Predisposing, Precipitating, Perpetuating, and Protective Factors Related to Distress in Family Members of Children with Cancer: A Systematic Review

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Thesis Abstract

Background

This systematic review aimed to identify factors related to psychological distress in family members of pediatric cancer patients on active treatment.

Methods

Search strategies were entered into six academic databases. Randomized, nonrandomized, quantitative descriptive and mixed method studies, examining factors related to psychological distress in the population of study were included. Identified factors were coded as *per* the 4P's of case formulation.

Results

59 studies were included. Parental factors identified: 24 predisposing factors; 12 precipitating factors; 35 perpetuating factors; and six protective factors. Sibling factors identified: five predisposing factors; one precipitating factor; 14 perpetuating factors; and two protective factors. A text-based, narrative synthesis and tabular summaries are presented.

Discussion

Findings can support the: (1) recognition of distress exhibited in family members; and (2) the timing of interventions specific to the chronological manifestations of distress. Assessment of risk of bias was not done.

Other

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List of Abbreviations

ACTH	Adrenocorticotropin
AMSTAR II	A Measurement Tool to Assess Systematic Reviews II
BMA	Bone Marrow Aspiration
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GVHD	Graft Versus Host Disease
FCR	Fear of Cancer Recurrence
FCC	Family Centered Care
HPA	Hypothalamic Pituitary Adrenal
HSCT	Hematopoietic Stem Cell Transplant
ICNP	International Classification for Nursing
LP	Lumbar Puncture
NANDA-I	North American Nursing Diagnosis Association International
PIPOH	Population, Intervention, Professionals, Outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PROSPERO	International Prospective Registry for Systematic Reviews
PTSD	Post-traumatic stress disorder
PTSD-RI	Post-traumatic Stress Disorder Reaction Index
PTSS	Post-traumatic stress symptoms
RCT	Randomized Control Trial
SCL-90	Symptom Distress Checklist

TBI	Total Body Irradiation
TSST	Trier Social Stress Test

Chapter One

Introduction

Introduction

Cancer is the second leading cause of death in Canadian children (Statistics Canada, 2015). Pediatric malignancies account for an estimated 23 deaths per million each year in Canada (Statistics Canada, 2015), and 80,000 deaths annually worldwide (American Childhood Cancer Organization, 2018). From 2009 to 2013, Canadian children and adolescents under the age of fourteen received a diagnosis of cancer at an estimated rate of 943 new cases per year (Canadian Cancer Society, 2017). Worldwide, approximately 300,000 cases of cancer are diagnosed in children and adolescents less than nineteen years of age each year (American Childhood Cancer Organization, 2018).

Advances in medical treatment over the last several decades have resulted in an increase in overall survival rates for children and adolescents diagnosed with cancer (Landier & Bhatia, 2008; Shepherd & Woodgate, 2010), and current estimated five-year survival rates in developed countries exceed 80% (Alderfer et al., 2010; Hudson et al., 2014; Tran et al., 2017). However, pediatric cancer survivors carry a high burden of morbidity (Landier & Bhatia, 2008; Tran et al., 2017). Exposure to antineoplastic agents potentiates the risk of subsequent iatrogenic complications: neurocognitive and growth deficits; disfigurement; functional impairment; neuroendocrine dysfunction; organ dysfunction; secondary malignancy; and psychosocial maladaptive processes (Bauld et al., 1998; Hile et al., 2014; Landier & Bhatia, 2008; Li et al., 2013; Meadows, 2006). Psychological consequences of the disease, including anxiety disorders, post-traumatic stress symptoms (PTSS), depression, and fear of cancer recurrence (FCR) are prevalent in children with cancer (American Psychiatric Association, 2013; Crist & Grunfeld, 2013). Pediatric oncology patients are therefore at risk of developing chronic medical problems that incite or worsen psychological or social difficulty requiring ongoing medical intervention

(Landier & Bhatia, 2008).

Indeed, pediatric cancer challenges the entire family system (Fainsilber Katz et al., 2018a; Fainsilber Katz et al., 2018b; Van Schoors et al., 2016). Therefore, the primary focus of this thesis was to explore the psychological impact of cancer on family members of children with cancer on active treatment.

Pediatric Cancer and the Family

The definition of family has evolved over recent decades to encompass the multiplicity of postmodern relational patterns, a distinct shift from the rigid obligations of the conventional nuclear family, focusing instead on the reality of the individual (Walsh, 2012). The family is recognized as a separate, social entity, with a unique structure, function, and set of requirements (Hallac & Oz, 2014). The perception of family and its functions vary, and in turn, may shape the identities of each individual family member (Hallac & Oz, 2014). For the purposes of this review, family encompasses parents, foster parents, surrogates, aunts and uncles, grandparents, and siblings.

In an attempt to incorporate the fluidity of family values into pediatric health initiatives, the philosophy of family centered care (FCC) was founded on the conviction that the family is a constant in children's lives (Harrison, 2010). The goal of FCC is not only to promote the physical aspects of health in children, but to also foster healthy emotional and psychological development that occurs within the context of the family (Harrison, 2010). The FCC philosophy highlights the importance of the family on the child's developmental processes and outcomes (Harrison, 2010) by extending the biopsychosocial definition of cure to all family members (Alderfer et al., 2010).

In the case of pediatric cancer, the child and their family are regarded as microsystems

with reciprocal patterns of effects (Long & Marsland, 2011; Kazak et al., 2003), which influence the child's developmental outcomes (Long & Marsland, 2011). There is a growing body of evidence to suggest that distress exhibited in parents of children with cancer is significantly correlated with a child's psychological health (van Warmerdam et al., 2019). Disruptions to the family, that impact on the child, may occur at multiple levels: (a) individual day-to-day experiences; (b) routines; (c) roles; (d) responsibilities; (e) relationships; and (f) functioning (Ostadhashemi et al., 2016; Van Schoors et al., 2016). The economic implications of pediatric malignant disease are also a cause for concern. Accrued medical and non-medical expenses (Dockerty et al., 2003), employment-related disruptions for caregivers (Miedema et al., 2008), and loss of annual income all contribute to the significant financial burden incurred by pediatric oncology patients and their families (Bemis et al., 2015; Tsimicalis et al., 2011; Warner et al., 2015).

Distress in Families of Children with Cancer

Definitions of psychological distress within the literature vary considerably (Gundelach, 2016; Vrijmoet-Wiersma et al., 2008). Psychological distress is conceptualized as an overarching construct comprising the specific domains of; depression, anxiety, PTSS, and somatization (Buchbinder et al., 2011; Ozono et al., 2010). This definition has also been used to conceptualize distress in the family members of pediatric cancer patients (Sultan et al., 2016; van Warmerdam et al., 2019).

Studies indicate that parents demonstrate increased distress within one year of their child's diagnosis, while approximately 27% of parents suffer from clinical levels of psychological distress up to five years post the initial diagnosis of pediatric cancer (Vrijmoet-Wiersma et al., 2008). In addition, a significant subset of siblings of children with cancer exhibit

internalizing symptoms (i.e., anxiety and depression), negative emotional reactions, and diminished quality of life (Alderfer et al., 2010; Prchal & Landolt, 2009). Specifically, an estimated 50-75% of siblings of children with cancer exhibit moderate to severe PTSS (Long et al., 2018). However, adolescent and young adult siblings of children with cancer also report posttraumatic growth, with estimates of mental health service use to achieve growth in range from 8 to 15% (Long et al., 2018).

Currently, a body of literature examining correlates of family distress within the context of malignant pediatric disease exists (Dahlquist et al., 1993; Knafl et al., 2013; McKenzie & Curle, 2012; Ostadhashemi et al., 2016; Sultan et al., 2016; Tsimicalis et al., 2011). To date, a small number of systematic reviews have been conducted in an attempt to collate and synthesize this literature. The most recent of these was a meta-analysis conducted by van Warmerdam et al. (2019). Study objectives were: (i) to determine the prevalence of anxiety, depression, and post-traumatic stress disorder (PTSD) in parents of children with cancer; and (ii) to ascertain whether the prevalence of anxiety, depression, and PTSD differed by parental gender or distinct phase of the pediatric cancer experience (i.e., active treatment, survivorship, bereavement). Prevalence data in 15 studies for anxiety, depression, and PTSD in 9262 parents of children with cancer across 14 countries were pooled. The pooled prevalence of anxiety was 21%, depression was 28%, and PTSD was 26%. Gender subgroup analyses showed that mothers had a higher pooled prevalence of depression than fathers but no significant difference in the prevalence of anxiety and PTSD was noted between mothers and fathers. Phase subgroup analyses showed depression in parents of children on active treatment did not increase significantly versus depression in bereaved parents and PTSD in parents of children on active treatment did not significantly exceed PTSD in parents of pediatric cancer survivors. Subgroup analyses also revealed

significant heterogeneity within the pooled prevalence of anxiety, depression, and PTSD. This is said to be consistent with the heterogeneity observed across study methodologies, underscoring a need to accurately measure distress within this population. Factors influencing distress manifest pre diagnosis and those occurring over time were not examined. Critical appraisal of the review using A Measurement Tool to Assess Systematic Reviews II (AMSTAR **II**) **(**Shea et al., 2017) is shown in Appendix **A** Table 1A. A detailed appraisal of the review is also presented in Appendix A Table 2A. Limitations of the review include absence of an adequate investigation of publication bias and its subsequent impact on the results of the review. Despite this, the meta-analysis obtained a high rating across the following AMSTAR II evaluation criteria: the research question and inclusion criteria included the components of PICO; review methods were established a priori; an explanation of selection of study design was stated; study selection and data extraction was performed in duplicate; eligible studies were described in adequate detail; appropriate methods for statistical combination of results were implemented; and an in depth discussion of heterogeneity of study findings was done.

Another systematic review by Sultan et al. (2016) examined factors and consequences of parental distress as related to childhood cancer (AMSTAR II-based appraisal available in Appendix **A** Table 1A). A detailed appraisal of the review is also summarized in Appendix A Table 3A. Study objectives were to: (i) conduct a synthesis of current literature on predictors and moderators of psychological distress in parents (i.e., mothers and fathers) of children or adolescents (< 18 years of age) diagnosed with cancer; and (ii) synthesize knowledge pertaining to the outcomes of emotional distress exhibited in this population. This review of 43 studies found the most probable factors of parental distress to be: (a) severity of the condition in the child with cancer and treatment intensity; (b) being a mother; (c) negative affectivity; (d) poor

personal resources; (e) and certain family stressors (e.g., divorce, poor family functioning) pre-diagnosis of cancer in the child. The experience of distress in other caregivers (e.g. foster parents, surrogates, grandparents) and siblings was not examined. Parameters specific to time since the pediatric cancer patient's diagnosis were also not explicit in the review. It is therefore unclear whether factors and consequences of parental distress may be attributed to distinctive phases of the pediatric oncology patient's treatment trajectory (e.g., pre-diagnosis period versus active treatment). In addition, the measures lacked homogeneity across distress domains (Sultan et al., 2016). The review did however yield a relatively high rating across AMSTAR II evaluation criteria. It should be noted that only those studies with a low risk of bias were selected for study inclusion. While findings from excluded reports may be subjected to higher risk of bias, it was acknowledged that results may well prove instrumental to understanding parental distress. Therefore, the authors presented findings from studies excluded on the basis of high risk of bias in a supplementary table.

Past systematic reviews examining the psychosocial repercussions incurred by healthy siblings of children and adolescents with cancer have produced mixed findings, possibly reflective of methodological limitations (i.e., study design, sampling methods, data collection procedures, and small sample size), and heterogeneity of study participants. In 2018, Long et al. conducted a systematic review of 102 studies examining psychosocial functioning and risk factors in siblings of children with cancer (AMSTAR II-based appraisal available in Appendix **A** Table 1A). A detailed appraisal of the review is also presented in Appendix A Table 4A. Parameters specific to time since the pediatric cancer patient's diagnosis were not explicit, thereby hindering understanding of the chronology and etiology of the individuals' presenting symptoms of psychological distress. However, the review demonstrated strong compliance with

AMSTAR II evaluation criteria. The research question and inclusion criteria encompassed each component of PICO, review methods were established a priori, study selection and data extraction was done in duplicate, a list of excluded studies and justification for exclusion was provided, included studies were described in detail, risk of bias of individual studies was assessed, and heterogeneity observed in results of the review was discussed.

Theoretical Framework

The 4Ps of case formulation was applied as a theoretical framework enabling the systematic organization of factors related to psychological distress exhibited in family members of pediatric oncology patients on active treatment (Henderson & Martin, 2014). The 4Ps model of case formulation categorizes an individual's presenting symptom into: (i) predisposing; (ii) precipitating; (iii) perpetuating; and (iv) protective factors (Henderson & Martin, 2014).

Predisposing factors are those that render the individual vulnerable to the presenting symptom (e.g., genetic loading, medical and psychiatric history, sociodemographic variables, socioeconomic variables, and chronic social stressors). Precipitating factors comprise inciting events that may cause the presenting symptom (e.g., trauma). Perpetuating factors are the constellation of features that result in symptoms enduring once they are present. Perpetuating factors may include: (i) the severity of the condition; and (ii) unresolved predisposing and precipitating factors. Protective factors are the available resources and supports, personal strengths, and resilience that prevent a symptom from presenting.

Rationale

International standards of care recommend the systematic assessment the psychosocial needs of childhood cancer survivors (Lown et al., 2015; Wiener et al., 2015). A comprehensive approach to the provision of psychosocial supports to both the child and the family unit is

warranted, as there is evidence to support that childhood cancer survivors and their family members experience lasting psychological effects related to the child's diagnosis and treatment (Barrett et al., 2020). Despite the implications of psychological distress on the psychosocial well-being of family members of children with cancer, no systematic review has reported on a chronology and etiology of the various related factors including those that may be associated with the development and maintenance of this distress, as well as factors protective against its development. Guidelines for psychosocial care in pediatric oncology recommend: (i) early and ongoing assessment of the mental health needs of family members (specifically parents); and (ii) timely access to interventions designed to optimize both parental and family wellness (Kearney, et al., 2015; van Warmerdam et al., 2019). Of crucial importance is an understanding of the temporality and variability of psychological distress within this population (Fainsilber Katz et al., 2018a; Fainsilber Katz et al., 2018b ; Pierce et al., 2017). Knowledge of the variability of psychological distress and its trajectories could: (i) mitigate potential adverse psychological outcomes in family members of children with cancer; and (ii) permit the efficacious allocation of psychosocial resources (Fainsilber Katz et al., 2018a; Fainsilber Katz et al., 2018b; Pierce et al., 2017).

Chapter Two

Methods

Introduction

Objectives and Research Questions

The primary aim of this research was to conduct a comprehensive, systematic search of the literature to identify factors related to psychological distress in family members of pediatric cancer patients on active treatment. Specifically: what are predisposing, precipitating, perpetuating, and protective factors related to self- or observer-reported psychological distress in family members of children with cancer on active treatment? Table 1 shows the population, intervention, professionals, outcomes, and health care setting and context (PIPOH) elements of the research question (The ADAPTE Collaboration, 2009).

Methods

Study Design

For the purposes of this review, a modified Cochrane Methodology for Systematic Review was implemented (Higgins et al., 2022). Reporting for this review is in accordance with the PRISMA checklist (Page et al., 2021). The description and evaluation of interventions to manage psychological distress was not conducted, as the focus of the systematic review was the identification of factors that cause psychological distress to develop and persist and the factors that protect against psychological distress in the population of interest.

For the purposes of this review, the 4Ps of case formulation was applied as a theoretical framework enabling the systematic organization of factors related to psychological distress exhibited in family members of pediatric oncology patients on active treatment (Henderson & Martin, 2014). The 4Ps model of case formulation categorizes an individual's presenting symptom into: (i) predisposing; (ii) precipitating; (iii) perpetuating; and (iv) protective factors (Henderson & Martin, 2014).

Table 1

Research Question: Population, Intervention, Professionals, Outcomes, Health Care Setting and Context (PIPOH) Format

	Description	Inclusion Criteria	Exclusion Criteria
Population	Study participants eligible for inclusion in the present systematic review	Family members (parents, foster parents, surrogates, aunts and uncles, grandparents, and siblings) of pediatric cancer patients (< 21 years) on active treatment	Children with cancer Bereaved family members Family members of end-of-life pediatric cancer patients
Intervention(s) of Interest		Not applicable	Interventions to manage psychological distress
Professionals		Healthcare professionals working in pediatric oncology	
Outcomes		Predisposing, precipitating, perpetuating, or protective factors described in the results section of identified studies as positively or negatively influencing psychological distress as a primary or secondary outcome	Outcomes only reported in the introduction or discussion sections of the manuscript
Health Care Setting and Context		All settings where pediatric oncology care is delivered	

	Description	Inclusion Criteria	Exclusion Criteria
Language		Studies must be published in the English language	
Study Design		Randomized and nonrandomized, mixed methods, and quantitative descriptive studies	Dissertations, book chapters, conference proceedings, non-peer reviewed publications or reports, editorials, qualitative studies and commentaries

Eligibility Criteria

In accordance with The Cochrane Methodology for Systematic Review, the methods used to identify studies eligible for inclusion in this review were developed a priori (McKenzie et al., 2022). Eligibility criteria are outlined in Table 1.

Inclusion Criteria

Studies published in peer-reviewed journals examining distress as a primary or secondary outcome in family members of pediatric cancer patients on active treatment were considered for inclusion.

Study Criteria

Randomized and nonrandomized quantitative, as well as quantitative descriptive and mixed method studies, examining factors related to psychological distress (at both clinical and subclinical levels) in family members of pediatric cancer patients on active treatment were

eligible for inclusion. Only quantitative results from mixed methods studies were included. Psychological distress was operationalized as an overarching construct comprising specific domains: (a) anxiety; (b) depression; and (c) PTSS. Studies must have been published in English and may have been conducted in any setting. Application of a date limit on the initial search of the literature was not done in order to retrieve as many relevant studies as possible (Polit & Beck, 2012).

Distress Measure Criteria

Psychological distress in family members of pediatric cancer patients (all types of cancer) on active treatment (as opposed to those parents of children in survivorship) were examined, as there is evidence to show that distress in family members is greater closer to time of the patient's diagnosis (Fainsilber Katz et al., 2018a; Fainsilber Katz et al., 2018b). Studies that employed an objective behavioral measure, as well as subjective self- or observer-report measure of psychological distress were included in the review.

Family Member Criteria

Family members of children and adolescents less than 21 years of age and on active cancer treatment including caregivers (parents, foster parents, surrogates, aunts and uncles, grandparents, etc.) and siblings were included.

Exclusion Criteria

Studies examining distress in bereaved family members, or family members of end-of-life pediatric oncology patients were excluded as distress related to the loss or anticipated loss of a child may incite protracted grief reactions which are unique to the bereavement process (Lichtenthal et al., 2015). To eliminate the risk of recall bias in the reporting of distress, retrospective reports of caregiver and sibling distress were excluded. Qualitative studies,

dissertations, book chapters, conference proceedings, editorials and commentaries were excluded.

