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# Parents of Children with Cancer

*Psychological Long-Term Consequences and  
Development of a Psychological Treatment for  
Parents of Survivors*

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ACTA  
UNIVERSITATIS  
UPSALIENSIS  
UPPSALA  
2016

ISSN 1651-6206  
ISBN 978-91-554-9745-3  
urn:nbn:se:uu:diva-306309

Dissertation presented at Uppsala University to be publicly examined in Auditorium minus, Museum Gustavianum, Akademigatan 3, Uppsala, Friday, 16 December 2016 at 09:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish. Faculty examiner: Professor Maria Tillfors (Örebro University, School of Law, Psychology and Social Work).

### **Abstract**

Ljungman, L. 2016. Parents of Children with Cancer: Psychological Long-Term Consequences and Development of a Psychological Treatment for Parents of Survivors. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1273. 65 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-554-9745-3.

The aims of this thesis were to increase the knowledge about the long-term psychological consequences in parents of children diagnosed with cancer, including parents of childhood cancer survivors (CCSs) and bereaved parents, and to take the first steps towards developing a psychological treatment for parents of CCSs.

Study I was a systematic review synthesizing the literature on psychological long-term consequences in parents of CCSs. Study II had a longitudinal design assessing posttraumatic stress symptoms (PTSS) from shortly after the child's diagnosis (T1, N=259) up to five years after end of the child's treatment or death (T7, n=169). Study I and II concluded that while most parents show resilience in the long-term, a subgroup report high levels of general distress and/or PTSS. In Study III, interview data from the last assessment in the longitudinal project (T7, n=168) was used. Participants described particularly negative and/or positive experiences in relation to their child's cancer, and results pointed to the wide range of such experiences involved in parenting a child with cancer. In Study IV and V, parents of CCSs reporting cancer-related psychological distress were included (N=15). In Study IV, a conceptualization of this distress was generated by aggregation of individual behavioral case formulations. The conceptualization consisted of two separate but overlapping paths describing development and maintenance of symptoms of traumatic stress and depressive symptoms. In Study V, cognitive behavior therapy (CBT) based on the individual case formulations were preliminarily evaluated in an open trial. The CBT appeared feasible, and at post-assessment participants reported significant decreases in PTSS ( $p<.001$ ), depression ( $p<.001$ ), and anxiety ( $p<.01$ ) with medium to large effect sizes (Cohen's  $d=0.65-0.92$ ).

Findings indicate that psychological long-term consequences in parents of children with cancer consist of a broad range of negative as well as positive experiences, and that while most parents show resilience in the long-term, a subgroup report high levels of psychological distress. For parents of CCSs this distress is suggested to primarily consist of symptoms of traumatic stress and depression, and a preliminary evaluation of CBT targeting hypothesized maintaining mechanisms showed promise in terms of feasibility and treatment effect.

**Keywords:** Cancer and oncology, Children, Parents, Survivors, Cognitive behavior therapy, Posttraumatic stress symptoms, Depression, Positive psychological consequences

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ISSN 1651-6206

ISBN 978-91-554-9745-3

urn:nbn:se:uu:diva-306309 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-306309>)

*Till Siri och Nils*



# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Ljungman, L., Cernvall, M., Grönqvist, H., Ljótsson, B., Ljungman, G., & von Essen, L. (2014). Long-term positive and negative psychological late effects for parents of childhood cancer survivors: A systematic review. *PLoS ONE*. 9(7): e103340.
- II Ljungman, L.\*, Hovén, E.\*, Ljungman, G., Cernvall, M., & von Essen, L. (2015). Does time heal all wounds? A longitudinal study of the development of posttraumatic stress symptoms in parents of survivors of childhood cancer and bereaved parents. *Psycho-Oncology*. 24(12), 1792–1798. (\*indicates joint first authorship)
- III Ljungman, L., Boger, M., Ander, M., Ljótsson, B., Cernvall, M., von Essen, L., & Hovén, E. (2016). Impressions that last: Particularly negative and positive experiences reported by parents five years after the end of a child's successful cancer treatment or death. *PLoS ONE*. 11(6): e0157076.
- IV Ljungman, L., Cernvall, M., Ghaderi, A., Kukkola, L., Ljungman, G., von Essen, L., & Ljótsson, B. A cognitive behavioral conceptualization of cancer-related psychological distress in parents of childhood cancer survivors. *Manuscript*.
- V Ljungman, L., Cernvall, M., Ghaderi, A., Ljungman, G., von Essen, L., & Ljótsson, B. Development and preliminary evaluation of individualized face-to-face cognitive behavior therapy for psychological distress in parents of childhood cancer survivors. *Manuscript*.

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# Contents

Introduction.....	11
Childhood cancer.....	11
Parents of children with cancer .....	11
During treatment.....	11
After end of successful treatment .....	12
Bereavement .....	13
Consequences of psychological distress .....	14
Conceptualization of cancer-related psychological distress .....	15
Positive psychological consequences .....	16
Psychological treatment .....	17
Cognitive behavior therapy and empirically supported psychological treatments.....	17
Psychological treatment for parents of children with cancer.....	18
Developing a psychological treatment.....	18
Concluding remarks .....	20
Aims .....	20
Study I.....	20
Study II .....	20
Study III.....	20
Study IV.....	21
Study V .....	21
Methods .....	22
Design .....	22
Procedure and participants .....	23
Study I.....	24
Study II and III .....	24
Study IV and V .....	25
Measures .....	25
Extraction of data.....	25
Self-assessments .....	26
Diagnostic interview.....	28
Semi-structured interview.....	28
Behavioral case formulations .....	28
Assessment of feasibility .....	28
Psychological treatment .....	29

Data analyses.....	30
Study I.....	30
Study II .....	31
Study III.....	32
Study IV.....	33
Study V .....	34
Results.....	35
Study I.....	35
Study II .....	36
Study III.....	37
Study IV.....	39
Study V .....	40
Discussion.....	43
Main findings .....	43
Long-term psychological consequences .....	43
Development of a psychological treatment for parents of CCSs .....	45
Methodological considerations.....	48
Study I.....	48
Study II and III .....	49
Study IV and V .....	50
Ethical considerations .....	51
Conclusions .....	52
Acknowledgements in Swedish .....	54
References.....	57



# Abbreviations

AD	Adjustment disorder
CBT	Cognitive behavior therapy
CFI	Comparative fit index
CCSs	Childhood cancer survivors
DSM	Diagnostic and statistical manual of mental disorders
LGC	Latent growth curve
MRC	Medical research council
PMTS	Pediatric medical traumatic stress
PTE	Potentially traumatic event
PTG	Posttraumatic growth
PTSD	Posttraumatic stress disorder
PTSS	Posttraumatic stress symptoms
RCT	Randomized controlled trial
RMSEA	Root-mean-square-error of approximation
SES	Socioeconomic status



# Introduction

## Childhood cancer

Each year approximately 350 children (<19 years of age) are diagnosed with cancer in Sweden, corresponding to an incidence of 16 per 100 000 children (Centre for Epidemiology, 2005; Gustafsson, Kogner, & Heyman, 2013). The main types of childhood cancers are: leukemia, CNS-tumors, lymphomas, and other solid tumors. Treatment for childhood cancer is often intensive, long-lasting and includes combinations of chemotherapy, radiation therapy, and surgery. Survival rates for childhood cancer have improved dramatically over the past 30 years, yielding a five-year survival of approximately 80% (Gatta et al., 2009; Gustafsson et al., 2013). Today, one in 650 adolescents and young adults is a childhood cancer survivor, and roughly twice as many are parents of childhood cancer survivors (CCSs) (Armstrong et al., 2009).

## Parents of children with cancer

### During treatment

The diagnosis of childhood cancer has been described as one of the most intense, disruptive, and enduring experiences that parents can have (Vrijmoet-Wiersma et al., 2008). Even with survival being expected for most children, childhood cancer poses a serious threat to life and presents numerous sources of stress for the affected child and its family. For parents these stressors involve seeing the child very ill and suffering from adverse treatment side effects e.g., nausea and mucositis (Bryant, 2003; Norris & Adamson, 2012), supporting the child through multiple medical procedures and recurrent surgery, experiencing occasional medical intensive care (Dalton, Slonim, & Pollack, 2003; Rosenman, Vik, Hui, & Breitbart, 2005), and importantly; having to cope with the potential risk that the child might die from its disease. Additionally, the demanding medical regimens involved in cancer treatment implies practical challenges for parents such as periods of residential care and temporary separation from the rest of the family (Wakefield, Mcloone, Butow, Lenthen, & Cohn, 2011) which may imply considerable changes in daily activities and disruption of social and family roles (Kazak, Simms, & Rourke, 2002; Rodriguez et al., 2012).

Parents often report psychological reactions such as intensive fear, sadness, uncertainty, and hopelessness during the child's treatment (Vrijmoet-Wiersma et al., 2008). In addition, psychiatric symptoms such as depressive symptoms and posttraumatic stress symptoms (PTSS), i.e. intrusive thoughts, avoidance, and hyperarousal (American Psychiatric Association, 2000), have been reported (Dolgin et al., 2007). PTSS at clinical levels have been reported by 22-68% of parents of children on cancer treatment (Dunn et al., 2012; Kazak, Boeving, Alderfer, Hwang, & Reilly, 2005; Pöder, Ljungman, & von Essen, 2008). Parents have also reported acute stress symptoms (ASS), anxiety, and excessive worry (Harper et al., 2013; Pai et al., 2007; Vrijmoet-Wiersma et al., 2008). Levels of psychological distress seem to be highest following the child's diagnosis and thereafter decrease as a function of time (Pai et al., 2007; Pöder et al., 2008).

### After end of successful treatment

When a child successfully completes cancer treatment it is often a celebrated milestone for the whole family (Wakefield et al., 2011). However, even after end of treatment, many challenges may remain for the child and its family (e.g., Patterson et al., 2004). These include the physical and medical late effects which are common in CCSs; two-thirds of CCSs experience at least one distressing late effect e.g., cardiopulmonary, endocrine, musculoskeletal, or neurocognitive deficits (Hewitt, Weiner, & Simone, 2003; Oeffinger et al., 2006). Survivors and their parents often have to struggle with such late effects in their daily life for many years, sometimes for the rest of their lives. Also, even when a cancer treatment is considered successful, there is a risk of disease relapse or occurrence of a secondary cancer disease which parents have to cope with. Additionally, stressors such as economical and occupational difficulties stemming from the time of the child's illness have been reported by parents of CCSs (Hovén, von Essen, & Norberg, 2013).

Previous studies indicate that, despite the ongoing stressors, most parents of CCSs report psychological distress within a normal range after end of the child's treatment, and thus demonstrate resilience in the long-term (Phipps, Long, Hudson, & Rai, 2005). However, a subgroup reporting high levels of psychological distress have been identified (Bruce, 2006; Grootenhuys & Last, 1997; Vrijmoet-Wiersma et al., 2008). In a systematic review of PTSS in parents of CCSs it was reported that 10-44% experiences severe levels of PTSS (Bruce, 2006). Additionally, parents of CCSs have reported anxiety, persistent worry, depressive symptoms and distressing thoughts about potential recurrence (Klassen et al., 2007; Manne, Du Hamel, Gallelli, Sorgen, & Redd, 1998). The prevalence rates of PTSS in parents of CCSs exceed those documented for the cancer survivors (Kangas et al., 2002), which suggests that parenting a child with cancer is more traumatic in the long-term than the actual cancer survivorship (Bruce, 2006). Furthermore, studies have shown that

parents may experience relationship difficulties after end of the child's treatment, such as marital strains and strains in relationships to the previously ill child or its siblings (Long & Marsland, 2011; Pai et al., 2007). It is important to highlight that many of the previous studies in this population have used mixed samples with regard to e.g., timing of assessment which precludes firm conclusions regarding the prevalence of psychological distress, and development of the distress over time.

Several predictors of psychological distress in parents of CCSs have been identified. In line with the general trauma literature, female gender has been associated with higher levels of PTSS (Bruce, 2006). Also, a lower level of social support and family functioning, and a higher number of prior stressful life events, has been related to higher levels of PTSS (Brown, Madan-Swain, & Lambert, 2003). Parents of children with cancer who are less educated, and parents with a lower socioeconomic status (SES) or a "perceived unsatisfactory financial status", have also reported higher degrees of depressive symptoms (Vrijmoet-Wiersma et al., 2008). Overall, subjective factors though seem to be more predictive of psychological distress than objective factors (Bruce, 2006). Parents' anxiety during treatment (particularly for mothers) has been reported to predict PTSS after end of treatment (Best, Streisand, Catania, & Kazak, 2001). Also, appraisals of the illness and treatment experience, including perceived treatment intensity and life threat have been related to PTSS (Barakat, Alderfer, & Kazak, 2006). These findings are conflicting with the general trauma literature where objective trauma features such as intensity of trauma and threat to life have been shown to correlate with severity of PTSS/posttraumatic stress disorder (PTSD) (Frans, Rimmö, Aberg, & Fredrikson, 2005). Furthermore, Bruce (2006) identified a significant association between levels of PTSS in parents of children with cancer and physical late effects in the child, indicating that PTSS in this population not only consist of *post*-traumatic reactions, but also of reactions to current and ongoing stressors.

