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Systematic Review of Psychosocial Morbidities among Bereaved Parents of Children with Cancer

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Abstract

The objective of this review was to comprehensively summarize existing studies utilizing validated instruments to measure psychosocial outcomes among bereaved parents of children with cancer. This population has increased risks of anxiety, depression, prolonged grief, and poor quality of life. Parental morbidity is associated with psychiatric co-morbidities, prior loss, economic hardship, duration and intensity of child's cancer-therapy, perceptions of medical care, child's quality of life, preparedness for and location of the child's death. Rigorous, prospective research is needed to identify risk-groups, define outcomes and design interventions which will improve parental outcomes after the death of a child due to cancer.

Keywords

Cancer; Parents; Bereaved; Palliative Care; Outcomes; Review

Introduction

Previous research has demonstrated that bereaved parents have the most intense grief reactions when compared to bereaved spouses or adults who lose their parents [1,2]. Not only do bereaved parents have increased risks of long-term psychosocial morbidities including anxiety, depression, suicidal ideation, prolonged grief, poor quality of life and poor social function [3], but their morbidities may persist 15 years following the death of their child [4]. Theoretical causes of this pronounced grief-response include the disruption of the natural life-order [5], parental guilt and feelings of failure [6], as well as the profound disruption of the family structure following the death of a child [7].

Nearly 20% of pediatric patients with cancer will die from their disease, and cancer remains the third-leading cause of death among children older than 1 year of age [8,9]. Parents of

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Conflict of Interest Statement

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children with cancer are often exposed to the prolonged physical and emotional suffering of their children; however, they may have more time to prepare for their child's death. It is unclear if the distinctive cancer-experience translates to unique psychosocial morbidities.

The primary objective of this review was to comprehensively summarize existing studies utilizing validated instruments to measure psychosocial outcomes among bereaved parents of children with cancer. Secondary objectives were to systematically evaluate the literature to identify areas for future research and intervention.

Methods

Medline, Embase, CINAHL and PsychInfo were searched using the term "[bereaved parent*] AND (neoplasm* OR cancer*)." The reference lists from relevant review articles and all eligible studies were also hand-searched. Studies were eligible if they included a population of bereaved parents of children with cancer, if the children were younger than 20 years-old at the time of death, and if the study utilized validated instruments to measure psychosocial outcomes. Studies of any methodology, including cross-sectional and longitudinal designs, were eligible; however, qualitative and other studies without validated instruments were excluded. The title and abstract of all citations obtained through the search strategy were screened and full-texts were obtained for potentially eligible studies.

Included studies were sorted by comparison groups as follows: those with no comparison group, those comparing bereaved to non-bereaved parents, and those with sub-group comparisons within populations of bereaved parents of children with cancer. Information was also collected regarding study design, follow-up period, measured psychosocial outcomes, instruments used, informant-source, as well as pertinent conclusions.

Results

Of the 121 initially identified studies, 102 failed to meet inclusion criteria based on abstract/title alone and 19 were potentially eligible. Of these, 6 were ultimately excluded because they either did not include validated instruments, assessed the immediate end-of life experience, assessed the initial diagnostic experience, or evaluated parents' reactions to the death of an adult child. Thirteen studies remained for qualitative synthesis (Figure 1).

Studies without Formal Comparison Groups

Four of the included studies had no formal comparison group (Table I) [10–13]. Rando first performed a cross-sectional analysis to describe the individual grief experiences of 54 parents (27 married dyads) 2 months-to-3 years following the death of their children from cancer (mean follow-up times were not reported) [10]. Study instruments were the Greif Experience Inventory (GEI) and the Parental Experience Assessment Form (PEAF). One of the first instruments to be used in bereavement research, the GEI is a 12-item, self-reported, objective tool to assess an individual's grief experience [14]. The PEAF was designed by the study authors to provide a comprehensive evaluation of parents' perceptions of factors such as social support, prior loss and coping, hospital staff interactions and satisfaction thereof, as well as parental behaviors during and after the child's illness [15]. Findings suggested that a child's duration of illness related to ultimate parental distress; parents of children whose cancer experience was shorter than 6 months or longer than 18 months had poorer adjustment. Previous loss was associated with worse outcomes and anticipatory grief was inversely related to abnormal grief responses. Data suggested that parental distress may intensify over time; some parents reported worse outcomes at the 3-year mark compared to those surveyed at the 2-month mark. Poor or abnormal responses were not well defined.

Later studies described bereaved parents' outcomes in comparison to normative population data [11,12]. Moore et al. cross-sectionally surveyed 75 bereaved parents approximately 24-months after their child's death and assessed current psychological and somatic symptomatology with the Symptom Checklist-90 (SCL-90) [11]. This self-administered instrument measures current psychological symptom-status in a broad array of clinical and medical contexts. It has good internal consistency and reliability (Cronbach's alpha 0.77–0.90) [16]. Bereaved parents tended to report more symptoms of anxiety and depression than population norms, but fewer than those of known psychiatric out-patients. Covariates were not described; however, the authors postulated that the observed differences may be related to "death-related events" or demographic information such as parent age or sex. Birenbaum et al. used the Duke-UNC Health Profile to longitudinally evaluate the general health status of 80 bereaved parents 2-weeks, 4- and 12-months after their child's death [12]. The Duke-UNC Health Profile is a self-administered, Likert-scale based instrument which measures physical, emotional and social function with good internal consistency (alpha 0.77–0.92) [17]. Results from this study suggested that bereaved parents' health did not differ significantly from normative adults. Unfortunately, only 28 parents completed all study-assessments, raising the question of a bias among those families willing to continue on-study compared to those who declined. Again, covariates were not described and authors suggested that demographic data such as education, income, age, sex and geographic location might affect outcomes.

McCarthy et al. described the prevalence and possible predictors of prolonged grief and depression in a cross-sectional study of 58 parents, an average of 4.5 years after their child's death from cancer [11]. Study instruments included the Inventory of Complicated Grief-Revised (ICG-R) and the Beck Depression Inventory-Second edition (BDI-II). The ICG-R is a self-report scale measuring clinical symptoms of prolonged grief disorder. It has considerable diagnostic power (sensitivity 0.93, specificity 0.93), and good internal consistency (alpha 0.94) [18]. The BDI-II is a self-report scale which assesses respondent depressive symptoms and includes threshold scores to grade their severity. Studies performed in bereaved populations have demonstrated high internal consistency (alpha 0.91) [19]. Forty-one percent of bereaved parents met diagnostic criteria for separation distress, while 10% of met full criteria for prolonged grief disorder. Twenty-two percent experienced clinically significant depressive symptoms. Time since death and parent-perception of the child's medical care predicted patterns of grief and depression. Furthermore, parent perceptions of the child's quality of life during the last month, preparedness for the child's death, and economic hardship were associated with both grief and depression.

Bereaved Compared to Non-Bereaved Parents

Three studies described outcomes among bereaved versus non-bereaved parents (Table I) [20–22]. Kriebel et al. used the Swedish National Registry to cross-sectionally evaluate 449 bereaved parents of children with cancer, plus 457 parents of well-children, matched by the child's age, sex, and region of residence [20]. Bereaved parents were surveyed 4–9 years following the death of their child (mean follow-up times were not reported). Instruments included the State-Trait Anxiety Inventory (STAI-T), the Center for Epidemiological Studies Depression Scale (CES-D) and the visual digital scale (VDS, Swedish Clinical Cancer Epidemiology Group).

The STAI-T is a self-report assessment of trait anxiety symptoms. It attempts to distinguish between anxiety and depression and has good internal consistency (alpha 0.86) [23]. The CES-D scale is a self-report scale designed to measure depressive symptoms in the general population. It has good sensitivity (0.80) and good overall consistency (alpha 0.88) [24]. Finally, the VDS uses visual keys to measure respondents' subjective symptoms of anxiety, depression, quality of life and psychological well-being. The scale correlates with

quantitative instruments for anxiety or depression ($r = 0.5\text{--}0.8$) [25]. In this study, bereaved parents had increased risks of self-reported anxiety (RR 1.5, 95% CI 1.1–1.9) and depression (RR 1.4, 95% CI 1.1–1.7). In comparison to parents 7–9 years beyond the child's death, those 4–6 years following the death had greater risks of low psychological well-being (RR 1.4; 95% CI 1.2–1.7) and poor quality of life (RR 1.3, 95% CI 1.1–1.5). Findings suggested the risk of psychosocial morbidity was greater in the first 4–6 years of bereavement and approached population standards in the 7–9 year period.

Two studies compared different populations of parents of children with cancer [21,22]. Morrow et al. performed a cross-sectional study using the Psychosocial Adjustment to Illness Scale (PAIS) [21]. It is unclear if the authors used the self-report or clinical interview format of this instrument which is designed to assess the psychological and social adjustment of family members to a patient's illness (alpha 0.86) [26]. Comparison groups consisted of 37 bereaved and 50 non-bereaved parents, including 28 whose children were still receiving cancer-directed therapy. Follow-up times were not reported. Bereaved parents demonstrated poorer adjustment than non-bereaved parents across all domains including family relationships, domestic, and social environments. Authors did not describe PAIS scores known to define poor adjustment. Norberg et al. conducted a longitudinal study to assess post-traumatic stress with the PTSD Checklist Civilian Version (PCL-C) among 35 bereaved and 185 non-bereaved parents at several time-points beginning at the time of diagnosis [22]. The PCL-C consists of subscales corresponding to the three symptom clusters of PTSD, according to the Diagnostic and Statistical Manual of mental disorders (DSM)-IV: re-experience (alpha 0.88), avoidance (alpha 0.82) and hyperarousal (alpha 0.89) [27]. Bereaved parents were assessed 1 year following their child's death; non-bereaved parents were assessed either 1 or 1.5 years after completing therapy, depending on the type of cancer-therapy the child had. Overall, 20% of mothers and 13% of fathers were identified as potential cases of PTSD; however, among bereaved parents, the rates were 53% and 33%, respectively. Bereaved parents' PTSD severity was positively associated with avoidance of disease and treatment-related stimuli at the time of their child's diagnosis ($r = 0.52$, $p < 0.001$) and early in therapy ($r = 0.36\text{--}0.47$, $p < 0.05$).

Bereaved Parents of Children with Cancer: sub-group comparisons

Six, cross-sectional studies described outcomes among sub-groups of bereaved parents of children with cancer (Table I) [28–33]. Goodenough et al. stratified bereaved parents by those whose child had died in the hospital ($n = 20$) versus those whose child had died at home ($n = 30$) and assessed depression, anxiety, and stress (DASS 21), complicated grief (ICG,) and family function (FAD) approximately 4.4 years following the child's death [28]. The DASS-21 is a self-report instrument providing clinically normalized scores on separate subscales for depression (alpha 0.71), anxiety (alpha 0.79), and stress (alpha 0.81) [34]. The FAD is a Likert-scale designed to assess overall family functioning (alpha 0.80–0.92) [35]. Other covariates for this study were not clearly defined. Parents whose child died in hospital were significantly more likely to meet criteria for complicated grief. In-hospital death was associated with significantly higher ratings of depression, anxiety and stress among fathers but not mothers. Place of death was not significantly associated with family functioning.

Three additional studies used the above-mentioned Swedish National Registries population of approximately 450 bereaved parents 4 to 9 years after the death of their children with cancer (mean follow-up times were not provided) [29–31]. Lannen et al. reported that 26% of this cohort subjectively “had not worked through their grief” [29]. Using the STAI-T, CES-D and VDS instruments described above, authors found that parents with unresolved grief reported significantly higher rates of anxiety (fathers: RR 4.9, 95% CI 2.2–10.8; mothers RR 3.6, 95% CI 2.0–6.5), depression (fathers: RR 4.3, 95% CI 2.1–8.9; mothers: RR 2.4, 95% CI 1.3–4.2), worsening psychological health (fathers: RR 3.6, 95% CI 2.0–6.4;

mothers: RR 2.9, 95% CI 1.9–4.4) and physical health (fathers: RR 2.8, 95% CI 1.8–4.4; mothers: RR 2.3, 95% CI 1.6–3.3). Among parents with unresolved grief, fathers reported significantly higher rates of sleep difficulties (RR 6.7, 95% CI 2.1–17.8); whereas, mothers reported significantly higher rates of physician visits (RR 1.7, 95% CI 1.1–2.6), and greater use of sick leave (RR 2.1, 95% CI 1.2–3.5).

Using the same instruments, Valdimarsdottir et al. aimed to determine whether the duration of parental awareness of a child's impending death due to cancer affected long-term morbidity [30]. Parents with intellectual awareness (implying rational acceptance of the child's prognosis) shorter than 24 hours ($n = 112$) were more likely to meet criteria for anxiety (RR 1.7, 95% CI 1.1–2.9) and to report symptoms of depression (RR 1.4, 95% CI 1.1–2.0). Parents with emotional awareness (implying psychological acceptance of the child's prognosis) shorter than 24 hours ($n = 195$) were more likely to report symptoms of anxiety (RR 1.6, 95% CI 1.1–2.2), depression (RR 1.5, 95% CI 1.1–2.0), or poor physical health (RR 1.1, 95% CI 1.0–1.3).

Jalmsell et al. retrospectively surveyed the same population using the VDS to assess the relationship between parents' perceptions of their child's unrelieved symptoms and their own long-term psychological well-being [31]. Bereaved parents who perceived their children as anxious endorsed greater psychological distress themselves, as reflected in higher rates of anxiety (RR 1.6, 95% CI 1.1–2.4); depression (RR 2.0, 95% CI 1.3–3.0), decreased psychological well-being (RR 1.6, 95% CI 1.2–2.0); and decreased quality of life (RR 1.5, 95% CI 1.2–1.8).

Two cross-sectional studies stratified sub-groups based on whether or not the child received hematopoietic stem cell transplant (HSCT) as part of his/her cancer-directed therapy [32,33]. Drew et al. used the DASS-21, ICG, FAD (described above), as well as the Core Bereavement Inventory (CBI) to study 28 parents of HSCT recipients compared to 28 non-recipients [32]. The CBI can assess the intensity and evolution of bereavement experiences among bereaved parents and has good internal consistency ($\alpha 0.91$) [36]. Parents of HSCT recipients had higher rates of anxiety than parents of non-recipients (35% versus 25%, respectively, $p = 0.039$). There were no significant differences in rates of depression or stress. Among parents of HSCT recipients, those whose child died in the hospital reported significantly higher ratings for depression, anxiety, and stress. Similarly, grief scores were significantly higher among those whose child received HSCT and died in the hospital.

Jalmsell et al. again used the above Swedish Registry and the STAI-T, CES-D, and VDS to assess the effect of HSCT on bereaved parents' psychological well-being [33]. Parents whose child underwent HSCT reported higher rates of anxiety (RR 1.5, 95% CI 1.0–2.1), lower quality of life (RR 1.4, 95% CI 1.2–1.7), poor psychological well-being (RR 1.3, 95% CI 1.1–1.5) and poor physical health (RR 1.9, 95% CI 1.1–1.5). Parents whose children had multiple HSCTs (versus one HSCT) had higher rates of anxiety (RR 3.5, 95% CI 1.5–8.2), symptoms of depression (RR 3.4, 95% CI 2.1–5.4), poor quality of life (RR 1.6, 95% CI 1.4–1.9), poor psychological well-being (RR 1.5, 95% CI 1.2–1.9) and poor physical health (RR 1.9, 95% CI 1.4–2.6).

Discussion

This systematic review confirms that bereaved parents have increased risks of poor psychosocial outcomes relative to other parents. Parents of children who die from cancer have elevated rates of anxiety, depression, prolonged grief, poor psychological well-being, poor physical health, and poor quality of life. Two studies found that bereaved parents have worse adjustment and higher rates of PTSD than parents of cancer survivors; however,

studies did not report other comparisons between those two groups. Similarly, this review did not find evidence to compare bereaved parents of children with cancer to other bereaved parent populations. Factors associated with psychosocial morbidity include parental history of loss, economic hardship, duration and intensity of the child's cancer-therapy, perception of medical care and the child's quality of life, location of death, as well as time since the child died. The included studies confirm that parents tend to do worse when they have less preparative time before their child's death, or if they have dual morbidities, such as prolonged grief as well as anxiety.

The included studies raise several new questions. Rando's findings suggest an optimal adjustment time for parents facing the death of their child from cancer [10]. Those whose child was ill for less than 6 months may not have had enough time to prepare for the death; whereas those whose child was ill for longer than 18 months may have been more adversely affected by the prolonged duration of their child's treatment and related suffering. Likewise, the particular morbidities assessed in these studies are diversely defined. McCarthy et al. reported that 10% of bereaved parents of children with cancer met criteria for prolonged grief [13], while Lannen et al. reported that 26% subjectively had "not worked through their grief" [29] and Rando described "abnormal grief" without formally quantifying or defining it [10]. Some investigators dichotomize outcomes (i.e., to the presence or absence of anxiety), while others use continuous instrument scores to evaluate associations. Not all studies report raw scores or quantitative values that could be broadly interpreted. In sum, there is little consensus regarding which of these methodologies are more informative.

Other methodological differences abound. First, studies used several different comparison groups. Moore et al. not only compared bereaved parents to well population norms, but also compared them to adults with documented psychiatric illness [11]. Kreicbergs et al. compared bereaved parents of children with cancer to parents of living, well children [20]. It remains unclear whether the increased risks of anxiety and depression among cancer parents is due to the child's death, the cancer experience, or both. Morrow et al. compared bereaved parents to those of surviving children both on- and off-therapy for cancer, but did not distinguish between the stresses of the cancer experience itself, completing therapy or losing a child to the disease [21]. Such distinction would be useful because previous studies have demonstrated that parents of survivors may also have increased rates of psychosocial morbidity [37]. Finally, Jalmsell et al. performed sub-analyses to compare parents of children who received multiple hematopoietic stem cell transplants to those whose children received a single transplant [33]. It is unclear if the increased risks seen in the multiple-transplant group are due to the trauma of relapsed disease, additional intensive therapy, or another unmeasured covariate.

This review highlights several challenges in the bereavement literature, especially among bereaved parents in the cancer setting. There is comparatively less research on long-term bereavement adaptation compared with that regarding the immediate end-of-life experience, including the elements of child suffering [38–40], child communication [41], physician communication [42,43], professional and social support [44], as well as advanced care planning [45]. Additionally, there is a rich qualitative literature base that does not rely on validated instruments [46–48]. There is a relative paucity of rigorous, multi-centered prospective research regarding long-term parent or family outcomes following the death of a child to cancer. Indeed, much of the data are descriptive, and/or from retrospective, cross-sectional studies.

There are several limitations to this review. First, despite the number of publications, there were, in fact, only a few distinct populations surveyed. Several papers were derived from the same Swedish Registry [20,30–33]. Similarly, two studies drew from the same Australian

database of cancer patients [28,29]. Our selection criteria deliberately limited the review to studies which used a validated instrument to assess psychosocial outcomes. The initial rationale for this design was to enable pooling of findings for a quantitative meta-analysis. Unfortunately, upon full review of the selected manuscripts, it became clear that such analyses were not possible given the diversity of measurements and reporting styles. The review therefore missed several critical and valuable papers which describe parental perspectives without formal instrumentation [39, 42–48]. Finally, the challenges that are pervasive in this literature, including small sample sizes and mixed methodologies, make it more difficult to draw strong conclusions.

This review has important implications for clinical practice and underscores an opportunity for further study. Parents of children with cancer have a unique experience which incorporates their child's prolonged physical and emotional suffering and the possibility of preparative time before their child's death. Factors associated with parental morbidity are many, including their baseline perceptions, on-going medical experiences and the timing of psychosocial evaluations. Investigations must be prospective and longitudinal so that true causal inferences can be made between these potential predictors and ultimate outcomes. Such work may inform who is at risk and may identify resilience factors that protect from psychological morbidities and consequent family disruption.

This type of research will continue to be challenging. Parents of children with cancer may be overwhelmed or distressed and less willing to participate. Death from pediatric cancer is becoming less common; this success makes the evaluable population of bereaved parents comparatively small. Likewise, it may not be feasible to prospectively follow all newly-diagnosed pediatric cancer families. Initial research may target the more discrete group of parents of children with progressive or refractory cancer. These children are at comparatively higher risk of death from their disease and their families may have had more time to prepare for the possibility of death. Further studies may elucidate outcomes that are not only unique in this population, but which also may be amenable to interventions. Ultimately, this research should enable the improvement of parent and family outcomes following the devastating experience of a child's death due to cancer.

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Figure 1.
Flow diagram of study selection and review.

Summary of Included Studies

Table 1

Study	Population (n =)	Comparison Group (n =)	Study Design	Follow-Up	Measured Outcome (Instrument); All by self-report	Results
Brenbaum et al. [12]	Bereaved parents (n = 80; 47 mothers, 33 fathers)	Normative adult data (n = 395; 295 women, 100 men)	Longitudinal	2 weeks, 4- and 12-months after child's death	General health status (Duke-UNC Health Profile);	Bereaved parents' health did not differ significantly from a normative group of adults on the emotional and symptoms scales. Bereaved mothers' social health was significantly lower than that of the normal group.
Drew et al. [32]	Bereaved parents whose child received HSCT as part of cancer therapy (n = 28)	Bereaved parents whose child did not receive HSCT (n = 28)	Cross-Sectional	Mean 4.2 years after child's death (SD not reported)	Depression, Stress and Anxiety (DASS-21); Bereavement Experience (CBI); Prolonged Grief (ICG); Family Function (FAD);	Parents of HSCT recipients reported higher rates of anxiety than parents of children who did not receive HSCT (35% versus 25%, respectively). Among parents whose child received HSCT, those whose child died in the hospital had significantly higher ratings for depression, anxiety, and stress. Among parents whose child died in the hospital, grief scores were significantly higher among those whose child received HSCT.
Goodenough et al. [28]	Bereaved parents whose child died in the hospital (n = 20; 10 mother-father dyads)	Bereaved parents whose child died at home (n = 30; 15 mother-father dyads)	Cross-Sectional	Mean 4.4 years after child's death (SD 2.1 years)	Depression, Stress, and Anxiety (DASS-21); Prolonged Grief (ICG); Family Function (FAD);	For fathers, those whose child died in hospital rather than at home reported significantly higher ratings of depression, anxiety and stress. For mothers, there were no statistically significant differences as a function of place of death. Place of death was not significantly associated with family functioning. Parents whose child died in hospital were significantly more likely to meet criteria for complicated grief.
Jalmsell et al. [31]	Bereaved parents whose child was affected by anxiety during the last month of life (n = 263)	Bereaved parents whose child was not affected by anxiety during the last month of life (n = 137)	Cross-Sectional	4-9 years after child's death (mean not reported)	Anxiety, depression, psychological well-being and quality of life (VDS);	Bereaved parents whose children were affected by anxiety had greater risks of anxiety (RR 1.6, 95% CI 1.1-2.4); depression (RR 2.0, 95% CI 1.3-3.0), decreased psychological well-being (RR 1.6, 95% CI 1.2-2.0); and decreased quality of life (RR 1.5, 95% CI 1.2-1.8).
Jalmsell et al. [33]	Bereaved parents whose child received HSCT as part of cancer therapy (n = 97)	Bereaved parents whose child did not receive HSCT (n = 336)	Cross-Sectional	4-9 years after child's death (mean not reported)	Anxiety (STAI-T & VDS); Depression (CES-D & Visual Digital Scale); Psychological well-being & Physical health (VDS); Quality of Life (VDS; Goteborg Instrument);	Parents whose child underwent HSCT reported higher rates of anxiety (RR 1.5, 95% CI 1.0-2.1), lower quality of life (RR 1.4, 95% CI 1.2-1.7), poorer psychological well-being (RR 1.3, 95% CI 1.1-1.5) and poorer physical health (RR 1.9, 95% CI 1.1-1.5). Parents whose children had multiple HSCTs (versus one HSCT) had higher rates of anxiety (RR 3.5, 95% CI 1.5-8.2), symptoms of depression (RR 3.4, 95% CI 2.1-5.4), poorer quality of life (RR 1.6, 95% CI 1.4-1.9), poorer psychological well-being (RR 1.5, 95% CI 1.2-

Study	Population (n=)	Comparison Group (n=)	Study Design	Follow-Up	Measured Outcome (Instrument); All by self-report	Results
Kreicbergs et al. [20]	Bereaved parents (n = 449; 251 mothers, 191 fathers, 7 unknown)	Non-bereaved parents of well-children, matched by child's age, sex, and region of residence (n = 457; 266 mothers, 191 fathers)	Cross-Sectional	4–9 years after child's death (mean not reported)	Anxiety (STAI-T & VDS); Depression (CES-D & VDS); Psychological well-being (VDS), Quality of Life (VDS);	1.9) and poorer physical health (RR 1.9, 95% CI 1.4–2.6). Bereaved parents had increased risks of anxiety based on self-assessment (RR 1.5, 95% CI 1.1–1.9). Bereaved parents had increased risks of depression based on self-assessment (RR 1.4, 95% CI 1.1–1.7) and CES-D (RR 1.4, 95% CI 1.0–2.0). The risk of anxiety and depression was higher in the period 4–6 years after bereavement than in the 7–9 years period. In the 4–6 years period, bereaved parents had greater risk of low psychological well-being (RR 1.4, 95% CI 1.2–1.7) and low quality of life (RR 1.3, 95% CI 1.1–1.5)
Lannen et al. [29]	Bereaved parents with unresolved grief (n = 116)	Bereaved parents who had "worked through" their grief (n = 333)	Cross-Sectional	4–9 years after child's death (mean not reported)	Anxiety (STAI-T & VDS); Depression (CES-D & VDS); Psychological well-being (VDS), Quality of Life (VDS);	Parents with unresolved grief reported significantly higher rates of anxiety (fathers: RR 4.9, 95% CI 2.2–10.8; mothers: RR 3.6, 95% CI 2.0–6.5), depression (fathers: RR 4.3, 95% CI 2.1–8.9; mothers: RR 2.4, 95% CI 1.3–4.2), worsening psychological health (fathers: RR 3.6, 95% CI 2.0–6.4; mothers: RR 2.9, 95% CI 1.9–4.4) and physical health (fathers: RR 2.8, 95% CI 1.8–4.4; mothers: RR 2.3, 95% CI 1.6–3.3). Among parents with unresolved grief: fathers reported significantly higher rates of sleep difficulties (RR 6.7, 95% CI 2.1–17.8); whereas mothers reported significantly higher rates of physician visits (RR 1.7, 95% CI 1.1–2.6), and greater use of sick leave (RR 2.1, 95% CI 1.2–3.5).
McCarthy et al. [13]	Bereaved parents (n = 58; 84% mothers)	None	Cross-Sectional	1.0–9.8 years after child's death (mean 4.5 years)	Prolonged Grief (ICG-R); Depression (BDI-II);	10% of bereaved parents fulfilled criteria for prolonged grief disorder; 22% reported clinically significant depressive symptoms Time since death and parent perception of child's medical care predicted parental grief, but not depression. Perception of child's quality of life during the last month, preparedness for the child's death, and economic hardship were associated with both grief and depression.
Moore et al. [11]	Bereaved parents (n = 75; 45 mothers, 30 fathers) representing 58 families	Normative non-patient and psychiatric adult data (n = 1002; 577 women, 425 men)	Cross-Sectional	24-months after child's death	Current psychological and somatic symptoms (SCL-90);	Bereaved parents' symptoms (including somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, and hostility) were significantly greater than normal populations, but less than psychiatrically diagnosed outpatients.

Study	Population (n=)	Comparison Group (n=)	Study Design	Follow-Up	Measured Outcome (Instrument); All by self-report	Results
Morrow et al. [21]	Bereaved parents (n = 37)	Non-bereaved parents of children with cancer (n = 50; 28 on-therapy; 22 off-therapy)	Cross-Sectional	Not Reported	Psychosocial adjustment (PAIS);	Bereaved parents demonstrated poorer adjustment than non-bereaved parents across all domains including family relationships, domestic environment, health care orientation and social environment.
Norberg et al. [22]	Bereaved parents (n=35, 17 mothers, 18 fathers)	Non-Bereaved parents of children with cancer (n=185, 94 mothers, 91 fathers)	Longitudinal	1 year following child's death; 1–1.5 years after end-of-therapy for survivors	Post-traumatic stress (PCL-C);	Post-traumatic stress among bereaved parents was positively associated with avoidance at the time of their child's diagnosis ($r = 0.52$, $p < 0.001$) and early in therapy ($r = 0.36$ – 0.47 , $p < 0.05$). Avoidance early on during a child's treatment seemed to be a greater risk factor for post-traumatic stress for bereaved than non-bereaved parents.
Rando [10]	Bereaved parents (n= 54; from 27 married couples)	None	Cross-Sectional	2-months to 3-years after child's death (mean time not reported)	Individual grief experience (GEL, PEAFF);	Parents of children who were ill < 6 months or >18 months had poorer adjustment. Previous loss tended to be associated with poorer outcomes. Anticipatory grief was inversely related to "abnormal" grief responses. Parental bereavement may intensify over time.
Valdimarsdottir et al. [30]	Bereaved parents with short "awareness times" (n = 112 for intellectual, n = 195 for emotional awareness)	Bereaved parents with longer "awareness times" (n = 324 for intellectual, n = 238 for emotional awareness)	Cross-Sectional	Mean 6.4 years after child's death (SD 1.7 years)	Anxiety (STAI-T & VDS); Depression (CES-D & VDS); Physical Health (VDS), Quality of Life (VDS);	Parents with "intellectual awareness" of child's impending death < 24 hours were more likely to meet criteria for anxiety (RR 1.7, 95% CI 1.1–2.9) and to report symptoms of depression (RR 1.4, 95% CI 1.1–2.0). Parents with emotional awareness < 24 hours were more likely to report symptoms of anxiety (RR 1.6, 95% CI 1.1–2.2), depression (RR 1.5, 95% CI 1.1–2.0), or poor physical health (RR 1.1, 95% CI 1.0–1.3). Fathers with short awareness times had increased risk of depression (RR 2.1, 95% CI 1.2–3.7) and use of sick leave (RR 8.5, 95% CI 1.1–67.8); Mothers had increased risk of anxiety (RR 2.2, 95% CI 1.2–3.9).

HSCT: Hematopoietic Stem Cell Transplant; DASS-21: Depression, Stress and Anxiety Scale-Short Form; CBI: Core Bereavement Inventory; ICG: Inventory of Complicated Grief; FAD: Family Assessment Device-General Functioning Scale; VDS: Visual Digital Scale; STAI-T: State-Trait Anxiety Inventory; CES-D: Center for Epidemiological Studies Depression Scale; RR: Relative Risk; ICG-R: Inventory of Complicated Grief-Revised; BDI-II: Beck Depression Inventory-Second Edition; SCL-90: Symptom Checklist 90-Revised; PAIS: Psychosocial Adjustment to Illness Scale; PCL-C: Post-Traumatic Stress Disorder Checklist Civilian Version; GEL: Grief Experience Inventory; PEAFF: Parental Experience Assessment Form