Information Sources

A systematic search of the literature was conducted in the following health related bibliographic academic databases: MEDLINE, CINAHL, EMBASE, PsycINFO, ERIC, and Cochrane Library from the date of database inception to May 25, 2018 (Lefebvre et al., 2022). Separate search strategies and search terms were developed for each academic database by two authors who are oncology nurses (MM and LJ) and a librarian working at an academic institution and specializing in the field of health sciences (LS).

Search strategy

The Cochrane Handbook of Systematic Reviews for Interventions guided the development of the search strategies (Lasserson et al., 2022; Lefebvre et al., 2022). Search strategies for all databases are presented in Appendix B. Sample articles of interest were supplied to the librarian by MM prior to the development of the search strategy to help establish keywords for the search strategy. An initial draft of the search strategy was conducted in MEDLINE and pilot tested. Pilot testing involved MM and LJ independently screening 200 titles and abstracts and finding the strategy to appropriately identify articles of interest (including those related to parental distress in pediatric cancer that the authors knew to be published). No changes to search strategies for any database were made following this pilot.

Study Records

Data Management

The titles and abstracts of articles retrieved from all database searches were uploaded to Covidence (Lefebvre et al., 2022). Covidence (https://www.covidence.org/) facilitates web-based

collaboration among screeners during the study selection process. Covidence was used to remove duplicate retrieved articles and to manage records throughout the review process.

Training was provided to members of the review team not familiar with Covidence or the content area prior to the review process. Training consisted of a brief 20- to 30-minute session and was led by MM and LJ. A digital presentation detailing the proposed research question, study design, population of interest, primary outcome variables, and theoretical framework (i.e., the 4Ps model of case formulation) were made accessible to review members electronically (i.e., *via* email). Review members were also given access to a screening guide created by MM (see Appendix C Table 1C), which included: (a) a table depicting the research question in PIPOH format; (b) a list of both inclusion and exclusion criteria; and (c) a section describing application of the theoretical framework. Review members were then: (a) introduced to Covidence; and (b) required to conduct a trial screening of approximately five to 20 articles with either MM or LJ present to ensure familiarity with the content and technology platform was achieved.

Selection Process

Titles and abstracts of the articles retrieved were independently screened by two authors (either MM, MG, LM or LJ) (Lefebvre et al., 2022). Disagreements regarding study inclusion were resolved through discussion with a third author (Lefebvre et al., 2022). Full-text reports that appeared to meet the inclusion criteria were then examined independently by two authors (either MM, MG, LM or LJ) to determine compliance with explicit eligibility criteria. Decision making reliability for inclusion decisions was evaluated. Specifically, inter-rater agreement was assessed by calculating the kappa statistic (Lefebvre et al., 2022). Disagreements regarding study inclusion at the full-text screening step were also resolved through discussion with a third author (Lefebvre et al., 2022). Rationale for the exclusion of each full-text study was recorded

(Lefebvre et al., 2022). See Appendix D.

Data Collection Process

A data extraction form (formatted in Excel) and coding manual was developed to guide authors in extracting relevant information regarding study characteristics (Li et al., 2022). The data extraction form was pilot tested using a sample of five studies selected for inclusion (Li et al., 2022). Two authors conducted data extraction and coding of information independently to reduce errors and the introduction of potential biases (Li et al., 2022). Disagreements were resolved through discussion with a third author (Li et al., 2022). It was agreed that in the event any uncertainties arose, the authors of included studies would be contacted, but this situation did not occur.

Data Items

The following methodological data items were coded for each included study: (a) data source, (b) study country, (c) language, (e) study design, (f) methods, and (g) source of funding. Characteristics of family members, as well as characteristics of the associated child with cancer, were also encoded. Specifically, data on the following items was collected: (a) age, sex, diagnosis, and treatment variables of children with cancer; and (b) age, sex, developmental stage, education level, language, culture, religion, residence (i.e., urban / rural), employment status, socioeconomic status, marital status, access to health services, and health literacy level of sibling(s) and caregiver(s). Type of caregiver (e.g., parent, guardian, foster parent, grandparent) were recorded. Data items described in the results section of identified studies as being positively or negatively associated with psychological distress (i.e., depression, anxiety, PTSS, and somatization) in family members of children with cancer on active treatment were recorded.

Risk of Bias in Individual Studies

Given the aim of this review was to include studies with an array of study designs, and the intent was always to include all studies that met inclusion criteria, quality appraisal of each individual study was not done.

Meta-bias(es)

Because studies of multiple designs that do not traditionally publish *a priori* protocols (e.g., studies other than RCTs) were included in this review, it was not possible to accurately assess risk of publication bias and selective reporting outcomes.

Analysis and Synthesis of Outcomes

The primary outcome for this systematic review comprised variables related to psychological distress in family members of children with cancer on active treatment. Variables related to psychological distress were coded as *per* pre-defined definitions of the 4P's of case formulation within the context of pediatric cancer (Henderson & Martin, 2014). Predisposing factors are those factors reported in the study as being present prior to a diagnosis of cancer in the child, and may include age, gender, medical and psychiatric history, and sociodemographic, and socioeconomic variables of the family (Kazak et al., 2012; Knafl et al., 2013). Precipitating factors are those that arise from the time a child is diagnosed with cancer to the initial onset of distress in the family member. Precipitating factors may include contextual factors associated with the initial diagnosis of cancer, and outcome favorability of the child (i.e., prognosis) (Knafl et al., 2013; Sultan et al., 2016). Perpetuating factors are those that contribute to the chronicity of psychological distress past its initial onset. Perpetuating factors may include treatment variables (e.g., treatment duration and intensity, the patient's exposure to central nervous system directed therapies), as exposure to anti-neoplastic agents associated with curative treatment potentiates

the incursion of subsequent iatrogenic complications (e.g., neurocognitive and growth deficits, disfigurement, neuroendocrine dysfunction, organ dysfunction, secondary malignancy, and psychosocial maladaptive processes) (Bauld et al., 1998; Landier & Bhatia, 2008; Meadows, 2006; Li et al., 2013). Acute medical events incurred by the child (e.g., septic shock) also may constitute perpetuating factors. Protective factors, which may present anywhere along the trajectory of pediatric malignant disease, are variables that promote resilience to the development of distress in family members. Protective factors may include innate characteristics (e.g., personal strengths) or those secondary to the individual's environment (e.g., healthcare professional support) (Knafl et al., 2013; Long et al., 2018; Sultan et al., 2016).

Data Synthesis Methods

Relevant evidence congruent with pre-specified eligibility criteria was collated (Page et al., 2021) *per* the 4Ps framework within the context of pediatric cancer (Henderson & Martin, 2014). Two authors (MM and CD) independently perused the results of the included studies. Factors related to psychological distress were identified and encoded as per the pre-defined definitions of the 4Ps of case formulation (Henderson & Martin, 2014). Data (i.e., factors related to psychological distress) were also organized with respect to category of the family member (e.g., sibling, parent, grandparent etc.). Resolution of conflict was done in consultation with a third author, LJ. Given the large number of identified factors, a mean number of factors was created. The calculated mean number of factors was 3.09. Therefore, only those factors with three or more supporting citations were discussed in a text-based narrative synthesis. All other factors were presented in a tabular summary. No meta-analysis was conducted, as the purpose of this systematic review was not to determine effect size.

Strength of the Body of the Evidence

Appraisal of the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was not done. A narrative overview of findings and tabular summaries of extracted data was completed. Appraisal of overall quality of the evidence was not done.

Addendum

Since registration with the International Prospective Register for Systematic Reviews (PROSPERO; CRD42018109802) , there were the following deviations from the study protocol. Initially, qualitative studies were to be included in the review. However, there were only three qualitative studies eligible for inclusion. Given the significant dominance of non-qualitative studies, qualitative studies were later excluded. In addition, quality appraisal of the studies using the Mixed Methods Appraisal Tool (MMAT) was not done (Pace et al., 2012; Pluye et al., 2011; Pluye et al., 2009). The primary aim of this review was to describe what is known of the 4Ps in the context of family members of children with cancer. The intent was to be inclusive of all findings, as opposed to appraising the quality of the studies and excluding those studies that failed to meet a pre-defined cut-off. Therefore, quality appraisal of the included studies was not done. Further, the psychometric properties of each measure of distress were to be evaluated using the Society of Pediatric Psychology assessment task force guidelines (SPP-ATF). However, the intent was always to include all studies that met inclusion criteria. Studies were not to be excluded based on the psychometric properties of the applied distress measure tool(s). Given the scale of this review, it was not feasible to proceed with this step. Finally, factors related to psychological distress identified within the population of interest were to be organized in concordance with Erikson's model of psychosocial development (Erikson, 1963). However,

studies did not report on developmental stage of sample participants. Given that age does not directly correlate with developmental stage, this was not done.

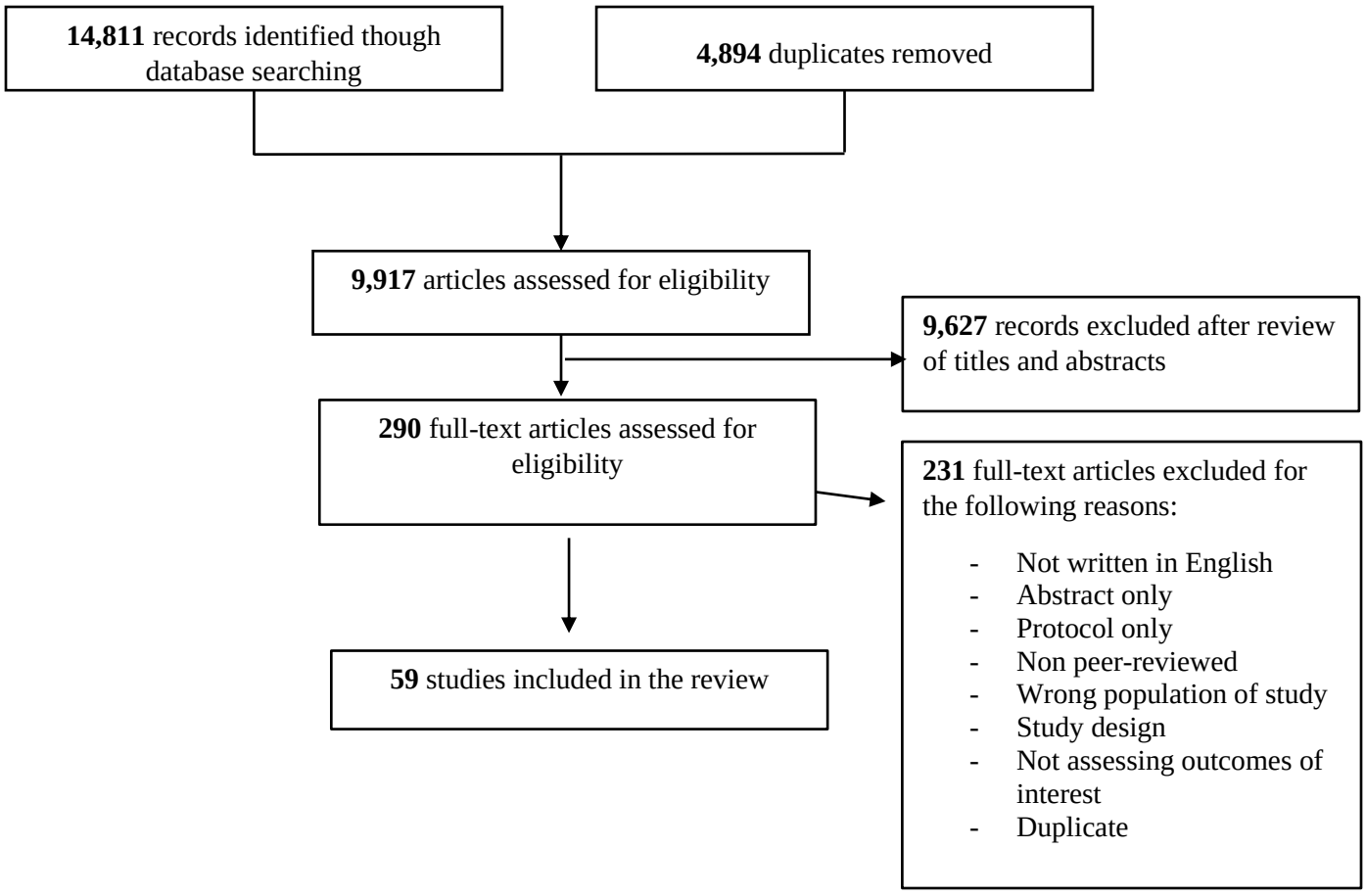
Chapter Three

Results

Results

Abstracts identified through database searches totaled 14,811. A total of 4,894 duplicates were removed. Four authors independently screened 9,917 abstracts against inclusion criteria in duplicate. Two-hundred and ninety full text articles were assessed for eligibility. Of these, 231 full text articles were excluded. Fifty-nine full text articles were included in the review.

Figure 1 PRISMA-P Diagram



Study Characteristics

Study designs include: 54 quantitative descriptive; one randomized control trial; two quantitative non-randomized; and two mixed-methods studies. Included studies reported on 7,703 family members: (i) 7,216 parents (i.e., biological, adoptive, foster, and stepparents) aged 18 to 59 years and (ii) 487 siblings aged seven to 19 years. Additionally, three studies included self-report outcomes for other family members that acted as caregivers for the childhood cancer patient and were categorized as other than parents or siblings (i.e., four aunts, three grandparents, and three 'other'). One study did not report on the number of sample participants. Eight studies did not report on the age of parents included in the sample population. Three studies reported missing data for age of parents included in the sample population (n = 11). This data was included in the systematic review. Study participants were from fourteen countries: Australia (four); Belgium (one); Canada (two); China (three); Egypt (one); Iran (two); Israel (five); Italy (five); Jordan (two); the Netherlands (five); Sweden (five); Taiwan (two); Turkey (two); the United Kingdom (one); and the United Sates (20). Pediatric cancer diagnoses, when reported, included: (i) leukemias (45 studies); (ii) lymphomas (26 studies); (iii) brain tumors (18 studies); (iv) solid tumors (32 studies); (v) tumors of the central nervous system (10 studies); and (vi) 25 studies reported other pediatric malignancies (i.e., germ cell tumors, hepatoblastoma, Wilm's tumor, choriocarcinoma, hematological malignancies, yolk sac tumors, tumors of the sympathetic nervous system, adrenal tumors, optic glioma, and reticuloendothelial neoplasms). Five studies did not report cancer diagnosis.

Outcome Measures

Across the 59 included studies, 37 instruments were implemented to measure distress. Identified distress measures included: (i) seven tools measuring anxiety; (ii) six tools assessing

depression; (iii) five tools assessing post-traumatic stress; (iv) one tool assessing somatization; and (v) 19 tools assessing generalized psychological distress. Thirty-five of these were self-report instruments, and two were observer-report instruments. The range of instruments used in any one study varied from one to six distress measure tools.

Factors Included in the Review

A detailed tabular summary of findings from the included studies is presented in Appendices E and F (see Tables 1E – 4E, and Tables 1F – 4F). A mean number of factors was calculated to determine which factors would be discussed in depth in a text-based, narrative synthesis. The calculated mean was 3.09. Therefore, only those factors with three or more supporting citations are discussed presently in text. All other factors are presented in the included tables.

Parental Factors Included in the Review

A tabular summary of findings from the included studies is presented in Appendix E: parent predisposing factors (Table 1E); parent precipitating factors (Table 2E); parent perpetuating factors (Table 3E); and parent protective factors (Table 4E). A total of 77 parent factors were identified: 24 predisposing factors; 12 precipitating factors; 35 perpetuating factors; and six protective factors. Of these, only those factors with three or more supporting citations are discussed presently in text. All other factors are presented in the tabular summaries.

Parent Predisposing Factors. Those factors that predisposed parents to psychological distress are depicted in Appendix E Table 1E**.**

***Female Parental Sex*.** Female sex of the parent was cited as predictor of both the development and maintenance of psychological distress (e.g., PTSS, PTSD, anxiety) across 11 studies. A single study indicated no statistical significance in the difference in self-reported

distress levels in mothers versus fathers of children with cancer (Magni et al., 1986). No studies reported higher distress in fathers versus mothers.

Authors Iranmanesh, Shamsi, and Dehghan, reported PTSS to be more prevalent in mothers (2015). In another study, a greater percentage of mothers (68%) reported PTSS within the moderate-to-severe range on the Post-traumatic Stress Disorder Reaction Index (PTSD-RI) compared to fathers (57%; Kazak et al., 2005). Further analyses revealed that mothers of children receiving active treatment for cancer reported more intrusive thoughts, avoidance, and arousal symptoms over a seven-day period when compared to a referent group of mothers whose children had transitioned into long-term survivorship (Kazak, et al., 2005).

PTSD levels were also found to be higher in mothers as opposed to fathers of children with cancer on active treatment (Masa'deh & Jarrah, 2017; Poder et al., 2008; Shi et al., 2017). A longitudinal study examining factors influencing PTSS in parents of children recently diagnosed with cancer found mothers reported higher levels of PTSD arousal, and that a greater proportion of mothers met requisite criteria on two of the three partial PTSD clusters when compared to fathers (McCarthy et al., 2012). Disparities in both the severity and prevalence of psychological distress between males and females were shown in a study conducted by Kostak and Avci (2013). Results from comparative analyses indicated mothers reported greater symptoms of moderate-to-severe depression than fathers (Kostak, & Avci, 2013). Magni et al. found that, compared to fathers, mothers of children with cancer reported higher distress scores across various subscales of the Symptom Distress Checklist (SCL 90) including: somatization; depressive symptoms; and phobic anxiety (1983). However, these findings were not statistically significant. Anxiety was found to be higher in mothers than in fathers of children with cancer (Sawyer et al., 1993). Mothers also reported experiencing more stressors that impacted daily role

functioning and caregiving (Rodriguez et al., 2012).

Pre-existing Anxiety and Depression. Findings across eight studies indicated pre-existing anxiety to be predictive of psychological distress in parents of children with cancer on active treatment. Results from nine studies supported that pre-existing depression may predispose parents to psychological distress. Two studies reported anxiety and depression to be both positively and significantly correlated with increased global psychological distress over time (Harper et al., 2016; Penner et al., 2016), and higher depression scores were predictive of anxiety in parents of children with cancer (Al Qadire et al., 2018). Additionally, higher self-reported symptoms of anxiety and depression were associated with elevated PTSS scores in this population (Dunn et al., 2012).

***Socioeconomic Status*.** Thirteen studies cited lower socioeconomic status, lower education level, and lower family income as factors predictive of psychological distress.

