Psychological adaptation to cancer in youth: An investigation into the mechanisms of psychopathology and resilience



Urška Košir

Magdalen College, University of Oxford

Supervisors: Dr. Lucy Bowes & Dr. Jennifer Wild

A thesis submitted for the degree of

Doctor of Philosophy

Michaelmas Term 2020

Mami and tatiju,
Roku in Lukatu,
Puncam in tamalim,
Tisočkrat hvala.

Acknowledgments

Somewhat paradoxically to the inherent nature and purpose of writing an acknowledgement, this part felt the least gratifying to compose; how does one go about recognizing all the important players and factors that contributed to the completion of this work? As the printing standards dictate, this section follows a linear structure, but as with many of my models, one ought to recognize that things are far more complex, and non-linear. So, without wasting any more ink, I am most grateful to:

My family. Mama and tata, thank you for teaching me all that really matters: to respond with kindness not contempt, to embrace the quest not just the goal, to dream the unimaginable without losing sight of the reality, to strive for excellence, but never forget where you started. Roki, thank you for making sure I was able to read and count before I even started first grade. Luka, thank you for instilling in me your voice of reason. Whenever faced with an obstacle, I think and act as you would: pause and find a solution. Together you have taught me patience only as older brothers can. Rok, Luka, Maja and Dragana, thank you for enriching me with 4 beautiful bundles of joy whose innocent laughter always lifts my spirits. And thanks to all the Koširs and non-Košir cousins, home and abroad.

Jean-Sébastien. Thank you for your loving and nurturing companionships on what is an inherently individualistic and oftentimes lonely pursuit that is the thesis writing. I am indebted to you for the endless support during a difficult year and grateful for all the laughs and sushis we continue to share.

My overseas family. Dori, David, Oliver, and Ava Hurwitz, thank you for supporting me throughout the years, for helping me mature, and for always offering me a second home on a foreign land. Your generosity and kindness are a source of inspiration.

Žana Šuran and Luca Sacher. Thank you for sticking around through ups and downs, through illness and health, through heartbreak and love. Thank you for keeping me grounded, and for being right there, even when thousands of miles away.

My friends and colleagues at Oxford. Anna Shpektor, Veronika Kubickova, and Hjördis Lorenz, your unwavering support and calming presence helped me persevere. Colleagues at OxCADAT: Milan Wiedemann, Esther Beierl, Graham Thew, Belinda Graham, Lawrence Yu, Gaby Tayson, and Hannah Murray. Colleagues at oRANGE Lab: Julia Badger, Aoife O'Higgins, Mirela Zaneva, Carolina Guzman, Michelle Degli Esposti. Thank you for showing me that our differences need not be divisive, but instead a source of strength and motivation. All my fellow compatriots in the UK, headed by Evelina and Marcus Ferrar, who always conjure up the taste of home when you most need it.

My supervisors and mentors. Dr Lucy Bowes, thank you for not once doubting in my ability to succeed, even when I tried to convince you otherwise. Your patience, selflessness and ability to see the bigger picture are unparalleled. You taught me that we should not only seek the right answers, but instead ask the right questions. And thank you for always prioritizing what was in my best interest and allowing me to

pursue my own aspirations. Dr Jennifer Wild, thank you for taking me under your wing, always providing with timely feedback, and encouraging me to think critically and independently. I am also grateful to Dr Alan Stein and Dr Elaine Fox who have seen me mature over the course of Oxonian graduate milestones and offered invaluable comments that improved my work.

The funders. Thanks to European Social Research Council for financing my doctorate studies, to Ad Futura, a stipend by the Public Scholarship, Development, Disability and Maintenance Fund of the Republic of Slovenia, to Magdalen College, and all who contributed and made my many travels, conferences, and research projects possible.

All of my collaborators, at home and overseas. In particular, I would like to thank Dr Maria Loades, Dr Rachel Taylor and Dr Ana Martins, Dr Robert Turcotte, Dr Argerie Tsimicalis, Dr Krista Goulding and Dr Nancy Mayo, Dr Serge Sultan and Dr Marco Bonanno, and Dr Kristine Sørensen. Thank you for always making me feel your equal despite the years-wide gap in experience, and for making me feel valuable and at home in your respective teams.

Cancer patient organizations and support groups. I appreciate all the young people who participated in my research and shared their intimate stories to help others. Youth Cancer Europe, Elephants and Tea, CATS, Onko Hub Slovenia, Young Adult Cancer Canada, AYA Community Canada. You haven't just helped me recruit for my research, but continue to give meaning to it, inspire new ideas, and offer a community I much sought during my own illness.

To all the stars that aligned. Because sometimes we have to believe in the stars. And thanks to all of you who have unobtrusively accompanied me on this pursuit of knowledge.

Thank you.

Urška Košir
Montreal, CA
December 2020

Abstract

Cancer diagnosis and treatment are a stressful experience for a patient of any age. However, compared to younger children or adults, adolescents and young adults (AYA) are a distinct group of patients with unique challenges due to their developmental period. Literature suggests that up to a third of AYA patients may be at risk for developing psychopathology. While there is an increasing interest in studying psychosocial outcomes in AYAs, little is understood about the mechanisms of psychosocial wellbeing in this population. This thesis uses a variety of research methods to examine factors associated with resilience and psychopathology in youth living with cancer and beyond cancer and aims to identify intervention targets to promote holistic recovery of young people with cancer.

Because psychosocial oncology is a young and rapidly evolving field, I begin by a short overview of some of the methodological challenges I faced in my research. In particular, I wanted to address the issue of not using cancer-specific questionnaires, and lack of longitudinal and data-driven approaches. To this end, I have innovatively used a mixed-methods approach to explore how individual, as well as socio-environmental factors are associated with psychological outcomes in young patients and survivors.

I begin by a systematic review of the literature, which provides an insight into the prevalence rates of psychopathology and identifies some of the risk factors for psychiatric disorders. Subsequently, I present qualitative analysis of in-depth interviews about life with and beyond cancer. For my third study, I developed an online survey to collect information about psychological wellbeing, including cancer-specific questionnaires. Using this data, I employed network analysis to explore if any symptoms of psychopathology and cancer worries are particularly salient and contribute more to the overall symptomatology than the rest. Lastly, I conclude with a longitudinal analysis of a clinical dataset in Canada, where I explored psychological wellbeing and its relationship with fatigue, a commonly endorsed symptom. Due to the global pandemic COVID-19 and its consequent disruption, I complemented my online survey with an auxiliary study that explored the impact of the pandemic on the wellbeing of young people with cancer who were considered at risk for infections.

Together, the research presented in this thesis contributes evidence to support that a subset of young people with cancer report psychopathology, and those at risk may be particularly vulnerable in the times of distress, such as the global pandemic. However, psychopathology may result from vastly different, individually led modifiable pathways, which can be addressed with a more personalized approach to care in the future.

Psychosocial adaptation to cancer in young people is a complex process with many factors at play. This thesis begins to uncover a few, introduces innovative methods to counteract the existing mythological pitfalls and concludes by proposing future directions for strengthening research in psychosocial oncology and reducing the inequalities of outcomes in young people with cancer.

Table of contents

Acknowledgments i
Abstract iii
Table of contents iv
List of figures ix
List of tables x
Declaration xii
List of publications xiii
List of abbreviations xv
Chapter 1 - Introduction 1
1.1 What is psycho-social oncology? 1
1.2 Cancer and young people 1
1.3 A case for adolescents and young adults 3
1.4 Defining resilience and psychopathology in youth with cancer 6
1.4.1 What constitutes resilience 7
1.4.2 What constitutes psychopathology 8
1.5 Current interventions in AYA psycho-social oncology: One size does not fit all 10
1.6 From brain tumors to sarcoma 11
1.7 From diagnosis to surveillance 12
1.8 From Slovenia to the world 14
1.9 A note on the language use and survivorship 16
1.10 An overview of the thesis 17
1.10.1 Research questions 18
Summary 21
Chapter 2 - Addressing the challenges through a mixed method approach 22
2.1 Conceptual challenges 23
2.1.1 How should we define adolescents and young adults? 23
2.1.2 Cancer as a single illness 25
2.2 Methodological challenges 26
2.2.1 Measuring psychological distress 26
2.2.2 Data collection and recruitment 28
2.2.3 Study design and data analysis 29
2.3 Summary: Addressing the challenges through a mixed method approach 31
Chapter 3 - Psychiatric disorders in adolescent and young adult cancer survivors: A systematic review of prevalence and predictors 32

3.1 Abstract 32
3.2 Introduction 33
3.3 Method 35
3.3.1 Search 35
3.3.2 Inclusion and Exclusion Criteria 35
3.3.3 Data Extraction 36
3.3.4 Quality Appraisal and Data Analysis 36
3.3.5 Analysis 37
3.4 Results 37
3.4.1 Prevalence of psychiatric disorders 39
3.4.2 Predictors of psychiatric disorders in adolescent cancer survivors 42
3.5 Discussion 47
3.5.1 Strengths and Limitations 49
3.5.2 Clinical implications 50
3.6 Contribution to this thesis 50
Chapter 4 - Psychological adaptation and recovery in youth with sarcoma: A qualitative study 52
4.1 Abstract 52
4.2 Introduction 53
4.3 Method 54
4.3.1 Participants and Recruitment 54
4.3.2 Design and Procedure 55
4.3.3 Data Analysis 56
4.4 Results 58
4.4.1 Participants 58
4.4.2 Factors that play a role in psychological adaptation and recovery in sarcoma 59
4.4.3 Individual level factors 59
4.4.4 Environmental level factors 66
4.5 Discussion 70
4.5.1 Limitations and future directions 72
4.5.2 Conclusion and clinical implications 72
4.6 Contribution to this thesis 73
Chapter 5 - Interconnectedness of anxiety, depression, and cancer-related worry in adolescents and young adults with cancer: A network analysis 74
5.1 Abstract 74
5.2 Introduction 75
5.2.1 Piloting the study 75

5.2.2 The present study 77
5.3 Method 78
5.3.1 Participants and study design 78
5.3.2 Measures 79
5.3.3 Data analysis 79
5.4 Results 81
5.4.1 Participants 81
5.4.2 Psychological functioning 83
5.4.3 Psychological networks 85
5.5 Discussion 88
5.6 Contribution to this thesis 92
Chapter 6 - Global pandemic COVID-19: Disruptions and impact on psychological functioning of young people with cancer 93
6.1 Abstract 93
6.2 Introduction 94
6.3 Method 96
6.3.1 Design and sample 96
6.3.2 Measures and survey description 97
6.3.3 Analysis 97
6.4 Results 98
6.4.1 Participants 98
6.4.2 COVID-19 impact on cancer care 99
6.4.3 COVID-19 impact on psychological well-being 100
6.4.4 COVID-19 information resources and satisfaction 104
6.5 Discussion 104
6.5.1 Strengths and Limitations 107
6.5.2 Clinical implications 107
6.6 Contribution to this thesis 108
Chapter 7 - Fatigue and psychological functioning in sarcoma over time: Application of group-based trajectory modelling 109
7.1 Abstract 109
7.2 Introduction 110
7.3 Method 111
7.3.1 Sample 111
7.3.2 Measures 112
7.3.3 Data analysis 115
7.4 Results 119

7.4.1 Sample....119
7.4.2 Trajectories of fatigue across the illness trajectory....121
7.4.3 Psychological profiles and associations between baseline factors and fatigue trajectories....125
7.4.4 Post Hoc analyses....128
7.5 Discussion....129
7.5.1 Strengths, limitations and future directions....130
7.5.2 Clinical implications....131
7.6 Contribution to this thesis:....132
Chapter 8 - Discussion....133
8.1 What are the factors associated with resilience and psychopathology in youth with cancer?....133
8.2 How do mechanisms of resilience and psychopathology change over the span of illness?....136
8.3 What should we target in early prevention to facilitate the holistic recovery of AYAs?....137
8.4 Overall strengths and limitations....137
8.4.1 Defining adolescents and young adults....139
8.4.2 Cancer as a single illness....140
8.4.3 Measuring psychological distress....141
8.4.4 Data collection and recruitment....142
8.4.5 Study design and analysis....143
8.4.6 Summary of overall strengths and limitations....145
8.5 Summary of future research directions....145
8.6 Broader implications....146
8.6.1 Clinical practice....147
8.6.2 Policy....148
8.6.3 A note on the COVID-19 and its aftermath:....149
8.7 Conclusion....153
Reference: 154
APPENDIX A: Selected quality indicators (Chapter 3)....187
APPENDIX B: Complete tables included in the systematic review (Chapter 3)....188
APPENDIX C: Sampling matrix with criteria (Chapter 4)....196
APPENDIX D: Supporting material (Chapter 5)....197
Description of deviations from the pre-registered protocol....198
Questionnaire details....200
Sensitivity analyses....203
Multiple imputation using chained equations (MICE) for missing data....205

APPENDIX E: Supplementary material for network analysis (Chapter 5) 206
All items included in the network analysis 207
Item-to-item correlations and post hoc networks sensitivity 208
Node predictability 209
Centrality indices for the two estimated networks 210
APPENDIX F: Abridged version of the online COVID-19 impact Survey (Chapter 6) 212
APPENDIX G: Supplementary tables (Chapter 6) 216
APPENDIX H: Supplementary material and tables (Chapter 7) 218
Details of the measures and questionnaires 219
Abbreviation of the FACIT questionnaire 226
Multiple imputation by chained equation (MICE) for missing data and sensitivity analyses 229
Complete tables with Group-based trajectory modelling (GBTM) indices for classes 1 through 6 234

List of figures

Figure 1.1: Cancer incidence per age group. 2
Figure 1.2: 5-year survival rate by age. 3
Figure 1.3: Relative levels of psychological distress along the illness trajectory. 14
Figure 2.1: Overlap in definitions of childhood, adolescent, and young adult cancer.24
Figure 3.1: PRISMA flowchart of literature search. 38
Figure 4.1: The steps included in the framework analysis. 56
Figure 4.2: The conceptual framework on which the themes were mapped. 57
Figure 4.3: Visual matrix of individual-level themes. 60
Figure 4.4: Visual matrix of environmental-level themes. 66
Figure 5.1: Individual scores on the GAD scale combined with Mental Defeat, Rumination and Cancer worry. 76
Figure 5.2: Prevalence of specific cancer worries. 84
Figure 5.3: Psychological network of depression and anxiety (N = 233). 85
Figure 5.4: Psychological network of depression, anxiety, and cancer worry. 86
Figure 5.5: Centrality indices. 88
Figure 6.1: Global and UK COVID-19 context at the time of this study. 96
Figure 6.2: Impact of COVID-19 on psychological wellbeing. 101
Figure 7.1: A diagram of data preparation. 112
Figure 7.2: Trajectories of fatigue across the span of illness, from diagnosis to 2 year after treatment. 124
Figure 7.3: Self-reported quality of life across the illness trajectory. 127
Figure 7.4: Mood disturbance by fatigue trajectory over time. 128
Figure H0.1: Correlation between old and new FACIT scales. 228

List of tables

Table 1.1: An overview of the main research questions and chapters. 18
Table 2.1: Addressing challenges in AYA psycho-social oncology. 23
Table 2.2: The most common types of cancer in a specific age range. 26
Table 3.1: Inclusion and exclusion criteria. 35
Table 3.2: Studies included in the review (abbreviated). 41
Table 4.1: Participant demographic and medical information. 58
Table 4.2: Supporting quotes from participants about individual level factors. 63
Table 4.3: Supporting quotes from participants about environmental level factors. 68
Table 5.1: Measures used in this study. 79
Table 5.2: Demographic and illness information. 81
Table 5.3: Descriptive statistics on the measures of psychological functioning. 83
Table 6.1: Demographic and medical information of the participants (N = 177). 99
Table 6.2: Psychological distress among adolescents and young adults. 100
Table 6.3: Categories devied from content analysis. 102
Table 7.1: Questionnaires from the IHRT Biobank used in this study. 115
Table 7.2: Demographic and medical information. 120
Table 7.3: Model enumeration comparisons with linear terms. 122
Table 7.4: Model enumeration comparisons with quadratic terms. 123
Table 7.5: Associations between baseline characteristics and fatigue trajectories in univariate multinomial models. 125
Table 7.6: Associations between baseline characteristics and fatigue trajectories in multivariate multinomial model. 126
Table 7.7: Mean scores for quality of life and function per fatigue trajectory across time. 127
Table 8.1: Summary of my approach, limitations, and future directions. 138
Table 8.2: A summary of recommendations for improvements in clinical care and policy 147
Table B.0.1: Measures for Posttraumatic Stress Disorder. 188
Table B.0.2: Measures for Depression and Anxiety. 189
Table B.0.3: Included studies (Complete table for Chapter 3, results section). 190
Table C.0.1: Sampling matrix used for the recruitment in the qualitative study with sarcoma. 196
Table D.0.1: Deviations from the pre-registered protocol and analysis. 198
Table D0.2: Comparison between the Slovenian and English-speaking participants. 203
Table D.0.3: Level of missingness. 205
Table D.0.4: Description of variables used in MICE. 205
Table E.0.1: Item (node) description and their assigned labels. 207
Table E.0.2: Zero-order correlations between items of psychological questionnaires. 208
Table E.0.3: Predictability of each node in the network. 209
Table E0.4: Network 1 centrality indices, standardized z-scores. 210
Table E0.5: Network 2 centrality indices, standardized z-scores. 211
Table G0.1: : Table showing the proportion of individuals feeling more anxious or distressed now, compared to the time prior to the pandemic, stratified by treatment phase. 216

Table G0.2: Table showing the proportion of individuals who received direct communication about COVID-19 from the health care team by treatment phase. 216
Table G0.3: Table showing the proportion of individuals who would have wanted more information about COVID-19, stratified by treatment phase. 217
Table G0.4: Table showing the most commonly used information resources for COVID-19, and reported satisfaction and perceived trustworthiness of these resources, stratified by treatment. 217
Table H0.1: Questionnaires from the IHRT Biobank used in Chapter 7. 219
Table H0.2: Abbreviated version of the FACIT scale. 227
Table H0.3: Model fit indices for testing measurement invariance of abbreviated FACIT scale. 228
Table H0.4: Table comparing complete cases with those who are missing 3-month appointment. 231
Table H0.5: Table comparing baseline characteristics of complete cases with those who dropped out at 24 months. 232
Table H0.6: Level of missingness for the main variables to be imputed. 233
Table H0.7: Description of variables used in MICE. 233
Table H0.8: Model enumeration comparisons with linear terms, classes 1 - 6. 234
Table H0.9: Model enumeration comparisons with quadratic terms, classes 1 - 6....234

Declaration

This thesis is interdisciplinary in nature and resulted from several successful collaborations that I established during my time at Oxford. Five chapters are based on published peer-review journal articles but have been formatted and edited for this thesis. Recruitment and data for Chapter 4 has been carried out by a team lead by Dr. Rachel Taylor at University College London and was supported by Sarcoma UK (grant number SUK102.2016LG) and Bone Cancer Research Trust (grant number BCRT/49/16). Chapters 5 and 6 are based on my own data collected online with the help from several charities from the UK and abroad. Chapter 7 is based on secondary data analysis of longitudinal data, which is systematically collected at McGill University Health Centre, in Montreal, Canada. During my DPhil I made several visits to Canada in order to gather and prepare the data, present the findings, and engage with the research teams at McGill University and McGill University Health Centre.

This thesis is original, and I led all work presented, unless otherwise acknowledged.

List of publications

Published:

1. **Košir, U**., Bowes, L., Taylor, R., Gerrand, C., Windsor, R., Onasanya, M., Martins, A. (2020). Psychological adaptation and recovery in youth with sarcoma: A qualitative study with practical implications for clinical care and research. *BMJ Open*. http://dx.doi.org/10.1136/bmjopen-2020-038799

2. **Košir, U**., Roškar, S., Wild, J., Bowes, L. (2020). Mapping the needs and psychological outcomes of Slovenian adolescent and young adult cancer patients: An exploratory mixed-methods study. *European Journal of Cancer Care*. https://doi.org/10.1111/ecc.13326

3. **Košir, U**., Loades, M., Wild, K., Wiedemann, M., Krajnc, A., Roškar, S., Bowes, L. (2020). What was the impact of COVID-19 on Adolescent and Young Adult cancer care and their wellbeing? Results from an online survey conducted in the early stages of the pandemic. *Cancer*. https://doi.org/10.1002/cncr.33098

4. **Košir, U**. & Sørensen, K. (2020). COVID-19: The key to flattening the curve is health literacy. *Perspectives in Public Health*. https://doi.org/10.1177/1757913920936717

5. **Kosir, U**., Denis Larocque, G., Tsimicalis, A., Freeman, C., Turcotte, R., Cury, F., Alcindor, T., Goulding, K. (2020). Psychological functioning, coping styles and their relationship to appraisal of physical limitations following invasive surgical procedures for soft tissue sarcoma: A qualitative study. *J Surg Oncol* 2020; 1-10. https://doi.org/10.1002/jso.25915

6. **Kosir, U**. Wiedemann M., Wild, J., Bowes, L. (2019). Cognitive and coping mechanisms in adolescent and young adult cancer patients and survivors: Feasibility and preliminary insights from the Cognitions and Affect in Cancer Resiliency Study. *J Adolesc Young Adult Oncol.* https://doi.org/10.1089/jayao.2019.0127

7. Sørensen, K., Trezona, A., Levin-Zamir, D., **Kosir, U**., Nutbeam, D. (2019). Transforming health systems and societies by investing in health literacy policy and strategy. *WHO Panorama* (5)2-3, p259-263. [link]

8. **Kosir, U**. (2019). Methodological issues in psychosocial research in adolescent and young adult (AYA) cancer populations. *J Adolesc Young Adult Oncol.* https://doi.org/10.1089/jayao.2019.0034

9. **Kosir, U**., Wiedemann M., Wild, J., Bowes, L. (2019). Psychiatric disorders in adolescent cancer survivors: A systematic review of prevalence and predictors. *Cancer Reports*. https://doi.org/10.1002/cnr2.1168

10. Kucukgoncu S, **Kosir U**, Zhou E, Sullivan E, Srihari VH, Tek C. Glucose metabolism dysregulation at the onset of mental illness is not limited to first episode psychosis: A systematic review and met-analysis. *Early Intervention in Psychiatry*. 2018;1-11. https://doi.org/10.1111/eip.12749

11. Annamalai, A., **Kosir, U**., & Tek, C. (2017). Prevalence of obesity and diabetes in patients with schizophrenia. *World J Diabetes*, 8(8), 390–396. https://doi.org/10.4239/wjd.v8.i8.390

12. Zhou, E. K., **Kosir, U**., Kucukgoncu, S., Reutenauer Sullivan, E. L., & Tek, C. (2017). How accurate are self-reported height and weight in the seriously mentally ill? *Psychiatry Research*, 257. https://doi.org/10.1016/j.psychres.2017.07.015

In preparation or under review:

1. Bonanno, M., Bourque, C. J., Aramideh, J., Cloutier, N., Dumont, E., Gomez-Tyo, M, Julien-Lacoste, A, **Kosir, U**., Provost, C., Laverdiere, C., Sultan, S. (Under review). Articulating viewpoints to better define and respond to the needs of adolescents and young adult survivors of brain tumors. *J Adolesc Young Adult Oncol.*

2. **Košir, U**., Loades, M., Wild, J. & Bowes, L. (In preparation). A network analysis of anxiety, depression, and cancer-related worry in adolescents and young adults with cancer. *Journal of Clinical Oncology*.

3. **Košir, U**., Bowes, L., Mayo, N., … & Turcotte, R. (In preparation). Fatigue and recovery in sarcoma over time: Application of group-based trajectory modeling. *JAMA Oncology*.

4. Menegatti, L., Roškar, S. & **Košir, U**. (In preparation). Beliefs about cancer causes and their relationship to psychological wellbeing. *Psycho-oncology.*

List of abbreviations

ab.	abstract
ACS	American Cancer Society
AeYA	Adolescent and early young adult
AIC	Akaike Information Criterion
ALL	Acute Lymphoblastic Leukemia
ALSPAC	Avon Longitudinal Study of Parents and Children
AML	Acute Myeloid Leukemia
ANOVA	Analysis of variance
AYA/AYAs	Adolescents and young adults
BIC	Bayesian Information Criterion
CBT	Cognitive Behavioral Therapy
CFI	Comparative Fit Index
CI	Confidence interval
CNS	Central Nervous system
COREQ	Consolidated criteria for reporting qualitative research
COVID-19	Coronavirus disease
DAG	Directed acyclic graph
DSM-IV/5	Diagnostic and Statistical Manual of Mental Disorders
Dx	Diagnosis
EBIC	Extended Bayesian Information Criterion
ESRC	Economic and Social Research Council
EU	European Union
FCR	Fear of cancer recurrence
FNLCC	French Federation of Cancer Centers Sarcoma Group
GBTM	Group-based trajectory modeling
GIST	Gastrointestinal stromal tumor
I4C	International Childhood cancer consortium
ICD	International Classification of Disorders
ICF	International Classification of Functioning
ICIDH	International Classification of Impairments, Disabilities, and Handicaps
IHRT	Interdisciplinary Health Research Team
m/M	mean
MAR	Missing at random
MI	Measurement invariance
MoBA	Norwegian Mother and Child Cohort Study
MSK	musculoskeletal
MUHC	McGill University Health Centre
n/N	number
NCI	National Cancer Institute

NHS	National Health Service
NIH	National Institute of Health
OR	Odds ratio
OSF	Open Science Framework
PPI	Patient and public involvement
PROSPERO	International prospective register of systematic reviews
PTG	Posttraumatic Growth
PTSD	Posttraumatic stress disorder
RCT	Randomized Controlled Trial
REB	Research Ethics Board
RMSEA	Root Mean Square Error of Approximation
RQ	Research question
RT	Radiation therapy
SABIC	sample-size-adjusted Bayesian Information Criterion
sd/SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SEM	Structural equation modelling
SES	Socio-Economic status
STS	Soft tissue sarcoma
TCT	Teenage Cancer Trust
ti.	title
UK	United Kingdom, English
US/USA	United States of America or American
WHO	World Health Organisation
YCE	Youth Cancer Europe

Chapter 1 - Introduction

1.1 What is psycho-social oncology?

From how far we have come today, it is difficult to imagine that until the 1950s the only treatment available for cancer was surgery (Kash, Mago, & Kunkel, 2005). Cancer is one of the oldest recognized diseases and remains among the leading causes of non-accidental death in youth (Cunningham, Walton, & Carter, 2018), and among the most prevalent causes of death by non-communicable diseases worldwide, second only to cardiovascular diseases (WHO, 2018). The advances in the modern medicine, the advent of chemotherapeutic agents, targeted immune therapies, and screening programs, which allow for early detection of cancer, result in an increasing number of people who reach remission (i.e. are disease free) and live for years after illness, with figures projecting over 20 million people who will have lived with cancer in the next decade (K. D. Miller et al., 2016; Shapiro, 2018). It is unsurprising that due to these advancements over the past few decades, the research and clinical care paradigm shifted from survival efforts to psycho-social wellbeing of patients (Kluetz et al., 2016).

Psycho-social oncology is thus a young and rapidly evolving field that considers the psychological and supportive care for people and families afflicted by cancer, (Care & Muriel, 2016; Lown, Phillips, Schwartz, Rosenberg, & Jones, 2015). Research spans broad areas of functioning, from physical to psychiatric outcomes (Dolbeault, Szporn, & Holland, 1999; Holland, 2002; Sansom-Daly & Wakefield, 2013), and there is a consensus among health care professionals and academics that everyone facing cancer should be considered holistically by an interdisciplinary team from the time they receive the diagnosis (Kash et al., 2005; Thomas, Albritton, & Ferrari, 2010). Even though attending to the psycho-social needs of all patients seems indisputable, it is far from the reality, and research and policy are just beginning to be shaped.

1.2 Cancer and young people

Cancer incidence increases with older age (Fitzmaurice et al., 2019), and the origins of cancer in young people are largely unknown (Kentsis, 2020). The incidence remains low, with cancer diagnoses under the age of 39 years accounting for less than 5% of all cancer cases (see Figure 1.1; Horner et al., 2008; Miller et al., 2016). Despite the low prevalence, the number of young cancer survivors is also growing globally

(Last, Grootenhuis, & Eiser, 2005; Yeh et al., 2019). However, a substantial proportion of them are not achieving full recovery; they live on with heightened distress and fear of illness recurrence (e.g. Barnett et al., 2016; Zeltzer et al., 2009), report difficulties establishing romantic relationships (e.g. Thompson, Long, & Marsland, 2013), experience difficulties or discrimination at work (e.g. Stone, Ganz, Pavlish, & Robbins, 2017), report increased suicidal ideation (Recklitis et al., 2010), and face higher risk for developing other chronic health conditions (Oeffinger et al., 2006).

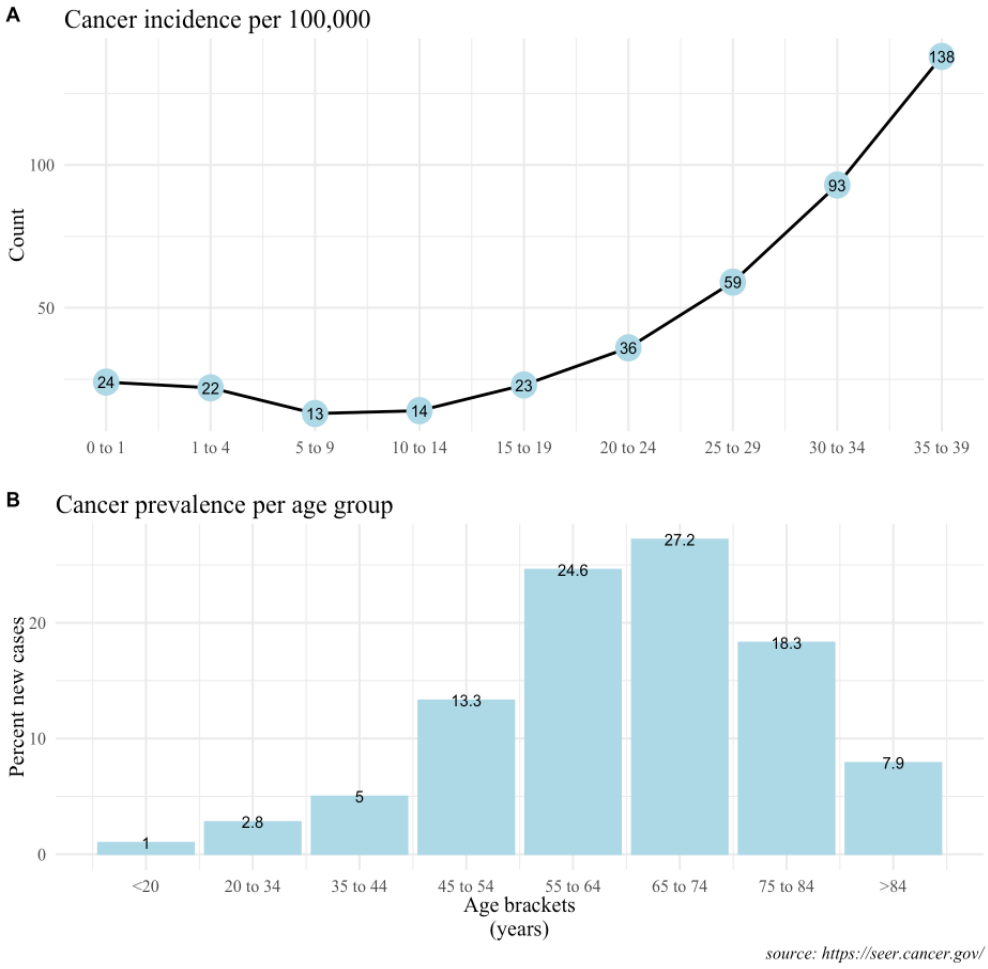


Figure 1.1: Cancer incidence per age group.

NOTE: **A)** Rate of cancer incidence per 100,000 based on the age bracket (numbers have been rounded to the nearest whole). **B)** Prevalence of cancer by age group (Data from SEER, accessed 22 March 2019 at https://seer.cancer.gov/).

While childhood cancers received ample attention over the past half of the century, adolescents and young adults (AYA) have only recently been recognized as a separate subgroup. Broadly defined as individuals between 15 and 39 years of age, AYAs have seen slower improvements in survival rates compared to younger children, (see Figure 1.2; Albritton & Bleyer, 2003; Barr, Ferrari, Ries, Whelan, & Bleyer, 2016), and may face more psychosocial difficulties during and after their cancer experience (Barnett et al., 2016; McDonnell et al., 2017; N. M. Schrag, McKeown, Jackson, Cuffe, & Neuberg, 2008).

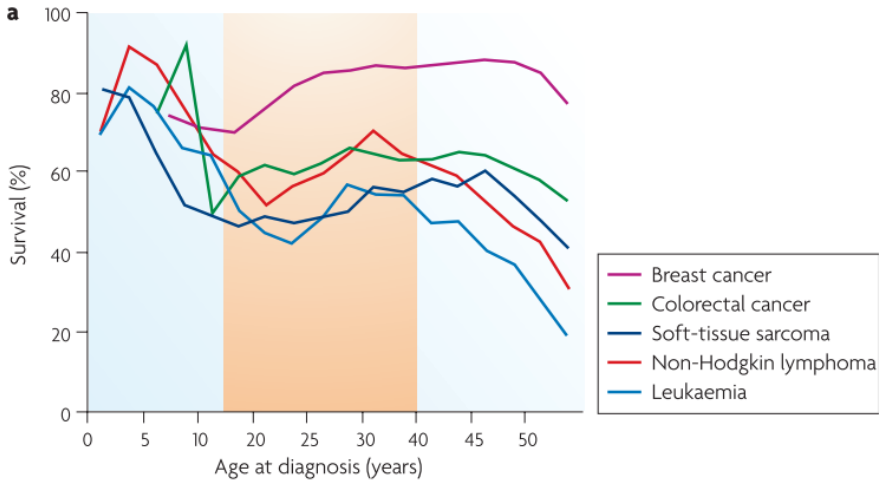


Figure 1.2: 5-year survival rate by age.

NOTE: Survival rates by age for some of the most commonly observed cancers in AYA. The figure has been adapted from Barr et al. (2016).

Large institutional bodies such as National Cancer Institute (NCI) recognize the disparity among supportive care programs for AYAs versus younger patients (B. Zebrack, Mathews-Bradshaw, & Siegel, 2010), and increasingly the initiatives that promote AYAs' empowerment emphasize the need for more developmentally appropriate and age-sensitive approaches to oncological care and highlight the importance of adjacent psychosocial care for young cancer patients (Aldiss, Fern, Phillips, & Gibson, 2018; Buchacz et al., 2018).

1.3 A case for adolescents and young adults

Reasons for the observed discrepancies in recovery and psycho-social outcomes between AYAs and younger or older patients may be many and multifaceted.

Adolescents and young adults find themselves at a distinct developmental period, marked by many changes due to the rapid development and several life transitions (Arnett, 2000; Hochberg & Konner, 2020; Richter, 2006). This is a period of physical, social, and emotional maturation, during which individuals strive to reach developmental milestones such as establishing autonomy, moving away from home, starting their university or career, developing intimate relationships, and even pursue family life, thus receiving a cancer diagnosis can significantly derail all of the above (Bibby, White, Thompson, & Anazodo, 2017; C. L. Daniel et al., 2015; Perez, Salsman, Fladeboe, & Kirchhoff, 2020). But while young people may have the cognitive maturity to understand the gravity of such diagnoses better than children, they might lack the emotional and decision-making capacity to cope, which can in turn compromise their well-being and adaptation (Patterson, McDonald, Zebrack, & Medlow, 2015). Maladaptive coping mechanisms such as substance use or avoidance have been reported in the AYA cancer literature, and may contribute to poorer physical, as well as psychosocial outcomes (Butow et al., 2015; Hobbie et al., 2000; Klosky et al., 2012; Milam et al., 2016).

Young people tend to be healthy, so having cancer in adolescence or young adulthood can feel isolating (Baird, Patterson, Medlow, & Allison, 2019; Pannier et al., 2019; B. J. Zebrack et al., 2013). Adolescents often have to miss school, or postpone their educational ambitions (H. M. Parsons et al., 2012; Prevatt, Heffer, & Lowe, 2000), which is associated with disruption in social circles (McLoone, Wakefield, Butow, Fleming, & Cohn, 2011). As peers and friends play an instrumental role in social support during emerging adulthood (Hochberg & Konner, 2020; Mascarin & Ferrari, 2019), disrupted education or early career, make the re-entrance difficult for many young people (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005; Glasson, 1995; Kaffenberger, 2006). Young people may also report feeling different from how they were before the illness, and different from their peers, which can act as another barrier to successful social and educational re-integration (Pini, Gardner, & Hugh-Jones, 2019; Vetsch et al., 2018). Moreover, young people don't always feel comfortable disclosing their medical history, or don't know how to talk about their cancer experience (Rabin, 2020), which can further contribute to the feelings of loneliness.

Cancer and its treatment are often associated with aggressive side-effects, that compromise physical appearance (e.g. hair loss) (Larouche & Chin-Peuckert, 2006). During a time in life, when the individuals are most striving to belong, AYAs with

cancer often report "looking sick" as a negative aspect, which contributes to lower self-esteem, and poorer body image (Fan & Eiser, 2009). Changes in appearance resulting from cancer treatment have been associated with psychological symptoms, such as depression (Enskär, Carlsson, Golsäter, & Hamrin, 1997), and behavioral maladjustment including somatization, withdrawal, and distress (Moore et al., 2003).

Furthermore, for many AYAs cancer diagnosis occurs before they start to think about fertility and family planning, and many young people do not fully understand the potential impact of their cancer treatment on current or future fertility (Crawshaw & Sloper, 2010; Tschudin & Bitzer, 2009). Fertility concerns are common and distressing to both males and females (Carpentier & Fortenberry, 2010; Nahata et al., 2018; Ruggeri et al., 2019). Equally disrupted may be AYAs exploration of their sexuality and romantic and intimate relationships (Acquati et al., 2018; Tolman & Mcclelland, 2011; Wettergren et al., 2017).

Lastly, AYAs may present with distinctive biology (Bleyer et al., 2008), and over the past few decades there were significantly fewer clinical trials that included AYAs than clinical trials available to younger or older patients, which stalled the research and innovation (Barr et al., 2016; Bleyer et al., 2008; L. A. Fern, Lewandowski, Coxon, & Whelan, 2014). Moreover, as cancer in youth is rare, symptoms may be missed or initially misdiagnosed, which can lead to a prolonged route to diagnosis and consequently poorer prognosis (Barr, 2014). Adolescents may also inadequately adhere to the treatment procedures (Kennard et al., 2004; KyngÄs, Kroll, & Duffy, 2000), and AYAs are not only less likely to comply with their cancer treatment, but also less likely to engage in long-term follow-up care (Rokitka et al., 2017).

The questions of fertility, body image, sexuality are salient to young people, but are still viewed as "taboo topics" and seldom discussed with physicians (Barlevy, Wangmo, Elger, & Ravitsky, 2016; Perez et al., 2020; Quinn et al., 2015; Quinn & Vadaparampil, 2009). Feeling supported and cared for by the medical team is beneficial to young people with cancer (Košir, Roškar, Wild, & Bowes, 2020; McNeil, Egsdal, Drew, McCarthy, & Sawyer, 2019; Osborn et al., 2019), and has the potential to ameliorate the outcomes by mediating the above described impact on one's development.

In this section I discussed what makes AYAs a unique group of patients and suggest that they might have been overlook and under-represented in the existing

literature. Other challenges pertaining specifically to the field of research in AYA psycho-social oncology are discussed at length in the following chapter (Chapter 2).

In my thesis I consider several aspects of cancer impact on AYAs and investigate the role of these factors in resilience and psychopathology along the cancer trajectory. Specifically, in my qualitative work I explore these factors (e.g. fertility, body image) in depth and demonstrate that modifiable factors (e.g. social support) can "moderate" the effect of illness. In Chapter 5 I also consider the role of coping mechanisms and cancer-specific worries on psycho-social adaptation.

1.4 Defining resilience and psychopathology in youth with cancer

Cancer diagnosis and treatment are a stressful experience for a patient of any age. Feelings of distress, anxiety, and depression are a common response at the time of cancer diagnosis (Chaturvedi & Uchitomi, 2012) and tend to subside with time (Kunin-Batson et al., 2016; Brad J. Zebrack et al., 2004). However, patients facing cancer at different developmental stages are likely to face distinct challenges. As already described, adolescent and young adult patients and survivors present with unique needs due to the nature of their developmental period; cancer, treatment and illness-associated changes can disrupt normative cognitive development (Wengenroth et al., 2015), interfere with social activities (Katz & Madan-Swain, 2006), and impose new demands on the survivor and their family (Rait, Ostroff, Smith, Cella, & Tan, 1992; Rashid, Saraykar, Makanjoula, Valentine, & De La Garza, 2016).

All of these can lead to adverse psychological outcomes, and research consistently shows that a smaller, yet significant subset of AYA patients and survivors reports a spectrum of adverse outcomes; from poorer physical health (Oeffinger et al., 2006), to somatic complaints (Chaturvedi, Peter Maguire, & Somashekar, 2006; L. Daniel et al., 2016), and psychopathology (Cousino et al., 2017; Gianinazzi et al., 2013; Kazak et al., 2004).

Due to methodological obstacles, which I discuss in the subsequent chapter (Chapter 2) the exact prevalence rates of psychopathology in adolescent and young adult cancer survivors are difficult to establish. But perhaps most identifiable and significant in this population is the persistent anxiety-related distress, which manifests

itself during all phases of illness and treatment trajectory (L. Curran, Sharpe, & Butow, 2017; McDonnell et al., 2017).

Labeled as the "Damocles syndrome," the analogy of a sword hanging above one's head on a horsehair that could snap at any time, has been used to describe the prevailing anxiety and uncertainty that young people experience despite having survived cancer (Koocher & O'Malley, 1981). Individuals often worry about their disease coming back or fear receiving a new, different cancer diagnosis. The so-called fear of recurrence (FCR) has been observed in 39 – 97% of all adult (>18 years) cancer survivors (Simard et al., 2013), however, some studies report that it may be particularly prominent in young people, with 62% of AYAs endorsing high levels of FCR (Thewes et al., 2018). Other cancer-specific worries (e.g. fertility; Gilleland Marchak et al., 2015) are also common among AYAs, with over half of them reporting at least some level of preoccupation related to late-effects in the years after treatment (R. Wang et al., 2015).

Understanding and addressing cancer worries and illness-related needs in young people is important in assuring optimal long-term outcomes and recovery. The aggressive nature of life-saving treatments can compromise health and lead to debilitating illness late effects (Oeffinger et al., 2006; Oeffinger & Tonorezos, 2011). Some level of concern and vigilance may be justified and even adaptive (Badr et al., 2013; Nathan et al., 2009). However, the problem is the current lack of consensus of what constitutes clinical levels of such worries and anxiety, and what exactly we should be targeting with psycho-social interventions in AYAs with cancer.

1.4.1 What constitutes resilience

To introduce the concept of resilience I want to begin with the very root of the word. To be 'resilient' comes from *resilientem*, which in Latin describes the proclivity to leap or spring back ("Online Etymology Dictionary," 2017). Most of the working definitions in today's psychological research are not too far off; they revolve around the idea that in light of adversity, some individuals cope better than expected (Masten, 2001; Michael Rutter, 2006). More recently it has been suggested that resilience be even more dynamic and implies a positive psychological outcome despite a significant adversity (Ungar, 2018). Moreover, inherent to the concept is the very multifactorial nature of resilience. Just as there exist substantial individual differences in the way

people behave or react emotionally, a uniform psycho-social adaptation to cancer should also not be expected (Luthar, Cicchetti, & Becker, 2000).

Even though resilience in oncological work is often talked about, the field lacks a common definition for it (Molina et al., 2014). Research conducted in oncological nursing defined resilience as a *process* through which individuals identify and develop resources and skills that allow them to manage and control stress which in turn brings about positive outcomes, a sense of accomplishment and confidence, and increases self-esteem (Haase, 1987; Haase, Kintner, Monahan, & Robb, 2014). This working definition may serve a particularly practical purpose. With the above definition in mind, medical professionals working with young patients sought to describe the *processes* that lead to positive outcomes and successfully identified several dispositions such as: optimism (Rooij et al., 2018; Sulkers et al., 2013), social support (Corey, Haase, Azzouz, & Monahan, 2008; Pennant et al., 2020), and spirituality (Park & Cho, 2017; Proserpio et al., 2020), which can be promoted in the clinical work.

Increasingly evidence depicts resilience as a dynamic process of response to stressors that can be the result of several factors, which can be biological, psychological, or environmental in nature (Bonanno, Romero, & Klein, 2015; Bonanno, Westphal, & Mancini, 2011; Kalisch et al., 2017; Kalisch, Müller, & Tüscher, 2015; Michael Rutter, 2012). With adequate data and appropriate statistical methods, such as network modelling (Kalisch et al., 2019) we can begin to reconceptualize the notion of resilience in AYAs with cancer too.

1.4.2 What constitutes psychopathology

Adolescence and young adulthood are not only the times of rapid developmental changes (Arnett, 2000; Crone & Dahl, 2012), but also the time when most mental health disorders arise (Kessler et al., 2005). The onset peaks around the mid-adolescence and grows higher in early adulthood (Merikangas et al., 2010). Anxiety disorders are the most prevalent, have the earliest onset, and their symptoms usually precede depression in adolescence (Merikangas et al., 2010; Reinherz, Paradis, Giaconia, Stashwick, & Fitzmaurice, 2003). Estimates suggest that 1 in 5 young people suffer from mental health disorders (Gore et al., 2011; Patton et al., 2012).

Some findings offer a more optimistic view, suggesting that most of adolescent mental health disorders resolve by the late 20s. Nevertheless, they also show that almost

30% of adolescent males and 54% of females, who have had at least one episode during adolescence, persist to report mental health difficulties throughout their 20s (Patton et al., 2014). Almost 20% of young adults are first diagnosed at the beginning of their 20s thus implying that the high-risk period persists into young adulthood (Patton et al., 2014).

During adolescence and young adulthood, significant or chronic stressors can derail the normative development and trigger psychopathology or contribute to life-long mental health disorders (Braithwaite, O'Connor, Degli-Esposti, Luke, & Bowes, 2017; Infurna et al., 2016; Lindert et al., 2014). Diagnosis and treatment for cancer may also be considered as a form of trauma. A chronic health condition like cancer can impact one's development and psychological wellbeing, and beyond the above described factors (see section 1.3) might even share common biological pathways to the expression of common mental health disorders (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Alternatively, the treatment and illness late-effects can compromise endocrinological functioning, which may increase the risk for psychopathology (Rose et al., 2016).

To date most of the psycho-oncological literature is relatively binary; most of the work has focused on evaluating risk factors and prevalence of psychopathology in cancer survivors. Only a minority of research studies have started to consider resilience and posttraumatic growth (e.g. Husson et al., 2017), however, the interlinked nature of resilience and psychopathology has been overlook, and average effects of either construct reported in most work do not offer a full picture. In my work I consider a cancer diagnosis as a significant adverse event in a young person's life and I operationalize psychosocial adaptation and recovery as a dynamic process that at once encompasses processes of resilience and psychopathology.

In order to develop novel psycho-social interventions in AYA oncology we need to take a more holistic and biopsychosocial approach, taking into account the multifactorial nature of adaptation, with biological, individual, and societal factors contributing varying degrees of risk and protection for psychological adaptation following a cancer diagnosis. As poor mental health remains the leading cause of disability among young people (Gore et al., 2011), identifying the factors that contribute to psychological distress in young cancer patients and survivors will not only

reduce the burden on individuals and their families, but also the burden posed on national health services.

1.5 Current interventions in AYA psycho-social oncology: One size does not fit all

Cancer and its treatment often cause disruption in a young person's life and in some cases result in persistent and high levels of psychological distress (e.g. Barnett et al., 2016). Moreover, AYAs are at an increased risk for developing chronic health conditions (Marjerrison & Barr, 2018) and have higher levels of disability compared to healthy peers (Tai et al., 2012). As such, AYAs present with many needs that have to be addressed not just to help them recover, but also to successfully reintegrate them into the society, educational system, and workforce (Ekwueme et al., 2014; H. M. Parsons et al., 2012; Vetsch et al., 2018). To meet these needs interventions for health promotion and psychological wellbeing have been developed.

Several systematic reviews looked at the existing interventions spanning from self-efficacy and coping mechanisms to treatment preference communication, and raised several criticisms; intervention studies of high quality are lacking, and many published reports are from feasibility and pilot studies (Bradford & Chan, 2017; Phillips & Davis, 2015; Walker, Martins, Aldiss, Gibson, & Taylor, 2016). The variety of inclusion criteria, heterogeneity of interventions as well as outcomes make it hard to compare the results or tease out the specific mechanisms of the intervention, and moreover, Bradford & Chan, (2017) noted that only 2 out of 17 studies targeted AYAs specifically. Additionally, the majority of psychosocial interventions focused on in-treatment populations (Walker et al., 2016), even though psychosocial wellbeing tends to become a priority after the active treatment phase for many young people (L. A. Fern et al., 2013).

More recently, group cognitive behavioral therapy (CBT) was proposed for AYAs, and while observational data from the therapists and qualitative responses from participants highlighted positive aspects of this approach, only 2 out of 17 participants attended all 6 sessions of the intervention (Hall, Short, Giberson, & Howe-Martin, 2020).

Even though many interventions seem beneficial, and face-to-face counselling and peer support show most promise in promoting psycho-social wellbeing in AYAs

(Bradford & Chan, 2017; Walker et al., 2016), the evidence to date suggests that one size fit all approach may not be appropriate. The population presents with many challenges that span multiple domains of functioning. Prior to developing and testing interventions, we need to conduct more research on the mechanisms of recovery and adaptation. My empirical work addresses this need and throughout the following empirical chapters I investigate several factors and mechanisms that might offer a target for future interventions for young people with cancer.

1.6 From brain tumors to sarcoma

Cancer is a broad term that describes an illness resulting from an abnormal and uncontrolled cell proliferation that can develop in virtually any tissue and impact any organ (Tomasetti, Li, & Vogelstein, 2017). The illness is often labelled based on the tissue of origin and location of occurrence (i.e. breast cancer).

Given that cancer describes many illnesses, it may be understandable to study psycho-social outcomes based on a cancer group. For example, some evidence suggests that individuals with brain tumors are a distinct group of cancer patients because of the specific neurocognitive, psychosocial, and physical difficulties resulting from the illness and treatment (D'Agostino & Edelstein, 2013; Kuhlthau et al., 2015). Direct radiotherapy to the developing brain may result in dysfunctions in memory, abstract thinking, and even IQ decline (Kuhlthau et al., 2015; Lassaletta, Bouffet, Mabbott, & Kulkarni, 2015) and leave brain tumor survivors at higher risk for long-term and chronic health complications compared to other cancer peers (Huang et al., 2017; Brad J. Zebrack et al., 2014). Although findings are inconclusive because studies have often excluded individuals with brain tumors for these reasons (de Ruiter et al., 2016).

Another distinct and understudied group may be young people with sarcoma. Sarcomas are very rare, though relatively prevalent in young people (Ferrari, Bleyer, et al., 2018). Due to the high heterogeneity within sarcomas and their rarity, the development of novel therapeutics has been slower, resulting not only in lower survival, but also lower awareness (Jacobs, Michels, Stein, & Levin, 2015; Weitz, Antonescu, & Brennan, 2003; Winnette, Hess, Nicol, Fritz, & Copley-merriman, 2017) compared to other cancer types. Moreover, because sarcomas often require invasive surgical procedures the research to date often overemphasized the physical toll of illness,

neglecting the psycho-social aspect, despite the fact that the latter is more important to patients (Martins et al., 2020).

Even though there may exist differences in the outcomes between distinct cancer groups, most of the literature in psycho-social oncology is seldom stratified by cancer type. Research suggests that objective clinical (e.g. tumour size) and demographic factors play a lesser role in adaptation than modifiable factors such as pre-existing distress (e.g. Olga Husson & Zebrack, 2017; Sansom-Daly & Wakefield, 2013). I elaborate on this limitation, as well as other challenges in the study of psycho-social outcomes in the following chapter (Chapter 2).

My thesis contains two chapters (Chapter 4 & Chapter 7) that focus exclusively on young people with sarcoma and contribute novel findings to the scarce literature in AYAs with sarcoma. The remaining work considers all cancer types, which allows me to consider mechanisms that may be independent from clinical characteristics, all the while controlling for any potential differences between the cancer types.

1.7 From diagnosis to surveillance

Receiving a diagnosis of cancer at a young age may be particularly difficult; when most individuals busy themselves with education, career goals, family relationships, and gaining their independence (Arnett, 2000; Richter, 2006; Waterman, 1982) a diagnosis of cancer can significantly delay the pursuit of important milestones and result in psychological distress (Suris, Michaud, & Viner, 2004). However, from the time of diagnosis to long-term survivorship, individuals undergo many phases, which also pose unique challenges (see Figure 1.3 for summary).

At the time of diagnosis, the levels of anxiety and distress tend to be higher compared to those in the post-treatment phase (Fritz & Williams, 1988; Yallop, McDowell, Koziol-McLain, & Reed, 2013). Initial response to learning the diagnosis is often described as a shock, and many young people talk about confronting their mortality for the first time (Ander, Thorsell Cederberg, von Essen, & Hoven, 2018; Mullan, 1985; Sodergren et al., 2018). AYAs who are newly diagnosed have shown the need to be actively involved in the care (Decker, Phillips, & Haase, 2004), which can lower the levels of distress by allowing young people to regain some level of control (DeRouen et al., 2015; Wilkins, D'Agostino, Penney, Barr, & Nathan, 2014).