## Bereavement

For about 20% of children diagnosed with cancer, treatment will not be successful, and the child will die as a consequence of its disease. In western countries cancer is the leading cause of disease-related deaths during childhood, and in Sweden approximately 60 children die of cancer every year (Gustafsson et al., 2013). Caring for a terminally ill child, and experiencing the death of one's own child, is among the most distressing human experiences (Kristensen, Elklit, Karstoft, & Palic, 2014). Parental bereavement is also associated with more intense and prolonged grief than other types of bereavement and implies significant and enduring psychological distress over a long period of time (McCarthy et al., 2010; Rando, 1983). In addition to the death of the child, parents of children lost to cancer have often experienced the long-

lasting physical and emotional suffering of the child preceding death (Wolfe et al., 2000). This has been argued to create distinct post-loss challenges for this population (Barrera et al., 2009; Rosenberg, Baker, Syrjala, & Wolfe, 2012) and that parents of children lost to cancer may not only experience intensive symptoms of grief, but also PTSS/PTSD. It has been shown that besides grief, other populations that have lost a close relative to a somatic illness are at risk for increased levels of PTSS (Zisook, Chentsova-Dutton, & Shuchter, 1998). However, studies on PTSS/PTSD in parents of children lost to cancer have been lacking.

Overall, the knowledge of the psychological long-term consequences in bereaved parents is sparse since these parents often have been excluded from previous studies. One of the few studies that have examined psychological reactions in this population reported an increased risk of psychological distress (including anxiety, depression, and prolonged grief) at four to nine years following the death of a child to cancer (Kreicbergs, Valdimarsdottir, Onelöv, Henter, & Steineck, 2004; McCarthy et al., 2010). Findings from the same study showed that bereaved mothers are at particular risk of high levels of psychological distress following the death of a child from cancer (Kreicbergs et al., 2004). High levels of suffering in the child before the death have been associated with higher levels of psychological distress in parents during bereavement (McCarthy et al., 2010). Furthermore, economic hardship, duration and intensity of the child's cancer treatment, and a parental history of loss, have been related to higher levels of psychological distress in parents following the death of a child (Rosenberg et al., 2012). As for distress in parents of CCSs, psychological distress in bereaved parents has been reported decrease with time (McCarthy et al., 2010). Importantly, the lack of longitudinal studies has precluded conclusions with regard to psychological long-term consequences, and predictors of these, in bereaved parents.

## Consequences of psychological distress

Clinical levels of psychological distress have serious consequences not only for the affected individual, but also for the society. For the individual the distress is associated with decreased quality of life, functional disability, and an increased risk for somatic morbidity such as coronary heart disease (Afari et al., 2014; Berg-Nielsen, Vikan, & Dahl, 2002; Denollet, Maas, Knottnerus, Keyzer, & Pop, 2009; Wittchen, Carter, Pfister, Montgomery, & Kessler, 2000). High levels of psychological distress in parents have also been reported to impair psychological recovery among children diagnosed with serious medical conditions (Bronner, Knoester, Bos, Last, & Grootenhuis, 2008). Furthermore, psychological distress such as PTSS/PTSD is related to increased costs due to increased health care utilization, productivity loss, and sick leave (Smit et al., 2006). Thus, the benefits of adequate care and treatment aiming at

reducing psychological distress can be expected to exceed the benefits of reduced suffering for the individual.

## Conceptualization of cancer-related psychological distress

There is an ongoing debate regarding how to best understand and conceptualize cancer-related psychological distress in parents of children with cancer (Kangas, Henry, & Bryant, 2002; Phipps et al., 2014). Since the DSM-IV (American Psychiatric Association, 1994) included parenting a child with a life-threatening disease such as cancer in the potentially traumatic events that can lead to PTSS and PTSD, a great part of the research in the area has applied a traumatic stress framework to these reactions. However, the application of a traumatic stress framework has been questioned and several arguments have been put forth in this debate (Kangas, 2013; Phipps et al., 2014). First, unlike traumatic events such as war and violence identifying a discrete precipitating stressor is difficult with regard to the cancer experience. Childhood cancer rather involves multiple and chronic stressors for parents such as learning about the diagnosis, supporting the child through invasive treatments, experiencing late effects, or even the death of the child. Secondly, the continuous risk of recurrence of the cancer implies a realistic, future orientated threat. Lastly, it has been argued that the decline of levels of psychological distress with time from the child's diagnosis indicates that these reactions are related to current stressors, rather than to previous events (Phipps et al., 2005). These arguments are reflected in the latest version of the DSM; the DSM-5 (American Psychiatric Association, 2013), where parenting a child with cancer no longer is included in the definition of potentially traumatic events that can lead to PTSS/PTSD. Instead adjustment disorder (AD) is suggested as the main psychiatric symptomatology accompanying somatic diseases in oneself or a close relative. The use of this diagnostic entity has also been questioned and researchers have put forth that AD is an ill-defined diagnosis that cannot be used to guide treatment (Hoge et al., 2016), and that by using the DSM-5 diagnostic criteria, parents of children with cancer may be left without adequate recognition and treatment.

Overall, there is a lack of specific theoretical models and conceptualizations of psychological distress in parents of children with cancer. However, Kazak et al. (2006) have suggested the pediatric medical traumatic stress (PMTS) model (Kazak et al., 2006; Price, Kassam-Adams, Alderfer, Christofferson, & Kazak, 2016) as a conceptual framework for psychological reactions in children and families across many different types of pediatric injuries and illnesses. The PMTS-model describes child and family adjustment across three consecutive phases; Phase I: Peri-trauma, which includes initial potentially traumatic events (PTE) and surrounding events such as receiving the information about the diagnosis of a life-treating disease; Phase II: The early, ongoing, and evolving phase which includes active medical treatment

and related demands; and Phase III: Longer-term PMTS which includes the time after end of active medical treatment and the potential traumatic reactions that may continue for months or years. The PMTS-model sets goals for interventions at each phase. These include changing the subjective experience of the potentially traumatic experiences in Phase I, preventing traumatic reactions during Phase II, and reducing traumatic reactions occurring in Phase III. The PMTS-model does however not specify the mechanisms to be targeted in such interventions. The psychological treatment for parents of CCSs based on the model did furthermore not show an effect in terms of reduction of psychological distress (Kazak et al., 2004).

Many ambiguities remain regarding cancer-related psychological distress in parents of children with cancer. These include uncertainties regarding symptom topography, development and prevalence of symptoms over time, and importantly; the mechanisms involved in development and maintenance of the distress. Accordingly, the best way to conceptualize psychological distress experienced by parents of children with cancer is still a matter of debate (Kangas, 2013; Phipps et al., 2014).

## Positive psychological consequences

It is a well described phenomenon that people who have undergone significant trauma and suffering may not only experience negative, but also positive psychological consequences (Calhoun & Tedeschi, 2006). Such consequences have been conceptualized as posttraumatic growth (PTG) and are often divided into five domains: personal strength, new possibilities, improved relationships, new appreciation of life, and spiritual change (Calhoun & Tedeschi, 2006). PTG has been reported in populations such as combat veterans, breast cancer survivors, sexual assault victims, people who have served time in prison, and in bereaved populations (Zoellner & Maercker, 2006). The relationship between PTG and psychological distress has been described as complex and studies have shown contradictory results, however overall suggesting that these processes occur independently (Zoellner & Maercker, 2006). It has also been shown that PTG and PTSD share some predictors, but not others. E.g., Dekel et al. (2011) showed that loss of control during the traumatic experience predicted both PTG and PTSD, whereas self-controllability predicted PTG but not PTSD. There are still many uncertainties regarding the concept of PTG, and more research is needed to fully describe and understand this phenomenon.

Barakat, Alderfer, and Kazak (2006) found that an overwhelming proportion of parents of CCSs reported at least one positive psychological consequence. Barakat et al. (2006) furthermore reported PTG and PTSS to be unrelated among parents of CCSs. On the other hand, a Swedish study reported a significant correlation between PTG and PTSS in parents of CCSs who had undergone stem cell transplantation (Forinder & Lindahl Norberg, 2014). In



the same study it was shown that PTG, and PTSS, were related to experiencing the trauma as more severe. Barakat et al. (2006) reported similar findings for fathers of survivors where subjective ratings of greater treatment intensity were associated with more PTG. These findings indicate that the interpretation of the severity of the trauma is important for the development of positive psychological growth. Besides in parents of CCSs, PTG has also been reported in parents of deceased children (Engelkemeyer & Marwit, 2008). Firm knowledge about the content of positive psychological consequences, as well as the prevalence, development and predictors of these, in the context of parenting a child with cancer is lacking.

## Psychological treatment

### Cognitive behavior therapy and empirically supported psychological treatments

CBT is the most widely studied form of psychological treatment and has been proven effective for a range of psychological disorders (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). There are today empirically supported CBT protocols for e.g., substance use disorder, schizophrenia and other psychotic disorders, depression and dysthymia, bipolar disorder, anxiety disorders, eating disorders, insomnia, personality disorders, anger and aggression, criminal behaviors, chronic pain and fatigue, and PTSD (Butler, Chapman, Forman, & Beck, 2006; Hofmann et al., 2012). Empirically supported treatments (ESTs) are generally based on protocols with reference to a diagnostic category (Farmer & Chapman, 2008). In the clinical practice, psychological treatments should therefore be assigned to clients on the basis of presenting symptomatology or diagnosis, and the EST will thus primarily fit clients whose needs are consistent with the objectives of the respective treatment protocol (Farmer & Chapman, 2008). For clients with comorbid-disorders or with problems in areas where there are no ESTs, the CBT protocols however provide limited treatment guidance. Importantly, there are also conditions (e.g., depression) where there is more than one EST available. In these cases, psychological treatment tailored to patients needs i.e., based on an ideographic case formulations approach can be applied. The empirical support for the use of a case formulations approach to CBT is limited, however individualized treatments based on ideographic assessment data, CBT-principles, and components from ESTs have shown results comparable to those of ESTs (Ghaderi, 2006; Persons, 2008). Due to the superior evidence base for standardized treatment protocols, it has been suggested that even when using an ideographic case formulations approach to CBT, evidence-based nomothetic formulations should be used as templates (Persons, 2008).

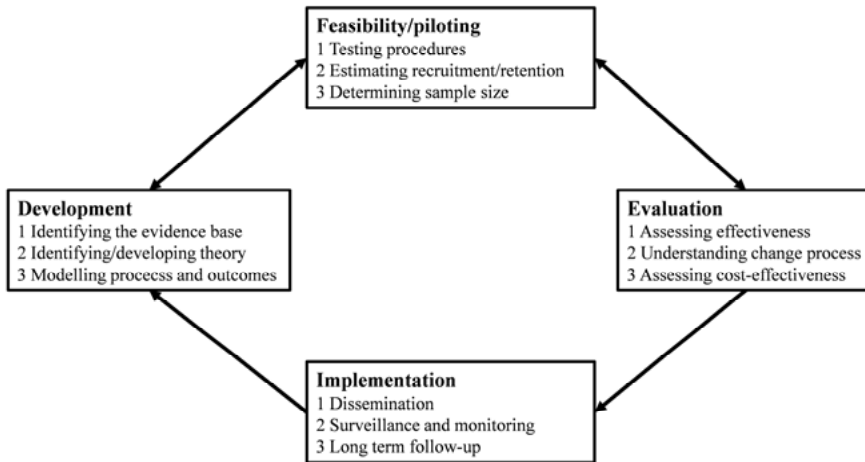
## Psychological treatment for parents of children with cancer

The few trials that have evaluated psychological treatments for parents of children with cancer have shown mixed results. For parents of newly diagnosed children two studies, one by Cernvall and co-workers (2015) and one by Sahler and colleagues (2013), have shown positive results. Sahler et al. (2005) developed a treatment consisting of structured problem-solving training and evaluated the treatment in a randomized controlled trial (RCT) (Sahler et al., 2013). The treatment was shown to be more effective in reducing negative affectivity (encompassing PTSS and symptoms of depression) than an active control condition consisting of non-directive support (Sahler et al., 2013). Cernvall and co-workers developed and evaluated internet-based CBT in a RCT with a wait-list control condition for parents of children recently diagnosed with cancer (Cernvall et al., 2015). The treatment was shown to reduce PTSS and depression at post-assessment. Other intervention studies for parents of children recently diagnosed with cancer have not shown reductions of psychological distress, such as the stress management intervention by Marsland et al. (2013). For parents of CCSs only one psychological treatment has been evaluated; the surviving cancer competently intervention program. This treatment was based on the PMTS-model (Kazak et al., 2004) and was a brief intervention targeting the whole family. Results showed no effect in terms of reduction of PTSS, except for intrusive thoughts among fathers (Kazak et al., 2006). Additionally, Wakefield et al. (2015) have recently developed an e-mental health intervention for parents of CCSs, which is described as an online group-based CBT intervention. The aim of this intervention is to improve quality of life in parents of CCSs, however evaluation of the effect of the intervention have not yet been published. To sum up, there is to date no EST targeting psychological distress in parents of CCSs.