Lower socioeconomic status, determined by the Hollingshead Four Factor Index, was predictive of global psychological distress in one study (Phipps et al., 2004). Having less years of formal education in parents was statistically and negatively correlated with self-reported depressive symptoms in five studies (Bemis et al., 2015; Cernvall et al., 2016; Demirtepe-Saygili, & Bozo, 2011; Dunn et al., 2012), PTSS in three studies (Bemis et al., 2015; Cernvall et al., 2016; Dunn et al., 2012), anxiety in two studies (Chen et al., 2015; Dunn et al., 2012), general perceived stress and post-traumatic stress in two studies (Shi et al., 2017; Tremolada et al., 2013), and cancer-related stress (Bemis et al., 2015).

Annual family income was negatively correlated with self-reported psychological distress in three studies (Bemis et al., 2015; Demirtepe-Saygili, & Bozo, 2011; Molzon et al., 2018); and both mothers' and fathers' role function stressors (Rodriguez et al., 2012). Lower income was

also found to be predictive of PTSS (Shi et al., 2017). In another study conducted by Harper et al., parent's self-reported PTSS showed a marginal positive relationship with household income (2013). Results from a study conducted by Chen et al. showed lower income level to exert a marginally predictive effect on parental anxiety (2015).

Unemployment status was associated with higher levels of psychological distress in parents of children with cancer (Poder et al., 2008). Analyses found unemployment to be marginally predictive of parental anxiety (Chen et al., 2015). Results from two studies indicated unemployment to be predictive of depression (Cernvall et al., 2016), post-traumatic stress symptoms (Masa'deh, & Jarrah, 2017), and post-traumatic stress disorder (Shi et al., 2017).

Younger Parental Age. Three studies cited younger parental age as a contributing factor to psychological distress. One study reported a negative correlation between self-reported PTSD and parental age (Masa'deh, & Jarrah, 2017). Results of multivariate regression analyses examining factors predictive of psychological distress indicated younger parental age to be an independent predictor of PTSS six to eight months following the initial diagnosis of pediatric cancer (McCarthy et al., 2012). In a study conducted by Poder et al., assessments at one week following the initial diagnosis of cancer in the child indicated younger parental age (i.e., < 30 years) potentiated the risk of acute stress disorder (ASD) in both mothers and fathers (2008).

Parent Precipitating Factors. Parental precipitating factors are depicted in Appendix E Table 2E.

Diagnosis of Pediatric Cancer. Seven studies reported the diagnosis of pediatric cancer incited the onset of psychological distress in this population. Following initial diagnosis, parents of children with cancer were more distressed than matched controls (Chen et al., 2015; Neu et al., 2014). A study by Cusinato et al. concluded that a subset of parents reported symptoms

falling within the clinical range, while the majority of participants exhibited subclinical levels of psychological distress, namely anxiety and depression (2017). It should be noted that the study's limited sample size (30 participants) and cross-sectional design limits generalizability of the findings. Prospective, longitudinal analyses are needed.

Higher Pediatric Cancer Treatment Intensity and Increased Number of Diagnostic and Treatment Procedures. In total, three studies measured and reported higher distress in parents of children undergoing more intensive procedures. Anxiety symptoms were more prevalent in mothers of children who underwent cranial irradiation and total body irradiation (TBI) compared to mothers of children who had a history of graft versus host disease (GVHD) (Barrera et al., 2012). Study findings also showed that increased paternal self-reported anxiety symptoms were associated with children who developed graft versus host disease during the course of treatment versus children who did not (Barrera et al., 2012). Findings from a longitudinal study reported greater parental catastrophizing about child procedural pain during lumbar puncture (LP) or bone marrow aspiration (BMA) elicited increased psychological distress in both mothers and fathers of children with leukemia undergoing intensive treatment (i.e., induction or consolidation) (Caes et al., 2014).

Parent Perpetuating Factors. Those factors that perpetuated psychological distress in parents are presented in Appendix E Table 3E**.**

Child Externalizing Problems. Results across four studies supported child externalizing problems to contribute to the chronicity of psychological distress in parents of children with cancer. Study findings support a positive association with increased maternal depressive symptoms and child externalizing problems (Barrera et al., 2012). Ultimately, more observed behavioral issues in the ill child were related to greater maternal depressive symptoms (Barrera

et al., 2012). Parental state anxiety (Dahlquist et al., 1994) was found to be positively correlated with observed procedural distress in those children aged eight years and older during LP and BMA (Dahlquist et al., 1994). Another study, conducted by Fedele et al., showed that child externalizing problems were associated with increased parenting stress in biological mothers (2011).

Female Parental Sex. Three studies cited sex as an important factor contributing to the maintenance of psychological distress in parents of children with cancer over time. Longitudinal analyses of temporal changes in parental psychological distress demonstrated that mothers experienced persistent distress across study time points (Barrera et al., 2012; McCarthy et al., 2012; Poder et al., 2008). Studies also showed mothers reported greater levels of psychological distress over time than fathers (McCarthy et al., 2012; Poder et al., 2008).

Disturbance to Maternal or Paternal Role. Loss of parental role (e.g., level of control within the family, extent to which the family is organized around enforcement of rules) was cited as a factor contributing to the chronicity of psychological distress in this population (Fife et al., 1987). Demirtepe-Saygili & Bozo reported that satisfaction with daily activities (e.g., leisure activities) was significantly related to increased anxiety symptoms exhibited in parents (2011). However, this finding was not consistent across studies as daily restrictions impacting parents' leisure activities, work, or studies 'all or most of the time' were associated with self-reports of partial PTSD symptoms (Hoven et al., 2017), and increased levels of parenting stress (Sherief et al., 2015).

***Increased Caregiver Stress*.** Two factors were cited as greatly contributing to stress in the caregiver. Lower income and greater barriers to care contributed to increased caregiver stress, thereby perpetuating psychological distress, specifically anxiety and depression, in parents of

children with cancer (Benaroya Milshtein et al., 2014; Molzon et al., 2018; Sulkers et al, 2015).

Parent Protective Factors. Those factors categorized as protective against psychological distress in parents are presented in Appendix E Table 4E**.**

Greater Time Elapsed Since Diagnosis. Time since diagnosis impacted both maternal and paternal reports of psychological distress. Notably, acute stress symptoms, clinical anxiety and depressive symptoms, and PTSD were most prevalent at the time of diagnosis, but decreased over time (Masa'deh, & Jarrah, 2017; Sulkers et al., 2015). Further, a significant decline in caregiving stress was reported at just three months post diagnosis, remaining stable thereafter (Sulkers et al., 2015). However, results indicate that distress symptoms that remain present at certain timepoints post-diagnosis may be associated with persistence of the symptom. One study concluded that those parents with more psychological symptoms at four months post-diagnosis were increasingly more likely to report PTSS twelve months after the successful completion of pediatric cancer treatment (Hoven et al., 2017).

Sibling Factors Included in the Review

A tabular summary of findings from the included studies is presented in Appendix F: sibling predisposing factors (Table 1F); sibling precipitating factors (Table 2F); sibling perpetuating factors (Table 3F); and sibling protective factors (Table 4F). Five predisposing factors, one precipitating factor, fourteen perpetuating factors, and two protective factors were identified.

Sibling Predisposing Factors. Six studies reported on factors that predisposed siblings to psychological distress are depicted in Appendix F Table 1F. No single factor was supported by the requisite number of citations (i.e., three or more). Still, to better understand factors influencing distress in siblings of children with cancer, those factors pertaining to the 4Ps will be

presented and discussed.

***Sociodemographic Variable*s.** Together, ethnicity, lower family income, and parental non-married status were associated with higher sibling distress in three studies (Houtzager et al., 2033; Houtzager et al., 2004; Long et al., 2013b). Subsequent analyses of a regression model of factors predicting sibling distress revealed that independent of each other, these factors were not significant (Long et al., 2013b). However, taken together ethnicity, lower family income, and parental non-married status were predictive of increased sibling distress (Long et al., 2013b).

***Increased Sibling Age*.** In a study conducted by Houtzager et al., siblings aged twelve to eighteen years reported greater anxiety than siblings aged seven to eleven years (2004). Conversely, findings from a study conducted by Long, Alderfer, Ewing, and Marsland (2013a) concluded that the effect of increased sibling age on reported distress within the sibling population was not significant.

Younger Birth Order Relative to the Child with Cancer. Findings from a mixed methods study conducted by Long, Alderfer, Ewing, and Marsland (2013a) concluded that, of the documented demographic and oncologic disease-related factors, younger birth order relative to the child with cancer was independently associated with greater sibling distress (Long et al., 2013a). The authors purported that a subset of sibling might therefore be at increased risk for greater psychological distress (Long et al., 2013a).

***Sibling Female Sex*.** A single study reported on the significance of female sex. One-month post initial diagnosis of pediatric cancer in the child, female adolescent siblings reported increased internalizing and externalizing problems at the clinical level when compared to peers in the normative sample population (Houtzager et al., 2003). These findings persisted six months after initial diagnosis (Houtzager et al., 2003).

Sibling Precipitating Factors. A single precipitating factor was identified across two studies (see Appendix F Table 2F). Increased perception of threat to lifestyle was cited as a factor that may precipitate distress in the sibling population. A study from 2011 found that increased depressive symptoms was related to lower satisfaction of basic needs amongst caregivers (Demirtepe-Saygili & Bozo). It should be noted however, that of the 100 study participants aged 18 to 51 years, only three were siblings. Distinctive findings for the three siblings represented in the sample population were not presented. However, Long et al. examined the effect of contextual threat on sibling-reported distress in a population of 30 siblings aged ten to seventeen years (2013a). Contextual threat, or threat to lifestyle, encompasses the following: (a) the frequency of hospital visits; (b) distance to the hospital; (c) inpatient versus outpatient status of the ill child; (d) recency of diagnosis of pediatric cancer; (e) typical sibling caretaker during hospital visits (e.g., parent, extended family, non-relative, none); (f) the frequency of the ill child being sick when at home; (g) change in employment status of parent(s) after diagnosis of cancer in the child; (h) presence of illness in other family members; (i) financial impact on the family; (j) the presence or absence of friends, (k) the presence or absence of someone to talk to; (l) other stressful events occurring since the ill child was diagnosed; and (m) other ongoing stressful situations (Long et al., 2013a). Greater perceived threat to lifestyle was positively associated with sibling-reported distress, independent of pediatric cancer treatment intensity, sibling age, and birth order relative to the child with cancer (Long et al., 2013a).

Sibling Perpetuating Factors. Two studies reported a single factor that perpetuated psychological distress in siblings (Appendix F Table 3F). A single factor identified as influencing the chronicity of psychological distress was supported by the requisite number of citations (i.e., three or more) and will therefore be discussed.

Increased Caregiver Burden. Family adaptation, or the extent to which a family adapts its power structure, redefines assigned roles within the family, and imposes new restrictions in response to both internal and external demands, was found to be associated with increased self-reported anxiety in siblings (Houtzager et al., 2004). This finding was reflected across the other two studies (Demirtepe-Saygili & Bozo, 2011; Hamama et al., 2008). Results indicated that the re-distribution of tasks, which otherwise would have been the responsibility of the parent or guardian, contributed to the chronicity of psychological distress within the sibling population.

Sibling Protective Factors. Three studies reported on two protective factors exhibited in siblings of children on active cancer treatment (see Appendix F Table 4F). No single factor was supported by the requisite number of citations (i.e., three or more). Despite this, to better understand factors influencing distress in siblings of children with cancer, factors pertaining to the 4Ps will be presented and discussed.

Greater Time Elapsed Since Diagnosis. Two studies reported a marked decrease in sibling's anxiety over time (Hamama et al., 2000; Houtzager et al. 2004). Select illness variables associated with the childhood cancer patient (i.e., type of cancer, prescribed treatment, duration of illness) and the subsequent emotional responses of the sibling were examined in a study conducted by Hamama et al. (2000). Duration of the child's illness was found to be strongly negatively correlated with siblings' anxiety. Further analysis revealed increased anxiety was exhibited in siblings within six months of the ill child's diagnosis. Comparatively, anxiety levels in siblings had decreased significantly after a period of twelve months or more since the date of diagnosis of cancer in the ill child. Houtzager et al. remarked that the observed stabilization trend in siblings' self-reported anxiety within six months of diagnosis is demonstrative of their adjustment to the illness over time (2004).

***Sibling's Increased Sense of Self-efficacy*.** Defined as the appraisal of a perceived threat and the subsequent exploration of possible courses of action to be implemented in response to said threat, self-efficacy is the individual's perceived capacity to effectively implement a behavior and achieve a desired outcome (Bandura, 1997). Findings reported by Hamama et al. suggested siblings' increased sense of self-efficacy correlated with lower anxiety and lower somatization (2008).

Chapter Four

Discussion

Discussion

The objective of this systematic review was to identify factors related to psychological distress in family members of pediatric cancer patients on active treatment. For the purposes of this research, psychological distress was conceptualized as an overarching construct comprising the specific domains of; depression, anxiety, PTSS, and somatization (Buchbinder et al., 2011; Ozono et al., 2010). The 4Ps of case formulation was applied as a theoretical framework enabling the systematic organization of these factors. Those factors that most influenced distress in parents of children with cancer included: (i) female sex; (ii) pre-existing psychological distress; (iii) lower socioeconomic status; and (iv) role disturbance. Those factors most frequently cited as impacting psychological distress in the sibling population include: (i) ethnicity; (ii) parental non-married status; (iii) increased caregiver burden; and (iv) greater time elapsed since diagnosis. With regard to outcomes related to both parental and sibling distress, it was stipulated that increased levels of distress were manifest closer to the time of diagnosis. Key findings will be discussed within the broader literature. Finally, implications for theory, research, clinical practice, and future directions will be highlighted.

Parent Factors Included in the Review

Parent Predisposing Factors. Broadly, predisposing factors comprised determinants of health and unmodifiable risk factors (e.g., sex, age etc.).

***Female Sex*.** Female sex was the single most cited predisposing factor identified in this systematic review. This finding may be indicative of disparate appraisals of traumatic events and stressors based on sex whereby females are more likely to exhibit a greater level of internalizing symptoms and report a stronger negative appraisal of the event (Kucharska, 2017). Increasingly, research published within the broader literature has sought to address discrepant cognitive

responses following exposure to traumatic events between the sexes (i.e., male versus female) (Herta et al., 2017). Findings, however, are inconsistent (Herta et al., 2017). Comparative analyses are made difficult given the heterogeneity of the data, possibly explained by differences in study methodology, and diverse demographic characteristics of the populations studied (Herta et al., 2017). It is therefore difficult to ascertain with certainty distinctive cognitive responses to trauma that are solely attributable to sex (Herta et al., 2017).

***Pre-existing Anxiety and Depression*.** Findings demonstrated the marked effects of pre-existing anxiety and depression in the population of study and made plain their role as antecedents to psychological distress in parents of children with cancer. Research into the cognitive processes that mediate the effects of trait anxiety is limited (Penner et al., 2016), and further research on this subject is warranted. Contemporary research purports that past exposure to traumatic events, and the experience of cumulative trauma may potentiate the risk of developing psychological distress symptoms (Kucharska, 2017). Future research directions should therefore focus on the delivery of targeted interventions to those parents at increased risk of developing psychological distress relative to their level of exposure to traumatic events.

***Socioeconomic Status*.** Our findings revealed that lower socioeconomic status, lower education level, and lower income significantly impacted the development of psychological distress in parents of children with cancer on active treatment. Financial constraints compounded by incurred medical expenses, or loss of parental income may incite the development of psychological distress in the context of a child's cancer diagnosis. This is reflected within contemporary research. Looking to the extant literature, a population-based study conducted in Ontario, Canada affirmed lower socioeconomic status was associated with an increased risk of adverse mental health outcomes in mothers and siblings of children with cancer (van

Warmerdam et al., 2020).

***Younger Parental Age*.** Younger parental age was cited as a predictor of psychological distress, possibly explained by the differences in developmental processes in younger versus older parents (Masa'deh & Jarrah, 2017). It was purported that older parents may, over time, adopt a changed perspective towards distress, and view it as chronic as opposed to episodic (Masa'deh & Jarrah, 2017). Thus, older parents may tactfully implement more routine management skills rather than seek to establish coping strategies (Masa'deh & Jarrah, 2017). This hypothesis is supported in the broader literature. Age-related differences in stress response and resultant coping mechanisms may be determinate of executive functioning (Nieto et al., 2020). Study findings support diminished executive performance potentiates the adoption of maladaptive coping (i.e. avoidant strategies), seemingly more prevalent in younger adults (Nieto et al., 2020). Over time inherent, age-related changes in the stress response may incite the development of more adaptive coping strategies, positively impact stress reappraisal, and incite a subsequent decrease in psychological distress.

Younger parental maternal age was found to be an independent predictor of psychological distress (McCarthy et al., 2012). It was postulated that this finding could be linked to other psychosocial risk factors (e.g., financial strain, parental demands), thereby impacting overall adjustment of young mothers (McCarthy et al., 2012). This could be further explained by physiological processes activated in response to stress. Past research serves to support this theory. Comparative data analyses from five independent studies examined the impact of age and sex on hypothalamic-pituitary adrenal (HPA) axis functioning in response to an acute psychosocial laboratory stress task, the Trier Social Stress Test (TSST) (Kudielka et al., 2004). Results indicated increased adrenocorticotropin (ACTH) levels in younger adults (reported mean

age 23.5 years) versus older adults (reported mean age 67.3 years) (Kudielka et al., 2004). Further, it was reported that younger females exhibited increased sensitivity to ACTH levels (Kudielka et al., 2004).

Contradictory findings, specific to paternal age, were also reported. Longitudinal analyses conducted by Barrera et al. found that, older fathers, except for those fathers of children diagnosed with leukemias other than ALL (otherwise unspecified), exhibited greater levels of anxiety and depressive symptoms than younger fathers (2012). The authors postulated that these findings were indicative of the fact that older fathers care for the ill child more often than younger fathers. This interpretation, however, requires empirical validation as this conclusion was drawn based on anecdotal evidence (Barrera et al., 2012). This finding is corroborated by results of another study conducted by McCarthy et al. (2012). Younger maternal, but not paternal age, was found to be predictive of PTSS.

Parent Precipitating Factors. Taken together, precipitating factors were found to be contextual, and related specifically to the diagnosis of pediatric cancer in the child, in addition to higher pediatric cancer treatment intensity. While these factors are not modifiable, steps can be taken to better support parents of children at the time of initial diagnosis, and those parents whose children are undergoing intensive treatment. A summary of findings is presented.

Diagnosis of Pediatric Cancer. Diagnosis of cancer in the child was identified as a precipitating factor in our findings. Termed a crucial life event, initial diagnosis may impact the assessment of psychosocial factors predictive of parental anxiety (Chen et al., 2015). Following diagnosis of ALL in the child, mothers reported significantly higher scores of depressive symptoms, greater perceived stress, and were increasingly likely to reports symptoms of anxiety and depression at the clinical level (Neu et al., 2014). Looking to the broader literature,

causative, or precipitative agents may include: (i) barriers to care (perceived or actual); and (ii) illness uncertainty.

Barriers to care, defined as those factors that: (i) obstruct an individual's access to the healthcare system; (ii) limit the level of engagement between that individual and the healthcare system; (iii) and engender a perceived lack of confidence in those individual's needs being met may present at any stage of the pediatric cancer treatment continuum (Perez et al., 2020). Socio-behavioral processes that interfere with or impede successful interaction with the healthcare system (e.g., language barrier, parental resistance to participating in the child's care) may also constitute barriers to obtaining healthcare for the ill child. Research examining the effects of barriers to care on parental distress within the context of pediatric cancer is scant (Perez et al., 2020).

Illness uncertainty, derived from the perceived unpredictability of illness-related outcomes, may incite maladaptive responses in parents of children newly diagnosed with cancer (Perez et al., 2020). Studies have demonstrated a strong relationship between illness uncertainty and psychological distress in parents of children with a chronic illness (Perez et al., 2018; Tackett et al., 2016). Barriers to care experienced upon initial diagnosis of pediatric cancer may engender illness uncertainty, and as a result exacerbate parental psychological distress (Perez et al., 2020). A recent study conducted by Perez et al. found illness uncertainty mediated the relationship between barriers to care, PTSS, and depressive symptoms (2020). Findings suggest that greater perceived barriers to care may increase illness uncertainty, which may precipitate psychological distress (i.e. PTSS, and depressive symptoms) in parents of children with cancer (Perez et al., 2020). It is important to note study limitations: (i) the cross-sectional study design precludes the assertion of the temporality of perceived barriers to care, its causal effect on illness

uncertainty, and the subsequent development of psychological distress; and (ii) the stated lack of heterogeneity in the sample population (Perez et al., 2020). Future research examining barriers to care within the context of pediatric oncology is warranted.

***Higher Pediatric Cancer Treatment Intensit*y.** Intensive antineoplastic therapy was defined as a prescribed course of treatment involving cranial irradiation, TBI, hematopoietic stem cell transplant (HSCT), stem cell transplant (SCT), LP, or BMA. A longitudinal study conducted by Barrera et al. determined that, pre-SCT, mothers' self-reported anxiety and depressive symptoms were comparable to those of mothers of children newly diagnosed with cancer (2012). Further, mothers whose child had undergone cranial radiation therapy and TBI reported more symptoms of anxiety (Barrera et al., 2012). Requisite critical and supportive care components following intensive antineoplastic therapy could necessitate extended inpatient stay, isolation practices, and invasive medical procedures. Higher pediatric cancer treatment intensity compounded by complex supportive care needs may precipitate distress in parents. Secondary cancer risk, treatment-related toxicities, neurocognitive and psychosocial sequelae following cranio-spinal irradiation, myeloablative TBI, and HSCT have been well documented (Bitsko et al., 2016; Ducassou et al., 2015). Knowledge of the risk of adverse treatment-related outcomes (e.g., chronic or acute graft versus host disease), neurocognitive and psychosocial sequelae may engender or precipitate psychological distress in parents of children on active cancer treatment. Of note, 24 months post-SCT anxiety and depressive symptoms reported by both mothers and fathers, while comparable, declined. This was thought to be explained by the fact that initial anxiety and depressive symptoms pre-SCT presented in response to a medical crisis.

Prospective analyses conducted by Caes et al. examined psychological distress in parents of children with leukemia (unspecified) following LP or BMA procedures (2014). Results

indicated that, while psychological distress in this population dissipated over time, elevated levels of psychological distress persisted in high catastrophizing parents and were manifest during subsequent LP/BMA procedures (Caes et al., 2014). Parental catastrophic thoughts were specific to child procedural pain (Caes et al., 2014).

In a study conducted by Molzon et al., researchers posited that a positive relationship existed between caregiver distress and intensity of treatment (2018). However, these findings were not significant.

Findings demonstrate a need for the provision of support to parents of children with cancer during periods of medical acuity and during invasive medical procedures. Given that distress in this population may recur during subsequent medical procedures, ongoing support is needed throughout the course of active treatment (Caes et al., 2014).

Parent Perpetuating Factors. It is at this level of the 4Ps where healthcare professionals, specifically nurses, may have the opportunity to enact the greatest impact. Unlike predisposing and precipitating factors, perpetuating factors were not solely unmodifiable risk factors. Those factors that contributed to the chronicity of distress in parents of children with cancer concerned aspects of the family dynamic and reciprocal effects of behaviors exhibited in the ill child. A summary of review findings is presented below.

***Child Externalizing Problems*.** Research identified high risk subgroups of mothers and fathers of children diagnosed with cancer based on specific factors that served to perpetuate distress in this population. In one study, mixed linear model analyses confirmed a significant positive relationship between child behavior scores (i.e., behavior problems exhibited in the child) and mothers' depressive symptoms (Barrera et al., 2012). Another study, conducted by Dahlquist et al., reported that, during the procedural phase, parental anxiety was significantly

related to observed distress in children aged eight years and older (1994). Similarly, findings presented by Fedele et al. concluded that a significant positive relationship existed between elevated parenting stress and greater externalizing problems exhibited in the child (2011).

Within the broader literature, research supports the child's behavior is predictive of parental adjustment following a diagnosis of pediatric cancer (Barrera et al., 2004). Fainsilber Katz et al. examined mean levels of externalizing symptoms in children with cancer, and psychological distress (i.e., anxiety, depression, and PTSS) in primary caregivers during the first year of treatment (2018a). Study findings suggest the majority of pediatric oncology patients remain well-adjusted during the first year of treatment with the highest level of mean symptoms exhibited within the first two months following diagnosis (Fainsilber Katz et al., 2018a). However, an increasing number of primary caregivers reported experiencing clinically significant symptoms of psychological distress (i.e. anxiety and depression) in relation to child externalizing symptoms during the first year of treatment (Fainsilber Katz et al., 2018a). Parents may interpret externalizing symptoms exhibited in the ill child to be a result of parental impaired self-efficacy. The appropriate screening and timely implementation of targeted interventions for those parents at increased risk of developing psychological distress is needed. Given that reciprocity exists between reports of increased psychological distress in the parent and the ill child, targeted interventions will also serve to better support pediatric oncology patients throughout the trajectory of their cancer treatment (Fainsilber Katz et al., 2018b).

Female Sex. Study findings evidenced that mothers consistently experienced increased levels of psychological distress across all time points. Of the sample population, one study reported that 99% of mothers acted as the primary caregiver (Barrera et al., 2012). It could therefore be speculated that parents of female sex may experience greater exposure to treatment

related stressors at more frequent intervals which could, in effect, contribute to the development or exacerbation of caregiver burden, and subsequent psychological distress. Results from a longitudinal population-based study indicated mothers of children with cancer experience an increased rate of mental-health related outpatient visits in the decades following initial diagnosis, with a subset of this population being at highest risk (van Warmerdam et al., 2020). It was stipulated that correlates of increased distress include decreased maternal age at the time of pediatric cancer diagnosis, lower socioeconomic status, and rural residence (van Warmerdam et al., 2020). It should be noted, however, that male caregivers lack representation in this area of study. The studies' sample populations predominantly consisted of biological mothers, thus constituting a limitation. This is also true of several studies included in this systematic review: (i) sample participants in the study conducted by Barrera et al. included 69 mothers and 42 fathers (2012); and (ii) McCarthy et al. sampled 135 mothers versus 85 fathers (2012). Future research in other caregiver groups is needed. Prospective research initiatives should therefore aim to incorporate this perspective into study objectives.

***Disturbance to Maternal or Paternal Role*.** Data from one study indicated that the level of daily activities fulfilled by parents of leukemic children was positively correlated to reported anxiety symptoms (Demirtepe-Saygili, & Bozo, 2011). Parents may experience guilt with regard to their ability to complete daily activities that are not specific to the provision of care for the child with cancer (Kish et al., 2019). Higher levels of parental anxiety relative to increased satisfaction of daily activities may indicate that parents frequently experience intrusive thoughts regarding the health status of the child.

While satisfactory fulfillment of daily activities engendered psychological distress in this population, research findings demonstrated that the inability to participate in leisure activities,

and limitations exerted on work or studies were also factors that served to perpetuate distress in parents. Parents' reports of said restrictions that occurred all or most of the time were found to be significantly correlated with parental reports of partial PTSD (Hoven et al., 2017). This finding was supported by data from another study which concluded that increased levels of parenting stress were found to be directly associated with restrictions on personal activities (unspecified) (Sherief et al., 2015). Further, Demirtepe-Saygili, & Bozo concluded that depressive symptoms in parents were significantly correlated with decreased satisfaction of basic needs (2011). This could be explained by the fact that mothers and fathers of children with cancer may be subject to restrictions (e.g., sleep disturbance, dissatisfaction of basic needs, social isolation, marital conflict) following the diagnosis of pediatric cancer (Coleman et al., 2018). These restrictions may prompt perceived self-inefficacy and disrupt maternal or paternal function(s) within the family dynamic. Indeed, family dysfunction was found to perpetuate paternal anxiety and depressive symptoms at 12 months post diagnosis (Fife et al., 1987). Research initiatives should therefore seek to identify factors that mediate the response to parental role disturbance.

***Increased Caregiver Stress*.** Study findings revealed parental depressive symptoms were significantly correlated with repeated exposure to stressors, termed major events, on the Hemato-oncology unit (Benaroya-Milshtein et al., 2014). Major events included: (i) LP performed on child; (ii) BMA; (iii) surgery; (iv) receiving discouraging information about child's prognosis; (v) decisions regarding a new medical procedure; (vi) an altercation with medical staff; (vii) emergency hospitalization; (viii) bone marrow transplantation; (ix) death of another patient; and (x) relapse of another patient in the ward. The study reported that repeated exposure to stressors may incite immunological changes in lymphocyte cell subsets in parents of children with cancer. Specifically, findings demonstrated decreased CD4 percentages and increased CD8+ percentages

in parent with depressive symptoms (Benaroya-Milshtein et al., 2014). Cancer-specific stressors, and increased caregiver burden may perpetuate symptoms of psychological distress following diagnosis and for the duration of treatment. Given the effects of chronic stress on the HPA axis and subsequent alteration in stress hormone regulation, increased caregiver stress may serve in the maintenance of distress, namely depressive symptoms (Benaroya Milshtein et al., 2014; Molzon et al., 2018; Sulkers et al, 2015). Within the context of pediatric oncology, these factors, compounded by maternal and paternal role conflict, may potentiate the risk of both the development and maintenance of psychological distress.

Parent Protective Factors. A factor that served to prevent or mitigate psychological distress in parents was temporal in nature. Based on the findings of the review, little emphasis has been placed on the identification of those factors that are protective of distress in this population.

Greater Time Elapsed Since Diagnosis. The length of time since diagnosis showed a significant negative association with maternal PTSS (Kazak et al., 2005). Masa'deh & Jarrah found that a significant negative correlation existed between time since diagnosis and parental (maternal and paternal) PTSD levels (2017). In the extant literature, it was posited that adaptive processes adopted by parents over time, coupled with parents' ability to effectively mobilize available supports and resources throughout the pediatric cancer trajectory may explain a protective effect of time since diagnosis (Sulkers et al., 2015). In effect, supports and resources permitting, parents may feasibly adjust to cancer-related stressors over a relatively short period of time. Identifying factors that enable parents to develop adaptive coping strategies is needed. Further, analyses of what fosters resilience in this population is warranted as this could inform the development of targeted interventions for parents of children with cancer on active treatment.

Sibling Factors Included in the Review

In general, more research is needed within the context of each of the 4Ps to determine factors related to psychological distress specific to this population.

Sibling Predisposing Factors. As seen with parental factors, sibling predisposing factors consisted of determinants of health and unmodifiable risk factors. Given the nature of these factors, there is little opportunity for healthcare professionals to intervene, however an understanding of which factors contribute to the development of distress in this population is of great importance as it may serve to identify which individuals may be at greater risk of psychological distress.

Sociodemographic Variables. Altogether ethnicity, lower family income, and parental non-married status were predictive of increased sibling distress in our review. Upon looking to the broader literature, research has shown the cumulative effect of overlapping and intersectional sociodemographic characteristics on health outcomes (Hauenstein et al., 2019). Identifying as an ethnic minority may place additional strain on the family as a whole, as cultural or linguistic differences may complicate the ability to effectively access medical and support services (Patterson et al., 2017). The mechanisms through which family income impacts developmental processes in the child have been critically examined using psychological and economic frameworks (Noonan et al., 2018). In a recent study, investigators examined the relationship between family income and socio-emotional behavioral problems in children aged eleven years (Noonan et al, 2018). The authors reported that increased permanent family income exerted a significant protective effect on externalizing problems exhibited in the child. Following a diagnosis of pediatric cancer, the resultant financial burden may exert significant strain on the family, predominantly single mothers (Santacroce & Kneipp, 2020). Parental non-married status

compounded by financial instability could exacerbate caregiver distress and incite maladaptive processes in children (Kalil & Ryan, 2010; Taylor & Conger, 2017), including healthy siblings. Parental non-married status coupled with economic constraints may greatly impact family functioning. Research has shown that increasing demands upon the family unit may require that roles be re structured, and afford siblings greater responsibilities (Huang et al., 2008; Patterson et al., 2017). The culmination of these factors contributes to the development of psychological distress in siblings of children with cancer. Therefore, efficacious screening to serve in the identification of those children who meet these criteria is needed. Clinicians should focus on the implementation of timely interventions to better support this lower SES population of siblings.

Increased Sibling Age. The impact of increased sibling age on distress was not conclusive based on included studies in this review. The concept of distress itself is difficult to conceptualize, and, depending on the child's age and developmental stage, siblings may be ill-equipped to articulate their distress (Emmott et al., 2017), especially if well-validated instruments are not being used consistently. Discrepant findings may also be attributed to methodological limitations, including small sample size; subsequent reduced power of the study; heterogeneity of the sample; the absence of comparative or normative data; and selective dropout of targeted participants (Houtzager et al., 2004).

Younger Birth Order Relative to the Child with Cancer. Findings indicated that a subset of siblings might be at increased risk for greater psychological distress (Long et al., 2013a). Younger birth order relative to the pediatric oncology patient was determinant of increased risk of psychological distress. Interestingly, the impact of developmental stage was not examined. Research into this concept is warranted.

***Sibling Female Sex*.** This factor was supported by mixed findings, likely attributed to variability in the quality of the data. Consensus and application of study findings is limited by non-representative sample populations, small sample size, design (i.e., cross-sectional design), and variability in the ages of sample participants. (Houtzager et al., 2003). Quality of the study should be noted. It was determined by Long et al. that sex was not significantly predictive of psychological distress in siblings of children with cancer (2013). Application of these findings is limited by the study's cross-sectional design, which impeded the ability to determine sibling functioning over time as it pertains to developmental processes, and variability in the sample population's ages. Clinical implications involve the need for research into the possibility of disparate appraisals of traumatic events and stressors based on sex within this population.

Sibling Precipitating Factors. Again, precipitating factors in the sibling population were contextual, and involved structural changes to the family unit, role disturbance, inconsistency or changes to daily routines, and caregiving demands placed upon the sibling.

***Increased Perception of Threat to Lifestyle*.** Unmet basic needs and impaired family functioning have been attributed to psychological sequelae exhibited in siblings of children with cancer (Long et al., 2018). Limitations of the study should be noted, including small sample size, selective dropout, and the absence of a comparator or normative sample group. However, these findings are congruent with conclusions from an earlier study by Hamama et al. (2008). Greater role overload, defined as an imbalance between, for example, various temporal, social, physical, or developmental demands placed on an individual and the resources available to meet the imposed demands, was found to be associated with increased state anxiety and somatization in siblings of children with cancer (Hamama et al., 2008). While much of the disruptions to lifestyle may be unavoidable given the serious implications of a pediatric cancer diagnosis, it is important

that siblings attain an understanding of why this shift in structured routines has occurred. Emphasis should be placed on fostering effective communication within the family, facilitating knowledge acquisition pertaining to the disease process and its treatment, and ensuring siblings are included in the family's decision-making processes, wherever possible (Long et al., 2018).

Sibling Perpetuating Factors. The perpetuation of distress within the sibling population was attributed to external demands placed upon the sibling by the family unit. As with the parent population, it is at this level of the 4Ps where the opportunity for intervention on behalf of the healthcare team is most feasible.

***Increased Caregiver Burden*.** Structural disruptions to the family unit may require that the sibling assume a number of caregiving behaviors that would otherwise have been the responsibility of the parent or guardian. This concept is described as "parentification", and may involve the provision of emotional support, the completion of household tasks, or assistance with the ill individual's activities of daily living (Tomeny et al., 2017). Greater levels of parentification have been linked to various negative outcomes, such as lower perceived acceptance and psychopathology (i.e., anxiety and depression) (Hooper et al., 2011). Therefore, efforts should be made to better support both the parent(s), guardian(s), and siblings during the pediatric cancer treatment trajectory. This will enable the allocation of increased responsibilities within the family in a sustainable way.

Sibling Protective Factors. Those factors protective of distress within this population were: (i) temporal; and (ii) indicative of the siblings' cognitive processes, and performance. Again, more research is needed to identify those factors protective of distress in this population.

***Time Elapsed Since Diagnosis*.** The effects of time elapsed since diagnosis on sibling adjustment are widely disputed. Study results are in direct contrast to Long et al.'s research

which concluded time elapsed since diagnosis was not significantly correlated with sibling distress (2013a). Comparatively, a recent systematic review by Long et al. reported shorter time elapsed since diagnosis to be predictive of poorer sibling adjustment (2018). Future longitudinal studies examining temporal changes in sibling adjustment are needed (Long et al., 2018).

***Increased Sense of Self-efficacy*.** Study findings supported a negative correlation between increased self-efficacy and the development and maintenance of psychological distress (Hamama et al., 2008). However, methodological limitations of the study, including the absence of a matched-control group, should be noted. In particular, the study's cross-sectional design prevented analysis of the temporal effects of perceived self-efficacy. Future longitudinal studies are needed. In addition, research should focus on factors that contribute to self-efficacy in this population. This will permit a better understanding of those processes that engender resilience in siblings of children with cancer.

Strengths and Limitations

There are several review strengths to be noted. According to the AMSTAR II, the following criteria were met: (i) an explicit statement that review methods were established a priori; (ii) the protocol for the review included all requisite components (with the exception of a risk of bias assessment) and was registered on PROSPERO; (iii) deviations from protocol explained; (iv) explanation of selection of study designs included; (v) a comprehensive literature search strategy was applied (i.e. greater than two databases were accessed, both a list of key words and the search strategy included in the review, and publication restrictions were justified); (vi) data extraction was performed in duplicate, inter-rater reliability calculated is presented in Table 2; (vii) justification for exclusion of ineligible studies provided; (viii) summative information of those studies selected for inclusion presented in a tabular summary; (ix) sources

of conflict disclosed (i.e. no competing interests to report). A tabular summary is presented in Appendix A (Table 1A). Further, no data restrictions were placed on studies eligible for inclusion, thereby permitting a more comprehensive review and synthesis of factors contributing to familial distress. However, a limitation was that the search was conducted four years ago. Parameters specific to time since the pediatric cancer patient's diagnosis were explicit, thereby enabling analysis of the chronology and etiology of the family members' presenting symptoms of psychological distress. In order to develop interventions to better support family members of children with cancer, it is important that we are conscious of the distinct phases of the treatment trajectory as we suspect this may be impactful.

Table 2

Inter-rater Reliability

Reviewer A	Reviewer B	Cohen's Kappa
M Murawsky	M Gladkikh	0.21
C Di Carlo	M Murawsky	0.54
M Murawsky	V Sanderson	0.42

This study has several limitations. Assessment of the risk of publication bias and selective reporting outcomes, in addition to a description of the quality of the cumulative evidence across domains of risk of bias, consistency, directness, and publication bias, was not conducted. While the results of included reports were informative, they may be subject to various levels of bias, which should be considered in the interpretation of the data. Even without an explicit assessment of bias, a number of methodological limitations (e.g., small sample sizes, heterogeneous sample groups) were identified across the studies included in this review,

indicating that bias may exist in these studies. An additional limitation of this study exists. The aim of this review was to include studies with an array of study designs, and the intent was always to include all studies that met inclusion criteria. Therefore, quality appraisal of each individual study was not done. Ultimately, this may have impacted the interpretation of study outcomes.

Categorization of study findings was done through content analysis. The subjectivity of this method of classification may constitute another limitation of the study. It should be noted, however, that measures were taken to limit the impact of this on study outcomes. Prior to analysis and synthesis of study findings, characteristics of the 4Ps were parsed out, and criteria for each, within the context of pediatric cancer, were clearly established. A framework enabling the systematic categorization of each factor of distress was established. Each factor of distress was then coded, and independently reviewed by a second author. Discrepancies were resolved through discussion with a third author.

Implications for Theory

Application of the 4Ps of case formulation permitted a consistent approach to the classification of factors related to distress in the population of study. While the framework's nonstandard format and the potential overlap of predisposing, precipitating, perpetuating, and protective factors of distress could be considered a limitation of the model (Henderson & Martin, 2014), the ability to contextualize distress through the imposition of a chronology and etiology on influential factors constitutes an overall strength. This study has demonstrated the feasibility of using the framework to categorize factors related to distress in family members of children with cancer. Results of this categorization may support an enhanced understanding of how and when distress arises in family members, thereby producing useful results for research and clinical

care and demonstrating the utility of the 4Ps model.

Implications for Research

The limited number of both parental and sibling protective factors cited within the literature stresses the need for future research to adopt a strength-based approach when examining distress in family members of children with cancer (Hamama et al., 2008; Sams et al., 2016). Placing sole emphasis on maladaptive processes adopted by caregivers within the context of pediatric oncology may be of detriment to our clinical understanding of how to promote effective coping (Walsh, 2016). Rather, future research should: (i) seek to examine those factors that are protective; and (ii) determine how those factors foster resilience to better support parents and siblings of children with cancer.

The psychological literature purports that resilience, an adaptive process, is the ability to cope with stress both psychologically, and physically (Caldeira & Timmins, 2016). As a concept, it is both dynamic and subjective (Caldeira & Timmins, 2016), and divergent definitions of resilience continue to emerge given the number of disciplines (e.g., biology, physics, medicine) that have sought to apply this concept in theory, research, and practice (Caldeira & Timmins, 2016). Post synthesis of elements of research on concept analyses, Caldeira & Timmins (2016) proposed the following definition of resilience to NANDA International (NANDA-I) and International Classification for Nursing Practice (ICNP®):

> Following our analysis of the results, we propose a definition of resilience which is the ability to recover from perceived adverse or changing situations, through a dynamic process of adaptation, influenced by personal characteristics, family and social resources, and manifested by positive coping, control and integration (Fig. 1). (p.194)

The proposed definition provides a framework for those factors that could be considered

protective of distress (i.e., personal attributes, resources available to the family) which align with the 4Ps of case formulation. Within the context of pediatric oncology, in depth analyses of those factors protective of distress, such as positive family functioning, could lead to the development of clinical interventions that compliment strengths of family members, which could serve to better promote resilience in this population (Walsh, 2016).

Additional implications for research include: (i) the need for adoption of rigorous study methodology to combat the limitations of past systematic reviews (i.e., study design, sampling methods, data collection procedures, heterogeneity of study participants, and small sample size) (Long et al., 2018); and (ii) longitudinal analyses examining distress in this population. When seeking to obtain empirical data specific to distress, emphasis should also be placed on the consistent use of well validated and reliable measurement tools to permit generalizability of study findings and cross-analyses.

Implications for Nursing Practice

Understanding those factors that influence psychological distress in family members of children with cancer is crucial as it will serve to guide clinical practice and improve clinical outcomes. With regards to the provision of care, study findings reinforce the importance of supporting the family unit, and not solely the ill child.

With respect to the findings from this systematic review, it is highly likely that pediatric oncology nurses will encounter, at a minimum, subclinical levels of distress manifest in family members of children with cancer on active treatment. Considering that nurses interact and engage with family members at the bedside, they are well positioned to actively assess for distress in this population. If this process of assessment is to be formalized, additional training and education to better support nurses in the recognition and timely assessment of psychological

distress is warranted. Further, the need for consistent use of a simple, validated distress measure tool cannot be overstated. The Distress Thermometer, for example, is a brief screening tool used to evaluate distress (Donovan et al., 2014; Tuinman et al., 2008). This tool has been validated for use in adult, and pediatric oncology patients, but not necessarily siblings. Given that the clinical management of pediatric cancer occurs over a continuum, it will also be of huge importance to facilitate recurrent screening for distress throughout the trajectory of active treatment. It should be noted that it may also be of benefit to perform focused assessments I order to identify those factors protective of distress, and to incorporate a strength-based approach when selecting interventions to better support the family member(s). Once an evidence-informed pathway for assessment has been implemented, it will then be necessary to ensure that responses to assessment findings are actionable. Examples, which will ultimately involve the multidisciplinary healthcare team, may include: (i) referral of family members to clinical specialists should the level of distress be deemed clinical; or (ii) established processes to better support family members experiencing subclinical levels of psychological distress at the bedside. Finally, the impact of caring for distressed family members with respect to nursing workload should be considered. While it is absolutely necessary to take into account acuity of the ill child when creating patient assignments, the needs of family members may also place additional caregiving demands upon the nurse. This should be broadly acknowledged in order to ensure that nurses are well supported in the delivery of care to patients and family members each shift.

Conclusion

The antecedents and resultant consequences of a diagnosis of cancer in the child impact the entire family. Disruptions to the family system, and subsequent distress exhibited in parents of children with cancer carry important implications for the psychological health and wellbeing

of the child. No systematic review has reported on the chronology and etiology of those factors influencing distress in family members of pediatric oncology patients on active treatment. This study applied the 4Ps of case formulation as a theoretical framework enabling the systematic categorization of factors related to psychological distress. This research carries important implications for nursing practice, as it may serve in the development and timely implementation of interventions specific to the chronological manifestations of psychological distress and its causative agents. Nurses should therefore have capacity to: (i) recognize manifestations of distress in family members of children with cancer; (ii) identify those predisposing, precipitating, perpetuating, factors unique to the family unit that may increase the risk of distress; (iii) determine those factors specific to the family that may protect against its development; (iv) develop and implement clinical interventions using a strength-based approach; and (v) evaluate the efficacy of clinical intervention(s) on an ongoing basis. Acquired knowledge of the etiology, temporality and variability of psychological distress and its trajectories could serve to: (i) mitigate potential adverse psychological outcomes in family members of children with cancer on active treatment; and (ii) permit timely and efficacious allocation of psychosocial resources tailored to meet the unique needs of family members.

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Appendices

Appendix A

Critical Appraisal of Systematic Reviews

Table 1A

Critical Appraisal of van Warmerdam et al. (2019) Meta-analysis, and Sultan et al. (2016), Long et al. (2018), and Murawsky (2022) Systematic Reviews

Criteria	**van Warmerdam et al. 2019**	**Sultan et al. 2016**	**Long et al. 2018**	**Murawsky, 2022**
1. Did the search questions and inclusion criteria for the review include components of PICO?	CM	CM	CM	CM
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	CM	CM	CNM	CM
3. Did the review authors explain their selection	CPM	CPM	CPM	CM

of the study designs for inclusion in the review?				
4. Did the review authors use a comprehensive literature search strategy?	CPM	CPM	CM	CM
5. Did the review authors perform study selection in duplicate?	CM	CM	CM	CM
6. Did the review authors perform data extraction in duplicate?	CM	CM	CM	CM
7. Did the review authors provide a list of excluded studies and justify the exclusion(s)?	CM	CM	CM	CM
8. Did the review authors describe the included studies in adequate detail?	CPM	CPM	CM	CM
9. Did the review authors use satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	CPM	CPM	CM	CNM
10. Did the review authors report on the source of funding for the studies included in the review?	CM	CNM	CM	CM
11. If meta-analysis was performed did the review authors use	CM	NA	NA	NA

appropriate methods for statistical combination of results?				
12. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?	CNM	NA	NA	NA
13. Did the review authors account for risk of bias in individual studies when interpreting / discussing the results of the review?	CM	CPM	CNM	CNM
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	CM	CNM	CM	CNM
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	CNM	NA	NA	NA
16. Did the review authors report any potential	CM	CNM	CM	CM

sources of conflict of interest, including any funding they received for conducting the review?				

Note. CM, criteria met; CNM, criteria not met; CPM, criteria partially met; NA, not applicable.

Table 2A

Critical Appraisal of van Warmerdam et al.'s (2019) Systematic Review

	Criteria Met	**Criteria Partially Met**	**Criteria Not Met**	**Not Applicable (N/A)**
17. Did the search questions and inclusion criteria for the review include components of PICO?	Population: parents of children with cancer Intervention: N/A Comparator group: N/A Outcome: determine the prevalence of mental illness in parents of children with cancer			
18. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	The authors stated the meta-analysis was done in accordance with PRISMA guidelines.			
19. Did the review authors explain their selection of the study designs for inclusion in the review?		Exclusion criteria were narrative reviews and studies not in full manuscript form.		
20. Did the review authors use a comprehensive literature search strategy?		Searched from database inception to December 2016: Ovid Medline, EMBASE, CINAHL, and PsychINFO. Key word(s) and search term(s) listed.		

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
21. Did the review authors perform study selection in duplicate?	Full text review was conducted independently by two authors. Discrepancies were resolved by consensus.			
22. Did the review authors perform data extraction in duplicate?	Data extraction was performed in duplicate. Discrepancies were resolved by consensus.			
23. Did the review authors provide a list of excluded studies and justify the exclusion(s)?	328 full text articles were discarded. Reasons for exclusion were listed.			
24. Did the review authors describe the included studies in adequate detail?		Study characteristics are presented in a tabular summary.		
25. Did the review authors use satisfactory technique for assessing the risk of bias in individual studies that were included in the review?		Study quality was evaluated independently by two authors using a tool based on the 9-item JBI Checklist for Studies Reporting Prevalence Data.		
26. Did the review authors report on the source of funding for the studies included in the review?	The authors reported the source of funding: Canadian Cancer Society Research Institute (Grant number: 704448).			

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
27. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	"The meta- analysis was performed using Review Manager version 5.3 with a random effects model given the diversity in samples and study methods.38 Result estimates were calculated as a weighted average of the interventional effects estimated in individual studies as defined by Cochrane Reviews." (van Warmerdam et al., 2019, p.7).			
28. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?			Not explicitly stated.	
29. Did the review authors account for risk of bias in individual studies when interpreting / discussing the results of the review?	Heterogeneity of study findings "…limited the interpretation of our pooled prevalence calculations and likely explained the conflicting results described by past literature. Thus, the current literature does not allow for robust findings that might guide clinical practice…" (van Warmerdam et al., 2019, p.6)		.	

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
30. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Authors addressed factors contributing to heterogeneity of study findings (e.g. varied use of measurement tools, populations studied etc).			
31. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?			Not specified.	
32. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No conflicts to disclose.			

Table 3A

Critical Appraisal of Sultan et al.'s (2016) Systematic Review

	Criteria Met	**Criteria Partially Met**	**Criteria Not Met**	**Not Applicable (N/A)**
1. Did the search questions and inclusion criteria for the review include components of PICO?	Population: parents of children (0 – 18 years) that suffered from cancer Intervention: N/A Comparator group: N/A Outcome: consequences of parental emotional distress (Sultan et al., 2016)			
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	The review protocol was registered on Prospero on the 20th of September 2013. The authors explicitly stated the review was conducted in accordance with the PRISMA (Moher at al., 2009) and AMSTAR (Shea et al., 2007) guidelines.			
3. Did the review authors explain their selection of the study designs for inclusion in the review?		The review authors stated that the intent was to focus on quantitative empirical studies that were able to yield association estimates.		

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
4. Did the review authors use a comprehensive literature search strategy?		Academic databases: PubMed, PsycINFO, and CINAHL. Key word(s) and search term(s) listed. Publication restrictions justified. Reference lists of eligible studies reviewed.		
5. Did the review authors perform study selection in duplicate?	Study selection was conducted independently by two authors. Discrepancies were resolved by consensus.			
6. Did the review authors perform data extraction in duplicate?	Data extraction was performed in duplicate. Discrepancies were resolved by consensus.			
7. Did the review authors provide a list of excluded studies and justify the exclusion(s)?	228 full text articles were discarded on the basis that they were not quantitative empirical studies.			
8. Did the review authors describe the included studies in adequate detail?		The review authors described the following study characteristics: population, interventions, comparators (where relevant), outcomes, and research designs.		

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
9. Did the review authors use satisfactory technique for assessing the risk of bias in individual studies that were included in the review?		Articles included in the review were assessed for risk of bias according criteria adapted from the Cochrane Handbook for systematic reviews of interventions. The following domains were rated independently: Selection, Attrition, Reporting, and Other. In the 'Other' domain, the Cochrane guideline to behavioral observational research was adapted. Criteria was rated on the basis of: Sample size, Measurement quality, Response rate maximization, Research design and Appropriateness of analyses for hypothesis testing. Domains were aggregated into one global rating. The rating of biases was performed independently by two review authors.		

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
10. Did the review authors report on the source of funding for the studies included in the review?			Sources of funding for individual studies included in the review were not reported.	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?				No meta-analysis conducted.
12. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?				No meta-analysis conducted.
13. Did the review authors account for risk of bias in individual studies when interpreting / discussing the results of the review?		Authors stated that, while excluded studies may have had a high risk of bias, findings may still well be informative. Findings from studies with a high risk of bias were presented in a supplementary table.		
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?			No discussion or explanation of heterogeneity observed in the results of the review provided.	

	Criteria Met	**Criteria Partially Met**	**Criteria Not Met**	**Not Applicable (N/A)**
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?				No meta-analysis conducted.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?			Sources of potential conflicts of interests were not acknowledged.	

Table 4A

Critical Appraisal of Long et al.'s (2018) Systematic Review

	Criteria Met	**Criteria Partially Met**	**Criteria Not Met**	**Not Applicable (N/A)**
1. Did the search questions and inclusion criteria for the review include components of PICO?	Population: siblings (≤25 years old at diagnosis) of children with cancer (≤19 years old at diagnosis) Intervention: N/A Comparator group: normative samples, controls, or standard scores Outcome: psychosocial outcomes (i.e., emotional, social, and behavioral functioning; psychopathology; QoL; health-related and/or physiological outcomes; social roles) (Long et al., 2018)			
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?			The review authors did not explicitly state compliance with the guidelines outlined per the Cochrane review guidelines.	

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
3. Did the review authors explain their selection of the study designs for inclusion in the review?		Quantitative, qualitative, and mixed methods studies included "to provide a comprehensive perspective on the developmental consequences of cancer for siblings" (Long et al.,2018).		
4. Did the review authors use a comprehensive literature search strategy?	The review authors searched the following academic databases for sibling-related articles published between January 2008 and July 2016: Medline / PubMed, PsycINFO, and CINAHL. Key word(s) and search term(s) were listed. Publication restrictions (i.e., language) were justified. References of all studies chosen for full-text review were manually searched for relevant studies.			
5. Did the review authors perform study selection in duplicate?	Study selection was conducted independently by two authors. Discrepancies were resolved by consensus. All authors were reported to have some level of expertise in either: (a) psychology; or (b) pediatric oncology.			
6. Did the review authors perform data extraction in duplicate?	Data extraction was performed in duplicate. Discrepancies were resolved by consensus.			

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
7. Did the review authors provide a list of excluded studies and justify the exclusion(s)?	Of the 221 articles selected for full-text review, 123 did not meet inclusion criteria.			
	Reasons for exclusion: (a) not sibling-related; (b) no context; (c) not empirical; (d) not concerning pediatrics; (e) not psychosocial; (f) not cancer-related; (g) unable to access article; (h) same sample / outcome already included.			
8. Did the review authors describe the included studies in adequate detail?	The review authors described the following study characteristics in detail: population, comparators (where relevant), psychosocial outcomes, and research designs.			
9. Did the review authors use satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	Studies were rated for scientific merit on criteria derived from both: (a) quantitative; and (b) qualitative publishing guidelines. All authors independently rated 3 papers. Ratings were then discussed. "Intra-class correlations demonstrated high inter-rater reliability (0.92 for qualitative and 0.95 for quantitative studies)" (Long et al., 2018, p2).			

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
10. Did the review authors report on the source of funding for the studies included in the review?			Sources of funding for individual studies included in the review were not reported.	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?				No meta-analysis conducted.
12. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?				No meta-analysis conducted.
13. Did the review authors account for risk of bias in individual studies when interpreting / discussing the results of the review?			The review did not provide a discussion of the likely impact of risk of bias on the results.	
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Limitations identified within the literature: - siblings to be compared with non-matched control groups (e.g., those matched to the patient/survivor) diminishes internal validity			

	Criteria Met	Criteria Partially Met	Criteria Not Met	Not Applicable (N/A)
	- non-diverse samples and low response rates raise questions of external validity and generalizability			
	of findings - lack of longitudinal designs leads to poor understanding of risk processes or adjustment trajectories - heterogeneity in sample characteristics (e.g., sibling age, treatment status) (Long et al., 2018)			
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?				No meta-analysis conducted.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Conflicts of interest reported as “none declared”. Sources of funding were acknowledged.			

Appendix B

Search Strategy

Family Distress + Cancer Systematic Review

Search Methods Section

Prepared by: Lindsey Sikora, University of Ottawa

Date: May 25, 2018

Methods

The following databases were searched by a health sciences librarian (LS) during the electronic component of the systematic review: Medline and Medline in Process (via OVID), Embase Classic + Embase (via OVID), Cochrane's Central Registry for Randomized Controlled Trials, CENTRAL (via OVID), PsycINFO (via Ovid), the Cumulative Index of Allied Health and Nursing Literature (CINAHL via EBSCOHost), ERIC (via Ovid) PubMed. A search strategy was developed in Medline, and then translated into the other databases, as appropriate. All databases were searched from the date of inception to May 22, 2018. There were no language exclusion criteria, nor any other publication restrictions. All references were entered into an Endnote file for processing (n = 14,811).

Database searches (numbers for PRISMA flowchart):

Medline in Process and Medline (via OVID): n = 4622

Embase (via OVID): n = 6102

ERIC (via OVID): n = 90

CENTRAL (via OVID): n = 276

PsycINFO: n = 2048

CINAHL: n = 956

PubMed: n = 717

Total: n = 14,811

Duplicates: n = 4894

Total with duplicates removed: n = 9917

Medline and CENTRAL:

1. exp NEOPLASMS/

2. (neoplasm* or cancer* or tumor* or tumour* or carcino* or malignan* or adenocarcinoma* or sarcoma* or adenoma* or chondrosarcoma* or fibrosarcoma* or dermatofibrosarcoma* or neurofibrosarcoma* or hemangiosarcoma* or leiomyosarcoma* or liposarcoma* or myosarcoma* or rhabdomyosarcoma* or myxosarcoma* or osteosarcoma* or lymphoma*).tw.

3. or/1-2

4. family/ or grandparents/ or nuclear family/ or exp parents/ or siblings/

5. (sibling* or sister* or brother*).tw.

6. Caregivers/

7. (famil* or mother or mothers or father or fathers or parent* or caregiver* or care giver* or carer*).tw.

8. (grandparent* or grandm* or grandfather* or grandpa*).tw.

9. (famil* adj2 member*).tw.

10. or/4-9

11. anxiety/ or catastrophization/

12. (anxiet* or catastroph* or distress* or nervous* or hypervigil* or frustrat* or stress* or agitat* or trauma* or externaliz* or externalis*).tw.

13. anxiety disorders/ or anxiety, separation/ or neurotic disorders/ or panic disorder/ or exp phobic disorders/

14. psychological trauma/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/

15. Somatoform Disorders/

16. fear/ or panic/ or frustration/

17. or/11-16

18. Adolescent/ or exp Child/ or exp Infant/ or Pediatrics/ or Young Adult/ or (child or children or childhood or infant or infants or baby or babies or newborn or newborns or neonate or neonatal or neonates or preemie or preemies or infancy or paediatric or pediatric or girl or girls or boy or boys or kid or kids or teen or teens or teenage or teenager or teenagers or youngster or youngsters or youth or youths or adolescent or adolescents or adolescence or preadolescent or preadolescence or pre adolescent or pre adolescence or preschooler or school age or school aged or schoolchildren or young adult*).tw.

19. 3 and 10 and 17 and 18

Embase

PubMed

((((((((((anxiety[MeSH Terms]) OR catastrophization[MeSH Terms]) OR anxiety disorders[MeSH Terms]) OR stress disorders, traumatic[MeSH Terms]) OR somatoform disorders[MeSH Terms]) OR fear[MeSH Terms]) OR panic[MeSH Terms]) OR frustration[MeSH Terms]) OR ((anxiet*[Title/Abstract] OR catastroph*[Title/Abstract] OR

distress*[Title/Abstract] OR nervous*[Title/Abstract] OR hypervigil*[Title/Abstract] OR frustrat*[Title/Abstract] OR stress*[Title/Abstract] OR agitat*[Title/Abstract] OR trauma*[Title/Abstract] OR externaliz*[Title/Abstract] OR externalis*)[Title/Abstract]))) AND ((((((Family[MeSH Terms]) OR grandparents[MeSH Terms]) OR nuclear family[MeSH Terms]) OR parents[MeSH Terms]) OR siblings[MeSH Terms]) OR ((sibling*[Title/Abstract] OR sister*[Title/Abstract] OR brother*[Title/Abstract] OR famil*[Title/Abstract] OR mother[Title/Abstract] OR mothers[Title/Abstract] OR father[Title/Abstract] OR fathers[Title/Abstract] OR parent*[Title/Abstract] OR caregiver*[Title/Abstract] OR care giver*[Title/Abstract] OR carer*[Title/Abstract] OR grandparent*[Title/Abstract] OR grandm*[Title/Abstract] OR grandfather*[Title/Abstract] OR grandpa*)[Title/Abstract]))) AND ((neoplasms[MeSH Terms]) OR (. (neoplasm*[Title/Abstract] OR cancer*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR carcino*[Title/Abstract] OR malignan*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR adenoma*[Title/Abstract] OR chondrosarcoma*[Title/Abstract] OR fibrosarcoma*[Title/Abstract] OR dermatofibrosarcoma*[Title/Abstract] OR neurofibrosarcoma*[Title/Abstract] OR hemangiosarcoma*[Title/Abstract] OR leiomyosarcoma*[Title/Abstract] OR liposarcoma*[Title/Abstract] OR myosarcoma*[Title/Abstract] OR rhabdomyosarcoma*[Title/Abstract] OR myxosarcoma*[Title/Abstract] OR osteosarcoma*[Title/Abstract] OR lymphoma*)[Title/Abstract])) Filters: Adolescent: 13-18 years; Child: 6-12 years; Child: birth-18 years; Infant: 1-23 months; Infant: birth-23 months; Newborn: birth-1 month; Preschool Child: 2-5 years; Adult: 19+ years; Young Adult: 19-24 years

CINAHL

#	Query
S14	S3 AND S9 AND S13
S13	S10 OR S11 OR S12
S12	(anxiet* or catastroph* or distress* or nervous* or hypervigil* or frustrat* or stress* or agitat* or trauma* or externaliz* or externalis*)
S11	(MH "Anxiety Disorders+") OR (MH "Somatoform Disorders")
S10	(MH "Anxiety") OR (MH "Fear") OR (MH "Frustration") OR (MH "Suffering") OR (MH "Separation Anxiety") OR (MH "Hopelessness")
S9	S4 OR S5 OR S6 OR S7 OR S8
S8	(grandparent* or grandm* or grandfather* or grandpa*)
S7	(famil* or mother or mothers or father or fathers or parent* or caregiver* or care giver* or carer*)

S6	(sibling* or sister* or brother*)
S5	(MH "Caregivers")
S4	(MH "Family") OR (MH "Nuclear Family+") OR (MH "Grandparents")
S3	S1 OR S2
S2	. (neoplasm* or cancer* or tumor* or tumour* or carcino* or malignan* or adenocarcinoma* or sarcoma* or adenoma* or chondrosarcoma* or fibrosarcoma* or dermatofibrosarcoma* or neurofibrosarcoma* or hemangiosarcoma* or leiomyosarcoma* or liposarcoma* or myosarcoma* or rhabdomyosarcoma* or myxosarcoma* or osteosarcoma* or lymphoma*)
S1	(MH "Neoplasms+")

Appendix C

Screening Guide

Table 1C

Research Question: Population, Intervention, Professionals, Outcomes, Health Care Setting and Context (PIPOH) Format

	Description	**Inclusion Criteria**	**Exclusion Criteria**
Population	Study participants eligible for inclusion in the present systematic review	Family members (parents, foster parents, surrogates, aunts and uncles, grandparents, and siblings etc.) of pediatric cancer patients (< 21 years of age) on active treatment	Children with cancer
Intervention(s) of Interest		Not applicable	Interventions to manage psychological distress
Professionals		Healthcare professionals working in pediatric oncology	

Outcomes		Any factors described in the results section of identified studies as positively or negatively influencing psychological distress as a primary or secondary outcome	Outcomes only reported in the introduction or discussion sections of the manuscript
Health Care Setting and Context		All settings where pediatric oncology care is delivered	
Language		Studies must be published in English	
Study Design		Randomized and nonrandomized, quantitative descriptive and mixed methods studies	Dissertations, book chapters, conference proceedings, non-peer reviewed publications or reports, systematic reviews, qualitative studies, editorials and commentaries

Eligibility Criteria

Inclusion criteria. Studies published in peer-reviewed journals examining distress as a primary or secondary outcome in family members of pediatric cancer patients on active treatment will be considered for inclusion.

Study criteria. Randomized and nonrandomized, as well as quantitative descriptive and mixed method studies, examining factors related to psychological distress (at both clinical and subclinical levels) in family members of pediatric cancer patients on active treatment will be eligible. Psychological distress will be operationalized as an overarching construct comprising specific domains: (a) anxiety; (b) depression; and (c) posttraumatic stress symptoms; (d) somatization. Themes and subthemes of psychological distress as reported in the qualitative literature will be included. Studies must be published in English and may have been conducted in any setting. Application of a date limit on the initial search of the literature was not done in order to retrieve as many relevant studies as possible (Polit & Beck, 2012).

Distress measure criteria. Psychological distress in family members of pediatric cancer patients (all types of cancer) on active treatment (as opposed to those parents of children in survivorship) will be examined, as there is evidence to show that distress in family members is greater closer to time of the patient's diagnosis (Fainsibler Katz et al., 2018a; Fainsilber Katz et al., 2018b). Studies that employ an objective behavioral measure, as well as subjective self- or observer-report measure of psychological distress will be included in the review.

Family member criteria. Family members of children and adolescents less than 21 years of age and on active cancer treatment including caregivers (parents, foster parents, surrogates, aunts and uncles, grandparents, etc.) and siblings will be included.

Exclusion criteria. Studies examining distress in bereaved family members, or family members of end-of-life pediatric oncology patients will be excluded. Psychological distress compounded by the loss or anticipated loss of a child may incite protracted grief reactions which are unique to the bereavement process (Lichtenthal et al., 2015). To eliminate the risk of recall bias in review findings, retrospective reports of caregiver and sibling distress will be excluded. Dissertations, book chapters, conference proceedings, systematic reviews, qualitative studies, editorials and commentaries will be excluded.

Data Extraction

Data Collection Process. A computerized data extraction form and coding manual will be developed to guide authors in extracting relevant information regarding study characteristics. The data extraction form will be pilot tested using a representative sample of the studies selected for inclusion ("Cochrane Handbook for Systematic Reviews of Interventions," 2011). Two authors will conduct data extraction and coding of information independently to reduce errors and the introduction of potential biases ("Cochrane Handbook for Systematic Reviews of Interventions," 2011). Disagreements will be resolved through discussion with a third author ("Cochrane Handbook for Systematic Reviews of Interventions," 2011). The authors of included studies will be contacted should any uncertainties arise.

Data Items

The following methodological data items will be coded for each included study: (a) data source, (b) study country, (c) language, (e) study design, (f) methods, and (g) source of funding. Characteristics of family members, as well as characteristics of the associated child with cancer, will also be encoded. Specifically, data on the following items will be collected: (a) age, sex, diagnosis, and treatment variables of children with cancer; and (b) age, sex, developmental stage,

education level, language, culture, religion, residence (i.e., urban / rural), employment status, socioeconomic status, marital status, access to health services, and health literacy level of sibling(s) and caregiver(s). Type of caregiver (e.g., parent, guardian, foster parent, grandparent) will also be recorded. Data items indicative of psychological distress (i.e., depression, anxiety, PTSS, and somatization) will be recorded.

Appendix D

Rationale for Exclusion of Full Text Articles

Table 1D

Conflict Resolution and Documentation of Exclusion of Full Text Articles

Conflicts [sort by author]	Conflict Resolution (1st look by MM)	Conflict Resolution FINAL w/ VS
Article #	INClude / EXClude [+reasoning]	INClude / EXClude
3088	EXC [population of study --> criteria --> child who recently finished chemo]	EXC population of study
14281	EXC [population of study --> criteria --> peds pts. on / off treatment]	EXC population of study
14227	EXC [population of study 60% of children NOT on active treatment]	EXC population of study
11343	EXC [population of study --> criteria --> 75.2% of peds pts. on active treatment]	EXC population of study
14110	EXC [population of study --> criteria --> includes pts. post chemo, RT and PHSCT]*	EXC population of study
14637	Possible EXC [qual. themes and subthemes are broad + do not explicitly align with outcomes of interest]*	EXC outcomes
14523	EXC [population of study --> do not include age of pediatric oncology patients]	EXC population of study
13980	EXC [population of study --> includes bereaved siblings]	EXC population of study
13971	INC vs. EXC [describes clinic visits contributing to anxiety]	EXC outcomes
13962	EXC [population of study --> includes siblings of pts. off treatment]	EXC population of study
13959	EXC [population of study --> includes siblings of pts. off treatment]	EXC population of study
13824	EXC [population of study --> includes siblings of pts. off treatment]	EXC population of study
13709	EXC [population of study --> 46.8% of pts. In remission --> not explicit if still receiving therapy]	EXC population of study
13648	EXC [population of study --> criteria --> peds pts. on / off treatment]	EXC population of study
13461	EXC [non-peer reviewed --> editorial]	EXC non-peer reviewed
13369	EXC [non-peer reviewed --> from a conference proceeding?]	EXC non-peer reviewed
13853	EXC [population of study --> includes peds pts. off treatment]	EXC population of study
13317	EXC [looks at efficacy of spiritual care training in pop. of interest]	EXC looking at an intervention

13016	INC [looks at LP/BPMA + catastrophizing + distress outcomes --> parent distress scale measures anxiety]	INC
12884	INC [looks at LP/BPMA + catastrophizing + distress outcomes]	EXC duplicate
12867	EXC [not explicit if peds pts. are on active treatment]	EXC population of study
12781	EXC [population of study --> includes peds pts. off treatment]	EXC population of study
12676	EXC [outcomes]	EXC outcomes
12606	EXC [outcomes --> structure + validity of PTSD models]	EXC outcomes
12599	EXC [outcomes --> efficacy + feasibility of an intervention--> guided self-help]	EXC outcomes
12585	EXC [outcomes --> efficacy + feasibility of an intervention --> internet based guided self-help]	EXC outcomes
12583	EXC [outcomes --> high PTSS / PTSD may result in attentional bias exacerbating symptoms and not VICE VERSA]	EXC outcomes
8354	INC [qualitative themes of psych. distress]	EXC study design
12918	EXC [population of study --> "fatally ill children"]	EXC population of study
12915	INC [looks at depression subscle in parents of kids w/ ca]	EXC does not operationalize depression as a form of psychological distress
12398	INC [waiting and not knowing categorized as distressing] *	EXC no themes RE umbrella of psychological distress
12067	EXC [population of study --> includes peds pts. off treatment]	EXC population of study
12015	INC [exmines state anxiety and depression]	INC
11388	EXC [pop. of study --> includes peds pts. off treatment]	EXC population of study
11981	EXC [outcomes --> marital distress]	EXC outcomes
11977	EXC [outcomes --> could also be pop. of study as is longitudinal] *	EXC outcomes
11880	EXC [includes peds pts > 5 years from diagnosis - likely off treatment but not explicit]	EXC population of study
11418	INC	INC
10987	EXC [looks at effects of narrative writing on depression]	EXC study design
12141	INC [not epxlicit about treatment satus] *	EXC population of study
11369	EXC outcomes --> looks at whether maternal distress predicts child adjustment	EXC outcomes
10844	EXC [outcomes --> what stressors increase sibling conflict?]	EXC outcomes
10449	EXC [population of study --> "13 years post diagnosis"]	EXC population of study
7160	EXC [non-peer reviewed --> conference presentation]	
10398	EXC [not explicit if peds pts. are on active treatment]	EXC population of study

10245	EXC population of study [does not explicitly palliative patients are excluded]	EXC population of study
9847	EXC [population of study --> 11 kids in "follow up"]	EXC population of study
9802	EXC [population of study --> 25% still receiving treatment]	EXC population of study
9751	EXC [populatio of study --> kids in remission / off treatment]	EXC population of study
10306	EXC [population of study --> includes diagnosis of langherhans cell histiocytosis]	EXC [population
9523	EXC [looks at efficacy of pedometer walkng intervention]	EXC outcomes
9500	EXC [population of study --> 1-12 years post diagnosis and treatment]	EXC population of study
10035	EXC [abstract only]	EXC abstract only
9605	EXC [outcomes --> does not use specific measures of psych distress]	EXC outcomes
9602	EXC [outcomes --> looks at coping]	EXC outcomes
9596	EXC [outcomes --> looks at effects of coping]	EXC outcomes
9032	EXC [population of study --> includes kids off treatment]	EXC population of study
8930	EXC [population of study --> 5 kids off treatment]	EXC population of study
8312	EXC [outcomes --> measures coping]	EXC outcomes
8228	EXC [population of study --> kids off treatment]	EXC population of study
8748	EXC population of study [kids off treatment ithin 2 years of diagnosis]	EXC population of study
8157	EXC [outcomes --> looking at resource use]	EXC outcomes
7887	EXC population of study [28 relapse free survivors]	EXC population of study
8386	EXC [population of study --> includes kids in "follo up" post treatment completion]	EXC population of study
7857	EXC [population of study --> follow up care]	EXC population of study
7564	INC [criterion that patient receive chemotherapy]	INC
7160	EXC [non-peer reviewed --> supplement]	EXC non-peer reviewed
7057	INC	INC
7772	EXC [outcomes --> looks at coping]	EXC coping]
7632	EXC [outcomes --> look at effects on marital relationships]	EXC outcomes
7284	EXC [retrospective]	EXC [retrospective]
6396	EXC [population of study --> some children off treatment --> no exclusion criteria for on treatment kids --> "16% just taking meds"]	EXC population of study
5626	EXC [population of study --> includes other non malignancies --> "only 84% peds onc]	EXC population of study
5206	EXC [population of study --> "treatment completion date"]	EXC population of study

5199	EXC population of study [age of peds patients > 21 years]	EXC
5459	EXC [population of study --> includes sibs of kids off treatment]	EXC population of study
5444	EXC popultion of study "16 kids off treatment"	EXC population of study
4792	EXC population of study "53% kids completed treatment"	EXC population of study
4767	EXC [population of study --> treatment completed]	EXC population of study
175	EXC [population of study --> kids five years out of treatment]	EXC population of study
4973	EXC [population of study --> bereaved siblings]	EXC population of study
4217	EXC [study design --> retrospective study]	EXC study design
5360	INC [looks at parental distress, perceived stress, global distress]	INC
5342	EXC [compare on / off treatment parents --> only one finding was significant --> PTSS]	EXC outcomes
5749	INC	INC
3961	EXC [outcomes] focuses on intervention compared to control	EXC
3818	"Most of kids undergoing chemotherapy" EXC population of study	EXC population of study
3708	EXC [population of study --> neurofibromatosis type 1]	EXC population of study
3561	EXC [outcomes --> looks at adjustment of the child on treatment --> moderators / association of child and parent distress]	EXC outcomes
3527	EXC [outcomes --> looks at coping]	EXC outcomes
3241	EXC [looks at coping]	EXC coping
2943	INC	INC
2940	EXC population of study [longitudinal - kids off treatment - duration of treatment 2 years]	EXC population of study
2563	EXC [mothers referred to peds care center seeking treatment for child]	EXC
2559	EXC [criterion to change DSM-IV-TR]	EXC [outcomes]
2539	EXC [population of study --> not clear if some off treatment kids included)	EXC population of study
2360	EXC [population of study --> 62% of kids still on treatment at time of study]	EXC population of study
1765	EXC [outcomes] --> looking at social isolation	EXC outcomes
1450	EXC [outcomes --> looks at metacognition / negative affect]	EXC outcomes
1381	EXC [population of study --> "not more than 1 year post treatment"]	EXC population of study
912	EXC population of study [included children in remission]	EXC population of study
869	EXC [looks at anxiety / depression in relation to caregiver burden]	EXC outcomes
855	EXC [behavioral outcomes]	EXC outcomes

524	EXC [population of study --> kids in follow up]	EXC population of study
299	EXC [population of study --> kids in follow up]	EXC population of study
	Data extraction completed by Mmurawsky and CDiCarlo May 16th at 2142hrs EST (commenced at 1930hrs EST).	

Note. Dx., diagnosis; EXC, exclude; INC, include; peds, pediatric; pop, population; pts., patients; w/, with.

Appendix E

Tabular Summaries of Parent Factors

Table 1E

Parent Predisposing Factors of Psychological Distress

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Parent Predisposing Factors					
Female parental sex					
Iranmanesh, 2015	F 34.12, M 37.07	F 100, M 100	Iran	ALL n = 146 Wilms Tumor n = 24 Other n = 16 Brain Tumor n = 14	QD, C
Kazak, 2005	F 38.1, M 41.7	F 119, M 52	United States	Leukemias n = 67 Solid Tumors n = 33 Brain Tumors n = 14 Lymphomas n = 11	QD, C
Kostak, 2013	F 33.5, M 36.9	F 44, M 44	Turkey	Leukemia 61.4%	QD, C
Masa'deh, 2017	40.5	F 87, M 30	Jordan	NR*	QD, C
Magni, 1983	F 34, M 38	F 13, M 12	Italy	Leukemia n = 13	QD, L
Magni, 1986	F 33.6, M 36.7	F 21, M 20	Italy	ALL n = 16 HL n = 5	QD, L
McCarthy, 2012	NR* Range: 20 – 39 n = 120 > 40 n = 95	F 135, M 85	Australia	Solid Tumors n = 65 Leukemia n = 58 Brain + CNS n = 20	QD, L

	Missing n = 5				
Poder, 2008	F 36.7, M 39.1	214	Sweden	Leukemia n = 50 Other Solid Tumors n = 51 CNS Tumors n = 14	QD, C
Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Rodriguez, 2012	F 37.9, M 39.5	F 193, M 97	United States	Leukemia n = 75 Other Solid Tumors n = 50 Lymphoma n = 49 Brain Tumor n = 21	QD, C
Sawyer, 1993	NR*	F 22, M 19	Australia	ALL n = 9 Lymphoma n = 4 AML n = 3 Neuroblastoma n = 1 Wilms Tumor n = 1 Ewing Sarcoma n = 1 Choriocarcinoma n = 1	QD, L
Schepers, 2018	40.35	F 130, M 62	Netherlands	NR*	QNR
Shi, 2017	F 34.16, M 36.56	F 192, M 87	China	ALL n = 102 Other Leukemias n = 54 Lymphomas n = 46 Other solid Tumors n = 23 Soft tissue Sarcomas n = 18 Bone n = 17 SNS n = 17 CNS n = 8	QD, C
Pre-existing anxiety					
Al Qadire, 2018	37.3	F 176, M 46	Jordan	Leukemias + Lymphomas n = 135 Solid Tumors n = 87	QD, C
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12	QD, L

				Blood Disorder n = 9	
Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Cernvall,2016	39.0 *Missing data for three participants	F 55, M 24	Sweden	Leukemia n = 42 Sarcoma n = 11 Lymphoma n = 6 CNS Tumor n = 10 Other n = 10	QD, C
Dunn, 2012	F 37.9, M 39.5	F 190, M 93	United States	NR*	QD, C
Harper, 2016	34.71	F 85, M 17	United States	ALL 83.3% Wilms Tumor 4.9% NHL 2% Other Lymphomas 2% Other (i.e., Ewing's sarcoma, osteosarcoma, unspecified) 5.8%	QD, L
Hoekstra-Weebers, 1999	35.9	F 66, M 62	Netherlands	Leukemia n = 28 Lymphomas n = 12 Brain Tumors n = 8 Wilms Tumors n = 6 Sarcomas n = 6 Neuroblastoma n = 2 Germ Cell Tumors n = 2 Hepatoblastoma n = 2	QD, L
McCarthy, 2012	NR* Range: 20 – 39 n = 120 > 40 n = 95 Missing n = 5	F 135, M 85	Australia	Solid Tumors n = 65 Leukemia n = 58 Brain + CNS n = 20	QD, L
Penner,2016	33.98	P 96, GP 3	United States	All 79%	QD, L

Study Pre-existing depression	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Al Qadire, 2018	37.3	F 176, M 46	Jordan	Leukemias + Lymphomas n = 135 Solid Tumors n = 87	QD, C
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9	QD, L
Benaroya-Milshtein,2014	F 40.0, M 47.0	F 23, M 9	Israel	Leukemia 50% Solid tumors 25% Lymphomas 21% Other 4%	QD, C
Cernvall,2016	39.0 *Missing data for three participants	F 55, M 24	Sweden	Leukemia n = 42 Sarcoma n = 11 Lymphoma n = 6 CNS Tumor n = 10 Other n = 10	QD, C
Dunn, 2012	F 37.9, M 39.5	F 190, M 93	United States	NR*	QD, C
Fife,1987	NR*	F 33, M 27	United States	Leukemia n = 34	QD, L
Sherief, 2015	F 30.11, M 32.74	178	Egypt	ALL n = 213	QD, C
Shi, 2017	F 34.16, M 36.56	F 192, M 87	China	ALL n = 102 Other Leukemias n = 54 Lymphomas n = 46 Other solid Tumors n = 23 Soft tissue Sarcomas n = 18 Bone n = 17	QD, C

				SNS n = 17 CNS n = 8	
Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Masa'deh, 2017	40.5	F 87, M 30	Jordan	NR*	QD, C
Socioeconomic status (low education level, unemployment status, low income)					
Bemis, 2015	37.5	F 318	United States	Leukemia n = 114 Other Solid Tumors n = 96 Lymphoma n = 79 Brain Tumors n = 28	QD, C
Chen, 2015	31.5	231	China	Acute lymphocytic leukemia n = 130 Acute non lymphocytic leukemia n = 34	QD, C
Cernvall, 2016	39.0 *Missing data for three participants	F 55, M 24	Sweden	Leukemia n = 42 Sarcoma n = 11 Lymphoma n = 6 CNS Tumor n = 10 Other n = 10	QD, C
Demirtepe Saygili, 2011	33.1 Range: 18 – 51	P(F)90, P(M)3, A 4 Sisters (n = 3), Aunts (n = 4)	Turkey	Leukemia n = NR*	QD, C
Dunn, 2012	F 37.9, M 39.5	F 190, M 93	United States	NR*	QD, C
Harper, 2013	35.65	F 60, M 15	United States	ALL 80% Other 7% Wilms Tumors 5% NHL 4 % Astrocytoma 3% Rhabdomyosarcoma 1%	QD, L

Masa'deh, 2017	40.5	F 87, M 30	Jordan	NR*	QD, C
Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Molzon, 2018	F 35.3, M 37.4	150	United States	Leukemias + Lymphomas n = 75 Non-CNS solid tumors n = 46 Brain Tumors n = 29	QD, C
Phipps, 2004	NR*	F 139, M 9, O 3	United States	ALL n = 23 AML n = 40 Other Leukemias n = 30 Neuroblastoma n = 16 Other Solid Tumor n = 16	QD, L
Poder,2008	F 36.7, M 39.1	214	Sweden	Leukemia n = 50 Other Solid Tumors n = 51 CNS Tumors n = 14	QD, L
Rodriguez, 2012	F 37.9, M 39.5	F 193, M 97	United States	Leukemia n = 75 Other Solid Tumors n = 50 Lymphoma n = 49 Brain Tumor n = 21	QD, C
Shi, 2017	F 34.16, M 36.56	F 192, M 87	China	ALL n = 102 Other Leukemias n = 54 Lymphomas n = 46 Other solid Tumors n = 23 Soft tissue Sarcomas n = 18 Bone n = 17 SNS n = 17 CNS n = 8	QD, C
Tremolada, 2012	37.39	F 94	Italy	ALL n = 104 AML n = 24	QD, L
Younger parental age					
Masa'deh, 2017	40.5	F 87, M 30	Jordan	NR*	QD, C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
McCarthy, 2012	NR* Range: 20 – 39 n = 120 > 40 n = 95 Missing n = 5	F 135, M 85	Australia	Solid Tumors n = 65 Leukemia n = 58 Brain + CNS n = 20	QD, L
Poder, 2008	F 36.7, M 39.1	214	Sweden	Leukemia n = 50 Other Solid Tumors n = 51 CNS Tumors n = 14	QD, L
Increased age of the ill child at time of diagnosis					
Tremolada, 2012	37.39	F 94	Italy	ALL n = 104 AML n = 24	QD, L
Decreased age of the ill child at time of diagnosis					
Al Qadire, 2018	37.3	F 176, M 46	Jordan	Leukemias + Lymphomas n = 135 Solid Tumors n = 87	QD, C
Impaired family functioning					
Patino-Fernandez, 2008	F 38.0, M 41.2	F 129, M 72	United States	Leukemias (ALL, AML, CML) n = 52 Brain tumors n = 31 Lymphomas n = 16 Neuroblastoma n = 11 Other sarcomas n = 10 HL n = 7 Ewing Sarcoma n = 4 Osteosarcomas n = 2 Germ Cell Tumors n = 2	QD, C

				Wilms Tumors n = 2 Carcinoma n = 1	
Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Schepers, 2018	40.35	F 130, M 62	Netherlands	NR*	QNR
Female sex (ill child)					
Poder, 2008	F 36.7, M 39.1	214	Sweden	Leukemia n = 50 Other Solid Tumors n = 51 CNS Tumors n = 14	QD, L
Gender role					
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9	QD, L
Higher number of children in the household					
Demirtepe-Saygili, 2011	33.1 Range: 18 – 51	P(F)90, P(M)3, A 4 Note: Sisters (n = 3), Aunts (n = 4)	Turkey	Leukemia n = NR*	QD, C
Vernon, 2016	F 36.0, M 38.99	F 41, M 25	Australia	Leukemia n= 3 Solid Tumors n = 17 Brain / CNS n = 1 Neuroblastoma n = 7 Wilm's Tumor n = 2 Other Solid Tumor n = 6 Other n = 3	QD, C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Higher paternal education level					
Mu, 2001	F 35.9, M 39.0	100	Taiwan	Leukemia 27% Brain Tumors 41% Osteosarcoma 12% Yolk Sac Tumor 7% Other 13%	QD, C
Mu, 2002	F 35.4, M 39.3	F 80, M 80	Taiwan	Leukemia n = 21 Brain Tumor n = 30 Osteosarcoma n = 9 Yolk Sac Tumor n = 4 Other n = 16	QD, C
Increased age of the ill child at diagnosis					
Molzon, 2018	F 35.3, M 37.4	150	United States	Leukemias + Lymphomas n = 75 Non-CNS Solid Tumors n = 46 Brain Tumors n = 29	QD, C
Increased maternal age					
Ben-Zur, 2017	39.1	F 197	Israel	Leukemia n = 80 Other NR*	QD, C
Chen, 2015	31.5	231	China	Acute lymphocytic leukemia n = 130 Acute non lymphocytic leukemia n = 34	QD, C
Increased paternal age and diagnosis of ALL or solid tumors in the child					
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16	QD, L

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
				Solid Tumors n = 12 Blood Disorder n = 9	
Non-married status of the mother					
Bemis, 2015	37.5	F 318	United States	Leukemia n = 114 Other Solid Tumors n = 96 Lymphoma n = 79 Brain Tumors n = 28	QD, C
Patino-Fernandez, 2008	F 38.0, M 41.2	F 129, M 72	United States	Leukemias (ALL, AML, CML) n = 52 Brain tumors n = 31 Lymphomas n = 16 Neuroblastoma n = 11 Other sarcomas n = 10 HL n = 7 Ewing Sarcoma n = 4 Osteosarcomas n = 2 Germ Cell Tumors n = 2 Wilms Tumors n = 2 Carcinoma n = 1	QD, C
Neuroticism					
Dolgin, 2007	35.0	F 217	Israel + United States	Leukemia n = 42 Other Tumor n = 32 Brain Tumor n = 12 NHL n = 7 HL n = 6	RCT
Parental negative affectivity and social inhibition (type D personality disorder)					
Chen, 2015	31.5	F 135, M 96	China	ALL n = 130 Acute Non-Lymphocytic Leukemia n = 34	QD, C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Past parental trauma					
Poder,2008	F 36.7, M 39.1	214	Sweden	Leukemia n = 50 Other Solid Tumors n = 51 CNS Tumors n = 14	QD, L
Tremolada, 2012	37.39	F 94	Italy	ALL n = 104 AML n = 24	QD, L
Pre-existing acute stress					
McCarthy, 2012	NR* Range: 20 – 39 n = 120 > 40 n = 95 Missing n = 5	F 135, M 85	Australia	Solid Tumors n = 65 Leukemia n = 58 Brain + CNS n = 20	QD, L
Pre-existing chronic stress					
Benaroya-Milshtein,2014	F 40.0, M 47.0	F 23, M 9	Israel	Leukemia 50% Solid tumors 25% Lymphomas 21% Other 4%	QD, C
Cernvall,2016	39.0 *Missing data for three participants	F 55, M 24	Sweden	Leukemia n = 42 Sarcoma n = 11 Lymphoma n = 6 CNS Tumor n = 10 Other n = 10	QD, C
Pre-existing global psychological distress					
Tackett, 2016	36.9	F 105	United States	Leukemia n = 46 Solid Tumors n = 44 Lymphomas n = 15	QD, C
Single child family					
Poder,2008	F 36.7, M 39.1	214	Sweden	Leukemia n = 50 Other Solid Tumors n = 51 CNS Tumors n = 14	QD, L

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Younger paternal age and diagnosis of non-acute lymphocytic leukemias in the child					
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9	QD, L

Note. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; C, cross-sectional; CNS, central nervous system; CR, case report; DP, descriptive phenomenological; E, exploratory; F, female; GT, grounded theory; HL, Hodgkin's Lymphoma; L, longitudinal; M, male; MM, mixed methods; NHL, Non-Hodgkin's lymphoma; NR*, not reported; O, other (i.e., stepparent / grandparent); P, parent; QD, quantitative descriptive; QNR, quantitative non-randomized; RCT, randomized control trial; SNS, sympathetic nervous system.

Table 2E

Parent Precipitating Factors of Psychological Distress

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Parent Precipitating Factors					
Diagnosis of pediatric cancer					
Chen, 2015	31.5	231	China	Acute lymphocytic leukemia n = 130 Acute non lymphocytic leukemia n = 34	QD, C
Cusinato, 2017	44.1	F 20, M 10	Italy	HL 33.3% Soft Tissue Sarcoma 20.8% CNS Tumor 16.7% Wilm's Tumor 12.5% Neuroblastoma 8.3% Osteosarcoma 4.2% Rare Tumor (unspecified) 4.2%	QD, C
Neu, 2014	32.4	F 24	United States	ALL (n NR*)	QNR
Magni, 1983	F 34, M 38	F 13, M 12	Italy	Leukemia n = 13	QD, L
Martinson, 1997	NR* F Range: 20 – 59 *Missing data for 3 participants M 20 – 59 *Missing data n = 3	F 89, M 80	China	Leukemia n = 53 Lymphoma n = 26 Osteosarcoma n = 6 Adrenal Tumor n = 2 Optic glioma n = 2	QD,C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Higher pediatric cancer treatment intensity (i.e, cranial radiation, total body irradiation, transplant, lumbar puncture, bone marrow aspiration)					
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9	QD, L
Caes, 2014	F 36.11, M 39.81	28	Belgium	ALL n = 22 AML n = 6	QD, L
Molzon, 2018	F 35.3, M 37.4	150	United States	Leukemias + Lymphomas n = 75 Non-CNS solid tumors n = 46 Brain Tumors n = 29	QD, C
Adverse response to prescribed curative treatment (e.g., GVHD)					
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9	QD, L
Barriers to obtaining health care for the ill child (e.g. language barrier, parental resistance to participating in the child's care)					
Molzon, 2018	F 35.3, M 37.4	150	United States	Leukemias + Lymphomas n = 75 Non-CNS solid tumors n = 46 Brain Tumors n = 29	QD, C
Cancer communication stressors (i.e. talking with my child about cancer, talking to my other children, family, and friends about cancer, understanding information about cancer and medical treatment, arguing with my child about taking medicines and other treatment)					
Rodriguez, 2012	F 37.9, M 39.5	F 193, M 97	United States	Leukemia n = 75 Other Solid Tumors n = 50 Lymphoma n = 49 Brain Tumor n = 21	QD, C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Child cancer relapse					
Dunn, 2012 (specifically in fathers)	F 37.9, M 39.5	F 190, M 93	United States	NR*	QD, C
Martinson, 1997 NR* F Range: 20 – 59 *Missing data for 3 participants M 20 – 59 *Missing data for 3 participants F 89, M 80	China	Leukemia n = 53 Lymphoma n = 26 Osteosarcoma n = 6 Adrenal Tumor n = 2 Optic glioma n = 2		QD,C	
Sawyer, 1997	NR*	NR*	Australia	ALL 66% Wilms Tumor 16% Rhabdomyosarcoma 5% AML 3% NHL 3% Hepatoblastoma 3% Histiocytosis 3%	QD, L
Tremolada, 2012	37.39	F 94	Italy	ALL n = 104 AML n = 24	QD, L
Diagnosis of neuroblastoma vs. other blood disorders [specifically affecting mothers]					
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9	QD, L

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Ill child's pre-procedural disruptive behaviors					
Dahlquist, 1994	NR*	NR*	United States	Leukemia 96% Other NR*	QD, C
Higher uncertainty related to child health outcomes					
Mu, 2001	F 35.9, M 39.0	100	Taiwan	Leukemia 27% Brain Tumors 41% Osteosarcoma 12% Yolk Sac Tumor 7% Other 13%	QD, C
Mu, 2002	F 35.4, M 39.3	F 80, M 80	Taiwan	Leukemia n = 21 Brain Tumor n = 30 Osteosarcoma n = 9 Yolk Sac Tumor n = 4 Other n = 16	QD, C
Maternal reported lack of social support after diagnosis of cancer in the child					
Tremolada, 2012	37.39	F 94	Italy	ALL n = 104 AML n = 24	MM
Shorter time elapsed since diagnosis					
Masa'deh, 2017	40.5	F 87, M 30	Jordan	NR*	QD, C
Poder, 2008	F 36.7, M 39.1	214	Sweden	Leukemia n = 50 Other Solid Tumors n = 51 CNS Tumors n = 14	QD, L
Stressful life events related to the pediatric cancer experience: (i) lumbar puncture performed on the child; (ii) bone marrow aspiration; (iii) surgery; (iv) receiving discouraging information about child's prognosis; (v) decisions regarding a new medical procedure; (vi) an altercation with medical staff; (vii) emergency hospitalization; (viii) bone marrow transplantation; (ix) death of another patient; and (x) relapse of another patient in the ward.					
Benaroya-Milshtein, 2014	F 40.0, M 47.0	F 23, M 9	Israel	Leukemia 50% Solid tumors 25% Lymphomas 21% Other 4%	QD, C

Note. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; C, cross-sectional; CNS, central nervous system; CR, case report; DP, descriptive phenomenological; E, exploratory; F, female; GP, grandparents; HL, Hodgkin's Lymphoma; L, longitudinal; M, male; MM, mixed methods; NHL, Non-Hodgkin's lymphoma; NR*, not reported; O, other (i.e., stepparent / grandparent); P, parent; QD, quantitative descriptive; QNR, quantitative non-randomized.

Table 3E

Parent Perpetuating Factors of Psychological Distress

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis		Design
Parent Perpetuating Factors						
Child externalizing problems						
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9		QD, L
Dahlquist, 1994	NR*	NR*	United States	Leukemia Other NR*	96%	QD, C
Fedele, 2011	33.09	F 22	United States	Leukemia n = 14 Neuroblastoma n = 2 CNS Tumors n = 2 Other n = 4		QD, L
Female parental sex						
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9		QD, L
McCarthy, 2012	**NR* Range: 20 – 39 n = 120 > 40 n = 95 Missing n = 5**	**F 135, M 85**	**Australia**	**Solid Tumors n = 65 Leukemia n = 58 Brain + CNS n = 20**		**QD, L**

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Poder, 2008	F 36.7, M 39.1	214	Sweden	Leukemia n = 50 Other Solid Tumors n = 51 CNS Tumors n = 14	QD, L
Disturbance to paternal or maternal role					
Demirtepe-Saygili, 2011	33.1 Range: 18 – 51	P(F)90, P(M)3, A 4, S 3	Turkey	Leukemia n = NR*	QD, C
Fife,1987	NR*	F 33, M 27	United States	Leukemia n = 34	QD, L
Hoven, 2017	38.0	F 122, M 121	Sweden	Leukemias + Lymphomas n = 77 Solid Tumors n = 40 CNS Tumors n = 16	QD, L
Sherief, 2015	F 30.11, M 32.74	178	Egypt	ALL n = 213	QD, C
Increased caregiver stress					
Benaroya-Milshtein, 2014	F 40.0, M 47.0	F 23, M 9	Israel	Leukemia 50% Solid tumors 25% Lymphomas 21% Other 4%	QD, C
Molzon, 2018	F 35.3, M 37.4	150	United States	Leukemias + Lymphomas n = 75 Non-CNS solid tumors n = 46 Brain Tumors n = 29	QD, C
Sulkers, 2015	*Reported [Mean] 8.4 Range 24 – 55	F 95	Netherlands	Hematological Tumor n = 41 Solid Tumor n = 31 Brain Tumor n = 23	QD, L
Higher number of children in the family					
Demirtepe-Saygili, 2011	33.1 Range: 18 – 51	P(F)90, P(M)3, A 4	Turkey	Leukemia n = NR*	QD, C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Impaired parental sense of self-efficacy (i.e., inability to mitigate child procedural distress)					
Harper, 2013	35.65	F 60, M 15	United States	ALL 80% Other 7% Wilms Tumors 5% NHL 4 % Astrocytoma 3% Rhabdomyosarcoma 1%	QD, L
Impaired family function					
Shi,2017	F 34.16, M 36.56	F 192, M 87	China	ALL n = 102 Other Leukemias n = 54 Lymphomas n = 46 Other solid tumors n = 23 Soft tissue sarcomas n = 18 Bone n = 17 SNS n = 17 CNS n = 8	QD, C
Increased time since diagnosis					
Vernon, 2016	F 36.0, M 38.99	F 41, M 25	Australia	Leukemia n= 3 Solid Tumors n = 17 Brain / CNS n = 1 Ewing's Sarcoma n = 1 Neuroblastoma n = 7 Wilm's Tumor n = 2 Other Solid Tumor n = 6 Other n = 3	QD, C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Long duration of disease					
Sherief, 2015	F 30.11, M 32.74	178	Egypt	ALL n = 213	QD, C
Low self-esteem in the ill child					
Sherief, 2015	F 30.11, M 32.74	178	Egypt	ALL n = 213	QD, C
Maternal reported behavioral problems (unspecified) exhibited in the ill child					
Barrera, 2004	36.66	F 69	Canada	ALL n = 47% Sarcomas n = 20% Brain tumors n = 10% Other n = 10% Hodgkin's Lymphomas n = 6% Non-Hodgkin's Lymphomas n = 4% Neuroblastoma n = 3%	QD, C
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9	QD, L
Medical expenses paid out of pocket					
Chen, 2015	31.5	231	China	Acute lymphocytic leukemia n = 130 Acute non lymphocytic leukemia n = 34	QD, C
Negative attachment to the ill child					
Sherief, 2015	F 30.11, M 32.74	178	Egypt	ALL n = 213	QD, C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Negative perceptions of the ill child's quality of life					
McCarthy, 2012	NR* Range: 20 – 39 n = 120 > 40 n = 95 Missing n = 5	F 135, M 85	Australia	Solid Tumors n = 65 Leukemia n = 58 Brain + CNS n = 20	QD, L
Parental catastrophic thoughts					
Caes, 2014	F 36.11, M 39.81	28	Belgium	ALL n = 22 AML n = 6	QD, L
Parental dysphoria					
Hoven, 2016	NR*	F 122, M 121	Sweden	NR*	QD, L
Parental emotion-focused coping					
Demirtepe-Saygili, 2011	33.1 Range: 18 – 51	P(F)90, P(M)3, A 4 Note: Sisters (n = 3), Aunts (n = 4)	Turkey	Leukemia n = NR*	QD, C
Paternal disengagement coping [positively related to psychological distress in mothers]					
Compas, 2015	F 37.5, 39.5	F 316, M 166	United States	NR*	QD, C
Paternal experience of adverse child response to prescribed curative treatment (i.e., GVHD)					
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9	QD, L
Poorer maternal emotional and cognitive adjustment					
Mahdavi, 2017	NR*	NR*	Iran	NR*	QD, C
Perceived lack of spousal support					

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Sherief, 2015	F 30.11, M 32.74	178	Egypt	ALL n = 213	QD, C
Poor parental health					
Sherief, 2015	F 30.11, M 32.74	178	Egypt	ALL n = 213	QD, C
Higher situational (unspecified) anxiety					
Fife,1987	NR*	F 33, M 27	United States	Leukemia n = 34	QD, L
Increased social isolation					
Sherief, 2015	F 30.11, M 32.74	178	Egypt	ALL n = 213	QD, C
Lower perceived social support					
Chen, 2015	31.5	F 135, M 96	China	ALL n = 130 Acute Non-Lymphocytic Leukemia n = 34	QD, C
Tremolada, 2012	37.39	F 94	Italy	ALL n = 104 AML n= 24	MM
Parental intrusive thoughts related to the pediatric cancer experience					
Hoven, 2016	NR*	F 122, M 121	Sweden	NR*	QD, L
Parental research involvement following perceived lack of information RE pediatric cancer from the physician					
Olcese, 2012	NR* Participants > 30 years n = 179	F 153, M 41	United States	Hematologic malignancy 56% Brain Tumor 23% Other Solid Tumor 22%	QD, C
Parental research involvement following the receipt of upsetting prognostic information					
Olcese, 2012	NR* Participants > 30 years n = 179	F 153, M 41	United States	Hematologic malignancy 56% Brain Tumor 23% Other Solid Tumor 22%	QD, C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Pediatric cancer treatment intensity (i.e., cranial radiation, total body irradiation)					
Barrera, 2012	F 36.6, M 39.55	111	Canada	ALL n = 17 Other Leukemias n = 15 Neuroblastoma n = 16 Solid Tumors n = 12 Blood Disorder n = 9	QD, L
Benaroya-Milshtein, 2014	F 40.0, M 47.0	F 23, M 9	Israel	Leukemia 50% Solid tumors 25% Lymphomas 21% Other 4%	QD, C
Side effects of antineoplastic therapy (e.g., nausea, vomiting)					
Al Qadire, 2018	37.3	F 176, M 46	Jordan	Leukemias + Lymphomas n = 135 Solid Tumors n = 87	QD, C
Unmet parental basic needs (e.g., sleep, nutrition, personal growth)					
Dahlquist, 1994	NR*	NR*	United States	Leukemia 96% Other NR*	QD, C
Demirtepe-Saygili, 2011	33.1 Range: 18 – 51	P(F)90, P(M)3, A 4 Note: Sisters (n = 3), Aunts (n = 4)	Turkey	Leukemia n = NR*	QD, C

Note. A, aunt; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; C, cross-sectional; CNS, central nervous system; CR, case report; DP, descriptive phenomenological; E, exploratory; F, female; GT, grounded theory; HL, Hodgkin's Lymphoma; L, longitudinal; M, male; MM, mixed methods; NHL, Non-Hodgkin's lymphoma; NR*, not reported; P, parent; QD, quantitative descriptive; QNR, quantitative non-randomized; S, sister.

Table 4E

Parent Protective Factors of Psychological Distress

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Parent Protective Factors					
Greater time elapsed since diagnosis					
Kazak, 2005	F 38.1, M 41.7	F 119, M 52	United States	Leukemias n = 67 Solid Tumors n = 33 Brain Tumors n = 14 Lymphomas n = 11	QD, C
Masa'deh, 2017	40.5	F 87, M 30	Jordan	NR*	QD, C
Sulkers, 2015	*Reported [Mean] 8.4 Range 24 – 55	F 95	Netherlands	Hematological Tumor n = 41 Solid Tumor n = 31 Brain Tumor n = 23	QD, L
Greater maternal optimism					
Fotiadou, 2008	38.4	F 20, M 30	United Kingdom	ALL n = 48 AML n = 4 Brain tumors n = 6 Lymphomas n = 5 Reticuloendothelial neoplasms n = NR*	QNR
Greater maternal emotional and cognitive adjustment					
Mahdavi, 2017	NR*	NR*	Iran	NR*	QD, C
Greater perceived social support					
Magni, 1986	F 33.6, M 36.7	F 21, M 20	Italy	ALL n = 16 HL n = 5	QD, L
Penner, 2016	33.98	P 96, GP 3	United States	All 79%	QD, L

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Increased parental age					
Masa'deh, 2017	40.5	F 87, M 30	Jordan	NR*	QD, C
Increased parental sense of self-efficacy (e.g., ability to mitigate child procedural distress)					
Harper, 2013	35.65	F 60, M 15	United States	ALL 80% Other 7% Wilms Tumors 5% NHL 4 % Astrocytoma 3% Rhabdomyosarcoma 1%	QD, L
Penner, 2016	33.98	P 96, GP 3	United States	All 79%	QD, L

Note. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; C, cross-sectional; CNS, central nervous system; CR, case report; DP, descriptive phenomenological; E, exploratory; F, female; GP, grandparents; HL, Hodgkin's Lymphoma; L, longitudinal; M, male; MM, mixed methods; NHL, Non-Hodgkin's lymphoma; NR*, not reported; O, other (i.e., stepparent / grandparent); P, parent; QD, quantitative descriptive; QNR, quantitative non-randomized.

Appendix F

Tabular Summaries of Sibling Factors

Table 1F

Sibling Predisposing Factors of Psychological Distress

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Sibling Predisposing Factors					
Ethnicity					
Long, 2013b	12.52 Range: 8.08 – 18.00	209 (54.8% F)	United States	Leukemia: 31.7%, Lymphoma: 13.9% Solid Tumor: 39.4% Brain Tumor: 13% Other: 1.9%	QD, C
Houtzager, 2004	11.0 Range: 7 – 18 years	83	Netherlands	Solid Tumor: 46.4%. Lymphoma: 23.2% Leukemia: 21.4% Brain Tumor: 8.9%	QD, L
Lower family income					
Long, 2013b	12.52 Range: 8.08 – 18.00	209 (54.8% F)	United States	Leukemia: 31.7%, Lymphoma: 13.9% Solid Tumor: 39.4% Brain Tumor: 13% Other: 1.9%	QD, C

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Parental non-married status					
Long, 2013b	12.52 Range: 8.08 – 18.00	209 (54.8% F)	United States	Leukemia: 31.7%, Lymphoma: 13.9% Solid Tumor: 39.4% Brain Tumor: 13% Other: 1.9%	QD, C
Houtzager, 2003	NR* Range: 7 – 18	F 46, M 37	Netherlands	Diagnosis – M1 Solid tumor: 46% Lymphoma: 23%. Leukemia: 21% Brain tumor: 9% M1 – M2 Lymphoma: 33%. Leukemia: 25% Solid tumor: 20%. Brain tumor: 11%	QD, L
Increased sibling age					
Houtzager, 2004	11.0 Range: 7 – 18 years	83	Netherlands	Solid Tumor: 46.4%. Lymphoma: 23.2% Leukemia: 21.4% Brain Tumor: 8.9%	QD, L
Younger Birth Order Relative to the Child with Cancer					
Long, 2013a	NR* Range: 10 – 17 years	30	United States	Leukemia n = 12 Brain Tumors n = 3 Rhabdomyosarcoma n = 3 Lymphoma n = 1 Neuroblastoma n = 1 Osteosarcoma n = 1 Thyroid n = 1	MM

Study Sibling female sex	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Houtzager, 2003	NR* Range: 7 – 18	F 46, M 37	Netherlands	Diagnosis – M1 Solid tumor: 46% Lymphoma: 23%. Leukemia: 21% Brain tumor: 9% M1 – M2 Lymphoma: 33%. Leukemia: 25% Solid tumor: 20%. Brain tumor: 11%	QD, L

Note. C, cross-sectional; F, female; L, longitudinal; M, male; NR*, not reported; QD, quantitative descriptive.

Table 2F

Precipitating Factors of Psychological Distress

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Sibling Precipitating Factors					
Increased perception of threat to lifestyle (e.g., frequency of hospital visits, distance to hospital, typical caretaker during hospital visits)					
Demirtepe-Saygili, 2011	33.1 Range: 18 – 51	F 3 Note: P(F)90, P(M)3, A 4	Turkey	Leukemia n = NR*	QD, C
Long, 2013a	NR* Range: 10 – 17 years	30	United States	Leukemia n = 12 Brain Tumors n = 3 Rhabdomyosarcoma n = 3 Lymphoma n = 1 Neuroblastoma n = 1 Osteosarcoma n = 1 Thyroid n = 1	MM

Note. A, aunt; C, cross-sectional; C, cross-sectional; F, female; M, male; MM, mixed methods; NR*, not reported; P, parent; QD, quantitative descriptive.

Table 3F

Perpetuating Factors of Psychological Distress

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Sibling Perpetuating Factors					
Increased caregiver burden					
Demirtepe-Saygili, 2011	33.1 Range: 18 – 51	F 3 Note: P(F)90, P(M)3, A 4	Turkey	Leukemia n = NR*	QD, C
Hamama, 2008	12.06 Range: 8 – 19 years	F 47, M 53	Israel	Leukemia n = 50 Bone Tumor n = 11 Soft Tissue Sarcoma n = 15 CNS n = 12 Lymphoma n = 11 Other n = 1	QD, C
Houtzager, 2004	11.0 Range: 7 – 18 years	83	Netherlands	Solid Tumor: 46.4%. Lymphoma: 23.2% Leukemia: 21.4% Brain Tumor: 8.9%	QD, L
Less autonomy granted to siblings					
Long, 2013b	12.52 Range: 8.08 – 18.00	209 (54.8% F)	United States	Leukemia: 31.7%, Lymphoma: 13.9% Solid Tumor: 39.4% Brain Tumor: 13% Other: 1.9%	QD, C
Lower sibling reported maternal acceptance					
Long, 2013b	12.52 Range: 8.08 – 18.00	209 (54.8% F)	United States	Leukemia: 31.7%, Lymphoma: 13.9% Solid Tumor: 39.4% Brain Tumor: 13% Other: 1.9%	QD, C

Increased reliance of the sibling on medical professionals					
Houtzager, 2004	11.0 Range: 7 – 18 years	83	Netherlands	Solid Tumor: 46.4%. Lymphoma: 23.2% Leukemia: 21.4% Brain Tumor: 8.9%	QD, L

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Sibling reported impaired family functioning					
Long, 2013b	12.52 Range: 8.08 – 18.00	209 (54.8% F)	United States	Leukemia: 31.7%, Lymphoma: 13.9% Solid Tumor: 39.4% Brain Tumor: 13% Other: 1.9%	QD, C
Unmet sibling basic needs (e.g., sleep, nutrition, personal growth)					
Demirtepe-Saygili, 2011	33.1 Range: 18 – 51	F 3 Note: P(F)90, P(M)3, A 4	Turkey	Leukemia n = NR*	QD, C

Note. ALL, acute lymphoblastic leukemia; C, cross-sectional; CNS, central nervous system; CR, case report; E, exploratory; F, female; M, male; NR*, not reported; P, parent; QD, quantitative descriptive.

Table 4F

Protective Factors of Psychological Distress

Study	Mean Age (years)	N	Country	Child Cancer Diagnosis	Design
Sibling Protective Factors					
Greater time elapsed since diagnosis					
Hamama, 2000	F 11.8, M 11.3 Range: 9 – 18	F 31, M 31	Israel	Leukemia 40% Lymphoma 17.5% Brain Tumor 9% Solid Tumor 9% Bone Tumor 7%	QD, C
Houtzager, 2004	11.0 Range: 7 – 18 years	83	Netherlands	Solid Tumor: 46.4%. Lymphoma: 23.2% Leukemia: 21.4% Brain Tumor: 8.9%	QD, L
Sibling's increased sense of self-efficacy					
Hamama, 2008	12.06 Range: 8 – 19 years	F 47, M 53	Israel	Leukemia n = 50 Bone Tumor n = 11 Soft Tissue Sarcoma n = 15 CNS n = 12 Lymphoma n = 11 Other n = 1	QD, C

Note. C, cross-sectional; CNS, central nervous system; ; F, female; L, longitudinal; M, male; QD, quantitative descriptive.