During the active phase of treatment, the levels of psychological distress vary, and are often related to the physical functioning and treatment tolerance; pain, nausea, and other side-effects that negatively impact individuals' quality of life, also compromise their psycho-social wellbeing (Schwartz & Brumley, 2017; Sodergren et al., 2017; Brad Zebrack, Kent, Keegan, Kato, & Smith, 2014).

Perhaps the most pronounced change and unexpected challenge is treatment completion; psychological distress in this phase may in part be due to the cognitive dissonance resulting from the fact that individuals at the end of the treatment often feel physically weak, yet are told that they are disease free, which is a positive result. The resulting change in services, and frequency of medical supervision leaves many AYAs feeling anxious and uncertain (Sansom-Daly & Wakefield, 2013; Walker et al., 2016). After the active treatment is over, young people also strive to continue with their "normal life" (Baird et al., 2019; Barnett et al., 2016; Bibby et al., 2017; B. J. Zebrack et al., 2013), and this is when most of them report having mental health and psychosocial difficulties (L. A. Fern et al., 2013; Mellblom, Ruud, Loge, & Lie, 2017).

For many AYAs, long-term survivorship and follow-up care include the change of services (e.g. from pediatric or AYA to adult units), and many individuals are lost in the transition (Oeffinger et al., 2006; Rokitka et al., 2017; Skinner, Wallace, & Levitt, 2006). Failing to adhere to follow up care can compromise long-term outcomes (Marjerrison & Barr, 2018; Oeffinger & Tonorezos, 2011), and psychosocial issues such as anxiety or lack of clear clinical recommendations have been shown to contribute to this loss (Smits-Seemann, Kaul, Zamora, Wu, & Kirchhoff, 2017). Addressing the psychosocial issues at all phases of cancer trajectory is important to assure for the best possible outcomes.

In my thesis I include individuals at different phases of their illness trajectory. My systematic review of the literature (Chapter 3) focuses on survivors post-treatment in order to determine the prevalence of psychiatric disorders that persist beyond treatment. The remaining chapters include individuals at all phases. The aim is to identify any factors that might be present in the earlier phases of illness trajectory, including learning about the diagnosis, and assess their relationship to the psychological outcomes. My longitudinal exploration of psychosocial wellbeing in sarcoma (Chapter 7) offers a novel view of individual, as well as group-based trajectories over time.

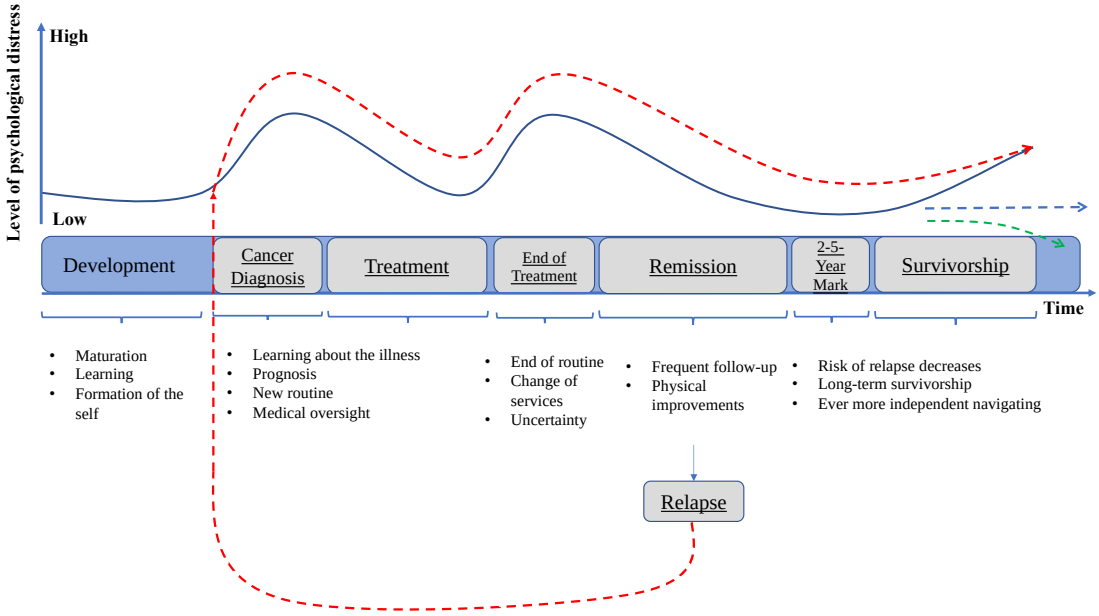


Figure 1.3: Relative levels of psychological distress along the illness trajectory.
NOTE: Based on my literature review, this figure describes a "typical" trajectory of distress across the different phases of cancer, from diagnosis through survival. Around the time of the diagnosis, the levels of distress increase, but tend to subside by the end of treatment. The end of treatment marks a period of changes in protocols, and often results in increased anxiety and uncertainty. Relapse of illness has been associated with higher levels of distress. In the long-term survivorship (>2 years), some individuals return to pre-illness levels of psychological functioning, some report doing better than they did before, and a subset reports increased levels of psychological distress.

1.8 From Slovenia to the world

Understanding cancer as a bio-psychosocial phenomenon that impacts the entire person and their environment, rather than a mere cluster of cells that have gone awry, highlights the need for a multidisciplinary approach in cancer care. However, the approach to treatment and care will inevitably depend on the cultural context, as well as on the health care system in a given society.

Large discrepancies in cancer care and outcomes exist between countries, and within the EU alone (Allemani et al., 2018; Hofmarcher et al., 2019). Countries with fewer or limited resources often fail to adhere to the recommended screening protocols or lack adequate access to novel medicines, yet alone are they able to offer individualized psychological evaluation and care. Similar problems may also occur in remote geographical locations or communities within high-income countries (e.g. northern territories in Canada) (Fernandez et al., 2011). Specialty care and age-appropriate hospital units are often reserved for large, rurally based medical centers.

The extent of cancer impact on societies at-large and an ever-increasing need to reduce its burden might best be understood by "Europe's Beating Cancer Plan," perhaps one of the Europe's most ambitious goals to diffuse preventative measures, early screening protocols, and improve treatment and follow-up care within the EU member states (*Roadmap: Europe's beating cancer plan*, 2020). Continuous work and EU-commissioned research has been informing novel policy recommendations such as those for fair pricing of new oncological agents, and cross boarder health care. These initiatives show promise but remain in the early phases of implementation. Novel research into long-term and psychological adaptation of young people with cancer will become instrumental for narrowing the gap in inequalities, because in parts of the world where access to oncological care alone remains limited, access to psycho-oncological care might be even less accessible.

These global, cancer-related challenges are important to keep in mind when considering the psychosocial impact of cancer. Not only will the social and economic gradients carry implications for cancer care and psychological outcomes, they will also impact the amount and quality of data available for conducting research (Hofmarcher et al., 2019). When reviewing and reading the literature it is thus not surprising that most of the work, particularly in the psycho-social domain is from the high-income countries and might not generalize to the low-income countries.

While acknowledging these discrepancies and the many challenges, my work relates findings from several different, mostly high-income countries, which in some respects broadens the generalizability of my work and allows for replication of findings across similar, yet different settings. The majority of participants in my research were recruited from the UK, Slovenia, Canada, and the USA. While nationally based health care systems are fairly similar between the UK, Slovenia, and Canada, perhaps the biggest and most significant difference is the national insurance (or lack thereof) in the USA (H. M. Parsons, Schmidt, Tenner, Bang, & Keegan, 2016). Even though issues relating to the insurance and associated financial difficulties add to the distress (Bleyer, 2005; Chino et al., 2017; Perez et al., 2020), other psycho-social challenges and needs unique to AYAs seem to transcend the international borders.

This may be attributable to two main factors. First, AYAs have only recently been recognized as a distinct group and services and calls for action have soared over the past few years. Many challenges that young people experience relate to the developmental phase rather than the health care system (e.g. disrupted education). As

such, the geographical location plays a lesser role. Secondly, with online and social media resources for AYAs gaining traction and credibility (Crook & Love, 2017; De Clercq et al., 2020), the global AYA cancer community is more tight-knit than ever. Despite the locally based hubs, many large organizations and initiatives advertise their trans-national scope. Youth Cancer Europe, a pan-European coalition which advocates for patients' rights at the EU level (YCE, 2020), or War on Cancer, an online platform which connects youth with cancer from every corner of the world ("War on Cancer," 2020) are just two notable examples.

The international scope of my work allows for a more thorough understanding of young patients' needs abroad, as well as in Slovenia, where no AYA-specific services exist. Such insights are crucial for continued progress on national levels, and have the potential to highlight important areas of need that might have been overlooked abroad.

1.9 A note on the language use and survivorship

It would be ignorant to dismiss the importance of language used in psycho-oncological settings. The definition of a cancer survivor has long been a contentious topic (Twombly, 2004), and deciding when survivorship begins is not yet clear (Marzorati, Riva, & Pravettoni, 2017).

In its broadest sense, the term survivor has been extended to describe all individuals impacted by cancer including the patients' parents, closest relatives, or spouses, which acknowledges the impact of illness on the entire family (Twombly, 2004). Some individuals embrace their new survivor identity and find strength and comfort in it, yet others find the label inappropriate and dislike that their identity be reduced to illness and its aftermath (Cheung & Delfabbro, 2016). While some researchers found that identification with cancer survivorship related to positive psychosocial outcomes in adults (Bellizzi & Blank, 2007; Park, Zlateva, & Blank, 2009), researchers in Australia suggested that higher level of identification with being a cancer survivor among AYAs was associated with higher levels of depressive symptomatology (Sansom-Daly et al., 2018). The exact relationship of the newfound cancer identity to psychopathology in young people is yet to be described.

Moreover, the language used in the popular media, as well as in clinical settings still often borrows from the combative spheres; phrases such as "beating cancer" or

"you won" are commonplace and are equally polarizing as the idea of the cancer identity (Seale, 2001). While describing remission as a *win* may sound positive, the underlying logic suggests that those who relapse have *failed* or *lost*, which could arise in overly ascribed personal responsibility, self-blame, and resultantly heightened psychological distress.

The use of language in relation to cancer goes beyond the scope of my work. Nevertheless, given that cancer can be considered as much an illness as a sociological phenomenon, and that language often shapes our reality, it is important to acknowledge that the way we speak about the illness may as well impact our adaptation to it. In my thesis I refer to *cancer patients* as those who are still undergoing treatment for their primary oncologic disease, and I use *cancer survivor* for individuals who have reached remission.

1.10 An overview of the thesis

Cancer diagnosis and treatment are a stressful experience for any patient, but patients facing cancer at different developmental stages also face unique challenges. Adolescents and young adults are gaining recognition as a distinct subgroup of patients and due to continuous developments in cancer treatments and subsequent improvements in survival rates, the focus has shifted from survival efforts to a more holistic approach, with emphasis on the psycho-social functioning during and after illness.

Even though a significant number of AYAs experience adverse outcomes upon reaching remission (e.g. Barnett et al., 2016; Zeltzer et al., 2009), others show positive psychological adaptation as well (e.g. Parry & Chesler, 2005). A better understanding of how and why some develop psychological difficulties, while others become more resilient is still needed. To this end, the research questions guiding my work are the following:

RQ1) What are the factors associated with resilience and psychopathology in youth with cancer?

RQ2) How do mechanisms of resilience and psychopathology change over the span of illness?

RQ3) What should we target in early prevention to facilitate the holistic recovery of AYAs?

1.10.1 Research questions

The following section describes how each of the research questions will be addressed through my empirical work. Table 1.1 provides a summary of the aims and chapters.

Table 1.1: An overview of the main research questions and chapters.

Overarching RQ	Chapter	Aim	Method
What are the factors associated with resilience and psychopathology in youth with cancer?	Chapter 3	Describe the prevalence and risk factors for psychopathology in AYA survivors	Systematic review of the literature
	Chapter 4	Explore the factors that AYAs describe in their road to recovery from sarcoma	Qualitative, semi-structured interviews; thematic analysis of the transcripts
	Chapter 5	To develop a better understanding of the relationship between different symptoms of psychopathology and cancer-specific worry	Online survey, undirected cross-sectional network approach (Gaussian graphical models)
	Chapter 6	Evaluate the impact of COVID-19 on psycho-social wellbeing of AYAs living with cancer	Online cross-sectional survey with questionnaires and open-ended questions; exploratory descriptive analysis
How do mechanisms of resilience and psychopathology change over the span of illness?	Chapter 7	Identify distinct trajectories of adaptation and recovery in sarcoma over time	Secondary analysis of longitudinal data; Group-based trajectory modeling
What should we target in early prevention to facilitate the holistic recovery of AYAs?	All	Contribute evidence towards the development of novel intervention targets	/

1.10.1.1 RQ1) What are the factors associated with resilience and psychopathology in youth with cancer?

Chapter 3 is a systematic review of the existing literature, which offers an insight into the prevalence rates of psychopathology in AYA survivors and reviews some of the

risk factors for psychiatric disorders. The chapter highlights the many discrepancies in the published literature, the need for a more rigorous approach to study of the holistic recovery in AYAs with cancer, and the presence of clinical anxiety in the survivorship phase. This systematic review was published in *Cancer Reports* (Kosir, Wiedemann, Wild, & Bowes, 2019b).

Chapter 4 offers an in-depth understanding of how AYAs with cancer perceive and live through their illness. This chapter relies on qualitative exploration of factors that are personally relevant to the individuals. In particular, the focus is on the youth with sarcoma across the UK. The emphasis is placed on the highly individualistic nature of recovery, with both positive and negative factors contributing to the recovery. The paper resulting from this chapter has been published in *BMJ Open* (Kosir et al., 2020).

Chapter 5 is an exploration of how cancer-specific worry, anxiety and depressive symptoms are interconnected. The data were analyzed using network approach, which accounts for the interactions between observable factors and allows us to identify the most central symptoms, which may offer potential targets for future interventions. The study was carried out online and collected novel and granular data on symptoms of psychopathology and cognitive mechanisms (e.g. mental defeat) from AYA cancer patients and survivors globally. A paper based on these findings is currently in preparation for submission to *Journal of Clinical Oncology*.

Chapter 6 is a cross-sectional survey, which was developed as an addendum in response to the global COVID-19 pandemic. The pandemic and associated measures (e.g. isolation, delayed cancer treatment) can be understood as risk factors, which may impact youth with cancer. The chapter evaluated psychological well-being of patients and survivors in the early phases of the pandemic. Being a cancer patient or survivor may not only make one more susceptible to infection, but further contribute to heightened distress and health-related anxiety. A paper based on this work was published in *Cancer* (Košir, Loades, et al., 2020) and the findings discussed in a panel discussion at the European Health Forum Gastein on September 30, 2020.

1.10.1.2 RQ2) How do mechanisms of resilience and psychopathology change over the span of illness?

Chapter 7 is a longitudinal exploration of clinical data of young individuals with sarcoma treated at a major sarcoma-specialty center in Montreal, Canada. Relying on person-centered statistical methods (group-based trajectory models) and controlling for clinical factors and tumor characteristics, this chapter explores distinct trajectories of fatigue and psychological functioning from diagnosis up to 2 years into remission. This work led to multi-institutional collaboration and the findings inform a publication in preparation for *JAMA Oncology*.

1.10.1.3 RQ3) What should we target in early prevention to facilitate the holistic recovery of AYAs?

This research question is underlining all of the above-described chapters. By studying the factors that contribute to the adaptation, and how they might change over time, we will be able to develop and test novel and targeted interventions for youth with cancer.

Chapter 8 is the concluding chapter with a general discussion that brings together the empirical findings and discusses the broader implications of this work for future research, clinical practice, and policy. The chapter also elaborates on the overall strengths and limitations of this thesis and highlights the remaining challenges in the field of psycho-social oncology. Appendices with the supporting documentation for the empirical chapters are found at the end.

Summary

Understanding the psychological well-being of AYA patients and survivors and examining the mechanisms of adaptation are the main focus on this thesis. I expand upon the current conceptualization of resilience and psychopathology in psycho-social oncology and rely on a mixed method approach[1] to better account for individual differences and to take a holistic approach in addressing psychosocial concerns of young people living with and beyond cancer. I take a bio-psycho-social approach and consider individual level factors, as well as broader environmental factors and their relationship to psychological outcomes in patients and survivors. Innovatively, my research draws from theoretical insights and models from the literature and is complemented with personal narratives and exploratory approach to addressing recovery in AYA cancer populations. This work may be directly informative for clinical practice, as well as policy development.

[1] I use the term "mixed method" only to describe the combination of qualitative and quantitative methods which I have employed in various studies. This thesis presents distinct studies, which were developed and designed separately, so the mixed method approach is not to be confused with any one specific and rigorously defined mixed method paradigm and methodological triangulation.

Chapter 2 - Addressing the challenges through a mixed method approach*

In the introductory chapter (Chapter 1) I briefly described what psycho-social oncology is, outlined some of the ongoing research efforts in the field, and introduced the main research questions underpinning my doctoral work:

RQ1) What are the factors associated with resilience and psychopathology in youth with cancer?

RQ2) How do mechanisms of resilience and psychopathology change over the span of illness?

RQ3) What should we target in early prevention to facilitate the holistic recovery of AYAs?

Understanding the overall recovery and how resilience and psychopathology develop in young people with cancer is a complex task and carries many public health implications. Despite many efforts to describe psychological adaptation in youth with cancer there remain conflicting and inconsistent findings, which can in part be attributed to the conceptual and methodological challenges of the current research practices in the field of AYA psycho-social oncology.

In this chapter I discuss some of the major limitations of the current research, offer directions for future work, and outline how I approached these challenges in my thesis.

Table 2.1 provides a quick summary and overview of the challenges and my approach to study of psychosocial outcomes in youth with cancer.

* Parts of this Chapter have been adapted from:

Kosir, U. (2019). Methodological issues in psychosocial research in adolescent and young adult (AYA) cancer populations. *J Adolesc Young Adult Oncol.* https://doi.org/10.1089/jayao.2019.0034

Table 2.1: Addressing challenges in AYA psycho-social oncology.

Conceptual challenges	**Description**	**My approach**
Defining AYA	There is no consensus on the most suitable age range for defining adolescents and young adults broadly, and specifically in the field of cancer treatment and recovery?	I focus on individuals between 15 – 39 years, and control for age in the analysis when possible.
Cancer as single illness	Cancer is often labeled as a single illness even though there is high heterogeneity in presentation, biology and outcomes between different cancer types.	In two of my empirical chapters I focus solely on patients with sarcoma, which most commonly begins in adolescence. For practical reasons I include all cancer types in my online study and control for type in the analysis.
Methodological challenges	**Description**	**My approach**
Measurement	Illness symptoms or treatment side effects might confound measurement of psychological distress.	I use several different measures for psychological distress, as well as a measure specifically validated in this population.
Data collection	Due to relatively low incidence of cancer in young people recruiting participants can be time-consuming and difficult.	I utilized secondary data analysis of a large clinical population in addition to collecting new data via online recruitment strategies to reach young people.
Study design and analysis	Current studies are mostly observational and cross-sectional in nature, often lacking adequate or appropriate statistical scrutiny. Moreover, purely quantitative analyses dismiss the importance of personal narratives and what is important to patients.	I utilize a mixed-method approach, combining qualitative exploration with advanced statistical methods.

2.1 Conceptual challenges

2.1.1 How should we define adolescents and young adults?

One commonly encountered limitation is the large variety of age ranges, and related terminology employed by different studies (JAYAO, 2011). “Pediatric”, “childhood”, “adolescent”, “AYA”, and “Adolescent and early Young Adult” (AeYA)

are all terms used to describe young cancer patients (see Figure 2.1). However, they often describe different groups. The terms "childhood" or "pediatric" cancer are very broad and, according to the National Cancer Institute and Surveillance, Epidemiology, and End Results (SEER) program, includes any cancer diagnosis that occurs between birth and 19 years of age (Horner et al., 2008). In the UK most people between 13 and 24 will receive local AYA services ("Teenage Cancer Trust," 2019). Again, in the United States, the definition of AYA seems to be broader yet, including all patients who are between 15 and 39 years of age. To add on to this confusion, some studies started utilizing a smaller age range, describing participants between 13 – 21 years as AeYA (e.g. Johnson, Torres, Sykes, Gibson, & Baker, 2017). While most researchers justify their choice of age, these differences make it hard to compare the findings between studies.

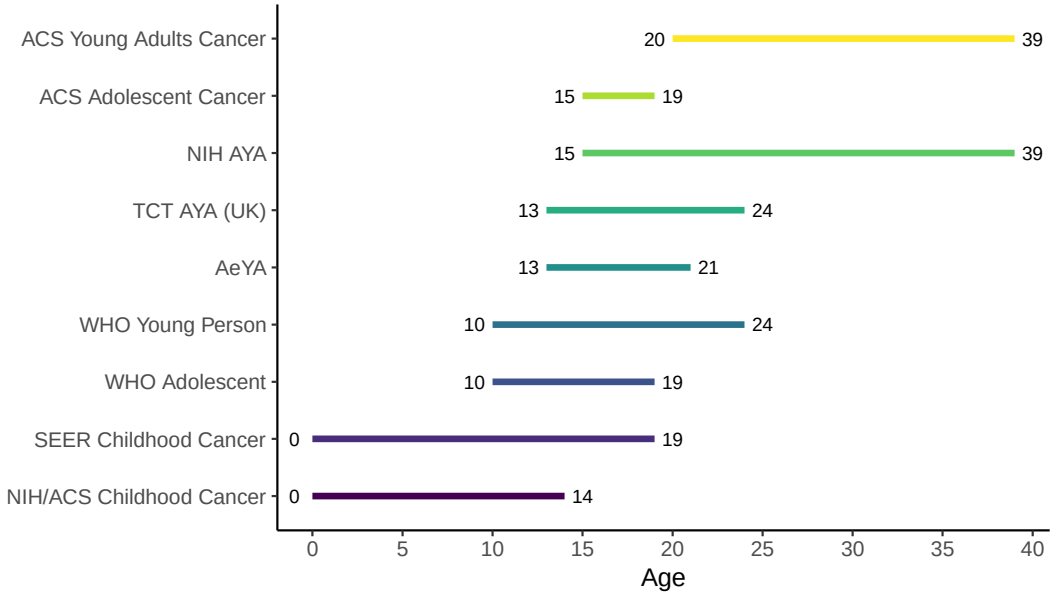


Figure 2.1: Overlap in definitions of childhood, adolescent, and young adult cancer.
NOTE: AYA = Adolescent and Young Adult; NIH = National Institute of Health; ACS = American Cancer Society; *SEER* = Surveillance, Epidemiology, and End Results; *WHO* = World Health Organization; *AeYA* = Adolescent and early Young Adult; *TCT* = Teenage Cancer Trust; *UK* = United Kingdom.

As the age range is not always clearly delineated, adolescents often end up being grouped with younger children or 'young' adults. And early young adults may be grouped with *older* young adults. In both cases, the important factors of psychological

adaptation might be overlooked. When studying psychological outcomes of cancer, we ought to consider distinct developmental periods and differences between children, adolescents, and young adults. While the youngest of the former might still depend on their parents, the oldest of the latter could already be living fully independent lives. Moreover, maturity levels and cognitive ability may contribute to understanding of the illness, and hence, impact one's psychological wellbeing.

Age differences between samples can make it hard to evaluate best-suited intervention strategies and limit generalizability of findings. While employing a broad age range is acceptable, researchers should strive to clearly outline their reasoning for inclusion, and whenever possible, conduct separate analyses in order to test for any age effects on the outcome of interest.

In my thesis I included all individuals between 15 and 39 years at the time of the study, who were diagnosed by age 10 or later. This allows us to study the impact of illness with onset during adolescence or young adulthood. I decided to include individuals who were diagnosed as early as 10 in order to account for any early-pubescent cases, as well as to facilitate the recruitment of participants.

2.1.2 Cancer as a single illness

Most of the existing literature and research treats childhood and AYA cancer diagnoses as a single illness. Although brain tumors are in some cases treated separately (e.g. Carpentieri et al., 2003) other tumors are seldom subcategorized. Cancer etiology will not only vary between different types but might also be significantly different between younger children, adolescents, and young adults (see Table 2.2; Bleyer et al., 2008). As such, different types of cancer may require different treatment modalities and, in turn, result in differential psychological outcomes, needs, and particularly illness late-effects (Marjerrison & Barr, 2018).

Table 2.2: The most common types of cancer in a specific age range.

<5 years	**5 – 14 years**	**15 – 19 years**	**20 – 39 years**
Acute Lymphoblastic Leukemia (58%)	CNS tumors (28%)	Lymphoma* (48%)	Breast Cancer (14%)
CNS tumors (36%)	Acute Lymphoblastic Leukemia (24%)	Germ cell, other gonadal (31%)	Lymphoma* (13%)
Neuroblastoma (27%)	Lymphoma* (18%)	CNS tumors (20%)	Melanoma (10%)
Wilms tumor (18%)	Astrocytoma (15%)	Soft tissue sarcoma (16%)	Thyroid cancer (9%)

NOTE: Percentages in the brackets account for the prevalence of a given cancer (among all cancers diagnosed) within a particular age group. Data obtained from Surveillance, Epidemiology, and End Results (SEER) (Accessed 22 March 2019 at https://seer.cancer.gov/). *CNS* = Central Nervous System; *Hodgkin's and non-Hodgkin's combined.

Cancer is a highly heterogeneous illness. Ideally, AYA patients with the same type of diagnosis would be grouped together in any analyses, however, if not feasible, researchers should aim to control and evaluate the extent to which different treatments or diagnoses contribute to psychosocial outcomes.

In my thesis I consider the differential impact of cancer diagnosis and elaborate on the differences between those with any type of cancer and brain tumors (Chapter 3). I then focus my qualitative work (Chapter 4) and longitudinal data exploration (Chapter 7) on an understudied population of patients with sarcoma, and finally, I consider all cancer cases in my online study, while acknowledging the differences in cancer types (Chapter 5).

2.2 Methodological challenges

2.2.1 Measuring psychological distress

When assessing psychological states and mental health in patients with AYA cancer we have to develop a better understanding of what a 'normal' trajectory is. Though new measures, e.g. for cancer-related worry (R. Wang et al., 2015), are being developed and used in research, most commonly, the measures in psychosocial oncology research for assessing psychological constructs are not adapted to AYA cancer experiences (Lazor et al., 2017). For example, a mood questionnaire might misinterpret one's fatigue as a depressive symptom instead of a side-effect of treatment.

We should therefore be cautious when using such measures so that we don't mistakenly label one's psychological functioning as pathological just because they might deviate from the norm.

Additionally, some studies reporting on post-traumatic stress disorder (PTSD) symptomatology make an *a priori* assumption that cancer was the most traumatic event in one's life, which is not always the case in young cancer survivors; for example, one study found that less than a third of respondents who do report trauma, report a cancer-related event as traumatic (Gerhardt et al., 2007). So, are these reported PTSD rates truly informative of how cancer survivors may cope? Further yet, some studies aiming to assess PTSD and related symptomatology reported participation rates as low as 45% and mentioned that majority of non-respondents did not participate in research because they wanted to avoid revisiting their illness (Kazak et al., 2004), precisely the construct they were trying to assess.

Another drawback, particularly in earlier studies which commonly grouped adolescents with younger children, is the reliance on parental reports of child's and adolescent's psychological functioning (e.g. Compas et al., 2014). Relying on parental proxy in youth with cancer may result in substantial bias; parental distress is normal and expected when having a sick child (Hoekstra-Weebers, Jaspers, Kamps, & Klip, 2001; Libov, Nevid, Pelcovitz, & Carmony, 2002; McCarthy et al., 2016), however, it may bias their perception to objectively report on their child's function. A study with leukemia survivors found large discrepancies between parental versus adolescents' self-reported psychological, which further calls into question the validity of parental reports in this population (Abate et al., 2018).

When designing future studies in AYA psycho-social oncology, researchers should carefully select measures for psychosocial outcomes, and whenever possible, try to adapt and validate them for a more accurate account of psychosocial outcomes in young cancer patients.

In my approach I relied on both, measures of general psychological distress (e.g. PHQ-9 for depression Kroenke, Spitzer, & Williams, 2001) and cancer and illness-specific questionnaires (e.g. cancer related worry Wang et al., 2015). The data used in the subsequent empirical chapters of my thesis is based on self-reported information by participants. Whenever appropriate, parent assent was sought.

2.2.2 Data collection and recruitment

Childhood and AYA cancers remain relatively rare, accounting for less than 5% of all cancer incidence (Horner et al., 2008). Therefore, recruiting participants is difficult, requires extensive efforts, and study samples are resultantly often small (Harlan et al., 2011). Despite employing the widest acceptable age range (e.g. 15 – 39 years), as well as grouping all cancer diagnoses together, one might still end up with a statistically underpowered sample. Moreover, low participation of AYAs has been described in clinical trials (L. Fern et al., 2008; Sender & Zabokrtsky, 2015) and may be particularly salient for studies with limited resources such as student-led projects.

Some of the barriers to recruitment have previously been stipulated; AYAs' lack of awareness, lack of availability and accessibility to clinical trials, and low acceptability (L. A. Fern et al., 2014). To address these issues, patient participation and public involvement (PPI) in all phases of research is becoming the norm (Pii, Schou, Piil, & Jarden, 2019), and the past two years have seen a proliferation of services and programs for youth with cancer that advocate for young patients' rights and set research priorities (Aldiss et al., 2018; Buchacz et al., 2018). PPI does not only allow for an easier route to recruitment, but also assures for shared decision-making between patients and health care professionals, thus tailoring the research efforts to the needs of the population.

In addition, online recruitment via social media platforms (Gorman et al., 2014), and even survey platforms like Amazon's Mechanical Turk (MTurk) have shown promise for reaching cancer populations (Arch & Carr, 2017). Patient support groups with a strong online presence often have a broad reach and the potential to gather information from previously under-represented individuals in psycho-oncological research (e.g. those living in remote areas). Researchers and health professionals should continue to work in tandem with patient organizations in order to better integrate research into routine clinical practice and streamline data collection.

In my work I overcame the difficulties with data collection and recruitment in several ways. First, I established two successful collaborations with researchers and experts in the UK (University College London) and Canada (McGill University and McGill University Health Centre) and relied on the already existing data on patients with sarcoma, which my collaborators were willing to share. Secondly, I have collected new data via Qualtrics (Qualtrics, 2020), a secure online software, where participants

were able to quickly respond to the questionnaires via an anonymous link. The online study was shared on patient support platforms and was open to participants in Slovenia, as well as anybody who could read and respond in English (see Chapter 5 for details). I consulted experts and patient organizations at various stages of my research and relied on PPI for guidance in my research.

2.2.3 Study design and data analysis

Studying psychosocial outcomes in youth with cancer is particularly difficult not only because cancer is rare, but also because one cannot simply conduct a randomized controlled trial (RCT), the 'gold standard' in research design (Barton, 2000), and randomly assign individuals to cancer versus cancer-free condition. While RCT could be conducted to study psycho-social interventions in AYAs, the outcomes are diverse and not yet well understood. As I briefly discuss in Chapter 1, there is no standard approach to psychosocial care in AYA oncology. Even though several psycho-therapeutic approaches show promising improvements in outcomes among young people, devising targeted and complex interventions requires better insights into the mechanisms of recovery, and warrants further study of which factors contribute to resilience and psychopathology.

Most of the published literature also relies on observational studies, which are often cross-sectional in nature and thus prevent us from making any causal inferences, or observations across the life course. An alternative route to studying outcomes in AYA cancer is by relying on prospectively collected information of large, nationally representative studies that collect an array of bio-psycho-social information from birth and follow individuals across lifespan. An example of a great collaborative effort is the establishment of the International Childhood Cancer Consortium (I4C) in 2005 (R. C. Brown et al., 2007). The consortium combines the wealth of data from several large longitudinal cohorts from across the world (e.g. Norwegian Mother and Child Cohort Study (MoBA; Magnus et al., 2006) or UK-based Avon Longitudinal Study of Parents and Children (ALSPAC; Golding, Pembrey, & Jones, 2001), containing rich information on disease and mental health variables at the individual and family level, repeated over time. Reliance on such approaches will not only help us understand the causes of cancer in young people but could also begin to uncover the risk and protective pathways in resilience and psychopathology in youth with cancer. However, the

downside of such approaches is the high cost of obtaining the relevant data and information for smaller-scale projects.

Working with small sample sizes in a relatively young field offers an opportunity to conduct qualitative research, which can greatly inform the development of new studies, as well as guide and complement our understanding and interpretation of the quantitatively derived findings. Qualitative research methods are as diverse and rigorous as quantitative approaches to analyses, but often serve in an initial exploration of the topic and allow for in-depth understanding of the subject as perceived by the participant (i.e. *What does recovery mean to a young person with cancer?*) (Pope & Mays, 1995). However, just as most observational quantitative studies, qualitative work also relies on retrospectively self-reported information, which is prone to recall bias, subjective perceptions, and psychological states (Coughlin, 1990; Queirós, Faria, & Almeida, 2017; Tuckett & Stewart, 2004; Williams, Boylan, & Nunan, 2020). As such, whenever possible, retrospective accounts should be replaced by prospective data collection.

Moreover, the nature and amount of the data available, as well as the study design will determine the type of statistical analysis that can be performed. Though longitudinal studies are increasing in number, we commonly observe analytical approaches that are variable-centered and focus on average effects, therefore failing to account for individual variability, which could be better described with person-centered statistical methods (e.g. Herle et al., 2020; Nagin & Odgers, 2010). Moreover, the direction of the effects and mental health outcomes post cancer is hard to assume without having adequate measurements of mental health prior to the illness diagnosis. Equally problematic is when advanced statistical methods such as structural equation modeling (SEM) are applied to statistically underpowered samples or led by poorly established theoretical models (Wolf, Harrington, Clark, & Miller, 2013). And as within other fields, studies are seldom pre-registered with pre-specified analysis, which does not exclude the possibility of over-testing and reporting only significant findings, which perpetuates the publication bias (Francis, 2012; Sanson-Fisher, Mackenzie, Butow, Rankin, & Paul, 2012).

The most robust and reliable evidence will emerge from the correctly applied and executed statistical methods that are best suited for the research question and data available, as well as transparent work that can be replicated in a different, yet similar population. One way to assure for that, is to carefully plan and pre-register studies in

line with the open science guidelines (Bartling & Friesike, 2014) , and rigorously test assumptions prior to conducting any statistical analysis.

To address biases in study design and data analysis, I use a mixed-method approach, in which the qualitative work serves to guide the subsequent study development, as well as to inform the interpretation of quantitatively derived models. To advance our understanding of the psychological constructs in youth with cancer I use network analyses (Epskamp & Fried, 2017), which allow high interpretability of the relationships between various symptoms of psychological functioning and cancer-specific worries (Borsboom & Cramer, 2013) (see Chapter 6). Moreover, I apply advanced, data-driven statistical methods, such as finite mixture modeling (i.e. group-based trajectory modelling; Nagin & Odgers, 2010) that allow for an examination of change over time on between- as well as within-person level (Herle et al., 2020) (see Chapter 7).

2.3 Summary: Addressing the challenges through a mixed method approach

Psycho-social oncology is a young, dynamic and rapidly evolving field. Despite the many limitations, the findings to-date lend us important insights, and though we are yet to understand why some young people who lived with cancer develop psychosocial difficulties, while others thrive, the first steps have been made. With novel applications of statistical methods, and an increasing number of initiatives that recognize the unique needs of AYA cancer populations we continue to make progress, which promises to reduce the inequalities in psychosocial outcomes in this vulnerable group of patients.

By adopting a mixed-method approach, my thesis combines the rigors of qualitative scrutiny and advanced quantitative analyses to addresses some of the above-described conceptual and methodological issues. The quantitative analyses in my thesis identify factors in psychological adaptation (**RQ1**) and describe the mechanisms of resilience or psychopathology over the course of the illness (**RQ2**). The qualitative work in my thesis aids in laying out hypothesis for future studies and informs the recommendations for intervention targets for young people with cancer (**RQ3**).

Chapter 3 - Psychiatric disorders in adolescent and young adult cancer survivors: A systematic review of prevalence and predictors*

3.1 Abstract

Objective: The aim of this systematic review was to establish prevalence rates and describe the predictors of psychiatric disorders in young cancer survivors, as well as highlight some areas for targeted interventions.

Method: We systematically reviewed four major online databases: Embase, PsychINFO, Scopus and Medline for quantitative studies evaluating mental health in adolescent cancer survivors. We used a narrative synthesis approach.

Results: Nineteen studies met our inclusion criteria (pooled N = 1,497). Across the sample up to 34% met criteria for PTSD, 13% for clinical depression, and 8% for anxiety. Maladaptive coping, illness relapse, higher number of late effects, brain tumor diagnosis, as well as poor family functioning and parental distress were associated with higher levels of psychological distress.

Conclusions: A significant subset of adolescent and young adult cancer survivors reports clinical levels of PTSD, anxiety and depressive symptoms. Individuals who present with more vulnerabilities and higher risk indices should be routinely assessed in order to reduce the psychological, social, and economic burden associated with poor mental health in this population. Early prevention strategies could target maladaptive coping mechanisms and promote healthy peer relationships, as well as family functioning.

* Chapter adapted from:

Kosir, U., Wiedemann M., Wild, J., Bowes, L. (2019). Psychiatric disorders in adolescent cancer survivors: A systematic review of prevalence and predictors. *Cancer Reports*. https://doi.org/10.1002/cnr2.1168

3.2 Introduction

The goal of this chapter was to systematically review the existing literature in order to: 1) establish the prevalence rates of psychiatric disorders in adolescent cancer survivors, and 2) identify and evaluate the predictors of psychiatric disorders in the specified population and compare it to healthy peers. A better understanding of adolescent mental health outcomes in cancer survivorship, as well as appraisal of the risk and protective factors, will allow for identification of intervention targets.

As discussed in the introductory chapter (Chapter 1), the survival rates in youth with cancer have dramatically increased over the past few decades (Horner et al., 2008), however, adolescents and young adults as a subgroup, have seen slower improvement (Barr et al., 2016) and face more psychosocial difficulties when confronting cancer and its aftermath (Barnett et al., 2016; McDonnell et al., 2017). It has become well-established that AYAs present with unique needs, which are often unmet (C. L. Daniel et al., 2015; Perez et al., 2020).

Adolescence is not only a time of rapid growth and psychosocial development (Arnett, 2000; Crone & Dahl, 2012; Richter, 2006) but also the time when most of the psychiatric disorders first arise (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Kessler et al., 2005). During adolescence, significant or chronic stressors can derail the normative development and trigger psychopathology or contribute to life-long psychiatric disorders (Carr, Martins, Stingel, Lemgruber, & Juruena, 2013; Compas, Orosan, & Grant, 1993). If a diagnosis and treatment for cancer coincide with major developmental milestones, they may act as a significant stressor, or even a form of trauma and, as such, impact one's psychological well-being (Patterson et al., 2015; Brad J. Zebrack, 2011). Cancer diagnosis and treatment are a stressful experience and feelings of distress, anxiety, and depression are a common response at the time of cancer diagnosis (Chaturvedi & Uchitomi, 2012; Sansom-Daly & Wakefield, 2013), however, a small subset of AYA cancer survivors reports a spectrum of adverse outcomes including psychopathology beyond active treatment phase (Cousino et al., 2017; Gianinazzi et al., 2013; Kazak et al., 2004). While the rates of clinical depression and anxiety in adult cancer survivors were found to be higher when compared with their spouses or other healthy adults (Mitchell, Ferguson, Gill, Paul, & Symonds, 2013) the findings in AYA survivors remain inconclusive.

The etiologies of psychiatric disorders are multifactorial, with biological, individual, and societal factors contributing varying degrees of risk. Even though heritability estimates suggest that between 30% and 40% of variance in depression and anxiety are attributable to genes (Sellick & Crooks, 1999; Sullivan, Neale, & Kendler, 2000), the rest can be attributed to environmental causes, including stressful life experiences. AYA cancer patients and survivors might endure significant stress as a result of painful procedures (Kuppenheimer & Brown, 2002), goal disruption (C. L. Daniel et al., 2015), or even bullying (Collins et al., 2019). While stress alone might not predict psychological ill health, it can impair emotion regulation, and cognitive functioning, which can result in maladaptive coping mechanisms, such as rumination or avoidance (Cisler et al., 2013; Watkins, 2008). These maladaptive coping styles have been associated with higher levels of psychological distress and more depressive symptomatology in adult cancer survivors (Manna et al., 2007; B. A. Morris & Shakespeare-Finch, 2011). The stress of illness can also impact family functioning (Pai et al., 2007; Rait et al., 1992). Risky family environment, marked by emotionally cold and distant relationships can interact with other biological factors and lead to the development of maladaptive behaviors and psychiatric disorders in the children and adolescents (Edwards & Clarke, 2004; Gutierrez-Colina, Lee, VanDellen, Mertens, & Marchak, 2017; Repetti, Taylor, & Seeman, 2002), so a young cancer patient with lesser family support may be at higher risk for poorer outcomes.

Due to methodological obstacles (see Chapter 2 for a detailed discussion), the exact prevalence rates of psychopathology in AYA cancer survivors are hard to establish. For the purposes of this review, we consider AYA survivors to be between 10 and 23 years of age, off cancer treatment, and free of disease. In the existing literature, studies employ various age cutoffs, in part due to the diverging views on how to define adolescent period, and some researchers group adolescents with younger children, while others group them with adults (Kosir, 2019; Lang, David, & Giese-Davis, 2015). Even though in my work I consider the broadest definition of AYAs to be between 10 and 39 years of age, the specified age range for this specific review was agreed upon between authors in order to capture an optimal sample for the analysis.

Studying psychiatric disorders in AYA survivors of cancer is important and will allow us to better understand to what extent psycho-social factors account for the variance in psychopathology. Identifying risk factors will offer insights for potential psycho-social interventions.

3.3 Method

3.3.1 Search

Our search strategy was developed in tandem with a librarian within our department. Via Ovid search platform, we conducted searches in Embase, PsychINFO, Scopus and Medline for articles examining the association between cancer survivorship and psychopathology from earliest point available through 20 January 2018. Our search terms were (child* OR adolesc*OR p*ediatric).ab. AND (child* OR adolesc* OR p*ediatric) ti. and (cancer or neoplasm or tumor or leuk*emia or lymphoma).ab. AND (cancer OR neoplasm OR leuk*emia OR lymphoma) ti. AND (depress* OR distress OR dysphoria OR dysthym* OR affective disorder OR mood disorder OR psychopathology OR psychiatric morbidity OR PTSD OR post-traumatic stress disorder OR adjustment OR anxiety OR suicide OR self-harm) ab. Additionally, reference lists were examined in order to retrieve any relevant papers not found in our initial search.

3.3.2 Inclusion and Exclusion Criteria

In order to be included in our systematic review the studies had to satisfy the following inclusion criteria presented in Table 3.1. In order to limit potential bias in sample representativeness, we excluded intervention studies that only recruited participants based on some pre-determined cut-off scores for a psychiatric disorder.

Table 3.1: Inclusion and exclusion criteria.

Inclusion criteria	**Exclusion criteria**

a) they had to be quantitative studies that looked at adolescent survivors of childhood cancer of any type, from any country, and of any type of research setting, b) the adolescent sample had to be between 10 – 23 years of age, with the mean age between 10 – 20 years, c) the mean age at first diagnosis had to be 5 years or older, d) participants were disease free at the time of the study and off-treatment for a mean of at least 12 months, e) the study employed a validated measure of psychopathology based on past or present DSM or ICD criteria for mental disorders, and f) the measures had to rely on self-reports by adolescent cancer survivors or clinician rating.	a) if the full-text was not available in English, b) case-report studies, c) if they relied solely on qualitative methods, d) if they employed only proxy measures of psychopathology (e.g. self-esteem, worry), e) if they only reported parental reports.

NOTE: *DSM* = Diagnostic and Statistical Manual for Mental Health Disorder, *ICD* = International Classification of Disorders.

3.3.3 Data Extraction

Data were independently extracted by myself and my colleague M. W. We extracted authors' names, year of publication, and titles. We also recorded sample characteristics with demographic information that was relevant for our analyses, information about cancer and treatment, measures of psychopathology, as well as other measures employed, overall findings, and conclusions of each paper. If two or more papers used the same sample, the study that reported more data relevant to the aims of this review was included. Authors of the studies that did not report relevant information were contacted to provide the missing data. If no answer was received upon two attempts of contact, the study was excluded.

3.3.4 Quality Appraisal and Data Analysis

With colleague M. W. we independently assessed the quality of the studies in the final sample using the shortened version of Downs and Black Quality Checklist (Downs & Black, 1998). Any inconsistencies in the ratings were resolved in a consensus meeting. The quality checklist has been utilized in previously published reviews (Barnett et al., 2016; McDonnell et al., 2017). The modified version employs 9 criteria, rated and scored as either "Yes" (1) or "No/Unable to determine" (0). Studies

that received a rating of 8 or above were considered to be of high quality. Appendix A contains the adapted version of the checklist.

3.3.5 Analysis

The aims of the current review were addressed by carrying out a narrative synthesis approach (Popay et al., 2006), and general recommendations from PRISMA 2009 statement for reporting of results were followed (Moher et al., 2009). Prior to beginning the search, the review was pre-registered (PROSPERO: CRD42018088884). Prevalence rates were extracted from individual studies wherever reported. In order to establish predictors, we extracted and evaluated variables that were significantly associated with psychiatric disorders within individual studies. Effect sizes (Cohen's *d*) were calculated and reported where possible.

3.4 Results

Our literature search yielded 2,245 unique articles of which we reviewed titles and abstracts for relevance against the inclusion and exclusion criteria. For the remaining 168 articles, the full text was reviewed and 149 excluded (see Figure 3.1 for details). The 21 articles that met our criteria were evaluated and data extracted from them. We contacted two authors, one of whom reported not having the requested data and another who had moved and no longer had access to the original study results. The final sample included in this review consisted of 19 articles. Meta-analysis was not performed due to high heterogeneity of analytic and outcome measurement approaches, cancer subtypes, and lack of control groups in 13 out of 19 studies.

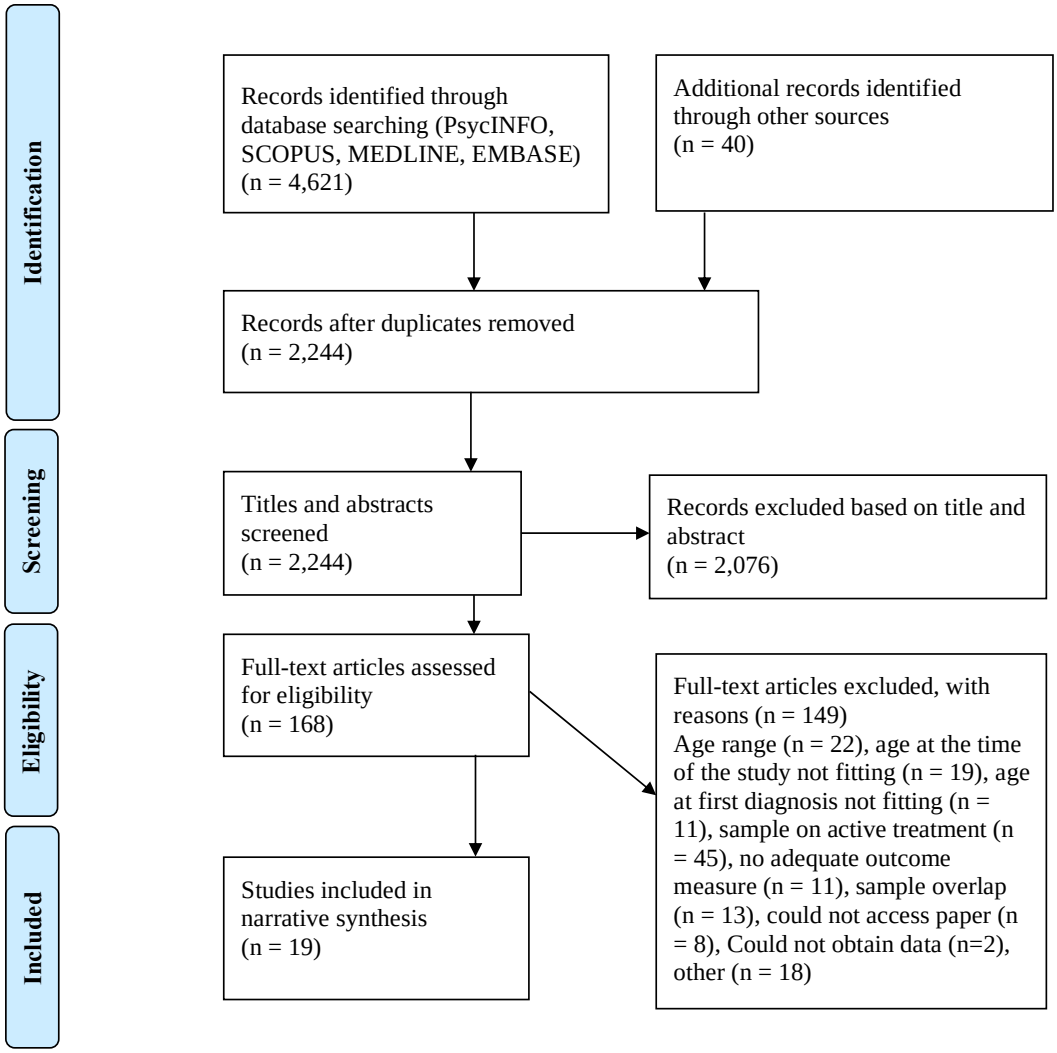


Figure 3.1: PRISMA flowchart of literature search.

Characteristics of the participants, type of cancer, and the main findings of the studies included in this review are summarized in Table 3.2. The mean sample age ranged from 13.7 to 20.2 years (*M* = 16.3 years), and the mean sample age at the time of cancer diagnosis ranged from 5 to 13.7 years (*M* = 8.4 years, range = 3 months to 18 years).

All studies that met our inclusion criteria were cross-sectional in nature, and most recruited their participants through tumor registries and at follow-up clinics. The sample sizes ranged from 21 to 407 young cancer survivors. Nine studies reported on post-traumatic stress disorder (PTSD), four of which used self-reported measures and three clinical interviews by a trained professional. Two studies used multiple measures to assess PTSD. Eight studies assessed depression, and eight measured anxiety among

adolescent cancer survivors, six of those measured both outcomes simultaneously. All studies employed self-report measures, and one included a clinician administered diagnostic interview. Details about the measures can be found in Appendix B.

Seven of the studies excluded brain tumor survivors, and two assessed only brain tumors survivors. The majority of the research had been conducted in the United States, while Canada, United Kingdom, Switzerland, Greece, Australia, New Zealand, and Japan each contribute one study. Based on our quality checklist, eight (42%) studies met criteria for high quality, and only one (5%) study missed more than three quality indicators (Fritz & Williams, 1988). Majority of the studies were penalized due to lack of random sampling and representativeness of the population studied (see Table 3.2 for summary, complete table is available in Appendix B).

3.4.1 Prevalence of psychiatric disorders

Rates of PTSD among adolescent cancer survivors ranged from none (R. T. Brown, Madan-Swain, & Lambert, 2003) to 35% (Pelcovitz et al., 1998). Additionally, Brown et al., (2003) reported that 36% (n = 18) of survivors self-endorsed subthreshold PTSD symptomatology, a significantly higher proportion than healthy controls (d = 0.6). Studies that utilized clinical interviews for the assessment of PTSD also found large variability in PTSD rates. Robinson, Gerhardt, Vannatta, & Noll, (2007) reported 3% of survivors meeting current or past PTSD criteria, with survivors experiencing lower levels of PTSD symptomatology (d = 0.36) than a control group. Alderfer, Navsaria, & Kazak, (2009) reported 8%, and Erickson, Gerstle, & Montague, (2008) reported 13.8% of survivors meeting full PTSD criteria, respectively. Kazak et al., (2004) who excluded any survivors who experienced relapse found that 4.7% of survivors met the criteria for current PTSD diagnosis, and 8% had PTSD sometime since the initial diagnosis. Based on the survivors' responses on Structured Clinical Interview for DSM-IV (SCID), arousal symptoms (cluster D) were predominant with 41.3% of adolescent survivors endorsing enough arousal symptoms to fulfill criteria for PTSD cluster D (Lang et al., 2015).

In a sample evaluated by Pelcovitz et al., (1998) 17.4% of adolescent survivors met current, and 34.8% met lifetime criteria for PTSD. The PTSD rates were higher in survivors than in abused children and healthy controls, though the study was statistically underpowered to detect significance (Pelcovitz et al., 1998). Overall, a

substantial subset of adolescent cancer survivors considers their cancer experience as traumatic and appear to be at risk for developing PTSD.

Depression and anxiety rates were modest in our sample, up to 8.5% (Bitsko, Stern, Dillon, Russell, & Laver, 2008) and 8% (Liptak, Manley, & Recklitis, 2012), respectively, when measured using self-reported questionnaires. In addition to 8.5% that scored in clinical levels of depression, Bitsko et al., (2008) reported that an additional 8.5% experienced mild depressive symptomatology, and Fritz & Williams, (1988) found an additional 12% of the sample that reached subthreshold levels of clinical depression.

Case-control studies reported higher levels of depression and anxiety among adolescent cancer survivors than in control groups. In an online survey study, 6% and 7% of adolescent cancer survivors scored in clinical levels for depression and anxiety, respectively, with cancer survivors reporting significantly more depression compared with a population-based control (d = 1.06) (Yallop et al., 2013). Gianinazzi et al., (2013) evaluated psychological functioning of adolescent survivors and compared it to that of siblings, population-based control, and functioning of psychotherapy patients prior to their engagement in therapy. Thirteen percent of survivors reported clinically significant distress based on the Global Severity Index (GSI). Adolescent survivors reported significantly more anxiety (d = 0.25) and more depression (d = 0.15) than control group. Survivors with higher GSI scores reported more anxiety than psychotherapy patients (d = 0.46) (Gianinazzi et al., 2013).

Two studies evaluated psychological outcomes of brain tumor survivors alone (Carpentieri et al., 2003; Liptak et al., 2012). Both studies found large discrepancies between self-ratings and clinician or parent ratings. Carpentieri et al., (2003) reported that 6.5% and 3.2% of adolescents self-reported at-risk levels of depression and anxiety, respectively, based on Behavioral Assessment System for Children (BASC-2), while parent and even teacher reports indicated higher levels of survivors' symptomatology. According to parental reports, 16% of brain tumor survivors experienced depressive symptomatology, and 12.5% experienced anxiety. Teachers reported higher anxiety among survivors than parents, with 19.4% of survivors having at-risk levels of anxiety and 9.7% experiencing at-risk levels of depressive symptomatology (Carpentieri et al., 2003).

Liptak, Manley, & Recklitis, (2012) similarly found large discrepancy between self-reported symptomatology and clinician ratings. Among adolescent brain survivors,

6% self-endorsed depression and 8% anxiety; however, 24% met criteria for depression and anxiety when evaluated by a trained clinician (Liptak et al., 2012).

Table 3.2: Studies included in the review (abbreviated).

Reference	**Country**	**Quality rating**	**N**	**Age at the time of the study** M(SD) [range]	**Main findings**
Alderfer et al. (2009)	USA	8	144	14.6 (2.4) [11 - 19 years]	8.3% of survivors met PTSD criteria. Survivors with PTSD were 5x more likely to emerge from families with poor functioning.
Bauld et al. (1998)	Australia	6	32	14.9 (1.6) [12 - 17 years]	Survivors reported higher state anxiety than healthy controls. Survivors employed more maladaptive coping mechanisms
Bitsko et al. (2008)	USA	7	50	20.2 [10 - 21 years]	Happiness is a stronger predictor of depression than intensity of treatment.
Brown et al. (2003)	USA	6	52	17 (3.4) [13 - 23 years]	36% endorsed sub-clinical levels; 25% of survivors' mothers met PTSD criteria. Late effects contributed to PTSD.
Carpentieri et al. (2003)	USA	8	31	14.5 [12 - 18 years]	6.5% and 3.2% of adolescent brain survivors reported depression and anxiety, respectively.
Cousino et al. (2017)	USA	8	65	14.1 (2.1) [10 - 17 years]	33.8% of survivors endorsed PTSD. Late effects contributed to PTSD.
Erickson et al. (2008)	USA	6	29	15.3 (1.82) [12 - 18 years]	13.8% of all survivors qualified for PTSD. Non-repressors reported poorer QOL, higher anxiety and depression.
Fritz & Williams (1988)	USA	4	41	17.3 (3.1) [13 - 21 years]	7% of survivors reported depression. 50% of the sample was preoccupied with their body, and 26% were hypochondrical.
Gianinazzi et al. (2013)	Switzerland	9	407	17.9 (1.5) [16 - 19 years]	13% of survivors reported clinical distress. Risk was female gender, late-effects and low perceived parental support.
Kazak et al. (2004)	USA	6	150	14.7 (2.4) [11 - 19 years]	8% of survivors met PTSD criteria since diagnosis, and 4.7% currently.
Liptak et al. (2012)	USA	7	84	15.7 (1.9) [12 - 18 years]	17% of adolescent survivors reported depression and anxiety.

Michel et al. (2009)	UK	8	41	13.7 (1.1) [12 - 16 years]	PTSD not associated with benefit finding. Diagnosis of leukemia, optimism, and illness impact associated with benefit finding.
Ozono et al. (2010)	Japan	9	88	16.2 (2.2) [12- 20 years]	Those from conflictive families report more PTSD, depression, and anxiety. Relapse associated with more PTSS.
Pelcovitz et al. (1998)	USA	7	23	17.6 (3.1) [15 - 19 years]	34.8% of survivors met lifetime, and 17.4% met current PTSD criteria. Chaotic families and maternal PTSD predicted survivors' PTSD.
Pendley et al. (1997)	USA	6	21	11 - 21 years	Those off treatment reported lower self-worth, more social anxiety and poorer body image.
Robinson et al. (2007)	USA	7	56	18.6 (0.8) years	3% of survivors met current or past PTSD criteria Late effects were associated with more PTSS. Only 31% of survivors described cancer as a traumatic event.
Servitzoglou et al. (2008)	Greece	8	45	19.8 [15 - 29 years]	Younger (at diagnosis) survivors reported higher anxiety than controls.
Turner-Sack et al. (2012)	Canada	6	31	15.7 (2.25) years	Younger (at diagnosis) and less avoidance predicted lower distress.
Yallop et al. (2013)	New Zealand	8	107	15.3 [12 - 18 years]	6% and 7% of survivors reported depression and anxiety, respectively. CNS tumors, older age, older at the time of diagnosis and lower SES associated with more psychosocial difficulties.

NOTE: *N* = Survivor sample size. Abbreviations: *ALL* = Acute Lymphoblastic Leukemia, *AML* = Acute Myeloid Leukemia, *CNS* = Central Nervous System, *PTG* = Posttraumatic Growth, *AYA* = Adolescent and Young Adult, *SES* = Socio-Economic Status.

3.4.2 Predictors of psychiatric disorders in adolescent cancer survivors

Studies in our review assessed a wide range of variables and their relationship to psychopathology. We identified several predictors of psychiatric disorders; some of these predictors are nonmodifiable (i.e. gender), while others are modifiable (i.e. coping styles).

3.4.2.1 Demographics

The majority of the studies included some demographic variables in their analyses. Two studies did not find evidence that gender, race, and parental education were associated with psychopathology in survivors (Cousino et al., 2017; Robinson et al., 2007), however, Gianinazzi et al., (2013) reported female gender to be a significant risk factor for greater psychological distress among adolescent survivors. Yallop et al., (2013) reported that older age at the time of the study, older age at diagnosis, and lower socioeconomic status were positively correlated with psychosocial difficulties; however, none of the demographic variables were significantly related to clinical levels of anxiety or depression.

3.4.2.2 Coping styles

Four studies assessed coping mechanisms and adaptive styles among adolescent cancer survivors (Bauld, Anderson, & Arnold, 1998; S. J. Erickson et al., 2008; Servitzoglou, Papadatou, Tsiantis, & Vasilatou-Kosmidis, 2008; Turner-Sack, Menna, & Setchell, 2012). Survivors employed maladaptive coping strategies more frequently than healthy peers. When faced with challenges, they relied more on wishful thinking and avoidance and distancing strategies (Bauld et al., 1998; Servitzoglou et al., 2008). In another sample, survivors who were rated as non-repressors endorsed more PTSD symptoms than repressors and reported lower quality of life (S. J. Erickson et al., 2008).

Contrary to the authors' prediction, (Turner-Sack et al., 2012) found that less avoidant coping (denial, behavioral disengagement, and substance use) was associated with lower levels of distress in survivors, a finding that the authors attributed to low statistical power and a small sample size.

3.4.2.3 Cognitive vulnerabilities

In a sample of Greek adolescents, the majority of survivors perceived their future with optimism; however, survivors were less likely to report long-term plans than healthy controls and reported significantly more worries about health-related issues (Servitzoglou et al., 2008). Fritz & Williams, (1988) who found low levels of depressive symptomatology in majority of the sample, also found that over 50% of adolescents expressed concern about their bodies, and 26% of them were affected with hypochondria. In yet another sample, greater levels of optimism among survivors were associated with better psychological adaptation and positive outlook (Michel, Taylor,

Absolom, & Eiser, 2009); however, none of these studies explored how cognitive constructs related to varying degrees of psychopathology in young survivors.

Bitsko et al., (2008) found that happiness and one's thinking about the past were stronger predictors of depression and quality of life in survivors than gender or treatment intensity, suggesting those areas could be targeted in interventions. Additionally, lower perceived parental support and lower levels of social desirability were associated with more anxiety and PTSD symptoms, respectively (Gianinazzi et al., 2013; Pelcovitz et al., 1998).

3.4.2.4 Late effects and treatment severity

Many survivors experience illness late effects that result from cancer treatment. Higher treatment severity is often associated with higher number of late effects, which can be physical, somatic, or psychological. Cousino et al., (2017) assessed the relationships between brain tumor survivors' late effects, illness-specific family burden, and psychosocial outcomes. Parental reports indicated that 11% of survivors exhibited clinically significant internalizing problems and that higher number of late effects predicted illness-specific family burden, which in turn predicted child's internalizing symptoms (Cousino et al., 2017).We found that higher number and severity of cancer late effects, as well as occurrence of illness relapse was also correlated with greater overall psychological distress, and more PTSD (Cousino et al., 2017; Gianinazzi et al., 2013; Ozono et al., 2010; Pelcovitz et al., 1998), as well as lower self-esteem and greater difficulties in social relationships among adolescent cancer survivors (Servitzoglou et al., 2008).

Though some studies in our review observed decreasing levels of psychological distress as more time elapsed since initial diagnosis (Servitzoglou et al., 2008; Turner-Sack et al., 2012), Pendley, Dahlquist, & Dreyer, (1997) found that survivors who were off-treatment for at least a year reported significantly lower self-worth (d = 1.1), more social anxiety (d = 1.11), and more negative body image (d = 0.88) compared with survivors within the first year since treatment completion. The authors suggested that this may be due to the slowing down of positive changes and late effects becoming more apparent after the first year of remission (Pendley et al., 1997).

3.4.2.5 Tumor type

All but two studies recruited survivors of various types and stages of childhood cancer, which makes differences between the impact of different types of diagnoses hard to detect. Brain tumor cases face more psychosocial difficulties particularly in the area of peer relationships and self-concept (Liptak et al., 2012). A discrepancy was observed between the self-ratings and clinician ratings; clinicians reported higher levels of social difficulties than brain tumor survivors, who either did not report any problems or did not perceive the nature of their social relationship as troublesome or developmentally inappropriate (Liptak et al., 2012). Moreover, when evaluated by teachers and parents, brain tumor survivors exhibited more problems with attention and leadership in school settings (Carpentieri et al., 2003).

In a sample that included all types of diagnoses, Michel et al., (2009) found that a diagnosis of leukemia predicted more benefit finding than a diagnosis of other tumors. Benefit finding implies a more positive disposition and has been associated with higher levels of optimism and self-esteem and lower levels of trait anxiety (Phipps, Long, & Ogden, 2007). Ozono et al., (2010) in a sample that exuded brain tumor cases, reported that the type of cancer diagnosis did not appear to be related to the levels of anxiety or depression among the adolescent survivors.

3.4.2.6 Peers

The relationship between psychological adaptation and cancer survivors' peer involvement and activities was directly evaluated by a single study in our review. Pendley et al., (1997) recruited 21 adolescent survivors, and healthy controls matched in age, gender, and ethnicity in order to evaluate social anxiety, body image, peer activities, loneliness, self- perceptions, and school attendance. The authors report that adolescent survivors participated in significantly fewer peer activities compared with healthy controls (d = 0.94); however, survivors did not report significant differences in feelings of loneliness or social anxiety (Pendley et al., 1997).

3.4.2.7 Family environment

Family environment and parental mental health are often implicated in an adolescent's adaptation to chronic illness and the life after it. Alderfer et al., (2009) assessed family functioning via Family Assessment Device (FAD) in areas of problem solving, communication, roles, affective responsiveness, affective involvement,

behavioral control, and general functioning. Cancer survivors who reported PTSD had a fivefold increased chance to come from poorly functioning families compared with healthy controls. Seventy-five percent of survivors meeting PTSD criteria came from families with poor family functioning, particularly in the areas of problem solving, affective responsiveness, and affective involvement (Alderfer et al., 2009).

Ozono et al., (2010) evaluated family functioning with the Family Relationship Index (FRI), which assesses the interpersonal relationships and organizational structure within a family unit. Additionally, the authors measured parental mental health and applied a clustering method to identify three different types of family environments that formed as a result of facing childhood cancer: supportive, intermediate, and conflictive type. These types varied on three main dimensions: family cohesiveness, expressiveness, and conflict. Thirteen percent of families fell within the conflictive type, marked by highest level of family conflict and lowest levels of family cohesiveness and expressiveness. Survivors from families that fell within the conflictive type reported the highest levels of clinically significant PTSD symptomatology, as well as depression and anxiety. Moreover, parents of cancer survivors in the conflictive type also reported highest rates of psychopathology, while adolescent survivors who came from the supportive families had the lowest levels of depression and anxiety symptoms (Ozono et al., 2010).

In addition to poorly functioning family environments, there is evidence for a strong positive association between mother's PTSD and child's PTSD symptoms (Bitsko et al., 2008; Kazak et al., 2004; Pelcovitz et al., 1998). The adolescent survivors who met the PTSD criteria reported their families to be more chaotic, and results show that 83% of them had mothers who met full PTSD criteria (Pelcovitz et al., 1998). Another study reported close to 30% of mothers and 12% of fathers of adolescent cancer survivors meeting full PTSD criteria,19 while Brown et al., (2003) reported 25% of mothers of survivors meeting PTSD compared with 7% of mothers in the control group. Kazak et al., (2004) found that 99% of the families that participated in the study had at least one member re-experiencing cancer-related events, suggesting that childhood cancer profoundly impacts all family members.

Only one study compared survivors' outcomes to those of siblings' and found that survivors reported clinically significant psychological distress at a higher frequency (Gianinazzi et al., 2013).

3.5 Discussion

Due to the continuing development of medical interventions, many childhood and adolescent cancer diagnoses are no longer synonymous with early death. Nevertheless, the illness and its treatment can be stressful and traumatic for everyone involved and can compromise psychosocial development and adaptation of a young survivor. It is important that researchers, medical workers, and clinicians understand the psychological profiles of adolescent cancer survivors and areas in which they might require most help and support. This systematic review was guided by two main research questions: (1) What is the prevalence of psychiatric disorders in adolescent cancer survivors? and (2) What are the predictors of psychiatric disorders in this population? We aimed to develop a better understanding of the nature of psychiatric disorders in adolescent survivors, and how to best address them.

Nineteen studies summarized in our review assessed PTSD, depression, and anxiety among adolescent cancer survivors. The rates of psychopathology showed large discrepancies between different samples, some reporting rates higher than population-established norms (Bitsko et al., 2008; Cousino et al., 2017; S. J. Erickson et al., 2008; Gianinazzi et al., 2013; Liptak et al., 2012), some similar to population levels (Servitzoglou et al., 2008), and others lower (R. T. Brown et al., 2003; Pelcovitz et al., 1998; Robinson et al., 2007). Nevertheless, our results suggest that a significant proportion of adolescent survivors are at risk for developing clinically significant symptoms of PTSD, anxiety, and depression.

Several studies in our review reported subthreshold levels of psychopathology (R. T. Brown et al., 2003; Kazak et al., 2004; Pelcovitz et al., 1998; Yallop et al., 2013). These individuals who do not meet full criteria for any given disorder should be equally attended to in order to prevent worsening of symptoms. There is growing evidence showing that subthreshold levels of psychopathology are associated with an array of adverse outcomes: suicidal ideation, higher comorbidity with other psychiatric disorders, and overall higher social and functional impairment (Cukor, Wyka, Jayasinghe, & Difede, 2010; Fergusson & Woodward, 2002; Marshall et al., 2001; Preisig, Kr, & Clinical, 2001; Zlotnick, Franklin, & Zimmerman, 2002). Young cancer patients should be regularly assessed from intake through treatment completion for their symptoms, even when they do not initially meet any psychiatric disorder criteria. Early

intervention strategies can contribute to better long-term adaptation and coping (Das et al., 2016; Durlak & Wells, 1998).

In addition to psychiatric disorders, two studies in our review assessed somatization as an independent construct (Carpentieri et al., 2003; Gianinazzi et al., 2013). The small number of studies that report somatization reflects cancer survivorship literature at large. Somatic symptoms are difficult to differentiate from the illness side effects, late effects, or mood symptomatology; however, findings in adult cancer patients show that somatization may be entirely independent from depression and anxiety (Hyphantis et al., 2009). Some patients exhibit significant somatic symptoms even upon full remission of cancer and report higher PTSD and distress levels (S. J. Erickson & Steiner, 2000). Somatization can affect pain perception, treatment outcomes, and quality of life (Chaturvedi et al., 2006). Research suggests that fatigue, one of the most common complaints in survivors (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007), might have a more significant negative impact on one's well-being than nausea, depression, or pain (Carlson et al., 2004; Curt, 2000). Managing somatic symptoms in adolescent survivors may help in reducing psychological distress and negative or excessive help-seeking behaviors.

Our data synthesis identified several predictors for psychiatric disorders in adolescent cancer survivors. Survivors at a higher risk for PTSD employed more repressive coping mechanisms (S. J. Erickson et al., 2008), reported lower levels of social desirability (R. T. Brown et al., 2003), came from families with poorer emotional functioning, lower support, and more conflict (Alderfer et al., 2009; Ozono et al., 2010), experienced a relapse (Ozono et al., 2010), or reported more illness late effects (Cousino et al., 2017; Gianinazzi et al., 2013; Pelcovitz et al., 1998). Consistent with the broader literature on the relationship between parental and child mental health (M. Smith, 2004), adolescent cancer survivors reporting PTSD were also more likely to have mothers with clinically elevated PTSD scores (Bitsko et al., 2008; Kazak et al., 2004). Higher levels of depressive and anxiety symptoms were also associated with poorer overall family functioning (Ozono et al., 2010), female gender (Gianinazzi et al., 2013), higher number of late effects (Cousino et al., 2017; Gianinazzi et al., 2013), lower perceived parental support (Gianinazzi et al., 2013), less time passed since diagnosis (Carpentieri et al., 2003), older age at assessment and at diagnosis, and lower socioeconomic status (Yallop et al., 2013).

Even though a meta-analytic review of the existing evidence did not find strong associations between overall adjustment and coping mechanisms in childhood cancer (Aldridge & Roesch, 2007), we found that wishful thinking and avoidance were associated with greater anxiety in adolescents (Bauld et al., 1998), while higher levels of happiness and less thinking about one's past predicted lower depression (Bitsko et al., 2008). Social anxiety was associated with poorer body image and larger illness impact and was significantly higher in adolescent survivors who had been off- treatment for at least a year (Pendley et al., 1997).

3.5.1 Strengths and Limitations

Our review is a thorough synthesis of prevalence and risk factors among the published papers that considered psychopathology in adolescent cancer survivors. However, there are several limitations and methodological issues, which also pertain to the field of psycho-oncology at large and have been discussed in the previous chapter (Chapter 2). The number of studies considering psychological adaptation to cancer in adolescence is scarce. The paucity of research, small sample sizes, grouping of all cancer types, and grouping of adolescents with either children or young adults may partially be explained by overall low number of cancer cases in this particular age range (Barr et al., 2016). We have tried to address this issue by selecting a wider age range (10-23 years), accounting for early adolescence, while reducing the number of studies that also include adults. Selecting the most appropriate age range proved difficult and the variability is still very large, with several studies including some childhood diagnoses.

Additionally, we were interested in the survivorship period after the first 12 months of treatment completion. This is the time when the rapid positive changes such as hair growth, and increases in energy slow down, and when patients are confronted with novel challenges of being in remission (Baird et al., 2019; Barnett et al., 2016; Bauld et al., 1998; L. A. Fern et al., 2013). The range of time since treatment completion also varied greatly in our sample, thus limiting our ability to suggest at what point in the survivorship adolescent survivors might be experiencing most clinically significant psychological symptoms. Future studies should carefully consider the age of participants, as well as the age at diagnosis, and conduct separate analyses for adolescent cancer survivors whenever possible.

Secondly, we mostly relied on self-report measures of psychiatric disorders in adolescent cancer survivors. Although some evidence suggests that these are more reliable than parental ratings in this specific population of adolescents (Abate et al., 2018), future work should aim to confirm this finding and further explore the discrepancies, particularly in patients with diagnosis of brain tumors.

Moreover, some studies report participation rates as low as 30% (Bitsko et al., 2008). Some authors noted that participants declined due to unwillingness to talk about their illness or reliving past events (Alderfer et al., 2009; Kazak et al., 2004), which might be, in cases like PTSD, the exact construct that the studies are trying to measure. Additionally, most studies lacked a control group, and an array of questionnaires not adapted to populations with cancer has been utilized.

3.5.2 Clinical implications

Adolescents cancer survivors are a unique and understudied group in oncological research, with lowest participation rates in clinical trials, and slowest progress in improvement of care (Barr et al., 2016; L. A. Fern et al., 2014; Sender & Zabokrtsky, 2015). Working with adolescents in medical settings requires establishing adolescent-friendly ways of discussing their concerns, expressing their needs following their illness, and reflecting back on it. Young cancer survivors should be monitored for signs of psychological distress and offered follow-up consultations even in case of subclinical presentations of psychiatric disorders. In particular, those adolescents that present at the clinic with more risk factors such as poorer family functioning or lower levels of optimism should be offered further psychological evaluations and interventions.

3.6 Contribution to this thesis

This systematic review addresses 2 of the research questions underpinning my doctoral thesis: **RQ1)** *What are the factors associated with resilience and psychopathology in youth with cancer?* And **RQ3)** *What should we target in early prevention to facilitate the holistic recovery of AYAs?* (See section 1.10.1).

In particular, this chapter highlights several risk factors for psychopathology in the survivorship phase, and points at the need to consider sub-threshold and pre-clinical levels of symptomatology in young people. The findings further stress the importance

of early interventions and suggest that due to the myriad factors spanning various domains, a one-size-fits-all approach is not suitable for this population.

The next chapter builds on the findings of this review and presents an in-depth exploration of young people's recovery from cancer, considering risk and protective factors at different phases of cancer trajectory, and extends the age range up to 39 years in order to account for young individuals at all developmental phases.

Chapter 4 - Psychological adaptation and recovery in youth with sarcoma: A qualitative study*

4.1 Abstract

Objective: This qualitative study explored factors that play a role in psychological adaptation and recovery of young people with sarcoma across the UK.

Method: Using purposive sampling, participants were recruited for semi-structured interviews over the telephone or face-to-face in order to answer questions about how cancer impacted various domains of their life. Data were analyzed using a framework approach.

Results: Thirty participants, aged 15 – 39 years with a primary sarcoma diagnosis provided in-depth accounts of their experience. Emerging themes from the interviews were grouped into two overarching themes that relate to one's adaptation to illness: individual and environmental level. The qualitative nature of our study sheds light on meaningful connections between various factors and their role in one's adaptation to sarcoma. We devised a visual matrix to illustrate how risk and protective factors in adaptation vary between individuals.

Conclusions: This study demonstrates that young people with sarcoma report an array of both positive and negative factors related to their illness experience. The route to holistic recovery is a multifactorial process and a one-size-fits-all approach to psychosocial care proves inadequate. We propose that moving beyond the latent constructs of resilience and psychopathology towards a dynamic model of psychological adaptation and recovery in this population can result in optimization of care.

* Chapter adapted from:

Košir, U., Bowes, L., Taylor, R., Gerrand, C., Windsor, R., Onasanya, M., Martins, A. (2020). Psychological adaptation and recovery in youth with sarcoma: A qualitative study with practical implications for clinical care and research. *BMJ Open*. http://dx.doi.org/10.1136/bmjopen-2020-038799

4.2 Introduction

The study presented in this chapter had 3 aims: 1) to describe factors that impact psychological adaptation and recovery in AYA with sarcoma and demonstrate variability of responses between individuals, 2) to contribute evidence towards a dynamic understanding of psychological adaptation and recovery in AYA with sarcoma, and 3) to provide recommendations for clinical care and research.

To best address these aims, we relied on qualitative methods that allow for an in-depth exploration of patient-reported outcomes, their personal circumstances, and response styles (Pope & Mays, 1995).

Sarcomas are a rare form of cancer but nevertheless represent an important health issue and often afflict young people (Ferrari, Gasparini, Gill, & Gorlick, 2018; Stiller et al., 2006). Over the past two decades the improvements in treatments for sarcomas resulted in higher survival rates, however, these remain low compared to other tumors, hovering around 50 – 60% (Allison et al., 2012; Jacobs et al., 2015). Patients with sarcoma are often subjected to an array of treatments; radiation and surgical procedures are the first line of treatment for soft tissue sarcoma (STS; Ramu et al., 2017), while osteosarcomas respond best to multimodal approach including multi-agent chemotherapy (Anninga et al., 2011). Due to these treatments many individuals do not reach full recovery; up to 50% report life-long disability and significantly compromised health-related quality of life (Gough, Smith, Ross, Riley, & Judson, 2011). Qualitative work with adults shows that sarcoma diagnosis and treatment can be burdensome and psychologically taxing (Ostacoli et al., 2014), however, a recent review of the literature revealed that the impact of sarcoma diagnosis and treatment on psychosocial wellbeing is not yet well understood (Storey et al., 2019).

Psychological adaptation and recovery in cancer are complex phenomena with biological, individual, and societal factors contributing varying degrees of risk for poor outcomes. In the recent years, national, as well as international initiatives have recognized the importance of psychosocial impact of cancer diagnosis in youth and are calling for research initiatives that investigate psychopathology and promote psychological wellbeing in young patients (Aldiss et al., 2018; Buchacz et al., 2018). However, the field lacks a common definition of resilience (Molina et al., 2014) and still relies on latent models of assessing mental health (i.e. having depression leads to fatigue and/or loss of interest) (Borsboom & Cramer, 2013).

We propose a different way of understanding psychological adaptation and recovery in cancer and conceptualize the two as interlinked and dynamic processes that encompass individuals' mental, physical, and social function along the illness trajectory and into survivorship. Resilience and mental health are malleable constructs contained within, brought about by complex interactions between different factors. While successful adaptation and recovery (i.e. maximized resilience factors and minimized risk factors for psychopathology beyond physical functioning) is a shared goal in increasingly patient-centered healthcare systems, we need to account for the fact that the configuration of these constructs will vary between people and may result from different pathways.

As the majority of patients with sarcoma experience life-long disability (J. A. Parsons & Davis, 2004) and the number of AYA sarcoma survivors keeps increasing, it is important to develop a novel model of understanding psychological adaptation and recovery in sarcoma and describe the factors that are important to individuals. This will allow us to better address the psychological needs of young patients with sarcoma.

4.3 Method

4.3.1 Participants and Recruitment

Individuals who responded to the study advertisement online (via social media) or in the recruiting UK hospitals were invited to participate. Eligible participants were those with any diagnosis of sarcoma, aged over 15 (current age) and able to communicate in English. Patients less than 16 years of age gave their assent after consent had been received from their legal guardians; the interviews proceeded following receipt of consent. Purposive sampling (Etikan, Musa, & Alkassim, 2016) was guided by a sampling framework (see Appendix C for details) to recruit participants across the cancer trajectory, with experience of multiple treatment modalities and aimed at approximately representative distribution of patients across demographic (e.g. gender, age) and illness characteristics (e.g. type of sarcoma). The final sample size was determined when data saturation was reached, and no new themes emerged from the individual semi-structured interviews.

The analysis presented in this paper represent a subgroup of the total sample (N=121) who were aged 15 – 39 years, corresponding to the National Institute of Health

definition of adolescents and young adults (AYAs), which has been identified as a unique subgroup of cancer patients and survivors (Kosir, 2019).

4.3.2 Design and Procedure

This study was part of a larger study of health-related quality of life in patients with sarcoma across the UK, which aimed to develop a patient-reported outcome measure specific for patients with sarcoma. The study was approved by London – Stanmore National Health Service (NHS) Research Ethics Committee (Reference: 16/LO/2152). Data were collected in this phase from February 2017 to August 2017.

Two modes of interviews were offered, in person, or over the phone. In-person interviews were held at home and at NHS premises and phone interviews were conducted with individuals far from the study site. People aged under 16 were interviewed face-to-face interviews and had their parents present at their request.

The interview guide was based on the existing theoretical models of health-related quality of life (Ferrans, Zerwic, Wilbur, & Larson, 2005; Wilson & Cleary, 1995) and refined with an advisory group that included patient advocates, sarcoma experts, members of the sarcoma unit, as well as the research team. This guide, previously published elsewhere (Martins et al., 2019) included questions such as: *Can you tell me about your feelings and experience of being diagnosed/treated for soft tissue sarcoma? How has sarcoma affected your psychological state? What has been the impact on your appearance and body image?*

The interview guide was not prescriptive and was purposefully flexible to enable the researcher to explore new and emerging experiences (Mason, 2002). The topic guide was shared with participants prior to the interview, so they knew the topics covered and allowed participants to have more control over the process. The participants were aware of the study aims, and the role of the researchers. No other information about the research team was shared with participants.

Researchers with graduate-level training in qualitative methods were responsible for conducting and moderating the semi-structured individual interviews. Individual interviews lasted on average 45 minutes, were audio recorded, and transcribed verbatim. Names, locations, or other identifiable information were omitted from the transcripts for confidentiality.

4.3.3 Data Analysis

This study is based on in-depth data analysis of 30 transcripts of the semi-structured interviews. The transcripts were analyzed using a framework approach (Ritchie & Lweis, 2003). Framework analysis allows a structured and organized approach for theme-based and case-based analyses, which produces a visual matrix of themes by participants. The approach is appropriate for semi-structured interviews that discuss similar topics, and results in sensible data reduction, which allows for multi-disciplinary and collaborative approaches to analysis (Gale, Heath, Cameron, Rashid, & Redwood, 2013). See Figure 4.1 for the detailed steps of the framework analysis approach.

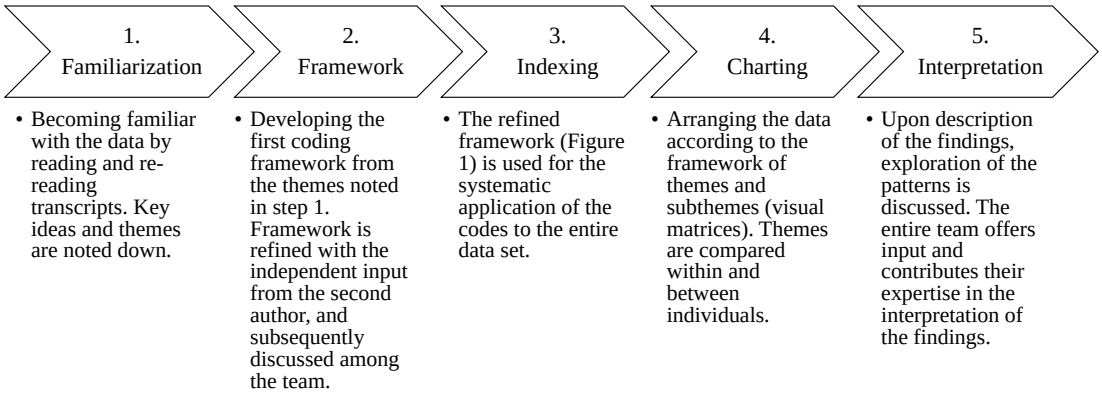


Figure 4.1: The steps included in the framework analysis.

My research colleague A.M. and I read the transcripts repeatedly to familiarize ourselves with the data, and then independently coded them. The first phase of the analysis followed a deductive approach by devising codes and key concepts, which were mapped onto the first conceptual framework of psychological adaptation and recovery which I developed initially. The conceptualization of some themes (i.e. function, activity, participation) was informed by the WHO International Classification of Functioning (ICF), Disability, and Health framework, which describes recovery a process of improvement in psychological, physical, and social domain (WHO, 2002). The second phase of the analyses relied on an inductive approach, adding themes from the initial coding in order to complement the framework and consolidate the findings

(Elo & Kyngäs, 2008). This resulted in a framework (see Figure 4.2) upon which the data were mapped. Themes were then compared within and between individuals with the help of visual matrices (see Figure 4.3 and Figure 4.4). The themes were described systematically, and the findings discussed among the team and embedded in the broader literature.

Throughout the analytical process I kept a reflexive journal to explore the concepts and repetitive themes. In order to account for participants' and researchers' cultural context and understanding of the interviews, meanings from data were produced jointly within the team discussions. Due to the nature of this analysis the exact inter-rater reliability was not determined (McDonald, Schoenebeck, & Forte, 2019). Interpretations on both sides enabled confirmation or rejection of researchers' perceptions of data (Pope, Ziebland, & Mays, 2000). The goal of this work was not to address the questions of prevalence and extent, therefore quasi-statistical phrases such as "some", "many", or "several" are used to not make the findings quantifiable and consequently misleading (Maxwell, 2010).

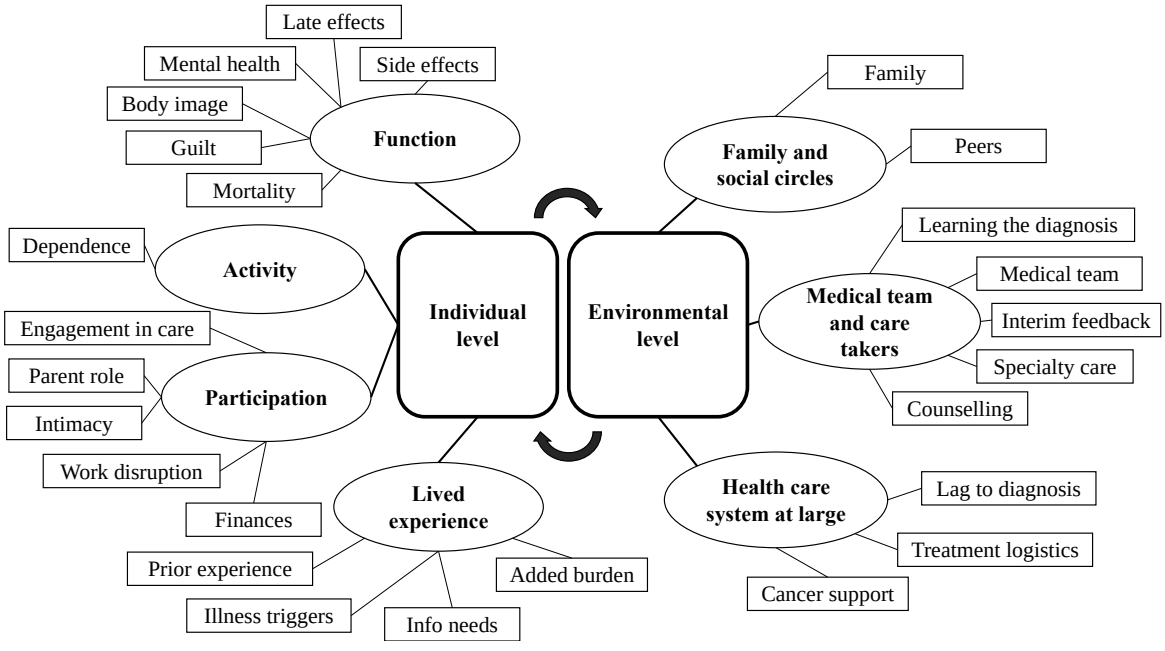


Figure 4.2: The conceptual framework on which the themes were mapped.

The conduct of the analysis and reporting of the results followed the consolidated criteria for reporting qualitative research (COREQ) guidelines (Tong, Sainsbury, & Craig, 2007).

4.4 Results

4.4.1 Participants

A total of 175 patients expressed interest in participating in the study, of whom 121 provided valid consent and were interviewed or joined a focus group. This study includes the 30 young people who were aged 15-39 years who participated in interviews. Descriptive demographic and medical information of our sample can be found in Table 4.1.

Table 4.1: Participant demographic and medical information.

	N %	**M (SD) range**
Gender		
Male	14 (47%)	
Female	16 (53%)	
Age at study		30.3 (5.5) [15 – 39]
15 – 24 y	5 (17%)	
25 – 39 y	25 (83%)	
Age at diagnosis		27.5 (6.4) [11 – 39]
11 – 24 y	11 (37%)	
25 – 39 y	19 (63%)	
Treatment status		
On treatment	10 (33%)	
Off treatment	20 (67%)	
< 3 years	13 (65%)	
3 – 6 years	6 (30 %)	
>6 years	1 (5%)	
Marital Status		
Single	16 (53%)	
Married/Cohabiting	12 (40%)	
Divorced	2 (7%)	
Employment		
Full-time student	4 (13%)	
Part-time employment	4 (13%)	
Full-time employment	12 (40%)	
Other	10 (34%)	
Ethnicity		
White	23 (77%)	
Other	7 (23%)	
Treatment type		
Surgery alone	6 (20%)	
Chemotherapy alone	1 (3%)	
Surgery and chemotherapy	10 (33%)	
Surgery, radiotherapy and chemotherapy	6 (20%)	
Surgery and radiotherapy	3 (10%)	

Chemotherapy and radiotherapy	3 (10%)
Other	1 (3%)
Sarcoma type	
Soft tissue sarcoma	13 (43%)
Bone sarcoma	17 (57%)
Sarcoma site	
Upper limb	4 (13%)
Lower limb	11 (37%)
Other*	15 (50%)
Amputation	
Yes	4 (13%)
No	23 (77%)
N/A	3 (10%)

*Other site: head and neck, pelvis, spine, finger, breast, abdominal origin.

4.4.2 Factors that play a role in psychological adaptation and recovery in sarcoma

Our analyses revealed seven grouping themes and twenty-six sub-themes that can be viewed as factors, which were grouped into two overarching themes: individual level factors or environmental level factors. When describing these factors, individuals' accounts were rated as either describing a given factor in a negative, positive, or ambivalent light. These factors form the basis for our conceptualization of psychological adaptation and recovery (See Figure 4.2).

Illustrative quotes from participants are provided within the text and fully anonymized for confidentiality reasons. The remaining quotes are included in the tables embedded within the text, which are organized to follow the themes' framework.

4.4.3 Individual level factors

Individual level factors encompass those that were individually bound and sometimes independent from external circumstances. These were not necessarily mutually exclusive with environmental level factors, and sometimes overlapped on the continuum between individual and societal. Figure 4.3 demonstrates the discussed themes by all participating individuals.

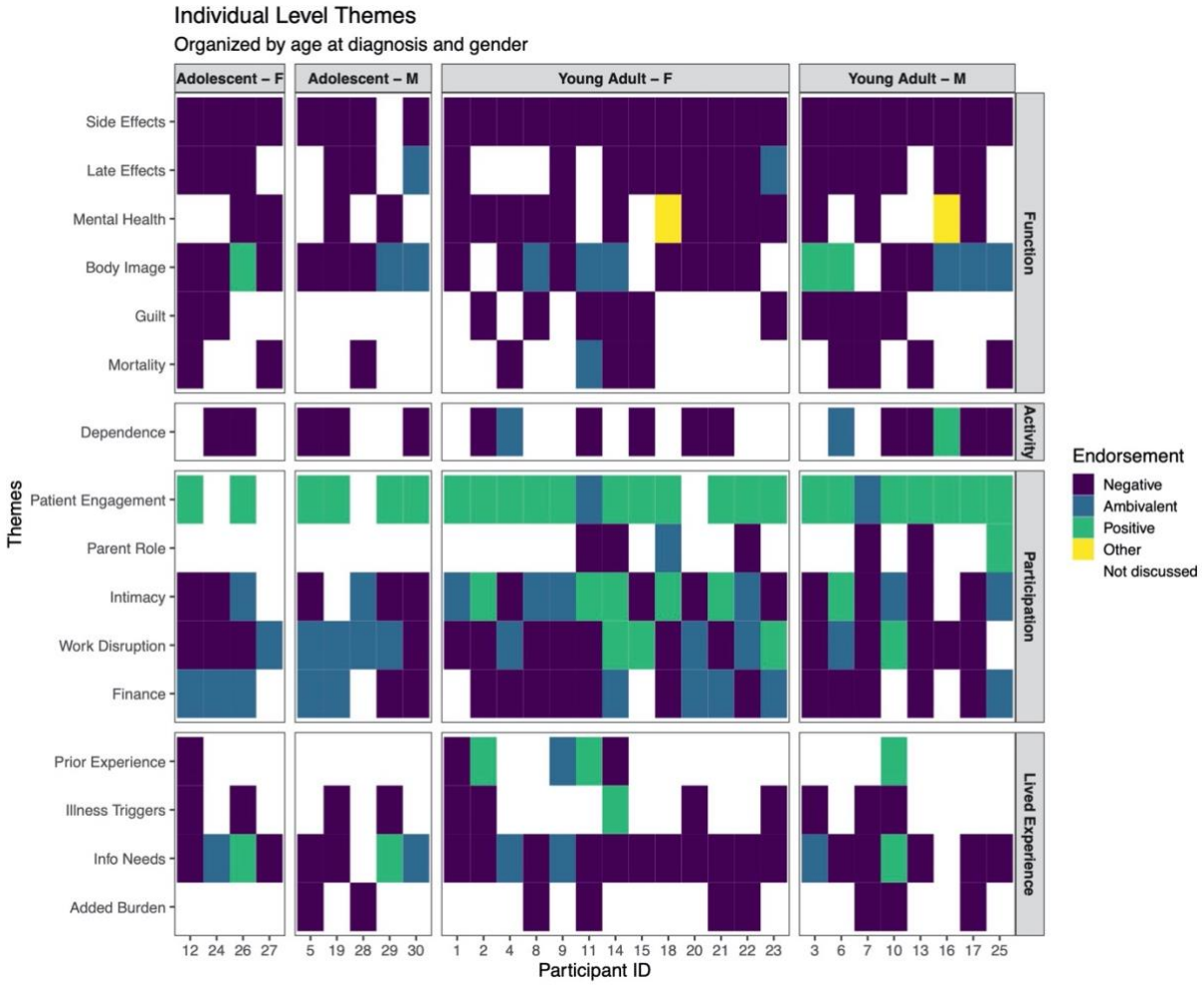


Figure 4.3: Visual matrix of individual-level themes.
NOTE: Adolescents are individuals who were diagnosed at 24 years or under, and young adults are those who were diagnosed above age 24 years. F, female; M, male.

4.4.3.1 Function

Function refers to an individual's physical or bodily functioning including psychological well-being and mental health (WHO, 2002). Treatment side-effects were endorsed entirely as negative, impacting participants' quality of life, and though they varied in magnitude and number, participants commonly reported trouble eating, feeling nauseous, and experiencing fatigue or pain. Side-effects limited individuals' participation in activities, however, they tended to subside after the treatment ended. For some participants symptoms persisted over time. Among the late effects, issues and worries related to fertility were the most commonly endorsed and discussed equally between genders.

Mental health concerns and acute episodes of psychopathology were reported by 17 participants. Two participants reported that their mental health was directly influenced by their physical function and resolved with physical recovery (see "Other"

in Figure 4.3). Several participants reported thoughts about their mortality, which provoked anxiety and negative emotions, and the majority emphasized that the mental health problems and psychopathology started after the phase of active treatment.

"I think the main thing that I struggled with was the bit afterwards when some people were 'You're alright now. It's finished, you're okay.' I found that hard to talk to some people about, because they saw that actually the physical side of it is over, but actually the mental side isn't."

Twelve participants also endorsed feelings of guilt, which tended to persist beyond active treatment. Young people expressed feeling guilty in relation to failing to fulfil their roles as partners or parents, unable to carry out their daily tasks or having to rely on their parents for financial or logistical support. Some participants experienced guilt in their relationship to other cancer peers who had a poorer prognosis, although others expressed feeling "lucky."

Body image concern was also prevalent, 15 participants reported negative feelings associated with it, and 3 individuals talked about their body image improving with illness due to weight loss or improved self-care and healthier lifestyle brought on by their illness (see Table 4.2).

4.4.3.2 Activity

Activity is the ability to carry out a task or an action (WHO, 2002). The most commonly described factor was loss of independence by 17 participants, which often resulted from physical limitations associated with treatment procedures. Among those who reported feeling dependent, two individuals did not perceive it as problematic because of the temporary nature of dependence and adjustments made to cope. One individual reported remaining relatively independent, which resulted in a sense of accomplishment, and resultantly positive attitude.

4.4.3.3 Participation

Participation involves active engagement in one's life and daily activities such as education or work, parenting, engagement in one's care, and romantic relationships and intimacy (WHO, 2002). The disruption in education or work was reported by 29 participants. Sixteen reported a negative impact and felt like they fell behind and had

to change their educational and vocational plans, which was "hard to accept". Nine participants felt ambivalent about their vocational disruption, most often explaining that it was a "small price to pay", or the disruption was temporary. Four participants, all of them young adults, endorsed disruption as a positive thing, allowing them to re-think their priorities and pursue more fulfilling endeavors (see Table 4.2).

Financial strain resulting from work disruption was discussed by 24 participants, and mostly felt by those with limited support from their family or partners. Young adults in particular reported hidden costs of sarcoma, which included traveling for treatment, parking, or family lodging at a hotel. A few participants reported limited impact because their employers continued to provide them with a salary, or they were financially secure.

Of 30 participants, seven were parents. Five of them reported that their parenting role was compromised by illness, and they expressed worry about their children. One individual reported that being a parent was his most important role and endorsed it as a positive factor, explaining that it provided him with a sense of purpose during treatment and recovery. Twenty-seven participants also spoke about romantic relationships and intimacy, which were commonly impacted by the diagnosis and treatment. Several talked about romantic relationship in a negative way and suggested that their relationships fell apart, describing illness and associated distress as the main reasons. Eight individuals felt ambivalent about sarcoma impact on their relationship, while six reported that their illness strengthened the appreciation of their romantic partner and made the relationship stronger as they learned ways to remain intimate despite the limitations imposed by illness.

A widely endorsed positive factor was individuals' participation in one's own care. Twenty-four young people reported being proactive about their care and sought ways to improve their health. Shared decision making and patient engagement were seen as empowering.

4.4.3.4 Lived experience

Lived experience describes other factors that are pertinent in one's participation and recovery. A common theme discussed by 28 participants was the need for information. Young people were not always satisfied with the amount of information

they were provided. In a few cases the information felt overwhelming, and several reported inadequate information at the time of diagnosis (see Table 4.2).

Twelve participants spoke about illness triggers or "reminders", which had a negative impact on all but one person. These triggers, ranging from bodily sensations to visits to the hospital, reminded participants of illness and caused feelings of distress and anxiety. One participant reported the illness reminder – a large scar – as a positive sign, giving her a sense of pride and strength.

Another aspect that proved important in one's understanding, and adaptation was prior experience. Prior experience defines one's experience with cancer, be it their own or familial, or significant prior experience with the medical care (e.g. major surgery, unrelated to cancer). Six participants discussed prior experience, two endorsed it as negative because they have lost a person close to them to cancer. They worried about their own prognosis and felt like they could not openly talk about it with their family because of the negative connotations. On the other hand, three participants reported their prior experience as a positive factor that allowed them to better manage their expectations, navigate the medical system, and advocate for themselves.

Finally, nine participants talked about the added burden resulting from external factors not related to their illness, for example, breaking a limb and family bereavement. This burden was an additional stressor and was exclusively negative.

Table 4.2: Supporting quotes from participants about individual level factors.

Function - an individual's physical or bodily functioning including psychological well-being and mental health	**Side effects**	*"I got the ulcers in my mouth a few times after my methotrexate, and the ulcers were quite bad. I'd probably go, like, three days without eating or drinking just because my mouth was so painful."*
	Late effects	*"I found out a couple of months ago that the chemo has made me totally infertile, and so that has probably been the thing that I've struggle with the most out of everything."*
	Mental Health	*"I was on a lot of diazepam to try and help me sleep and just really get through those first few days [after diagnosis]. I think I just cried probably for the first few weeks because I didn't know what was going to happen. Nobody seemed to be giving me any indication as to what the next steps were…"* *"I got put on the antidepressants. That was, kind of, the worst thing, how it affects you mentally. I just couldn't even get out of bed. […] Depression was that bad. That's one of the worst side effects."*

	Body Image	Negative: *"Losing my hair didn't really bother me that much at the beginning. Towards the end it kind of did bother me. I got really tired of just looking like a cancer patient."* Positive: *"I think my physical condition, in terms of body, like, I've lost a lot of weight compared to, I think I'm 15kg down pre-cancer, which I love and I take very much pride in the fact that I'm a lot fitter than I was…"*
	Guilt	*"The hardest thing is when you see how much pain and upset you caused other people […]. So that's what I really struggle with today all the time. It's horrible that you've ruined someone's life for a year."*
	Mortality	*"You've got your kids and your family, and you've got to work, because you need the money. In your head, you're thinking, 'I'm dying. I'm literally dying as I'm working."*
Activity - ability to carry out a task or an action	**Dependence**	Negative: *"I couldn't do anything. So, during this time, my husband had to wash my feet, change my underwear and dress me. […] I didn't have a shower for four months, just stand-up washes because I didn't want to get the dressings wet, and my husband had to wash my hair and do all the housework."* Positive: *"I had family around, but in terms of people helping me get dressed and everything, I didn't need that."*
Participation - active engagement in one's life and daily activities such as education or work, parenting, engagement in one's care, and romantic relationships and intimacy	**Patient engagement in care**	*"I think it's still important to have an element of control and be involved in your decisions. […] I've always had the final say, but I think it's always important to feel as though you're part of your treatment. So you know what's going on, and you're not, kind of, just letting it happen to you."*
	Parent role	Negative: *"It was really hard from things like-, so I had to stop breastfeeding."* Positive: [interviewer]: *"Being able to see your daughter grow up as being something that has helped you throughout this period…"* [participant]: *"Most definitely, yes."*
	Romantic relationship & intimacy	Negative: *"[Partner] was essentially my carer throughout the whole treatment, because obviously she was there… and our relationship unfortunately fell apart after. We were made aware of this. They did say, 'Look, after [cancer], people can change."* Positive: *"Sex life, basically that was non-existent for nine months,[…] we'd have to spend quality time doing something else together, instead of duvet action, so we might watch a DVD or a TV programme, or play cards, and just make it a special quality time, doing something together."*

	School & work disruption	*"I had a really good relationship with my manager, so it wasn't hard to tell my manager about it. They were very supportive, you know, I obviously had to go for chemo almost immediately, so I had to leave work straight away, and I told them. They were very good, they offered to continue paying me until I come back, and stuff. They kept in touch with me, so that was really good."* *"I still did all my exams, and so I've had to work harder than anyone to make it up, and I feel really short changed that I'm only graduating with an ordinary degree, and I worry that it's going to hold me back."*
	Financial strain	Negative: *"I mean obviously when I got ill I was supporting myself via my student loans and my grant, and my part-time job, and that all ended obviously when I had to interrupt my studies, so they stopped paying me."* Ambivalent: *"Paying for taxis is not exactly cheap, so my friends help. My brothers help, obviously. They drive. My parents help and my colleagues help as well, so I wouldn't say it's dire if you know what I mean? It's manageable."*
Lived experience - describes other factors that are pertinent in one's participation and recovery	**Prior experience**	Negative: *"Because my mum died of cancer, and having cancer now really kind of reopened a lot of my grief over that, because I just felt like I was reliving her history."* Positive: *"I have a genetic predisposition to cancer, and so it's not my first cancer. In fact it's not my first sarcoma. I know it might sound weird to say but to be honest since of [other medical condition] diagnosis I've kind of been waiting for osteosarcoma. Yes, I was just kind of-, well, kind of prepared."*
	Illness triggers	Negative: *"Again, you get what I call shadowy pain where the tumour was, so I'll get a sore shoulder or something and that, sort of, leans on your mind because it takes you back to the exact same symptom that gave away the fact that you had cancer originally."* Positive: *"Now my scar is extremely neat and tidy, even though it's large. I think it reminds me that I've fought something and won, at the moment, and I'm still here."*
	Information needs	*"[Interviewer] When you were with that first appointment where you received the diagnosis, she [Dr.] mentioned reconstructive surgery, at that time did you understand why she was talking about that? To be honest, I didn't. [Interviewer]: She just gave you the information? Yes. She didn't really mention what it would entail. She just said, you know, they do great reconstructive surgery, so I'm, like, 'Oh,*

		okay. It sounds like I'm going to have to have surgery,' but she didn't go into detail about what the treatment would be." "*Obviously all the information's bombarding, coming into you, so you can't process it all."*
	Added burden	*"I had moved to new jobs at the time. I was going through a break-up in a relationship at the time also which added to the problems, you see."* *"I mean, my mum used to be my best friend. Just after I got into remission, she had her cancer back again, and she passed."*

4.4.4 Environmental level factors

Environmental level factors refer to aspects of individuals' social and environmental context within which they found themselves during their illness experience. They range from more intimate circles of friends and family to one's medical team. Figure 4.4 demonstrates the discussed themes by all participants.

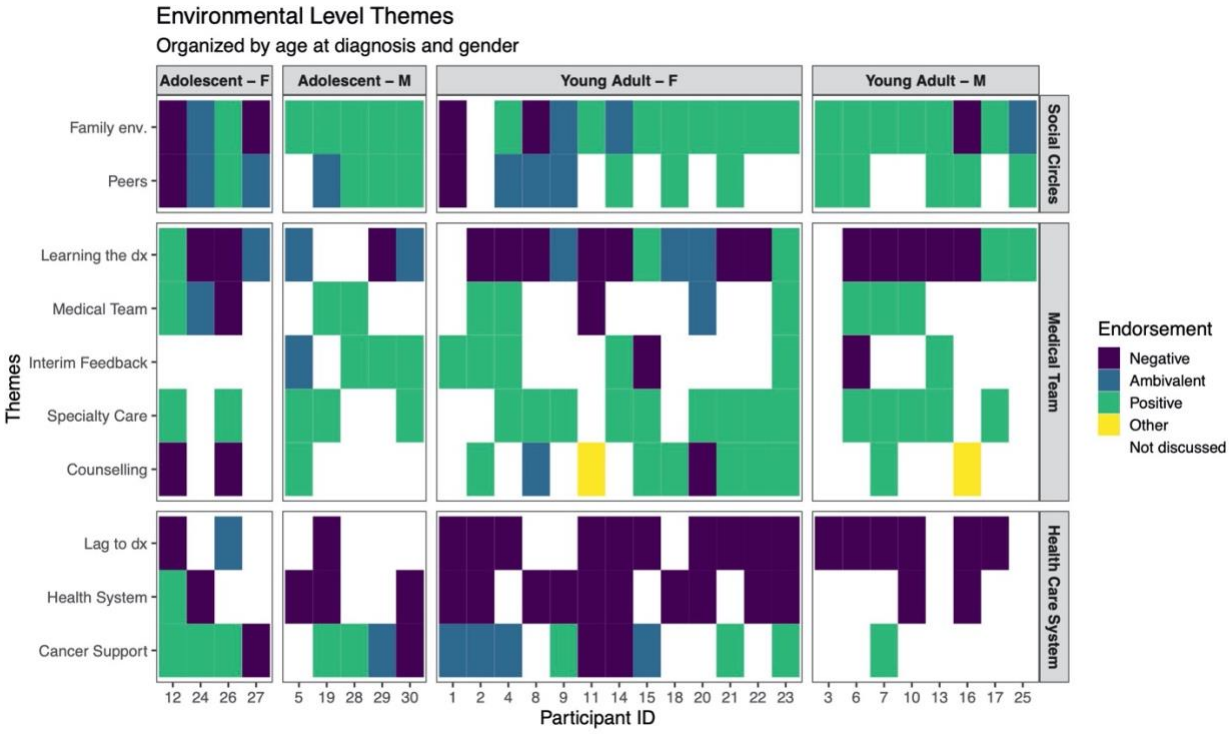


Figure 4.4: Visual matrix of environmental-level themes.
NOTE: Adolescents are individuals who were diagnosed at 24 years or under, and young adults are those who were diagnosed above age 24 years. F, female; M, male.

4.4.4.1 Family and social circles

Twenty participants endorsed family as a positive factor. Many reported their relationship within the family improving and resulting in a more cohesive environment due to support and greater appreciation of one another. Some individuals could only draw partial support from their family, and for a few, family was not a source of support but rather an impediment (see Table 4.3).

Twelve participants spoke about peers and close friends in a positive light. Close friends provided additional support for the individual, which was different from familial support and provided them with a sense of normalcy. However, several participants reported that they also lost friends and felt abandoned due to illness.

4.4.4.2 Medical team

Participants often spoke about their medical teams and healthcare professionals. The initial impact of diagnosis often stemmed from the time they learned their diagnosis. Learning the diagnosis was a negative experience for 15 individuals and almost entirely resulted in feelings of shock and distress. Seven participants learned the news over the phone, which did not allow them to ask questions. Some felt that the bad news were attenuated by the fact that they were not alone at the time of diagnosis, and some found great relief in getting an answer for their previously unexplained symptoms.

Nine participants spoke about their positive relationship with the medical team. Those who reported feelings of trust and being able to openly express their concerns reported greater levels of satisfaction with their care and less distress associated with treatment. Additionally, interim feedback on disease and treatment status was desired. Several individuals emphasized that receiving positive news during treatment was encouraging. Two participants reported feeling negative impact due to the lack of positive news.

In addition to the medical team, the specialist nurses or in some cases AYA coordinators were endorsed as the most helpful resource by 19 participants. Specialist nurses were able to spend more time with participants and answer questions related to their illness and its impact.

"My MacMillan nurse, she's phenomenal. If I'm ever feeling a bit low or anything, when I was on chemo or anything, she was there. She was fantastic. Absolutely fantastic."

Fourteen participants spoke about psychotherapy and counselling. Some received it as part of their oncological care, while others sought it externally. For 8, counselling was a positive experience, teaching them adaptive coping mechanisms. However, four participants found counselling services inadequate in addressing their needs as sarcoma patients, which resulted in frustration. Two individuals explicitly asked for and wanted psychological support but were unable to obtain any (see Figure 4.4, "Other").

4.4.4.3 Healthcare system at large

Two thirds of our participants reported a prolonged route to diagnosis. In all but one case this was a negative factor. Participants reported several months, in one case 2 years, before their symptoms were recognized and treated seriously. Several individuals resorted to private care in order to speed up the diagnostic process. Two individuals reported an initial misdiagnosis.

Sixteen individuals also discussed difficulties in navigating the healthcare system. Some individuals had to travel long distances for their treatment, and two reported that their care was not age appropriate. Managing the logistics of care was burdensome.

Participants were often encouraged to join cancer support groups, face-to-face or online, some of which were specific to sarcoma. Nine participants endorsed them as positive, but young adult males rarely discussed the topic or engaged with the services. Among cancer peers, participants felt supported, understood, and less isolated due to their illness. However, half of the participants felt as though the groups were not tailored to their needs, found them too depressing due to generally poor prognoses, or hard to relate due to different outlooks or age differences.

Table 4.3: Supporting quotes from participants about environmental level factors.

Family and social circles	**Family environment**	Negative: *"I'm just not very close to them, so it was quite strange to have bring them to something and they don't talk to each other. They said that I needed to bring them both, and at the time it was almost extra stressful having to bring them."* Positive: *"I would say, out of everything, it's brought us closer. The impact has been far more positive than negative, because I think everyone just values life a bit more now."*

	Peers and friends	Negative: *"I feel a slight disconnect with my friends, and it's hard because you can't just kind of slot back in…. It's just a sense of feeling so disconnected because my problems are just different and it's not relatable. […] It's hard for my friends to see me sick, and it's hard for them to see me really suffering."* Positive: *"Quite a few of my mates had all arranged a big charity bike ride for me and they'd arranged it at this time because that was when it was going to fit in with my surgery, you see, and before I started my chemo again."*
Medical team and care takers	**Learning the diagnosis**	Negative: "*I actually got told over the phone. I found it just really shocking…. Yes, to have it through a phone call, it was a bit, I don't know, strange to be told that through a phone call, really."* Ambivalent: *"It was a bit conflicting because obviously it's not something that you expect to hear, and it's not something you want to hear, but at the same time it was kind of nice to know that I wasn't crazy."*
	Relationship with the medical team	*"I do have quite a good relationship with Dr.[…] I trust that he'll tell me what he thinks is the best thing for me to do."*
	Interim feedback	*"There's actually been a small reduction in size in my largest mass and everything else has stayed perfectly stable. There's nothing else in my body so really, really pleased. My consultant's very, very pleased with how everything's working so it's very, very positive."*
	Specialty sarcoma and/or AYA care	*"I hear about people who don't have a clinical nurse specialist and they don't understand how important it is until you have one. You realise she does so much for us. She makes it easy. She knows when you don't understand something. She'll stay behind and explain things. When I had surgery, she travelled to the different hospitals, she came to see us. She looks after your family, friends, everything. Everyone knows her, but it's the fact that she takes time to explain. She listens to you."*
	Counselling or psychotherapy	Negative: *"One of the hospices arranged for some therapy, but I didn't really get on with it very well, so I only went a couple of times… I just didn't really like it, I found it made me feel more worried than less worried."* Positive: *"I did have some professional support at the very beginning. I had four or five sessions with a counsellor. Again, that was all done privately because I wasn't offered anything on the NHS, […]. It was really useful to go and talk to somebody and just open up and explain everything to*

		them. She gave me lots of advice and tips on how to deal with the days when I feel down."
Health care system at large	**Prolonged route to diagnosis**	*"So, I went to my GP about 1,000 times, and they said I had growing pains and prescribed me diclofenac, which I took for a long time. Then because I couldn't sleep because the pain was so bad, and I was trying to do my exams, my mum decided to send me privately."* *"Every time I went to the GP, they, kind of, still said, 'Oh, look, you're just doing a lot of overtime. You're just standing on your legs a lot. It's just, you've probably got a shin splint."*
	Health system & treatment logistics	*"Travel can be quite hectic. […] Yes, the thing is on the travel days it is about muscling through it, you know."*
	Cancer support groups	Negative: *"I did look on some sarcoma websites, but I found them quite depressing. A lot of people were sort of-, some people were not as successful as I'd been and I felt that I couldn't relate to them because they were in a different situation to me, so I found that those forums didn't really help because they were people offloading because they'd been dealt a bad card."* Positive: *"Yes, these support groups are fantastic because you can communicate with people the same age as you at any time.[…]They may have a very different cancer and be at a very different stage in their treatment or their journey but they understand because they're the same and they have the same feelings and the same thoughts and the same worries. Those groups are priceless."*

4.5 Discussion

This qualitative study aimed to describe both positive and negative factors along the illness trajectory in young people with sarcoma. By relying on qualitative methodology, we demonstrated the extent of between-individual variability in mental, physical, and social function along the illness trajectory and contribute evidence towards a dynamic approach to understanding of psychological adaptation and recovery. Practical recommendations for clinical care and future research are discussed below.

Thirty AYA participants from across the UK provided in-depth subjective accounts about their experience with sarcoma. The present study contributes to the existing body of knowledge with a thorough investigation and description of commonly

reported factors and demonstrates that when faced with cancer, individuals stem from vastly different backgrounds and life experience. Consequently, different individual level factors or environmental level factors will contribute to one's psychological adaptation and recovery. As psychosocial well-being remains an unmet need and among the most important topics for AYAs with cancer (Aldiss et al., 2018), we have to develop a better understanding of how different sub-groups of patients, though afflicted with the same diagnosis, respond differently based on their individual bio-psycho-social profile.

We propose that successful psychological adaptation and recovery may not be considered as latent entities, but rather as dynamic systems composed of factors or symptoms. As such, the concept extends on the static models of psychopathology (i.e. meeting the symptom threshold for a mental disorder), and resilience (i.e. absence of psychopathology given adversity; Rutter, 2006), and accounts for the fact that one might at once experience psycho-social growth, as well as symptoms of psychopathology.

Moving beyond the latent constructs of resilience and psychopathology in youth with sarcoma may be particularly important because unlike the general population where mental health disorders are thought to occur via the activation of symptoms through adverse life events (Cramer, Borsboom, Aggen, & Kendler, 2012; Keller, Neale, & Kendler, 2007), in patients with chronic conditions (i.e. cancer) the pathway to psychopathology may be different (De Jonge et al., 2006; Marusak et al., 2018). The illness may be perceived as both an adverse life event, as well as a chronic health condition, we suggest that psychological adaptation and recovery in AYA with sarcoma will follow unique pathways and factor or symptom presentation. For example, our results imply that education and work are salient aspects of AYAs' identities and often disrupted by illness. So, we might have two individuals experiencing anxiety (i.e. not achieving full recovery) who are of the same age, gender, same type of sarcoma, and with a comparable treatment plan. While one's feelings of anxiety will revolve around the thoughts of mortality and follow-up consultations (*follow-up consultation → thoughts of mortality → anxiety*), another might experience anxiety due to occupational disruption and financial strain (*work disruption → financial strain → anxiety*). Similarly, we show that certain concepts such as body image, which most commonly carry negative connotations (Fan & Eiser, 2009; Sodergren et al., 2017), can in fact act as resilience factors if appraised as positive (*healthier lifestyle → improved body image*

after cancer → improved self-image). This further strengthens our claim that individual circumstances vary in important ways and should be accounted for in clinical practice. The high level of individual variability also suggests that the use of person-centred statistical approaches (e.g. growth mixture models; Nagin & Odgers, 2010) would be informative in further study of this heterogeneous population.

It would be erroneous to expect young people exposed to cancer to show uniform outcomes in facing their illness. Most of the existing literature in AYA cancer survivorship addressing psychological well-being relies on the conceptualizations of psychopathology and resilience from healthy populations, which have not been adapted to young people with cancer. Therefore, an understanding of psychological adaptation and recovery as dynamic systems is needed to take into account the interplay between many resilience and risk factors on an intra, as well as inter-individual level. Our study offers a first step in this conceptualization and provides invaluable insights for future work in this field.

4.5.1 Limitations and future directions

Certain limitations are important to note in the present study. Our sample was heterogeneous, including individuals with all types of sarcoma, from a broad age range, and is limited to the UK, which might limit generalizability of the findings, particularly in the domain of the health care system. Additionally, participants were a self-selected group and mostly provided retrospective accounts, which may have been impacted by recall bias. Though asked about their illness and sarcoma history, this information was self-reported. Lastly, this study relies on secondary data analysis, which might explain why some concepts were not explored in-depth by all the participants, or in greater detail. The themes mapped onto the framework were not mutually exclusive and often spanned across domains. Despite its limitations, this study is the largest in-depth exploration of the impact of sarcoma on AYA, which adds important insights for future research and targeted therapeutic approaches for this vulnerable population of patients.

4.5.2 Conclusion and clinical implications

Sarcoma impacts young people on psychological, physical and social levels. Understanding the subjective experience and individual circumstances is at the centre of personalized approach to health care. Our findings suggest that young people with

sarcoma require holistic guidance and care beyond active treatment. One-size-fits-all approach is inadequate and healthcare professionals working with this population should actively engage with their patients from the time of diagnosis. Considering individual context will aid in identifying those in need of help in a specific domain (e.g. return to work). While certain factors cannot be prevented (i.e. infertility), promoting a cohesive atmosphere between the patients and medical professionals can result in better management of an individual and optimization of service and resources utilization. Furthermore, across the UK, nationally-based services for AYAs mostly end at age of 24 years (L. A. Fern et al., 2013). In our study we included individuals up to the age 39 and demonstrated that young individuals who are ineligible for the NHS AYA services also present with needs that may not be adequately addressed in adult cancer units. We recommend that special attention is paid to young people outside the dedicated AYA services.

4.6 Contribution to this thesis

This chapter is the largest in-depth exploration of the impact of sarcoma on AYA and answers to **RQ1**) What are the factors associated with resilience and psychopathology in youth with cancer? (see Section 1.10.1).

The qualitative nature of this study sheds light on meaningful connections between various factors and their role in psychological adaptation and recovery in young people with sarcoma. Psychopathology and resilience in AYA with sarcoma may result from vastly different pathways, therefore, understanding one's unique trajectory may help us in developing a more personalized approach to care.

By demonstrating the need to move beyond the latent constructs of resilience and psychopathologyand consider the dynamic nature of adaptation process, the following chapter builds on this notion and uses network analysis to consider individual symptom-to-symptom connections.

Chapter 5 - Interconnectedness of anxiety, depression, and cancer-related worry in adolescents and young adults with cancer: A network analysis*

5.1 Abstract

Objective:

The objective of this study was 1) to use network analysis and explore how cancer-specific worries, anxiety and depressive symptoms are interconnected, and 2) identify the most central symptoms, which may offer potential targets for psychological interventions.

Method:

Participants were 233 self-identified cancer patients and survivors (87% female) aged 18 – 39 primarily from the EU and North America. Data were collected online via Qualtrics. We estimated two cross-sectional network models of symptom-to-symptom relationships of anxiety and depression symptoms, as well as cancer-specific worries and their interconnectedness to psychopathology in a subset of participants off-treatment (N=160).

Results: Clinical levels of anxiety and depression were present in 59% and 39%, respectively. Cancer-specific worries ranged from 43% to 81%, with worry about relapse being the most commonly endorsed. Centrality analyses and predictability indices highlighted trouble relaxing and low mood as the most central nodes in our networks.

Conclusions: Network analysis allows us to complement our current conceptualizations of psychological adaptation to cancer by highlighting important connections between symptoms and illuminating trouble relaxing and low mood as the critical symptoms. Future directions and clinical implications are discussed.

* Chapter adapted from:

Košir, U., Loades, M., Wild, J. & Bowes, L. (Submitted). A network analysis of anxiety, depression, and cancer-related worry in adolescents and young adults with cancer. *Journal of Clinical Oncology*.

5.2 Introduction

As discussed throughout the preceding chapters, receiving a cancer diagnosis can significantly derail achievement of developmental milestones and impact one's psychosocial wellbeing (Bibby et al., 2017; C. L. Daniel et al., 2015; Perez et al., 2020). Many AYAs report ongoing difficulties (re-)integrating at school or work (Pini et al., 2019; Vetsch et al., 2018), poorer body image and self-esteem (Fan & Eiser, 2009), difficulties establishing and maintaining intimate relationships (Acquati et al., 2018; Tolman & Mcclelland, 2011; Wettergren et al., 2017), as well as psychopathology (Kosir et al., 2019b; McDonnell et al., 2017; Recklitis et al., 2010).

A particularly salient worry for cancer survivors is fear of cancer recurrence (FCR; commonly defined as cancer relapse or progression in the original site or a new part of the body) (Simard et al., 2013), which has been reported by up to two thirds of AYAs (Thewes et al., 2018). FCR has been associated with lower quality of life and increased depressive and anxious symptomatology (Simard & Savard, 2015; Simard et al., 2013). However, the field lacks a consensus on what consists a clinical level of cancer-related worry, or which worries most strongly link to specific symptoms of depression and anxiety among AYAs (Kosir, Wiedemann, Wild, & Bowes, 2019a; Mutsaers et al., 2016).

5.2.1 Piloting the study

Prior to launching the online study, we conducted a small cross-sectional feasibility study to 1) assess the feasibility of online research with AYAs, 2) to provide preliminary insights into which factors play a role in psychological adaptation in AYA cancer populations, and 3) to guide the subsequent study development.

Twenty-one participants aged 18 – 39 years, 57% female, answered questionnaires about mental defeat, rumination, cancer worry, anxiety, and experience participating in such research. Seven participants scored in the clinical range for anxiety. Cancer-related worry was common with *worry about receiving a new cancer diagnosis* being the most prevalent (66.7 %). More than half of the participants also worried about experiencing a relapse or experiencing late effects related to their cancer treatment. Rumination (measured by Ruminative Response Style (RRS-10; Treynor, Gonzales, & Nolen-Hoeksema, 2003) and mental defeat were positively associated

with anxiety (Figure 5.1). The participants reported the length and type of questions to be appropriate and not distressing.

We carried out exploratory analysis to visualize the associations between anxiety and other variables of interest described above, and also report Spearman's correlations (Figure 5.1). The complete report, as well as the analysis scripts can be found at https://psyarxiv.com/d3cjy.

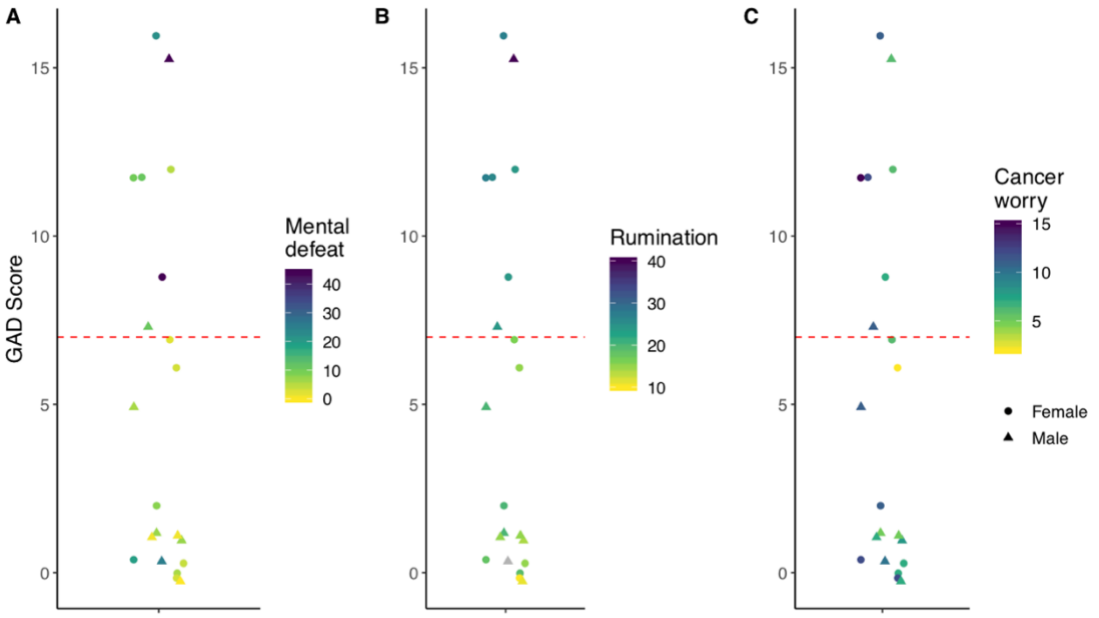


Figure 5.1: Individual scores on the GAD scale combined with Mental Defeat, Rumination and Cancer worry.
NOTE: GAD-7 = Generalized Anxiety Disorder, MDQ = Mental Defeat Questionnaire, RRS = Ruminative Response Style questionnaire.

The graphs represent individual scores of anxiety on y-axis against MDQ, RRS, and Cancer Worry. The horizontal dashed line corresponds a clinical cut off score on the GAD-7. Seven participants scored in the clinical range for anxiety. Darker color of the data points corresponds to higher scores on the MDQ, the RRS and Cancer worry scales. The pattern of results indicates that those scoring highest in anxiety also score higher in the three subscales. The GAD-7 was positively associated with mental defeat (r = 0.40, p = 0.07), and ruminative response style (r = 0.743, p < 0.001), while there was no association between GAD-7 and cancer worry. Interestingly, the pattern is least pronounced among individuals scoring high in cancer worry on both ends of the anxiety scale.

Out of 23 respondents who consented to participate in the pilot, 20 (87%) completed the entire survey, and 1 respondent did not complete 2 questionnaires. Participants reported the length, type, and number of questions to be appropriate. Only 1 participant found the survey distressing (80/100), and none found it burdensome.

A direct link to the survey was circulated on Twitter and Facebook. Additionally, several patients, health professionals, and cancer charities based in the UK reposted our ad. Most participants were recruited on the day or the day after the ad appeared, suggesting that continued social media engagement is required for larger samples and broader reach.

5.2.2 The present study

The study described in the remainder of this chapter was based upon the pilot study described above. The methodology is outlined in the following section (5.3).

Because psychosocial wellbeing remains a primary concern and an unmet need for many young people with cancer (Aldiss et al., 2018; C. L. Daniel et al., 2015; Perez et al., 2020), understanding and addressing cancer worries and symptoms of psychopathology in young people is important in assuring optimal long-term outcomes and recovery. Extending upon the pilot findings, we wanted to go beyond the correlational analysis between latent constructs and instead wanted to further uncover the relationship between different symptoms of psychopathology and cancer worries. We included a measure for depression (Patient Health Questionnaire, PHQ-9; Kroenke, Spitzer, & Williams, 2001) in order to obtain more granular data on psychopathological symptoms.

We used network analysis to explore the psychological networks of young cancer patients and survivors in a cross-sectional sample. Specifically, we were interested in exploring how cancer-specific worry, anxiety and depressive symptoms are interconnected, and identify the most central symptoms, which might offer potential targets for future interventions.

Recent advances in psychometric theory have propelled the application of network analysis to the study of psychopathology (Borsboom & Cramer, 2013), and offer a promising avenue to explore the intricate relationships between FCR and associated symptoms in cancer populations (Schellekens et al., 2019). This data-driven approach posits that individual symptoms of a construct (e.g. anxiety) are interrelated

and covary, and produces graphical networks of nodes (symptoms), which are positioned based on their interconnectedness, thus nodes on the periphery, are the nodes with fewer connections to the other nodes in the network (Epskamp & Fried, 2017). These peripheral symptoms may be considered more independent or "stand-alone" symptoms. Network modeling allows for an inspection of the reciprocal relationships between specific symptoms of different constructs, identify the most central symptoms, and as such identify which nodes might carry more weight and offer potential intervention targets, as well as offer insight for new research questions (Fried, 2015; Fried & Cramer, 2017).

Relying on network approach in AYAs with cancer will allow us to advance beyond the descriptions of symptoms groups (cancer worry, anxiety, depression), and complement the current literature with a deeper understanding of variation of these constructs at a symptom level. This could advance our understanding of etiology of psychopathology in AYAs with cancer. To the best of our knowledge, no study has yet looked at symptom-to-symptom relationships in psychopathology of AYAs with cancer.

5.3 Method

5.3.1 Participants and study design

This study analysed baseline data of an online longitudinal survey study aimed at investigating how cognitive and emotional wellbeing impacts psychological adaptation and holistic recovery in AYA cancer patients. The complete study protocol was published on Open Science Framework (OSF) and can be viewed at: https://osf.io/zy9hj/. The study was approved by the Medical Sciences Inter-Divisional Research Ethics Committee at the University of Oxford (R61437/RE005).

Data were collected via Qualtrics (Qualtrics, 2020), secure online survey software, via an anonymous link distributed on social media outlets and online via patient organizations' web posts or newsletters. All participants were provided brief information about the study, eligibility criteria, the study aims, and provided informed consent prior to participating. Participants were all self-identified cancer patients or survivors aged between 18 and 39 years, diagnosed with any form of malignant cancer at age 10 or later. The survey had two equal arms: Slovenian and English.

5.3.2 Measures

The measures used in this study are described in Table 5.1. Complete item list can be viewed in Appendix E. All participants self-reported their age, gender, geographical region, and current living arrangements. They also reported their current health status, treatment status, and whether or not they had a pre-existing mental health condition.

Table 5.1: Measures used in this study.

Measure name	**Description**	**Internal reliability in the current study (Cronbach's α)**
Generalized Anxiety Disorder (GAD-7) (Plummer, Manea, Trepel, & McMillan, 2016)	7-item measure of anxiety symptoms rated on 4-point Likert scale from 0 (not at all) to 3 (nearly every day). A sum score of ≥7 or indicates probable clinical anxiety.	0.89
Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001)	9-item measure of depressive symptoms rated on 4-point Likert scale from 0 (not at all) to 3 (nearly every day). A sum score of ≥10 indicates probable clinical depression.	0.88
Cancer-related Worry (Klassen et al., 2015)	6-item scale rated on a 4-point Likert scale ("Strongly disagree" to "Strongly agree") about the degree of cancer-specific worries. Agreement with any statement indicates presence of worry. Only administered to those off treatment.	0.81

5.3.3 Data analysis

The aims and analysis of the current paper were pre-registered on the Open Science Framework (OSF; https://osf.io/gu52d/). The limitations resulting from the data resulted in minor deviations from the pre-registered protocol. The changes and justification are described in Appendix D. The associated code for the analysis is available on the project repository. The analysis was performed in R/R Studio (Team, 2020).

To minimize data loss, we imputed missing values for GAD-7 (6.9%), PHQ-9 (7.3%) and cancer worry (9%). Data were imputed (n = 5) using multiple imputation using chained equation in *mice* package (van Buuren & Groothuis-Oudshoorn, 2011) and pooled using *sjmics* (Lüdecke, 2018). The networks were estimated using the imputed data set. Table 5.3 contains the description of complete and imputed cases. The variables used for the imputation are outlined in Appendix D.

5.3.3.1 Network estimation and graphical representation

To address our aims, we estimated two separate undirected Gaussian graphical models. Networks are composed of nodes that represent the psychological variables and symptoms, which are described in Figure 5.3 and Figure 5.4. The nodes in the network are linked with edges, which represent the partial correlation between two nodes while controlling for all other nodes, thus estimating a covariation that cannot be explained by other nodes in the network (Epskamp & Fried, 2017). We estimated networks using graphical least absolute shrinkage and selection operator (glasso), which limits the sum of absolute partial correlation coefficients that shrinks the edges, and results in a more spurious network that is easier to interpret. This was done by tuning the parameter lambda (λ), which was set at a *qgraph* (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012) default 0.5 (Foygel & Drton, 2010). The selection of λ parameter is guided by Extended Bayesian Information Criterion (EBIC). Minimizing EBIC has been suggested to feature high model specificity (i.e. excluding false positives) (Foygel Barber & Drton, 2015).

The networks were graphically represented using a modified version of the Fruchterman-Reingold algorithm for weighted networks (Epskamp et al., 2012; Fruchterman & Reingold, 1991), which places nodes in an informative way, positioning connected networks close to each other.

5.3.3.2 Node stability estimates

Post-hoc network stability was assessed using bootstrapping method performed using *bootnet* package (Epskamp, Borsboom, & Fried, 2017). Edge weights were assessed using a non-parametric bootstrap, which results in confidence intervals (CI) around the regularized edge weights (Costenbader & Valente, 2003). Statistical significance test is performed on the difference between the different edge weights.

Stability of centrality indices are computed using case-dropping bootstrap, which results in a correlation stability (CS) coefficient, quantifying the proportion of the data that can be dropped to retain 95% certainty. To establish network stability CS coefficient should be at least 0.25, and ideally above 0.5 (Epskamp et al., 2017).

5.3.3.3 Node centrality and predictability

Node centrality refers to the importance of each node in the network and it is based on node strength, betweenness, closeness (Opsahl, Agneessens, & Skvoretz,

2010), and expected influence (Robinaugh, Millner, & Mcnally, 2016). Node strength is the sum of absolute edge weights connected to each node, betweenness refers to how often one node is in the shortest paths between other nodes, and closeness is the inverse sum of distances from one node to all other nodes in the network. Expected influence provides the sum of edge weights, but unlike node strength, it accounts for the negative edges.

Additionally, we report node predictability, which describes the shared variance with the surrounding nodes. The value provides an absolute value of interconnectedness and quantifies the level of influence we can exert on that particular node by intervening on the surrounding nodes (Fried et al., 2018).

5.4 Results

5.4.1 Participants

Between June 2019 and January 2020, 233 (87% female) AYA cancer patients and survivors participated in the study and completed at least 80% of the baseline survey. Of those, 74 were from the Slovenian arm and 159 from the English arm. Slovenian participants were older compared to the English-speaking sample but did not differ on psychological measures. Appendix D contains a detailed comparison between the two samples. Participants' demographic and medical information is presented in Table 5.2. On average, cancer patients were 30.1 (SD = 5.79) years old.

Table 5.2: Demographic and illness information of the total sample.

	N (%)	**M (SD) range**
Gender		
Male	27 (12)	
Female	204 (87)	
Other	2 (1)	
Age at study		30.1 (5.79) [18 –
18 – 30 years	39]	
31 – 39 years	110 (47)	
	123 (53)	
Age at diagnosis		25.3 (7.53) [10 –
10 – 20 years	39]	
21 – 30 years	71 (30)	
31 – 39 years	90 (39)	
	72 (31)	
Treatment status (months)		
On treatment	73 (31)	
Off treatment	160 (69)	50.8 (58.6) [1 – 282]
< 1 year	50 (31)	
1 – 5 years	66 (41)	

>6 years	44 (28%)
Relationship Status	
Single	73 (31)
In a relationship	62 (27)
Married/Cohabiting	89 (38)
Separated/Divorced	9 (4)
Children	
Yes	68 (29)
No	165 (71)
Education	
Elementary school	2 (1)
High school/higher degree below university	90 (39)
Bachelor's	82 (35)
Master's	44 (19)
PhD/Doctorate	10 (4)
Prefer not to answer	5 (2)
Cancer type	
Hematologic cancers	79 (34)
Breast	50 (22)
Sarcomas	29 (12)
CNS	19 (8)
Reproductive organs	18 (8)
Colorectal cancers	13 (6)
Thyroid	8 (3)
Melanoma	5 (2)
Testicular	4 (2)
Head and neck	4 (2)
Other	4 (2)
Multiple cancers	
Yes	5 (2)
No	228 (98)
Metastasis	
Yes	68 (29)
No	142 (61)
Don't know	23 (10)
Relapse*	
Yes	23 (12)
No	168 (88)
Treatment type	
Chemotherapy alone	33 (14)
Chemotherapy and radiotherapy	17 (7)
Surgery alone	11 (5)
Surgery and chemotherapy	38 (16)
Surgery and radiotherapy	11 (5)
Surgery, radiotherapy and chemotherapy	46 (20)
Other	77 (33)
Self-reported mental Health diagnosis	
Yes	77 (33)
Diagnosed after cancer	40/77 (52)
No	152 (65)
Prefer not to answer	4 (2)

NOTE: *Only those off-treatment responded about relapse (n=191)

5.4.2 Psychological functioning

Descriptive statistics of the means and SD for the psychological measures are reported in Table 5.3. We estimated networks on the imputed dataset. Figure 5.2 shows the prevalence of specific cancer worries. Level of worries ranged from 43% (thinking about cancer every day) to 81% worrying about cancer relapse.

Table 5.3: Descriptive statistics on the measures of psychological functioning.

	Complete cases **N mean (SD) [range]**	**Imputed cases (*N*=233)** **mean (SD) [range]**
Anxiety Proportion clinical range, N (%) *In treatment* *Off treatment*	N=217 8.14 (5.31) [0-21] 124 (57%) *44/124 (35%)* *80/124 (65%)*	 8.15 (5.15) [0-21] 137 (59%) *47/137 (34%)* *90/137 (66%)*
Depression Proportion clinical range, N (%) *In treatment* *Off treatment*	N=216 8.57 (6.34) [0-27] 82 (38%) *31/82 (38%)* *51/82 (62%)*	 8.64 (6.18) [0-27] 92 (39%) *33/92 (36%)* *59/92 (64%)*
Cancer worry*	149 11.2 (4.15) [0-18]	N=160 11.2 (4.04) [0-18]

NOTE: Clinical range for anxiety is defined as ≥ 7 and ≥ 10 for GAD-7 and PHQ-9, respectively. Clinical levels of anxiety and depression were present in 36% [84 out of 233].
*only administered to those off treatment.

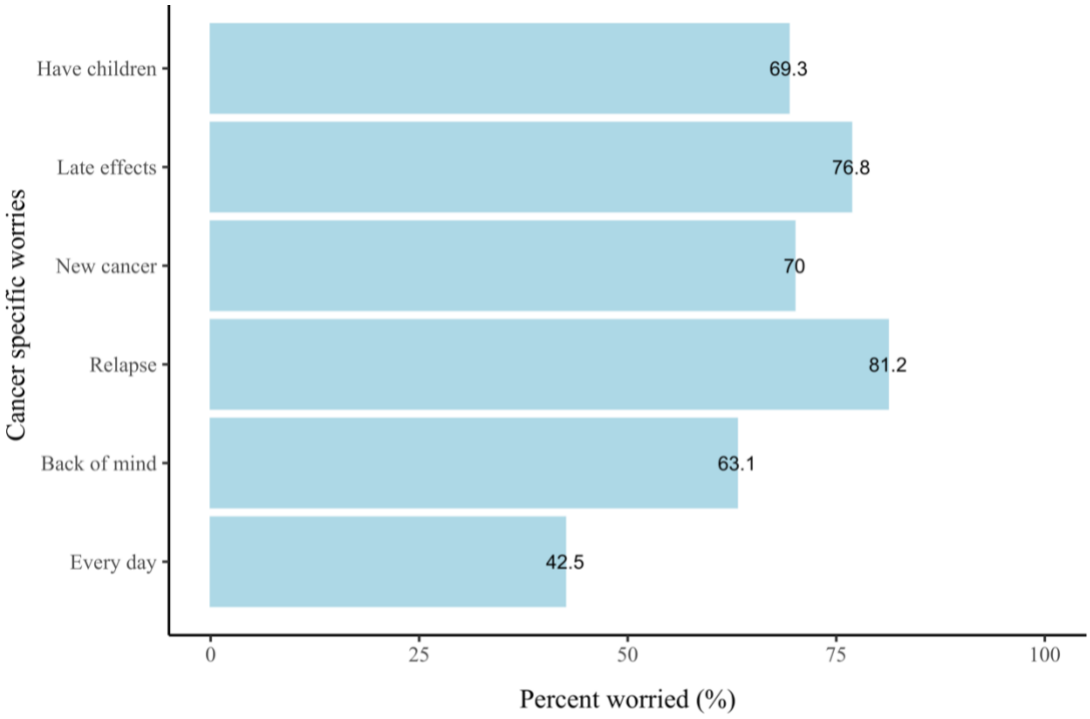


Figure 5.2: Prevalence of specific cancer worries.
NOTE: Worry was marked as present if individuals responded to an item with "agree" or "strongly agree." Description of the items: Have children = worry about having children in the future; Late effects = worry about experiencing late effects related to treatment; New cancer = worry about receiving a new cancer diagnosis; Relapse = worry about their cancer coming back; Back of mind = cancer being always at the back of their mind; Every day = worry about cancer every day.

5.4.3 Psychological networks

We estimated 2 separate networks. Figure 5.3 (**A**) shows the items of anxiety and depression, and Figure 5.4 (**B**) shows items of anxiety, depression and cancer worry in the subset of cancer survivors who were off treatment at the time of the study. Both networks reached acceptable stability, 0.52 and 0.36, respectively Network 1 was estimated using Spearman correlation instead of polychoric correlations (Epskamp et al., 2017).

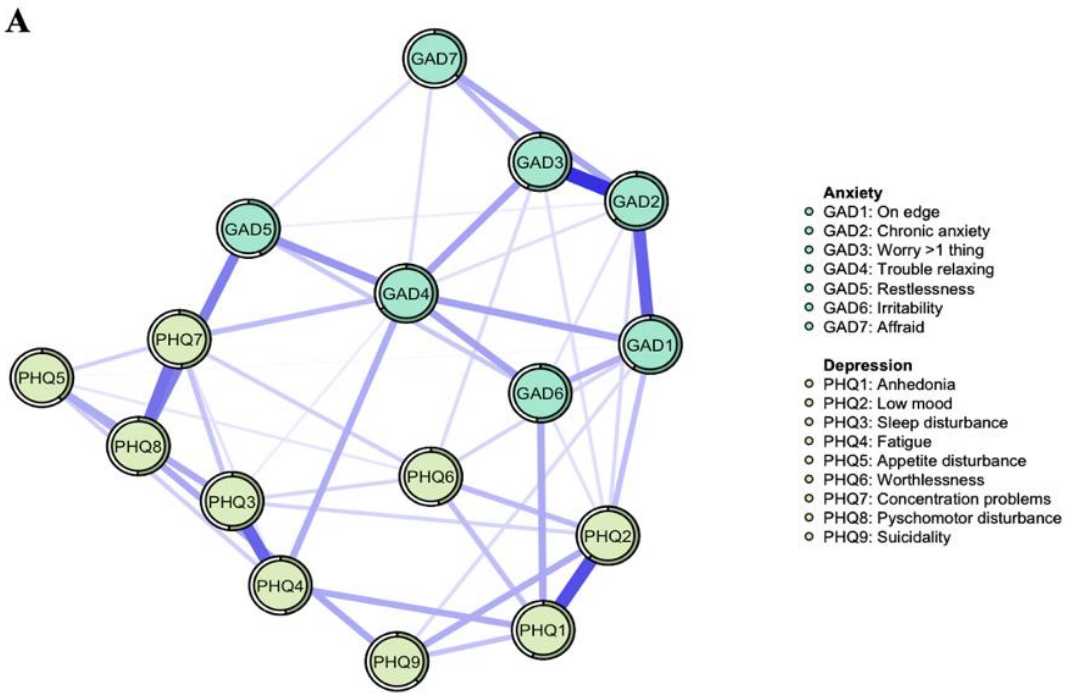


Figure 5.3: Psychological network of depression and anxiety (N = 233).
NOTE: The figure shows a network of anxiety and depression symptoms estimated on the entire sample of patients and survivors (*N*=233). Edges between nodes represent partial correlations between items, controlling for all other items in the network. The thicker the edge between the two nodes, the stronger the connection between those two items. All edges are blue, which correspond to positive connections. Each node is an item from the questionnaire, and their colors correspond to the construct measured, as described in the figure legend. The pie chart around each node corresponds to the level of predictability of that particular node. The network is graphically represented using Fruchterman–Reingold algorithm, which places more strongly connected nodes closer together.

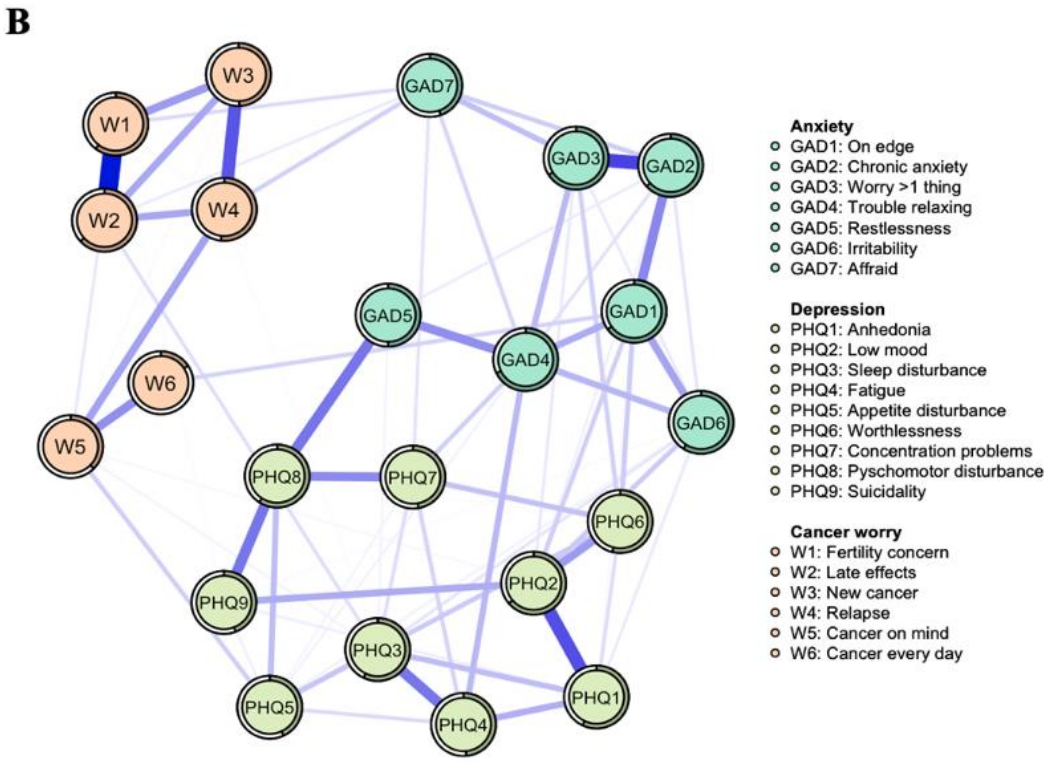


Figure 5.4: Psychological network of depression, anxiety, and cancer worry.
NOTE: The figure shows a network of anxiety, depression, and cancer specific worries on a subsample of survivors (*N*=160). Edges between nodes represent partial correlations between items, controlling for all other items in the network. The thicker the edge between the two nodes, the stronger the connection between those two items. All edges are blue, which correspond to positive connections. Each node is an item from the questionnaire, and their colors correspond to the construct measured, as described in the figure legend. The pie chart around each node corresponds to the level of predictability of that particular node. The network is graphically represented using Fruchterman–Reingold algorithm, which places more strongly connected nodes closer together.

Network 1 (Figure 5.3 (**A**)) showed the strongest relationships between GAD2 and (GAD3), PHQ1 and PHQ2, as well as PHQ3 and PHQ4. The symptoms of depression and anxiety form two relatively distinguished clusters. Item *restlessness (GAD5)* from anxiety cluster exhibits the strongest connection to *psychomotor disturbance (PHQ8)* in depression cluster.

Network 2 (Figure 5.4 (**B**)) which included cancer-specific worry items was estimated on a smaller sample (those off treatment only, *N* = 160), but nevertheless showed acceptable stability. Adding six items of worry did not alter the network significantly, and all of the worry items clustered on periphery, suggesting that cancer-specific worry is a separate construct. The relationship between worry about late effects and fertility issues showed the strongest connection. Strong connection was observed

also between the worry about a *new cancer diagnosis* and *cancer relapse*. These worries have received ample attention in the literature (Simard et al., 2013) and are common among AYA survivors in our sample, ranging from 70 to 82.2%, respectively (see Figure 5.2).

Two items, namely *having cancer on one's mind*, and *thinking about cancer every day*, were fairly poorly connected, which was confirmed with low predictability scores (0.37, 0.16, respectively). This suggests that the 2 nodes are largely conditionally independent from other nodes in the network. One plausible explanation is that these 2 items fit poorly with the scale that otherwise describes specific cancer worries. Another possible explanation is the floor effect, and because of the low parameters, the node shares few connections with other nodes.

Despite the fact that the network of anxiety and depressive symptoms didn't change, and that we found no strong relationship between any cancer specific worry and a specific symptom of depression and anxiety, we observed that adding cancer worry to the network, raised predictability of all nodes. Overall, average node predictability was 0.50 and 0.53 for network 1 and 2, respectively. This suggests that most nodes are well-explained by the surrounding nodes, with *worrying about more than 1 thing (GAD3), low mood* (*PHQ2)* and *late effects (W2)* having over 60% of variance explained by the surrounding nodes. Appendix E contains complete table and information on node predictability.

Considering the expected influence of nodes, we observe that *trouble relaxing (GAD4)* and *low mood (PHQ2)* have the highest values (see Figure 5.5). This suggests that they share the strongest connections within the networks and may be most influential or influenced by the surrounding nodes.

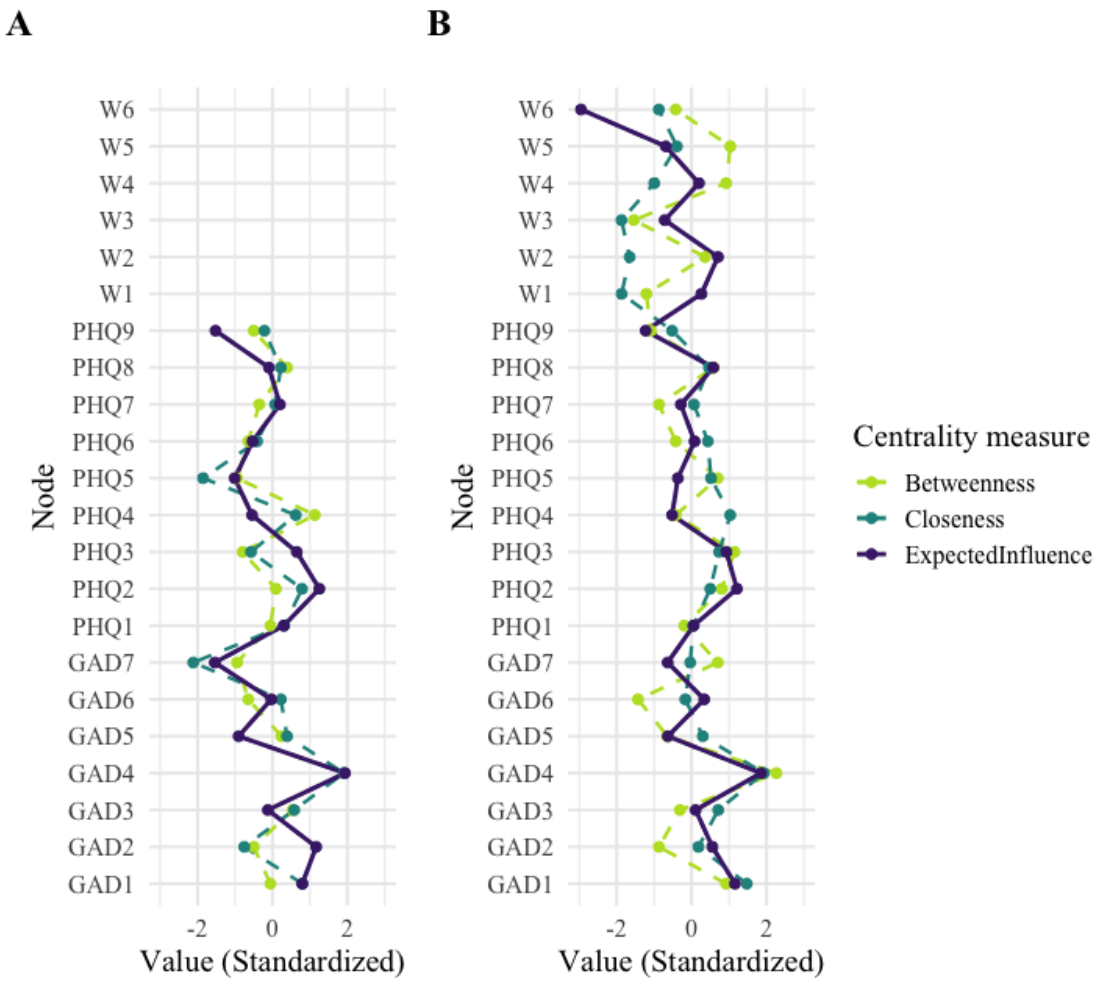


Figure 5.5: Centrality indices.
NOTE: **Panel A** shows centrality indices for the psychological network 1. Cancer-specific worries were not included in the network, therefore the values from *W1-W6* are empty cells. This network was estimated on the entire sample (*N* = 233). **Panel B** shows centrality indices for the psychological network 2, which was estimated on the subset of individuals off treatment (*N* = 160). Node abbreviations on y-axis are detailed in Figure 5.4. X-axes represent standardized z-scores. In particular we highlight expected influence of each node, which is the sum of edge weights. In our example it equals to node strength due to absence of any negative edges. The complete table with the exact z-scores for each node can be found in Appendix E.

5.5 Discussion

In the first study to use a network approach to studying psychological wellbeing in AYAs with cancer, we aimed to investigate the interconnectedness of depression and anxiety symptoms as well as cancer-specific worries by estimating two separate networks. The first included symptoms of depression and anxiety across the entire sample, and the second network included cancer-specific worry in addition to symptoms of depression and anxiety across the subset of participants who were off-treatment.

Both networks in our study showed uniformly positive connections between all nodes within the network (see Figure 5.3 and Figure 5.4). This homogeneity is not surprising when considering symptoms of psychopathology, and especially due to high levels of comorbidity between anxiety and depression (T. A. Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Hirschfeld, 2001). Our results show a high level of covariance between symptoms of anxiety, depression and cancer worry. However, we suggest that this may be due to direct interactions between the observed symptoms rather than a common latent cause. For example, compromised fertility is in fact one of the most common and relevant late effects of cancer treatment. It is plausible that the strong correlation between the two items stems from the fact that if one is worried about late effects, they will also worry about fertility. Fertility is also the most central node among cancer worries, a finding that may in part be attributable to our sample being primarily female (87%), although literature suggests that both men and women affected by cancer report preoccupation about fertility (Carpentier & Fortenberry, 2010; Nahata et al., 2018; Ruggeri et al., 2019). Further consistent with the existing literature, we demonstrated that FCR is common among survivors (Simard et al., 2013; Thewes et al., 2018), and worry about relapse, and of new cancer are strongly connected. However, despite previous findings which suggest that fear of cancer recurrence is positively associated with psychopathology (Simard et al., 2013), we found no strong connections between any specific cancer worry and symptoms of depression and anxiety.

An interesting feature of our networks is the presence of the most central node, namely *trouble relaxing (GAD4)*. Its predictability was also the highest, increasing from 0.66 to 0.68 in network 2, when cancer worry was included. This suggest that 66% or 68% of variance in trouble relaxing may be explained by the surrounding nodes. Although we cannot conclude if *trouble relaxing* is a cause or an effect, this finding illuminates previously overlooked aspect of anxiety in AYA with cancer. We discuss the potential clinical implication of this finding below.

Additionally, fatigue is a commonly discussed effect among AYA cancer populations and can contribute to lower quality of life and poorer psychological functioning (Nowe et al., 2017; Hanneke Poort et al., 2017). Unlike in a network analysis of adult cancer survivors, where fatigue was more centrally embedded (Schellekens et al., 2019), we observed *fatigue (PHQ4)* on the periphery (see Figure 5.3 and Figure 5.4). This difference may be sample specific or could have resulted from

the measurement differences. Unlike the work by Schellekens et al. (Schellekens et al., 2019), in our study, fatigue was assessed by a single item from the PHQ-9. Positive relationships between fatigue and sleep problems have been observed before, and associated with psychological distress (L. Daniel et al., 2016; Roscoe et al., 2007). Unsurprisingly, we found that fatigue was strongly connected to sleep problems (see Figure 5.3), which indicates that the two symptoms may be causally linked. However, fatigue did not appear central to our networks and had lower predictability than other nodes (see Appendix E).

Previously, network analysis has been applied in adult cancer populations to explore fatigue and psychopathology (Schellekens et al., 2019), quality of life (Kossakowski, Epskamp, & Kieffer, 2016), death anxiety (Vehling et al., 2017) and continues to show promise in understanding and studying psychopathology in this population of patients. Because psychological adaptation to a chronic illness is a complex process involving mental and physical health (Cramer et al., 2012; De Jonge et al., 2006; Keller et al., 2007), and because young people present with different needs and challenges than adults (e.g. more worry about fertility), exploring the interconnectedness of symptoms is a crucial first step to understanding the etiology of psychopathology in AYAs with cancer. Studies continue to demonstrate inequality in psychosocial outcomes of AYA cancer patients and survivors and a novel approach such as network analysis may help us to overcome the current limitations in the study of mental health in AYA with cancer.

Strengths and limitations

Several limitations of our study are important to note. We recruited a small and highly heterogeneous sample. However, we nevertheless obtained 2 stable networks. Because only 13% of our participants were men the findings may be more generalizable to female populations. Due to the low numbers, and vastly different sizes between groups, we could not make any meaningful comparisons between networks estimated on each subset of the sample (male vs. female or in vs. off-treatment). We wanted to prevent inflation of cancer-specific worry and only administered the questionnaire to those off-treatment. Future studies might want to consider the level of preoccupation with cancer-specific thoughts (late effects, fertility) in individuals who are still undergoing treatment. Moreover, due to the disruption caused by COVID-19, we were only able to estimate cross-sectional networks on data that were collected prior to the

pandemic. This precludes us from making any assumptions of causality or changes over time.

Additionally, one of the assumptions in network modeling is that symptoms (nodes) represent distinct processes. High correlation between some items on the scales may also result from conceptual overlap. For example, *being on edge (GAD1)* and *trouble relaxing (GAD4)* may result from a common cause, and thus show an inflated association. This topological overlap has been noted before (E. E. Bernstein, Heeren, & McNally, 2019; Levinson et al., 2018), and analytical tools have been developed to address it (Jones, 2018). Future analyses in AYAs with cancer could consider condensing items.

Despite the many limitations, our findings illuminate previously unexplored relationships between psychopathological symptoms and cancer-related concerns in AYAs with cancer and highlight several areas for subsequent research relying on network analysis and implications for treatment.

Clinical and future research implications

From a psychometric point of view, we found that the structure of anxiety, depression, and cancer-worry remained relatively stable and robust, which supports the validity of the scales we used. However, our findings also offer insights for intervention approaches. The underlying premise in network analysis that symptoms causally relate to one another, and some symptoms are more central than others (Borsboom & Cramer, 2013), suggests that by targeting the most central symptom within the network could alleviate the overall burden of endorsed symptoms or worries.

Although psychological interventions for AYAs with cancer exist, their effectiveness has been limited (Bradford & Chan, 2017; Phillips & Davis, 2015). Rather than employing a one-size-fits-all approach, interventions may instead target the most central symptoms, which are most likely to have an impact on the entire network. In our sample, the most central and predictable symptom was *trouble relaxing*, which may be easier to address than other symptoms such as worthlessness. Promoting relaxation may alleviate a significant level of the surrounding symptoms, and subsequently lead to lower level of anxiety, or render other concerns more manageable. Relaxation techniques, including meditation (targeting trouble relaxing), have been shown to reduce depression and anxiety (Campo et al., 2017; Jorm, Morgan, & Hetrick, 2008; Manzoni, Pagnini, Castelnuovo, & Molinari, 2008), which remain prevalent concerns

among AYA cancer patents and survivors (Košir, Loades, et al., 2020; McDonnell et al., 2017).

Though we cannot establish causal relationships in our networks, longitudinal studies with larger samples could investigate the interconnectedness of anxiety and depression symptoms, as well as cancer worries. Moreover, our networks show how symptoms are interrelated on average, it may be that individual profiles of psychopathology vary as well. A method that will allow exploration of psychological profiles using network theory is network trees. The recently published method (Jones, Mair, Simon, & Zeileis, 2020) allows for statistical comparison of networks by demographic or other covarying factors and offers exciting possibilities for future studies.

Psychological adaptation remains a complex construct, and network analysis might help us to reconceptualize mental health in AYA with cancer, as well as promote new avenues for research and intervention approaches.

5.6 Contribution to this thesis

Building on the idea of moving beyond the latent constructs of psychopathology presented in the previous chapter (Chapter 4), this chapter also addresses **RQ1** and **RQ3** of my doctoral thesis.

Psychological adaptation to cancer is a complex construct and there are many factors and symptoms that play a role and interact to produce psychosocial outcomes. The network approach allows for an exploration of these intricate systems of symptoms and factors. The findings provide preliminary evidence to show that trouble relaxing and low mood may be the driving symptoms of poorer psychological functioning in AYAs. Targeting these specific symptoms may help alleviate the overall level of distress.

The following chapter extends the online survey to assess the impact of the COVID-19 pandemic, which disrupted the data collection for the present study.

Chapter 6 - Global pandemic COVID-19: Disruptions and impact on psychological functioning of young people with cancer*

6.1 Abstract

Objective: The global COVID-19 pandemic and its disruptions carry important implications for young patients. We wanted to understand the impact of COVID-19 pandemic on young people living with and beyond cancer in the initial phases of the pandemic.

Method: This was a cross-sectional study in which we surveyed 177 cancer patients and survivors, aged 18 – 39 years. Participants were asked about the impact of COVID-19 on their cancer care and psychological wellbeing. Participants also reported their information needs relating to COVID-19. Short qualitative responses were summarized using content analysis approach.

Results: Data were collected during the first weeks of the COVID-19 pandemic (from early April through early May 2020). Close to a third of our respondents reported clinical levels of psychological distress, and 60% reported feeling more anxious than they did prior to COVID-19. More than half also wanted information tailored to them as young cancer patients and survivors.

Conclusions: Young people living with and beyond cancer might be more vulnerable during a pandemic compared to their healthy peers. There is a need to screen for psychological distress and attend to young people whose cancer care has been delayed or disrupted. In the times ahead, any changes in cancer protocols should be updated according to this population's needs.

* Chapter adapted from:

Košir, U., Loades, M., Wild, K., Wiedemann, M., Krajnc, A., Roškar, S., Bowes, L. (2020). What was the impact of COVID-19 on Adolescent and Young Adult cancer care and their wellbeing? Results from an online survey conducted in the early stages of the pandemic. *Cancer*. https://doi.org/10.1002/cncr.33098

6.2 Introduction

The objective of this chapter was to respond to the sudden and unexpected turn of events associated with the COVID-19 outbreak. We wanted to understand the psycho-social impact of the pandemic on young people living with and beyond cancer.

COVID-19 was first identified in China, in December 2019 (Lu, Stratton, & Tang, 2020) and is an infectious disease caused by the novel SARS-CoV-2 virus (WHO, 2020). In most patients, COVID-19 infection results in mild symptoms such as a fever and a dry cough, but in some cases, and particularly in those with underlying health conditions and those who are immune compromised, COVID-19 can be more severe and can result in serious complications such as Acute Respiratory Distress Syndrome or even death (Rothan & Byrareddy, 2020). To date, findings suggest that COVID-19 poses little threat to children and young people (Chen et al., 2020), however, cancer patients and survivors may be a vulnerable population. Individuals undergoing active treatment or taking immunosuppressive medication are known to be at higher risk for viral infections (Kamboj & Sepkowitz, 2009), while those in survivorship might experience distress due to changes in their follow-up care. Most young people living beyond cancer worry about cancer recurrence (Koch, Jansen, Brenner, & Arndt, 2013; Kosir et al., 2019a) and resultantly the disrupted follow-up care, which includes physical exams and screening may lead to heightened anxiety. As such, adolescent and young adult (AYA) cancer patients and survivors remain a group with unique needs during a pandemic outbreak like the current COVID-19, even though the relative risk of infection and mortality for this population have not yet been established at the time of writing this chapter.

In response to the global spread of the novel SARS-CoV-2, oncology departments quickly acted and adapted measures and protocols for cancer care. Most centers sought to balance the risk of delaying cancer treatment with that of exposing a vulnerable cancer patient to the virus, which resulted in a crucial reprioritization; the most essential and necessary treatments remained on schedule, while early preventative screenings, follow-up appointments, and non-essential surgeries were often delayed (Dinmohamed et al., 2020).These changes were made rapidly and the newly devised guidelines were operationalized with increased survival in mind, and in hopes to render the oncology centers ‘pandemic proof’ (D. Schrag, Hershman, & Basch, 2020; van de Haar et al., 2020). While taking such measures is necessary for successful infection

control, the subsequent steps will have to involve consideration of the psychological impact of COVID-19 and related changes on cancer patients, survivors, and their families.

Even though the scientific, as well as patient support communities were quick to recognize the need to provide information about COVID-19 to cancer patients (Nekhlyudov et al., 2020), the sudden increase and a plethora of resources available was not necessarily tailored to AYA patients' and survivors' needs. We do not know if the information available is adequate, and if AYAs living with or beyond cancer feel confident about making sense of and applying it.

As after any major global disaster, the COVID-19 pandemic is also likely to result in increased mental health symptomatology (Galea, Merchant, & Lurie, 2020; Holmes et al., 2020). Considering that a subset of AYA cancer patients experiences significant levels of psychological distress even under normal circumstances (Barnett et al., 2016; Kosir et al., 2019b), it is important to recognize that worries associated with the pandemic, and any delays in life-saving treatments are likely to contribute to the anxiety in this population. Furthermore, the social distancing measures imposed to contain the spread of the infection may have unintended consequences for mental health via changes in social support, economic consequences and changes to daily routines (Brooks et al., 2020). In AYAs who are already vulnerable to experiencing distress, this may further compound their anxiety. To ensure that the needs of AYAs continue to be met during and after the COVID-19 outbreak, developing new strategies that will help manage, and attenuate worries about the COVID-19 exposure should be a priority. This effectively requires an understanding of what the needs of AYAs are in this unprecedented context.

In order to adapt and better prepare for any future outbreaks, it is important to understand the impact of the novel SARS-CoV-2 on AYAs cancer care and their wellbeing. The aim of this study was 1) to gather initial evidence of the impact of COVID-19 on AYA cancer patients' and survivors' psychological well-being and cancer care, and 2) to understand where they received the information about the pandemic and how satisfied they were with the resources on COVID-19.

In order to provide the readership with context, Figure 6.1 provides an overview with all the relevant dates and facts known at the time of writing this article (May 12, 2020).

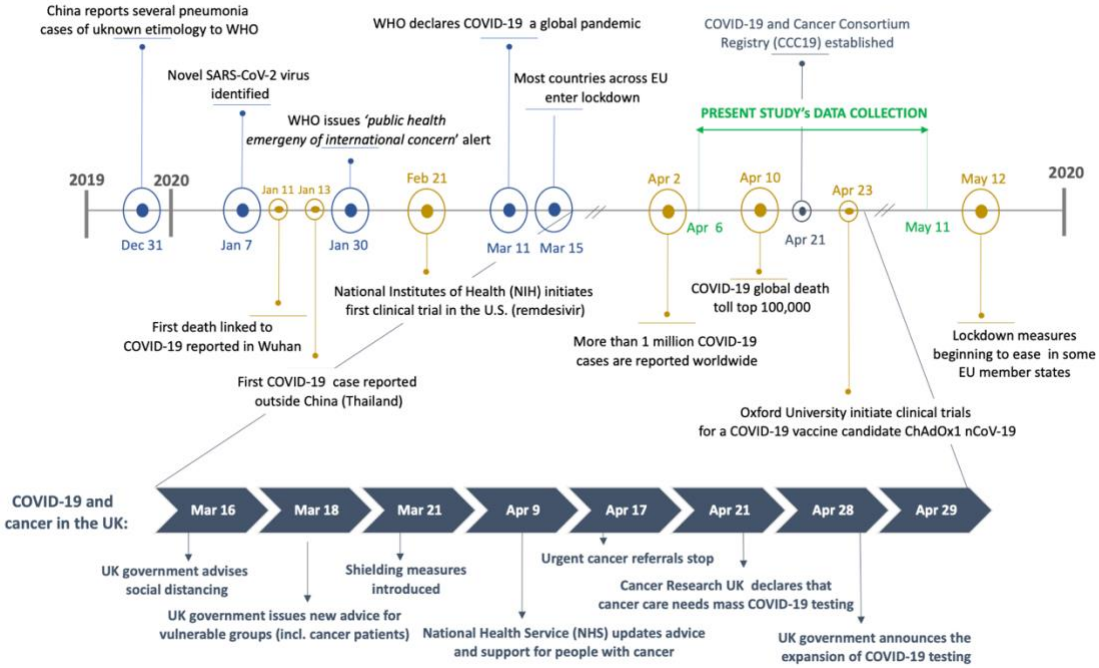


Figure 6.1: Global and UK COVID-19 context at the time of this study.
NOTE: This figure aimed at providing future readership with COVID-19 context at the time of writing (May 12, 2020). By mid-March, most countries across Europe began nation-wide lockdowns. At the beginning of April, most cancer centers began adapting their treatment protocols. By late April COVID-19 a Cancer Consortium Registry was established with currently over 100 participating institutions globally reporting results about COVID-19 outcomes in cancer patients. There are currently several vaccine trials which have already began testing in healthy human participants.

6.3 Method

6.3.1 Design and sample

This cross-sectional survey was an extension of my online study exploring the predictors of psychological well-being and holistic recovery in AYA cancer patients (see Chapter 5). This study has been approved by the Medical Sciences Inter-Divisional Research Ethics Committee at the University of Oxford (R61437/RE005).

Data were collected using Qualtrics (Qualtrics, 2020), a secure online survey software, via an anonymous link distributed on social media outlets and online via patient organizations' web posts or newsletters. Participants were provided brief information about the study, eligibility criteria, and the current aims; understanding what was the COVID-19 impact on their cancer care and wellbeing. The survey had two equal arms: a Slovenian and an English arm, accessible to anyone who was able to read and respond in English. Participants were all cancer patients or survivors aged between 18 and 39 years, diagnosed with any form of malignant cancer at age 10 or later.

6.3.2 Measures and survey description

6.3.2.1 Demographic and Medical information

Participants reported their age, gender, geographical region, and current living arrangement. They also reported their current health status, treatment status, whether or not they had a pre-existing mental health condition or other chronic illness, or if they were taking any immunosuppressant medication (i.e. steroids).

6.3.2.2 Psychological distress

Psychological distress was measured using the Patient Health Questionnaire for Depression and Anxiety (PHQ-4), a 4-item measure of the frequency of two anxiety and two depressive symptoms on a 4-point Likert scale from 0 (not at all) to 3 (nearly every day). Reliability and validity of the brief PHQ-4 scale have been established in general and clinical populations, and a score of 3 or above on either sub-scale, and a total score of 6 or above is indicative of clinically relevant distress (Kroenke, Spitzer, Williams, & Löwe, 2009; Löwe et al., 2010). Cronbach's α for PHQ-4 in our study was 0.84, and 0.83 and 0.78 for anxiety and depression subscales, respectively.

6.3.2.3 COVID-19: impact on care and information resources

Respondents self-reported if and how the pandemic related events disrupted their cancer treatment and care, what the pandemic impact was on their psychological well-being, where they received the information about the novel SARS-CoV-2, and how satisfied they were with the information available on a scale from 0 (least satisfied/trustworthy) to 10 (most satisfied/trustworthy). Some of the questions can be seen in Appendix E, and the complete details of the survey can be online viewed online at https://osf.io/ncpv8/.

6.3.3 Analysis

Survey data were analyzed in an exploratory and descriptive manner in order to provide preliminary evidence of the impact of the COVID-19 pandemic on the subjective well-being of cancer patients.

Qualitative responses were analyzed using content analysis approach (Krippendorf, 2018). The approach has been described as suitable for mixed method

research, allowing for a more positivistic approach to analysis and phenomena description (Elo et al., 2014). I independently read and coded all of the responses to open-ended questions about COVID-19 impact on cancer patients and caretakers' psychological well-being. With the help of two colleagues, the rest of the responses were coded, both deductively by organizing them around the present study aims and survey questions, as well as inductively by devising a list of categories to describe impact on cancer care and the most common worries from participants' descriptions. The formulated categories were refined and operationalized into a coherent list upon which all qualitative responses were mapped. The inter-rater reliability for this procedure was 96%. Lastly, the classification of responses was checked by another colleague, and discrepancies were resolved through a discussion. All illustrative quotes in this chapter are from different participants.

6.4 Results

6.4.1 Participants

During the period between April 6 and May 12, 2020, 177 AYA cancer patients and survivors participated in the study and completed at least 80% of the survey. Of those, 39 were from the Slovenian arm and 138 from the English arm. Participants' demographic and medical information is presented in Table 6.1. On average, cancer patients were 29.33 (*SD* = 6.17) years old. A third [57 out of 177] of responders were in active treatment at the time of the study, 14% [24 out of 177] completed treatment within the previous 6 months, and 54% [96 out of 177] completed their cancer treatment more than 6 months ago. Of the latter, 14 (15%) individuals were still taking immunosuppressive medication.

Table 6.1: Demographic and medical information of the participants (*N* = 177).

Variable	**Value**
Age, mean (SD) [range]	29.33 (6.17) [18 – 39]
Sex, N (%)	
Female	154 (87)
Male	20 (11)
Prefer not to answer	3(2)
Region, N (%)	
North America	93 (53)
Central and South America	2 (1)
Europe	78 (44)
Middle East	1 (1)
Asia	1 (1)
Oceania	3 (2)
Living arrangement, N (%)	
Alone	24 (14)
Shared house	13 (7)
Partner only	45 (25)
Parents	20 (11)
Family	72 (41)
Other	4 (2)
Treatment status, N (%)	
Undergoing treatment	57 (32)
Completed within 6 mo	24 (14)
Completed more than 6 mo ago	96 (54)
Immunosuppressant medication, N (%)	
Yes	41 (23)
No	122 (69)
Prefer not to answer	14 (8)
Mental health diagnosis, N (%)	
Yes	66 (37)
No	108 (61)
Prefer not to answer	3 (2)

NOTE: mo = months.

6.4.2 COVID-19 impact on cancer care

Forty-five percent [79 out of 177] of AYA cancer patients reported that COVID-19 had an impact on their cancer treatment or care, and 21% [38 out of 177] reported no impact at the time, but worried that there might be.

According to the short answers, the analyses revealed six categories of most commonly reported changes in cancer care. These categories were: follow-up appointments being postponed or cancelled, appointments carried out over the phone or virtually, cancer treatment and/or surgery being postponed, having to be alone during the treatment, reduced access to medicine, and changes in treatment protocols, such as reduced blood-work or oral instead of intravenous chemotherapy.

6.4.3 COVID-19 impact on psychological well-being

Over a third of AYA participant scored in the clinical range for psychological distress. Individuals undergoing treatment or within 6 months of treatment completion, on average, reported higher levels of psychological distress. Symptoms of anxiety were more common than depressive symptomatology. The mean scores and proportions of participants scoring in the clinical range of psychological distress are reported in Table 6.2.

Additionally, participants were asked how they felt compared to before the pandemic. Sixty-two percent [109 out of 177] of respondents reported feeling more anxious than before, 34% [52 out of 177] reported feeling the same, and 9% [16 out of 177] reported feeling less anxious than before. The proportion of individuals feeling more anxious was the same for those currently in treatment, as well as those who have completed treatment over 6 months ago (see Appendix F for complete breakdown).

Table 6.2: Psychological distress among adolescents and young adults.

		Mean (SD)		
	N	**Anxiety**	**Depression**	**Total**
Total sample	177	2.61 (1.94)	1.92 (1.71)	4.53 (3.29)
Undergoing treatment	57	2.84 (1.89)	2.07 (1.69)	4.91 (3.22)
Completed within 6 mo	24	3.54 (2.02)	2.29 (1.90)	5.83 (3.60)
Completed more than 6 mo ago	96	2.24 (1.87)	1.73 (1.66)	3.97 (3.15)
		N (%)		
	N	**Anxiety**	**Depression**	**Total**
Total sample	177	56 (32%)	34 (19%)	51 (29%)
Undergoing treatment	57	20 (35%)	10 (18%)	17 (30%)
Completed within 6 mo	24	12 (50%)	6 (25%)	12 (50%)
Completed more than 6 mo ago	96	24 (25%)	18 (19%)	22 (23%)

NOTE: *PHQ-4* = Patient Health Questionnaire. PHQ-4 items are rated on a 4-point Likert scale ranging from 0 to 3. The upper half of the table contains means and *SD* (standard deviation), while the bottom half contains number and proportion of individuals scoring in the clinical range. *mo* = months.

The short responses revealed that the most common concerns among the AYAs related to COVID-19 and their health status were not being sure how big of a risk COVID-19 posed for them, how their body would react to the infection, anxiety about experiencing serious complications if they were to catch the virus, and having their cancer care delayed. Figure 6.2 depicts the worries and impact of COVID-19 on their psychological wellbeing as reported by the AYA participants in their short answers.

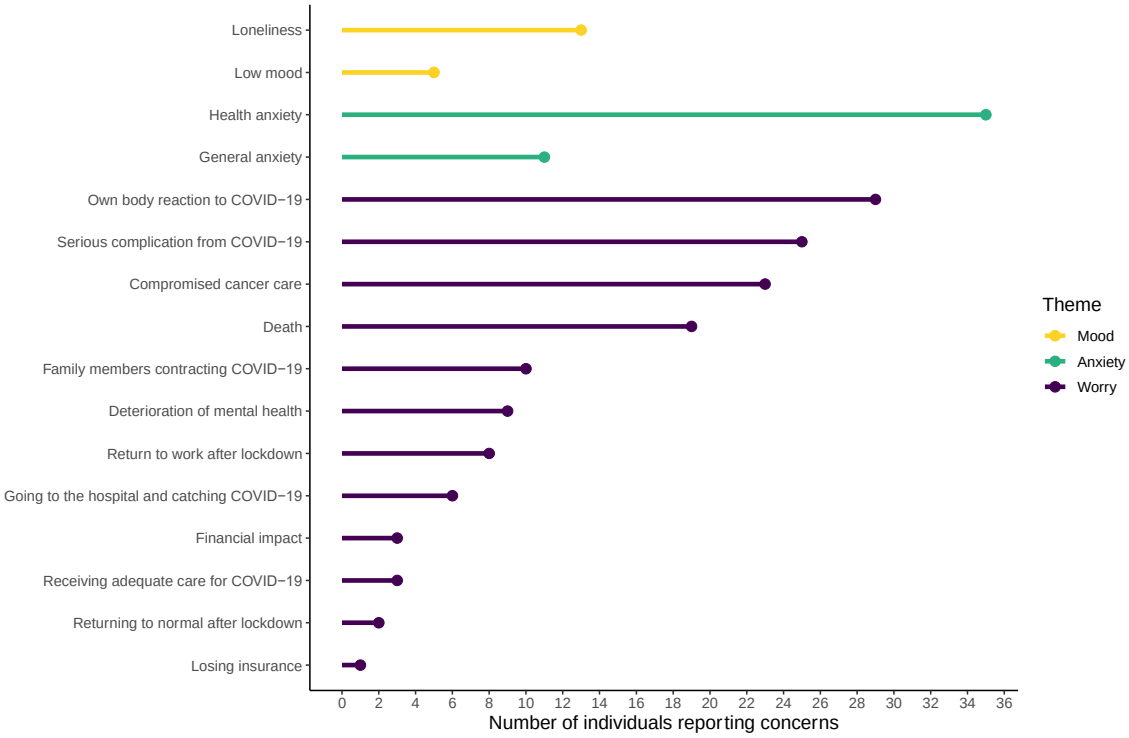


Figure 6.2: Impact of COVID-19 on psychological wellbeing.
NOTE: This figure summarizes qualitative responses on impact of COVID-19 on individuals' psychological wellbeing. Three overarching themes emerged: low mood, anxiety, and worries. The values on the x-axis show the number of individuals reporting a specific concern. Anxiety and worries were more common than low mood, which is also reflected in the PHQ scores. Several individuals spoke broadly about feeling more anxious, others reported their feelings of anxiety being linked to health – their own health, and the magnitude of COVID-19 risk for them. The majority of individuals who reported feeling anxious talked about specific worries, which are listed in the ascending order. Some individuals listed more than one concern.

However, individuals also reported impact on mood, as well as worries about their family members, returning to "the normal" and finances. The categories and examples of participants' responses can be viewed in Table 6.3.

Table 6.3: Categories devied from content analysis.

Category	Definition	Example
General anxiety	Broad statements and descriptions of anxiety and worries that are not specified or described in detail	*"My anxiety levels tend to be quite high. I had felt like I had my anxiety under control, but this situation has thrown me off."*
Health anxiety	Broad statements about worries of own health, hypochondria, includes concerns about individuals' mental health and illness triggers	*"I worry that my current health problems will not be taken as seriously in the healthcare system as they were before."*
Loneliness	Mentions of lacking support, feeling low and sad due to isolation, feelings of loneliness	*"Whereas I was isolated prior to the global lockdown, I was still able to have the physical support of my family given that they were healthy. I have now lost that, making navigating cancer treatment all the more lonely."*
Low mood	Broader descriptions of low mood or morale, depression	*"Increased feelings of depression and overeating."*
Disruptions	Refers to the impact on mental health and wellbeing due to disruptions in daily living and activities	*"My biggest source of happiness was my job and not being able to see my students is heartbreaking."*
Death/dying	Explicit mentions about dying and mortality	*"I am constantly worried that if I fall sick, I will end up dying considering my cancer history and weak immune system."*
Worry about COVID-19 – self	Worries about how one's body would react to COVID-19, worries about severe complications due to COVID-19, including worries about receiving adequate care if they contracted COVID-19	*"I am worried that if I caught it, I would be one of the ones that do not do well as I have had radiation to my spleen and still have low lymphocytes."*
Worry about COVID-19 – others	Worries about close individuals or family members contracting the virus	*"Mostly worried about family/elder members of the family wanting to get outside more."*
Cancer care	Changes and disruptions in cancer care, which are unfavorable; worry about	*"I worry about what stage my cancer will be when they*

	continuing with care and going to the hospital where many people are infected	*are finally able to do my surgery/treatment."*
Return to normal	Concerns about how to return to normal, what normal will look like; worries about returning back to work	*"Going back to work eventually stresses me."*
Finance	Direct financial impact from job loss or disruption; loss of insurance	*"I have lost my job, risk losing my insurance, and will be in active treatment until late summer."*

Moreover, physical distancing measures imposed by many authorities resulted in social isolation with 52% [90 out of 173] of AYAs reported feeling more isolated than prior to the pandemic. On the other hand, 39% [68 out of 173] reported feeling about the same, and 9% [15 out of 173] reported feeling less isolated than before, and better understood by their friends and family.

"Even though I am still as isolated as I was when going through treatment and recovery, I find I feel less isolated than before because now my friends and family understand a lot better how it feels."

The qualitative responses highlighted that despite an increase in social interactions online, many individuals missed a more intimate human connection with others. While a few individuals reported having more time for themselves and their families, others reported that the isolation made them more anxious, depressed, and claustrophobic. Their needs as cancer patients were felt to have become secondary:

"People are so concerned with COVID-19 that they don't care about my cancer anymore."

For some, isolation also acted as a trigger, reminding them of their cancer:

"It makes me feel like I am in the first steps of my treatment all over again."

6.4.4 COVID-19 information resources and satisfaction

Participants were asked what sources they relied on for obtaining information related to the COVID-19 pandemic. The majority of respondents [159 out of 172] relied on a minimum of 2 different sources, with the general news being most read [135 out of 172], followed by social media [used by 109 out of 172]. Less than a third [46 out of 172] relied on cancer support groups and patient organizations for COVID-19 specific information. Individuals in different illness phases reported relying on the same information resources. Satisfaction and trustworthiness of the available information related to COVID-19 were perceived to be moderate, 6.2/10 and 6.1/10 respectively, with individuals currently undergoing treatment reporting least satisfaction and trustworthiness for the available information (see Appendix F for breakdown by treatment status).

Only 24% [42 out of 173] of respondents reported receiving direct communication regarding COVID-19 from their oncologists or health care teams, majority (64%) of whom was undergoing treatment at the time of this study. Over half of the participants, 56% [96 out of 170] reported wanting more information about how to cope with the pandemic (see Supplementary material for breakdown by treatment status). Furthermore, 35% [60 out of 172] of AYAs would have preferred information about COVID-19 tailored to their needs as young cancer patients and survivors.

"It would be nice to have something to read designed with me in mind." (Female, 32)

On the other hand, a few individuals reported that having more information would be overwhelming, and some reported the need for information specifically for mental health resources for cancer patients during a pandemic.

6.5 Discussion

Evidence to-date suggests that young people are at lower risk for contracting the novel SARS-CoV-2 virus or developing serious complications from it (Boulad, Kamboj, Bouvier, Mauguen, & Kung, 2020; Chen et al., 2020), however, youth living with and beyond cancer might be at an increased risk because due to the compromised

immunity resulting from illness and/or cancer late-effects (Desai, Sachdeva, Parekh, & Desai, 2020; Kamboj & Sepkowitz, 2009). Moreover, changes in cancer care protocols may increase the levels of anxiety and uncertainty not only for those undergoing active treatment, but also for individuals in the long-term care. Our cross-sectional study of youth living with and beyond cancer, conducted in the initial weeks of the COVID-19 pandemic, found that 3 in 10 AYAs experienced increased levels of psychological distress, with anxiety being more prominent than depressive symptomatology. As many as 6 in 10 AYAs reported feeling more anxious during the COVID-19 pandemic than they had been previously.

Higher levels of distress during a pandemic outbreak might be expected (Holmes et al., 2020) and a variety of psychological problems such as panic disorder, anxiety, and depression due to COVID-19 pandemic have already been observed in general population (Qiu et al., 2020). It may be that this is compounded for cancer patients, given the salience of risks to their health and their vulnerability due to immunosuppression. The themes driving anxiety and worry for our participants were predominantly related to physical health and cancer-related concerns. A recent study of Italian adolescent cancer patients and survivors revealed that both groups worried about contracting the virus, and felt personally at risk for severe complications, with survivors reporting more worry than those in follow up care (Casanova et al., 2020). When stratified by treatment status, our results revealed the highest levels of anxiety in those who have completed treatment within the past 6 months, followed by those in treatment at the time of the study. We speculate that this may in part be due to the uncertainty often experienced upon treatment completion, when individuals often have to wait for scans before remission can be confirmed. These treatment transitions can be burdensome for patients (Barr et al., 2016; Wilkins et al., 2014). The first few months after treatment are also often marked by frequent follow up appointments, all of which were likely postponed or cancelled due to the current pandemic. The added uncertainty is likely to contribute to anxiety symptoms.

The lowest levels of clinically elevated psychological distress were present in those off treatment, for whom the care was also least impacted by the pandemic and associated events. Nevertheless, a high proportion of those off treatment also reported feeling more anxious now than compared to the times prior the pandemic.

The social impact of the disease containment measures has been considerable. Most governments and authorities across the world have imposed physical distancing as a way to slow the spread of the virus within communities. For many, these measures resulted in social isolation, which can result in increased feelings of loneliness and further contribute to the feelings of low mood and anxiety (Matthews et al., 2019). The majority of our participants recounted being familiar with isolation measures due to their cancer experience. For some AYAs, de novo isolation acted as a negative reminder of their illness, while on the other hand, almost 10% reported feeling less anxious and isolated compared to the time prior the pandemic. The qualitative responses revealed that this may be due to the fact that they felt better understood, spent more time with their families, or even found more time for themselves.

Research to date suggests that AYAs with cancer like to be involved in their care and need tailored, age-appropriate information about their cancer, care, late-effects, and resources (Drew, Kable, & van der Riet, 2019; Greenzang, Fasciano, Block, & Mack, 2020). Only a quarter of our participants reported receiving direct communication related to COVID-19 from their health care providers and we demonstrated that more than half of AYAs would like to have received more information on how to cope during the COVID-19 pandemic, specifically, information tailored to them as young cancer patients and survivors. Regardless of the time passed since diagnosis, the most common worry was knowing the extent of the risk for contracting the virus and how their body would react if they were to contract the infection.

Unlike Italian adolescents (Casanova et al., 2020), our AYA participants consumed most of the news related to the pandemic via general news sources, followed by social media outlets. This difference may be due to the older age of our sample. The fact that AYAs received most information from general news sources could also explain the reported need for more tailored information. The utility of social media as a way to deliver reliable information, as well as interventions to AYA cancer communities is gaining traction and could pave the way for an eHealth approach to oncological AYA care (Ramsey et al., 2019). Preliminary evidence supports the feasibility and acceptability of online psychosocial interventions for AYAs in treatment (Chalmers, Sansom-Daly, Patterson, McCowage, & Anazodo, 2018) or early post-treatment phases (Sansom-Daly et al., 2019), however, future research should carefully evaluate if online support and digital approaches to care respond equally well to the needs of AYAs living with and beyond cancer.

6.5.1 Strengths and Limitations

While the global reach and early data collection add the largest contribution to the growing body of knowledge about the COVID-19 pandemic, there are several limitations that limit the generalizability of our work. Our sample size was relatively small, highly heterogeneous, mostly female, and with most responses submitted from North America and Europe. While a geographically diverse sample offers broad and preliminary insights into COVID-19 related concerns of AYAs globally, it also limits generalizability due to the diverse health care systems, time-lags between peaks of the pandemic across different countries, and measures taken to prevent the spread of COVID-19.

Participants were a self-selected group who responded to the online study post, and we collected only minor, though relevant details relating to their medical and cancer history. Moreover, the survey was cross-sectional in nature and psychological distress was assessed using a very brief measure, and relied on short answer questions, to which many individuals provided responses with limited context and detail. We relied on retrospective self-report of changes in psychological distress since the advent of COVID-19, which are subject to reporting biases. Nevertheless, have provided important preliminary evidence, which offers invaluable directions for the future research on the impact of COVID-19, and also captured the experiences of this vulnerable population in the early weeks of the COVID-19 pandemic. Our sample included respondents at different stages of cancer treatment and beyond.

6.5.2 Clinical implications

The COVID-19 pandemic is rapidly evolving, and we learn new details every day. Even though the disruptions in our daily routines and health care systems pose many challenges, therein lie many opportunities for improvement of AYA cancer care in the future. The current situation highlights the continued need to screen for psychological distress and attend to those who might be experiencing distress even under normal circumstances. Finding ways of doing this whilst providing follow-up care remotely is particularly important within the current ways of working, and the brief PHQ-4 used in this study may offer a promising way to monitor psychological distress in clinical contexts.

The health care teams should actively engage and provide relevant and reliable information about COVID-19 for cancer patients and survivors, as well as information about any mental health resources. This will be important as the lockdown measures begin to ease in the coming months. Individuals whose care was delayed should receive adequate support so that they follow through with their appointments and continue the necessary treatment. While attending to those who are undergoing treatment or just recently completed it has been a priority, our results emphasize that the needs of long-term survivors should not be overlooked, as many may be experiencing higher levels of distress due to their illness history.

Telemedicine and eHealth might offer a favorable approach for some AYAs, however, in scaling them up, we have to ensure we do not leave behind those with limited access to digital technologies.

6.6 Contribution to this thesis

This chapter supplements and extends the online study presented in the previous chapter by acknowledging the sudden and profound impact of the global COVID-19 pandemic on vulnerable populations. This chapter too, addressed **RQ1** and **RQ3**. We demonstrate that young people who live with and beyond cancer may be vulnerable to psychological distress in the time of crisis, which directly threatens their health. The findings provide evidence to support that modifiable factors may contribute to the level of distress more than the clinical factors. Having adequate support and information is important in the times of crises, while the time from treatment completion was not found to be associated with the level of psychological distress. Going forward young patients' and survivors' psychosocial and informational needs need not be overlooked.

The following and concluding empirical chapter builds on the work from the online study and zooms in and investigates fatigue, a commonly endorsed symptom among the AYAs. The relationship between fatigue and psychological functioning are explored over time.

Chapter 7 - Fatigue and psychological functioning in sarcoma over time: Application of group-based trajectory modelling*

7.1 Abstract

Objective: The aim of this study was to explore and describe distinct trajectories of fatigue from baseline through 24 months into recovery and identify demographic and psychological factors associated with different fatigue trajectories.

Method: This study relies on secondary analysis of longitudinal clinical data from sarcoma-specialty clinic in Montreal, Canada. Data were available from 150 adolescents and young adults diagnosed and treated for sarcoma. Demographic and illness characteristics were extracted from the medical records, and participants responded to the questionnaires about quality of life, physical and psychosocial functioning at baseline, 1 year, and 2 years post-treatment.

Results: We identified 3 distinct fatigue trajectories over time: Low, decreasing (14.9%), Stable (35.4%), and Elevated, increasing (49.7%). Those in *Elevated, increasing* fatigue trajectory had significantly higher odds (p=0.05) of reporting moderate to severe mood disturbance [OR = 3.34, 95% CI, 0.98 – 11.44], as well as significantly lower scores of optimism [p=0.05; OR = 0.74, 95% CI, 0.55-1.00] than those in *Low, decreasing* fatigue trajectory. No demographic or illness factors were associated with fatigue trajectories.

Conclusions: Fatigue is a common problem among AYAs with cancer. Mood disturbance and lower levels of optimism were associated with increasing levels of fatigue over time. Psychosocial support for AYAs exhibiting lower levels of optimism at the time of diagnosis, and higher levels of mood disturbance over time may help alleviate persistent fatigue.

* Chapter adapted from:

Košir, U., Bowes, L., Mayo, N., … & Turcotte, R. (In preparation). Fatigue and recovery in sarcoma over time: Application of group-based trajectory modeling. *JAMA Oncology*.

7.2 Introduction

Cancer is an illness that impacts many domains of psychosocial functioning, particularly in adolescents and young adults (AYAs). Illness and its associated disruptions may leave lasting effects on peer relationships, professional pursuits, or mental health (C. L. Daniel et al., 2015; Perez et al., 2020; Sansom-Daly & Wakefield, 2013). Despite the efforts to address the inequalities in psychosocial outcomes, many young people report difficulties long into survivorship (Baird et al., 2019; Marjerrison & Barr, 2018). One particularly common problem is fatigue, which is considered to be a multidimensional construct including physical, emotional, as well as cognitive fatigue (De Raaf, De Klerk, & Van Der Rijt, 2013; Scott, Lasch, Barsevick, & Piault-Louis, 2011). While cancer and treatment often directly contribute to the levels of fatigue (Bower et al., 2000; L. F. Brown & Kroenke, 2009), the problem sometimes persists years after treatment completion (Bower et al., 2000; Spathis et al., 2017).

Persisting fatigue has been reported by children and adults with cancer (Barsevick et al., 2013). Many studies have focused on fatigue in older adults (>39 years) (Campos, Hassan, Riechelmann, & Del Giglio, 2011; Oh & Seo, 2011), and literature has comprehensively described fatigue in children and younger adolescents (<18years) (J. M. Erickson, 2004; Spathis et al., 2017). However, a recent review of the literature suggests that evidence on fatigue in AYA patients and survivors lags behind (Nowe et al., 2017).

Nevertheless, studies to date suggest that AYAs with cancer report higher levels of fatigue compared to age-matched healthy peers (Geue et al., 2014). Other factors associated with higher levels of fatigue were female gender and poorer quality of life (Geue et al., 2014), lack of health insurance, radiation therapy, treatment side effects, and being currently in treatment (A. W. Smith, Bellizzi, et al., 2013), as well as expressed need for mental and physical support (A. W. Smith, Parsons, et al., 2013).

These findings should be interpreted with caution as they are based on small sample sizes, and often focus on active treatment phases (Singer et al., 2011; Spathis et al., 2017), or a short time-frame post-treatment (6 – 14 months) (Hauken, Holsen, Fismen, & Bogsnes Larsen, 2015). Lack of longitudinal evidence and systematically collected clinical data further limit the existing evidence on fatigue in AYAs. Moreover, as discussed in section (Chapter 2), studies commonly employ variable-centered approaches, relying on a single mean, which risks to obscure important between-subject

variability. We address these limitations and complement the existing literature by conducting comprehensive analyses of clinical data of young people with sarcoma from the time of diagnosis through 24 months post-treatment. Relying on group-based trajectory modeling, we investigate how different patterns of fatigue may emerge over time. Understanding how different trajectories of fatigue evolve over time and identifying psychological and illness factors associated with them will help us develop more targeted approaches to care.

Even though fatigue affects the great majority of cancer patients, regardless of their age or diagnosis (Bower, Crosswell, & Slavich, 2014; L. F. Brown & Kroenke, 2009), this study focuses on young people with sarcoma in order to minimize the potential confluence of different diagnoses (Bleyer et al., 2008). Previous sections of this thesis have introduced sarcomas in young people (see section 1.6 and Chapter 4).

The aim of this study was two-fold: First, to explore and describe distinct trajectories of fatigue from baseline through 24 months into recovery and identify demographic and psychological factors associated with different fatigue trajectories. The second part aimed to describe the psychological functioning of young people with sarcoma across time and explore any differences in psychological profiles across different fatigue trajectories. In particular, we were interested in the relationship between mood and fatigue.

7.3 Method

7.3.1 Sample

Data were extracted from Interdisciplinary Health Research Team (IHRT), a biobank and a centralized database established for collecting and maintaining information on patients with musculoskeletal (MSK) neoplasia. The main purpose behind creating this biobank was to investigate the pathogenesis, treatment, treatment-related morbidity, as well as quality of life and psychosocial outcomes of primary malignant tumors (sarcomas) of the bones and soft tissues. The data collection started in 2001 and is ongoing. Eligible participants are all patients with a biopsy-confirmed primary diagnosis of an MSK tumor from broader Montreal region. They are invited to participate sequentially, and in case of minors, parental consent is sought. Data is collected prospectively, and questionnaires are administered by the research team personnel during routine appointments at baseline (pre-operative), and subsequently at

3, 6, 12 and 24 months post-operatively. If participants need help, research coordinators hired to maintain and collect the data assist in filling out the questionnaires. All questionnaires are available to participants in English and French. Data are collected and continuously managed at McGill University Health Centre (MUHC), Montreal, Canada. The sample which we requested contained 1,085 individual entries who provided informed consent prior to June 2020. The analyses in this chapter are based on 489 cases who have completed baseline and at least one other time point, and 150 cases of adolescents and young adults (see Figure 7.1).

Ethical approval was given for secondary data analysis by the MUHC Research Ethics Board (REB), with reference number 2021-7013.

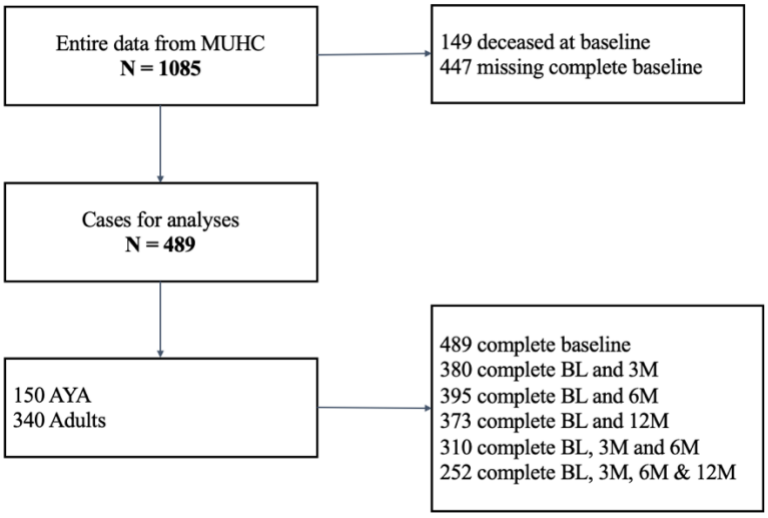


Figure 7.1: A diagram of data preparation.
NOTE: *MUHC* = McGill University Health Centre, *AYA* = Adolescent and Young Adults
BL = baseline measurement completed, 3, 6, 12M = 3, 6, 12 months measurements completed

7.3.2 Measures

7.3.2.1 Demographic and clinical characteristics

Self-reported demographic (e.g. gender, education level) and medical information (e.g. tumor size, grade, and other chronic conditions) was collected at baseline, and revised at each time point.

7.3.2.2 Fatigue

Fatigue was assessed with Functional Assessment of Chronic Illness Therapy (FACIT) – fatigue scale, which is a 13-item scale that asks about fatigue, tiredness,

weakness, listlessness, lack of energy, and the impact of these on social activities, as well as functioning (i.e. sleeping). The scale was originally developed to assess cancer-related fatigue and has shown good reliability and validity in a sample of cancer patients (Webster, Cella, & Yost, 2003). It has subsequently been used and validated in other populations of patients with chronic health conditions (e.g. inflammatory bowel syndrome or anemia; Acaster et al., 2015; Tinsley, MacKlin, Korzenik, & Sands, 2011). In the current study we used an abbreviated version of the scale (7 items), which we adapted in order to meet the assumption of measurement invariance (MI). The scale adaptation process is described in detail in Appendix H. Higher scores indicate higher levels of fatigue. Cronbach α for of our subsample was 0.89.

7.3.2.3 Functional outcomes

Toronto Extremity Salvage Score (TESS) is a 31-item measure, which was developed to measure physical and functional impairment and disability in daily living activities of patients with sarcoma. It includes restrictions in mobility, personal care, and social activities. The sum score is converted to the percentage score which describes physical function according to the International Classification of Impairments, Disabilities, and Handicaps (ICIDH; WHO, 2002). The measure has been developed and validated for use in patients with sarcoma from age 12 to 80 years (Davidge et al., 2009; Davis et al., 1996). The scale has 2 versions, one for the lower extremity, and one for the upper extremity. Even though Cronbach α appeared acceptable (0.8), our confirmatory factor analysis of the scale on the entire sample (*n*=489) showed a poor fit (for upper extremity CFI = 0.55, RMSEA = 0.29; for lower extremity CFI = 0.75, RMSEA = 0.165)[†]. We have decided to consider TESS as a covariate only.

7.3.2.4 Quality of life

Health-related quality of life was assessed with European Quality of Life Questionnaire (EQ-5D), which is a self-reported questionnaire with two analysis

[†] CFI stands for Comparative Fit Index and RMSEA stands for Root Mean Square Error of Approximation. Both are commonly used fit indices to assess how well the model fits the data. CFI values range from 0 to 1, with values ≥ 0.9 indicating acceptable model fit. RMSEA values between 0.05 and 0.08 indicate acceptable fit. RMSEA value ≥ 0.10 indicate poor model fit (Hu & Bentler, 1999). Our confirmatory factor analysis demonstrated poor fit for both versions of the measure.

variables. The first is a visual analog scale (VAS), from 0 (worst imaginable) to 100 (best imaginable), which asks about patients' health status on the day. The second part contains variables that are a descriptive system, which defines health across five domains: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each domain has 3 possible levels: no problem (1), some problem (2), and moderate or severe problem (3) (Shaw, Johnson, & Coons, 2005). In this study we treated VAS as a continuous variable, and each of the five domains as separate categorical variables with 2 levels; no problem and moderate or extreme problem/disturbance. In particular, we focused on mood disturbance and self-reported levels of pain.

7.3.2.5 Optimism

Optimism was measured using Life Orientation Test (LOT), a 12-item measure designed to assess the personality trait of dispositional optimism (Scheier & Carver, 1985). The scale asks individuals to express their agreement with statements on a 5-point Likert scale, from Strongly disagree (1) to Strongly Agree (5). Six items are filler items (e.g. *It's easy for me to relax.*), 3 items measure pessimism (e.g. *Things never work out the way I want them to.*), and 3 items measure optimism (e.g. *I'm always optimistic about my future*.). Optimism score is created by a sum score of the 3 items. Higher scores indicate higher levels of optimism. Cronbach α for of our subsample was 0.7.

Table 7.1 describes the measures used in this study at different time points. Complete measures can be viewed in Appendix H.

Table 7.1: Questionnaires from the IHRT Biobank used in this study.

Time point	**Pre-op**	**3m**	**6m**	**12m**	**24m**
Data collected	Demographic and medical information	TESS	TESS	EQ-5D	EQ-5D
				FACIT	FACIT
	LOT (Optimism)			TESS	TESS
	EQ-5D				
	FACIT				
	TESS				

NOTE: *Pre-op* = administered post-diagnosis, in the pre-operative phase; *m* = months post treatment; *LOT* = Life Orientation Test, *EQ-5D* = European Quality of Life Questionnaire, self-reported measure for quality of life; *FACIT* = Functional Assessment of Chronic Illness Therapy; *TESS* = Toronto Extremity Salvage Score.

7.3.3 Data analysis

This study relies on secondary data analysis of a prospective, longitudinal dataset of sarcoma patients at the MUHC. All the analysis and data visualizations were carried out in R (Team, 2020).

Aim 1: ***To devise the trajectories of fatigue from baseline through two years into recovery and identify demographic and psychological factors associated with different fatigue trajectories*****.**

In order to estimate different trajectories of fatigue over time we used group-based trajectory modelling (GBTM), from intake (i.e. baseline) through 24 months post-surgery. GBTM are finite mixture models, which assume that subgroups of individuals who form a trajectory (i.e. latent class) are taxonomically similar in their responses on the outcome variable (D S Nagin, 2014; Daniel S. Nagin & Odgers, 2010).

In its most traditional sense, GBTM models the mean level of responding within each trajectory, overlooking within-class variability, thus allowing us to make comparisons between different classes (Daniel S. Nagin & Odgers, 2010). However, assuming class homogeneity has been contested and within-group heterogeneity has only recently begun to be addressed (Saunders, 2010). The methodological advancements now allow for the inclusion of variation in the latent growth terms (i.e.

random effects). Allowing for the random effects in the intercept and slope factors we generally require fewer number of latent classes to capture different trajectories, however, this must be balanced against a less parsimonious and more complex model with higher number of parameters.

We used a three-step approach to estimate GBTM, thus estimating the trajectories without auxiliary variables (i.e. unconditional model) and performed subsequent analyses after the trajectories have been established. The three-step approach has been shown to outperform the one-step approach where auxiliary variables (i.e. covariates) are used in GBTM (Asparouhov & Muthén, 2014). Using *lcmm* package (Proust-Lima, Philipps, & Liquet, 2017), we ran all the possible permutations of linear and quadratic functions and estimated models with 1 to 6 latent classes.

7.3.3.1 Model fit

One of the challenges in GBTM is the model selection, since there is no single statistical test of model fit. It is recommended that a variety of statistical criteria are examined along with the theoretical fit of the trajectories (D S Nagin, 2005; Nylund, Asparouhov, & Muthén, 2007). For each model we recorded if the model converged, the number of parameters it included, and several fit indices such as Akaike information criterion (AIC), Bayesian information Criterion (BIC), sample-size-adjusted BIC (SABIC) and entropy. Entropy describes the classification accuracy of individuals to into the correct class. Each individual has a nonzero posterior probability of being classified into the most likely class of a given model. Entropy values range from 0 to 1, with 0.7 or above indicating acceptable level of classification (J. Wang & Wang, 2012).

The best model is the most parsimonious model (with fewest possible classes and parameters estimated, e.g. linear over quadratic; Bauer & Curran, 2003). The selection is further informed by lower AIC and BIC values, entropy, and size of each class, which is recommended to be at least 5%, although it is important to consider absolute numbers when sample size is limited (Daniel S. Nagin & Odgers, 2010). In our case, we considered size-adjusted BIC, which is recommended for limited samples ($n < 500$) (Henson, Reise, & Kim, 2007).

7.3.3.2 Model validity

Irrespective of how the best model is defined, class members will never follow their trajectories perfectly (D S Nagin, 2005; D S Nagin & Tremblay, 2005; D S Nagin, Tremblay, Sampson, & Laub, 2005). This may be particularly true when the random effects are specified as part of the model. Class membership may change when individual class members are allowed to vary, so the degree of heterogeneity within a class becomes a key issue (Kreuter & Muthén, 2008; Raudenbush, 2005). Because the aim is to describe the trajectories in terms of the measured outcome (i.e. fatigue), class membership must be meaningful. Validity is often established by further evaluation of the class, and a generally accepted method is creating profiles of the trajectories and descriptively characterize them (Saunders, 2010).

Aim 2: ***Describe the associations between baseline factors and fatigue trajectories and describe the psychological profiles of young people with sarcoma across the illness trajectory*****.**

Psychological functioning was further explored and described graphically. Self-reported mood symptomatology and quality of life scores were stratified by different fatigue trajectories.

In order to further characterize our trajectories, we ran a multivariate multinomial logistic regression, and assessed the unique contribution of baseline variables. The trajectory with the lowest overall level of fatigue was used as a reference group.

7.3.3.3 Covariates

Covariates tested in multinomial logistic regression were identified by theory a priori, as well as based on their statistical significance. They were individual, family, and medical characteristics, which were associated with fatigue in previous research (Curt, 2000; Nowe et al., 2017; Spathis et al., 2017). These included: gender (male; female), age at diagnosis, tumor type (osteosarcoma, soft tissue sarcoma; Ewing sarcoma), tumor site (upper; lower), education level, relationships status, other chronic conditions (yes/no), expectations of outcomes, optimism, and baseline EQ-5D information. Individuals who experienced illness recurrence were not included in the

analysis. Covariates that were not found to be significant in univariate multinomial logistic regression were not included in the multivariate analysis.

7.3.3.4 Missing data

Questionnaire data was routinely collected during patients' appointments, however, several variables of interest had missing data. Attrition was observed in fatigue (6 – 43.1%), functional scores (TESS; 0 – 42.7%) and EQ-5D (7 – 43.5%). Individuals who passed away throughout the study were excluded from the analysis. We compared complete cases with those with missing data at 24 months on main predictors (e.g. age, gender, baseline quality of life, baseline functioning). There were no significant differences between complete and drop-out cases on any variables. Additionally, the Principal Investigator (Dr. Robert Turcotte) who manages the data collection reported that some data was missing due to administrative errors and technical difficulties (i.e. server not working). Thus, assuming that data was missing at random (MAR) and in order to minimize data loss, we imputed missing variables for up to 2 years using chained equations with *mice* package (van Buuren & Groothuis-Oudshoorn, 2011) and pooled the data using *sjmisc* package (Lüdecke, 2018). In line with recommendations for the level of missingness, we imputed 30 data sets (Little & Rubin, 2014). Observations were similar in imputed versus complete cases, therefore we report the results of the imputed data. Details on which variables were used in multiple imputations, as well as description of the complete cases are reported in Appendix H.

7.3.3.5 Measurement invariance

When modeling individual scores across time (i.e. fatigue), we assume that the measure we are using is equivalent between different time points (time-invariant), which allows us to assume that any change in the measured (observed) construct is attributable to real change rather than error or changes in the understanding of the construct (Meredith, 1993). Because fatigue was the main outcome of interest, we checked the reliability of FACIT measure using longitudinal confirmatory factor analysis, which fits a series of measurement models, each adding a constraint in order to simulate measurement invariance (MI) over time (Liu et al., 2017; Widaman, Ferrer, & Conger, 2010). The full FACIT scale did not meet the assumption of MI, therefore we used exploratory confirmatory factor analysis and abbreviated the scale. The MI

analyses were done using package *lavaan* (Rosseel, 2012). All the subsequent analyses were performed using the abbreviated version.

The details of testing for MI, model fits, as well as the abbreviated scale are described in detail in Appendix H.

7.3.3.6 Post Hoc analyses

Post Hoc ANOVA was used to compare the baseline level of fatigue across different trajectories. In order to further assess the relationship between fatigue trajectories and mood at 1 year, we ran multinomial logistic regression that included mood at 1 year and fatigue trajectories.

7.4 Results

7.4.1 Sample

The sample included in the analysis is described in Table 7.2 on the following page.

Table 7.2: Demographic and medical information.

	Imputed cases (*N*=150) **N (%) *or*** **M (SD)**	**Complete cases (*N*=150)*** **N (%) *or*** **M (SD)**
Gender		
Male	95 (64)	96 (64)
Female	54 (36)	52 (36)
Age at diagnosis	28.9 (7.53)	29 (7.51)
13 – 25 y	49 (33)	49 (33)
26 – 39y	100 (67)	98 (67)
Age at baseline	29.8 (8.23)	29.6 (8.11)
Education		
Primary school	88 (59)	83 (59)
Secondary school	40 (27)	36 (26)
University level	17 (11)	16 (11)
Graduate school	5 (3)	5 (4)
Relationship Status		
Single	73 (49)	72 (52)
In a relationship	72 (48)	62 (45)
Married/Cohabiting	4 (3)	4 (3)
Separated/Divorced	/	/
Tumor type		
Osteosarcoma/Bone	49 (33)	48 (33)
Soft tissues sarcoma	44 (30)	45 (31)
Ewing sarcoma	8 (5)	8 (5)
N/A	48 (32)	46 (31)
Tumor site		
Upper	41 (28)	41 (28)
Lower	108 (72)	106 (72)
Tumor size (cm)	6.60 (4.30)	6.60 (4.30)
Range (cm)	0.2-21	0.2-21
Tumor grade[a]		
GX	27 (18)	27 (18)
G1	32 (21)	32 (21)
G2	27 (18)	27 (18)
G3	27 (18)	27 (18)
Unknown	37 (25)	37 (25)
Relapse		
Yes	12 (8)	12 (8)
No	138 (92)	138 (92)
BL QoL	70.6 (18.1)	71.0 (18.0)
BL FACIT	6.5 (5.81)	6.51 (5.93)
BL TESS	74.0 (19.4)	74.4 (18.9)

NOTE: *N/A* – information was missing. *QoL* – quality of life, as measure by visual analog scale on EQ-5D, *FACIT* = Functional Assessment of Chronic Illness Therapy; *TESS* = Toronto Extremity Salvage Score.

*because some information (e.g. gender) was available for all cases, the total number is the same across both groups

[a] – Tumor grade is determined by a common grading system from the French Federation of Cancer Centers Sarcoma Group (FNLCC); *GX* = may indicate benign or cannot be evaluated, *G1* = low grade, *G2* = medium grade, *G3* = high grade. A lower grade means that the tumor is less aggressive and that a patient's prognosis I better.

7.4.2 Trajectories of fatigue across the illness trajectory

Prior to estimating the trajectories, we performed a log transformation of fatigue values in order to correct the asymmetry in the scores (Herle et al., 2020; Muthén, 2004). We identified 3 trajectories of fatigue over time, which were best fit with quadratic terms and including random effects. Comparison of different models with 1 to 4 classes can be seen in Table 7.3 and Table 7.4. Complete tables with values for 6 classes can be viewed in Appendix H.

Our trajectory model depicted heterogeneity in fatigue scores across different levels of baseline fatigue (see Figure 7.2). Trajectories were assigned names that best described the trajectory of fatigue: 1) *Stable* (n=52; 35.4%), characterized by individuals whose fatigue at 2 years was comparable to their baseline level, 2) *Elevated, increasing* (n=76; 49.7%), which was characterized by individuals who reported elevated levels of fatigue, which increased after the first year, and 3) *Low, decreasing* (n=22; 14.9%), characterized by a decrease in fatigue after treatment completion. Post hoc ANOVA confirmed that individuals in *Elevated, increasing* fatigue trajectory had a significantly higher baseline fatigue (M = 8.91, SD = 6.47) compared to *Low, decreasing* (M = 3.45, SD = 3.29), and *Stable* (M = 4.27, SD = 3.87) fatigue trajectory ($F[1,147] = 16.1$, $p < 0.01$). There was no difference in baseline fatigue between *Stable* and *Low, decreasing* fatigue trajectories.

Table 7.3: Model enumeration comparisons with linear terms.

No variance	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**
M1	3	440.80	449.77	440.28	1	100%			
M2	6	340.98	358.92	339.94	0.77	60.54%	39.56%		
M3	**9**	**337.76**	**364.67**	**336.19**	**0.73**	**55.8%**	**8.2%**	**36%**	
M4	12	340.46	376.35	338.37	0.59	11.6%	31.3%	13.6%	43.5%

Random intercept, fixed slope	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**
M1	4	350.41	362.37	349.71	1	100%			
M2	7	334.81	355.74	333.59	0.66	37.4%	62.6%		
M3	**10**	**337.23**	**367.14**	**335.49**	**0.74**	**2.7%**	**63.3%**	**34%**	
M4	13	339.12	378.00	336.86	0.73	32.6%	56.5%	3.4%	7.5%

Random intercept, random slope	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**
M1	6	346.72	364.66	345.67	1	100%			
M2	**9**	**334.83**	**361.74**	**333.26**	**0.69**	**36.7%**	**63.3%**		
M3	12	340.83	376.71	338.74	0.41	0%	57.8%	42.2%	
M4	15	341.50	386.36	338.89	0.74	55.1%	2.7%	34.7%	7.5%

NOTE: The table presents the results from the most to least restrictive models with linear terms. *M1 – 4* stands for number of classes specified. The emboldened line presents the best model fit in each category. *NPM* – Number of parameters, *AIC* – Akaike Information Criterion, *BIC* – Bayesian Information Criterion, *SABIC* – sample-size-adjusted BIC, *Class 1 – 4* give the proportion of the sample in that specific class for each specified model.

Table 7.4: Model enumeration comparisons with quadratic terms.

No variance	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**
M1	4	440.94	452.90	440.25	1	100%			
M2	8	339.41	363.34	338.02	0.77	59.9%	40.1%		
M3	**12**	**335.47**	**371.35**	**333.38**	**0.71**	**10.9%**	**35.4%**	**53.7%**	
M4	16	332.36	380.21	329.57	0.72	12.9%	35.4%	42.2%	9.5%

Random intercept, fixed slope	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**
M1	5	348.84	363.79	347.97	1	100%			
M2	9	331.67	358.58	330.10	0.65	63.3%	36.7%		
M3	**13**	**331.09**	**369.97**	**328.83**	**0.67**	**8.8%**	**37.4%**	**53.8%**	
M4	17	326.17	377.00	323.21	0.66	39.5%	20.4%	29.9%	10.2%

Random intercept, random slope	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**
M1	10	345.84	363.79	347.97	1	100%			
M2	14	324.43	366.29	321.99	0.80	61.9%	38.1%		
M3	**18**	**314.98**	**368.81**	**311.85**	**0.84**	**35.4%**	**49.7%**	**14.9%**	
M4	22	297.66	363.45	293.83	0.92	6.8%	46.9%	24.5%	21.8%

NOTE: The table presents the results from the most to least restrictive models with quadratic terms. *M1 – 4* stands for number of classes specified. The emboldened line presents the best model fit in each category. *NPM* – Number of parameters, *AIC* – Akaike Information Criterion, *BIC* – Bayesian Information Criterion, *SABIC* – sample-size-adjusted BIC, *Class 1 – 4* give the proportion of the sample in that specific class for each specified model.

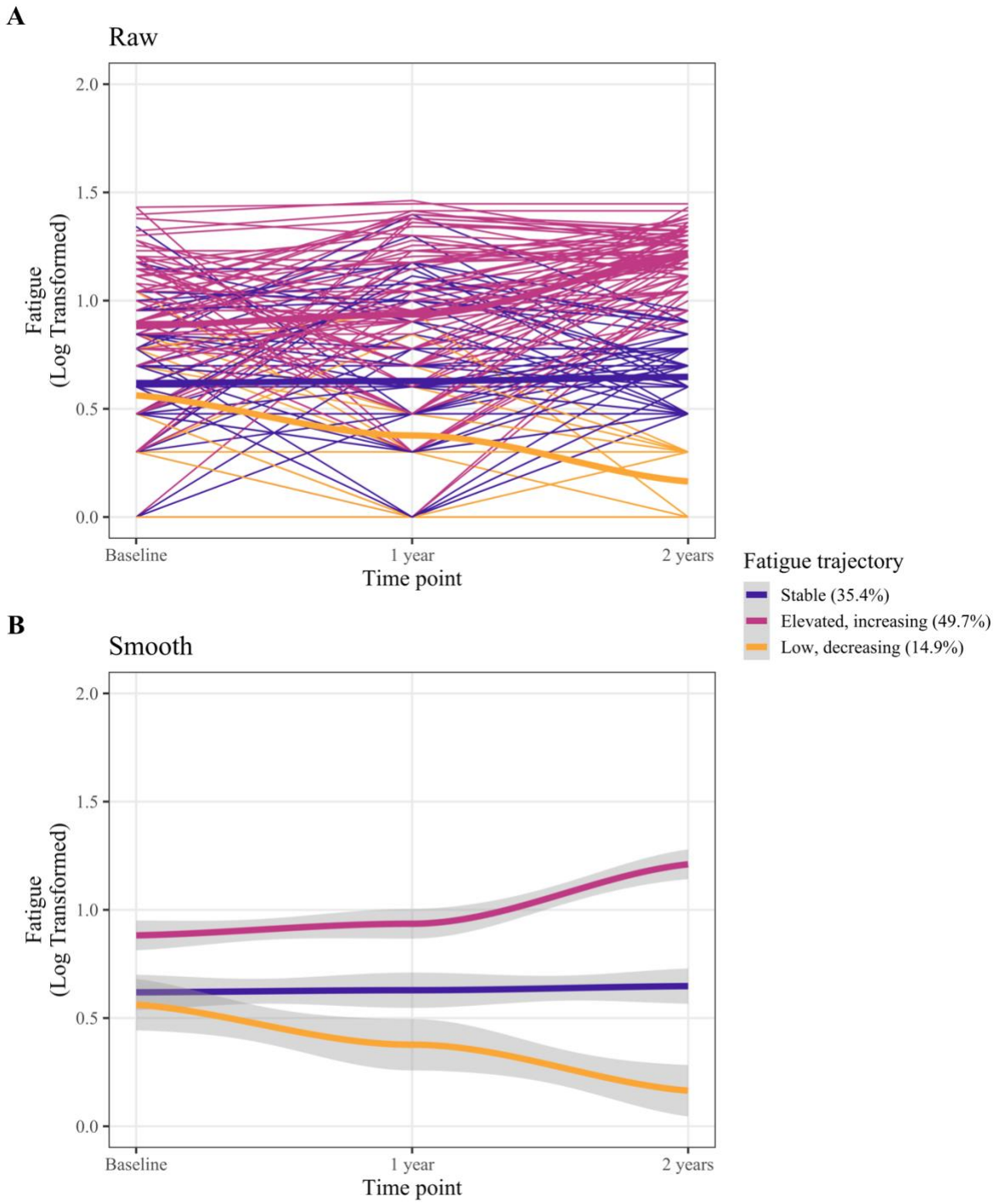


Figure 7.2: Trajectories of fatigue across the span of illness, from diagnosis to 2 year after treatment.
NOTE: **Panel A** shows the raw data with each individual trajectory. Color corresponds to the assigned fatigue trajectory as indicated in the legend. **Panel B** shows the 3 trajectories smoothed out. The gray band around the line indicates a 95% confidence interval. The y-axes show log-transformed fatigue scores, which were used to correct for the skew in the analysis. Section 7.4.2 in the results describes the differences in fatigues scores between the trajectories.

7.4.3 Psychological profiles and associations between baseline factors and fatigue trajectories

The univariate models revealed significant association between mood at baseline and fatigue trajectory. Those in *Elevated, increasing* fatigue trajectory had significantly higher odds (p=0.006) of reporting moderate to severe mood disturbance (elevated anxiety and depression as measured by EQ-5D) than those in *Low, decreasing* fatigue trajectory [OR = 5.16, 95% CI, 1.59 – 16.75]. Similarly, individuals in *Elevated, increasing* fatigue trajectory had significantly lower levels of optimism (p=0.01) compared to individuals in *Low, decreasing* fatigue trajectory [OR = 0.68, 95% CI, 0.51 – 0.91]. No other baseline variable was significantly associated with any of the specified trajectories. Table 7.5 shows the results of univariate models.

Table 7.5: Associations between baseline characteristics and fatigue trajectories in univariate multinomial models.

	Stable (*n* = 52)		**Elevated, increasing (*n* = 76)**	
Variable	OR (*p*)	95% CI	OR (*p*)	95% CI
Female	0.74 (0.58)	0.25-2.15	0.87 (0.80)	0.31-2.34
Age at dx	1.04 (0.23)	0.97-1.11	1.02 (0.42)	0.96-1.09
Type[a]				
Osteo	0.36 (0.38)	0.03-3.52	0.76 (0.77)	0.11-5.01
Soft tissue	1.54 (0.58)	0.31-7.50	1.14 (0.86)	0.25-5.15
Tumor size	1.02 (0.82)	0.87-1.18	1.06 (0.42)	0.91-1.23
Relapse	0.52 (0.43)	0.10-2.58	0.44 (0.29)	0.09-2.04
Chronic diagnosis	1.56 (0.60)	0.29-8.16	3.27 (0.13)	0.69-15.39
Baseline activity *(problems performing usual activities)*	1.34 (0.57)	0.48-3.67	1.96 (0.0.17)	0.74-5.15
Baseline pain *(moderate or extreme pain)*	1.11 (0.84)	0.40-3.06	1.60 (0.34)	0.59-4.30
Baseline mood *(moderate or extreme mood disturbance)*	2.38 (0.16)	0.70-8.11	5.16 (**0.006**)	1.59-16.75
Baseline QoL (VAS)	0.99 (0.75)	0.96-1.02	0.98 (0.24)	0.95-1.01
Baseline TESS	0.99 (0.78)	0.96-1.03	0.98 (0.19)	0.95-1.01
Baseline optimism	0.76 (0.07)	0.56-1.02	0.68 (**0.01**)	0.51-0.91

NOTE: *dx* = diagnosis, *VAS* = Visual Analog Scale, *OR* = Odds Ratio, *CI* = Confidence Intervals; Emboldened values are statistically significant.
[a] – compared to bone sarcoma

We subsequently ran a multivariate model which included optimism and baseline mood (see Table 7.6). The results revealed significant association between optimism and mood at baseline and fatigue trajectory. Those in *Elevated, increasing* fatigue trajectory had significantly higher odds (p=0.05) of reporting moderate to severe mood disturbance [OR = 3.34, 95% CI, 0.98 – 11.44], as well as significantly lower scores of optimism [p=0.05; OR = 0.74, 95% CI, 0.55-1.00] than those in *Low, decreasing* fatigue trajectory.

Table 7.6: Associations between baseline characteristics and fatigue trajectories in multivariate multinomial model.

	Stable (*n* = 52)		**Elevated, increasing (*n* = 76)**	
Variable	OR (*p*)	95% CI	OR (*p*)	95% CI
Optimism	0.78 (0.12)	0.57-1.07	0.74 (**0.05**)	0.55-1.00
Baseline mood *(moderate or extreme mood disturbance)*	1.65 (0.44)	0.45-5.98	3.34 (**0.05**)	0.98-11.44

NOTE: *OR* = Odds Ratio, *CI* = Confidence Intervals; Emboldened values are statistically significant.

We further explored data visually. Figure 7.3 shows density plots of quality of life scores as measured by VAS on the EQ-5D scale. Individuals in *Elevated, increasing* fatigue trajectory show a broader distribution of scores, with a lower mean at 2 years (M = 52.5, SD = 23.1) compared to those in *Stable* (M = 81.3, SD = 14.5), and *Low, decreasing* (M = 92.5, SD = 7.7) fatigue trajectories. Similar pattern was observed with functional scores as measured by TESS. Those in the *Elevated, increasing* fatigue trajectory reported lower functional scores on average. See Table 7.7 for a breakdown of quality of life and TESS scores for different fatigue trajectory across time.

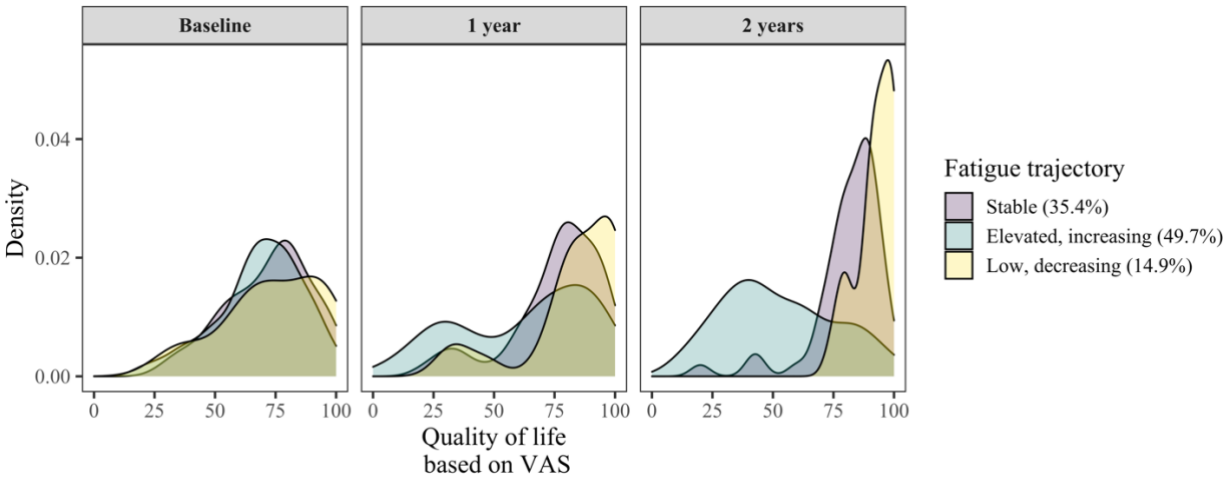


Figure 7.3: Self-reported quality of life across the illness trajectory.
NOTE: *VAS* = visual analog scale. Individuals in different trajectories showed different distribution of scores on the quality of life measure. Those in *Elevated, increasing* fatigue trajectory show a broader distribution of scores, with a lower mean at 2 years (*M* = 52.5, *SD* = 23.1) compared to those in *Stable* (*M* = 81.3, *SD* = 14.5), and *Low, decreasing* (*M* = 92.5, *SD* = 7.7) fatigue trajectories. At 2 years, individuals with the lowest average fatigue scores (*Low, decreasing* fatigue trajectory) report the highest scores on quality of life.

Table 7.7: Mean scores for quality of life and function per fatigue trajectory across time.

	Baseline			**1 year**			**2 years**		
	Stable (*n*=52)	In-creasing (*n*=76)	Low (*n*=22)	Stable (*n*=52)	Increasing (*n*=76)	Low (*n*=22)	Stable (*n*=52)	Increasing (*n*=76)	Low (*n*=22)
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
QoL	72.1 (17.6)	68.8 (17.8)	73.5 (20.6)	76.0 (18.9)	62.3 (27.3)	82.8 (20.5)	81.3 (14.5)	52.6 (23.1)	92.5 (7.7)
TESS Score	76.6 (15.1)	71.1 (21.3)	77.8 (20.7)	83.4 (8.90)	80.7 (11.4)	88.1 (4.41)	84.3 (9.04)	78.8 (14.2)	89.0 (3.18)

NOTE: QoL = Quality of life as measured by EQ-5D VAS scale, TESS = Toronto Extremity Salvage Score; Increasing = abbreviated for Elevated, increasing fatigue trajectory; Low = abbreviated for Low, decreasing fatigue trajectory.

Furthermore, we observed changes within fatigue trajectories and mood across time. Figure 7.4 depicts number of individuals in each trajectory that reported no mood problems versus mood disturbance (i.e. moderate to severe anxiety or depression). *Elevated, increasing* fatigue trajectory is accompanied with an increase in self-reported mood disturbance. Conversely, *Low, decreasing* fatigue trajectory is accompanied with a decrease in mood disturbance, with no individuals reporting mood problems at 2 years post treatment.

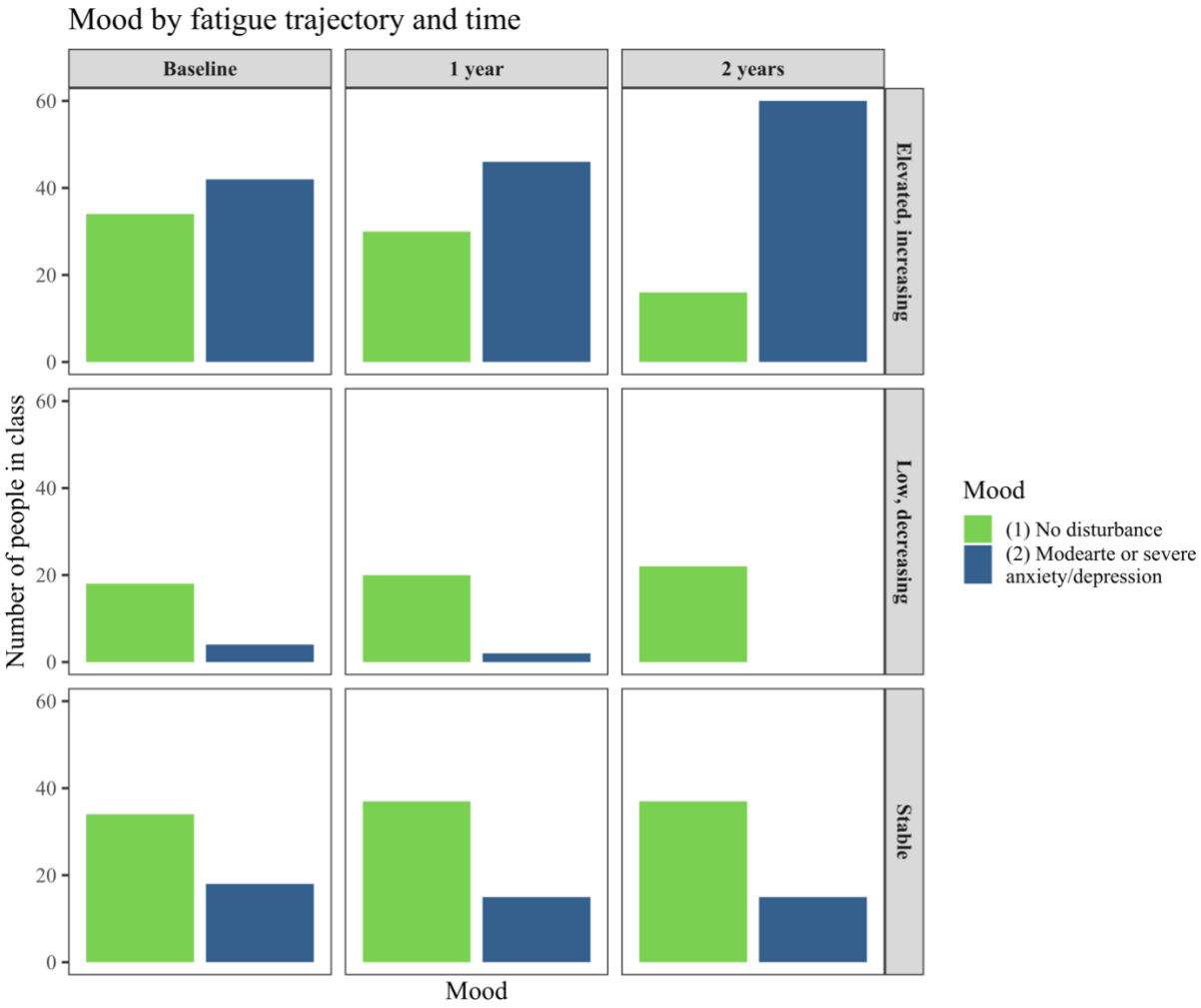


Figure 7.4: Mood disturbance by fatigue trajectory over time.
NOTE: This figure depicts the absolute number of individuals that reported no mood problems versus mood disturbance (i.e. moderate to severe anxiety or depression) in each fatigue trajectory. *Elevated, increasing* fatigue trajectory is accompanied with an increase in self-reported mood disturbance. Conversely, *Low, decreasing* fatigue trajectory is accompanied with a decrease in mood disturbance, with no individuals reporting mood problems at 2 years post treatment. *Stable* fatigue trajectory is accompanied with almost zero change in mood across time.

7.4.4 Post Hoc analyses

Post Hoc analyses revealed that mood disturbance at 1-year post treatment remained significantly associated with fatigue trajectories. Compared to *Low, decreasing*, *Elevated, increasing* fatigue trajectory had significantly higher odds (p=0.005) of reporting mood disturbances at 1-year post treatment, even after controlling for baseline mood and optimism [OR = 9.37, 95% CI, 1.96-44.79].

7.5 Discussion

In this study we explored trajectories of fatigue in AYAs with sarcoma and aimed to describe associations between psychological functioning and distinct fatigue trajectories. We identified 3 distinct trajectories of fatigue over time: *Stable, Low, decreasing*, and *Elevated, increasing*. Almost half of the sample was assigned to the latter trajectory and characterized by elevated and increasing levels of fatigue. This finding is in line with the existing literature; fatigue is a commonly endorsed problem in patients with cancer, and for some, it persists over time (Hofman et al., 2007).

Moreover, we conducted multinomial logistic regressions and assessed the association between baseline variables and distinct fatigue trajectories. The largest differences were found between *Low, decreasing* and *Elevated, increasing* fatigue trajectories. Our analyses revealed that dispositional optimism and mood were significantly associated with fatigue, and those in *Elevated, increasing* fatigue trajectory reported lower levels of optimism, and increased mood disturbance over time compare to individuals in *Low, decreasing* fatigue trajectory. In fact, our Post Hoc analyses revealed that mood disturbance at 1-year post treatment remained significantly associated with *Elevated, increasing* fatigue trajectory, even after controlling for baseline mood and optimism. We found no evidence of association between other factors and distinct fatigue trajectories, however, previous research suggests that gender, and illness characteristics may also play a role in fatigue (Nowe et al., 2017; Spathis et al., 2017). Though the association was not statistically significant, visual exploration of self-reported quality of life (see Figure 7.3) suggests that higher levels of fatigue are related to lower quality, a finding previously reported (Carlson et al., 2004; Curt, 2000; Nowe et al., 2017).

In patients with cancer, fatigue may be particularly difficult to characterize as it could be a symptom of illness, result from treatment, or describe a psychosomatic concern. Positive associations between mood symptomatology and fatigue have been noted before (Carlson et al., 2004; Curt, 2000; Schellekens et al., 2019), and some evidence suggests that cognitive behavioral therapy (CBT) may alleviate the symptoms (H Poort et al., 2019). However, despite great efforts, fatigue remains poorly understood (Hofman et al., 2007), and particularly so in young people (Nowe et al., 2017). In part this may be due to the fact that traditionally, studies have used variable-

centered approaches to study fatigue and looked at association between average levels of fatigue and psychological factors (e.g. Spathis et al., 2017).

In our study we employed group-based trajectory modeling, which is a person-centered approach (D S Nagin, 2005; Daniel S. Nagin & Odgers, 2010). In particular, we wanted to address the issue of high heterogeneity in data, and thus complemented the traditional GBTM with random effects models. By doing so, we explored *between-*, as well as *within-group* heterogeneity in fatigue responses over time. Theoretically, this approach proves advantageous; not everyone with cancer experiences fatigue or suffers from chronic levels of it. With our approach we were able to model heterogeneity in intercepts and slopes, which may result from different time-varying (e.g. mood disturbance) or time-invariant factors (e.g. optimism) (P. J. Curran & Bauer, 2011; D S Nagin, 2014; Saunders, 2010).

Our work highlights that fatigue over time is linked to psychological functioning at the time of diagnosis. Our findings contribute evidence that persisting fatigue may be associated with a less optimistic outlook, which may in turn contribute to more mood disturbance in years after treatment. Our modeling approach offers potential for future theory development.

7.5.1 Strengths, limitations and future directions

This is the first extensive analysis of psychosocial functioning and recovery of AYA individuals with sarcoma that utilized longitudinal and person-centered approach. We conducted rigorous analysis and facilitate the interpretation with transparent and visual exploration of data. Nevertheless, several limitations are important to note.

Though the data are systematically collected during routine care, there was a high level of missingness beyond 2 years' time point, which prevented us from modeling fatigue across a longer period into survivorship. Furthermore, the data are from a major clinical and sarcoma-specialty center in Montreal, Canada, which might limit generalizability to other geographical regions. Future studies should aim to replicate the findings in a separate, and larger dataset.

Moreover, several measures used in the study were sub-optimal. We had to adapt the measure for fatigue (FACIT) and found poor reliably for the scale for functioning (TESS). As such, we could not reliably test the association between functioning and fatigue. Further studies should aim to confirm the validity of our

abbreviated scale for fatigue, and aim to adapt TESS, which did not meet the assumptions of a single factor structure, nor measurement invariance in our study. Additionally, a more granular scale for anxiety and depression may reveal if the relationship between mood disturbance and fatigue remains, and if so, further studies may investigate if any particular symptoms are more strongly related to fatigue. Moreover, our results indicate associations, and do not imply causal mechanisms. Future studies should consider utilizing cross-lagged models or directed acyclic graphs (DAGs).

We also report optimism as a personality trait, measured at a single time point, after a person has already learned their cancer diagnosis. As with many existing data sets in cancer populations, we do not have information on individuals' psychological functioning prior to their diagnosis. This could be addressed by analyzing population-based cohort studies, where data may be available prior to one's diagnosis.

Lastly, even though our model selection was informed by theory, any data-driven approaches may be sample-specific, especially when including random effects (Saunders, 2010). This further calls for the need to replicate our findings in an external dataset.

7.5.2 Clinical implications

Addressing mental health and wellbeing of young individuals remains a challenge. Sarcomas are a rare type of cancer, associated with a high level of physical morbidity (Gough et al., 2011). However, despite the physical limitations and comorbid chronic conditions, our findings suggest that modifiable factors may contribute to fatigue and its persistence over time more than clinical and medical characteristics. It may be particularly valuable to attend to the psychosocial needs of young patients who are displaying lower levels of optimism at the time of diagnosis. This may not only help to alleviate the levels of fatigue, but may also contribute to better mood, as well as higher quality of life.

7.6 Contribution to this thesis:

This chapter provides longitudinal evidence to support that psychological functioning of young people with cancer may primarily be driven by modifiable factors. The findings suggest that optimism and mood may be closely related to fatigue even long into remission.

The results add to the existing literature and directly address the **RQ2** of this thesis: *How do mechanisms of resilience and psychopathology change over the span of illness?* (see section 1.10.1), establishing that distinct trajectories of fatigue over time exist and are associated with psychological functioning rather than demographic and illness characteristics. Fatigue, which is a commonly reported problem among survivors may begin as an illness or treatment side effect, but could become a self-sustained problem through the interactions of symptoms of psychopathology. Future research should further investigate this intricate relationship. In the meantime, psychosocial support may benefit those who present with lower levels of optimism at the time of diagnosis.

Chapter 8 - Discussion

The overarching aim of this thesis was to investigate the mechanisms of resilience and psychopathology in adolescents and young adults (AYA) living with and beyond cancer, an understudied group of patients, and to provide recommendations for the future research and development of more personalized approaches to cancer care for young people. Relying on a mixed method approach, this thesis addresses some of the methodological challenges in the field of psycho-social oncology and complements our current conceptualizations of resilience and psychopathology.

In order to investigate the mechanisms associated with resilience and psychopathology in AYAs, I systematically reviewed the existing literature and first addressed the question of prevalence of psychiatric disorders and risk factors in AYA cancer survivors (Chapter 3). To complement the quantitative findings and to better understand the psychological wellbeing and factors that are personally relevant to young people with cancer, I conducted in-depth qualitative analysis of semi-structured interviews (Chapter 4). The qualitative work informed the development of an online study, which collected novel and more granular information on psychological wellbeing, including cancer-specific worries (Chapter 5). An auxiliary study conducted during the COVID-19 pandemic investigated the impact of an exogenous factor (i.e. the pandemic) and its influence on this population of young patients, who may be at risk for infections (Chapter 6).

In order to investigate the mechanisms of resilience and psychopathology over the course of illness, I conducted longitudinal analyses of a clinical dataset in Montreal, Canada, exploring the relationship between psychological factors and fatigue from the time of cancer diagnosis through two years into remission (Chapter 7).

8.1 What are the factors associated with resilience and psychopathology in youth with cancer?

Addressing the inequalities in psychosocial outcomes in young people with cancer requires a better understanding of the factors that contribute to resilience and psychopathology. The empirical part of this thesis begins with a comprehensive and systematic review of the literature up until early 2018 (Chapter 3). The review addressed the question of prevalence of psychiatric disorders in AYA survivors and

aimed at synthesizing evidence on risk factors, which were found to be associated with the development of the said disorders. The review included 19 peer-reviewed articles from 4 major existing databases (PsychINFO, SCOPUS, MEDLINE, EMBASE). This review extended the previously published systematic review by Sansom-Daly & Wakefield, (2013) by including several more recent studies, and complemented a systematic review by McDonnell et al., (2017), which focused exclusively on anxiety. Even though our findings confirmed that anxiety and PTSD symptoms were among the most prevalent, we also found that up to 13% of AYAs reported depressive symptomatology. Using broader criteria for the diagnosis (i.e. including depression) but restricting the age range to exclude samples with younger children (< 10 years) allowed us to get a better understanding of the AYAs' psychological functioning. Importantly we found that several modifiable factors were associated with psychopathology: maladaptive coping mechanisms (i.e. avoidance), poor family functioning, and parental, particularly maternal distress. On the other hand, resilience factors were good family functioning and peer support. Non-modifiable factors associated with higher levels of psychopathology were illness relapse, higher number of illness late-effects, and having a brain tumor diagnosis. In addition to highlighting these factors, the systematic review, which was conducted in the early phases of this thesis highlighted many discrepancies in the published literature (discussed in Chapter 2) and inspired a mixed method approach to my work.

Chapter 4 was a qualitative study in which I used a framework analysis to gather evidence from 30 semi-structured interviews with young people with sarcoma from across the UK. Participants who were interviewed at different phases of their illness provided in-depth accounts of their personal experiences with their diagnosis, treatment, medical team, and life in remission. While the qualitative nature of this work prevents us from making claims about people's mental health, the analyses shed light on meaningful connections on several factors that play a role in AYAs' adaptation to life with and beyond sarcoma. These factors were broadly grouped into two overarching themes, individual- and environmental-level factors. This chapter demonstrated that young people report an array of positive and negative factors that play a role, and that the way a specific factor is described will mostly be guided by individual circumstances.

This chapter extended the findings which previously described factors and their impact on average levels of psychological functioning. The qualitative analysis allowed

for a better understanding of what specific factors mean to young people with cancer. Considering the personal experience of a young person provided invaluable context for the quantitative studies. The results also highlighted the high level of variation in responses, for which a more dynamic understanding and conceptualization of psychological adaptation in AYAs would be suited (Kosir et al., 2020).

Chapter 5 offered a more granular look at specific symptoms of psychological functioning. Moving beyond the latent construct, this chapter explored how unique cancer-specific worries, anxiety and depressive symptoms are interconnected. Launching an online survey study, I collected novel data from AYAs globally. The chapter relied on network analysis (Gaussian graphical models), with which I explored the interactions between observable factors. The modeling allowed me to identify two most central symptoms, *trouble relaxing* and *low mood* within clusters of psychopathology and cancer worries. The centrality implies that these symptoms may be the most influenced or influencing on the entire symptom cluster, and thus most strongly related to the overall level of psychological distress. The findings also showed high prevalence of cancer-specific worry regardless of treatment status, suggesting that late effects and cancer relapse often trouble young people, years beyond the active treatment.

Chapter 6 resulted as a response to the onset of the global COVID-19 pandemic, which consumed the world by mid-March 2020 and overwhelmed many health care systems. The pandemic and associated measures caused disruptions across multiple domains. Oncology clinics had to make significant changes to the cancer care protocols. To complement my then ongoing work, I devised a cross-sectional survey in order to understand how the pandemic and the disruption affected AYAs' wellbeing in the initial weeks. Psychological distress was measured using a brief questionnaire (Patient Health Questionnaire 4), as well as open-ended questions, which allowed participants to elaborate on their mental state. The results showed that a third of the participants scored in the clinical levels of anxiety, and up to two thirds reported higher levels of distress at the time of the study compared to the time before the pandemic. Even though the disruptions in care were most pronounced for the individuals undergoing treatment and active follow up care, the level of psychological distress was heightened among the long-term survivors as well. AYAs reported the need for tailored information for their needs, which was scarce at the time, and seldom conveyed from the medical professionals (Košir, Loades, et al., 2020).

Together these chapters show that adaptation to illness is a multifactorial process, with modifiable and non-modifiable factors. Cancer in young people impacts multiple domains, from educational pursuits to family environment and peer relationships, all of which can play an important role in mental health. Illness-related, as well as exogenous factors can interact with individual characteristics and produce an array of psychosocial outcomes.

8.2 How do mechanisms of resilience and psychopathology change over the span of illness?

Receiving a cancer diagnosis often marks just the beginning of a sequalae of events in a young person's life. Due to the paucity of longitudinal research in AYA psycho-social oncology, one of my thesis' aims was to explore the process of adaptation and resilience and psychopathology factors as they evolve over the course of illness. In particular, the chapter explored how fatigue, a prevalent yet poorly understood symptom persists over time. Chapter 7 addresses the question of *between-*, as well as *within-individual* change in fatigue over time by employing group-based trajectory modeling (GBTM) with random effects. The analyses were based on a prospectively collected clinical dataset of AYAs with sarcoma treated at a major medical center in Montreal, Canada. Questionnaire data were collected at baseline (i.e. diagnosis), and at 1- and 2-years post treatment.

GBTM revealed that our data was best described with 3 trajectories of fatigue over time: low and decreasing, stable, and elevated and increasing. The largest proportion, close to half of individuals, reported increasing levels of fatigue over time. Lower levels of optimism at the time of diagnosis and increasing levels of mood disturbance over time were significantly associated with fatigue. On the other hand, the smallest proportion of individuals experienced decreasing levels of fatigue, which was also associated with decreased mood disturbance and increasing quality of life 2 years into remission. No evidence of association between demographic or clinical factors and fatigue over time was found. By using a person-centered statistical method, I was better able to account for the high level of heterogeneity of responses to illness and show that a subset of individuals continues to report higher levels of fatigue, and progressively poorer mood, even 2 years after their cancer treatment has ended.

This chapter contributes novel evidence to support that psychological functioning of AYA is a dynamic process and may be primarily driven by modifiable factors (e.g. personality characteristics such as optimism or mood).

8.3 What should we target in early prevention to facilitate the holistic recovery of AYAs?

Over the recent decades, the health care services in high-income countries have seen the shift towards a more patient-centered care with the aim of a holistic approach, treating an entire person beyond their ailments. In oncology this means focusing on the psychosocial impact of the disease beyond the physical aspect. However, in order to best address the problems and reduce the inequalities in psychosocial outcomes of AYAs with cancer, we ought to recognize that one-size-fit-all approach proves inadequate. To facilitate the holistic recovery of a young person with cancer, we need to target factors that promote resilience and contribute to psychopathology.

The evidence presented in this thesis suggests that there may be a myriad of bio-psycho-social factors that are individually based yet interact with the environmental factors and circumstances to produce the outcomes. The research question "*what should we target in early prevention*" is inherent to all empirical chapters of this thesis. Early prevention would likely benefit individuals. As our evidence from Chapter 3 suggests, a proportion of young people endorse sub-threshold levels of psychopathology. Early prevention measures may lower the risk of sub-threshold symptomatology worsening over time (Balázs et al., 2013). Modifiable factors (e.g. trouble relaxing) described in the studies offer feasible early prevention and intervention targets.

Moreover, in light of the findings presented in this thesis, we may also rephrase the question to ask "*whom should we target*" with early prevention efforts. This may be particularly important where routine psychosocial evaluation is not yet the norm. In countries or clinics where the resources are limited, health care professionals could rely on identification of "warning signals" such as lower levels of optimism at the time of diagnosis and offer additional psychological consultation to those most at risk.

8.4 Overall strengths and limitations

The research in this thesis has several strengths and limitations. Specific strengths and limitations for each study are described in the discussion of each

empirical chapter. This section describes my original contributions to the field of AYA psycho-social oncology, the broader methodological challenges that remain, and how those may be addressed in the future research. A brief summary of the section is presented in Table 8.1.

Table 8.1: Summary of my approach, limitations, and future directions.

Conceptual challenges	**My approach**	**Limitations**	**Future research**
Defining AYA	I focused on individuals between 15 – 39 years, diagnosed at 10 years or later. In my analysis I accounted for age differences when possible.	Underpowered samples to stratify by narrower age groups. Online study only included people 18 years or above, which may have resulted in an older sample.	Large and adequately powered studies should stratify the data analysis by narrower age groups in order to study the differences between younger and older adolescents, and young adults. Rather than age alone it would be important to consider the age-appropriateness of cancer care settings.
Cancer as single illness	Two of my empirical chapters focus on patients with sarcoma only. Other chapters include all cancer types and discuss any differences where observed.	My online study was underpowered to control for any differences. Sarcomas are still a highly heterogeneous group of tumors.	Large studies should stratify the data analysis by cancer type and consider cancer characteristics and prognostic factors when possible
Methodological challenges	**My approach**	**Limitations**	**Future research**
Measurement	I used several different measures for psychological distress, along with cancer-specific worry questionnaire and adapted several questions to cancer experience.	Many measures were not adapted to AYAs with cancer. Slovenian questionnaires need to be further validated. Outdated scales did not meet reliability criteria.	Researchers should continue to develop and adapt measures to the needs of adolescents and young adults with cancer. Novel findings need to be replicated in separate samples, and outdated scales should be revised.
Data collection	I conducted secondary data analysis of a large clinical dataset. New data was collected online approaching AYAs through online support systems for young patients and survivors.	Limited generalizability: Online participants are a self-select group and primarily female, the clinical dataset comes from a single medical center in Canada.	Researchers should work in tandem with health professionals and patient organizations in order to facilitate recruitment and improve the representativeness and generalizability of the findings.

…continued

Methodological challenges	My approach	Limitations	Future research
Study design and analysis	Non-experimental, mixed-method approach, combining qualitative and advanced quantitative methods. In line with open science practices, I pre-registered my study protocols, used transparent reporting, and share my analytical code freely.	Cross-sectional and observational evidence limits causal inference. Missing data and attrition were present in longitudinal data.	Researchers should adhere to open science practices and transparent reporting; sharing the analytical code and replication should become the norm. When analyzing longitudinal data, appropriate methods should be selected, and all the assumptions checked.

8.4.1 Defining adolescents and young adults

Adolescents and young adults are often found at the cusps between pediatric and adult clinics and services, even though they present with many unique needs (C. L. Daniel et al., 2015; Perez et al., 2020). The field lacks a consensus on how AYAs should be defined (Lang et al., 2015), and the definitions vary geographically (see Section 2.1.1). Because of the global scope of my research, I employed the broadest age range, including individuals from 15 to 39 years of age at the time of studies and diagnosed at age 10 or later with the aim to account for the impact of illness from adolescence onwards. The broad age range allowed me to account for the many transitions and milestones that young people face – from completing education to starting their families. Moreover, because the incidence of cancer increases into emerging adulthood (Fitzmaurice et al., 2019), this allowed me to recruit larger samples.

Even though I considered age differences in my analyses and how they may impact psychosocial outcomes, I did not observe any meaningful patters in my qualitative work (Chapter 4), nor any significant difference in longitudinal analysis (Chapter 7). The quantitative studies in my thesis lacked adequate power to subset the data into narrower age groups and further investigate if any difference exist. Additionally, due to the ethical constraints, my online studies (Chapter 5 & Chapter 6) only allowed me to recruit individuals who were 18 years or older at the time of the study. This may have resulted in an older sample, consequently less generalizable to younger AYAs.

Although evidence to date suggests that age at diagnosis may not play a significant role in psychosocial outcomes, future studies should aim to employ larger samples and stratify the analysis by narrower age groups in order to study any differences. More importantly, recent findings from Canada suggest that AYAs treated in pediatric settings fare better than AYAs treated in adult clinics (Gupta et al., 2019). Future analysis should not only focus on the chronological age, but also consider the treatment settings and their age-appropriateness.

8.4.2 Cancer as a single illness

Cancer is an umbrella term for an illness with many different types that merely shares the etiology; unconstrained proliferation of cells due to a mutation (Weinberg, 1996). Different types of cancer occur at different ages, may have distinctive biology, and require different treatment procedures (Barr et al., 2016; Bleyer et al., 2008). Throughout my thesis I distinguished between cancer types whenever possible. In Chapter 3 I found that having a brain tumor diagnosis may carry more severe ramifications for psychosocial wellbeing in AYAs compared to other types (Liptak et al., 2012), which often leaves them excluded from research (de Ruiter et al., 2016; Michel et al., 2009; Ozono et al., 2010). Chapter 4 and Chapter 7 focused exclusively on young patients with sarcoma, an understudied group (see Section and Chapter 4 for details). The unique nature and pronounced physical impact of sarcomas has previously made this group underrepresented in psychological research, and recent findings show that their psychosocial needs are yet to be met (Martins et al., 2020).

However, despite the same overarching diagnostic labels (e.g. breast, hematologic cancer), many cancers remain highly heterogeneous. Over the recent decade, nearly a 100 different subtypes of sarcoma alone have been identified (Fletcher, 2014). This makes the differences in tumor pathophysiology very difficult to control or adjust for. Nevertheless, my research suggests that modifiable factors rather than illness characteristic play a role in psychosocial outcomes. While I could not observe any differences between the cancer types in my online study (Chapter 5 & Chapter 6), my longitudinal work with AYAs with sarcoma revealed no association between tumor subtype, or tumor size and fatigue over time (Chapter 7).

Similar to the question of age differences, cancer type should be considered in the future studies. Larger samples could stratify the analysis by broader cancer type, or control for cancer or treatment characteristics when possible.

8.4.3 Measuring psychological distress

Measuring psychological distress in AYAs with cancer remains a challenge. In my systematic review I found evidence that majority of studies used questionnaires that were not adapted to the needs of this population (see Appendix B). This may be particularly problematic and result in inaccurate rates of psychopathology due to the symptomatic overlap between cancer and treatment side effects and mood or anxiety disorders.

In my work I overcame the challenge of measurement in several ways. Firstly, I conducted a qualitative study, which often precedes measure development (Snyder, Jensen, Segal, & Wu, 2013). My in-depth analysis provided invaluable context for the understanding of psychological wellbeing of an understudied population. For example, Chapter 4 highlighted that some individuals could experience symptoms of psychopathology primarily as side effects of the medication, a previously described phenomenon (Mehnert et al., 2014; Qato, Ozenberger, & Olfson, 2018).

Secondly, when designing my online study, in addition to the well-established measures for depression and anxiety (GAD-7 and PHQ-9; Kroenke, Spitzer, & Williams, 2001; Plummer, Manea, Trepel, & McMillan, 2016), I included a cancer-specific worry questionnaire, designed for the needs of AYAs (Klassen et al., 2015). I also devised several open-ended questions, which provided context to the quantitative answers, and I adapted the instructions to prompt individuals to think about their cancer experience when answering about the level of mental defeat (see Appendix D and Appendix H).

Thirdly, in Chapter 5 I used network analysis, which allowed me to explore the relationships between specific symptoms of psychopathology rather than latent constructs (i.e. depression), and evaluate each individual symptom's influence on the other symptoms (Borsboom & Cramer, 2013). This allowed me to overcome the possibility of inflating the sum scores of psychopathology in case where cancer-related fatigue (a side-effect) and fatigue (a symptom of depression) may have been mistakenly endorsed. Network modeling approach may prove invaluable for understanding the unique nature of psychological distress in young people living with and beyond cancer.

Lastly, prior to conducting the longitudinal analysis in Chapter 7, I rigorously tested the main measures of interest (Functional Assessment of Chronic Illness Therapy

(FACIT) for fatigue and Toronto Extremity Salvage Score (TESS) for functional outcomes). FACIT was originally developed for cancer patients (Webster et al., 2003) but was abbreviated for the analysis in order to meet reliability and measurement invariance criteria (see Appendix H for details). TESS showed poor model fit in our confirmatory factor analysis (see section 7.3.2.3) and was thus included as a covariate only.

Despite the many ways in which I addressed the problem of measurement there remain important limitations. Majority of the measures for psychological distress are still not adapted to AYAs with cancer. Moreover, the online study included Slovenian translations of the questionnaires. Even though the translation was carried out in forward and backward manner, and checked by 2 independent Slovenian psychologists for accuracy, the questionnaires need to be validated in a larger sample for the future use.

Chapter 5 and Chapter 7 present novel findings that warrant replication. When using generic measures such as GAD-7 and PHQ-9, and conducting network analysis, including a control group may shed light on any differences in the constellation of symptoms of psychopathology. Even though I observed no differences in levels of psychological distress between individuals in versus off treatment (Chapter 6), future studies should control for the treatment status, and rule out the potential contribution of symptoms resulting from active cancer treatment or medication use. Additionally, researchers should continue to complement the questionnaires with cancer-specific measures, and revise and update or adapt the outdated scales such as TESS.

8.4.4 Data collection and recruitment

Recruiting AYAs with cancer is challenging. Firstly, cancer in youth remains rare (K. D. Miller et al., 2016), and secondly, once treated, a lot of young people are lost to follow up and resultantly more difficult to track down (Harlan et al., 2011; Rokitka et al., 2017). The presence of social media and an increasing number of online support groups and charities devoted to youth with cancer has helped in making research opportunities easier to advertise, and more accessible to AYAs (Gorman et al., 2014).

By relying on social media and online platforms I was able to recruit internationally, and allowed participants to respond anonymously at their convenience,

which resulted in a diverse and larger sample (Chapter 5). Alternatively, Chapter 7 presents secondary data analysis based on a previously unexplored clinical dataset, aiming to recruit all newly diagnosed patients sequentially. The data is collected prospectively, and follows individuals from the time of diagnosis onwards, minimizing the biases resulting from retrospective data collection.

Despite the two different approaches to data collection in my empirical work, generalizability may be limited in both. Participants recruited online are a self-selected group and often skew the gender distribution, with higher female participation (Chapter 5 & Chapter 6). Even though the recruitment was open internationally, the sample was primarily limited to high-income countries. On the other hand, the clinical dataset is bound to a single medical center in Montreal, Canada, thus limiting representativeness to a limited geographical region.

In order to facilitate the recruitment and increase the representativeness of AYA samples, researchers should continue to employ diverse recruitment methods, advertising their research in clinics, as well as online. Strengthening the involvement of patient groups in clinical settings may further incentivize participation in research across the AYAs.

8.4.5 Study design and analysis

The empirical chapters of this thesis are based on non-experimental, observational study designs. Observational studies are practical in studying psychosocial outcomes in AYA with cancer and combined with the wealth of different methodological approaches I was able to address my research questions; which are the factors associated with resilience and psychopathology and how these may change over the course of illness.

The former question was addressed with rich qualitative data from semi-structured interviews, as well as questionnaire data from the online studies. Change over time was examined by secondary analysis of a longitudinal and prospective clinical dataset of young patients with sarcoma in Montreal, Canada. Particularly novel is the network approach to analysis of psychological functioning in AYA with cancer (Chapter 5) and application of group-based trajectory modeling to help us parcel the high level of variation in fatigue over time (Chapter 7). Network analysis offers a different way of conceptualizing psychopathology in AYAs (Borsboom & Cramer,

2013), while using growth mixture modeling such as GBTM with random effects, allows for a more accurate description of populations with high variability in the outcome of interest (i.e. fatigue) (D S Nagin, 2014; Saunders, 2010).

Nevertheless, an important limitation of the observational work, and particularly cross-sectional studies is that we cannot draw any causal inference or assume directionality of effects. Moreover, due to the emerging nature of evidence in AYA psycho-social oncology, and novel application of advanced psychometrics, majority of the work presented in this thesis is exploratory and warrants further investigation. As with any secondary data analysis, I was limited to the variables available and collected by the original study. Missing data and attrition are a common problem in the longitudinal studies (Twisk & de Vente, 2002) and prevented me to explore changes over longer period of time. To overcome this challenge, I imputed the missing data under the Missing at Random (MAR) assumption (Little & Rubin, 2014; van Buuren & Groothuis-Oudshoorn, 2011) The method and the sensitivity analyses are reported in the relevant chapters and respective appendices.

Lastly, studying psychosocial outcomes in young people with cancer is difficult because we do not have information about their psychological wellbeing prior to cancer. This limitation may be addressed only with large, population based epidemiological studies that collect a wealth of data from an early age and follow individuals over time.

In order to minimize bias in my work, I pre-registered my systematic review protocol prior to beginning the search (PROSPERO: CRD42018088884), as well as the analytical plan for network analysis on Open Science Framework (OSF; https://osf.io/3rnv6/). Further in line with the open science best practices, I used transparent reporting of the results and analysis along with the freely available analytical code for R, data descriptions, and changes to the original protocols (Košir, Loades, et al., 2020; Košir, Roškar, et al., 2020; Kosir et al., 2019a). For example, I also devised a novel way to visualize qualitative data (visual matrices, Figure 4.3, Figure 4.4 in Chapter 4), and present all the individual trajectories along the smooth, group-based trajectories in order to highlight the level of heterogeneity and allow a critical reader to interpret the findings in light of the limitations.

Future studies should build on the existing literature and systematically evidence the analytical protocols and openly share the code. Doing so will help in making psychological research more transparent and reproducible (Gilmore, Diaz,

Wyble, & Yarkoni, 2017; Nosek et al., 2015). Replication of findings in an emerging field is key. Moreover, future studies should not only aim to conduct longitudinal analyses, but also strive to apply statistical methods best suited for the research questions and the data at hand, and check all of the necessary assumptions prior to the analysis.

8.4.6 Summary of overall strengths and limitations

The limitations described in this section are important to consider when reading and interpreting the results of this thesis. Overall, the biggest strength of this thesis is the mixed method approach, which allowed me to complement the quantitative findings with qualitative work in an emerging field where many voices need yet to be heard. All of the empirical studies of this thesis made an original contribution to the existing literature and offer intriguing findings upon which the future studies can expand.

8.5 Summary of future research directions

To assure progress and reduce the inequalities in psychosocial outcomes for young people with cancer, we need to continue investing into research. The findings presented in this thesis suggest that at least a third of AYAs report clinical levels of psychopathology or psychosocial difficulties during and after cancer treatment. Future research should continue to address the challenges and limitations outlined in the section above (section 8.4). Above all, my work demonstrates the need to a) develop, adapt, validate, and standardize AYA cancer-specific measures for psycho-social outcomes, b) establish larger data sources, c) conduct research in an open and transparent fashion, and share the data and analytical code when possible, and d) expand the research efforts to mid- and low-income countries.

The need for new and cancer-specific measures has been recognized before (Lazor et al., 2017), but because measure development can be a lengthy and resource-intensive process (Boateng, Neilands, Frongillo, Melgar-Quiñonez, & Young, 2018), researchers could rely on adapting the existing measures, and test the reliability assumptions when conducting secondary data analysis.

My work demonstrated the need for establishing novel and larger data sources. Large and longitudinal epidemiological studies will allow future studies to examine change over longer time period more reliably. Efforts to collect large psychosocial

dataset in childhood cancer are well-underway. For example, Swiss Childhood Cancer Survivor Study in Europe is a prospective cohort study actively recruiting since 2007 and plans to follow individuals over 50 years (Kuehni et al., 2012), and Childhood Cancer Survivor Study funded by National Cancer Institute (NCI) began in 1994 in order to assess health-related as well as psychological sequalae of childhood cancer (Robison et al., 2009). Similar data sources for AYAs are lacking (Pollock, 2020).

The process of improving measurement, as well as psychological research in AYA oncology will be further facilitated by open science practices (Bartling & Friesike, 2014). Open sharing of data and code can aid younger researchers, help them learn new methodologies, and allows replication and important scrutiny of published research (e.g. Nosek et al., 2015). Conducting research in an open manner also carries the potential to expand the research efforts to currently underrepresented populations from low- and mid-income countries.

8.6 Broader implications*

Despite our best efforts many young people continue to report difficulties in the years after cancer treatment. These psychosocial difficulties, spanning across many domains, pose a burden on the individual as well as societal level. The academic, patient, and care provider communities have recognized the unmet needs for support for AYAs with cancer and began prioritizing work that will help us tailor our approaches to care (Aldiss et al., 2018; Buchacz et al., 2018).

I highlighted clinical implications of each empirical study at the end of each chapter. This section provides an overview of the clinical and policy implications. A summary of recommendations for clinical care and policy is presented in Table 8.2.

* Parts of this section have been adapted from:

Košir, U., Bowes, L., Taylor, R., Gerrand, C., Windsor, R., Onasanya, M., Martins, A. (2020). Psychological adaptation and recovery in youth with sarcoma: A qualitative study with practical implications for clinical care and research. *BMJ Open*. http://dx.doi.org/10.1136/bmjopen-2020-038799

Košir, U., Roškar, S., Wild, J., Bowes, L. (2020). Mapping the needs and psychological outcomes of Slovenian adolescent and young adult cancer patients: An exploratory mixed-methods study. *European Journal of Cancer Care*. https://doi.org/10.1111/ecc.13326

Table 8.2: A summary of recommendations for improvements in clinical care and policy.

Individual level	**System-wide level**
Better management of individual needs; from side effects to psychological support	Shorter waiting times, and reduced lag to diagnosis for young people
More time with one's oncologist	Structured support service for return to school or work
Education and information needs; illness late effects (management & prevention)	Streamlined schemes for financial aid for those in need (addressing the "hidden" costs, e.g. parking)
Health literacy & promotion of patient engagement in care, feeling heard and listened to	Age-appropriate services for AYA
Consultation for family, partners and peers	Assuring for quality care at smaller, non-specialty clinics
Psychoeducation (Promoting adoption of adaptive coping techniques such as optimism)	Better organized and multidisciplinary approach to diagnosis and treatment
Early physical rehabilitation (*prehabilitation*) and improved uptake of available resources	Family planning and fertility preservation services
	Signposting to support for mental health when active treatment ends

8.6.1 Clinical practice

In Chapter 1 I introduced the constructs of resilience and psychopathology in AYAs with cancer. The latter is described uniformly in the existing literature: experiencing clinical levels of psychological distress, which compromise one's functioning and interfere with daily living (APA, 2013; WHO, 2019). On the other hand, resilience remains difficult to define (Molina et al., 2014). Though the studies presented in this thesis often describe psychopathology in a binary fashion (one either meets the threshold for depression or anxiety or not), together my chapters highlight that resilience and psychopathology are not necessarily mutually exclusive, and that psychological adaptation to cancer is a complex process with many positive and negative factors at play, some of which can change across time.

Because the existing psychosocial interventions fail to adequately address the needs of AYAs (see Walker, Martins, Aldiss, Gibson, & Taylor, (2016), or section 10), I proposed to move beyond the latent constructs of resilience and psychopathology and instead consider the psychological adaptation as a dynamic process. This carries

implications for clinical work, and in particular encourages health care professionals to consider individual circumstances of young patients so as to account for individually based modifiable risk and resilience factors. Rather than developing and testing novel psychological interventions, using the existing interventions in a targeted manner may improve the outcomes. Based on the findings presented, targeting low mood and promoting relaxation with the existing approaches may lessen the overall level of symptomatology (Chapter 5), and reduce fatigue over time (Chapter 7).

Moreover, I found that young people want to be engaged in their cancer care, and adequately informed about their illness. A good relationship with a medical team may help alleviate a young patient's distress (Kosir et al., 2020; Košir, Roškar, et al., 2020), and may even improve adherence to the preventative measures and surveillance of health in the future (Kennard et al., 2004), all of which are crucial in improving outcomes in the long-term.

8.6.2 Policy

An overview of translational research suggests that the lag between implementation of new findings in policy is approximately 17 years (Z. S. Morris, Wooding, & Grant, 2011). This presents a challenge, especially in a young and rapidly evolving field such as AYA psycho-social oncology. Future policies should make it a priority to revise and update the practices in a timely manner.

My work highlights the need for a continued collaboration and international effort to recruit and collect high quality data from AYAs with cancer. Policies that fund, promote, and facilitate novel and cross-border data collection and sharing will not only offer the potential for larger interdisciplinary studies, but potentially also increase the representativeness of individuals from different regions and backgrounds.

Europe has begun to outline an ambitious plan – Europe Beating Cancer plan (*Roadmap: Europe's beating cancer plan*, 2020) which covers policies across many domains, from clinical trials accessibility to cancer prevention, and post-cancer care. Such large efforts need to continue to recognize AYAs as a unique group of patients with specific needs. Chapter 2 and Chapter 3 have shown that AYAs are often placed with younger children or older adults, which has slowed the progress for this particular age group. Prioritizing age-appropriate services for AYAs should be part of any new policy.

Research is an endeavor that has the potential to benefit the health of the entire societies. While recognizing the patients' autonomy and respecting voluntarily participation, research should become a core indicator of health (EU, 2013). Making participation in research a norm and integrating it within clinical practices could help us advance faster. However, researchers, health care professionals, policy makers and patient organizations should continue to work in tandem to assure accessible, acceptable, safe, and ethical research practices.

8.6.3 A note on the COVID-19 and its aftermath:

Chapter 6 is based on a small study, which was my best attempt to recognize the impact of the pandemic on the vulnerable population I work with. At the time of this writing (December 10, 2020), the pandemic and associated restrictive measures are still in place in many countries even though the vaccination of the most vulnerable already began in some places.

I have shown that the onset of the pandemic caused increases in psychological distress in young people with cancer who may be at risk due to immunosuppressive effects of treatment or illness itself (Kamboj & Sepkowitz, 2009). Measures aiming at preventing the spread of the virus and hoping to serve those at highest risk of dying (i.e. people with advanced cancer; Garrett-Mayer & Rini, (2020) have not been inconsequential for some young people whose cancer has spread or became inoperable due to the delays (BBC, 2020b, 2020a).

Some of the changes in cancer care protocols may be temporary, others might last for months or years after the pandemic is over. As we approach the next phase of this global pandemic, I wanted to highlight some challenges, as well as opportunities resulting from it. Most importantly, any crucial decisions and guidelines taken in the coming months should be as transparent, impartial, and as evidence-based as possible.

8.6.3.1 Backlog of patients

Most cancer centers reduced the number of face-to-face consultations and delayed treatments, weighing the risks and benefits of doing so (van de Haar et al., 2020). As the governments begin to loosen up the restrictive measures, the first challenge in the oncological settings will be managing the backlog of patients who had their treatments or appointments postponed. Moreover, a gradual return to the clinics

implies a slower reuptake, and de novo reprioritization of cases. Clear guidelines for management of gradual re-opening should become a priority and be established ahead of time.

8.6.3.2 Equitable approach to cancer care

It is clear that the pandemic disproportionally affects populations already marginalized: socio-economically disadvantaged, minorities, and elderly (Wilder, 2020; Winskill et al., 2020). Such differences exist within AYA cancer populations as well, and future measures taken should aim to not further exacerbate the status of those most affected.

8.6.3.3 Information gaps and needs

Peer-reviewed evidence about the novel SARS-CoV-2 is accumulating daily. As scientific literature rapidly grows, it will become increasingly important to translate the findings and the technical jargon into useful guidance for young cancer patients and their caretakers. An overwhelming number of online resources and information for cancer patients sprung quickly and is just clicks away (Nekhlyudov et al., 2020). However, we do not know if the information provided is addressing patients' needs and concerns, to what extent they find it trustworthy, and if they are able to successfully filter through the plethora of resources advertised.

8.6.3.4 COVID-19 vaccine safety

Though the vaccination began, and medical professionals are urging populations at risk to be vaccinated, the efficacy and safety of these vaccine in cancer patients has not yet been fully established, with some evidence suggesting a poorer response for cancer patients receiving treatment on transplant (Fanciullino, Ciccolini, & Milano, 2020). When and if the safety is established for young cancer patients, efforts should be made to promote the uptake of the vaccine, which may be limited to the general skepticism of the novel agents (Dror et al., 2020; B. L. Miller, 2020).

8.6.3.5 Mental Health

Experts warn about the lingering impact of the current pandemic on mental health and emphasize the need for increased care and research (Holmes et al., 2020). Countless and rapid changes in daily routines combined with the uncertainty about the

future have taken a toll on our collective well-being. In oncology departments, the decisions taken were largely driven by efforts to increase survivorship, paying little attention to the potential mental health impact of delaying life-saving treatments. In the months to come, it will be important to recognize that subsets of cancer populations experience increased psychological distress even under normal circumstances (H. R. Smith, 2015). Loss to follow up care was already a problem for many young people with cancer. Individuals who experience anxiety due to COVID-19 might struggle to follow up with their care, which could lead to poorer outcomes in the long-term.

Opportunities

Despite the many challenges that lie ahead, post-COVID-19 era also presents with opportunities for improvements in the holistic cancer care for AYAs.

8.6.3.6 Streamlined care

Whenever possible oncologists switched from intravenous to oral chemotherapy agents and posted the medication to patients' home in order to prevent overcrowding and unnecessary exposure. Many follow-up consultations occurred digitally, paving the way for telemedicine. Both, at-home care and telemedicine offer novel ways of cancer care, which might be equally effective and sometimes preferred among the AYAs (Abrol et al., 2017).

8.6.3.7 Health literacy

With an increasing number of cancer care procedures taking place in patients' own homes, health literacy becomes increasingly important (Sørensen et al., 2020). Defined as one's ability to find, appraise, understand, and apply health information (World Health Organization, 2013), health literacy will be key to sustained and effective at-home cancer care. Increasing health literacy of patients will contribute to better outcomes and has the potential to lessen the burden on the health care systems in the long run. Efforts should be placed on training the medical professionals in delivering adequate and reliable directions via digital technologies, as well as assuring patients' successful engagement with digital health technologies.

8.6.3.8 Holistic approach to care

The time ahead presents an opportunity for bridging the gaps between many departments implicated in cancer care. Oncology departments have to recognize the increased and imminent need for psychological support and should liaise with psychiatry, social work and other relevant departments in order to deliver the necessary psychosocial support for AYA cancer patients and their families. Patient-centered approach recognizes that successful oncological outcomes are a result of multiple domains, all of which need to be addressed (i.e. physical, psychosocial, occupational).

8.7 Conclusion

Cancer, a socio-biological phenomenon is increasingly common, not just due to the augmenting prevalence of this disease, but also due to the increasing number of people who live long beyond their diagnosis. Despite the ever-improving treatments and survival outcomes, the disease presents a burden. A subset of adolescents and young adults report psychopathology and psychosocial difficulties during and after treatment, which are currently not adequately addressed. By investigating the mechanisms of resilience and psychopathology in youth with cancer my work contributes to the existing evidence by emphasizing the need to evaluate individual circumstances and by shedding light on factors that contribute to the psychosocial adaptation. Most encouragingly, modifiable factors, which we may be able to target with interventions are the ones contributing to the psychosocial outcomes in young people living with and beyond cancer.

The AYA research community has grown substantially since I began my doctoral work, which fills me with enthusiasm and hope. Young people who were previously overlooked were given a voice, and as the new evidence accumulates, we will be able to continue making our strides to improve the holistic approach to care and reduce the taboos around cancer in youth.

Reference:

Abate, C., Lippe, S., Bertout, L., Drouin, S., Krajinovic, M., Rondeau, E., … Sultan, S. (2018). Could we use parent report as a valid proxy of child report on anxiety, depression, and distress? A systematic investigation of father-mother-child triads in children successfully treated for leukemia. *Pediatric Blood & Cancer*, *65*(2). https://doi.org/https://dx.doi.org/10.1002/pbc.26840

Abrol, E., Groszmann, M., Pitman, A., Hough, R., Taylor, R. M., & Aref-Adib, G. (2017). Exploring the digital technology preferences of teenagers and young adults (TYA) with cancer and survivors: a cross-sectional service evaluation questionnaire. *Journal of Cancer Survivorship*, *11*(6), 670–682. https://doi.org/10.1007/s11764-017-0618-z

Acaster, S., Dickerhoof, R., DeBusk, K., Bernard, K., Strauss, W., & Allen, L. F. (2015). Qualitative and quantitative validation of the FACIT-fatigue scale in iron deficiency anemia. *Health and Quality of Life Outcomes*, *13*(1). https://doi.org/10.1186/s12955-015-0257-x

Acquati, C., Zebrack, B. J., Faul, A. C., Embry, L., Aguilar, C., Block, R., … Cole, S. (2018). Sexual functioning among young adult cancer patients: A 2-year longitudinal study. *Cancer*, *124*(2), 398–405. https://doi.org/10.1002/cncr.31030

Albritton, K., & Bleyer, W. A. (2003). The management of cancer in the older adolescent. *European Journal of Cancer*, *39*(18), 2584–2599. https://doi.org/10.1016/j.ejca.2003.09.013

Alderfer, M. A., Navsaria, N., & Kazak, A. E. (2009). Family Functioning and Posttraumatic Stress Disorder in Adolescent Survivors of Childhood Cancer. *Journal of Family Psychology*, *23*(5), 717–725. https://doi.org/10.1037/a0015996

Aldiss, S., Fern, L. A., Phillips, B., & Gibson, F. (2018). *Teenage and Young Adult Cancer: Research Priorities. Final Report of the James Lind Alliance Priority Setting Partnership.*

Aldridge, A. A., & Roesch, S. C. (2007). Coping and adjustment in children with cancer: A meta-analytic study. *Journal of Behavioral Medicine*, *30*(2), 115–129. https://doi.org/http://dx.doi.org/10.1007/s10865-006-9087-y

Allemani, C., Matsuda, T., Di Carlo, V., Harewood, R., Matz, M., Nikšić, M., … Lewis, C. (2018). Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *The Lancet*, *391*(10125), 1023–1075. https://doi.org/10.1016/S0140-6736(17)33326-3

Allison, D. C., Carney, S. C., Ahlmann, E. R., Hendifar, A., Chawla, S., Fedenko, A., … Menendez, L. R. (2012). A meta-analysis of osteosarcoma outcomes in the modern medical era. *Sarcoma*, *2012*. https://doi.org/10.1155/2012/704872

Ander, M., Thorsell Cederberg, J., von Essen, L., & Hoven, E. (2018). Exploration of psychological distress experienced by survivors of adolescent cancer reporting a need for psychological support. *PloS One*, *13*(4), e0195899. https://doi.org/10.1371/journal.pone.0195899

Anninga, J. K., Gelderblom, H., Fiocco, M., Kroep, J. R., Taminiau, A. H. M., Hogendoorn, P. C. W., & Egeler, R. P. (2011). Chemotherapeutic adjuvant treatment for osteosarcoma: Where do we stand? *European Journal of Cancer*, *47*(16), 2431–2445. https://doi.org/10.1016/j.ejca.2011.05.030

APA. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th Editio). Vancouver: American Psychiatric Association.

Arch, J. J., & Carr, A. L. (2017). Using Mechanical Turk for research on cancer survivors. *Psycho-Oncology*, *26*(10), 1593–1603. https://doi.org/10.1002/pon.4173

Arnett, J. J. (2000). Emerging adulthood: A theory of development from the late teens through the twenties. *American Psychologist*, *55*(5), 469–480. https://doi.org/10.1037/0003-066X.55.5.469

Asparouhov, T., & Muthén, B. (2014). Auxiliary Variables in Mixture Modeling: Three-Step Approaches Using Mplus. *Structural Equation Modeling*, *21*(3), 329–341. https://doi.org/10.1080/10705511.2014.915181

Badr, H., Chandra, J., Paxton, R. J., Ater, J. L., Urbauer, D., Cruz, C. S., & Demark-Wahnefried, W. (2013). Health-related quality of life, lifestyle behaviors, and intervention preferences of survivors of childhood cancer. *Journal of Cancer Survivorship*, *7*(4), 523–534. https://doi.org/10.1007/s11764-013-0289-3

Baird, H., Patterson, P., Medlow, S., & Allison, K. R. (2019). Understanding and improving survivorship care for adolescents and young adults with cancer. *Journal of Adolescent and Young Adult Oncology*, *8*(5), 581–586. https://doi.org/10.1089/jayao.2019.0031

Balázs, J., Miklõsi, M., Keresztény, Á., Hoven, C. W., Carli, V., Wasserman, C., … Wasserman, D. (2013). Adolescent subthreshold-depression and anxiety: Psychopathology, functional impairment and increased suicide risk. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *54*(6), 670–677. https://doi.org/10.1111/jcpp.12016

Barlevy, D., Wangmo, T., Elger, B. S., & Ravitsky, V. (2016). Attitudes, Beliefs, and Trends Regarding Adolescent Oncofertility Discussions: A Systematic Literature Review. *Journal of Adolescent and Young Adult Oncology*, *5*(2), 119–134. https://doi.org/10.1089/jayao.2015.0055

Barnett, M., McDonnell, G., DeRosa, A., Schuler, T., Philip, E., Peterson, L., … Jennifer, S. (2016). Psychosocial outcomes and interventions among cancer survivors diagnosed during adolescence and young adulthood (AYA): a systematic review. *J Cancer Surviv*, *10*(5), 814–831. https://doi.org/10.1007/s11764-016-0527-6

Barr, R. D. (2014). "Delays" in diagnosis: A misleading concept, yet providing opportunities for advancing clinical care. *Journal of Pediatric Hematology/Oncology*, *36*(3), 169–172. https://doi.org/10.1097/MPH.0000000000000108

Barr, R. D., Ferrari, A., Ries, L., Whelan, J., & Bleyer, W. A. (2016). Cancer in adolescents and young adults: A narrative review of the current status and a view of the future. *JAMA Pediatrics*, *170*(5), 495–501. https://doi.org/10.1001/jamapediatrics.2015.4689

Barrera, M., Shaw, A. K., Speechley, K. N., Maunsell, E., & Pogany, L. (2005). Educational and social late effects of childhood cancer and related clinical, personal, and familial characteristics. *Cancer*, *104*(8), 1751–1760. https://doi.org/10.1002/cncr.21390

Barsevick, A. M., Irwin, M. R., Hinds, P., Miller, A., Berger, A., Jacobsen, P., … Cella, D. (2013). Recommendations for high-priority research on cancer-related fatigue in children and adults. *Journal of the National Cancer Institute*, *105*(19), 1432–1440. https://doi.org/10.1093/jnci/djt242

Bartling, S., & Friesike, S. (2014). *Opening science: The evolving guide on how the internet is changing research, collaboration and scholarly publishing*. (S. Bartling & S. Friesike, Eds.), *Indian Journal of Environmental Health* (Vol. 44). Springer

open. https://doi.org/10.1007/978-3-319-00026-8

Barton, S. (2000). Which clinical studies provide the best evidence? The best RTC still trumps the best observational study. *Bmj*, *321*, 255–256. https://doi.org/DOI 10.1136/bmj.321.7256.255

Bauer, D. J., & Curran, P. J. (2003). Distributional Assumptions of Growth Mixture Models: Implications for Overextraction of Latent Trajectory Classes. *Psychological Methods*, *8*(3), 338–363. https://doi.org/10.1037/1082-989X.8.3.338

Bauld, C., Anderson, V., & Arnold, J. (1998). Psychosocial aspects of adolescent cancer survival. *Journal of Paediatrics and Child Health*, *34*(2), 120–126. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=9588632

BBC. (2020a). Cancer: woman urges young people to be aware of disease. Retrieved November 20, 2020, from https://www.bbc.com/news/uk-wales-54576604

BBC. (2020b). Cancer patient left inoperable after Covid-19 delay. Retrieved October 28, 2020, from https://www.bbc.com/news/uk-england-nottinghamshire-53935643

Bellizzi, K. M., & Blank, T. O. (2007). Cancer-related identity and positive affect in survivors of prostate cancer. *Journal of Cancer Survivorship*, *1*(1), 44–48. https://doi.org/10.1007/s11764-007-0005-2

Bernstein, D., & Rubin, D. (2006). The Centrality of Event Scale: A Measure of Integrating a Trauma into One's Identity and its Relation to Post-Traumatic Stress Disorder Symptoms. *Behavior Research and Therapy*, *44*(2), 219–231. https://doi.org/10.1016/j.brat.2005.01.009

Bernstein, E. E., Heeren, A., & McNally, R. J. (2019). Reexamining trait rumination as a system of repetitive negative thoughts: A network analysis. *Journal of Behavior Therapy and Experimental Psychiatry*, *63*(May 2018), 21–27. https://doi.org/10.1016/j.jbtep.2018.12.005

Bibby, H., White, V., Thompson, K., & Anazodo, A. (2017). What Are the Unmet Needs and Care Experiences of Adolescents and Young Adults with Cancer? A Systematic Review. *Journal of Adolescent and Young Adult Oncology*, *6*(1), 6–30. https://doi.org/10.1089/jayao.2016.0012

Bitsko, M. J., Stern, M., Dillon, R., Russell, E. C., & Laver, J. (2008). Happiness and time perspective as potential mediators of quality of life and depression in adolescent cancer. *Pediatric Blood & Cancer*, *50*(3), 613–619. https://doi.org/https://dx.doi.org/10.1002/pbc.21337

Bleyer, A. (2005). The adolescent and young adult gap in cancer care and outcome. *Current Problems in Pediatric and Adolescent Health Care*, *35*(5), 182–217. https://doi.org/10.1016/j.cppeds.2005.02.001

Bleyer, A., Barr, R., Hayes-Lattin, B., Thomas, D., Ellis, C., Anderson, B., & Oncology, on behalf of the B. and C. T. S. of the U. N. C. I. P. R. G. in A. and Y. A. (2008). The distinctive biology of cancer in adolescents and young adults. *Nature Reviews Cancer*, *8*(4), 288–298. https://doi.org/10.1038/nrc2349

Boateng, G. O., Neilands, T. B., Frongillo, E. A., Melgar-Quiñonez, H. R., & Young, S. L. (2018). Best Practices for Developing and Validating Scales for Health, Social, and Behavioral Research: A Primer. *Frontiers in Public Health*, *6*(June), 1–18. https://doi.org/10.3389/fpubh.2018.00149

Bonanno, G. A., Romero, S. A., & Klein, S. I. (2015). The Temporal Elements of Psychological Resilience: An Integrative Framework for the Study of Individuals,

Families, and Communities. *Psychological Inquiry*, *26*(2), 139–169. https://doi.org/10.1080/1047840X.2015.992677

Bonanno, G. A., Westphal, M., & Mancini, A. D. (2011). Resilience to Loss and Potential Trauma. *Annual Review of Clinical Psychology*, *7*, 511–535. https://doi.org/10.1146/annurev-clinpsy-032210-104526

Borsboom, D., & Cramer, A. O. J. (2013). Network Analysis: An Integrative Approach to the Structure of Psychopathology. *Annual Review of Clinical Psychology*, *9*(1), 91–121. https://doi.org/10.1146/annurev-clinpsy-050212-185608

Boulad, F., Kamboj, M., Bouvier, N., Mauguen, A., & Kung, A. L. (2020). COVID-19 in children with cancer in New York City. *JAMA Oncology*, *Published*, 3–4. https://doi.org/doi:10.1001/jamaoncol.2020.2028 Author

Bower, J. E., Crosswell, A. D., & Slavich, G. M. (2014). Childhood adversity and cumulative life stress: Risk factors for cancer-related fatigue. *Clinical Psychological Science*, *2*(1), 108–115. https://doi.org/10.1177/2167702613496243

Bower, J. E., Ganz, P. A., Desmond, K. A., Rowland, J. H., Meyerowitz, B. E., & Belin, T. R. (2000). Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *Journal of Clinical Oncology*, *18*(4), 743–753.

Bradford, N. K., & Chan, R. J. (2017). Health promotion and psychological interventions for adolescent and young adult cancer survivors: A systematic literature review. *Cancer Treatment Reviews*, *55*, 57–70. https://doi.org/10.1016/j.ctrv.2017.02.011

Braithwaite, E. C., O'Connor, R. M., Degli-Esposti, M., Luke, N., & Bowes, L. (2017). Modifiable predictors of depression following childhood maltreatment: A systematic review and meta-analysis. *Translational Psychiatry*, *7*(7), 1–10. https://doi.org/10.1038/tp.2017.140

Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N., & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *The Lancet*, *395*, 912–920. https://doi.org/10.1016/S0140-6736(20)30460-8

Brown, L. F., & Kroenke, K. (2009). Cancer-related fatigue and its associations with depression and anxiety: A systematic review. *Psychosomatics*, *50*(5), 440–447. https://doi.org/10.1176/appi.psy.50.5.440

Brown, R. C., Dwyer, T., Kasten, C., Krotoski, D., Li, Z., & Linet, M. S. (2007). Cohort Profile : The International Childhood Cancer Cohort Consortium (I4C), *36*(August), 724–730. https://doi.org/10.1093/ije/dyl299

Brown, R. T., Madan-Swain, A., & Lambert, R. (2003). Posttraumatic Stress Symptoms in Adolescent Survivors of Childhood Cancer and Their Mothers. *Journal of Traumatic Stress*, *16*(4), 309–318. https://doi.org/http://dx.doi.org/10.1023/A:1024465415620

Brown, T. A., Campbell, L. A., Lehman, C. L., Grisham, J. R., & Mancill, R. B. (2001). Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. *Journal of Abnormal Psychology*, *110*(4), 585–599. https://doi.org/10.1037/0021-843X.110.4.585

Buchacz, A., Farrington, T., Gudger, B., Leppänen, E., Narbutas, Š., Rizvi, K., … Voß, A. (2018). *White Paper on the needs of young people living with cancer: 5 Calls to action*. Brussels, Belgium.

Butow, P., Kelly, S., Thewes, B., Hruby, G., Sharpe, L., & Beith, J. (2015). Attentional bias and metacognitions in cancer survivors with high fear of cancer recurrence. *Psycho-Oncology*, *24*(4), 416–423. https://doi.org/10.1002/pon.3659

Campo, R. A., Bluth, K., Santacroce, S. J., Knapik, S., Tan, J., Gold, S., … Asher, G. N. (2017). A mindful self-compassion videoconference intervention for nationally recruited posttreatment young adult cancer survivors: feasibility, acceptability, and psychosocial outcomes. *Supportive Care in Cancer*, *25*(6), 1759–1768. https://doi.org/10.1007/s00520-017-3586-y

Campos, M. P. O., Hassan, B. J., Riechelmann, R., & Del Giglio, A. (2011). Cancer-related fatigue: A practical review. *Annals of Oncology*, *22*(6), 1273–1279. https://doi.org/10.1093/annonc/mdq458

Care, M., & Muriel, A. C. (2016). *Pediatric Psychosocial Oncology: Textbook for Multidisciplinary Care*. https://doi.org/10.1007/978-3-319-21374-3

Carlson, L. E., Angen, M., Cullum, J., Goodey, E., Koopmans, J., Lamont, L., … Bultz, B. D. (2004). High levels of untreated distress and fatigue in cancer patients. *British Journal of Cancer*, *90*(12), 2297–2304. https://doi.org/10.1038/sj.bjc.6601887

Carpentier, M. Y., & Fortenberry, J. D. (2010). Romantic and sexual relationships, body image, and fertility in adolescent and young adult testicular cancer survivors: A review of the literature. *Journal of Adolescent Health*, *47*(2), 115–125. https://doi.org/http://dx.doi.org/10.1016/j.jadohealth.2010.04.005

Carpentieri, S. C., Meyer, E. A., Delaney, B. L., Victoria, M. L., Gannon, B. K., Doyle, J. M., & Kieran, M. W. (2003). Psychosocial and behavioral functioning among pediatric brain tumor survivors. *Journal of Neuro-Oncology*, *63*(3), 279–287. https://doi.org/10.1023/A:1024203323830

Carr, C. P., Martins, C., Stingel, A. M., Lemgruber, V., & Juruena, M. (2013). The Role of Early Life Stress in Adult Psychiatric Disorders: A Systematic Review According to Childhood Trauma Subtypes. *The Journal of Nervous and Mental Disease*, *201*(12), 1007–1020. https://doi.org/10.1097/NMD.0000000000000049

Casanova, M., Bagliacca, E. P., Silva, M., Patriarca, C., Veneroni, L., Clerici, C. A., … Ferrari, A. (2020). How young patients with cancer perceive the Covid-19 (coronavirus) epidemic in Milan, Italy: is there room for other fears? *Pediatric Blood & Cancer*, (March), e28318. https://doi.org/10.1002/pbc.28318

Chalmers, J. A., Sansom-Daly, U. M., Patterson, P., McCowage, G., & Anazodo, A. (2018). Psychosocial assessment using telehealth in adolescents and young adults with cancer: A partially randomized patient preference pilot study. *Journal of Medical Internet Research*, *7*(8), e168. https://doi.org/10.2196/resprot.8886

Chaturvedi, S., Peter Maguire, G., & Somashekar, B. (2006). Somatization in cancer. *International Review of Psychiatry*, *18*(1), 49–54. https://doi.org/10.1080/09540260500466881

Chaturvedi, S., & Uchitomi, Y. (2012). Psychosocial and Psychiatric Disorders. In L. Grassi & M. Riba (Eds.), *Clinical Psycho-Oncology: An International Perspective* (1st ed., pp. 55–69). NJ: Wiley.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., … Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, *395*(10223), 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

Cheung, S. Y., & Delfabbro, P. (2016). Are you a cancer survivor? A review on cancer identity. *Journal of Cancer Survivorship*, *10*(4), 759–771. https://doi.org/10.1007/s11764-016-0521-z

Chino, F., Peppercorn, J. M., Rushing, C., Kamal, A. H., Altomare, I., Samsa, G., & Zafar, S. Y. (2017). Out-of-Pocket costs, financial distress, and underinsurance in cancer care. *JAMA Oncology*, *3*(11), 1582–1584.

https://doi.org/10.1001/jamaoncol.2017.2148

Cisler, J. M., James, G. A., Tripathi, S., Mletzko, T., Heim, C., Hu, X. P., … Kilts, C. D. (2013). Differential functional connectivity within an emotion regulation neural network among individuals resilient and susceptible to the depressogenic effects of early life stress. *Psychological Medicine*, *43*(3), 507–518. https://doi.org/10.1017/S0033291712001390

Collins, D. E., Ellis, S. J., Janin, M. M., Wakefield, C. E., Bussey, K., Cohn, R. J., … Fardell, J. E. (2019). A Systematic Review Summarizing the State of Evidence on Bullying in Childhood Cancer Patients/Survivors. *Journal of Pediatric Oncology Nursing*, *36*(1), 55–68. https://doi.org/10.1177/1043454218810136

Compas, B. E., Desjardins, L., Vannatta, K., Young-Saleme, T., Rodriguez, E. M., Dunn, M., … Gerhardt, C. A. (2014). Children and Adolescents Coping With Cancer: Self- and Parent Reports of Coping and Anxiety/Depression. *Health Psychol*, *33*(8), 853–861. https://doi.org/10.1037/hea0000083

Compas, B. E., Orosan, P. G., & Grant, K. E. (1993). Adolescent stress and coping: implications for psychopathology during adolescence. *Journal of Adolescence*, *16*, 331–349.

Corey, A. L., Haase, J. E., Azzouz, F., & Monahan, P. O. (2008). Social support and symptom distress in adolescents/young adults with cancer. *Journal of Pediatric Oncology Nursing*, *25*(5), 275–284. https://doi.org/http://dx.doi.org/10.1177/1043454208321117

Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry*, *60*(8), 837–844. https://doi.org/10.1001/archpsyc.60.8.837

Costenbader, E., & Valente, T. W. (2003). The stability of centrality measures when networks are sampled. *Social Networks*, *25*(4), 283–307. https://doi.org/10.1016/S0378-8733(03)00012-1

Coughlin, S. S. (1990). Recall bias in epidemiologic studies. *Journal of Clinical Epidemiology*, *43*(1), 87–91. https://doi.org/10.1016/0895-4356(90)90060-3

Cousino, M. K., Hazen, R., Josie, K. L., Laschinger, K., de Blank, P., M.K., C., … P., de B. (2017). Childhood Cancer and Brain Tumor Late Effects: Relationships with Family Burden and Survivor Psychological Outcomes. *Journal of Clinical Psychology in Medical Settings*, *24*(3–4), 279–288. https://doi.org/http://dx.doi.org/10.1007/s10880-017-9519-6

Cramer, A. O. J., Borsboom, D., Aggen, S. H., & Kendler, K. S. (2012). The pathoplasticity of dysphoric episodes: Differential impact of stressful life events on the pattern of depressive symptom inter-correlations. *Psychological Medicine*, *42*(5), 957–965. https://doi.org/10.1017/S003329171100211X

Crawshaw, M. A., & Sloper, P. (2010). "Swimming against the tide" - the influence of fertility matters on the transition to adulthood or survivorship following adolescent cancer. *European Journal of Cancer Care*, *19*(5), 610–620. https://doi.org/10.1111/j.1365-2354.2009.01118.x

Crone, E. A., & Dahl, R. E. (2012). Understanding adolescence as a period of social-affective engagement and goal flexibility. *Nature Reviews Neuroscience*, *13*(9), 636–650. https://doi.org/10.1038/nrn3313

Crook, B., & Love, B. (2017). Examining the Light and Dark of an Online Young Adult Cancer Support Community. *Qualitative Health Research*, *27*(6), 938–948. https://doi.org/10.1177/1049732316672638

Cukor, J., Wyka, K., Jayasinghe, N., & Difede, J. A. (2010). The nature and course of subthreshold PTSD. *Journal of Anxiety Disorders*, *24*(8), 918–923.

https://doi.org/10.1016/j.janxdis.2010.06.017

Cunningham, R. M., Walton, M. A., & Carter, P. M. (2018). The major causes of death in children and adolescents in the United States. *New England Journal of Medicine*, *379*(25), 2468–2475. https://doi.org/10.1056/NEJMsr1804754

Curran, L., Sharpe, L., & Butow, P. (2017). Anxiety in the context of cancer: A systematic review and development of an integrated model. *Clinical Psychology Review*, *56*(June), 40–54. https://doi.org/10.1016/j.cpr.2017.06.003

Curran, P. J., & Bauer, D. J. (2011). The Disaggregation of Within-Person and Between-Person Effects in Longitudinal Models of Change. *Annual Review of Psychology*, *62*(1), 583–619. https://doi.org/10.1146/annurev.psych.093008.100356

Curt, G. A. (2000). Impact of Cancer-Related Fatigue on the Lives of Patients: New Findings From the Fatigue Coalition. *The Oncologist*, *5*(5), 353–360. https://doi.org/10.1634/theoncologist.5-5-353

Curtis, R., & Mackinnon, S. P. (2020). A Tutorial in Longitudinal Measurement Invariance Using Lavaan. *PsyarXiv*, 1–30.

D'Agostino, N. M., & Edelstein, K. (2013). Psychosocial challenges and resource needs of young adult cancer survivors: Implications for program development. *Journal of Psychosocial Oncology*, *31*(6), 585–600. https://doi.org/10.1080/07347332.2013.835018

Daniel, C. L., Emmons, K. M., Fasciano, K., Nevidjon, B., Fuemmeler, B. F., & Demark-Wahnefried, W. (2015). Needs and lifestyle challenges of adolescents and young adults with cancer: Summary of an institute of medicine and livestrong foundation workshop. *Clinical Journal of Oncology Nursing*, *19*(6), 675–681. https://doi.org/10.1188/15.CJON.19-06AP

Daniel, L., Kazak, A. E., Li, Y., Hobbie, W., Ginsberg, J., Butler, E., & Schwartz, L. (2016). Relationship between sleep problems and psychological outcomes in adolescent and young adult cancer survivors and controls. *Supportive Care in Cancer*, *24*(2), 539–546. https://doi.org/https://dx.doi.org/10.1007/s00520-015-2798-2

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, *9*(1), 46–56. https://doi.org/10.1038/nrn2297

Das, J. K., Salam, R. A., Lassi, Z. S., Khan, M. N., Mahmood, W., Patel, V., & Bhutta, Z. A. (2016). Interventions for adolescent mental health: An overview of systematic reviews. *Journal of Adolescent Health*, *59*, S49–S60. https://doi.org/http://dx.doi.org/10.1016/j.jadohealth.2016.06.020

Davidge, K., Bell, R., Ferguson, P., Turcotte, R., Wunder, J., & Davis, A. M. (2009). Patient expectations for surgical outcome in extremity soft tissue sarcoma. *Journal of Surgical Oncology*, *100*(5), 375–381. https://doi.org/10.1002/jso.21301

Davis, A. M., Wright, J. G., Williams, J. I., Bombardier, C., Griffin, A., & Bell, R. S. (1996). Development of a measure of physical function for patients with bone and soft tissue sarcoma. *Quality of Life Research*, *5*(5), 508–516.

De Clercq, E., Rost, M., Gumy-Pause, F., Diesch, T., Espelli, V., & Elger, B. S. (2020). Moving Beyond the Friend-Foe Myth: A Scoping Review of the Use of Social Media in Adolescent and Young Adult Oncology. *Journal of Adolescent and Young Adult Oncology*, *00*(00). https://doi.org/10.1089/jayao.2019.0168

De Jonge, P., Ormel, J., Van Den Brink, R. H. S., Van Melle, J. P., Spijkerman, T. A., Kuijper, A., … Schene, A. H. (2006). Symptom dimensions of depression

following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *American Journal of Psychiatry*, *163*(1), 138–144. https://doi.org/10.1176/appi.ajp.163.1.138

De Raaf, P. J., De Klerk, C., & Van Der Rijt, C. C. D. (2013). Elucidating the behavior of physical fatigue and mental fatigue in cancer patients: A review of the literature. *Psycho-Oncology*, *22*(9), 1919–1929. https://doi.org/10.1002/pon.3225

de Ruiter, M. A., Schouten-van Meeteren, A. Y. N., van Vuurden, D. G., Maurice-Stam, H., Gidding, C., Beek, L. R., … Grootenhuis, M. A. (2016). Psychosocial profile of pediatric brain tumor survivors with neurocognitive complaints. *Quality of Life Research*, *25*(2), 435–446. https://doi.org/10.1007/s11136-015-1091-7

Decker, C., Phillips, C. R., & Haase, J. E. (2004). Information needs of adolescents with cancer. *Journal of Pediatric Oncology Nursing*, *21*(6), 327–334. https://doi.org/10.1177/1043454204269606

DeRouen, M. C., Smith, A. W., Tao, L., Bellizzi, K. M., Lynch, C. F., Parsons, H. M., … Keegan, T. H. M. (2015). Cancer-related information needs and cancer's impact on control over life influence health-related quality of life among adolescents and young adults with cancer. *Psycho-Oncology*, *24*(9), 1104–1115. https://doi.org/10.1002/pon.3730

Desai, A., Sachdeva, S., Parekh, T., & Desai, R. (2020). Covid-19 and cancer: Lessons from a pooled meta-analysis. *JCO Global Oncology*, *6*, 557–559. https://doi.org/10.1200/GO.20.00097

Dinmohamed, A. G., Visser, O., Verhoeven, R. H. A., Louwman, M. W. J., van Nederveen, F. H., Willems, S. M., … Siesling, S. (2020). Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. *The Lancet Oncology*. https://doi.org/10.1016/S1470-2045(20)30265-5

Dolbeault, S., Szporn, A., & Holland, J. C. (1999). Psycho-oncology: Where have we been? Where are we going? *European Journal of Cancer*, *35*(11), 1554–1558.

Downs, S., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions. *Journal of Epidemiology Community Health*, *52*(377–384), 377–384.

Drew, D., Kable, A., & van der Riet, P. (2019). The adolescent's experience of cancer: An integrative literature review. *Collegian*, *26*(4), 492–501. https://doi.org/10.1016/j.colegn.2019.01.002

Dror, A. A., Eisenbach, N., Taiber, S., Morozov, N. G., Mizrachi, M., Zigron, A., … Sela, E. (2020). Vaccine hesitancy: the next challenge in the fight against COVID-19. *European Journal of Epidemiology*, *35*(8), 775–779. https://doi.org/10.1007/s10654-020-00671-y

Dunmore, E., Clark, D. M., & Ehlers, A. (2001). A prospective investigation of the role of cognitive factors in persistent Posttraumatic Stress Disorder (PTSD) after physical or sexual assault. *Behaviour Research and Therapy*, *39*(9), 1063–1084. https://doi.org/10.1016/S0005-7967(00)00088-7

Durlak, J. A., & Wells, A. M. (1998). Evaluation of Indicated Preventive Intervention (Secondary Prevention) Mental Health Programs for Children and Adolescents. *American Journal of Community Psychology*, *26*(5), 775–802.

Edwards, B., & Clarke, V. (2004). The psychological impact of a cancer diagnosis on families: The influence of family functioning and patients' illness characteristics on depression and anxiety. *Psycho-Oncology*, *13*, 562–576. https://doi.org/10.1002/pon.773

Ekwueme, D. U., Yabroff, K. R., Guy, G. P., Banegas, M. P., de Moor, J. S., Li, C., …

Virgo, K. S. (2014). National Cancer Survivors Medical Costs and Productivity Losses of Cancer Survivors — United. *Morbidity and Mortality Weekly Report (MMWR)*, *63*(23), 505–510.

Elo, S., Kääriäinen, M., Kanste, O., Pölkki, T., Utriainen, K., & Kyngäs, H. (2014). Qualitative Content Analysis. *SAGE Open*, *4*(1), 215824401452263. https://doi.org/10.1177/2158244014522633

Elo, S., & Kyngäs, H. (2008). The qualitative content analysis process. *Journal of Advanced Nursing*, *62*(1), 107–115. https://doi.org/10.1111/j.1365-2648.2007.04569.x

Enskär, K., Carlsson, M., Golsäter, M., & Hamrin, E. (1997). Symptom distress and life situation in adolescents with cancer. *Cancer Nursing*, *20*(1), 23–33. https://doi.org/10.1097/00002820-199702000-00004

Epskamp, S., Borsboom, D., & Fried, E. I. (2017). Estimating psychological networks and their accuracy: A tutorial paper. *Behavior Research Methods*, *50*(1), 195–212. https://doi.org/10.3758/s13428-017-0862-1

Epskamp, S., Cramer, A. O. J., Waldorp, L. J., Schmittmann, V. D., & Borsboom, D. (2012). Qgraph: Network visualizations of relationships in psychometric data. *Journal of Statistical Software*, *48*(4). https://doi.org/10.18637/jss.v048.i04

Epskamp, S., & Fried, E. I. (2017). A Tutorial on Regularized Partial Correlation Networks. *ArXiv*.

Epskamp, S., Waldorp, L. J., Mõttus, R., & Borsboom, D. (2013). The Gaussian Graphical Model in Cross-sectional and Time-series Data.

Erickson, J. M. (2004). Fatigue in adolescents with cancer: a review of the literature. *Clinical Journal of Oncology Nursing*, *8*(2), 139–145. https://doi.org/10.1188/04.cjon.139-145

Erickson, S. J., Gerstle, M., & Montague, E. Q. (2008). Repressive adaptive style and self-reported psychological functioning in adolescent cancer survivors. *Child Psychiatry and Human Development*, *39*(3), 247–260. https://doi.org/10.1007/s10578-007-0085-2

Erickson, S. J., & Steiner, H. (2000). Trauma spectrum adaptation: Somatic symptoms in long-term pediatric cancer survivors. *Psychosomatics*, *41*(4), 339–346. https://doi.org/10.1176/appi.psy.41.4.339

Etikan, I., Musa, S. A., & Alkassim, R. S. (2016). Comparison of convenience sampling and purposive sampling. *American Journal of Theoretical and Applied Statistics*, *5*(1), 1–4. https://doi.org/10.11648/j.ajtas.20160501.11

EU. (2013). *Evaluation of the use and impact of the European Community Health Indicators ECHI by Member States*.

Fan, S.-Y., & Eiser, C. (2009). Body image of children and adolescents with cancer: A systematic review. *Body Image*, *6*(4), 247–256. https://doi.org/http://dx.doi.org/10.1016/j.bodyim.2009.06.002

Fanciullino, R., Ciccolini, J., & Milano, G. (2020). COVID-19 vaccine race: watch your step for cancer patients. *British Journal of Cancer*, (November), 3–4. https://doi.org/10.1038/s41416-020-01219-3

Fergusson, D. M., & Woodward, L. J. (2002). Mental Health, Educational, and Social Role Outcomes of Adolescents With Depression. *Archives of General Psychiatry*, *59*(3), 225–231. https://doi.org/10.1001/archpsyc.59.3.225

Fern, L. A., Lewandowski, J. A., Coxon, K. M., & Whelan, J. (2014). Available, accessible, aware, appropriate, and acceptable: A strategy to improve participation of teenagers and young adults in cancer trials. *The Lancet Oncology*, *15*(8), e341–e350. https://doi.org/10.1016/S1470-2045(14)70113-5

Fern, L. A., Taylor, R. M., Whelan, J., Pearce, S., Grew, T., Brooman, K., … Gibson, F. (2013). The art of age-appropriate care: Reflecting on a conceptual model of the cancer experience for teenagers and young adults. *Cancer Nursing*, *36*(5), 27–38. https://doi.org/10.1097/NCC.0b013e318288d3ce

Fern, L., Davies, S., Eden, T., Feltbower, R., Grant, R., Hawkins, M., … Whelan, J. (2008). Rates of inclusion of teenagers and young adults in England into National Cancer Research Network clinical trials: Report from the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group. *British Journal of Cancer*, *99*(12), 1967–1974. https://doi.org/10.1038/sj.bjc.6604751

Fernandez, C., Fraser, G. A. M., Freeman, C., Grunfeld, E., Gupta, A., Mery, L. S., … Schacter, for the Canadian Task For, B. (2011). Principles and Recommendations for the Provision of Healthcare in Canada to Adolescent and Young Adult–Aged Cancer Patients and Survivors. *Journal of Adolescent and Young Adult Oncology*, *1*(1), 53–59. https://doi.org/10.1089/jayao.2010.0008

Ferrans, C. E., Zerwic, J. J., Wilbur, J. E., & Larson, J. L. (2005). Conceptual model of health-related quality of life. *Journal of Nursing Scholarship : An Official Publication of Sigma Theta Tau International Honor Society of Nursing / Sigma Theta Tau*, *37*(4), 336–342. https://doi.org/http://dx.doi.org/10.1111/j.1547-5069.2005.00058.x

Ferrari, A., Bleyer, A., Patel, S., Chiaravalli, S., Gasparini, P., & Casanova, M. (2018). The challenge of the management of adolescents and young adults with soft tissue sarcomas. *Pediatric Blood and Cancer*, *65*(7), 1–8. https://doi.org/10.1002/pbc.27013

Ferrari, A., Gasparini, P., Gill, J., & Gorlick, R. (2018). Challenges of Clinical Management of Adolescent and Young Adults with Bone and Soft Tissue Sarcoma. *Cancer Journal (United States)*, *24*(6), 301–306. https://doi.org/10.1097/PPO.0000000000000337

Fitzmaurice, C., Abate, D., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdel-Rahman, O., … Murray, C. J. L. (2019). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-Adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. *JAMA Oncology*, *5*(12), 1749–1768. https://doi.org/10.1001/jamaoncol.2019.2996

Fletcher, C. D. M. (2014). WHO classification of soft tissue tumours: An update based on the 2013 (4th) edition. *Pathology*, *46*(2), 2–11. https://doi.org/10.1111/his.12267

Foygel Barber, R., & Drton, M. (2015). High-dimensional Ising model selection with Bayesian information criteria. *Electronic Journal of Statistics*, *9*(0000), 567–607. https://doi.org/10.1214/15-EJS1012

Foygel, R., & Drton, M. (2010). Extended Bayesian information criteria for Gaussian graphical models. *Advances in Neural Information Processing Systems 23: 24th Annual Conference on Neural Information Processing Systems 2010, NIPS 2010*, 1–9.

Francis, G. (2012). Publication bias and the failure of replication in experimental psychology. *Psychonomic Bulletin and Review*, *19*(6), 975–991. https://doi.org/10.3758/s13423-012-0322-y

Fried, E. I. (2015). Problematic assumptions have slowed down depression research: Why symptoms, not syndromes are the way forward. *Frontiers in Psychology*, *6*(MAR), 1–11. https://doi.org/10.3389/fpsyg.2015.00309

Fried, E. I., & Cramer, A. O. J. (2017). Moving Forward: Challenges and Directions for Psychopathological Network Theory and Methodology. *Perspectives on Psychological Science*, *12*(6), 999–1020. https://doi.org/10.1177/1745691617705892

Fried, E. I., Eidhof, M. B., Palic, S., Costantini, G., Huisman-van Dijk, H. M., Bockting, C. L. H., … Karstoft, K. I. (2018). Replicability and Generalizability of Posttraumatic Stress Disorder (PTSD) Networks: A Cross-Cultural Multisite Study of PTSD Symptoms in Four Trauma Patient Samples. *Clinical Psychological Science*, *6*(3), 335–351. https://doi.org/10.1177/2167702617745092

Fritz, G. K., & Williams, J. R. (1988). Issues of adolescent development for survivors of childhood cancer. *Journal of the American Academy of Child & Adolescent Psychiatry*, *27*(6), 712–715. https://doi.org/http://dx.doi.org/10.1097/00004583-198811000-00008

Fruchterman, T. M. J., & Reingold, E. M. (1991). Graph drawing by force-directed placement. *Software: Practice and Experience*, *21*(11), 1129–1164. https://doi.org/10.1002/spe.4380211102

Gale, N. K., Heath, G., Cameron, E., Rashid, S., & Redwood, S. (2013). Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*, *13*(1), 117. https://doi.org/10.1186/1471-2288-13-117

Galea, S., Merchant, R. M., & Lurie, N. (2020). The mental health consequences of COVID-19 and physical distancing. *JAMA Internal Medicine*, E1–E2. https://doi.org/10.1001/jamainternmed.2020.1562

Garrett-Mayer, E., & Rini, B. I. (2020). To Treat or Not to Treat—Balancing Benefits and Risks ofTreatment Delay Among PatientsWith Cancer During the COVID-19 Pandemic. *JAMA Oncology*, (October 2020), E1–E2. https://doi.org/doi:10.1001/jamaoncol.2020.4886

Gerhardt, C. A., Yopp, J. M., Leininger, L., Valerius, K. S., Correll, J., Vannatta, K., & Noll, R. B. (2007). Brief report: post-traumatic stress during emerging adulthood in survivors of pediatric cancer. *Journal of Pediatric Psychology*, *32*(8), 1018–1023. https://doi.org/jsm038 [pii]\r10.1093/jpepsy/jsm038

Geue, K., Sender, A., Schmidt, R., Richter, D., Hinz, A., Schulte, T., … Stöbel-Richter, Y. (2014). Gender-specific quality of life after cancer in young adulthood: a comparison with the general population. *Quality of Life Research*, *23*(4), 1377–1386. https://doi.org/10.1007/s11136-013-0559-6

Gianinazzi, M. E., Rueegg, C. S., Wengenroth, L., Bergstraesser, E., Rischewski, J., Ammann, R. A., … for Swiss Pediatric Oncology, G. (2013). Adolescent survivors of childhood cancer: are they vulnerable for psychological distress? *Psychooncology*, *22*(9), 2051–2058. https://doi.org/https://dx.doi.org/10.1002/pon.3249

Gilleland Marchak, J., Elchuri, S. V., Vangile, K., Wasilewski-Masker, K., Mertens, A. C., & Meacham, L. R. (2015). Perceptions of Infertility Risks among Female Pediatric Cancer Survivors Following Gonadotoxic Therapy. *Journal of Pediatric Hematology/Oncology*, *37*(5), 368–372. https://doi.org/10.1097/MPH.0000000000000349

Gilmore, R., Diaz, M., Wyble, B., & Yarkoni, T. (2017). Progress Toward Openness, Transparency, and Reproducibility in Cognitive Neuroscience. *Annals of the New York Academy of Sciences*, *1396*(1), 5–18. https://doi.org/doi:10.1111/nyas.13325

Glasson, J. E. (1995). A descriptive and exploratory pilot study into school re-entrance

for adolescents who have received treatment for cancer. *Journal of Advanced Nursing*, *22*(4), 753–758. https://doi.org/10.1046/j.1365-2648.1995.22040753.x

Golding, G., Pembrey, P., & Jones, J. (2001). ALSPAC - The Avon Longitudinal Study of Parents and Children I. Study methodology. *Paediatric and Perinatal Epidemiology*, *15*(1), 74–87. https://doi.org/10.1046/j.1365-3016.2001.00325.x

Gore, F. M., Bloem, P. J. N., Patton, G. C., Ferguson, J., Joseph, V., Coffey, C., … Mathers, C. D. (2011). Global burden of disease in young people aged 10-24 years: A systematic analysis. *The Lancet*, *377*(9783), 2093–2102. https://doi.org/10.1016/S0140-6736(11)60512-6

Gorman, J. R., Roberts, S. C., Dominick, S. A., Malcarne, V. L., Dietz, A. C., & Su, H. I. (2014). A Diversified Recruitment Approach Incorporating Social Media Leads to Research Participation Among Young Adult-Aged Female Cancer Survivors. *Journal of Adolescent and Young Adult Oncology*, *3*(2), 59–65. https://doi.org/10.1089/jayao.2013.0031

Gough, N. J., Smith, C., Ross, J. R., Riley, J., & Judson, I. (2011). Symptom burden, survival and palliative care in advanced soft tissue sarcoma. *Sarcoma*, *2011*. https://doi.org/10.1155/2011/325189

Greenzang, K. A., Fasciano, K. M., Block, S. D., & Mack, J. W. (2020). Early Information Needs of Adolescents and Young Adults About Late Effects of Cancer Treatment. *Cancer*, *0*, 1–8. https://doi.org/10.1002/cncr.32932

Gupta, S., Pole, J. D., Baxter, N. N., Sutradhar, R., Lau, C., Nagamuthu, C., & Nathan, P. C. (2019). The effect of adopting pediatric protocols in adolescents and young adults with acute lymphoblastic leukemia in pediatric vs adult centers: An IMPACT Cohort study. *Cancer Medicine*, *8*(5), 2095–2103. https://doi.org/10.1002/cam4.2096

Gutierrez-Colina, A. M., Lee, J. L., VanDellen, M., Mertens, A., & Marchak, J. G. (2017). Family functioning and depressive symptoms in adolescent and young adult cancer survivors and their families: A dyadic analytic approach. *Journal of Pediatric Psychology*, *42*(1), 19–27. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc13&NEWS=N&AN=2017-44778-003

Haase, J. E. (1987). Components of courage in chronically ill adolescents: a phenomenological study. *Advanced Nursing Science*, *9*(2), 64–80.

Haase, J. E., Kintner, E. K., Monahan, P. O., & Robb, S. L. (2014). The Resilience in Illness Model (RIM) Part 1: Exploratory Evaluation in Adolescents and Young Adults with Cancer, *37*(3), 1–25. https://doi.org/10.1097/NCC.0b013e31828941bb

Hall, B. C., Short, V. M., Giberson, S., & Howe-Martin, L. (2020). A Cognitive Behavioral Therapy Group for Adolescent and Young Adult Cancer Patients: A Review of a Pilot Program. *Journal of Adolescent and Young Adult Oncology*, *9*(3), 422–425. https://doi.org/10.1089/jayao.2019.0104

Harlan, L. C., Lynch, C. F., Keegan, T. H. M., Hamilton, A. S., Wu, X. C., Kato, I., … Potosky, A. L. (2011). Recruitment and follow-up of adolescent and young adult cancer survivors: The AYA HOPE Study. *Journal of Cancer Survivorship*, *5*(3), 305–314. https://doi.org/10.1007/s11764-011-0173-y

Hauken, M. A., Holsen, I., Fismen, E., & Bogsnes Larsen, T. M. (2015). Working toward a good life as a cancer survivor: A longitudinal study on positive health outcomes of a rehabilitation program for young adult cancer survivors. *Cancer Nursing*, *38*(1), 3–15. https://doi.org/10.1097/NCC.0000000000000138

Henson, J. M., Reise, S. P., & Kim, K. H. (2007). Detecting mixtures from structural

model differences using latent variable mixture modeling: A comparison of relative model fit statistics. *Structural Equation Modeling*, *14*(2), 202–226. https://doi.org/10.1080/10705510709336744

Herle, M., Micali, N., Abdulkadir, M., Loos, R., Bryant-waugh, R., Hübel, C., … Stavola, B. L. De. (2020). Identifying typical trajectories in longitudinal data : modelling strategies and interpretations. *European Journal of Epidemiology*, (March). https://doi.org/10.1007/s10654-020-00615-6

Hirschfeld, R. M. A. (2001). The comorbidity of major depression and anxiety disorders: Recognition and management in primary care. *Primary Care Companion to the Journal of Clinical Psychiatry*, *3*(6), 244–254. https://doi.org/10.4088/pcc.v03n0609

Hobbie, W. L., Stuber, M., Meeske, K., Wissler, K., Rourke, M. T., Ruccione, K., … Kazak, A. E. (2000). Symptoms of posttraumatic stress in young adult survivors of childhood cancer. *Journal of Clinical Oncology*, *18*(24), 4060–4066. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-0034671370&partnerID=40&md5=e1314452f614cf6ef0d63289647f91b0

Hochberg, Z., & Konner, M. (2020). Emerging Adulthood, a Pre-adult Life-History Stage. *Frontiers in Endocrinology*, *10*(January), 1–12. https://doi.org/10.3389/fendo.2019.00918

Hoekstra-Weebers, J. E., Jaspers, J. P., Kamps, W. A., & Klip, E. C. (2001). Psychological adaptation and social support of parents of pediatric cancer patients: a prospective longitudinal study. *Journal of Pediatric Psychology*, *26*(4), 225–235. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11329482

Hofman, M., Ryan, J. L., Figueroa-Moseley, C. D., Jean-Pierre, P., & Morrow, G. R. (2007). Cancer-Related Fatigue: The Scale of the Problem. *The Oncologist*, *12*(S1), 4–10. https://doi.org/10.1634/theoncologist.12-s1-4

Hofmarcher, T., Brådvik, G., Jönsson, B., Lindgren, P., Jönsson, B., & Wilking, N. (2019). Comparator Report on Cancer in Europe 2019 – Disease Burden, Costs and Access to Medicines, 230. Retrieved from https://ihe.se/wp-content/uploads/2020/01/IHE-Report-2019_7_.pdf

Holland, J. C. (2002). History of psycho-oncology: Overcoming attitudinal and conceptual barriers. *Psychosomatic Medicine*, *64*(2), 206–221. https://doi.org/10.1097/00006842-200203000-00004

Holmes, E. A., O'Connor, R. C., Perry, V. H., Tracey, I., Wessely, S., Arseneault, L., … Bullmore, E. (2020). Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *The Lancet Psychiatry*, *0366*(20), 1–14. https://doi.org/10.1016/S2215-0366(20)30168-1

Horner, M., Ries, L., Krapcho, M., Neyman, N., Aminou, R., & Howlader, N. (2008). SEER Cancer Statistics Review, 1975-2006. Retrieved May 24, 2018, from http://www.joplink.net/prev/201003/ref/16-001.html

Hu, L. T., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*, *6*(1), 1–55. https://doi.org/10.1080/10705519909540118

Huang, I. C., Brinkman, T. M., Armstrong, G. T., Leisenring, W., Robison, L. L., & Krull, K. R. (2017). Emotional distress impacts quality of life evaluation: a report from the Childhood Cancer Survivor Study. *Journal of Cancer Survivorship*, *11*(3), 309–319. https://doi.org/10.1007/s11764-016-0589-5

Husson, O., Zebrack, B., Block, R., Embry, L., Aguilar, C., Hayes-Lattin, B., & Cole,

S. (2017). Posttraumatic growth and well-being among adolescents and young adults (AYAs) with cancer: a longitudinal study. *Supportive Care in Cancer*, *25*(9), 2881–2890. https://doi.org/10.1007/s00520-017-3707-7

Husson, Olga, & Zebrack, B. J. (2017). Perceived impact of cancer among adolescents and young adults: Relationship with health-related quality of life and distress. *Psycho-Oncology*, *26*, 1307–1315. https://doi.org/http://dx.doi.org/10.1002/pon.4300

Hyphantis, T., Tomenson, B., Paika, V., Almyroudi, A., Pappa, C., Tsifetaki, N., … Creed, F. (2009). Somatization is associated with physical health-related quality of life independent of anxiety and depression in cancer, glaucoma and rheumatological disorders. *Quality of Life Research*, *18*(8), 1029–1042. https://doi.org/10.1007/s11136-009-9527-6

Infurna, M. R., Reichl, C., Parzer, P., Schimmenti, A., Bifulco, A., & Kaess, M. (2016). Associations between depression and specific childhood experiences of abuse and neglect: A meta-analysis. *Journal of Affective Disorders*, *190*, 47–55. https://doi.org/10.1016/j.jad.2015.09.006

Jacobs, A. J., Michels, R., Stein, J., & Levin, A. S. (2015). Improvement in Overall Survival from Extremity Soft Tissue Sarcoma over Twenty Years. *Sarcoma*. https://doi.org/http://dx.doi.org/10.1155/2015/279601

JAYAO. (2011). What Should the Age Range Be for AYA Oncology? *Journal of Adolescent and Young Adult Oncology*, *1*(1), 3–10. https://doi.org/10.1089/jayao.2011.1505

Johnson, L.-M., Torres, C., Sykes, A., Gibson, D. V, & Baker, J. N. (2017). The bereavement experience of adolescents and early young adults with cancer: Peer and parental loss due to death is associated with increased risk of adverse psychological outcomes. *PloS One*, *12*(8), e0181024. https://doi.org/https://dx.doi.org/10.1371/journal.pone.0181024

Jones, P. (2018). Networktools: Tools for identifying important nodes in networks, *R Package*.

Jones, P., Mair, P., Simon, T., & Zeileis, A. (2020). Netowrk trees: A method for recursively partitioning covariance structures. *Psychometrika*. https://doi.org/10.1007/s11336-020-09731-4

Jorm, A. F., Morgan, A., & Hetrick, S. E. (2008). Relaxation for depression. *Cochrane Database of Systematic Reviews*, (2). https://doi.org/10.1002/14651858.CD007142

Kaffenberger, C. (2006). School Reentry for Students with a Chronic Illness: A Role for Professional School Counselors. *Professional School Counseling*, *9*(3), 223–230. https://doi.org/10.5330/prsc.9.3.xr27748161346325

Kalisch, R., Baker, D. G., Basten, U., Boks, M. P., Bonanno, G. A., Brummelman, E., … Kleim, B. (2017). The resilience framework as a strategy to combat stress-related disorders. *Nature Human Behaviour*, *1*(11), 784–790. https://doi.org/10.1038/s41562-017-0200-8

Kalisch, R., Cramer, A. O. J., Binder, H., Fritz, J., Leertouwer, Ij., Lunansky, G., … van Harmelen, A. L. (2019). Deconstructing and Reconstructing Resilience: A Dynamic Network Approach. *Perspectives on Psychological Science*, *14*(5), 765–777. https://doi.org/10.1177/1745691619855637

Kalisch, R., Müller, M. B., & Tüscher, O. (2015). A conceptual framework for the neurobiological study of resilience. *The Behavioral and Brain Sciences*, *38*(2015), e92. https://doi.org/10.1017/S0140525X1400082X

Kamboj, M., & Sepkowitz, K. A. (2009). Nosocomial infections in patients with cancer.

The Lancet Oncology, *10*(6), 589–597. https://doi.org/10.1016/S1470-2045(09)70069-5

Kash, K. M., Mago, R., & Kunkel, E. J. S. (2005). Psychosocial oncology: Supportive care for the cancer patient. *Seminars in Oncology*, *32*(2), 211–218. https://doi.org/10.1053/j.seminoncol.2004.11.011

Katz, E. R., & Madan-Swain, A. (2006). Maximizing School, Academic, and Social Outcomes in Children and Adolescents With Cancer. *Comprehensive Handbook of Childhood Cancer and Sickle Cell Disease: A Biopsychosocial Approach.*, 313–338. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc5&NEWS=N&AN=2006-07718-017

Kazak, A. E., Alderfer, M., Rourke, M. T., Simms, S., Streisand, R., & Grossman, J. R. (2004). Posttraumatic stress disorder (PTSD) and posttraumatic stress symptoms (PTSS) in families of adolescent childhood cancer survivors. *Journal of Pediatric Psychology*, *29*(3), 211–219. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=15131138

Keller, M. C., Neale, M. C., & Kendler, K. S. (2007). Association of different adverse life events with distinct patterns of depressive symptoms. *American Journal of Psychiatry*, *164*(10), 1521–1529. https://doi.org/10.1176/appi.ajp.2007.06091564

Kennard, B. D., Stewart, S. M., Olvera, R., Bawdon, R. E., O'Hailin, A., Lewis, C. P., & Winick, N. J. (2004). Nonadherence in adolescent oncology patients: Preliminary data on psychological risk factors and relationships to outcome. *Journal of Clinical Psychology in Medical Settings*, *11*(1), 30–39. https://doi.org/http://dx.doi.org/10.1023/B:JOCS.0000016267.21912.74

Kentsis, A. (2020). Why do young people get cancer? *Pediatr Blood Cancer*, *e28335*, 1–6. https://doi.org/10.1002/pbc.28335

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*, *62*(June), 593–602. https://doi.org/10.1001/archpsyc.62.6.593

Klassen, A. F., Rosenberg-Yunger, Z. R. S., D'Agostino, N. M., Cano, S. J., Barr, R., Syed, I., … Nathan, P. C. (2015). The development of scales to measure childhood cancer survivors' readiness for transition to long-term follow-up care as adults. *Health Expectations*, *18*(6), 1941–1955. https://doi.org/10.1111/hex.12241

Klosky, J. L., Howell, C. R., Li, Z., Foster, R. H., Mertens, A. C., Robison, L. L., & Ness, K. K. (2012). Risky health behavior among adolescents in the childhood cancer survivor study cohort. *Journal of Pediatric Psychology*, *37*(6), 634–646. https://doi.org/10.1093/jpepsy/jss046

Kluetz, P. G., Slagle, A., Papadopoulos, E. J., Johnson, L. L., Donoghue, M., Kwitkowski, V. E., … Pazdur, R. (2016). Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials : Symptomatic Adverse Events , Physical Function , and Disease-Related Symptoms, 1553–1559. https://doi.org/10.1158/1078-0432.CCR-15-2035

Koch, L., Jansen, L., Brenner, H., & Arndt, V. (2013). Fear of recurrence and disease progression in long-term (≥5 years) cancer survivors - A systematic review of quantitative studies. *Psycho-Oncology*, *22*(1), 1–11. https://doi.org/10.1002/pon.3022

Koocher, G. P., & O'Malley, J. E. (1981). *The Damocles syndrome*. New York: McGraw-Hill.

Kosir, U. (2019). Methodological Issues in Psychosocial Research in Adolescent and Young Adult Cancer Populations. *Journal of Adolescent and Young Adult Oncology*, *00*(00), 1–4. https://doi.org/10.1089/jayao.2019.0034

Kosir, U., Bowes, L., Taylor, R. M., Gerrand, C., Windsor, R., Onasanya, M., & Martins, A. (2020). Psychological adaptation and recovery in youth with sarcoma: a qualitative study with practical implications for clinical care and research. *BMJ Open*, *10*(11), e038799. https://doi.org/10.1136/bmjopen-2020-038799

Košir, U., Loades, M., Wild, J., Wiedemann, M., Krajnc, A., Roškar, S., & Bowes, L. (2020). The impact of COVID-19 on the cancer care of adolescents and young adults and their well-being: Results from an online survey conducted in the early stages of the pandemic. *Cancer*, 1–9. https://doi.org/10.1002/cncr.33098

Košir, U., Roškar, S., Wild, J., & Bowes, L. (2020). Mapping the needs and psychological outcomes of Slovenian adolescent and young adult cancer patients: An exploratory mixed-method study. *European Journal of Cancer Care*, (July), 1–10. https://doi.org/10.1111/ecc.13326

Kosir, U., Wiedemann, M., Wild, J., & Bowes, L. (2019a). Cognitive Mechanisms in Adolescent and Young Adult Cancer Patients and Survivors: Feasibility and Preliminary Insights from the Cognitions and Affect in Cancer Resiliency Study. *Journal of Adolescent and Young Adult Oncology*, *00*(00), 1–6. https://doi.org/10.1089/jayao.2019.0127

Kosir, U., Wiedemann, M., Wild, J., & Bowes, L. (2019b). Psychiatric disorders in adolescent cancer survivors: A systematic review of prevalence and predictors. *Cancer Reports*, (December 2018), e1168. https://doi.org/10.1002/cnr2.1168

Kossakowski, J. J., Epskamp, S., & Kieffer, J. M. (2016). The application of a network approach to Health-Related Quality of Life (HRQoL): introducing a new method for assessing HRQoL in healthy adults and cancer patients. *Quality of Life Research*, *25*(4), 781–792. https://doi.org/10.1007/s11136-015-1127-z

Kreuter, F., & Muthén, B. (2008). *Analyzing criminal trajectory profiles: Bridging multilevel and group-based approaches using growth mixture modeling*. *Journal of Quantitative Criminology* (Vol. 24). https://doi.org/10.1007/s10940-007-9036-0

Krippendorf, K. (2018). *Content analysis: An introduction to its methodology* (Fourth Edi). Los Angeles: SAGE Publications Ltd.

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9 Validity of a Brief Depression Severity Measure. *Journal of General Internal Medicine*, *16*, 606–613.

Kroenke, K., Spitzer, R. L., Williams, J. B. W., & Löwe, B. (2009). An Ultra-Brief Screening Scale for Anxiety and Depression: The PHQ–4. *Psychosomatics*, *50*(6), 613–621. https://doi.org/10.1016/s0033-3182(09)70864-3

Kuehni, C. E., Rueegg, C. S., Michel, G., Rebholz, C. E., Strippoli, M. P. F., Niggli, F. K., … Rischewski, J. (2012). Cohort profile: The swiss childhood cancer survivor study. *International Journal of Epidemiology*, *41*(6), 1553–1564. https://doi.org/10.1093/ije/dyr142

Kuhlthau, K., Luff, D., Delahaye, J., Wong, A., Yock, T., Huang, M., & Park, E. R. (2015). Health-Related Quality of Life of Adolescent and Young Adult Survivors of Central Nervous System Tumors: Identifying Domains From a Survivor Perspective. *Journal of Pediatric Oncology Nursing*, *32*(6), 385–393. https://doi.org/10.1177/1043454214563752

Kunin-Batson, A. S., Lu, X., Balsamo, L., Graber, K., Devidas, M., Hunger, S. P., … Kadan-Lottick, N. S. (2016). Prevalence and predictors of anxiety and depression after completion of chemotherapy for childhood acute lymphoblastic leukemia: A

prospective longitudinal study. *Cancer*, *122*(10), 1608–1617. https://doi.org/https://dx.doi.org/10.1002/cncr.29946

Kuppenheimer, W. G., & Brown, R. T. (2002). Painful procedures in pediatric cancer. *Clinical Psychology Review*, *22*(5), 753–786. https://doi.org/10.1016/S0272-7358(02)00105-8

KyngÄs, H. A., Kroll, T., & Duffy, M. E. (2000). Compliance in adolescents with chronic diseases: a review. *Journal of Adolescent Health*, *26*, 379–388. https://doi.org/10.1016/s1054-139x(99)00042-7

Lang, M. J., David, V., & Giese-Davis, J. (2015). The age conundrum: A scoping review of younger age or adolescent and young adult as a risk factor for clinical distress, depression, or anxiety in cancer. *Journal of Adolescent and Young Adult Oncology*, *4*(4), 157–173. https://doi.org/http://dx.doi.org/10.1089/jayao.2015.0005

Larouche, S. S., & Chin-Peuckert, L. (2006). Changes in body image experienced by adolescents with cancer. *Journal of Pediatric Oncology Nursing*, *23*(4), 200–209. https://doi.org/10.1177/1043454206289756

Lassaletta, A., Bouffet, E., Mabbott, D., & Kulkarni, A. V. (2015). Functional and neuropsychological late outcomes in posterior fossa tumors in children. *Child's Nervous System*, *31*(10), 1877–1890. https://doi.org/10.1007/s00381-015-2829-9

Last, B. F., Grootenhuis, M. A., & Eiser, C. (2005). International comparison of contributions to psychosocial research on survivors of childhood cancer: Past and future considerations. *Journal of Pediatric Psychology*, *30*(1), 99–113. https://doi.org/10.1093/jpepsy/jsi021

Lazor, T., Tigelaar, L., Pole, J. D., De Souza, C., Tomlinson, D., & Sung, L. (2017). Instruments to measure anxiety in children, adolescents, and young adults with cancer: a systematic review. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer*, *25*(9), 2921–2931. https://doi.org/https://dx.doi.org/10.1007/s00520-017-3743-3

Levinson, C. A., Brosof, L. C., Vanzhula, I., Christian, C., Jones, P., Rodebaugh, T. L., … Fernandez, K. C. (2018). Social anxiety and eating disorder comorbidity and underlying vulnerabilities: Using network analysis to conceptualize comorbidity. *International Journal of Eating Disorders*, *51*(7), 693–709. https://doi.org/10.1002/eat.22890

Libov, B. G., Nevid, J. S., Pelcovitz, D., & Carmony, T. M. (2002). Posttraumatic stress symptomatology in mothers of pediatric cancer survivors. *Psychology and Health*, *17*(4), 501–511. https://doi.org/10.1080/0887044022000004975

Lindert, J., Von Ehrenstein, O. S., Grashow, R., Gal, G., Braehler, E., & Weisskopf, M. G. (2014). Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: Systematic review and meta-analysis. *International Journal of Public Health*, *59*(2), 359–372. https://doi.org/10.1007/s00038-013-0519-5

Liptak, C., Manley, P., & Recklitis, C. J. (2012). The feasibility of psychosocial screening for adolescent and young adult brain tumor survivors: the value of self-report. *Journal of Cancer Survivorship*, *6*(4), 379–387. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med7&AN=22903638

Little, R. J. A., & Rubin, D. B. (2014). *Statistical analysis with missing data*. Hoboken, NJ: John Wiley & Sons.

Liu, Y., Millsap, R. E., West, S. G., Tein, J., Tanaka, R., & Grimm, K. J. (2017). Testing Measurement Invariance in Longitudinal Data with Ordered-Categorical

Measures. *Psychological Methods*, *22*(3), 486–506. https://doi.org/doi:10.1037/met0000075

Löwe, B., Wahl, I., Rose, M., Spitzer, C., Glaesmer, H., Wingenfeld, K., … Brähler, E. (2010). A 4-item measure of depression and anxiety: Validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. *Journal of Affective Disorders*, *122*(1–2), 86–95. https://doi.org/10.1016/j.jad.2009.06.019

Lown, E. A., Phillips, F., Schwartz, L. A., Rosenberg, A., & Jones, B. (2015). Psychosocial follow-up in survivorship as a standard of care in pediatric oncology. *Pediatric Blood Cancer*, *62*, S514–S584. https://doi.org/DOI 10.1002/pbc.25783

Lu, H., Stratton, C. W., & Tang, Y. W. (2020). Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *Journal of Medical Virology*, *92*(4), 401–402. https://doi.org/10.1002/jmv.25678

Lüdecke, D. (2018). sjmisc: Data and Variable Transformation Functions. *Journal of Open Source Software*, *3*(26), 754. https://doi.org/10.21105/joss.00754

Luthar, S. S., Cicchetti, D., & Becker, B. (2000). The Construct of Resilience. *Child De*, *71*(3), 543–562. https://doi.org/10.1111/1467-8624.00164.

Magnus, P., Irgens, L. M., Skjærven, R., Stoltenberg, C., Haug, K., & Nystad, W. (2006). Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). *International Journal of Epidemiology*, *35*(5), 1146–1150. https://doi.org/10.1093/ije/dyl170

Manna, G., Foddai, E., Di Maggio, M. G., Pace, F., Colucci, G., Gebbia, N., & Russo, A. (2007). Emotional expression and coping style in female breast cancer. *Annals of Oncology*, *18*(SUPPL. 6), 77–80. https://doi.org/10.1093/annonc/mdm231

Manzoni, G. M., Pagnini, F., Castelnuovo, G., & Molinari, E. (2008). Relaxation training for anxiety: A ten-years systematic review with meta-analysis. *BMC Psychiatry*, *8*. https://doi.org/10.1186/1471-244X-8-41

Marjerrison, S., & Barr, R. D. (2018). Unmet Survivorship Care Needs of Adolescent and Young Adult Cancer Survivors. *JAMA Network Open*, *1*(2), e180350. https://doi.org/10.1001/jamanetworkopen.2018.0350

Marshall, R. D., Olfson, M., Hellman, F., Blanco, C., Guardino, M., & Struening, E. L. (2001). Comorbidity, impairment, and suicidality in subthreshold PTSD. *American Journal of Psychiatry*, *158*(9), 1467–1473. https://doi.org/10.1176/appi.ajp.158.9.1467

Martins, A., Bennister, L., Fern, L. A., Gerrand, C., Onasanya, M., Storey, L., … Taylor, R. M. (2020). Development of a patient-reported experience questionnaire for patients with sarcoma: the Sarcoma Assessment Measure (SAM). *Quality of Life Research*. https://doi.org/10.1007/s11136-020-02481-x

Martins, A., Whelan, J. S., Bennister, L., Fern, L. A., Gerrand, C., Onasanya, M., … Taylor, R. M. (2019). Qualitative study exploring patients experiences of being diagnosed and living with primary bone cancer in the UK. *BMJ Open*, *9*(9), 1–10. https://doi.org/10.1136/bmjopen-2018-028693

Marusak, H. A., Iadipaolo, A. S., Harper, F. W., Elrahal, F., Taub, J. W., Goldberg, E., & Rabinak, C. A. (2018). Neurodevelopmental consequences of pediatric cancer and its treatment: applying an early adversity framework to understanding cognitive, behavioral, and emotional outcomes. *Neuropsychology Review*, *28*(2), 123–175. https://doi.org/10.1007/s11065-017-9365-1

Marzorati, C., Riva, S., & Pravettoni, G. (2017). Who Is a Cancer Survivor? A Systematic Review of Published Definitions. *Journal of Cancer Education*, *32*(2), 228–237. https://doi.org/10.1007/s13187-016-0997-2

Mascarin, M., & Ferrari, A. (2019). The concept of friendship in adolescents with cancer: Reflections and experiences. *Tumori*, *105*(1), 5–11. https://doi.org/10.1177/0300891618792464

Mason, J. (2002). *Qualitative researching*. London: SAGE Publications Ltd.

Masten, A. S. (2001). Ordinary Magic: Resilience Processes in Development. *American Psychologist*. Retrieved from http://graphics.uk.ovid.com.ep.fjernadgang.kb.dk/ovftpdfs/PDHFFNEGDAFHFJ00/fs046/ovft/live/gv023/00000487/00000487-200103000-00004.pdf

Matthews, T., Danese, A., Caspi, A., Fisher, H. L., Goldman-Mellor, S., Kepa, A., … Arseneault, L. (2019). Lonely young adults in modern Britain: Findings from an epidemiological cohort study. *Psychological Medicine*, *49*(2), 268–277. https://doi.org/10.1017/S0033291718000788

Maxwell, J. A. (2010). Using numbers in qualitative research. *Qualitative Inquiry*, *16*(6), 475–482. https://doi.org/10.1177/1077800410364740

McCarthy, M. C., McNeil, R., Drew, S., Dunt, D., Kosola, S., Orme, L., & Sawyer, S. M. (2016). Psychological Distress and Posttraumatic Stress Symptoms in Adolescents and Young Adults with Cancer and Their Parents. *Journal of Adolescent and Young Adult Oncology*, *5*(4), 322–329. https://doi.org/10.1089/jayao.2016.0015

McDonald, N., Schoenebeck, S., & Forte, A. (2019). Reliability and inter-rater reliability in qualitative research: Norms and guidelines for CSCW and HCI practice. *Proceedings of the ACM on Human-Computer Interaction*, *3*(CSCW). https://doi.org/10.1145/3359174

McDonnell, G. A., Salley, C. G., Barnett, M., DeRosa, A. P., Werk, R. S., Hourani, A., & Hoekstra, A. B. (2017). Anxiety Among Adolescent Survivors of Pediatric Cancer. *Journal of Adolescent Health*, *61*(4), 409–423. https://doi.org/http://dx.doi.org/10.1016/j.jadohealth.2017.04.004

McLoone, J. K., Wakefield, C. E., Butow, P., Fleming, C., & Cohn, R. J. (2011). Returning to school after adolescent cancer: A qualitative examination of Australian survivors' and their families' perspectives. *Journal of Adolescent and Young Adult Oncology*, *1*(2), 87–94. https://doi.org/http://dx.doi.org/10.1089/jayao.2011.0006

McNeil, R., Egsdal, M., Drew, S., McCarthy, M. C., & Sawyer, S. M. (2019). The changing nature of social support for adolescents and young adults with cancer. *European Journal of Oncology Nursing*, *43*(September), 101667. https://doi.org/10.1016/j.ejon.2019.09.008

Mehnert, A., Brähler, E., Faller, H., Härter, M., Keller, M., Schulz, H., … Koch, U. (2014). Four-week prevalence of mental disorders in patients with cancer across major tumor entities. *Journal of Clinical Oncology*, *32*(31), 3540–3546. https://doi.org/10.1200/JCO.2014.56.0086

Mellblom, A. V., Ruud, E., Loge, J. H. H., & Lie, H. C. (2017). Do negative emotions expressed during follow-up consultations with adolescent survivors of childhood cancer reflect late effects? *Patient Education and Counseling*, *100*(11), 2098–2101. https://doi.org/http://dx.doi.org/10.1016/j.pec.2017.06.008

Meredith, W. (1993). Measurement invariance, factor analysis and factorial invariance. *Psychometrika*, *58*(4), 525–543.

Merikangas, K. R., He, J. P., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., … Swendsen, J. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: Results from the national comorbidity survey replication-adolescent supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry*,

49(10), 980–989. https://doi.org/10.1016/j.jaac.2010.05.017

Michel, G., Taylor, N., Absolom, K., & Eiser, C. (2009). Benefit finding in survivors of childhood cancer and their parents: Further empirical support for the Benefit Finding Scale for Children. *Child: Care, Health and Development*, *36*(1), 123–129. https://doi.org/10.1111/j.1365-2214.2009.01034.x

Milam, J., Slaughter, R., Meeske, K., Ritt-Olson, A., Sherman-Bien, S., Freyer, D. R., … Hamilton, A. S. (2016). Substance use among adolescent and young adult cancer survivors. *Psycho-Oncology*, *25*(11), 1357–1362. https://doi.org/http://dx.doi.org/10.1002/pon.3958

Miller, B. L. (2020). Science Denial and COVID Conspiracy Theories. *JAMA*, (November 2), E1–E2. https://doi.org/doi:10.1001/jama.2020.21332

Miller, K. D., Siegel, R. L., Lin, C. C., Mariotto, A. B., Kramer, J. L., Rowland, J. H., … Jemal, A. (2016). Cancer treatment and survivorship statistics, 2016. *CA: A Cancer Journal for Clinicians*, *66*(4), 271–289. https://doi.org/10.3322/caac.21349

Mitchell, A. J., Ferguson, D. W., Gill, J., Paul, J., & Symonds, P. (2013). Depression and anxiety in long-term cancer survivors compared with spouses and healthy controls: A systematic review and meta-analysis. *The Lancet Oncology*, *14*(8), 721–732. https://doi.org/10.1016/S1470-2045(13)70244-4

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Altman, D., Antes, G., … Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7). https://doi.org/10.1371/journal.pmed.1000097

Molina, Y., Yi, J. C., Martinez-Gutierrez, J., Reding, K. W., Yi-Frazier, J. P., & Rosenberg, A. R. (2014). Resilience among patients across the cancer continuum: diverse perspectives. *Clinical Journal of Oncology Nursing*, *18*(1), 93–101. https://doi.org/10.1188/14.CJON.93-101

Moore, I. M., Challinor, J., Pasvogel, A., Matthay, K., Hutter, J., & Kaemingk, K. (2003). Behavioral adjustment of children and adolescents with cancer: teacher, parent, and self-report. *Oncology Nursing Forum*, *30*(5), E84-91. https://doi.org/10.1188/03.ONF.E84-E91

Morris, B. A., & Shakespeare-Finch, J. (2011). Rumination, post-traumatic growth, and distress: Structural equation modelling with cancer survivors. *Psycho-Oncology*, *20*(11), 1176–1183. https://doi.org/10.1002/pon.1827

Morris, Z. S., Wooding, S., & Grant, J. (2011). The answer is 17 years, what is the question: understanding time lags in translational research. *Journal of Royal Society of Medicine*, *104*, 510–520.

Mullan, F. (1985). Seasons of survival: Reflections of a physician with cancer. *New England Journal of Medicine*, *313*(4), 270–273.

Muthén, B. (2004). Latent variable analysis: growth mixture modeling and related techniques for longitudinal data. In D. Kaplan (Ed.), *The SAGE handbook of quantitative methodology for the social sciences* (pp. 346–369). Thousand Oaks: Sage Publications.

Mutsaers, B., Jones, G., Rutkowski, N., Tomei, C., Séguin Leclair, C., Petricone-Westwood, D., … Lebel, S. (2016). When fear of cancer recurrence becomes a clinical issue: a qualitative analysis of features associated with clinical fear of cancer recurrence. *Supportive Care in Cancer*, *24*(10), 4207–4218. https://doi.org/10.1007/s00520-016-3248-5

Nagin, D S. (2005). *Group-based modeling of development*. Cambridge, MA: Harvard University press.

Nagin, D S. (2014). Group-based trajectory modeling: An overview. *Annals of Nutrition and Metabolism*, *65*, 205–210. https://doi.org/10.1159/000360229

Nagin, D S, & Tremblay, R. E. (2005). What has been learned from group-based trajectory modeling? Examples from physical aggression and other problem behaviors. *Annals of the American Academy of Political and Social Science*, *602*(November), 82–117. https://doi.org/10.1177/0002716205280565

Nagin, D S, Tremblay, R. E., Sampson, R. J., & Laub, J. H. (2005). Developmental trajectory groups: Fact or a useful statistical fiction? *Criminology*, *43*(4), 873–904. https://doi.org/10.1111/j.1745-9125.2005.00026.x

Nagin, Daniel S., & Odgers, C. L. (2010). Group-Based Trajectory Modeling in Clinical Research. *Annual Review of Clinical Psychology*, *6*(1), 109–138. https://doi.org/10.1146/annurev.clinpsy.121208.131413

Nahata, L., Caltabellotta, N. M., Yeager, N. D., Lehmann, V., Whiteside, S. L., O'Brien, S. H., … Gerhardt, C. A. (2018). Fertility perspectives and priorities among male adolescents and young adults in cancer survivorship. *Pediatric Blood and Cancer*, *65*(e27019), 1–4. https://doi.org/10.1002/pbc.27019

Nathan, P. C., Ford, J. S., Henderson, T. O., Hudson, M. M., Emmons, K. M., Casillas, J. N., … Oeffinger, K. C. (2009). Health behaviors, medical care, and interventions to promote healthy living in the Childhood Cancer Survivor Study cohort. *Journal of Clinical Oncology*, *27*(14), 2363–2373. https://doi.org/10.1200/JCO.2008.21.1441

Nekhlyudov, L., Duijts, S., Hudson, S. V, Jones, J. M., Keogh, J., & Love, B. (2020). Addressing the needs of cancer survivors during the COVID-19 pandemic. *Journal of Cancer Survivorship*. https://doi.org/https://doi.org/10.1007/s11764-020-00884-w

Nosek, B. A., Alter, G., Banks, G. C., Borsboom, D., Bowman, S. D., Breckler, S. J., … Yarkoni, T. (2015). Promoting an open research culture. *Science*, *348*(6242), 1422–1425. https://doi.org/https://doi.org/10.1126/science.aab2374

Nowe, E., Stöbel-Richter, Y., Sender, A., Leuteritz, K., Friedrich, M., & Geue, K. (2017). Cancer-related fatigue in adolescents and young adults: A systematic review of the literature. *Critical Reviews in Oncology/Hematology*, *118*(August), 63–69. https://doi.org/10.1016/j.critrevonc.2017.08.004

Nylund, K. L., Asparouhov, T., & Muthén, B. O. (2007). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural Equation Modeling*, *14*(4), 535–569. https://doi.org/10.1080/10705510701575396

Oeffinger, K. C., Mertens, A. C., Sklar, C. A., Kawashima, T., Hudson, M. M., Meadows, A. T., … Childhood Cancer Survivor, S. (2006). Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*, *355*(15), 1572–1582. https://doi.org/10.1056/NEJMsa060185

Oeffinger, K. C., & Tonorezos, E. S. (2011). The cancer is over, now what?: Understanding risk, changing outcomes. *Cancer*, *117*(SUPPL. 10), 2250–2257. https://doi.org/10.1002/cncr.26051

Oh, H. S., & Seo, W. S. (2011). Systematic Review and Meta-Analysis of the Correlates of Cancer-Related Fatigue. *Worldviews on Evidence-Based Nursing*, *8*(4), 191–201. https://doi.org/10.1111/j.1741-6787.2011.00214.x

Online Etymology Dictionary. (2017). Retrieved September 16, 2020, from https://www.etymonline.com/word/resilient#etymonline_v_30471

Opsahl, T., Agneessens, F., & Skvoretz, J. (2010). Node centrality in weighted networks: Generalizing degree and shortest paths. *Social Networks*, *32*(3), 245–

251. https://doi.org/10.1016/j.socnet.2010.03.006

Osborn, M., Johnson, R., Thompson, K., Anazodo, A., Albritton, K., Ferrari, A., & Stark, D. (2019). Models of care for adolescent and young adult cancer programs. *Pediatric Blood and Cancer*, *66*(12), 1–13. https://doi.org/10.1002/pbc.27991

Ostacoli, L., Saini, A., Zuffranieri, M., Boglione, A., Carletto, S., De Marco, I., … Comandone, A. (2014). Quality of Life, Anxiety and Depression in Soft Tissue Sarcomas as Compared to More Common Tumours: An Observational Study. *Applied Research in Quality of Life*, *9*(1), 123–131. https://doi.org/10.1007/s11482-013-9213-2

Ozono, S., Saeki, T., Mantani, T., Ogata, A., Okamura, H., Nakagawa, S.-I. I., … Yamawaki, S. (2010). Psychological distress related to patterns of family functioning among Japanese childhood cancer survivors and their parents. *Psycho-Oncology*, *19*(5), 545–552. https://doi.org/10.1002/pon.1606

Pai, A. L. H., Greenley, R. N., Lewandowski, A., Drotar, D., Youngstrom, E., & Peterson, C. C. (2007). A meta-analytic review of the influence of pediatric cancer on parent and family functioning. *Journal of Family Psychology*, *21*(3), 407–415. https://doi.org/http://dx.doi.org/10.1037/0893-3200.21.3.407

Pannier, S. T., Warner, E. L., Fowler, B., Fair, D., Salmon, S. K., & Kirchhoff, A. C. (2019). Age-Specific Patient Navigation Preferences Among Adolescents and Young Adults with Cancer. *Journal of Cancer Education*, *34*(2), 242–251. https://doi.org/10.1007/s13187-017-1294-4

Park, C. L., & Cho, D. (2017). Spiritual well-being and spiritual distress predict adjustment in adolescent and young adult cancer survivors. *Psycho-Oncology*, *26*(9), 1293–1300. https://doi.org/http://dx.doi.org/10.1002/pon.4145

Park, C. L., Zlateva, I., & Blank, T. O. (2009). Self-identity after cancer: " survivor", " victim", " patient", and " person with cancer." *Journal of General Internal Medicine*, *24*(SUPPL. 2), 430–435. https://doi.org/10.1007/s11606-009-0993-x

Parry, C., & Chesler, M. A. (2005). Thematic Evidence of Psychosocial Thriving in Childhood Cancer Survivors. *Qualitative Health Research*, *15*(8), 1055–1073. https://doi.org/10.1177/1049732305277860

Parsons, H. M., Harlan, L. C., Lynch, C. F., Hamilton, A. S., Wu, X. C., Kato, I., … Keegan, T. H. M. (2012). Impact of cancer on work and education among adolescent and young adult cancer survivors. *Journal of Clinical Oncology*, *30*(19), 2393–2400. https://doi.org/10.1200/JCO.2011.39.6333

Parsons, H. M., Schmidt, S., Tenner, L. L., Bang, H., & Keegan, T. H. M. (2016). Early impact of the Patient Protection and Affordable Care Act on insurance among young adults with cancer: Analysis of the dependent insurance provision. *Cancer*, *122*(11), 1766–1773. https://doi.org/10.1002/cncr.29982

Parsons, J. A., & Davis, A. M. (2004). Rehabilitation and quality-of-life issues in patients with extremity soft tissue sarcoma. *Curr Treat Options Oncol*, *5*(6), 477–488. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L39591807%5Cnhttp://va8ef7lf8s.search.serialssolutions.com/?sid=EMBASE&issn=15272729&id=doi:&atitle=Rehabilitation+and+quality-of-life+issues+in+patients+with+extremity+soft+tissue+s

Patterson, P., McDonald, F. E. J., Zebrack, B., & Medlow, S. (2015). Emerging issues among adolescent and young adult cancer survivors. *Seminars in Oncology Nursing*, *31*(1), 53–59. https://doi.org/10.1016/j.soncn.2014.11.006

Patton, G. C., Coffey, C., Cappa, C., Currie, D., Riley, L., Gore, F., … Ferguson, J. (2012). Health of the world's adolescents: A synthesis of internationally

comparable data. *The Lancet*, *379*(9826), 1665–1675. https://doi.org/10.1016/s0140-6736(12)60203-7

Patton, G. C., Coffey, C., Romaniuk, H., Mackinnon, A., Carlin, J. B., Degenhardt, L., … Moran, P. (2014). The prognosis of common mental disorders in adolescents: A 14-year prospective cohort study. *The Lancet*, *383*(9926), 1404–1411. https://doi.org/10.1016/S0140-6736(13)62116-9

Pelcovitz, D., Libov, B. G., Mandel, F., Kaplan, S., Weinblatt, M., & Septimus, A. (1998). Posttraumatic stress disorder and family functioning in adolescent cancer. *Journal of Traumatic Stress*, *11*(2), 205–221. https://doi.org/http://dx.doi.org/10.1023/A:1024442802113

Pendley, J. S., Dahlquist, L. M., & Dreyer, Z. (1997). Body image and psychosocial adjustment in adolescent cancer survivors. *Journal of Pediatric Psychology*, *22*(1), 29–43. https://doi.org/10.1093/jpepsy/22.1.29

Pennant, S., C. Lee, S., Holm, S., Triplett, K. N., Howe-Martin, L., Campbell, R., & Germann, J. (2020). The Role of Social Support in Adolescent/Young Adults Coping with Cancer Treatment. *Children*, *7*(2), 1–25. https://doi.org/10.3390/children7010002

Perez, G. K., Salsman, J. M., Fladeboe, K., & Kirchhoff, A. C. (2020). Taboo Topics in Adolescent and Young Adult Oncology : Strategies for Managing Challenging but Important Conversations Central to Adolescent and Young Adult Cancer Survivorship. *ASCO Educational Book*, 171–185. https://doi.org/https://doi.org/10.1200/EDBK_ 279787

Phillips, C. R., & Davis, L. L. (2015). Psychosocial Interventions for Adolescents and Young Adults with Cancer. *Seminars in Oncology Nursing*, *31*(3), 242–250. https://doi.org/10.1016/j.soncn.2015.05.004

Phipps, S., Long, A. M., & Ogden, J. (2007). Benefit finding scale for children: Preliminary findings from a childhood cancer population. *Journal of Pediatric Psychology*, *32*(10), 1264–1271. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L351011038%5Cnhttp://dx.doi.org/10.1093/jpepsy/jsl052%5Cnhttp://sfx.metabib.ch/sfx_locater?sid=EMBASE&issn=01468693&id=doi:10.1093/jpepsy/jsl052&atitle=Benefit+finding+scale+for+chil

Pii, K. H., Schou, L. H., Piil, K., & Jarden, M. (2019). Current trends in patient and public involvement in cancer research: A systematic review. *Health Expectations*, *22*, 3–20. https://doi.org/10.1111/hex.12841

Pini, S., Gardner, P., & Hugh-Jones, S. (2019). How and why school is important to teenagers with cancer: Outcomes from a photo-elicitation study. *Journal of Adolescent and Young Adult Oncology*, *8*(2), 157–164. https://doi.org/10.1089/jayao.2018.0068

Plummer, F., Manea, L., Trepel, D., & McMillan, D. (2016). Screening for anxiety disorders with the GAD-7 and GAD-2: A systematic review and diagnostic metaanalysis. *General Hospital Psychiatry*, *39*, 24–31. https://doi.org/10.1016/j.genhosppsych.2015.11.005

Pollock, B. H. (2020). What's Missing in the Assessment of Adolescent and Young Adult (AYA) Cancer Outcomes? *Journal of the National Cancer Institute*, *112*(10), 975–976. https://doi.org/10.1093/jnci/djaa015

Poort, H, Peters, M., van der Graaf, W., Nieuwkerk, P., van de Wouw, A., Nijhuis-van der Sanden, M., … Knoop, H. (2019). Cognitive behavioral therapy or graded exercise therapy compared to usual care for severe fatigue in patients with advanced cancer during treatment: a randomized controlled trial. *Annals of*

Oncology, *In Press*(1), 115–122. https://doi.org/10.1016/j.annonc.2019.09.002

Poort, Hanneke, Kaal, S. E. J., Knoop, H., Jansen, R., Prins, J. B., Manten-Horst, E., … van der Graaf, W. T. A. (2017). Prevalence and impact of severe fatigue in adolescent and young adult cancer patients in comparison with population-based controls. *Supportive Care in Cancer*, *25*(9), 2911–2918. https://doi.org/10.1007/s00520-017-3746-0

Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., & Britten, N. (2006). Narrative Synthesis in Systematic Reviews: A Product from the ESRC Methods Programme. *ESRC Methods Programme*, (2006), 93. https://doi.org/10.13140/2.1.1018.4643

Pope, C., & Mays, N. (1995). Reaching the parts other methods cannot reach: an introduction ot qualitative methods in health and healthervices research. *Bmj*, *311*(1), 109–112.

Pope, C., Ziebland, S., & Mays, N. (2000). Analysing qualitative data. *Bmj*, *320*(January), 114–116. https://doi.org/10.1136/bmj.320.7227.114

Preisig, M., Kr, M., & Clinical, A. J. (2001). Clinical significance and comorbidity of subthreshold depression and anxiety in the community. *Acta Psychiatrica Scandinavica*, *104*, 96–103.

Prevatt, F. F., Heffer, R. W., & Lowe, P. A. (2000). A review of school reintegration programs for children with cancer. *Journal of School Psychology*, *38*(5), 447–467. https://doi.org/http://dx.doi.org/10.1016/S0022-4405%2800%2900046-7

Proserpio, T., Pagani Bagliacca, E., Sironi, G., Clerici, C. A., Veneroni, L., Massimino, M., & Ferrari, A. (2020). Spirituality and Sustaining Hope in Adolescents with Cancer: The Patients' View. *Journal of Adolescent and Young Adult Oncology*, *9*(1), 36–40. https://doi.org/10.1089/jayao.2019.0058

Proust-Lima, C., Philipps, V., & Liquet, B. (2017). Estimation of extended mixed models using latent classes and latent processes: The R package lcmm. *Journal of Statistical Software*, *78*(2). https://doi.org/10.18637/jss.v078.i02

Qato, D. M., Ozenberger, K., & Olfson, M. (2018). Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *JAMA - Journal of the American Medical Association*, *319*(22), 2289–2298. https://doi.org/10.1001/jama.2018.6741

Qiu, J., Shen, B., Zhao, M., Wang, Z., Xie, B., & Xu, Y. (2020). A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: Implications and policy recommendations. *General Psychiatry*, *33*(2), 19–21. https://doi.org/10.1136/gpsych-2020-100213

Qualtrics. (2020). Qualtrics. Provo, Utah, USA. Retrieved from https://www.qualtrics.com

Queirós, A., Faria, D., & Almeida, F. (2017). Strengths and Limitations of Qualitative and Quantitative Research Methods. *European Journal of Education Studies*, *3*(9), 369–387. https://doi.org/10.5281/zenodo.887089

Quinn, G. P., Block, R. G., Clayman, M. L., Kelvin, J., Arvey, S. R., Lee, J. H., … Hayes-Lattin, B. (2015). If you did not document it, it did not happen: Rates of documentation of discussion of infertility risk in adolescent and young adult oncology patients' medical records. *Journal of Oncology Practice*, *11*(2), 137–144. https://doi.org/10.1200/JOP.2014.000786

Quinn, G. P., & Vadaparampil, S. T. (2009). Fertility Preservation and Adolescent/Young Adult Cancer Patients: Physician Communication Challenges. *Journal of Adolescent Health*, *44*(4), 394–400. https://doi.org/10.1016/j.jadohealth.2008.08.014

Rabin, C. (2020). Cancer-Related Self-Disclosure in the Workplace/School by Adolescent and Young Adult Cancer Survivors. *Journal of Adolescent and Young Adult Oncology*, *00*(00), 1–6. https://doi.org/10.1089/jayao.2019.0159

Rait, D. S., Ostroff, J. S., Smith, K., Cella, D. F., & Tan, C. (1992). Lives in a balance: perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. *Family Process*, *31*(4), 383–397. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=23871589

Ramsey, W. A., Heidelberg, R. E., Gilbert, A. M., Heneghan, M. B., Badawy, S. M., & Alberts, N. M. (2019). eHealth and mHealth interventions in pediatric cancer: A systematic review of interventions across the cancer continuum. *Psycho-Oncology*, *29*(1), 17–37. https://doi.org/10.1002/pon.5280

Ramu, E. M., Houdek, M. T., Isaac, C. E., Dickie, C. I., Ferguson, P. C., & Wunder, J. S. (2017). Management of soft-tissue sarcomas; treatment strategies, staging, and outcomes. *Sicot-J*, *3*(1), 20. https://doi.org/10.1051/sicotj/2017010

Rashid, A., Saraykar, S., Makanjoula, T. B., Valentine, A. D., & De La Garza, R. (2016). Sleep disturbances predict higher levels of depression, anxiety and fatigue in cancer patients. *Psychooncology*, *25*, 51–52.

Raudenbush, S. W. (2005). How do we study "what happens Next"? *Annals of the American Academy of Political and Social Science*, *602*(November), 131–144. https://doi.org/10.1177/0002716205280900

Recklitis, C. J., Diller, L. R., Li, X., Najita, J., