CIS-20R severe fatigue (≥35)	2.11	[.81; 5.50]	.126	-	-	-	-	-	-	-	-	-

Table 3, continued.

	Lifestyle & Health (76.2%, N=115)^a			School and work (29.8%, N=45)^a			Future perspective (49.0%, N=74)^a			Insurance and mortgage (54.3%, N=82)^a		
	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*
Socioeconomic												
Sex (ref=male)	2.39	[1.01; 5.66]	.047	-	-	-	1.96	[.86; 4.49]	.110	1.76	[.81; 3.84]	.152
Attained Education (ref=low)												
Middle	2.14	[.77; 5.93]	.146	-	-	-	-	-	-	-	-	-
High	6.90	[1.89; 25.19]	.003	-	-	-	-	-	-	-	-	-
Medical												
Age at diagnosis	-	-	-	-	-	-	-	-	-	1.10	[1.02; 1.20]	.019
Time since diagnosis	-	-	-	-	-	-	-	-	-	-	-	-
Diagnosis (ref = hematological)				-	-	-	-	-	-	-	-	-
CNS tumor	-	-	-	-	-	-	-	-	-	-	-	-
Solid tumor	-	-	-	-	-	-	-	-	-	-	-	-
Recurrence	-	-	-	-	-	-	-	-	-	3.11	[.95; 10.22]	.062
Surgery	-	-	-	-	-	-	-	-	-	-	-	-
Chemotherapy	-	-	-	-	-	-	-	-	-	-	-	-
Radiotherapy	.52	[.23; 1.22]	.135	-	-	-	-	-	-	-	-	-
Psychosocial												
PedsQL-YA Physical Functioning	-	-	-	1.00	[.97;1.03]	.978	1.01	[.98;1.04]	.499	.92	[.96;1.01]	.187
PedsQL-YA Social Functioning	-	-	-	.96**	[.93;.99]	.005	.96	[.93;.99]	.012	1.00	[.98;1.03]	.937
PedsQL-YA Work/School Functioning	-	-	-	.98	[.96;1.01]	.247	.98	[.95;1.01]	.114	1.00	[.97;1.02]	.511
HADS (sub)clinical anxiety (≥8)	3.61	[1.08;12.15]	.038	1.54	[.59;3.99]	.378	2.44	[.96;6.23]	.061	1.76	[.70;4.42]	.231
HADS (sub)clinical depression (≥8)	-	-	-	.48	[.12;1.98]	.312	1.12	[.24;5.15]	.886	1.76	[.42;7.36]	.439
CIS-20R severe fatigue (≥35)	-	-	-	2.31	[.92;5.83]	.075	1.42	[.57;3.55]	.455	1.00	[.40;2.48]	1.0

- not included in model; The following variables were not included in any model: Time since diagnosis,

diagnosis, surgery (yes/no), chemotherapy (yes/no)

[a] YACCS with any need for support (%, N)

Abbreviations: YACCS Young Adult Childhood Cancer Survivor; CNS Central Nervous System; PedsQL-YA Pediatric Quality of Life – Young Adults; HADS Hospital Anxiety and Depression Scale; CIS-20R Individual Strength Revised.

APPENDIX A - Support needs questionnaire (translated)

In which domains do you need support?
In the first column there are domains in which support may be needed. In every other column, there is a type of support that you could need.
For each domain, please indicate which support types you need. You can tick multiple boxes for each domain. If you do not need any support in a domain, you can make this known by choosing the 'none' option.

Domain	Concrete information	Counseling	Peer support	Other	None
Physical consequences	○	○	○	○ …………………	○
Social/emotional consequences	○	○	○	○ …………………	○
Relationships and sexuality	○	○	○	○ …………………	○
Fertility	○	○	○	○ …………………	○
Lifestyle and health risks	○	○	○	○ …………………	○
School/work	○	○	○	○ …………………	○
Future perspective	○	○	○	○ …………………	○
Mortgages and insurance	○	○	○	○ …………………	○
Other areas	○	○	○	○ …………………	○

8

CHAPTER 8

ONLINE COGNITIVE-BEHAVIORAL GROUP INTERVENTION FOR YOUNG ADULT SURVIVORS OF CHILDHOOD CANCER: A PILOT STUDY

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Abstract

Background

Young adult childhood cancer survivors (YACCS) are a vulnerable group in need of psychosocial support, but tailored interventions are lacking.

Aim

To examine feasibility and explore preliminary effectiveness of an online group intervention (Op Koers Online for YACCS) aimed at teaching active coping skills and providing peer-contact, thereby reducing and preventing psychosocial problems in YACCS. The intervention is based on psycho-education, cognitive behavioral therapy, and aspects of acceptance and commitment therapy.

Methods

YACCS completed questionnaires pre- and post-intervention. Feasibility was based on attendance, drop-out, and an evaluation questionnaire. Preliminary effectiveness was evaluated with the Distress Thermometer, Mastery Scale, Illness Cognition Questionnaire, Impact of Cancer - Childhood Survivors, and Pediatric Quality of Life Inventory. Preliminary effectiveness was investigated by testing differences on the psychosocial outcomes between T0 and T1 within respondents, using paired samples t tests and Cohen's *d*.

Results

10 YACCS participated in the intervention and completed all questionnaires. There was no drop-out; 90% of participants attended five out of six sessions. Overall, participants were satisfied with the intervention; 7.6 on a 0-10 scale. Distress (Cohen's *d*=-.6, p=.030) and feelings of helplessness (Cohen's *d*=-.8, *p*=.001) reduced from T0 to T1, while self-efficacy (Cohen's *d*=.8, *p*=.013,) improved. Other outcomes displayed small effects, but did not change significantly.

Conclusions

This first, small pilot study showed short term decrease in distress and feelings of helplessness and improvement of self-efficacy. The pilot also indicated that Op Koers Online is a feasible intervention, filling a gap in psychosocial services for YACCS.

Introduction

Thanks to significant medical advancements, most children diagnosed with childhood cancer now survive into adulthood[1]. As a consequence of intensive treatments, many childhood cancer survivors (CCS) are faced with long-term physical and some with mental health problems, called late effects[2-7]. Young adult childhood cancer survivors (YACCS) are potentially vulnerable for adverse psychosocial outcomes, because of the combination of their developmental (e.g. starting a career, living independently) and survivorship challenges[8-10]. Despite this pressing issue and current psychosocial standards of care recommending screening and psychosocial care for survivors[11], psychosocial interventions specifically aimed at preventing or reducing psychosocial problems in YACCS are lacking.

Interventions tailored for YACCS could focus on teaching coping skills, so that YACCS are better equipped to deal with the challenges of survivorship and the demands of development in young adulthood. The disability-stress-coping model of Wallander and Varni (1998)[12] assumes that coping, known as the way people react to stressful situations, plays an important role in adaptation to disease. The model of Wallander and Varni (1998)[12] was adapted for the current study to explain outcomes for YACCS (Figure 1). Elements from known effective therapies such as Cognitive Behavior Therapy (CBT) and Acceptance and Commitment Therapy (ACT) could be used in psychosocial interventions for YACCS, as they aim to improve coping by targeting unhelpful cognitions that elicit negative feelings and behaviors. CBT is a widely used evidence-based method that focuses on identifying and challenging unhelpful thoughts in an effort to replace them with helpful ones[13]. Cancer specific CBT-based interventions have been developed and evaluated and found effective in the past, for example for reducing fear of cancer recurrence in adults[14], and for persistent severe fatigue in CCS[15]. A recent RCT of a CBT-based online group intervention for survivors of adolescent and young adult cancers, showed that participants in the intervention used more CBT skills than a peer support and waitlist control group, indicating that conveying the principles of CBT is possible with such an intervention[16]. ACT is a third wave CBT that focuses on acceptance of thoughts and situations to reduce the impact of unhelpful thoughts on daily life. ACT includes various techniques, such as value elicitation which encourages participants to discover and live by their values even when faced with challenges[17]. Specifically, ACT could be useful for YACCS because they are confronted with situations that cannot be changed. Components of ACT can teach YACCS to cope with such situations.

E-health interventions can make psychosocial interventions more accessible and less demanding while connecting to the online world of young people today[18, 19]. It eliminates logistical barriers such as travel time and distance. These barriers apply especially for CCS because they are living all over the country[20, 21]. In addition, online therapy may be more cost-effective than face to face therapy, especially when delivered in a group since that allows therapists to use their time on several patients simultaneously[22-24]. Finally, group therapy gives participants an opportunity to share experiences with peers which was previously suggested to be beneficial for mental health[19, 25-27].

Op Koers (English On Track) is a program of CBT and ACT-based face-to-face and online group courses developed at the Emma Children's hospital in Amsterdam, The Netherlands, to prevent and/or decrease psychosocial problems in children with

chronic illness, including cancer, their siblings and parents. Op Koers courses have shown promise with regard to teaching coping strategies and improving psychosocial outcomes in pilot studies among various populations and in a randomized controlled trial (RCT) among children with a chronic illness and their parents[28-31]. After adjustment of the content, to specifically fit the developmental and survivorship needs of YACCS, while using the components of CBT and ACT as in the previously developed courses, Op Koers has potential to fill the current gap in interventions for this population.
This study aimed to evaluate the first experiences with Op Koers Online for YACCS, an online group intervention based on psycho-education, CBT, peer support, and with influences from ACT, by examining feasibility and exploring preliminary effectiveness of Op Koers Online for YACCS.

Materials and methods

Design and procedure

This study was a pilot of the group intervention Op Koers Online for YACCS, conducted between February and June of 2019. Participants completed a set of paper-pencil questionnaires 1-4 weeks before (T0) and 1-4 weeks after (T1) the intervention to explore preliminary effectiveness. To examine feasibility, they completed an evaluation questionnaire at T1. Additionally, the intervention was evaluated in person with the participants as part of the sixth course session and with course leaders in an evaluation meeting (Figure 2). Participants provided written informed consent and the Medical Ethical Committee of the University Hospital Utrecht reviewed this study (case number 18/256).

Participants

Participants (N=151) in a study about the psychosocial well-being and need for psychosocial support in YACCS[8] (aged 18-30, age at diagnosis ≤17 and time since diagnosis ≥ 5 years) were asked whether or not they would be interested in an online group course for YACCS. A total of 40 (opt-in rate 26.4%) reported to be interested and were invited to participate in the pilot study. In the end, a total of 13 YACCS wanted and were able to participate in the pilot study. Others replied they were too busy at the moment or not available at the times suggested for the intervention. A few YACCS were no longer interested to participate or did not reply.

We offered the course at two different times, one during the day and one during the evening. Due to limitations on group size and availability of the YACCS, 10 YACCS were included in this pilot study (enrollment rate 25%). One group contained 4 and the other 6 participants. The researchers and/or course leaders did not intervene in the assignment of participants to groups, which was completely based on scheduling and availability of the participants.

Exclusion criteria for this pilot study were a cancer diagnosis in the past 3 years, current treatment for cancer, or severe psychological problems (clinical depression, severe PTSD, etc.). These were assessed during the intake via telephone by asking “Did you receive a diagnosis of cancer in the past 3 years or are you currently being treated?” and “Do you currently suffer from mental health problems, or did you receive a mental health related diagnosis in the past?”. One participant mentioned a PTSD diagnosis, but no current complaints of heightened arousal, nightmares or spontaneous flashbacks. No participants were excluded as a result of the screening.

Intervention

Op Koers Online is an online group intervention aimed at teaching active coping skills (e.g. cognitive restructuring and relaxation) and providing peer-contact, thereby preventing or decreasing psychosocial problems (e.g. (health)anxiety or difficulties in (family) relationships and friendships). Op Koers makes extensive use of the principles of CBT. In order to explain the basic principles of CBT, course leaders use the thinking-feeling-doing model, with a focus on restructuring negative thoughts about the disease (e.g. opinions of others, not being able to participate in activities with peers) and thereby increasing coping skills[13]. Furthermore, psycho-education and components of Acceptance and Commitment Therapy (e.g. living your values) are used[17].

A preliminary outline for Op Koers Online for YACCS was based on topics from the available literature about YACCS' challenges and their psychosocial well-being as well as a previous study from the authors into YACCS' need for psychosocial support[32]. To validate the content of Op Koers Online for YACCS, two focus groups were organized. One focus group was held with health care providers (HCP) involved in survivorship care and survivor representatives from the Dutch parent and survivor association (N=7). Another focus group was held with 5 YACCS who had participated in the previous study about need for psychosocial support. During the focus groups the preliminary content of Op Koers Online for YACCS was presented and participants were asked to respond to the topics meant to be included in the intervention as well as to mention any topics they missed. Because the preliminary content was mostly in agreement with the input of YACCS and HCP, the course was finalized by grouping the discussed topics into topics for the 6 sessions: 1) introduction, 2) 'my body', 3) 'my family', 4) 'friendships and relationships', 5) 'school, work, future', 6) 'looking back and evaluation'.

The intervention contains six consecutive weekly 90-minute sessions, and a 90-minute booster session after three months. Sessions are led by two psychologists (course leaders). Course leaders are trained and follow a detailed manual that was reviewed by the psychosocial staff of the Princess Máxima Center beforehand.

The sessions take place in a secure chatroom. The chatroom offers no video or audio communication, in order to allow participants to take their time thinking about their response and remain anonymous. Participants (min. 3, max. 6 in a fixed group) log on to the Op Koers website (www.opkoersonline.nl) to see their personal environment, from which they can enter the chatroom, submit homework assignments, and view psycho-educational texts.

Each session follows a similar structure. Firstly, the group discusses their experiences since the last session. After that, the homework exercises are discussed; YACCS can share their answers or ask questions to each other or the course leaders. Then, the majority of the time is spent on the topic of the session. To discuss this topic, the course leaders ask questions about that topic to be answered by the YACCS and discussed in the group. The course leaders moderate the discussion, answer questions, and keep an eye on chats from YACCS that can be used for a teaching moment, e.g. about cognitive restructuring, relaxation, living your values. To close the session, YACCS are reminded of the homework for next week and there is time to ask questions that were left unanswered by the session.

Before the intervention, each participant had a 45-60 minute intake with one of the course leaders over the telephone. During the intake, the intervention was discussed, and also YACCS' employment and/or education and living situation, childhood cancer history, survivorship care, late effects, and coping with late effects in daily life. Also, the interviewer screened for exclusion criteria.

After each session, participants gain access to homework and psycho-educational texts, which is meant to consolidate the knowledge and skills from the completed session and prepare for the next session. All homework and information remains accessible for the duration of the course. Table 1 provides a global overview of the topics and used therapeutic techniques, homework exercises, and psycho-educational texts for each session. For the exact contents of our intervention, the manual is available upon request to the corresponding author.

Measures

Feasibility: After the intervention, an evaluation questionnaire was used to assess satisfaction with the content, the course leaders and the technical aspects of Op Koers Online. Participants were asked to give the course an overall grade (1-10). Furthermore, they were asked to indicate how much they agreed with statements on a 5-point Likert-scale, see table 3. In addition to the questionnaire, YACCS' input from session 6 as well as input from an evaluation meeting with the course leaders was used to find specific points for improvement.

Sociodemographic characteristics: YACCS were asked to report their date of birth, gender, marital status, number of children, employment, and educational level (table 1) in a questionnaire.

Medical characteristics: Data about the diagnosis and treatment of the initial cancer as well as recurrences was obtained from the Dutch LATER registry, which contains detailed information about diagnosis and treatment from the medical files of Dutch CCS.
Distress: Distress was measured using the Distress Thermometer (DT)[33]. The DT is a thermometer (0-10) on which CCS can indicate their overall distress (physical, emotional, social, as well as practical). Higher scores indicate more distress. The DT is a quick screening tool that accurately identifies distress in CCS[34].

Sense of control over changes in life: The Mastery Scale (MS) is a seven-item questionnaire measuring sense of control over changes in life[35]. Every item is a statement to which a respondent can respond on a 5-point Likert scale from 1 "totally agree" to 5 "totally disagree". Higher scores indicate higher sense of control. A total score is calculated (5-35). Internal consistency of the MS is sufficient with Cronbach alpha .79[36].

Illness cognitions: cognitions about childhood cancer were measured using the illness cognition questionnaire (ICQ). YACCS responded to 18 statements on a 4-point Likert scale to indicate how much they agreed with the statement from 1 "not" to 4 "completely". The ICQ has three scales: Helplessness, acceptance, and perceived disease benefit. Higher scores indicate higher levels of the constructs (6-24). The ICQ has good psychometric properties, with Cronbach alpha ranging from .84 to .91[37, 38].

Impact of cancer: The Dutch IOC-CS is a survivor-specific questionnaire for perceived impact of childhood cancer[8, 39]. It includes five scales measuring positive impact and six scales measuring negative impact (table 3). Survivors respond to statements on a 5-point Likert scale from 1 "none at all" to 5 "very much". Higher scores indicate more

positive or negative impact. The original version has good psychometric properties[39]. Cronbach's alphas in a previous study with Dutch YACCS ranged from .59 to .92[8].

Health-related quality of life: The Pediatric Quality of Life Inventory Young Adults (PedsQL-YA) measures HRQOL. The PedsQL-YA has four scales: Physical, Emotional, Social, and Work/School functioning, a total scale and a Psychosocial Summary Scale combining emotional, social, and work/school functioning. Higher scores indicating better HRQOL (0-100). The PedsQL-YA has good psychometric properties and a Dutch young adult reference group is available[40]. Internal consistency in a previous study with Dutch YACCS was satisfactory ($.80 \leq \alpha \leq .92$)[8].

Statistics

All statistics were performed using IBM SPSS Statistics version 26. Descriptive statistics were used to create an overview of participants' characteristics. Feasibility was assessed using attendance rates and descriptive statistics from the evaluation questionnaire.
Preliminary effectiveness was investigated using paired samples t tests to compare psychosocial outcomes between T0 and T1 within respondents. For all tests, α was set at .05. Cohen's *d* was calculated to assess the effect size of the differences between T1 and T0.

Results

Sample characteristics

Ten YACCS (mean age = 25.1, 60.0% female) participated in this pilot study. There were two group courses, one with 4 and one with 6 participants. Sociodemographic and medical characteristics of participants are displayed in table 2.

Feasibility

Attendance logs showed that of the 10 participants, 90% attended at least 5 out of 6 sessions and the drop-out rate was 0%.

Results from the evaluation questionnaire (table 3)

On average, YACCS rated the intervention a 7.6 (range 7.0-8.0) on a 0-10 scale. Most YACCS indicated that they implemented at least one thing they learned during the course into their daily lives. YACCS most often mentioned implementing the thinking-feeling-doing model. All participants would (maybe) recommend the course to others. YACCS were mostly positive about their experiences with the intervention.

In terms of points for improvement, the number of 6 sessions was not enough according to 60% of YACCS. Also, participants were not all satisfied with the homework. Even though 70% thought that the quantity of the exercises was good, and 90% agreed that the difficulty of the exercises was good, no participants considered the exercises to be useful.
For more details see table 3.

Results from the evaluation during the sixth session

The group with six participants mentioned that there was often not enough time to discuss topics as thoroughly as they would want. YACCS indicated that to solve this problem, they would rather have had more sessions than longer sessions, as they expected that longer sessions would be unattainable in terms of energy and attention.

Results from the evaluation session with course leaders

In a separate evaluation, course leaders, who were mostly positive about the intervention, agreed that a group of six was too large to thoroughly discuss certain topics. Furthermore, conversations were slower than expected, due to the fact that the group was often waiting for someone to type a message. Lastly, homework was often not completed by all participants, which made plenary discussion of the homework exercises more difficult.

Preliminary effectiveness

Participants' distress (DT, $Mean_{T0}$=5.1, $Mean_{T1}$=3.7, p=.030, Cohen's d=-.6) and feelings of helplessness (ICQ, $Mean_{T0}$=10.4, $Mean_{T1}$=8.7, p=.001, Cohen's d=-.8) reduced significantly from T0 to T1, while their self-efficacy (MS, $Mean_{T0}$=20.1, $Mean_{T1}$=22.8, p=.013, Cohen's d=.8) improved. Impact of cancer (IOC-CS) and HRQOL (PedsQL-YA) did not change significantly. See table 4 for all outcomes.

Discussion

Results from this first, small pre-post-test, pilot study indicate that Op Koers Online for YACCS seems to be a feasible intervention that is positively evaluated by both YACCS and course leaders. YACCS rated the intervention satisfactory in terms of their user experiences with the chat box as well as content, and most YACCS reported that they implemented the main CBT skills in their daily lives. The pilot study showed promising results shortly after the intervention regarding distress, illness related helplessness and self-efficacy. This could indicate that YACCS feel more prepared to deal with challenges, which fits well with the learning goals that the course aims to fulfill through the combination of CBT, ACT, peer support, and psycho-education.

Besides these significant results, a few small-to medium effects that were not significant stood out with regard to improved acceptance, perceived positive impact of cancer on one's body and health, and health literacy, as well as decreased concerns about the impact of cancer on siblings. These results align with the use of ACT and topics discussed during the sessions 'my body' and 'my family'. However, to be able to draw sound conclusions about effectiveness of the intervention, results should be replicated in a RCT, with sufficient power and measuring also effects on the long term.

The preliminary, short-term results of this small pilot study are in line with the results of Op Koers Online in adolescents treated for cancer or with a chronic illness and their parents[28, 29, 31]. Like the present study, the recently published RCT about Op Koers Online for parents, which offers CBT to another adult population in a similar manner as Op Koers Online for YACCS, found a significant decrease of helplessness. Furthermore, a significant increase of acceptance was found in parents, while the present study found a trend towards significance.

Although there was no drop-out in this pilot and attendance was high, adherence to the homework exercises was low. This is unfortunate, because homework exercises are a core component of CBT and low adherence could jeopardize the effectiveness of the intervention. Nevertheless, implementation of CBT principles into daily life was high, indicating that repeatedly addressing them during the sessions was probably sufficient to achieve retention. This result is in line with the short-term results of a recent RCT of Recapture Life, an Australian online group intervention for survivors of adolescent and young adult cancers, showing that participants have adopted CBT-skills over the course of the intervention[16]. Because of the low adherence and limited perceived usefulness, the homework exercises will be revisited while further developing Op Koers Online for YACCS.

While this study provides some important new insights, there are a few limitations to consider. Caution is warranted when drawing conclusions from this pilot study as there were only 10 participants, who were recruited after showing interest to participate in the intervention in the questionnaire of the previous needs assessment study. Explorative comparison of the group of YACCS that were interested to participate and those who were not, revealed that interested YACCS reported poorer psychosocial functioning. Additionally, the prior needs assessment study found that YACCS with worse psychosocial outcomes reported more support needs[32].

Furthermore, there was no control group and only short term effects were measured in a small sample. While this design was sufficient to answer the research questions in this pilot testing phase, further evaluation is necessary in order to draw conclusions about the effectiveness and feasibility of the intervention. While our study design could raise concerns for bias, nevertheless, the results seem to indicate that self-referral to low-threshold interventions such as Op Koers Online is appropriate for a subset of YACCS that may achieve improvement.

No CNS tumor survivors participated, so we cannot generalize the findings from this pilot to them. Survivors of CNS tumors are a risk group for poor outcomes after childhood cancer[4, 9, 41-45], but Op Koers Online could be less appropriate for those with neurocognitive deficits, due to the high speed of the chat conversations at times.

Survivors in this pilot study varied from 18 to 31 in current age and from 3 to 17 in age at diagnosis, but we did not experience this to be a barrier in conversations between the YACCS. The content of Op Koers Online focuses mainly on experiences that YACCS have in their current life that may be related to their childhood cancer history. By centering each session around each survivor answering questions from their own experience, course leaders fostered an environment where differences and similarities between survivors could be discussed in a safe and supportive manner.

With Op Koers Online for YACCS, we can now offer a first psychosocial intervention to YACCS receiving survivorship care in The Netherlands. The intervention fills a gap because to date no psychosocial intervention for YACCS was available in the Netherlands. Op Koers Online for YACCS made use of an existing platform and format that has previously shown positive results in various other patient populations[28, 29, 31]. Researching the needs of YACCS and pro-actively asking YACCS for input has allowed us to create an intervention that matches what YACCS need and want in a psychosocial intervention[32]. It is important to note that an online group intervention does not fit every YACCS. Survivorship care should include a wide range of psychosocial care, so that tailored care can be delivered to YACCS. Since the first development of Op Koers Online in the early 2000s, e-health has become more popular and technological advancements have changed the way in which e-health interventions are delivered to patients. Although previous experiences with Op Koers Online as a chat box intervention were positive for most participants (e.g. anonymity), it could be time to explore more modern delivery methods such as video conferencing software or Voice over IP (VoIP). Notably, this pilot study took place before the COVID-19 pandemic. As the use of e-health has increased and evolved during the pandemic, Op Koers Online may now match even more closely with the demand for innovative e-health care.

Op Koers Online for YACCS shows promise, but continuous development could help make the intervention more effective and more fitting to the needs of YACCS. All points of improvement from the present study will therefore be taken along in developing the next version of the intervention. Op Koers Online for YACCS is not suitable for YACCS with severe mental health problems. Therefore, survivorship care clinics should still offer or refer to more intensive and personalized psychosocial support for YACCS.

Conclusions

The first pilot study of Op Koers Online for YACCS indicated that the intervention is feasible, having been evaluated positively by both YACCS and course leaders. Short term results of this small pilot showed decrease in distress and feelings of helplessness and improvement of self-efficacy. This intervention fills a gap in psychosocial services for YACCS during survivorship care. Points of improvement for the intervention include reducing the number of participants per group, revision of the homework, and adding one or more sessions.

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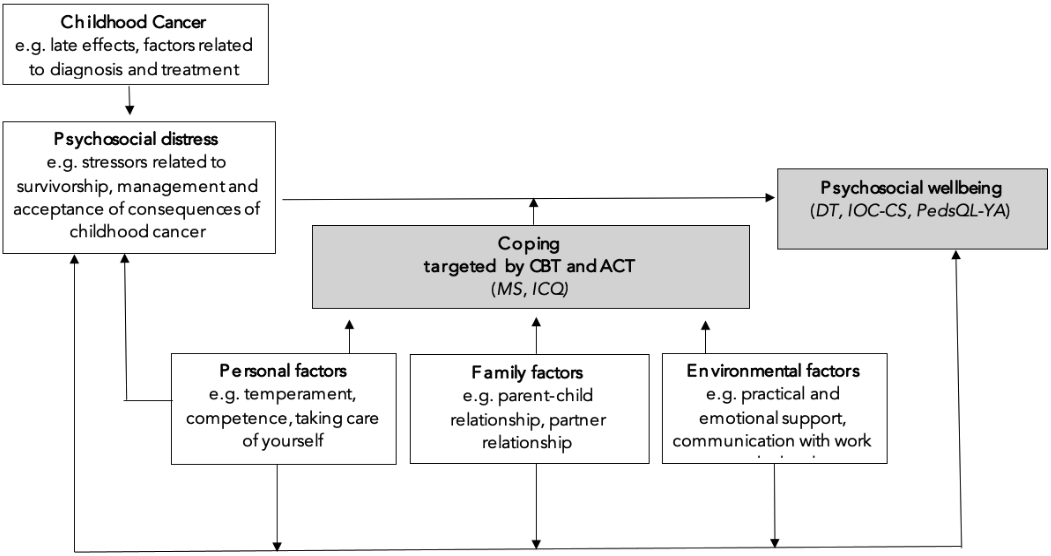
Figure 1
Conceptual model: adapted version of the disability-stress-coping model of Wallander and Varni (1998)[12] to explain psychosocial wellbeing of young adult survivors of childhood cancer.



MS Mastery Scale; ICQ Illness Cognition Questionnaire; DT Distress Thermometer; IOC-CS Impact of Cancer – Childhood Survivors; PedsQL-YA Pediatric Quality of Life Inventory for Young Adults.

Figure 2 *Design of the pilot study Op Koers Online for YACCS*

	Participants	Course leaders
week 1-4	**T0 – Questionnaires:** *Preliminary effectiveness*: - Distress Thermometer (DT) - Mastery Scale (MS) - Illness Cognition Questionnaire (ICQ) - Impact of Cancer – Childhood Survivors (IOC-CS) - Pediatric Quality of Life Inventory (PedsQL-YA)	
week 5-10	**6 Group sessions via the chat** *Feasibility* Course leaders evaluated the intervention with the participants as part of the sixth group session (week 10)	
week 11-14	**T1 – questionnaires:** *Feasibility* - Evaluation questionnaire *Preliminary effectiveness*: - Distress Thermometer (DT) - Mastery Scale (MS) - Illness Cognition Questionnaire (ICQ) - Impact of Cancer - Childhood Survivors (IOC-CS) - Pediatric Quality of Life Inventory (PedsQL-YA)	*Feasibility* Evaluation meeting with the researcher
week 27	**Booster session via the chat**	

Table 1: Overview of Op Koers Online for YACCS sessions

tw	Topics	Homework	Psycho-educational texts
Introductions + CBT-model	- Introduction to the course, each other and the CBT-model.	- Practice with the CBT-model, application to self and others. - Finding information	- The CBT-model - Disability
My body	- Physical late effects - Finding information	- Coping with late effects - Finding information - Practice with CBT-model	- Late effects - Reliable information - Independence from parents
My family	- Impact childhood cancer on family life	- Leisure activities with others - Talking to brothers/sisters about illness and late effects - Practice with the CBT-model, application to self and family members - Dealing with impact of own disease on family members	- Impact of childhood cancer on brothers and sisters - Complimenting others - Thinking errors - Finding distraction or relaxation
My friendships and relationships	- Telling others about childhood cancer - Impact of childhood cancer on current friendships and relationships	- Complimenting others - Writing 'your story' - Deciding when to disclose illness history - Thinking error 'mindreading'	- Talking about childhood cancer - Friendships after childhood cancer - Assertiveness - Creating a common vision in a romantic relationship
My education, work and future	- Support system in the context of education, work and future plans - Trouble at work/school - Reactions from others regarding childhood cancer - Contact with school or employer - Ambitions for the future	- Writing down your support system - Difficult questions about history with childhood cancer - Practicing the CBT-model in the context of work or school - Value-driven living (ACT)	- Asking for help and getting help - Looking for a job - Studying with a disability - Formulating ambitions SMART
Looking back	- Complimenting each other - Looking back at course - Evaluation	N.A.	N.A.

Table 2: Characteristics of participants (N=10)

	Mean±SD (range)	% (N)
Socio-demographic		
Age (years)	25.1±4.5(18.3-30.1)	
Sex (female)		60 (6)
Partner		
Yes		30 (3)
No		70 (7)
Employment status		
Paid occupation		50 (5)
No paid occupation		50 (5)
Educational attainment[a]		
Low		10 (1)
Middle		50 (5)
High		40 (4)
Current education (N=4)[a]		
Low		0 (0)
Middle		25 (1)
High		75 (3)
Medical characteristics		
Age at diagnosis	12.0±5.2 (3.8-17.4)	
Time since diagnosis	13.1±2.8 (7.2-16.4)	
Diagnosis		
Hematologic cancers		80 (8)
CNS tumors		0 (0)
Solid tumors		20 (2)
Recurrence		40 (4)
Treatment[b,c]		
Surgery		60 (6)
Chemotherapy		100 (0)
Radiotherapy		60 (6)
SCT/BMT		20 (2)

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

[b] *More than one category possible*

[c] *Treatments for primary tumor and (if applicable) recurrence(s).*

Table 3: Feasibility of Op Koers Online for YACCS (N=10)

How do you feel about the following components? %(N)			
	Too short	Good	Too long
Duration of sessions	10(1)	80(8)	10(1)
	Too few	Good	Too many
Number of sessions	60(6)	40(4)	0 (0)
	Too small	Good	Too large
Group size	10(1)	80(8)	10 (1)

How do you feel about the homework exercises? %(N)			
	Too few	Good	Too many
Quantity	0(0)	70(7)	30(3)
	Too easy	Good	Too hard
Difficulty	0(0)	90(9)	10(1)
	Not useful	Somewhat useful	Useful
Usefulness	30(3)	70(7)	0(0)

Would you recommend this course to others? %(N)				
Certainly	Probably	Maybe	Probably not	Certainly not
50(5)	30(3)	20(2)	0(0)	0(0)

Indicate how much you agree with the following statements %(N)					
	Completely disagree	Disagree	Nor agree, nor disagree	Agree	Completely agree
I could follow the sessions well	0(0)	0(0)	10(1)	40(4)	50(5)
I could express myself well in the chat	10(1)	0(0)	20(2)	30(3)	40(4)
During the sessions, I was (mostly) able to say what I wanted to say	0(0)	0(0)	20(2)	60(6)	20(2)
I found the course instructive	0(0)	0(0)	20(2)	60(6)	20(2)

Do you use something you have learned in the course in your daily life? %(N) (missing data = 1)	
Yes	No
78(7)	22(2)

Table 4: Preliminary effectiveness: Psychosocial wellbeing of YACCS after versus before the intervention 'Op Koers Online for YACCS' (N =10).

	Before		After			
	Mean	SD	Mean	SD	*t*	Cohen's *d*
Distress Thermometer	5.1	2.0	3.7	2.6	-2.6*	-.6
Mastery Scale	20.1	4.1	22.8	2.3	3.1*	.8
Illness Cognition List						
Helplessness	10.4	2.2	8.7	2.2	-5.1**	-.8
Acceptance	18.2	3.1	19.1	3.2	1.5	.3
Perceived disease benefit	19.6	3.0	19.6	3.9	.0	.0
IOC-CS						
Positive impact of cancer						
Body/Health	3.5	.5	3.7	.5	1.6	.4
Talking With Parents	3.5	1.0	3.3	1.1	-1.4	-.2
Personal Growth	3.1	.5	3.2	.7	1.8	.2
Health Literacy	3.5	.8	3.7	.7	1.4	.3
Socializing	3.6	1.0	3.8	.7	1.2	.2
Negative impact of cancer						
Life Challenges	2.3	.8	2.3	.7	.0	.0
Thinking/Memory Problems	2.5	.6	2.4	.6	-1.3	-.2
Financial Problems	1.5	.7	1.6	.8	.6	.1
Sibling Concerns	3.1	1.2	2.7	1.2	1.3	-.3
Relationship Concerns	2.6	.5	2.5	.5	-1.6	-.2
PedsQL (total score)	76.1	10.5	76.0	10.2	.0	.0
Physical	76.9	17.9	78.1	16.7	.5	.1
Emotional	71.0	22.0	69.5	18.3	-.3	-.1
Social	79.5	11.1	79.5	7.9	.0	.0
Work/school	76.5	17.6	75.5	17.9	-.2	-.1
Psychosocial	75.7	12.3	74.8	10.4	-.2	-.1

** significant at $\alpha = .05$*
*** significant at $\alpha = .01$*

9

CHAPTER 9
GENERAL DISCUSSION

Childhood cancer survivors (CCS) are a growing population facing unique challenges, in need of specialized survivorship care throughout their lifespan. This thesis reported results from the Dutch CCSS LATER cohort and the young adult childhood cancer survivors (YACCS) project. The thesis aimed to increase the understanding of psychosocial challenges of childhood cancer survivorship

Part I provided an overview of HRQOL and risk factors of impaired HRQOL in Dutch adult CCS. (Chapter 2 and 3). In part II, the focus was on YACCS, arguing that YACCS and adolescent and young adult cancer survivors (AYACS) are distinct groups (Chapter 4). We examined several psychosocial outcomes, including developmental milestones (Chapter 5) and survivor-specific outcomes (Chapter 6). In addition, we examined support needs of YACCS (Chapter 7) and developed and evaluated an online group intervention for YACCS (Chapter 8).

The discussion of this thesis begins with a summary of and reflection on the main findings, followed by a critical review of the research, recommendations for clinical care and future research, and concluding with key messages.

Main findings and reflections

Part I: Health-Related Quality of Life (HRQOL) of adult survivors of childhood cancer

The first part of this thesis contains two reports of large nation-wide cohort studies of HRQOL in Dutch adult childhood cancer survivors; one using the SF-36, the other using the TAAQOL. From both nation-wide cohort studies, we concluded that adult CCS are at a higher risk of worse HRQOL compared to peers from the general population, but that differences were generally small to medium-sized. The main findings are discussed below and listed in table 1.

The SF-36 enabled us to investigate physical and mental HRQOL separately, illustrating that a few sociodemographic risk factors (low educational attainment and not having a partner) can threaten both aspects of HRQOL. Besides these risk factors, impaired physical HRQOL was predicted by female sex and some medical characteristics: older age at diagnosis, disease recurrence, and exposure to radiotherapy, specifically to the lower extremities. Impaired mental HRQOL was associated with male sex, and age 26-35 but not with medical characteristics.

A benefit of using the TAAQOL is that this questionnaire does not only measure health problems but also the perceived impact of these problems. In this way, the TAAQOL adds valuable information to that of the SF-36. Furthermore, despite being a generic HRQOL measurement, the TAAQOL measures some specific subscales that are potentially very relevant to CCS, such as cognition and sleep, and sexuality.

The results of the TAAQOL-project revealed that CCS were more often impaired than the general population in gross and fine motor function, cognitive function, sleep, and vitality. Especially the domain of cognition, in which 50% of survivors experienced impairment, is in need of more research and (early) interventions. Besides these domains, female CCS were also more likely to be impaired in daily activities, pain, and sexuality. Apart from female sex and older age, a few medical risk factors for some aspects of impaired HRQOL were found: diagnosis of a CNS or bone tumor or retinoblastoma, and exposure to cranial, pelvic or lower extremity radiation. Most associations between the medical factors and HRQOL were of small to medium size.

In both studies, CCS scored less favorable than the general population in most domains of HRQOL, and effect sizes were mostly small to medium. This is consistent with most HRQOL research in survivors(1-7). However, some studies found HRQOL of CCS to be comparable to the general population (6-9). These conflicting results can be explained by differences in the survivor groups that were included, such as differences in diagnosis or follow-up time, as well as the use of different reference groups (siblings, healthy peers, or the general population).

Looking at the rate of impairment, which was around 10% for both physical and mental HRQOL on the SF-36 and varied between 10% on aggressive emotions and 50% on cognitive function for women on the TAAQOL, CCS were at a higher risk for impaired HRQOL overall. Looking at the specific domains where CCS differ the most from the general population, both studies stress the need for attention for vitality and the TAAQOL-study emphasizes cognition.

The two nation-wide cohort studies showed that, when compared to norms specifically for women, female CCS seem to be impacted more severely by childhood cancer survivorship than their male counterparts. This stresses the need for looking at men's and women's HRQOL and other psychosocial outcomes separately, for example in clinical studies designing and evaluating interventions that are expected to improve HRQOL.

Nation-wide cohort studies have two important benefits. First of all, large cohort studies provide an overview of the outcome that is potentially more generalizable. Furthermore, a large sample, through statistical power, allows for the investigation of more potential risk factors than a smaller sample would. Therefore, in both studies, we aimed to identify characteristics that are associated with a higher risk of impaired HRQOL. In line with previous research, our results confirm that investigating medical characteristics did not yield sufficient leads to identify specific (groups) of CCS at risk for psychosocial problems, other than CCS diagnosed with CNS cancer and treated with radiotherapy. It highlights the importance of looking at sociodemographic and psychosocial characteristics that can put survivors at risk for poor HRQOL in more detail. Because of the large sample size, we were able to investigate the role of sociodemographic characteristics, such as educational attainment and having a partner in the SF-36 cohort-study. Both seemed to have a bigger influence on HRQOL than diagnosis and treatment did. However, besides being risk factors for impaired HRQOL, both have been identified as outcomes of childhood cancer in the past (8-10). Thus, it is important to intervene early and provide interventions for children related to peer activities and school in order to support social functioning.

	Aims	Sample characteristics	Outcome measures	Main findings and conclusions
Part I: Health-Related Quality of Life of adult survivors of childhood cancer				
Chapter 2	To investigate the HRQOL of adult CCS and to identify risk factors of impaired HRQOL.	2301 adult CCS, aged ≥18, diagnosed <18, ≥5 years since diagnosis, mean age = 35.4 years (range 18.3-69.0), 49.6% female, mixed diagnoses	HRQOL: SF-36	- CCS reported significantly worse HRQOL than the general population on almost all scales of the SF-36, but differences were small to medium-sized (-.11≤d≤-.56). - The largest differences were found regarding general health perceptions and vitality. - Risk factors for impaired physical HRQOL were: female sex, older age at diagnosis, not having a partner, low educational attainment, disease recurrence, exposure to radiotherapy, specifically to lower extremity radiation. ORs ranged from 1.6 to 3.7. - Risk factors for impaired mental HRQOL were: age 26-35, male sex, not having a partner, and low educational attainment. ORs ranged from 1.3 to 2.0. - Adult CCS could benefit from routine surveillance of their HRQOL. - Special attention for CCS' vitality and health perceptions and beliefs is warranted.
Chapter 3	To compare HRQoL of adult male and female CCS to the general population and study medical determinants.	1766 adult CCS, aged ≥18, diagnosed <18, ≥5 years since diagnosis, mean age = 35.9 years (range 18-71), 49% female, mixed diagnoses	HRQOL: TAAQOL	- CCS scored worse in most domains, but differences were small (-.05≤d≤-.34). - CCS were more often impaired in gross and fine motor function, cognitive function, sleep and vitality than the norm with ORs >1.4. - Female CCS were also more impaired in daily activities, pain, and sexuality (ORs:1.4-1.9) but were less often aggressive (OR:0.6) than the norm. - Survivors of CNS tumors, bone tumors and retinoblastoma, and those exposed to cranial, abdominopelvic, or lower extremity radiation were at risk of impairment in ≥1 domains. - Surveillance of HRQOL and multidisciplinary survivor care are recommended.

Part II: Age-specific psychosocial challenges of young adult childhood cancer survivors

The second part of this thesis started with a commentary about the urgent need for research into young adult childhood cancer survivors (YACCS, diagnosed before the age of 16) as a distinct group, separately from young adult survivors who were diagnosed with cancer during adolescence or young adulthood (AYACS, diagnosed from age 16 to 25). Furthermore, we described the results about psychosocial development in YACCS from the DCCSS LATER study part 2. In the final three chapters of part II, we described the results of the YACCS-project in which we investigated the age-specific challenges of YACCS and evaluated the newly developed online group intervention Op Koers Online for YACCS. The results of our research on YACCS is recapped in table 2.

From our studies, we conclude that YACCS are a vulnerable population who, as a group, report worse psychosocial well-being than the general population. YACCS reported more anxiety and depression than the norm, lower HRQOL, and more fatigue. Despite this vulnerability, many YACCS have normal psychosocial development, are resilient, with scores within the norms, and also experience positive impact of cancer besides negative impact.

However, young adult survivors of CNS tumors are at risk for delayed or disrupted autonomy, psychosexual and social development. Certain subsets of YACCS, in particular survivors of CNS tumors, women, and those with lower education, are at risk for worse well-being. Therefore, we can conclude that risk factors in YACCS are similar to those found in adult CCS as described in part I.

The investigation of survivor-specific outcomes in YACCS and their association with other psychosocial outcomes is innovative and therefore makes an important contribution to the literature. Previous research has mostly focused on generic outcomes and psychopathology. The YACCS well-being study showed that the perceived impact of cancer is important in predicting the psychosocial outcomes of YACCS, though statements about causality cannot be made. The highest positive impact was experienced with regard to socializing, while the highest negative impact was experienced concerning thinking and memory problems.

Not just survivor-specific outcomes are deserving of more attention, YACCS' support needs are understudied as well. Increased knowledge on support needs can help shape and improve survivorship care. In the YACCS-needs study, over 80% of YACCS reported a need for support. Especially information and counseling needs in domains related to late effects of childhood cancer and lifestyle were often reported. This is in line with the sparse previous research on support needs (11-13). YACCS with worse psychosocial well-being reported more needs. Quantifying YACCS' support needs and looking at needs with a broader scope than information needs added to the already existing, mostly qualitative literature. We conclude that information provision is crucial in providing adequate survivorship care. Through starting information provision at an earlier stage than during young adulthood, we can potentially inform CCS better about their health in order to prevent high unmet needs for information. Also, as a large portion of YACCS indicated to need information about lifestyle, we believe this topic should be addressed not just in survivorship care, but from the first day of treatment. Developing a healthy lifestyle during childhood, and being aware of the special importance of a healthy lifestyle after childhood cancer, could be helpful in our goal of giving children

with cancer and survivors the best possible quality of life. It is important to note that addressing lifestyle in children cannot be done without involving their parents.

Striving for optimal quality of life can also be supported by psychosocial interventions. In the final part of our YACCS project, we developed and evaluated Op Koers Online for YACCS. This online group intervention based on cognitive behavior therapy (CBT) with inclusion of a few excercises based on Acceptance and Commitment Therapy (ACT), was evaluated positively by YACCS and course leaders and appeared to be feasible. Furthermore, participants in the pilot study reported lower distress and helplessness, as well as more self-efficacy after the intervention. This study provided a first indication of the potential effectiveness of Op Koers Online for YACCS in improving psychosocial outcomes.

	Aims	Sample characteristics	Outcome measures	Main findings and conclusions
Part II: Age-specific challenges of young adult childhood cancer survivors				
Chapter 4	To explore and describe differences between the cancer and survivorship experiences of YACCS and AYACS. To provide arguments for research of YACCS and AYACS as distinct groups.	Presents information from previous literature.		- The interruption of development by the cancer diagnosis and treatment of YACCS differs from the interruption of AYACS. - We expect YACCS and AYACS to have some similar psychosocial outcomes caused by similar experiences, some similar psychosocial outcomes caused by different experiences, and some different psychosocial outcomes because of differing interruptions to their development. - The lack of clear delineation between these two groups in the literature makes it difficult to understand, and therefore meet, the psychosocial needs of these two growing populations. - Future researchers should: - Document age at diagnosis and current age to conduct subgroup analyses to explore any differences - Consider survivors' developmental stage at cancer diagnosis/ treatment when interpreting research findings
Chapter 5	To compare the psychosocial developmental trajectory of YACCS with young adults from the general population.	558 YACCS, aged 18-30, mean age 25 years, 51% female, diagnosed <18, ≥5 years since diagnosis, mixed diagnoses (CNS tumor survivors N = 61)	Psychosocial developmental milestones: Course of Life Questionnaire (CoLQ)	- The total group of survivors scored as favorable as the norm group. - CNS tumor survivors scored lower than the norm group on the scales autonomy and psychosexual development. Differences were of small to medium size. - CNS tumor survivors were less likely than the norm group to achieve half of the milestones from autonomy, psychosexual and social development; OR [0.23 – 0.48]. - Monitoring psychosocial development is recommended. - Personalized interventions should be offered to improve the psychosocial development in an early stage.

Chapter 6	To increase our understanding of the psychosocial well-being of young adult YACCS as well as the positive and negative impacts of cancer.	151 YACCS, aged 18-30, mean age 24 years, 61% female, diagnosed <18, ≥ 5 years since diagnosis mixed diagnoses	Impact of cancer: IOC-CS HRQOL: PedsQL 4.0 YA Depression and anxiety: HADS Fatigue: CIS-20R	- YACCS reported lower HRQOL, more anxiety, depression, and fatigue than the norm; effect sizes were small to medium ($.3 \leq d \leq -5$). - YACCS were at an increased risk for (sub)clinical anxiety; OR 1.8. - YACCS were at an increased risk for severe fatigue; OR 2.4. - YACCS experience both positive and negative impact of cancer. - Especially higher negative impact on 'Life Challenges' and higher positive impact on 'Body & Health' were related to psychosocial outcomes. - Monitoring of psychosocial outcomes and offering targeted interventions are necessary to optimize psychosocial long-term follow-up care for YACCS.
Chapter 7	To assess support needs and its determinants (sociodemographic, medical and psychosocial functioning) in YACCS.	See chapter 6	Sociodemographic questionnaire Need for support questionnaire HRQOL: PedsQL 4.0 YA Depression and anxiety: HADS Fatigue: CIS-20R	- The majority (88%) of YACCS had support needs. - YACCS report the strongest needs in the domains lifestyle (76.2%), fertility (68.2%) and physical consequences of childhood cancer (69.5%) - Factors associated with support needs were mostly socioeconomic and psychosocial in nature; YACCS with worse psychosocial well-being reported more needs. - Psychosocial care should be an integral part of survivorship care for YACCS, including: - Screening for psychosocial problems, - Information provision including psycho-education - Tailored interventions - Adequate referrals to more specialized care if necessary.

Chapter 8	To examine feasibility and preliminary effectiveness of an online group intervention Op Koers Online for YACCS.	10 YACCS, aged 18-30, diagnosed ≤18, mean age 25 years, 60% female, ≥ 5 years since diagnosis, mixed diagnosis, no CNS	Distress: Distress Thermometer Sense of control/ Self-efficacy: Mastery Scale Illness cognitions: ICQ Impact of cancer: IOC-CS HRQOL: PedsQL 4.0 YA	- Overall satisfaction with the course was high (7.6 out of 10). - Op Koers Online is feasible, 90% of participants attended ≥5 out of 6 sessions, and no one dropped out. - Op Koers Online is potentially effective in reducing distress and helplessness, and improving self-efficacy, based on pre-post tests within participants.

Critical review

When interpreting the results of the research described in this thesis, there are some considerations to keep in mind.

First of all, as a general consideration for survivorship research, it is important to realize that the survivors we are currently researching have received treatment that is different from the treatment given to children with cancer today. Childhood cancer treatment is continuously evolving. Therefore, it is of tremendous importance to continue researching survivorship challenges, outcomes, and determinants. However, with regard to psychosocial survivorship research, the findings in this thesis have shown that diagnosis and treatment characteristics have a limited influence on psychosocial outcomes, except from a few clearly defined risk factors (CNS tumors, cranio-spinal radiation, and radiation to the lower extremities). It could therefore be the case that research of psychosocial outcomes in childhood cancer survivors is less sensitive to changing treatment protocols than physical late-effect research. However, treatment protocols are not the only thing that is changing. The experiences associated with childhood cancer have changed over the years, with more attention for psychosocial support, supportive care, and a development centered approach. Furthermore, societal changes may influence how children with cancer and survivors compare to peers in the general population. While it is encouraging to see that survivors' psychosocial development seemed to be changed for the better, this improvement unfortunately does not apply to all survivors. CNS tumor survivors remain at risk for delayed psychosocial development. Therefore, survivorship research and care remain an absolutely necessary part of pediatric oncology.

Secondly, in a few of our studies (SF-36, YACCS well-being, YACCS needs) we found that sociodemographic characteristics of survivors are of importance when predicting psychosocial outcomes. However, when looking at these characteristics, such as relationship status or educational attainment, we have to remind ourselves that they can be outcomes of childhood cancer as well (8-10). Therefore, chances to influence problems in these domains may benefit more from a focus on prevention during and shortly after treatment. For example, more focus on children's cognitive functioning during and after treatment may help survivors' academic achievements later in life. Nevertheless, challenges regarding education or relationships should receive explicit attention in survivorship care, for example by monitoring satisfaction with relationship status or academic achievements.

Thirdly, we were unable to include any data on disease burden of physical late effects in predictive models in our studies. Previous studies showed that the presence of physical late effects can influence HRQOL in survivors (2, 14, 15). In addition, we did not examine the role of psychosocial factors in relation to HRQOL and mental health outcomes, while it is known that coping style, for example, plays an important role in adaptation to disease in general (32), and in adaptation to cancer in particular (33,34) Future research projects should try to include these important factors whenever possible. The DCCSS LATER study part 2 Psycho-oncology includes these factors, and will therefore provide important additions to the work described in this thesis.

Lastly, the representation of CNS tumor survivors is lower in our study than one would expect looking at the composition of the LATER-cohort. For those most severely affected by late effects, especially after cranial radiation, it could have been difficult to fill out the self-report questionnaires from our study. This hampers the generalizability of the results of our studies to all Dutch YACCS. For the pilot study of Op Koers Online, we invited YACCS who had indicated to be interested in participation in the study. Unfortunately, the final sample was small and did not contain any survivors of CNS tumors. Because no survivors of CNS tumors participated in the Op Koers Online pilot, we cannot conclude whether or not this intervention is suitable for them. It may be difficult for them to participate in a chat intervention like Op Koers Online, due to the speed of chat conversations and the prolonged attention required during a session. It could also be that survivors of CNS tumors have needs that go beyond what is offered with Op Koers Online. One possibility is to offer Op Koers both face-to-face as well as online or using videoconferencing. Possibly, the face-to-face version of the course could be more appropriate for those with neurocognitive deficits. In developing interventions that are specifically designed for survivors of CNS tumors, inspiration could be drawn from interventions for psychosocial problems in patients with traumatic brain injury or from interventions in rehabilitation.

Main recommendations

Recommendations for clinical practice

Survivorship care

The combination of physical and mental health problems in this population makes holistic survivorship care absolutely necessary. Recognizing the importance of holistic survivorship care at all ages, and more attention for various transitional moments after childhood cancer treatment is warranted; the first moment being at the transition from follow-up care to survivorship care, and the second from pediatric survivorship care to adult survivorship care. We recognize that these moments are not universal across centers or across countries. It is important to identify relevant transition moments and investigate the needs of survivors at those stages.

With regards to supporting the psychosocial well-being of survivors, it is recommended that survivorship care includes monitoring of survivors' HRQOL, achievement of psychosocial developmental milestones, and other psychosocial outcomes, such as depression, anxiety, fatigue, and cognitive complaints. Clinicians should view these concepts from a biopsychosocial perspective, acknowledging their interrelationships, for example the association between fatigue and cognitive complaints (35,36). Using patient reported outcomes (PROs) with questionnaires in clinical practice for this purpose, has previously shown to be an effective way to increase attention for and discussion of patient outcomes, improve patient-clinician communication, as well as improve patient satisfaction and HRQOL (16-19). Monitoring should continue throughout the lifespan and can be especially important at transition moments, such as when survivors move on from primary to secondary school or from pediatric to adult survivorship care. Monitoring moments could be linked in timing and frequency to survivors' visits to the survivorship care clinic, enabling health care providers to see if there are any changes since the last appointment. Questionnaires that can be used are the PedsQL and TAAQOL for HRQOL, the HADS for anxiety and depression, the CIS-20R for fatigue and the course of life questionnaire (CoLQ) for developmental milestones. In the past years, positive experience with these questionnaires have been gained in the Princess Máxima Center within the KLIK PROM portal. In the future, PROMIS (Patient Reported

Outcomes Measurement Information System) questionnaires need to have a place in this system as well.

Interventions

The research described in this thesis showed that childhood cancer survivors are at risk for psychosocial difficulties, besides the more well-known physical late effects of their past treatment. As part of the holistic survivorship care, interventions could be used to meet the specific needs of (subgroups of) CCS. In order to improve survivors' attendance of survivorship care, it is crucial to inform them about their health, the importance of lifestyle, and the goals of survivorship care from a young age. Information provision programs should include psycho-education. A step-by-step information provision and lifestyle program that teaches children and their parents about life with and after childhood cancer from the start of treatment could improve attendance, prevent high information needs at a later age, as well as stimulate behavior and lifestyle that promote healthy aging of survivors.

YACCS reported support needs beyond information. Therefore, it is important to expand the availability of psychosocial support for YACCS. It is important to provide survivors with information about available health care providers in their own environment. Social support can be offered through psychosocial interventions (e.g. group interventions like Op Koers Online), or by referring CCS to someone in a network of health care providers that are sensitive to the needs of those who have had cancer. In accordance with previous research, the studies described in this thesis indicate that survivors of CNS tumors are an especially vulnerable group. Consequences of CNS tumors are complex and vary widely between survivors. We therefore recommend a personalized approach that focuses on supporting survivors' psychosocial development (e.g. social skill training, cognitive rehabilitation, or academic support).

Transitions in survivorship care can be optimized through the use of transition programs. Transition programs or interventions can be to help survivors navigate the change of center and/or health care provider by strengthening independence in the years prior to the transition from child survivorship care to adult survivorship care without undermining the involvement of parents in their child's care (20). In this way, transition programs can help empower CCS and support their autonomy development, so they can become responsible for their own health and care decisions as much as possible.

Vitality, or rather fatigue (as a state of lacking vitality) after cancer has received increased attention from researchers over the past years. Most studies conclude that fatigue is an important problem for survivors that needs to be monitored and guidelines were developed (21-25). Fortunately, previous studies suggest that cognitive behavior therapy (CBT) can be effective in reducing or coping with fatigue in various populations, including CCS (26). Therefore, clinicians could consider referral for CBT as an option for survivors who suffer from fatigue. Furthermore, in order to improve survivors' vitality and meet their need for support regarding a healthy lifestyle, it could be beneficial to develop and offer interventions that focus on healthy diet, exercise, and stress management as early as possible. Finally, it is crucial to acknowledge the association between fatigue and cognitive functioning, another frequently reported problem among CCS, and to develop interventions that could impact both.

Recommendations for research

In terms of future psychosocial survivorship research, there are a few recommendations to be made based on the work in this thesis.

Well-being

In the future, researchers should keep studying CCS' well-being, as their outcomes could potentially change as childhood cancer treatments change over time. Based on the findings (worse HRQOL, increased anxiety, depression, fatigue) and arguments discussed in this thesis, it is necessary to research YACCS specifically and separately from other groups of survivors (AYACs, younger and older survivors). YACCS are simultaneously dealing with a challenging developmental stage and potentially with (emerging) late effects of their treatment.

Researching survivor-specific outcomes enrich the perspective of findings, in the sense that they allow us to better represent the experiences of CCS. Therefore, we recommend continued use of survivor-specific psychosocial measures in research in addition to generic outcomes. The results of the survivor-specific outcomes in the YACCS project raise concern for health literacy. The focus groups and conversations with YACCS further illuminate survivor guilt as an important theme. From these results we can conclude that these topics are very relevant to the daily lives of survivors, however very little research focuses on these topics specifically.

Besides YACCS, there is a growing population of potentially vulnerable middle aged and elderly CCS who have thus far received little attention as a separate group. As survivorship care remains crucial to survivors' health throughout the lifespan, researching these groups should become a priority in the coming years. Discovering age specific challenges at a later age and, at a later stage, could yield input for tailored interventions. There is increasing evidence that survivors of childhood cancer experience premature physiologic aging, which puts them at risk for health problems that would occur much later in the general population (27). As middle aged and elderly CCS are a relatively small but growing population, very little is known about the challenges they face.

Apart from researching separate groups of survivors based on their age, sex-specific long-term outcomes of survivors need more attention from researchers. The findings from the TAAQOL-study and the SF-36-study indicate that female survivors experience impairment of their HRQOL more often and in more domains than male survivors.

Psychosocial well-being of survivors is of tremendous importance, and yet, it cannot be appreciated separately from their physical health situation. We therefore recommend future researchers to not only include survivors' past medical characteristics, such as diagnosis and treatment variables, but to include the burden of late effects in studies. Fortunately, this effort has been kick started in the Netherlands through the DCCSS LATER 2 Psycho-oncology study. Collaborations between researchers of physical and psychosocial late effects will be of great importance to the future of childhood cancer survivorship research and care. In addition to physical factors, it is of great importance to examine psychosocial factors that play a role in coping with the long-term consequences of childhood cancer.

Subjective cognitive complaints, a specific late effect, was found to be an important challenge for (young) adult survivors in both the TAAQOL-project and the survivor-specific part of the YACCS-project. In the past decades, more and more studies have objectified these complaints and investigated cognitive impairment in survivors of childhood cancer. Previous studies that include neuropsychological assessment showed that neurocognitive late effects affect many survivors and can be severe (28-30). Future research should focus on the development of subjective cognitive problems and objective cognitive impairments throughout the lifespan of survivors.

Needs

Future research should focus on accumulating more information about YACCS' needs, as our study was one of the first. As we have seen in the results of our research, well-being in survivorship is different for men and women and is impacted by age. We therefore recommend taking both sex and age into account when further researching needs, and to research needs in understudied groups like YACCS or middle-aged and elderly survivors.

Another group that should be specifically researched are those with cognitive complaints. As researchers learn more about subjective cognitive complaints and objective deficits in survivors, it is crucial to learn also more about the needs of those faced with this late effect of treatment, in order to better understand how to deliver care that is appropriate for those with cognitive deficits.

In conclusion, more knowledge about needs of CCS and vulnerable groups of CCS can help tailor survivorship care and develop more interventions.

Interventions

In general, research and development of psychosocial interventions for survivors is not yet very advanced and should therefore receive more attention. Interventions for specific groups of survivors (e.g. elderly or survivors of CNS tumors or those with cognitive impairment), or interventions focusing on specific challenges (e.g. cognitive complaints of survivorship), should be developed in the future.

The results of HRQOL in adult survivors and well-being and support needs of YACCS raise specific concerns about fatigue, which is important to focus at in interventions. Survivors' perception of their own health and their body image were the strongest predictors of well-being, though causality was not examined. Well-being may be sensitive to change by lifestyle interventions, another topic that YACCS expressed high needs on in our study.

Besides lifestyle interventions, more psychosocial interventions for YACCS need to be developed, as very few interventions specifically for YACCS are available. Our own intervention, Op Koers Online for YACCS, was based on CBT. While this approach may be effective in improving outcomes like fatigue, or in the case of Op Koers Online for YACCS distress and self-efficacy, the applicability of newer cognitive behavioral techniques for YACCS could be put to the test in future research. Acceptance and Commitment Therapy (ACT) is a third wave behavior therapy that focuses on acceptance of the challenges presented by your life or situation and living in alignment with your values (31). Op Koers Online for YACCS contained one ACT-based exercise. Interventions based on ACT or with a larger component of ACT could be especially fitting for survivors, as many of the health related challenges they face cannot be changed or avoided.

Conclusions

Survivors of childhood cancer are a growing population facing unique challenges to both their physical and mental health. This thesis aimed to contribute to the base of evidence on the long-term psychosocial outcomes of childhood cancer survivors. Above all, this thesis yields insight into the needs of young adult survivors as a vulnerable group and presents a promising online group intervention tailored to these needs.

The first part of this thesis shows that survivors, as a group, experience worse HRQOL than the norm, with small to medium effect sizes. Impairment in some areas, such as vitality and cognitive functioning, was rather high. Monitoring HRQOL should become standard practice in survivorship care. Clinicians should pay special attention to risk groups: female survivors, CNS tumor survivors, survivors with lower educational attainment and those without a partner.

The second part of this thesis focused especially on YACCS. YACCS are a vulnerable group that needs to be researched separately from younger and older childhood cancer survivors because of the unique combination of developmental and survivorship challenges they face. While YACCS reported to experience positive impact of cancer beside negative impact of cancer, some psychosocial outcomes were worse than the norm. A large portion of survivors reported anxiety or fatigue. A large majority of YACCS reported needs for support, and those with worse well-being reported more needs. Needs were especially high regarding information about late effects, lifestyle, and fertility. A portion of survivors also reports a need for counselling, for example regarding social and emotional consequences of their cancer history.

To meet YACCS' needs for psychosocial support, Op Koers Online for YACCS was developed and pilot tested. With this version of Op Koers Online, the first psychosocial intervention especially for YACCS in the Netherlands has become available. While this intervention needs fine-tuning and could benefit from additional research about effectiveness, the results from our first small pilot study were promising with regard to feasibility and potential effectiveness on improving distress, self-efficacy and feelings of helplessness.

The final conclusions are summarized as key messages.

Key Messages

- Survivorship care must be holistic and development centered, throughout the lifespan.
- Routinely monitor the HRQOL and other psychosocial outcomes of survivors.
- Consider survivor's sociodemographic background because sex, education, and marital status can be risk factors for worse psychosocial wellbeing.
- Make vitality, lifestyle, and cognition top priorities in pediatric oncology and survivorship care and research.
- Start providing survivors with information about their health as soon as possible.
- Pay special attention in care and research to the needs of CNS tumor survivors, as a vulnerable group who are often underrepresented in research.

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CHAPTER 10
ENGLISH SUMMARY

Childhood cancer survivors (CCS) are a growing population. Thanks to the advancement of childhood cancer treatments, average overall five-year survival rates have increased to approximately 80%. As a consequence of intensive treatments, CCS may be faced with long-term physical and mental health problems, called late effects. The experience of childhood cancer and late effects can affect all aspects of survivors' life.

A lot of research focuses on the physical health outcomes of CCS. Over the years, generic psychosocial outcomes and psychopathology have gotten much attention but do not paint a full picture of the functioning and experiences of CCS. Therefore, it is crucial to investigate survivor-specific outcomes as well. Besides this, survivors' self-reported needs should be assessed in research and clinical practice, so that survivorship care can be further tailored to the needs of CCS.

The work described in this thesis aimed to increase the understanding of psychosocial challenges of childhood cancer survivorship. **Chapter 1, General introduction**, describes the background, outline and aims of the research included in this thesis. The research described in this thesis focuses on Health-Related Quality of Life (HRQOL) of adult survivors of childhood cancer in part I and on psychosocial challenges of young adult survivors in part II.

Part I: Health-Related Quality of Life of adult survivors of childhood cancer

Part I of this thesis describes the results of two nation-wide cohort studies, the SF-36 project and the TAAQOL project. Both projects were part of the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort part 2. These studies aimed to provide an overview of Health-Related Quality of Life (HRQOL) in Dutch adult CCS. Previous studies of HRQOL in Dutch CCS were mostly smaller in sample size. The added benefit of nation-wide cohort studies is that the large numbers allow us to identify potential risk factors for poor HRQOL, using detailed diagnosis and treatment characteristics from the LATER registry.

In **Chapter 2**, the nation-wide cohort study of HRQOL with use of the SF-36 is described. The SF-36 is a well-known and widely used measurement of both the physical and mental components of HRQOL.

Between 2016 and 2018, 2301 CCS completed the SF-36. Both male and female CCS reported significantly worse HRQOL than the norm on almost all scales of the SF-36. The differences with the norm were small to medium-sized. Largest differences were found on vitality and general health perceptions.

Identified risk factors were both sociodemographic and cancer-related in nature, but it is important to mention that for impaired mental HRQOL, no cancer-related risk factors were identified. CCS most at risk were those with low educational attainment and without a partner. Systematic attention for HRQOL is necessary during survivorship care and should include special consideration of vitality and general health perceptions, especially for CCS who display one or more risk factors for impairment.

In **Chapter 3**, we describe the HRQOL of the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort part 2. Between 2016 and 2020, HRQOL was assessed with

the TAAQOL. The unique attribute of the TAAQOL is that besides impairment, it asks responders to quantify the burden they experience because of the impairments. This allows us to paint a more complete picture of how an individual experiences their HRQOL.
TAAQOL scores of 1766 adult CCS differed from references on most domains with small effect sizes. Both male and female CCS were more often impaired in gross and fine motor functioning, cognitive functioning, sleep and vitality than the general population. Compared to male CCSs, female CCSs had impaired HRQOL more often and in more domains, and accordingly may need more attention. Central nervous system (CNS) tumor, bone tumor and retinoblastoma CCS and those with cranial, abdominopelvic or lower extremity radiotherapy were at increased risk of impairment in ≥1 domains.

Regular HRQOL surveillance is recommended in CCSs, especially for cognitive functioning and fatigue, and in particular for CCSs treated for CNS tumors and/or with cranial radiotherapy. A multidisciplinary approach to the prevention and treatment of impairments in HRQOL is required.

Both HRQOL studies underline previous findings that CCS' HRQOL can be vulnerable, although most CCS are resilient. Vitality of CCS was significantly impacted in both studies, in line with the literature and earlier recommendations for surveillance of fatigue.

Part II: Age-specific psychosocial challenges of young adult childhood cancer survivors

In Part II, the age-specific psychosocial challenges of young adult childhood cancer survivors (YACCS) were described. YACCS are potentially vulnerable for adverse psychosocial outcomes, because of the combination of their developmental and survivorship challenges. This is a pressing issue and the current psychosocial standards of care recommend screening and psychosocial care for survivors. Nevertheless, little is known about YACCS self-reported needs and preferences for support, and psychosocial interventions specifically aimed at preventing or reducing psychosocial problems in YACCS are lacking.

This part starts with **Chapter 4**, a commentary about the urgent need for research into young adult childhood cancer survivors (YACCS, diagnosed before the age of 16) as a distinct group, separate from young adult survivors who were diagnosed with cancer during adolescence or young adulthood (AYACS, diagnosed from age 16 to 25). The interruption of development by the cancer diagnosis and treatment of YACCS differs from the interruption of AYACS in four aspects:

1. For YACCS parents are responsible for most decisions during treatment, while AYACS are involved in medical decision making;
2. YACCS may have fewer memories of cancer and treatment due to their often young age, and rely on the family cancer narrative, whereas AYACS have their own recollection of cancer experience;
3. For YACCS the development of early social skills is disrupted, for AYACS later social milestones are disrupted;

4. For YACCS, most of their psychosexual development occurs after cancer, while AYACS psychosexual development is directly interrupted by diagnosis and treatment.

As a result, we expect that in young adulthood, YACCS and AYACS have some similar psychosocial outcomes caused by similar experiences, some similar psychosocial outcomes caused by different experiences, and some different psychosocial outcomes because of differing interruptions to their development. The lack of clear delineation between YACCS and AYACS in the literature makes it difficult to understand, and therefore meet, the psychosocial needs of these two growing populations. Therefore we recommended future researchers to document age at diagnosis and current age in all survivorship research, and to avoid merging the outcomes and needs of CCS and AYACS within one study and where possible, conducting subgroup analyses to explore any differences, and, consider survivors' developmental stage at cancer diagnosis/treatment when interpreting research findings.

Chapter 5 describes the psychosocial developmental trajectory of survivors participating in the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort part 2. From 2017 to 2020, 558 YACCS 18-30 years completed the Course of Life Questionnaire (CoLQ), that assesses achievement of milestones in Autonomy, Psychosexual and Social development. The total group of YACCS did not report a less favorable psychosocial development than the norm group. However, survivors of CNS cancer scored lower than norm on the scales Autonomy and Psychosexual development. Additionally, on half of the items of Autonomy, Psychosexual and Social development, survivors of CNS cancer were less likely than the norm group to have achieved the milestones.

This study once again emphasizes the vulnerability of CNS cancer survivors, which is in accordance with earlier literature on psychosocial outcomes. Monitoring psychosocial development should be included in the standards of psychosocial care, especially for patients with and survivors of CNS tumors, to be able to trace delay in the psychosocial development in an early stage. Considering the complex and individual consequences of CNS cancer, especially CNS cancer survivors need a personalized approach.

Chapter 6, 7 and 8 describe the three parts of the YACCS-project. The YACCS-project was a research project specifically aimed at increasing our understanding of psychosocial outcomes in YACCS, their support needs, and develop and evaluate a psychosocial group intervention. It falls apart into three chapters: YACCS well-being, YACCS needs, and the pilot study of Op Koers Online for YACCS.

In **Chapter 6**, the well-being study is described, aiming to increase our understanding of the psychosocial well-being of YACCS as well as the positive and negative impacts of cancer with the use of a survivor-specific questionnaire. In 2018, 151 YACCS filled out the survivor-specific IOC-CS (positive and negative impact of cancer), the HADS (anxiety and depression), the PedsQL 4.0 YA (HRQOL), and the CIS-20R (fatigue).

The YACCS reported lower HRQOL and more anxiety, depression, and fatigue than young adults from the general Dutch population. The IOC-CS scale scores showed more impact on domains representing positive impact (Socializing, Talking with parents, Body & Health) than on domains representing negative impact (Thinking & Memory problems, Life Challenges). Various domains of impact of childhood cancer were related to HRQOL, anxiety, depression, and fatigue .

Based on these findings, we recommend routine psychosocial screening as part of survivorship care. Survivorship care clinics need to have mechanisms in place to follow-up when screening results call for psychosocial support for a YACCS, e.g. in-house psychologists or adequate referral options.

Chapter 7 describes the YACCS needs study. Data for this study was collected at the same time and in the same sample as the well-being project (Chapter 6). In 2018, support needs were assessed in 151 YACCS using a questionnaire developed specifically for this study. YACCS were asked to indicate need for information, counselling, and/or peer contact regarding physical consequences of childhood cancer, social and emotional consequences of childhood cancer, relationships and/or sexuality, fertility, lifestyle and health risks after childhood cancer, choices relating to school and work, future perspective, insurance and mortgages.

Most of the 151 YACCS reported a need for support in one or more domains (88.0%). Over 50% of participants reported a need for concrete information about lifestyle and health risks, fertility, and physical consequences of childhood cancer and 25-50% in the domains insurance and mortgages, future perspective and social-emotional consequences of childhood cancer. In the domains lifestyle, physical as well as emotional consequences of childhood cancer, 25-50% reported a need for counselling. Previous, qualitative studies similarly found YACCS' information and psychosocial support needs to be high. YACCS with worse psychosocial well-being reported more needs.

Based on the findings, we recommended making psychosocial survivorship care more tailored to the needs of CCS. Tailored care could benefit both the physical and mental well-being of YACCS, and improve survivorship care attendance. Furthermore, this study stresses the need for adequate provision of information and information sources to YACCS. Having an accessible and age-appropriate information program could improve the participation of YACCS in their survivorship care. Also, it is important to povide survivors with information about avaialble health care providers (with experience in psycho-oncology) in their own environment.

In **Chapter 8**, we describe our first experiences with Op Koers Online for YACCS, in a pilot study. Op Koers Online is an online group intervention aimed at teaching active coping skills and providing peer-contact, thereby preventing or decreasing psychosocial problems. The intervention is based on psycho-education, cognitive behavioral therapy, and includes exercises for value-based living from acceptance and commitment therapy.

Op Koers Online for YACCS takes place in a secure chat box, where a fixed group of YACCS meet with two psychologists for 6 weekly 90-minute sessions, discussing topics such as physical and emotional late effects, the impact of cancer history on family life, education, and work. These topics were chosen based on the literature and the results of the YACCS needs study (see Chapter 7) and focus groups with YACCS and health care professionals.

During the pilot study, 10 YACCS participated in the intervention and completed a feasibility questionnaire, the Distress Thermometer, the Mastery Scale, the Illness Cognitions List, the Pediatric Quality of Life Inventory for Young Adults, and the Impact of Cancer – Childhood Survivors. There was no drop-out; 90% of participants attended five out of six sessions.

Results from this pilot study indicate that Op Koers Online for YACCS is a feasible intervention that is positively evaluated by both YACCS and course leaders. Overall, participants were satisfied with the intervention; 7.6 on a 0-10 scale. Preliminary effectiveness was promising; shortly after the intervention positive results were found on distress, illness related helplessness and self-efficacy. This could indicate that, after the intervention, YACCS feel more prepared to deal with challenges, which fits well with the learning goals that the course aims to fulfill through the combination of CBT with one ACT-based exercise, peer support, and psycho-education.

General discussion and conclusions

Chapter 9, General discussion, contains a reflection on the main findings, a critical review of the research and an outline our recommendations for childhood cancer survivorship research and care as well as the conclusions and key-messages.

This thesis shows that, on the group level, adult CCS experienced worse HRQOL than the norm. While most survivors were resilient, subgroups, especially survivors of CNS cancer, were at risk of impairment in some HRQOL areas, such as vitality and cognitive functioning, and had an unfavorable psychosocial development trajectory. YACCS were another vulnerable subgroup of survivors. While YACCS reported to experience positive impact of cancer beside negative impact of cancer, their psychosocial outcomes were worse than the norm. Almost a third of survivors reported anxiety or fatigue.

The YACCS needs project showed that almost 90% reported needs for support. To meet YACCS' needs for psychosocial support, Op Koers Online for YACCS was developed and pilot tested. With Op Koers Online for YACCS, the first psychosocial intervention for YACCS in the Netherlands has become available. While this intervention needs fine-tuning and could benefit from additional research about effectiveness, the results from the first pilot study were promising with regard to feasibility and potential effectiveness; decrease of distress and feelings of helplessness, and improvement of self-efficacy.

When interpreting the results of the research described in this thesis, there are some considerations to keep in mind. Importantly, the studies presented in this thesis did not include any data on disease burden of physical late effects and did not examine psychososocial factors such as coping style, while this may be important predictors of psychosocial well-being. Also, the representation of CNS tumor survivors seemed to be lower in our studies than one would expect looking at the composition of the LATER-cohort.

To improve **survivorship care**, we argue for holistic care, tailored to the needs of CCS. With regards to supporting psychosocial well-being, it is recommended to monitor survivors' HRQOL, achievement of psychosocial developmental milestones and other psychosocial outcomes, such as depression, anxiety, and fatigue. Preferably, the KLIK PROM portal should be used to achieve this by routinely administering questionnaires. Clinicians should pay special attention to risk groups: female survivors, YACCS, CNS tumor survivors, survivors with lower educational attainment and those without a partner. This means that clinicians should make themselves familiar with survivors' sociodemographic background.

Holistic care should further include step-by-step information provision and lifestyle programs about life with and after childhood cancer from the start of treatment. It could improve attendance to survivorhip care appointments, prevent high information needs at a later age, as well as stimulate behavior and lifestyle that promote healthy aging of survivors.

Besides, it is crucial to expand the availability of psychosocial support in survivorship care. Ensuring that CCS receive appropriate support can be done through psychosocial interventions (e.g. group interventions like Op Koers Online for YACCS), or by referring CCS to someone in a network of health care providers with expertise in psycho-oncology.

In accordance with previous research, the studies described in this thesis indicate that survivors of CNS tumors are at risk for unfavorable psychosocial outcomes. Consequences of CNS tumors are complex and vary widely between survivors. Therefore a personalized approach is recommended, that focuses on supporting survivors' psychosocial development (e.g. social skill training, cognitive rehabilitation, or academic support) within their capabilities.

For **future research** endeavors, it is recommended to study YACCS separately from other groups of survivors such as AYACS, and to give attention to elderly CCS. Apart from researching separate groups of survivors based on their age, sex-specific long-term outcomes of survivors need more attention. Besides, continued use of survivor-specific psychosocial measures in research in addition to generic outcomes is recommended.

It is important to realize that psychosocial well-being of survivors cannot be appreciated separately from their physical health situation. Therefore, future researchers should not only include survivors' past medical characteristics, such as diagnosis and treatment variables, but include the burden of late effects in studies. It is of importance to examine also psychosocial factors that play a role in the adaptation to the long-term consequences of childhood cancer.

Furthermore, future research should focus on accumulating more information about needs in understudied groups of CCS, because literature about needs is scarce. A specific focus should be put on CCS with cognitive complaints.

Finally, research and development of psychosocial interventions for survivors of childhood cancer is not yet very advanced and should therefore receive more attention. Interventions focusing on psychosocial challenges of childhood cancer survivorship in general, or on the challenges of specific groups of survivors, survivors of CNS cancer in particular, should be developed and studied in the future.

The final conclusions are summarized as key messages.

Key Messages

- Survivorship care must be holistic and development centered, throughout the lifespan.
- Routinely monitor the HRQOL and other psychosocial outcomes of survivors.
- Consider survivor's sociodemographic background because sex (female), educational attainment (low), and marital status (no partner) are risk factors for worse psychosocial wellbeing.
- Make vitality, lifestyle, and cognition top priorities in pediatric oncology and survivorship care and research.
- Start providing survivors with information about their health as soon as possible.
- Pay special attention in care and research to the needs of CNS tumor survivors, as a vulnerable group who are often underrepresented in research.

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CHAPTER 11
NEDERLANDSE SAMENVATTING

Survivors van kinderkanker (childhood cancer survivors; CCS) vormen een steeds grotere groep. Dankzij de vooruitgang in de behandeling van kinderkanker is de gemiddelde overleving 5 jaar na diagnose gestegen tot ongeveer 80%. Als gevolg van intensieve behandelingen kunnen CCS te maken krijgen met fysieke en mentale gezondheidsproblemen op de lange termijn, zogenaamde late effecten. De ervaring van kanker op de kinderleeftijd en de late effecten kunnen alle aspecten van het leven van CCS beïnvloeden.

Veel onderzoek onder CCS richt zich op fysieke gezondheidsuitkomsten. In de loop der jaren hebben generieke psychosociale uitkomsten en psychopathologie veel aandacht gekregen maar geven geen volledig beeld van het functioneren en de ervaringen van CCS. Daarom is het van cruciaal belang om ook survivor-specifieke uitkomsten te onderzoeken. Daarnaast is het belangrijk om de zelfgerapporteerde behoeften van survivors vast te stellen in onderzoek en in de klinische praktijk, zodat de zorg voor survivors verder kan worden afgestemd op deze behoeften.

Het werk beschreven in dit proefschrift had tot doel het inzicht in de psychosociale uitdagingen van overleving van kanker op de kinderleeftijd te vergroten. **Hoofdstuk 1, algemene inleiding**, beschrijft de achtergrond, de opzet en de doelen van het onderzoek in dit proefschrift. Het onderzoek in dit proefschrift richt zich op gezondheidsgerelateerde kwaliteit van leven (Health-Related Quality of Life; HRQOL) van volwassen CCS, in deel I, en op psychosociale uitdagingen van jongvolwassen survivors (Young Adult Childhood Cancer Survivors; YACCS) in deel II.

Deel I: Gezondheidsgerelateerde kwaliteit van leven van volwassen survivors van kinderkanker

Deel I van dit proefschrift beschrijft de resultaten van twee landelijke cohortstudies, het SF-36 project en het TAAQOL project. Beide projecten maken deel uit van de Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohortstudie deel 2. Deze studies hadden tot doel een overzicht te geven van de HRQOL in Nederlandse volwassen CCS. Eerdere studies naar HRQOL in Nederlandse CCS hadden meestal een kleinere steekproef. Het voordeel van landelijke cohort studies was dat de grote aantallen ons in staat stelden potentiële risicofactoren voor verminderde HRQOL te identificeren, waarbij gedetailleerde diagnose- en behandelingskenmerken uit de LATER registratie beschikbaar waren.

In **hoofdstuk 2** wordt de landelijke cohort studie naar HRQOL beschreven met de SF-36 als meetinstrument. De SF-36 is een bekende en veelgebruikte vragenlijst die zowel de fysieke als mentale componenten van HRQOL meet. Tussen 2016 en 2018 vulden 2301 CCS de SF-36 in. Zowel mannelijke als vrouwelijke CCS rapporteerden significant slechtere HRQOL dan de norm op bijna alle schalen van de SF-36. De verschillen met de norm waren klein tot middelgroot. De grootste verschillen werden gevonden op vitaliteit en algemene gezondheidspercepties.

De geïdentificeerde risicofactoren waren zowel sociodemografisch als kankergerelateerd van aard, maar het is belangrijk te vermelden dat kankergerelateerde factoren niet samenhingen met mentale HRQOL. CCS met een laag opleidingsniveau en zonder partner liepen het meeste risico op verminderde HRQOL. Systematische aandacht voor HRQOL is noodzakelijk in de zorg voor CCS. Extra aandacht moet worden besteed aan vitaliteit en algemene gezondheidspercepties, en aan CCS die een of meer risicofactoren voor verminderde HRQOL hebben.

Hoofdstuk 3 gaat over de HRQOL van het Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort deel 2, gemeten met de TAAQOL tussen 2016 en 2020. Het unieke kenmerk van de TAAQOL is dat het naast beperkingen in functioneren ook meet hoeveel last respondenten ervaren van deze beperkingen. Hierdoor ontstaat een completer beeld van de HRQOL.
De TAAQOL scores van 1766 volwassen CCS waren in de meeste TAAQOL domeinen lager dan in de referentiegroep. De verschillen waren klein. Zowel mannelijke als vrouwelijke CCS waren vaker beperkt in grove en fijne motoriek, cognitief functioneren, slaap en vitaliteit dan de algemene bevolking. Vergeleken met mannelijke CCS hadden vrouwelijke CCS vaker, en op meer domeinen, een verminderde HRQOL. Daarom hebben vrouwen mogelijk meer aandacht nodig. CCS van een centraal zenuwstelsel (CZS) tumor, bottumor of retinoblastoom, en CCS die zijn behandeld met craniale of abdominopelvische radiotherapie, of met radiotherapie op de onderste extremiteiten, hadden een verhoogd risico op beperkingen in ≥1 domein.

Monitoring van HRQOL wordt aanbevolen bij CCS, met name voor cognitief functioneren en vermoeidheid, en in het bijzonder bij CCS die zijn behandeld voor CZS tumoren en/of met craniale radiotherapie. Preventie en behandeling van beperkingen in HRQOL vereist een multidisciplinaire aanpak.

Beide HRQOL studies onderstrepen eerdere bevindingen dat CCS kwetsbaar kunnen zijn voor verminderde HRQOL, hoewel de meeste CCS veerkrachtig zijn. De vitaliteit van CCS was in beide studies verminderd, in lijn met de literatuur en eerdere aanbevelingen voor monitoring van vermoeidheid.

Deel II: Leeftijdsspecifieke psychosociale uitdagingen van jongvolwassen survivors van kinderkanker

Deel II beschrijft de leeftijdsspecifieke psychosociale uitdagingen van jongvolwassen survivors van kinderkanker. YACCS zijn potentieel kwetsbaar voor ongunstige psychosociale uitkomsten vanwege de combinatie van de uitdagende ontwikkelingsfase en late effecten. Dit is een belangrijke kwestie en volgens de huidige psychosociale zorgstandaarden is screening en psychosociale zorg voor CCS aanbevolen. Desondanks is er weinig bekend over de behoeften van YACCS en over hun voorkeuren voor ondersteuning, en psychosociale interventies specifiek gericht op het voorkomen of verminderen van psychosociale problemen bij YACCS ontbreken.

Dit deel begint met **Hoofdstuk 4**, een beschouwend hoofdstuk waarin de dringende noodzaak wordt beschreven van onderzoek naar jongvolwassen survivors van kinderkanker (YACCS, gediagnosticeerd voor de leeftijd van 16 jaar) als een aparte groep, los van jong volwassen survivors die gediagnosticeerd zijn met kanker tijdens de adolescentie of jong volwassenheid (Adolescent and Young Adult Cancer Survivors; AYACS, gediagnosticeerd tussen de leeftijd van 16 tot 25 jaar). De kankerdiagnose en behandeling verstoort de ontwikkeling van zowel YACCS als AYACS maar verschilt in vier opzichten:

1. Bij YACCS waren de ouders verantwoordelijk voor de meeste beslissingen tijdens de behandeling, terwijl AYACS zelf betrokken werden bij de medische besluitvorming;
2. YACCS kunnen minder herinneringen hebben aan kanker en de behandeling vanwege hun vaak jonge leeftijd. Zij moeten daarom vertrouwen op het verhaal van de familie over de ziekteperiode, terwijl AYACS hun eigen herinnering aan de ervaring met kanker hebben;
3. Bij YACCS is de ontwikkeling van vroege sociale vaardigheden verstoord, bij AYACS heeft de diagnose en behandeling invloed op latere sociale mijlpalen;
4. Bij YACCS vindt het grootste deel van hun psychoseksuele ontwikkeling plaats na kanker, terwijl bij AYACS sprake is van een directe verstoring van de psychoseksuele ontwikkeling door de diagnose en behandeling.

Als gevolg hiervan verwachten we bij YACCS en AYACS in de jongvolwassenheid een aantal vergelijkbare psychosociale uitkomsten als gevolg van vergelijkbare ervaringen, een aantal vergelijkbare psychosociale uitkomsten als gevolg van verschillende ervaringen, en een aantal verschillen in psychosociale uitkomsten als gevolg van verschillen in verstoringen in hun ontwikkeling. Hoewel het duidelijk is dat YACCS en AYACS verschillende ontwikkelingstrajecten hebben doorlopen, maakt het gebrek aan een duidelijke afbakening tussen deze twee groepen in de literatuur het moeilijk om de psychosociale behoeften van deze twee groeiende populaties te begrijpen, en dus, om er aan te voldoen. Daarom bevelen wij toekomstige onderzoekers aan om de leeftijd bij diagnose en de huidige leeftijd te documenteren in elk onderzoek onder survivors van kanker, en om de uitkomsten en behoeften van CCS en AYACS niet binnen één onderzoek samen te voegen. Verder bevelen wij aan om waar mogelijk subgroepanalyses uit te voeren om eventuele verschillen tussen YACCS en AYACS te onderzoeken, en om bij het interpreteren van onderzoeksbevindingen rekening te houden met de ontwikkelingsfase ten tijde van de diagnose/behandeling van kanker.

Hoofdstuk 5 beschrijft het psychosociale ontwikkelingstraject van survivors uit de Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort deel 2. Van 2017 tot 2020 vulden 558 YACCS (18-30 jaar) de Levensloop Vragenlijst voor Jong Volwassenen (LVJV) in, die het bereiken van mijlpalen in Autonomie, Psychoseksuele en Sociale ontwikkeling meet. De psychosociale ontwikkeling van YACCS als geheel was niet minder gunstig dan de psychosociale ontwikkeling van de normgroep. Survivors van CZS kanker scoorden echter slechter dan de norm op de schalen Autonomie en Psychoseksuele ontwikkeling. Bovendien was de kans dat survivors van CZS kanker een mijlpaal hadden bereikt minder groot op de helft van de items van Autonomie, Psychoseksuele en Sociale ontwikkeling.

Deze resultaten benadrukken nogmaals de kwetsbaarheid van survivors van CZS kanker, hetgeen in overeenstemming is met eerdere literatuur over psychosociale uitkomsten. Het monitoren van de psychosociale ontwikkeling zou moeten worden opgenomen in de standaarden van de psychosociale zorg vooral voor de patiënten met en de survivors van CZS kanker, om vertraging in de psychosociale ontwikkeling in een vroeg stadium te kunnen opsporen. Gezien de complexe en individuele gevolgen van CZS kanker, hebben survivors van CZS kanker een gepersonaliseerde aanpak nodig.

Hoofdstuk 6, 7 en 8 beschrijven de drie onderdelen van het YACCS-project. Het

YACCS-project was een onderzoeksproject specifiek gericht op het vergroten van het inzicht in de psychosociale uitkomsten en behoefte aan ondersteuning van YACCS, en op het ontwikkelen en evalueren van een psychosociale groepsinterventie voor YACCS. Het YACCS-project valt uiteen in drie hoofdstukken: YACCS well-being, YACCS needs, en de pilot studie van Op Koers Online voor YACCS.

In **Hoofdstuk 6** wordt de YACCS well-being studie beschreven. Het project was gericht op het vergroten van het inzicht in het psychosociale welzijn van YACCS, alsmede de positieve en negatieve gevolgen van kanker gemeten met een survivor-specifieke vragenlijst. In 2018 vulden 151 YACCS de survivor-specifieke IOC-CS (positieve en negatieve impact van kanker), de HADS (angst en depressie), de PedsQL 4.0 YA (HRQOL), en de CIS-20R (vermoeidheid) in.

De YACCS rapporteerden een lagere HRQOL en meer angst, depressie en vermoeidheid dan jongvolwassenen uit de algemene Nederlandse bevolking. Hun IOC-CS schaalscores lieten zien dat kanker meer impact had in domeinen die de positieve impact van kinderkanker betreffen (Sociale contacten, Praten over kanker met ouders, Lichaam & Gezondheid) dan in domeinen die staan voor een negatieve impact (Aandacht- en geheugenproblemen, Uitdagingen in het leven). De scores in verschillende domeinen van de impact van kanker waren gerelateerd aan HRQOL, angst, depressie, en vermoeidheid.
Op basis van deze bevindingen bevelen wij psychosociale screening aan als vast onderdeel van zorg voor CCS. Poliklinieken voor CCS zouden zo georganiseerd moeten zijn dat psychosociale ondersteuning geboden kan worden als uit de screeningsresultaten blijkt dat dat nodig is, bijvoorbeeld door de beschikbaarheid van psychologen of een adequate sociale kaart met doorverwijsmogelijkheden.

Hoofdstuk 7 beschrijft de YACCS needs studie, een onderzoek naar de behoeften aan ondersteuning van YACCS. De gegevens voor dit onderzoek werden op hetzelfde moment en in dezelfde steekproef verzameld als bij de YACCS well-being studie (Hoofdstuk 6). In 2018 werd de behoefte aan ondersteuning van 151 YACCS gemeten met behulp van een vragenlijst die speciaal voor dit onderzoek was ontwikkeld. YACCS werd gevraagd of zij behoefte hadden aan informatie, counseling en/of lotgenotencontact over fysieke gevolgen van kinderkanker, sociale en emotionele gevolgen van kinderkanker, relaties en/of seksualiteit, vruchtbaarheid, levensstijl en gezondheidsrisico’s na kinderkanker, school- en beroepskeuze en werk, toekomstperspectief, verzekeringen en hypotheken.

Het merendeel van de 151 YACCS gaf aan behoefte te hebben aan ondersteuning op een of meer gebieden (88%). Meer dan 50% van de YACCS rapporteerde behoefte aan concrete informatie over levensstijl en gezondheidsrisico’s, vruchtbaarheid en lichamelijke gevolgen van kinderkanker, en 25-50% in de domeinen verzekeringen en hypotheken, toekomstperspectief, sociaal-emotionele gevolgen van kanker bij kinderen. In de domeinen levensstijl en gezondheidsrisico’s, lichamelijke zowel als emotionele gevolgen van kinderkanker gaf 25-50% aan behoefte te hebben aan counseling. Uit eerdere, kwalitatieve studies kwam eveneens naar voren dat de behoefte aan informatie en psychosociale ondersteuning bij YACCS groot is. YACCS wiens psychosociaal welzijn minder goed was, rapporteerden meer behoeften.

Op basis van de bevindingen bevelen wij aan de psychosociale zorg voor survivors meer af te stemmen op hun behoeften. Zorg op maat zou zowel het fysieke als het mentale welzijn van de CCS ten goede kunnen komen, en zou ervoor kunnen zorgen dat CCS naar de poli voor survivors blijven komen. Verder benadrukken de resultaten de noodzaak van adequate informatievoorziening en informatiebronnen voor YACCS. Een toegankelijk en op de leeftijd afgestemd informatieprogramma zou de participatie van CCS in de voor hen bestemde zorg kunnen verbeteren. Daarnaast is het belangrijk om CCS informatie te geven over zorgprofessionals (met ervaring in de psycho-ocnologie) in hun eigen omgeving.

In **Hoofdstuk 8** beschrijven we onze eerste ervaringen met Op Koers Online voor YACCS, in een pilot studie. Op Koers Online is een online groepsinterventie gericht op het aanleren van actieve copingvaardigheden en het bieden van lotgenotencontact, waardoor psychosociale problemen voorkomen of verminderd worden. De interventie is gebaseerd op psycho-educatie, cognitieve gedragstherapie (CGT), en bevat oefeningen voor waardegericht leven uit de acceptance and commitment therapy (ACT).

Op Koers Online voor YACCS wordt gegeven in een beveiligde chatbox, waar een vaste groep YACCS samenkomt met twee psychologen. De cursus bestaat uit 6 wekelijkse sessies van 90 minuten, waarin onderwerpen worden besproken zoals fysieke en emotionele late effecten, de impact van kinderkanker op het gezinsleven, opleiding en werk. Deze onderwerpen zijn gekozen op basis van de literatuur, de resultaten van het YACCS needs onderzoek (zie Hoofdstuk 7) en focusgroepen met YACCS en professionals uit de gezondheidszorg.

Tijdens de pilotstudie hebben 10 YACCS deelgenomen aan de interventie en vragenlijsten ingevuld; een haalbaarheidsvragenlijst, de Lastthermometer, de Mastery Scale, de Ziektecognitielijst, de PedsQL voor jongvolwassenen, en de IOC-CS. Er was geen uitval; 90% van de deelnemers woonde vijf van de zes sessies bij.

De resultaten van deze pilotstudie geven aan dat Op Koers Online voor YACCS een haalbare interventie is die positief is beoordeeld door zowel YACCS als cursusleiders. Over het geheel genomen waren de deelnemers tevreden over de interventie; 7,6 op een schaal van 0-10. De eerste indruk van de effectiviteit was veelbelovend; kort na de interventie waren er positieve resultaten te zien op distress, ziektegerelateerde hulpeloosheid en self-efficacy. Dit zou erop kunnen wijzen dat de YACCS zich na de interventie beter in staat voelden om met uitdagingen om te gaan, hetgeen goed past bij de leerdoelen die de cursus beoogt te bereiken door de combinatie van CGT met een paar oefeningen uit de ACT, peer support en psycho-educatie.

Algemene discussie en conclusies

Hoofdstuk 9, Algemene discussie, bestaat uit een reflectie op de belangrijkste bevindingen, een kritische reflectie op het onderzoek, en het bevat aanbevelingen voor het onderzoek naar en de zorg voor survivors van kinderkanker, evenals de conclusies en key messags.

Dit proefschrift laat zien dat volwassen CCS op groepsniveau een slechtere HRQOL ervaren dan de norm. Hoewel de meeste CCS veerkrachtig zijn, lopen subgroepen, met name survivors van CZS kanker, het risico op verlaagde HRQOL op sommige gebieden, zoals vitaliteit en cognitief functioneren, en op een ongunstig verloop van hun psychosociale ontwikkeling. YACCS zijn een andere kwetsbare subgroep van CCS. Hoewel de YACCS naast negatieve gevolgen van kanker ook positieve gevolgen rapporteerden, waren hun psychosociale uitkomsten slechter dan de norm. Bijna een derde van de survivors rapporteerde angst of vermoeidheid.

Uit de YACCS-needs studie bleek dat bijna 90% behoefte had aan ondersteuning. Om tegemoet te komen aan de behoeften aan psychosociale ondersteuning, werd Op Koers Online voor YACCS ontwikkeld en geëvalueerd in een pilot studie. Met Op Koers Online voor YACCS is de eerste psychosociale interventie voor YACCS in Nederland beschikbaar gekomen. Hoewel deze interventie nog verfijnd moet worden en er nog aanvullend onderzoek naar de effectiviteit gedaan zou kunnen worden, zien de resultaten van de eerste pilotstudie er veelbelovend uit met betrekking tot de haalbaarheid en mogelijke effectiviteit; afname van distress en gevoelens van hulpeloosheid, en toename van self-efficacy.

Bij het interpreteren van de resultaten in dit proefschrift, is het belangrijk om in gedachten te houden dat de in dit proefschrift gepresenteerde onderzoeken geen gegevens bevatten over ziektelast door lichamelijke late effecten en dat psychosociale factoren zoals copingstijl niet zijn onderzocht, terwijl dit belangrijke voorspellers kunnen zijn van psychosociaal welbevinden. Ook lijken survivors van CZS kanker minder te zijn vertegenwoordigd in onze studies dan verwacht op basis van de samenstelling van het LATER-cohort.

Om de **zorg** voor CCS te verbeteren, pleiten wij voor holistische zorg, afgestemd op de behoeften van CCS. Ten aanzien van de ondersteuning van het psychosociale welzijn wordt aanbevolen om HRQOL van de survivors te monitoren, als ook psychosociale ontwikkelingsmijlpalen en andere psychosociale uitkomsten, zoals depressie, angst en vermoeidheid. Voor het regelmatig afnemen van vragenlijsten om het psychosociale welzijn te monitoren is het gebruik van het KLIK PROM-portaal aan te raden. Clinici moeten speciale aandacht besteden aan risicogroepen: vrouwelijke survivors, YACCS, survivors van CZS kanker, survivors met een lager opleidingsniveau en survivors zonder partner. Dit betekent dat clinici bekend moeten zijn met de sociodemografische achtergrond van survivors.

Holistische zorg zou stapsgewijze informatievoorziening en leefstijlprogramma’s moeten bevatten die kinderen en hun ouders vanaf het begin van de behandeling leren over het leven met en na kinderkanker. Dit zou opkomst op de polikliniek voor CCS kunnen verbeteren, hoge informatiebehoeften op latere leeftijd kunnen voorkomen en gedrag en leefstijl kunnen stimuleren die gezond ouder worden van CCS bevorderen.

Daarnaast is het van cruciaal belang om de beschikbaarheid van psychosociale ondersteuning voor CCS te vergroten. Met psychosociale interventies (bijv. groepsinterventies zoals Op Koers Online) en goede doorverwijzing naar netwerken van zorgverleners met expertise in de psycho-oncologie kan CCS passende ondersteuning worden geboden.

In overeenstemming met eerder onderzoek wijzen de in dit proefschrift beschreven studies uit dat survivors van CZS kanker risico lopen op ongunstige psychosociale uitkomsten. Gevolgen van CZS kanker zijn complex en variëren sterk tussen CCS. Daarom is een gepersonaliseerde aanpak aan te raden die zich richt op het ondersteunen van de psychosociale ontwikkeling van CCS (bijv. sociale vaardigheidstraining, cognitieve rehabilitatie, of academische ondersteuning) binnen hun mogelijkheden.

Het is belangrijk om in **toekomstig onderzoek** YACCS apart te onderzoeken van andere groepen survivors zoals AYACS, en om aandacht te besteden aan oudere CCS. Naast het onderzoeken van aparte groepen survivors op basis van hun leeftijd, moeten sekse-specifieke langetermijnuitkomsten van survivors meer aandacht krijgen. Daarnaast is het belangrijk om survivor-specifieke psychosociale uitkomstmaten op te nemen in onderzoek naast generieke uitkomstmaten.

Het psychosociale welzijn van survivors kan niet los worden gezien van hun lichamelijke gezondheidssituatie. Daarom zouden toekomstige onderzoekers niet alleen de diagnose en behandelgegevens van survivors in onderzoek moeten mee te nemen, maar ook de ziektelast van late effecten. Het is belangrijk om ook psychosociale factoren die een rol spelen in de aanpassing aan de langetermijn gevolgen van kinderkanker, zoals coping, te onderzoeken.

Verder zou toekomstig onderzoek zich moeten richten op het vergroten van de kennis over de behoeften van YACCS, aangezien de literatuur hierover nog schaars is. Een specifieke focus van onderzoek zou moeten liggen op behoeften van CCS met cognitieve klachten.

Ten slotte, het onderzoek en de ontwikkeling van psychosociale interventies voor survivors staat nog in de kinderschoenen en zou daarom meer aandacht moeten krijgen. Interventies gericht op de psychosociale uitdagingen van leven met een voorgeschiedenis van kinderkanker in het algemeen, en gericht op specifieke groepen survivors, moeten verder worden ontwikkeld en onderzocht.

In het kader worden de belangrijkste conclusies samengevat als key messages.

Key messages

- Zorg voor survivors moet holistisch en ontwikkelingsgericht zijn.
- Monitor regelmatig HRQOL en andere psychosociale uitkomsten van survivors.
- Houd rekening met de sociaaldemografische achtergrond van survivors. Sekse (vrouw), opleidingsniveau (laag), en burgerlijke staat (geen partner) zijn risicofactoren voor slechter psychosociaal welbevinden.
- Vitaliteit, leefstijl en cognitie moeten een hoge prioriteit krijgen in kinderoncologische zorg en onderzoek.
- Informeer survivors zo vroeg mogelijk over hun gezondheid.
- Besteed in zorg en onderzoek extra aandacht aan de behoeften van survivors van een CZS tumor omdat dit een kwetsbare groep is en vaak ondergerepresenteerd in onderzoek.

Appendices

APPENDICES

Abbreviations
List of co-authors
Curriculum Vitae
PhD portfolio
List of publications
Dankwoord

Abbreviations

ACT	Acceptance and Commitment Therapy
ALL	Acute Lymphoblastic Leukemia
AYA	Adolescent and Young Adult (cancer patients)
AYACS	Adolescent and Young Adult Cancer Survivor(s)
BMT	Bone Marrow Transplant
CBT	Cognitive Behavior Therapy
CCS	Childhood Cancer Survivor(s)
CI	Confidence Interval
CIS-20R	Checklist Individual Strength 20 Revised
CNS	Central Nervous System
CoLQ	Course of Life Questionnaire
CZS	Dutch: Centraal Zenuw Stelsel
DCCSS	Dutch Childhood Cancer Survivor Study
DT	Distress Thermometer
HADS	Hospital Anxiety and Depression Scale
HCPs	Health Care Providers
HRQOL	Health-Related Quality of Life
ICCC-3	International Classification of Childhood Cancer
ICQ	Illness Cognition Questionnaire
IOC-CS	Impact of Cancer – Childhood Survivors
LATER	Dutch: LAngeTERmijn, English: Long term
LTFU	Long Term Follow-Up care
MS	Mastery Scale
OR	Odds Ratio
PedsQL-YA	Pediatric Quality of Life Inventory Young Adults
PROMS	Patient Reported Outcome Measures
PTSD	Post-Traumatic Stress Disorder
QOL	Quality of Life
RCT	Randomized Controlled Trial
SCT	Stem Cell Transplant
SES	Socio-Economic Status
SF-36	Short Form-36
TAAQOL	TNO-AZL Questionnaire for Adult Health-Related Quality of Life
TBI	Total Body Irradiation
YACCS	Young Adult Childhood Cancer Survivor(s)

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Curriculum Vitae

Loes van Erp was born on the 28th of June 1994, in Diessen, the Netherlands. She grew up with her parents and younger sister, Sarah. In 2012 she finished secondary school (Koning Willem II College in Tilburg) and started her bachelor in psychology and health at Tilburg University. During her bachelor education, she succesfully completed the extracurricular Outreaching Honors Program. In 2015 she graduated cum laude from the bachelor of psychology and health, and was accepted into the master's program Medical Psychology at Tilburg University. In 2017, during the final year of her studies, she worked as an apprentice psychologist at the Máxima Medical Center in Eindhoven and Veldhoven while writing her master's thesis on sleep quality and hypoglycemic control in patients with diabetes. After graduating as Master of Science in 2017, she started her PhD trajectory on psychosocial challenges of childhood cancer survivorship with a specific focus on young adult childhood cancer survivors at the Princess Máxima Center for Pediatric Oncology under the supervision of prof. dr. Martha Grootenhuis, dr. Heleen Maurice-Stam and dr. Gea Huizinga. During her PhD trajectory she gave various oral and poster presentations at national and international conferences. Besides her academic work, she was a member of the PriMá PhD Committee at the Princess Máxima Center, advocating for PhD students and organizing various activities. In September of 2021 she started working as a psychologist at Topklinisch Centrum Lichaam, Geest, en Gezondheid for patients with psychosomatic disorders of GGz Breburg in Tilburg. In her free time, Loes enjoys playing video games and board games, traveling, fitness, and running. She has been involved with a team representing pediatric oncology professionals in the Roparun running event for quality of life of patients with cancer since 2019. Furthermore, she has been active as a volunteer organizing activities for young adults with autism since 2015. Loes is living together with Tobias in Tilburg.

PhD Portfolio

Name	Loes M.E. van Erp
PhD period	September 2017 – August 2021
Graduate School	Graduate School of Life Sciences (GSLS), Utrecht University
PhD Program	Clinical and Translational Oncology (CTO)
Promotor	Prof. dr. Martha A. Grootenhuis
Co-promotoren	Dr. Heleen, Maurice-Stam & Dr. Gea A. Huizinga

PhD training	Year
Courses	
Research planning & time management (GSLS)	2018
Writing a scientific paper (GSLS)	2018
Writing a patient information letter (GSLS)	2018
Basiscursus regelgeving en organisatie voor klinische onderzoekers (BROK, NFU)	2018
Clinical trial development (CTO, GSLS)	2019
The art of presenting science (GSLS)	2019
Introductory biostatistics (GSLS, online)	2020
Conceptual and methodological issues in intervention research (Graduate school of social and behavioral sciences)	2020, 2021
CTO Introduction course	2021
Seminars and workshops	
Research retreat Princess Máxima Center	2017, 2019
Nederlandse Vereniging voor Psycho-oncologie Early Career Researchers Network	2018
DCCSS LATER research day	2018, 2019
PhD retreat CTO	2019, 2020
Weekly research seminars Princess Máxima Center	2018-2021
Weekly meetings Grootenhuis research group	2018-2021
Bi-weekly PhD meetings DCCSS LATER study group	2018-2021
Conferences and symposia	
ISOQOL Symposium	2017
LATER voor LATER	2017
Tulips Young Investigators Day	2017
21st PanCare Meeting, Prague, Czech Republic	2018
5th National Space4AYA Symposium	2018
Princess Máxima Center Scientific Symposium	2018
23rd PanCare Meeting, Opatija, Croatia (oral presentation)	2019
24rd PanCare Meeting, Basel, Switzerland (oral presentation)	2019
51st Annual Congress of the SIOP, Lyon, France (poster presentation)	2019
Annual Conference of the Association of Researchers in Psychology and Health (ARPH) (oral presentation)	2020
52nd Annual Congress of the SIOP, online (poster presentation)	2020

25th PanCare Meeting, Utrecht, the Netherlands (oral presentation)	201
53rd Annual Congress of the SIOP, online (oral presentation, poster presentation)	2021
LATER voor LATER	2021

Teaching	
Childhood cancer and late effects lecture for Tilburg University’s Medical Psychology Master’s program	2019, 2020, 2021

Other activities	
Two week working visit to prof. Anne-Sophie Darlington at the University of Southampton, England	2020
PriMá PhD Group	2019-2021

List of Publications

This thesis

van Erp LME, Maurice-Stam H, Kremer, LCM, Tissing WJE, van der Pal HJH, de Vries ACH, van den Heuvel-Eibrink MM, Versluys BAB, van der Heiden-van der Loo M, Huizinga GA, Grootenhuis MA. A vulnerable age group: the impact of cancer on the psychosocial well-being of young adult childhood cancer survivors. Supportive Care in Cancer. 2021; 29(8): 4751–4761.

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van Erp LME, Maurice-Stam H, Beek LR, Kremer LCM, den Hartogh J, van Gorp M, Huizinga GA, Grootenhuis MA. Online cognitive-behavioral group intervention for young adult survivors of childhood cancer: A pilot study. Submitted for publication.

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