## Developing a psychological treatment

There are important guidelines to follow when developing a psychological treatment. The Medical Research Council (MRC) guidance to developing and evaluating complex interventions (including psychological treatments) (Craig, 2008; Craig et al., 2013) emphasizes that such work should be conducted as an iterative process where the formal evaluation wait until thorough feasibility and pilot work have been conducted. The MRC guidance also stress the importance of an in-depth understanding of the symptoms/problems addressed by the intervention, and of the likely process of change. According to the MRC guidance, best practice is to develop interventions systematically, using the best available evidence and appropriate theory, and to thereafter test these using a carefully phased approach. The process should start with feasibility and pilot studies targeting each of the key uncertainties in the design, and then

moving on to formal evaluations. See Figure 1 for an illustration of this process.



*Figure 1.* Key elements of the development and evaluation process as described by the MRC guidelines for developing and evaluating complex interventions.

Guidance on development of psychological treatments can also be found in the stage model for behavioral therapies described by Rounsaville, Carroll, and Onken (2001). This model identifies three stages in the scientific processes of developing and evaluating a psychological treatment which lead from initial innovation (Stage I), through efficacy research (Stage II), and finally to effectiveness research (Stage III). This guidance puts emphasis on Stage I studies, which include innovation work i.e., development of the treatment protocol and pilot testing of this. The authors furthermore stress the importance of a theoretical understanding of the disorder/the distress experienced by the population, and underscore the need to identify the mechanisms involved in the distress. Further, the stage model, as the MRC guidance, highlight that the treatment protocol should be carefully tested including feasibility outcomes concerning the treatment and the study procedures at early stages of the development process. Finally, Rounsaville et al. (2001) recommend that if there is limited knowledge regarding the population at hand, Stage I studies could include identification of needs and development of instruments.

## Concluding remarks

In the previous literature, negative as well as positive psychological consequences have been reported by parents of CCSs and bereaved parents. Still, firm knowledge about the nature of these consequences is lacking. Regarding parents of CCSs, studies indicate that while most parents report resilience in the long-term, a subgroup experience high levels of psychological distress. There is however a paucity of knowledge in the existing literature about this distress including prevalence, specifications of symptom topography and the mechanisms involved in development and maintenance of the symptoms. There is also a lack of consensus in this field regarding how to best conceptualize cancer-related psychological distress and how to describe it in terms of a potential psychiatric diagnosis. Lastly, there is no EST targeting cancer-related psychological distress in parents of CCSs, which implies an important gap in the clinical care of families of children diagnosed with cancer.

## Aims

The overall aims of this dissertation project were to increase the knowledge about the long-term psychological consequences in parents of children diagnosed with cancer, including parents of survivors and bereaved parents, and to take the first steps towards developing a psychological treatment for parents of CCSs. The specific aims of Study I-V were:

### Study I

To describe the nature and prevalence of the long-term psychological late effects of childhood cancer for parents of childhood cancer survivors.

### Study II

To describe the development of PTSS and the prevalence of full and/or partial PTSD in parents of children diagnosed with cancer from shortly after diagnosis up to long-term survivorship or aftermath of a child's death.

### Study III

To examine particularly negative and positive experiences reported by parents of childhood cancer survivors and parents of children lost to cancer.

#### Study IV

To develop a cognitive behavioral conceptualization of cancer-related psychological distress in parents of childhood cancer survivors.

#### Study V

To preliminary evaluate the effect and test the feasibility of individualized face-to-face cognitive behavior therapy (CBT) for parents of childhood cancer survivors.

# Methods

## Design

An overview of the characteristics of Study I-V is presented in Table 1.

Study I was a systematic review which was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009). In Study I, systematic literature searches were performed and data was collected from studies matching the inclusion criteria.

For Study II and III data was collected within a project with the overall aim to investigate psychological and economic consequences of parenting a child diagnosed with cancer. The project had a longitudinal design and included (up to now) seven assessments (T1-T7). T1-T3 were administered in relation to the time of the child's diagnosis and during the child's treatment: one week (T1), two (T2) and four months (T3) after diagnosis. T4-T7 was administered in relation to the end of successful treatment or stem cell/organ transplantation, or the child's death (T5-T7). For parents whose child had completed a successful treatment data was collected: one week after treatment (T4), three months after treatment (T5), one year (T6) and five years (T7) after treatment. For bereaved parents, data was collected: nine (T5) and 18 months (T6), and five years (T7) after the child's death. In Study II longitudinal data from all assessment (T1-T7) was used, and in Study III data collected at the last assessment (T7) was used.

Study IV and V utilized data collected in an open trial with the overall aim to identify and describe parents' suffering related to parenting a child treated for cancer, and to develop, refine, and evaluate CBT for cancer-related psychological distress experienced by these parents. In Study IV data from the behavioral case formulations conducted as part of the CBT was used, and in Study V data from baseline, post-assessment, and follow-up assessment was used to evaluate the feasibility and preliminary effect of the CBT.

Table 1. *Design, participants, time of assessment, and data collection in Study I-V.*

Study design	Participants	Time of data collection	Type of data collection
I. Systematic literature review	1045 parents of CCSs	≤Five years after child's diagnosis and/or ≤two years after end of child's treatment	Systematic literature searches, extraction of data from included studies
II. Longitudinal	T1: N= 259; T7=169 parents of CCSs/bereaved parents	All parents: T1-T3=one week to four months after diagnosis Parents of CCSs: T4-T7=one week to five years after end of treatment Bereaved parents: T5-T7=nine months to five years after child's death	Structured self-reports via telephone
III. Cross-sectional	168 parents of CCSs/bereaved parents	T7=five years after end of treatment/child's death	Semi-structured interviews via telephone
IV. Exploratory	15 parents of CCSs	Baseline: three months to five years after end of child's treatment	Individual behavioral case formulations
V. Open trial, within-group pre-/post-/follow-up design	15 parents of CCSs	Baseline: three months to five years after end of child's treatment Post-assessment: after completion of CBT Follow-up assessment: three months after completion of CBT	Structured self-reports, structured diagnostic interview, and feasibility outcomes

*Note.* CCSs=Childhood cancer survivors

## Procedure and participants

There is no single definition of the time when a person is considered a childhood cancer survivor and different definitions of CCSs have been used in the previous literature (Feuerstein, 2007; Pui et al., 2014). In Study I we used a very conservative definition of CCSs, i.e., a person who had completed a successful treatment and was diagnosed with cancer at least five years prior to

study participation and/or had completed treatment at least two years prior to study participation. In Study II to V we used to a more inclusive definition of a CCS, i.e., a person who had completed cancer treatment at the time considered successful. The latter definition has been recommended to researchers in this field e.g., by the editor of *Journal of Cancer Survivorship* (Feuerstein, 2007).

## Study I

Inclusion criteria for the systematic review were: observational study using quantitative and/or qualitative methodology, published in the English language in a peer-reviewed journal during the last 30 years (the search was conducted in November 2012 and thereby studies published 1982-2012 matched the inclusion criteria), and reporting psychological effects of childhood cancer for parents of CCSs who were diagnosed with cancer at the age of 0-18 years and had completed treatment and were diagnosed at least five years prior to study participation and/or had completed treatment at least two years prior to study participation. A search strategy was developed and the following databases were searched: CINAHL, EMBASE, PsycINFO, and PubMed. Reference lists of included studies were screened for additional studies not found via the searches in the databases. A total of 15 studies were included in the review and 1045 participants participated in these studies. Gender was reported for 913 participants of which 624 (68%) were mothers.

The objectives and methods for Study I were specified in advance, documented in a protocol, and registered at PROSPERO (21/12-2012, CRD42012003521).

## Study II and III

Parents of children treated at four of the six Swedish pediatric oncology centers (Gothenburg, Linköping, Umeå, and Uppsala) were consecutively included from 2002-2004, during 18 months. Eligibility included: Swedish- and/or English-speaking parents (including step-parents) of children aged 0-18 years, diagnosed  $\leq 14$  days previously with a primary cancer diagnosis, and scheduled for chemotherapy and/or radiotherapy. To be eligible at T2 and T3, the child had to be on curative treatment. At T1, 259 parents, representing 139 families, participated (80% response rate). At T7, 132 parents of survivors and 37 bereaved parents participated. The retention rate between T1 and T7 was 65%; 64% among parents of survivors and 69% among bereaved parents. At T1, 50% ( $n=130$ ) of the participants were mothers, at T7 this figure was 52% ( $n=88$ ). At all assessments the PTSD-Checklist Civilian Version (Weathers, Litz, Herman, Huska, & Keane, 1993) was administered, data from these assessments was analyzed and reported in Study II. In Study III parents' ( $n=168$ ) answers to open-ended questions at T7 regarding particularly positive and/or



negative experiences in relation to the child's cancer disease were analyzed and reported.

Ethical approval of the study procedures was obtained from the local research committees in 2002 (DNR: 02-006) and from the Regional Ethical Review Board in Uppsala in 2008 (DNR: 2008/109).

## Study IV and V

Inclusion to Study IV and V was initiated in February 2013 and completed in February 2014. Parents were eligible if they had a child who had completed successful cancer treatment at the pediatric oncology center at the Children's University Hospital, Uppsala, three months to five years earlier; spoke Swedish; were able to commute to the clinic in Uppsala or Västerås, and reported psychological distress of any kind related to their child's cancer disease. Parents were excluded if they suffered from a psychiatric disorder in immediate need of treatment (for example severe depression or suicidal ideation) or if they were undergoing psychological treatment. Of the 80 potential participants, 15 were included, representing an inclusion rate of 19%. The sample consisted of eight mothers (53%) and seven fathers. One participant did not speak Swedish as native language, and parts of the data collection and psychological treatment with this participant was therefore performed with support from an interpreter. All but one participant completed the treatment, resulting in a treatment retention rate of 93%. All participants completed the follow-up assessment.

The study was approved by the Regional Ethical Review Board in Uppsala in 2012 (Dnr: 2012/440).

## Measures

### Extraction of data

In Study I, data was extracted according to a data extraction sheet developed for the study. Data comprised all aspects of parental distress and adjustment and factors associated with/predicting these, and included quantitative and qualitative data.

## Self-assessments

Studies in which the respective measure was used are indicated in the parentheses.

### **PTSD-Checklist Civilian Version (Study II and V)**

PTSS/PTSD was assessed with The PTSD Checklist-Civilian Version (PCL-C) (Weathers et al., 1993) which consists of 17 items measuring PTSS as defined in the B (re-experiencing), C (avoidance), and D (hyperactivity) criteria in the DSM-IV (American Psychiatric Association, 2000). The total score ranges from 17 to 85 points. The PCL-C has good test-retest reliability and concurrent validity (Ruggiero, Del Ben, Scotti, & Rabalais, 2003; Weathers et al., 1993). In the version used in the current work items were keyed to the child's cancer disease. Interpretation of the PCL-C scores can be done in two ways: 1. Level of PTSS can be identified by the mean score of the PCL-C. By using this method, a value of 44 or above indicates a PTSD diagnosis (Manne et al., 1998); 2. The symptom-criteria method can be applied to identify a potential PTSD diagnosis. By this method a score of  $\geq 3$  on at least one of the items assessing symptoms of re-experience, three items assessing symptoms of avoidance, and two items assessing symptoms of hyper-arousal indicates a PTSD diagnosis (Weathers et al., 1993). This method directly corresponds with the DSM-IV criteria for PTSD and is the most rigorous self-assessment of PTSD (Manne et al., 1998). Furthermore, partial PTSD can be assessed using the sub-symptom criteria method where a score of  $\geq 3$  on at least one symptom of re-experience, avoidance, and hyper-arousal indicates partial PTSD (Ruggiero et al., 2003).

### **Beck Anxiety Inventory (Study V)**

Anxiety was assessed with the Beck Anxiety Inventory (BAI: Beck, Epstein, Brown, & Steer, 1988) which consists of 21 items rated on a four point scale ranging from never (0) to almost all the time (3), indicating how often the respondent has experienced anxiety symptoms during the past week. The BAI has high internal consistency ( $\alpha=.94$ ), good test-retest reliability ( $r=.67$ ), and robust convergent validity ( $r=.54$ ) (Fydrich, Dowdall, & Chambless, 1992).

### **Montgomery Åsberg Depression Rating Scale-Self Assessment (Study V)**

Depressive symptoms were assessed with the Montgomery Åsberg Depression Rating Scale Self-assessment (MADRS-S: Svanborg & Åsberg, 2001; Svanborg & Åsberg, 1994) which consists of nine items measuring depressed mood over the past three days with scores ranging from 0 to 6 points. MADRS-S has good convergent validity with the Beck Depression Inventory ( $r=.87$ ) (Svanborg & Åsberg, 2001) and good internal consistency and satisfactory test-retest reliability (Fantino & Moore, 2009).

### **Penn State Worry Questionnaire (Study V)**

Worry was assessed with the Penn State Worry Questionnaire (PSWQ) which encompasses 16 items measuring excessive worry (Meyer, Miller, Metzger, & Borkovec, 1990). The items are statements with answers ranging from 1 to 5 where 0 indicates “not at all typical” and 5 indicates “very typical”. PSWQ has high internal consistency (Cronbach's  $\alpha=.91-.95$ ) and good test-retest reliability ( $r=.92$ ) (Meyer et al., 1990), and correlates highly with other questionnaires measuring anxiety and repetitive thinking in terms of rumination ( $r=.67-.73$ ) (Rijsoort, Emmelkamp, & Vervaeke, 1999).

### **Rumination scale of the Response Style Questionnaire (Study V)**

The rumination scale of the Response Style Questionnaire (R-RSQ: Nolen-Hoeksema, 1991) was used to assess rumination. R-RSQ measures rumination as a response to symptoms of depression, consists of 22 statements ranging from almost never (1) to almost always (4), and has high internal consistency (Cronbach's  $\alpha=.89$ ) (Nolen-Hoeksema, 1991) and good test-retest reliability ( $r=.67$ ) (Trenor, Gonzalez, & Nolen-Hoeksema, 2003).

### **Acceptance and Action Questionnaire-II (Study V)**

Experiential avoidance was assessed with the Acceptance and Action Questionnaire-II (AAQ-II: Bond et al., 2011). AAQ-II in its original form consists of 10 items measuring experiential avoidance. Each item is scored from never true (1) to always true (7). The instrument has good internal consistency and test-retest reliability (Bond et al., 2011). The convergent validity of the AAQ-II is good as it correlates positively with measures of depression, anxiety, and thought suppression (Bond et al., 2011). In the present study the items were cued to the child's cancer, and six extra items measuring avoidance of cancer-related experiences were included (Cernvall, Carlbring, Ljungman, & von Essen, 2013).

### **Satisfaction with Life Scale (Study V)**

Quality of life was assessed with the Satisfaction with Life Scale (SWLS) which consists of five items comparing current situation with a hypothetical standard (e.g., "I am satisfied with my life") (Diener, Emmons, Larsen, & Griffin, 1985). Statements are rated on a seven-point scale from strongly disagree (1) to strongly agree (7). The instrument has good test-retest reliability ( $r=.82$ ), high internal consistency (Cronbach's  $\alpha=.87$ ) (Diener et al., 1985), and adequate convergence with related measures (Pavot & Diener, 1993).

## Diagnostic interview

In Study V, the diagnostic interview M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.) for DSM-IV and ICD-10 was administered by a psychologist to assess psychiatric disorders (Sheehan et al., 1998).

## Semi-structured interview

In Study III, a telephone interview was conducted in which participants were asked to describe particularly negative and positive experiences in relation to their child's cancer disease. Participants were asked the following questions: "Have you had any particularly negative experience in relation to your child's cancer disease?" and "Have you had any particularly positive experience in relation to your child's cancer disease?" Participants who answered "Yes" or "I am not sure" were thereafter asked to describe their experiences. The answers were simultaneously transcribed by the interviewer.

## Behavioral case formulations

The individual behavioral case formulations in Study IV were conducted with each participant in line with Persons (2008) and Sturmey (2008). The case formulations included a description of the patient's problems, specification of the topography of symptoms, and functional analyses containing hypotheses about the mechanisms causing and, most importantly, maintaining the problems/symptoms (Persons, 2008; Tarrier, 2006). Besides the theoretical foundation in operant theory, the concept of experiential avoidance which has been identified as a core pathogenic mechanism with trans-diagnostic features, was used as a framework when conducting the individual behavior analyses and aggregating these (Dougher, 2000; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). The CBT-interventions (evaluated in Study V) were chosen, applied, and evaluated based on the emerging hypotheses about the maintaining factors (Persons, 2008). The behavioral case formulations were mainly conducted during the first two to three sessions of each CBT by the psychologist delivering the CBT in cooperation with a group of supervisors.

## Assessment of feasibility

To assess the feasibility of the recruitment, the data collection, and the delivery of the treatment in Study V the following data was documented; number of potential and included participants, reasons for not participating, retention to treatment and data collection, and drop-out rates and reasons for drop-out. Furthermore, duration of treatments i.e., number and frequency of treatment sessions, and number of cancelled/re-scheduled sessions were documented. Potential adverse effects were indicated by the number of participants report-

ing a higher level of psychological distress on the outcomes of primary interest at post- and follow-up assessment.

## Psychological treatment

Due to the lack of previous evaluations of psychological treatments for parents of CCSs and the lack of knowledge regarding cancer-related psychological distress in this population, we chose to base the treatment on a behavioral case formulation approach (Persons, 2008; Sturmey, 2008). Intervention techniques were selected to address the hypothesized maintaining mechanisms in accordance with the ideographic assessment data, previous literature describing best practice, i.e., ESTs, and by using nomothetic CBT-principles (O'Donohue & Fisher, 2009). Treatment sessions were structured according to standard CBT methodology (Persons, 2008) i.e., initially the homework assignments were discussed, thereafter specific interventions (according to the behavioral case formulation) were administered, and lastly homework assignments for the next week were discussed and planned. Importantly, in line with the CBT approach to psychological treatment, all interventions used, including homework, were decided upon together with the participant.

Overall, participants reported symptoms of traumatic stress (anxiety when reminded of the child's cancer, hyperarousal, and emotional numbing), and symptoms of depression (lack of motivation, low degree of positive emotions, and lack of energy). According to the case formulations, symptoms of traumatic stress were hypothesized to be maintained by avoidance of cancer-related stimuli and internal events such as thoughts and emotions related to the cancer experience (Foa, Hembree, & Rothbaum, 2007; Hayes et al., 1996). Interventions chosen to address these mechanisms were exposure to cancer-related stimuli, exposure to memories from the time of the child's illness, and mindfulness techniques to increase contact with emotions and present moment experiences overall (Baer, 2003; McLean & Foa, 2011). Health-related control behaviors that were identified to often accompany these thoughts and emotions were targeted by exposure with response-prevention (Hedman et al., 2011). Symptoms of depression were hypothesized to mainly be maintained by a low degree of engagement in potentially positively reinforcing activities, implying a low degree of positive reinforcement (Martell, Addis, & Jacobson, 2001). Behavior activation (BA) was the primary intervention chosen to address this maintaining mechanism (Dimidjian et al., 2006; Martell, Dimidjian, & Herman-Dunn, 2010). In addition to these specific interventions, standard CBT techniques such as setting goals for the treatment, providing psychoeducation, and teaching the participant to conduct functional analyses, were used. Also, and importantly, the therapists applied an accepting and validating approach towards the participants' expressions of thoughts and emotions in relation to the child's cancer disease. This approach also implied not avoiding

conversations about difficult thoughts and emotions, and thus provided participants with many opportunities to talk about their experiences related to the child's cancer throughout the treatments. For a presentation of specific interventions used see Table 2.

Table 2. *Intervention techniques used in Study V (N=15) and number of participants for whom the respective intervention was used.*

<b>Intervention</b>	<b>n(%)</b>
Mindfulness	11(73)
Behavior activation	9(60)
Exposure to cancer-related stimuli	8(53)
General affect exposure	8(53)
Relationship skills training	7(47)
Defining values	6(40)
Applied relaxation	4(27)
Scheduling positive activities with the partner	4(27)
Scheduling positive activities with the child	3(20)
Targeting the worry process	3(20)
Breathing training	2(13)
Exposure to health anxiety	2(13)
Sleep hygiene	2(13)
Anger management	1(7)
Perfectionism exposure	1(7)

## Data analyses

### Study I

As recommended when conducting a systematic review, we performed a detailed analysis of quality of the included studies (Moher et al., 2009). This analysis was conducted according to an aggregate of two quality assessment tools; the quality criteria for observational studies developed by Leboeuf-Yde and Lauritsen (1995) and the assessment tool QALSYST for studies using quantitative and qualitative methodology (Kmet, Lee, & Cook, 2004). Separate aspects of quality were assessed for studies using quantitative and qualitative methodology. Each study was provided a total quality score and the ratio between the study score and the possible maximum score was calculated. A ratio of <0.5 was assessed as low quality, 0.5-0.75 as moderate quality, and >0.75 as high quality. Total score for each item were also calculated to assess risk of bias across studies.

The synthesis of the extracted data was made with guidance from two sources. According to the Centre for Reviews and Dissemination (2009) the aim of the synthesis in a systematic review is to draw results together, explore whether results are consistent across studies, and investigate possible reasons for inconsistencies. Mays, Pope, and Popay (2005) suggest a narrative synthesis to move beyond a summary of study findings to a synthesis where conclu-

sions can be drawn within and across studies to generate new insights and reveal previously unknown patterns. Based on these two sources, a synthesis was made by a categorization of all extracted data and analyses were made within each category, and across all categories. Due to the low number of studies utilizing consistent measures it was not possible to conduct a meta-analysis.

## Study II

Latent growth curve (LGC) analysis was used to analyze development of PTSS over time. LGC analysis can be seen as a special case of structural equation modeling which is a general modeling framework for testing relationships among variables, using observed (measured) and unobserved (latent) variables. In LGC analyses the observed variables are repeated measures of the same outcome variable (Duncan & Duncan, 2010). The latent variables represent aspects of initial status and change in this outcome variable. A minimum of two latent factors are defined in a LGC-model; an intercept factor representing level of the outcome when time equals zero, and a slope factor representing change over time in the outcome variable. For Study II, LGC-analyses were performed in a hierarchy of increasing complexity. Overall model fit was analyzed using the Steiger-Lind Root-Mean-Square-Error of Approximation (RMSEA) and Bentler Comparative Fit Index (CFI). RMSEA values  $<.05$  indicate good fit and values between  $.05$  and  $.08$  moderate fit (Browne & Cudeck, 1992; Steiger, 1990), and CFI values close to  $.95$  indicate good fit and values  $>.90$  acceptable fit (Bentler, 1990).

A visual inspection of the observed means and individual growth trajectories indicated that the rate of change was different during the child's treatment (T1-T4) and after the end of treatment (T4-T7) or the child's death (T5-T7). Also, the study design was based on time counted from these different events, i.e., child's diagnosis and end of the child's treatment (survivorship) or the death of the child. Together these facts suggested two separate slope factors (Slope 1 and Slope 2) to allow separate estimates of growth during these different stages of the child's disease trajectory. A piecewise LGC-model was therefore chosen as the overall modeling strategy. The intercept factor was estimated to represent the initial status in PTSS at T1. Slope 1 was estimated to represent change during treatment up to the assessment directly after end of treatment (T1-T4) and Slope 2 was estimated to represent change after end of treatment (T4-T7) or the child's death (T5-T7). Time scores used in the model were specified to represent time since diagnosis, and time since end of treatment/child's death according to mean days from diagnosis and end of treatment/child's death respectively.

First an unconditional piecewise linear growth model (without covariates), Model 1, was estimated to examine the overall group growth and to test for variability in the model estimates. When fitting the unconditional piecewise

LGC-model significant residual variance in intercept and slope revealed substantial individual differences in initial levels of PTSS and development over time. Model 1 showed poor fit (RMSEA=0.13, 90% Confidence Interval [CI]=0.11-0.16; CFI=0.87). Model 1 was extended by adding a third slope factor, a quadratic slope factor at T1-T4 to improve fit, yielding Model 2. The addition of the quadratic slope factor at T1-T4 allowed the change during T1-T4 to be non-linear. Model 2 showed improved fit (RMSEA=0.11, 90% CI=0.084-0.14; CFI=0.93). The time-variant covariate; child's vital status, i.e., if the child is alive or deceased, and the time-invariant covariates parent age and gender, child age and gender, and child diagnosis (CNS-tumor vs. non CNS-tumor) were added, yielding Model 3. Model 3 showed improved and adequate fit (RMSEA=0.079, 90% CI=0.062-0.096; CFI=0.92). In Model 4 only the significant covariates child's status, parent gender, and child gender were included (RMSEA=0.084, 90% CI=0.066-0.10; CFI=0.92). Modification indices for Model 4 suggested that the time score for T4 should be freely estimated, thus allowing the estimate at this time-point to deviate from the overall growth. As this corresponded with the visual inspection indicating that this time-point deviated from overall growth pattern, and as previous literature has reported that the time after end of the child's treatment might be challenging for parents (Wakefield et al., 2011), we choose to free the intercept factor at T4, resulting in the final model, Model 5. Model 5 fit data well (RMSEA=0.043, 90% CI=0.013-0.066; CFI=0.98).

### Study III

The manifest verbal content of the answers about particularly negative and/or positive experiences were analyzed with content analysis in accordance with Graneheim and Lundman (2004). Negative and positive experiences were analyzed separately. The analyses was conducted in five steps and carried out by five of the co-authors. Answers by fathers of survivors, mothers of survivors, bereaved fathers and bereaved mothers were analyzed separately in the first three steps of the analysis. The analysis was conducted via the following steps: 1. Meaning units were identified and reduced to condensed meaning units by author 2 (MB). The meaning units and condensed meaning units were reviewed independently by author 4 (MC) and author 6 (EH). Disagreements, for example with regard to the level of condensing were discussed until consensus was reached; 2. The condensed meaning units were abstracted into codes by author 1 (LL) and author 3 (MA). This step was first conducted by the authors working independently, thereafter the codes were compared and disagreements discussed and negotiated; 3. The codes were compared based on differences and similarities and categorized into subcategories, first independently by author 1 (LL) and author 3 (MA), and then by these two authors working together. Disagreements were discussed until consensus was reached; 4. All identified subcategories for the four subgroups (fathers of survivors,



mothers of survivors, bereaved fathers and bereaved mothers) were reviewed by author 1 (LL), author 2 (MB), author 3 (MA), and author 6 (EH), resulting in a new set of mutually exclusive subcategories; 5. The subcategories were analyzed and organized by author 1 (LL), author 2 (MB), author 3 (MA), and author 6 (EH) into mutually exclusive categories. When the categories emerged it was apparent that these were related to either the past or the present, and the categories were therefore classified within these two overarching themes. Finally author 1 (LL) and author 3 (MA) re-read all transcripts, through each meaning unit, condensed meaning unit, code, subcategory, and category to check the agreement of the data. The few disagreements found were resolved by re-coding a few codes and re-sorting these into another subcategory until consensus was reached. The analytical procedure, including the initial steps of independent coding and the complementary confirmatory analyses, was applied to increase the trustworthiness of the analysis (Malterud, 2001). To further increase the credibility of the results, a parent of a child who had completed treatment for cancer approximately five years previously carefully read the results of the analyses and reflected upon these together with the authors.

## Study IV

To derive a nomothetic conceptual model from the ideographic behavioral case formulations, the case formulations were aggregated according to the following procedure: Continuous discussions were held during the course of the study (which lasted for approximately 19 months) between the supervisors and the psychologists working as therapists in the study. The supervision was organized in three forms: 1. Once a week with a licensed psychologist (Author 1 [MC]) where the progress of the individual therapies was discussed and adjustments to case formulations and interventions were made if needed; 2. Bi-weekly with a licensed psychologist with experience of developing CBT protocols (Author 7 [BL]); and 3. Approximately twice every semester with a licensed psychologist and psychotherapist who had extensive experience of working with severe emotional disorders. The aim of the supervisions (2 and 3) was to discuss all the case formulations in terms of commonalities and differences, and to identify general themes. The general conceptualization gradually evolved during the course of the study. A summarizing meeting where all the case formulations were read and discussed by the psychologists working with the treatments and the supervisors was held with the goal to assure that the conceptualization was representative for all the case formulations. After completion of the study, all documentation about each patient, including the behavioral case formulations, the treatment summary and all patient journal data, was carefully re-read by the first author (LL) and once again summarized with regard to each patient's presenting problems and interventions used in the treatments, to ensure that no relevant information had been omitted in the

analyses. Furthermore, respondent validation was used with four of the participants who also participated as research partners in a participatory action research (Kindon, Pain, & Kesby, 2007) study aiming at developing an easily accessible online treatment manual for parents of children previously treated for cancer on the basis of the conceptualization of distress formulated in Study IV. The participants provided feedback on the conceptualization (depicted in Figure 2) in terms of categorization of psychological distress as consisting of symptoms of traumatic stress and depressive symptoms, and the hypotheses regarding developmental and maintaining factors. Overall, the participants considered the model to be relevant and representative of their experiences and coherent with their perceptions of the maintaining mechanisms that had been targeted during the CBT.

## Study V

Potential changes from baseline to post-assessment, and from baseline to follow-up assessment, were analyzed using dependent t-test. Within-group effect sizes were estimated using Cohen's  $d$  based on baseline to post-assessment and baseline to follow-up assessment change scores. According to Cohen (1988), effect sizes of  $d=0.2$ ,  $d=0.5$ , and  $d=0.8$  are considered small, medium, and large, respectively. For the outcomes of primary interest (PCL-C, BAI, MADRS-S) the proportion of participants who reported a reliable change according to Jacobson and Truax (1991) was calculated. Furthermore, potential differences and/or associations between the outcomes of primary interest and the site of delivery of the intervention, having the partner included in the study or not, and time since end of the child's treatment were calculated using independent t-test or Pearson correlation.

# Results

## Study I

Fifteen studies, published between 1989 and 2010, met the inclusion criteria. Thirteen of these were based on quantitative methodology, one on quantitative and qualitative methodology, and one on qualitative methodology.

Results from the quality assessment indicated that three of the 14 studies using quantitative methodology were of low quality, six of moderate quality, and five of high quality. Summation of each item score across studies indicated that overall the studies were of low quality regarding response rate, comparison of responders and non-responders, and sample size. These issues are all related to a risk of selection bias. One of the studies using qualitative methodology was assessed as of moderate quality and one as of low quality. Summation of item scores across the qualitative studies showed that these studies were of low quality regarding analytic method, use of verification process, and reflexivity of the account.

Main results were categorized under the sub-categories: general psychiatric symptoms and psychological distress; PTSS; worry; disease-related thoughts and feelings; adjustment and coping adequacy; family functioning; marital adjustment; and positive long-term psychological late effects. In addition, factors associated with/predicting long-term psychological late effects were reported. The results showed that at group-level parents reported general psychological distress within a normal range in all nine studies reporting on general distress. Levels within a normal range were also reported regarding family functioning and coping. However, subgroups reporting clinically relevant levels of psychological distress were identified; 20-30% reported general psychological distress at a level indicative of seeking help and 21-44% reported PTSS at a severe level. Additionally negative psychological consequences such as anger, guilt, self-blame, and fear of relapse were reported. Positive consequences were also reported and included “a growth experience”, “being tougher”, and “seeing what is really important in life”. Overall, results for factors associated with parental outcomes showed that parents’ coping and adjustment were stronger predictors of emotional function than the children’s medical and disease-related variables, however, that late effects in the child was associated to disease-related hopelessness in parents.

## Study II

The final LGC-model, see Figure 2, showed a significant linear and quadratic development between T1 and T4 confirming an initial decline in PTSS following the time of the child's diagnosis. The free intercept factor loading at T4 was significant, suggesting that the level of PTSS at T4 deviated from the overall estimated growth (Est=4.65;  $p<.001$ ). In the final model, the second slope factor (T4-T7) was non-significant, implying that no further decline in PTSS occurred after end of the child's treatment (T4-T7). Importantly, the second slope factor was significant before the free intercept at T4 was included in the final model, implying that the non-significant change occurred from T5. Mothers reported a higher initial level of PTSS than fathers (Est=6.82;  $p<.001$ ). Parent gender did not predict change in PTSS, i.e. mothers continued to report higher levels than fathers. The initial level of PTSS was related to a greater decline between T4-T7 (Est=-1.38;  $p<.01$ ). Having a girl was related to a higher initial level of PTSS ( $p<.05$ ) and a greater decline between T1-T4 ( $p<.05$ ). Parent age, child age, and child diagnosis (CNS tumor/non-CNS tumor) did not predict initial level or development of PTSS. Finally, bereaved parents reported higher levels of PTSS at T5-T7 than parents of survivors.

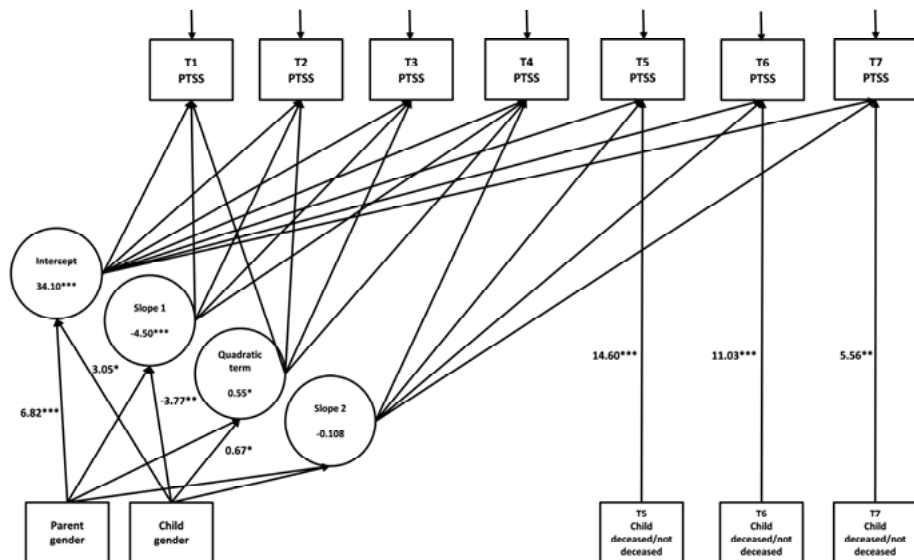


Figure 2. LGC-model in Study II. \* $p<.05$ ; \*\* $p<.01$ ; \*\*\* $p<.001$

The prevalences of full and partial PTSD for mothers and fathers of survivors at T4-T7 and bereaved mothers and fathers at T5-T7 are presented in Table 3. Among mothers of survivors there was a decline in the prevalence of full and partial PTSD from T4 to T5 ( $p<.001$ ) and a decline of partial PTSD from T5 to T6 ( $p<.05$ ). For fathers of survivors, there was a decline in the prevalence of partial PTSD from T4 to T5 ( $p<.01$ ). Among bereaved parents there was a decline for mothers of full and partial PTSD between T6 and T7 ( $p<.01$ ). Comparisons of the prevalence of full/partial PTSD between mothers of survivors and bereaved mothers, and between fathers of survivors and bereaved fathers are also reported in Table 3. Bereaved mothers reported higher prevalences of full and partial PTSD than mothers of survivors at T5 and T6. Bereaved fathers reported higher prevalences of full and partial PTSD at all assessments, besides at T5 regarding full PTSD.

Table 3. *Comparisons of prevalence of full/partial PTSD between mothers of survivors and bereaved mothers, and between fathers of survivors and bereaved fathers in Study II.*

	Mothers			Fathers		
	Survivors	Bereaved	$\chi^2$	Survivors	Bereaved	$\chi^2$
<b>T4</b>						
Full PTSD	30/109(27.5)	NA	NA	15/103(14.6)	NA	NA
Partial PTSD	49/109(45.0)	NA	NA	33/103 (32.0)	NA	NA
<b>T5</b>						
Full PTSD	16/109(14.7)	6/9(66.7)	14.81**	6/101(5.9)	2/11(18.2)	2.24
Partial PTSD	32/109(29.4)	8/9(88.9)	13.15**	16/101(15.8)	6/11(54.5)	9.41**
<b>T6</b>						
Full PTSD	10/98(10.2)	9/18(50.0)	17.58***	6/94(6.4)	5/19(26.3)	7.15*
Partial PTSD	16/98(16.3)	11/18(61.1)	17.08***	14/94(14.9)	8/19(42.1)	7.46*
<b>T7</b>						
Full PTSD	7/68(10.3)	2/20(10.0)	0.01	1/64(1.6)	3/17(17.6)	7.40*
Partial PTSD	13/68(19.1)	4/20(20.0)	0.04	5/64(7.8)	6/17(35.3)	8.64**

Note. NA=not applicable; \* $p<.05$ ; \*\* $p<.01$ ; \*\*\* $p<.001$

### Study III

The number of fathers and mothers who answered yes to the questions “Have you had any particularly negative/positive experience in relation to your child’s cancer disease?” is depicted in Table 4.

Table 4. *The number of fathers' and mothers' who answered yes to the questions "Have you had any particularly negative/positive experience in relation to your child's cancer disease?" at T7 in Study III.*

	Parents of survivors n(%)			Bereaved parents n(%)		
	Fathers (n=64)	Mothers (n=68)	Total (n=132)	Fathers (n=16)	Mothers (n=20)	Total (n=36)
Negative experience/s						
Yes	40(62.5)	47(69.1)	87(65.1)	13(81.3)	15(75.0)	28(77.8)
Don't know	1(1.6)	2(2.9)	3(2.3)	1(6.3)	1(5.0)	2(5.6)
No	23(35.9)	19(27.9)	42(31.8)	2(12.5)	4(20.0)	6(16.7)
Positive experience/s						
Yes	59(92.2)	61(89.7)	120(90.1)	10(62.5)	18(90.0)	28(77.8)
Don't know	2(3.1)	4(5.9)	6(4.5)	0(0)	1(5.0)	1(2.8)
No	3(4.7)	3(4.4)	6(4.5)	6(37.5)	1(5.0)	7(27.8)

Results from the content analyses revealed eight categories of negative experiences and seven categories of positive experiences, see Figure 3. The categories were related to past events or to the present situation. Categories of negative experiences related to the past were: distressing events; healthcare; own reactions; surrounding institutions; and the fact that the child got cancer. Negative experiences related to the present were: impaired relationships; child late effects; and long-term psychological consequences. Categories of the positive experiences related to the past were: healthcare; support systems; treatment outcome; and unexpected joy, and categories of positive experiences related to the present were: improved relationships; long-term consequences for the child; and personal development.

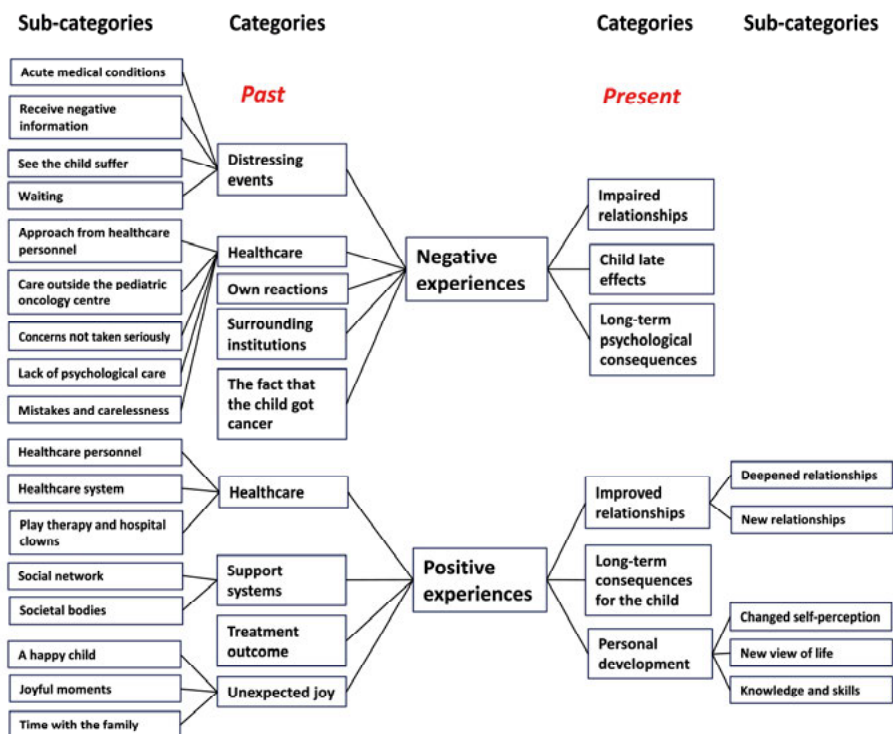
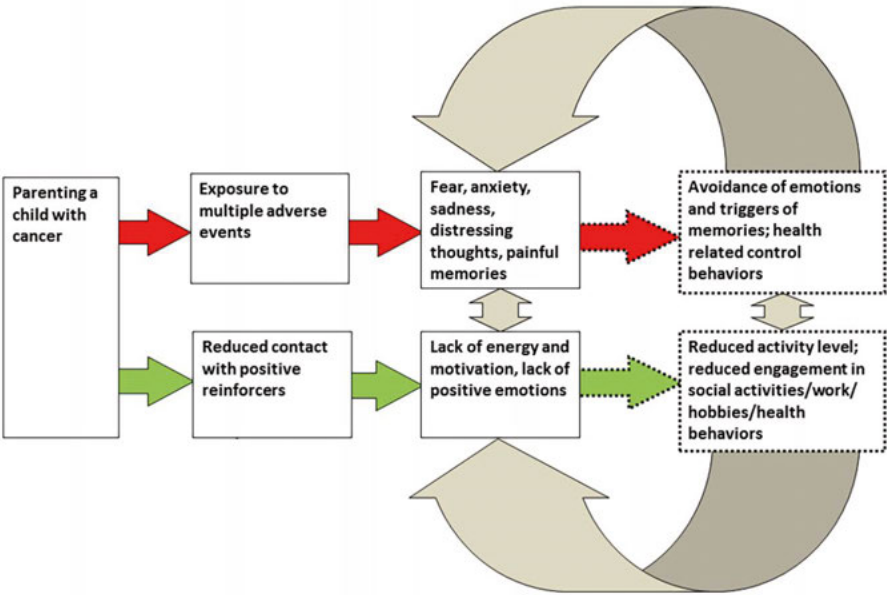


Figure 3. Categories and subcategories of parents' answers about negative and positive experiences in Study III.

## Study IV

The conceptualization consisted of two separate but overlapping paths describing development and maintenance of symptoms of traumatic stress and symptoms of depression, see Figure 4. The behavioral responses hypothesized as maintaining for symptom of traumatic stress were avoidance of cancer-related stimuli which included external stimuli and internal stimuli such as thoughts and emotions related to the cancer experience. Hypothesized maintaining behaviors for depressive symptoms were low engagement in potentially reinforcing activities. The psychologically relevant experiences involved in parenting a child with cancer, and the reactions to be expected in response to these are specified in the conceptualization, see Figure 4. Importantly, the maintaining behaviors were hypothesized to have been established through the adaptation to the challenging circumstances at the time of the child's illness since these behaviors served adaptive functions at the time. An example is the behavioral strategy emotional avoidance which may have served adaptive functions such as helping the parent to manage repeated exposure to adverse experiences during the time of the child's illness. However, after end of the child's treatment, the continuous use of emotional avoidance instead hinders

emotional processing, and thus will serve maladaptive functions. We suggested the term ‘state of emergency behaviors’ (SEBs) to label these behaviors. Importantly, the conceptualization can provide guidance for developing a psychological treatment for parents of CCSs who experience cancer-related distress. Based on the conceptualization, such treatment should address the maintaining mechanisms, i.e., internal and external avoidance of cancer-related stimulus and low engagement in potentially reinforcing activities.



*Figure 4.* Conceptualization of cancer-related psychological distress in parents of survivors of childhood cancer in Study IV. Red arrows indicate the traumatic stress pathway; green arrows indicate the depressive symptoms pathway. Dashed lines indicate maintaining behaviors, i.e., SEBs.

## Study V

Overall, the recruitment, data collection, and delivery of the treatment appeared feasible and acceptable to participants. Of the 15 participants included in the study, all but one completed the treatment, representing a treatment retention rate of 93%. Follow-up assessment was completed by all participants indicating that the treatment and the study procedures were acceptable to participants. Furthermore, the treatment seemed to be safe to use as only two minor increases in the outcomes of primary interest at post-assessment (one participant reported an increase by four points on the PCL-C and one partici-



pant reported an increase by one point on the MADRS-S), and as there was no increases on the PCL-C or the MADRS-S at follow-up compared to baseline.

Participants reported significant improvements on all outcomes from baseline to follow-up assessment. For the outcomes of primary interest (PTSS, symptoms of depression, and symptoms of anxiety) reductions from baseline to follow-up assessment were all significant at least at the level of  $p < .01$  and effect sizes were in the medium to large range ( $d = 0.69-1.30$ ). Mean values and standard deviations for all measures at baseline, post-assessment, and follow-up assessment are presented in Figure 5. At baseline eight participants (53%) fulfilled the criteria for at least one psychiatric diagnosis, compared to three (20%) at post-assessment and three (20%) at follow-up assessment. At baseline, major depressive disorder was the most common diagnosis (criteria fulfilled by seven participants), followed by PTSD (criteria fulfilled by four participants). At post- and follow-up assessment, no participant fulfilled the criteria for either major depressive disorder or PTSD.

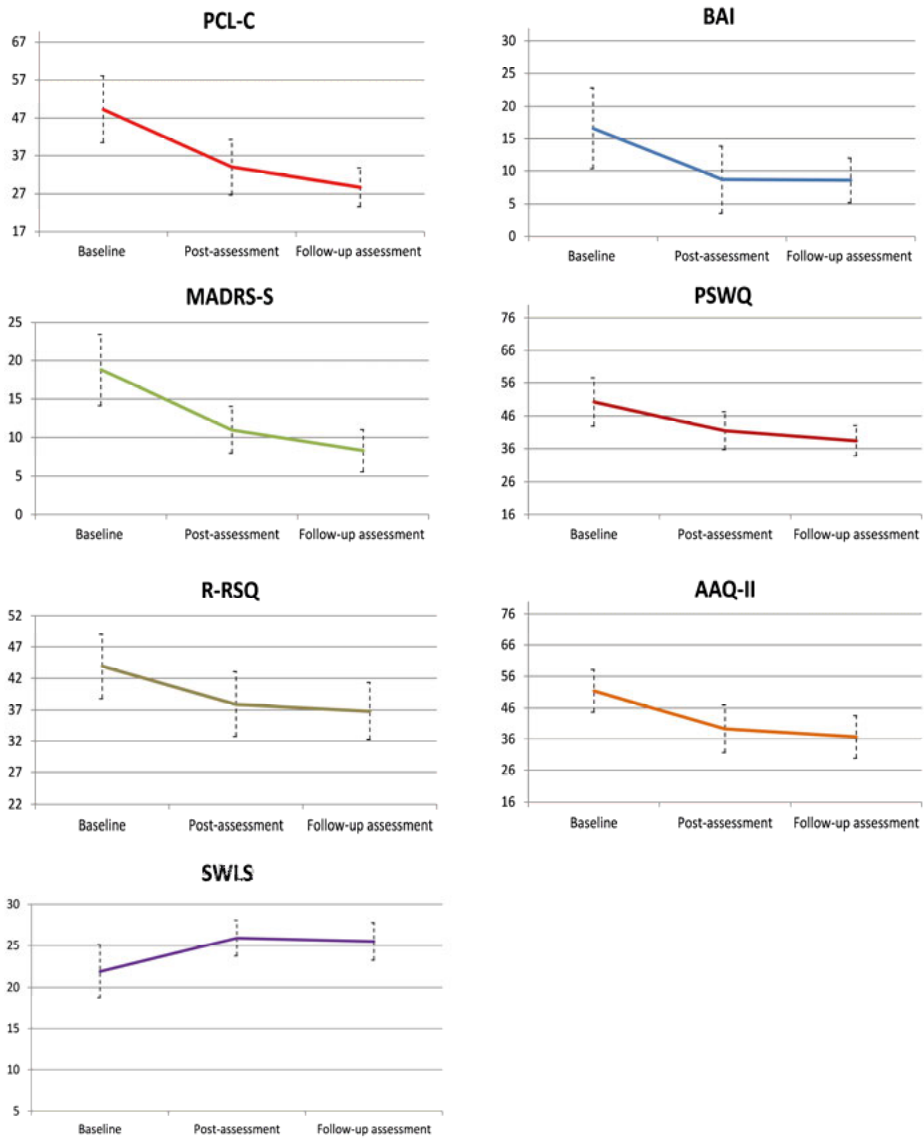


Figure 5. Mean values and standard deviations on all measures at baseline, post-assessment, and follow-up assessment in Study V (N=15). Dashed lines represent standard deviations.

# Discussion

## Main findings

### Long-term psychological consequences

One of the aims of this dissertation project was to increase the knowledge about the long-term psychological consequences in parents of children diagnosed with cancer, including parents of survivors and bereaved parents. In Study I the literature on long-term psychological consequences in parents of CCSs was synthesized and results revealed that while worry, anger, sorrow, fear, and marital strains were reported, levels of psychological distress were in general within normal ranges. However, a substantial subgroup reporting clinical levels of general psychological distress and/or high levels of PTSS was identified; general psychological distress was reported by 20-30% and high levels of PTSS by 21-44%. Importantly, the quality analyses conducted pointed to methodological limitations in the previous studies, mainly related to a risk of selection bias. A conclusion from Study I was therefore that firm knowledge e.g., regarding the size of the subgroup reporting high levels of psychological distress was precluded due to a risk of selection bias in the reviewed studies. In Study II the development of PTSS, and the prevalence of full and/or partial PTSD, was examined in parents of children diagnosed with cancer, from shortly after diagnosis up to long-term survivorship or aftermath of a child's death. Study II had a longitudinal design, a large sample including both mothers and fathers, and high response- and retention rates, and did thus not include the methodological shortcomings identified in the previous literature. For parents of CCSs the estimates of PTSS/PTSD, at the assessments corresponding to timing of assessments in Study I, were in general lower than in Study I. In Study II, 16% of the mothers and 15% of the fathers reported at least partial PTSD one year after end of treatment, and 19% of the mothers and 8% of the fathers reported at least partial PTSD five years after end of treatment. Due to the lower risk of bias in Study II, these estimates were assumed to be more accurate. It has been argued previously (e.g., Phipps et al., 2015) that prevalence rates of PTSS/PTSD in parents of children with cancer have been overestimated due to methodological limitations in studies. Our results give some support to such a conclusion.

The design of Study II allowed examination of development of PTSS over time and results demonstrated that the levels of PTSS decrease over time from

the child's diagnosis, however, that the decline abates. The results from Study II furthermore identified the time directly after end of the child's treatment as a time of particular vulnerability. This pattern has been suggested in the previous literature (Wakefield et al., 2011), however was for the first time validated in Study II.

In Study II PTSS/PTSD was also examined in bereaved parents. Bereavement following the loss of a child in cancer has been suggested to imply a traumatic form of grief (Barrera et al., 2009; Rosenberg et al., 2012). Studies assessing PTSS/PTSD in this population have however been lacking. The results from Study II showed high levels of PTSS and high prevalence of potential PTSD among bereaved parents. Nine months after the death of the child, 89% of the mothers and 55% of the fathers reported at least partial PTSD. Five years after the death of the child these figures were 20% for mothers, and 35% for fathers. Over time, the prevalence of potential PTSD decreased among bereaved mothers, but not among bereaved fathers. Future research, using larger samples, should examine PTSS/PTSD further in parents of children lost to cancer to determine if there is an interaction effect between parental gender and time. Importantly, results from Study II support the assumption that grief in this population has traumatic implications. In a previous study, the prevalence of prolonged grief disorder was estimated to 10% in parents of children lost to cancer (mean time since child's death=4.5 years) (McCarthy et al., 2010). Our results indicate that PTSD may occur at similar, or even higher, prevalences in this population. It was beyond the scope of this dissertation work to conduct in-depth analyzes of psychological distress following the death of a child to cancer. However, future research should explore symptoms of psychological distress in this population further and determine the occurrence and prevalence not only of PTSS/PTSD, but also of symptoms of grief, depressive symptoms and potentially other dimensions of the distress.

In Study III parents' particularly negative and positive experiences were identified. Negative experiences related to past and/or present events were reported by 65% of parents of CCSs and 78% of bereaved parents. Negative experiences related to the past concerned distressing events; healthcare; own reactions; surrounding institutions; and the fact that the child got cancer. The category distressing events included experiences labelled as potentially traumatic in previous research in this population (Bruce, 2006). The other categories included negative or adverse experiences related to the time of the child's illness which additionally may be of significance to parents in a long-term perspective. E.g., were the reports of previous own reactions an interesting finding, pointing to the potential benefit of offering psychological treatments to help parents to cope with their emotional reactions during time of the child's treatment. Negative experiences related to the present situation pointed to ongoing stressors for parents of children previously treated for cancer and highlighted the long-lasting impact of childhood cancer for parents. The prevalence and intensity of the negative experiences identified in Study III and the

effect of these on parental well-being however needs to be further explored in upcoming studies.

With regard to positive psychological consequences, Study I only identified very few studies exploring this phenomenon and therefore, even though some aspects of PTG were reported, conclusions could not be drawn with regard to the nature or prevalence of these. In Study III, positive experiences were explored in a broader sense and the findings demonstrated that the great majority of the parents reported such experiences; 90% of parents of survivors and 78% of bereaved parents. These experiences were related to past events or to the present situation. Positive experiences related to the past concerned healthcare; support systems; the outcome of the treatment; and unexpected joy. Unexpected joy involved answers such as having got to spend time with the sick child and the family, and intense moments of joy during the hospital stay. Such experiences have almost exclusively been overlooked in the previous literature which has focused on the adverse aspects of parenting a child on treatment for cancer. Positive experiences related to the present situation involved improved relationships; long-term consequences for the child; and personal development. Personal development and improved relationships can be seen as aspects of PTG. Answers regarding positive long-term consequences for the child could be descriptions of a similar phenomenon occurring in the child. Future studies should explore the concept of PTG further in this population, and other positive experiences in relation to a child's cancer disease, to determine their relationship with overall psychological functioning. It has been argued that promoting positive psychological outcomes in parents of children with cancer is just as critical as minimizing negative ones (Rosenberg et al., 2013). Future research examining these experiences further will provide important knowledge to reach such an end.

## Development of a psychological treatment for parents of CCSs

Another aim of this dissertation project was to take the first steps towards developing a psychological treatment for parents of CCSs who suffer from high levels of cancer-related psychological distress. This aim was mainly reached by Study IV and V however findings from Study I-III informed the process. The MRC guidelines (Craig, 2008; Craig et al., 2013) state that careful identification of the existing evidence, preferably by using systematic reviews, should precede the development of a new treatment. Study I was conducted as a mean towards this end. Study II investigated PTSS/PTSD in parents of children with cancer, and Study III shed light on the content of the particularly negative and/or positive experiences involved in parenting a child with cancer. The MRC guidelines highlight the need for a clear rationale for the treatment, including how the therapeutic changes are expected to be achieved. A key task in the beginning of the process of developing a treatment is therefore to generate a theoretical understanding of the likely process of

change (Craig, 2008; Craig et al., 2013). Since such an understanding was lacking for cancer-related psychological distress in parents of CCSs, we conducted Study IV. The conceptualization generated in Study IV included hypotheses on pathogenic mechanisms to target in a treatment for this group. In Study V, the treatment based on the individual case formulations (aggregated in Study IV) was evaluated with regard to feasibility and preliminary effect.

In Study IV a conceptualization of cancer-related psychological distress in parents of CCSs was generated. The conceptualization suggests that this distress consist of symptoms of traumatic stress and symptoms of depression, and that these symptoms are developed and maintained by two separate but overlapping pathways. These findings should be related to the ongoing debate on how to best conceptualize and understand psychological distress in this population (Kangas, 2013; Phipps et al., 2015). Of interest is that all participants in Study IV and V reported symptoms of traumatic stress, which supports previous literature suggesting PTSS to be a relevant symptomatology in parents of CCSs (Bruce, 2006). We did however also observe high degree of overlap with depressive symptoms (11 of the 15 participants also reported depressive symptoms). This finding can be discussed in relation to the psychological sequelae seen in other populations exposed to prolonged and repeated traumatic experiences. After experiences where the victim has been exposed to serious threat to life or integrity whilst being in a state of captivity, unable to flee, over a prolonged period of time e.g., traumatic prison stays, repeated sexual abuse, and domestic violence, a specific type of PTSD called complex PTSD has been reported (Cloitre et al., 2011). The symptoms characterizing complex PTSD are high levels of general distress, somatic symptoms, dissociation (including thought and emotion suppression), and affective changes (Herman, 1992; Resick et al., 2012). The features of complex PTSD resembles our findings regarding the psychologically relevant stressors involved in parenting a child with cancer (exposure to repeated adverse events and change of context implying and reduced contact with positive reinforcement and low degree of control over own activities, see Figure 4), and has clear parallels to the symptoms that we identified. One could argue that cancer-related psychological distress in parents of CCSs might be phenomenologically more similar to complex PTSD than simple PTSD, but importantly, likely presents with milder symptoms. Our findings in Study I, II, IV and V all point to the fact that parents of children with cancer experience symptoms of traumatic stress. The experiences of long-term psychological consequences mentioned in Study III also resembled symptoms of traumatic stress (e.g., intense anxiety when reminded of the child's disease). However, in the diagnostic nomenclature used today (the DSM-5), parenting a child with cancer is not included as an event qualifying for PTSD. It is important that future research determine how cancer-related distress best can be conceptualized, and what diagnostic entity it should be denoted to enable adequate recognition and treatment.

The conceptualization suggested in Study IV is the first cognitive behavioral conceptualization of cancer-related psychological distress in parents of CCSs. This conceptualization can be seen as a complement to the PMTS-model for psychological reactions in parents of children with serious illnesses (Kazak et al., 2006; Price et al., 2016). In the PMTS-model the third phase refers to long-term traumatic responses occurring after end of active medical treatment. The PMTS-model does however not include specifications with regard to how these responses are developed and maintained, and does not specify mechanisms to be targeted in treatment. Our conceptualization provides such hypotheses regarding symptom development and maintenance, and thus gives clear guidance for treatment. The maintaining mechanisms that we suggest are well documented in the literature, and interventions targeting them have been proven effective in other populations (Baer, 2003; Hedman et al., 2011; Martell et al., 2001; McLean & Foa, 2011). The preliminary evaluation of these interventions for parents of CCSs in Study V showed promise in terms of symptom reduction; however, it is up to future studies to corroborate the conceptualization and the effect of a treatment derived from this.

An important result from Study V is that the recruitment, data collection, and administration of the psychological treatment were conducted with relative ease, indicating that the study procedures and the treatment were acceptable and engaging to participants. These results contradict results from previous psychological treatment trials with parents of children newly diagnosed with cancer, which have struggled with low recruitment and retention rates (e.g., Cernvall et al., 2015). This may indicate that the timing of the treatment in Study V, i.e., when the child no longer is on cancer treatment, is more suitable to parents. The recently published evaluation of feasibility and acceptability of the online group intervention developed by Wakefield et al. (2016) for parents of young cancer survivors reported similar findings. This intervention was reported to be highly acceptable and feasible, supporting the conclusion that psychological treatments might be suitable for parents after end of the child's cancer treatment. The high retention rate in Study V may also reflect the high degree of individualization in terms of the treatment content and length of the treatment. Further development of a psychological treatment for this population should consider whether a treatment protocol should include elements of flexibility.

It is important to stress that the conceptualization generated in Study IV at this stage merely is based on hypotheses and that future studies are needed to determine the clinical value of this conceptualization. Such studies could preferably use a variation of designs e.g., interview studies exploring the SEBs identified in Study IV both during the time of the child's illness and after end of treatment. Structured assessment of these behaviors should also be conducted and such studies should consider development of a specific instrument for assessment. Development of an instrument for assessment of the specific symptoms of psychological distress in this population should also be consid-

ered, which is in line with suggestions in the stage model for behavioral therapies (Rounsaville et al., 2001). Further, parents of CCSs who do not experience psychological distress could be interviewed and assessed to identify the adaptive strategies involved in resilience outcomes. Also, longitudinal studies examining depressive symptoms, PTSS and the suggested pathogenic mechanisms over the child's full disease trajectory should be conducted to determine the causal relationships between these. Importantly, a psychological treatment targeting the suggested maintaining mechanisms in the conceptualization should be evaluated in future controlled studies to determine its efficacy and clinical effectiveness. In our research group, a project that is an elongation of the results from Study IV and Study V has been launched; ParentsCan. This project aims at developing an easily accessible online treatment manual for parents of children previously treated for cancer on the basis of the conceptualization of distress formulated in Study IV and in close corporation with parents of children previously treated for cancer. The results from ParentsCan will provide further information about the clinical value of the conceptualization, and of the effect of an online treatment based on the hypothesized mechanisms involved in distress in this population.

## Methodological considerations

The studies in this thesis used various designs and data collection methods. This can be considered as methodological triangulation, which has been related to increased confidence in research data, innovative ways of understanding a phenomenon, revealing of unique findings, and to provision of a clearer understanding of a problem (Thurmond, 2001). Thus, the variation of designs, data collections, and analytic methods can be considered as important strengths of this thesis work. There are however also methodological concerns which should be addressed. First, it is important to recognize that the samples used in Study II and III were drawn from the same cohort. Study IV and V were also based on the same participants. This should be kept in mind when interpreting the results since potential bias in these samples will affect results in both studies. It has been suggested that analyzing data from the same participants more than once should be made with caution since it can lead to biased estimates, exaggerated accuracy, and false impressions of e.g., treatment effect and safety (Choi et al., 2014). Even though unique data was used in all the studies, this issue should be acknowledged. Specific methodological considerations of the respective studies are presented below.

### Study I

In Study I reference lists of included studies were screened to identify additional studies possibly omitted in the data base searches. As many of the in-



cluded studies were old, it could have been beneficial to also conduct a “forward citation tracking” procedure. By using this procedure studies that have cited an article are identified, which could have resulted in additional studies found and included in the review. Furthermore, we choose to assess quality by combining the quality criteria for observational studies developed by Leboeuf-Yde and Lauritsen (1995) and the assessment tool QUALSYST (Kmet et al., 2004). A benefit of using tools and pre-designed scales is that a total score can be generated for each study and for each assessed item. This enables a comparison between studies and allows identification of risk of bias in the combined reviewed literature. An alternative scoring method could however been applied by which different weights had been assigned to different items. If such a scoring method had been used, risks of important biases such as selection bias would have been more eminent in the results. Also, we chose to include all studies in the review regardless of their level of quality. The methodological shortcomings of these studies may therefore impede the validity of the results from the review. We chose to include all studies due to the limited numbers of studies in this field, however, the methodological shortcomings identified in the studies was an important result from Study I per se.

## Study II and III

Study II and III addressed several of the methodological limitations in the literature identified in Study I. In Study II and III the samples were large, included about 50% of fathers, and the inclusion and retention rates were high. Still, at the last assessment attrition may have resulted in a more biased sample. Also, the number of bereaved parents was low, precluding firm conclusions regarding this population.

In Study II, the level of PTSS and prevalence of PTSD was assessed by self-reports without confirmation by a structured diagnostic interview. However, the PCL-C has shown high diagnostic effectiveness in this population when using the symptom criteria method (Manne et al., 1998). Also, even though the number of participants was relatively high, there might be a power issue precluding detection of a decline in level of PTSS between T5 and T7. The analytic method chosen for Study II (LGC-modeling) has benefits such as: enabling inclusion of all available data; adjustment of standard errors due to dependency in data (individuals that were partners provided data); use of unequal time distances between measurement points; and inclusion of time-invariant and time-variant covariates in the model. However, the complexity in this particular data set resulted in statistical challenges. First, the study design implied somewhat different timing of assessment for parents of survivors and bereaved parents. When specifying the LGC-model we used time scores representing the mean distance from end of treatment/child’s death, however, the time scores in the model deviated somewhat from actual observed time, especially for bereaved parents. This should be recognized when interpreting

the results. Furthermore, the low number of bereaved parents precluded a specification of a separate slope factor for this subgroup, and thus development of PTSS over time following the death of the child could not be examined. An important issue regarding Study II is also the limited data regarding psychological distress. It would have been beneficial if data had also been collected on e.g., depressive symptoms, anxiety, worry, and importantly, symptoms of grief for bereaved parents.

In Study III attempts to increase the credibility of the findings were made such as involving several authors in the different steps of the analysis and keeping a dialogue between the authors throughout the analysis. Also, a form of participant validation of the findings was applied (i.e., a parent of a CCSs commented on the analysis and the results) to increase the credibility of the results. To enhance the transferability we provided a rich and detailed presentation of the findings including appropriate quotations. The use of simultaneous transcription of interview answers in Study III is an important limitation which may have resulted in nuances in the answers being overlooked. It is also important to highlight that the experiences that parents acknowledged as particularly negative or positive in relation to past events should be understood in the context of being a parent of a long-term survivor, or several years following the death of the child, and that these are part of the long-term experience.

## Study IV and V

Potential participants for Study IV and V were the total population of parents of children who at study-start had completed a successful cancer treatment three months to five years previously at the Uppsala Akademiska children's hospital. In order to identify those belonging to the subgroup experiencing high levels of psychological distress the question "do you experience psychological distress of any kind that you relate to your child's cancer disease?" was posed. Since there was a lack of knowledge in the previous literature regarding the nature of the psychological distress experienced by the population no cut-off on any specific measure was used. The included participants reported high levels of distress at baseline, indicating that the inclusion procedure successfully identified the target population. However, with increased knowledge on the nature of the distress experienced by the population specific assessments could be developed and used for screening and evaluation of treatment effects. Furthermore, the sample in Study IV and V consisted of almost an equal number of mothers and fathers and had adequate variation in terms of educational level and work status. Taken together, the sample must be considered as a strength of Study IV and V.

In Study IV the ideographic behavioral case formulations were aggregated by a process mainly based on discussions during supervisions. The aims of these discussions were to identify general themes in the case formulations. Steps were taken to increase the trustworthiness of the procedure such as the

summarizing meeting that was held where all case formulations were discussed in relation to the conceptualization. Re-reading of all participant documentation at the end of the process was also done to ensure that no relevant information had been omitted in the conceptualization. To increase the credibility of the results, member checking or respondent validations were used with four participants who also participated in the ParentsCan project. In spite of these strengths there were methodological limitations of the procedures. One important such is that the therapy sessions were not recorded. If this had been done, preferably by video recording, a more structured analysis of the content of the therapy sessions could have been conducted. This could have enabled additional interpretations and conclusions regarding participants' presenting problems and their progress in therapy. It is also important to stress that the conceptualization generated in Study IV was dependent on the interpretations and conclusions made by the individuals working with the study, and thus on the theoretical knowledge and experience that these individuals had. Future research could explore potentially different hypotheses of development and maintenance of symptoms of psychological distress in this population and evaluate the clinical value of these, as well as of the conceptualization presented in Study IV.

For Study V the use of an open trial with a within group design precluded conclusions with regard to treatment effect. It is however important to stress that this was not the aim of the study and that it is up to future studies to evaluate the effect of the treatment. The design of Study V could however have been improved by using more frequent assessments of distress throughout the course of the study to enable studying the development of symptoms throughout the treatments. Feasibility outcomes could also have been formally assessed including assessment of treatment satisfaction and therapeutic alliance. Lastly, interviews regarding these issues with participants after having participated in the treatments could have been conducted to further explore the participants' acceptability of the treatments, and the mechanisms involved in distress and treatment effect.

## Ethical considerations

For Study II, ethical approval of the study procedure, including the process to obtain consent, was obtained in 2002 from the local research ethics committees at the faculties of medicine in Gothenburg, Linköping, Umeå and Uppsala (DNR:02-006). In 2004 the organization of ethical vetting in Sweden changed, from being administered by local ethical research committees to regional ethical committees. The study procedures, including the procedure to obtain oral consent, for Study II and III was approved by the Regional Ethical Review Board in Uppsala in 2008 (DNR: 2008/109). Oral informed consent was collected via telephone and carefully documented; still the lack of written in-

formed consent could be considered an ethical concern with the study procedure. Since data collection was completed over telephone this procedure was however chosen. In Study II, the design with different time points for parents of CCSs and bereaved parents were chosen for ethical reasons where respect for parents recently losing their child was regarded as more crucial than concerns for the research design. Furthermore, reporting PTSS and particularly negative experiences related to the child's cancer could elicit discomfort for parents. Parents were however asked for consent to participate at each assessment point, and were able to decline participation if they perceived participation to cause emotional distress at any assessment. These ethical concerns should be put in relation to not conducting research on parents' psychological reactions in relation to a child's cancer disease which could be considered more unethical, since these reactions thereby would possibly not be adequately recognized and addressed in clinical care.

For Study IV and V ethical approval was obtained from the Regional Ethical Review Board in Uppsala in 2012 (DNR: 2012/440). For Study V we chose an open trial design without the use of a control group which allowed us to offer the treatment to all participants. This can be considered an ethical strength. The results regarding treatment effect though need to be followed up in future controlled research. Furthermore, since there is no EST for this population, we per definition had to provide participants with a treatment which was not empirically supported. We chose to base the specific interventions used in the treatments on individual behavioral case analyses which enabled us to target each participant's specific needs. Also, to assure safety of the treatments careful supervision of the therapies were carried out throughout the course of the study.

## Conclusions

Within this thesis work psychological long-term consequences for parents of CCSs and bereaved parents have been examined. In Study I, PTSS, worry, anger, sorrow, fear, and positive psychological consequences were reported for parents of CCSs. Although levels of psychological distress in general were within normal ranges, subgroups reporting high levels of general psychological distress and/or PTSS were identified. General psychological distress was reported by 20-30% and high levels of PTSS were reported by 21-44%. In Study II levels of PTSS and prevalence of potential PTSD was examined, and results corresponded to the findings in Study I since parents of CCSs overall reported low levels of PTSS, and not were identified as potential PTSD cases. The size of the subgroup reporting at least partial PTSD (at the assessments corresponding to the timing of assessment in Study I) was however somewhat smaller in Study II. This can be related to the risk of selection bias in the previous literature, and the estimates in Study II for parents of CCSs are therefore

considered more accurate. Study II also examined PTSS/PTSD in bereaved parents, and high levels of PTSS/incidence of PTSD were reported for this group pointing to the traumatic implications of grief following the death of a child in cancer. For bereaved fathers, the prevalence of PTSD did not decrease over time which is a finding that should be further explored in future research. In Study III, particularly negative and positive experiences reported by parents of CCSs and bereaved parents were identified. Such experiences were mentioned by the vast majority of parents, and content analyses revealed that these were related to past events or to the present situation. Interestingly, parents reported several positive experiences related to the time of the child's illness. Such experiences have been overlooked in the previous literature, and should be further evaluated in future studies.

In Study IV and V parents belonging to the subgroup reporting high levels of cancer-related psychological distress were included. Both these studies contributed in the process of developing a psychological treatment for parents of CCSs. In Study IV a cognitive behavioral conceptualization of cancer-related psychological distress in parents of CCSs was generated, including a specification of symptom topography and mechanisms involved in maintenance of the distress. In Study V individualized CBT based on the case formulations generated in Study IV was evaluated in terms of feasibility and preliminary effect. Results indicated that the CBT was feasible to participants, and after having completed the treatment participants reported lower levels of PTSS and symptoms of depression and anxiety. In order to continue the process of developing a psychological treatment for parents of CCSs, the hypotheses generated in Study IV and the treatment based on these should be corroborated in upcoming studies. If future research shows that such a treatment is effective, steps should be taken to implement this in the standard after-care of parents of children with cancer. Thus, the process to develop a psychological treatment for parents of CCSs, initiated within this thesis work, has the potential to result in an EST and thereby in important improvement in the care of this population. It is my sincere hope that such a treatment will be available to parents of children with cancer who suffer from long-term cancer-related psychological distress in the future.

# Acknowledgements in Swedish

Att skriva en avhandling är inte alltid lätt. Men har man människor kring sig som vägleder, diskuterar, stöttar, läser, lyssnar, korrläser, och inspirerar så är det i alla fall inte omöjligt. Tydligen. Och till stora delar kan det då även vara riktigt roligt! Jag vill rikta mitt varmaste tack till er viktiga människor vid min sida, professionellt såväl som privat.

*Louise von Essen.* Min huvudhandledare tillika forskargrundsledare och chef. Tack för ditt stöd genom hela mitt doktorandarbete! Du har varit nära involverad i allt det jag arbetat med, du har verkligen tagit dig tid att handleda och att guida i stort som smått. Jag har lärt mig så mycket om forskning från dig. Du är verkligen otroligt bra på att driva projekt framåt, är lyhörd för bra idéer och vågar satsa. Tack!

*Brjánn Ljótsson.* Biträdande handledare och en mycket viktig person för mitt avhandlingsarbete. Tack för alla kloka synpunkter, ditt engagemang, och ditt smittande intresse för psykologi och forskning. Och inte minst, tack för all stöttning och pepp under de här åren, det har betytt väldigt mycket!

*Ata Ghaderi.* Biträdande handledare och en mycket klok och erfaren forskare. Tack för att du tagit dig tid att diskutera teoretiska utvecklingar och hypoteser om psykopatologiska processer, att du gett feedback på projektidéer, och inte minst läst och kommenterat på mina manus och andra texter. Varmt tack!

*Martin Cernvall.* Formellt har du inte varit min handledare vad gäller doktorandarbetet, men i praktiken har du ändå ofta fyllt en sådan funktion. Jag har alltid känt att jag kan fråga dig och vetat att jag får kompetenta och genomtänkta svar. För ibland kan svaret ju faktiskt vara både ja och nej. Tack för de här åren, och jag hoppas verkligen att jag får möjligheten att fortsätta samarbeta med dig framöver!

*Gustaf Ljungman.* Tack för att du introducerade mig till detta intressanta och viktiga forskningsområde. Tack också för att du delat med dig av din kunskap och kompetens, och för att du alltid tagit dig tid att hjälpa mig med mina frågor och funderingar. Ditt stöd under de här åren har betytt väldigt mycket. Tack också för att all hjälp med barnvakteri som skapat viktiga tillfällen för återhämtning.

*Malin Ander.* Tänk hur många mil vi vandrat tillsammans genom de långa korridorerna på BMC för att nå det efterlängtrade kaffet. De här promenaderna har ofta varit det som jag sett fram emot när jag är på väg till jobbet! Du är en oerhört bra kollega; kompetent, generös, varm, intelligent, intresserad och inte minst väldigt trevlig. Samma egenskaper gör dig också till en väldigt bra vän.

*Emma Hovén.* Vad vi har slitit med analyser, revideringar och tabellkorrigeringar. Du är otroligt duktig, klok, effektiv, lätt att samarbeta med och en finfin vän. Jag vill särskilt tacka dig för att du tog hela korrekturen av vårt manus när den dök upp samtidigt som jag satte mig på ett plan mot Berlin. Det (DU) räddade min semester!

*Helena Grönquist.* Tack för att du peppat och stöttat mig under de här åren! Ser mycket fram emot nästa stora utmaning i livet som jag ska ta mig an tillsammans med dig; nio mil på skidor.

*Laura Kukkola.* Det har varit mycket trevligt att dela rum med dig och att få vara med och introducera dig till det här forskningsområdet. Du gör verkligen ett jättebra jobb med det fortsatta arbetet med att ta fram en psykologisk behandling för föräldrar till barn med cancer.

*Sven Alfonsson.* En underfundig, klok och mycket trevlig kollega. Tack för delad doktorandtid och för trevligt häng utanför jobbet!

*Sandra Waara.* Min partner i Petra-studien. Tack för ditt bidrag i denna studie som terapeut, diskussions-partner, och inte minst som den mer begåvade av oss två vad gäller organisation och administration. Det var därtill mycket trevligt att jobba tillsammans med dig!

*Kata och Malin F.* Tack för all hjälp med dokumentering, bokningar, och praktiska frågor i stort och smått. Som till exempel när jag inte kunnat stänga mina fönster på BMC. Tack också för att ni alltid bidragit med trevlig stämning i vårt lilla hörn av korridoren.

Stort tack också till alla ni andra fantastiska kollegor i forskargruppen som på olika sätt varit med och gjort jobbet intressant, meningsfullt och trevligt: *Linda, Fredrika, John, Anders, Erik, Anna, Claudia, Ian, Fabian, Ylva, Kim och Tove.* Tack!

Och så mina vänner utanför jobbet. Först, *Bea Lötstedt.* Min allra bästa vän. Tack för att du lyssnat, analyserat, ifrågasatt, stöttat, skrattat och gråtit med mig i mer än 20 år nu. *Sussie och Elina;* fina, fina kvinnor. Tack för att ni finns. Och sen är ni också många, många till. Ni vet vilka ni är och att ni är viktiga!

*Familjen Ljungman* (alltså den som funnits lite längre tid). *Laila, Gustaf* (igen), *Karin, Lotta och Henke.* Tack för många härliga stunder tillsammans, och verkligen; stort tack för hjälp med barnen. Dom och jag tycker mycket om er!

*Åsa och Ola.* Syster och bror. Mina intelligenta, roliga, vackra och vilda syskon. Tack för alla gånger ni skrattat med, och åt, mig. Jag är så glad att jag numera har er på geografiskt hanterbart avstånd (alltså nära). Ni är ju bäst ju!

*Mamma och pappa.* Först, tusen tack för all hjälp med praktiska saker som verkligen avlastat och underlättat. Ni har vaktat barn, hjälpt till vid flyttar och bil-köp, ni har lagt cykelpunkor, bjudit på resor, stylat lägenheter. Men allra mest, tack för det riktigt viktiga: att ni tar så fantastiskt bra hand om mina barn, precis som ni gjorde och fortfarande också gör, om mig.

*Gudrun.* Tack för att du varit en solstråle i mitt liv, att du alltid har mött mig med ett leende och fått mig att känna mig viktig. Fina, kloka, varma, mormor!

*Siri och Nils.* Tack för att ni så obarmhärtigt krävt min fulla uppmärksamhet, att ni så sällan uppmuntrat mig att prata om jobbet, och för att ni alltid påmint mig vad som är viktigt på riktigt. Siri och Nils, mina älskade ungar. Nu åker vi till Spanien och lämnar ”boken” hemma!

*Markus.* Den intelligentaste, roligaste, varmaste, vackraste och bästa människa jag känner. Tack för att jag får dela familjeliv, föräldraskap, äktenskap och galenskap med dig. Nu är vi dr Ljungman och dr Ljungman!

Slutligen, till alla föräldrar som deltagit i studierna i det här avhandlingsarbetet: stort tack för att ni så modigt och generöst delat med er av era erfarenheter.



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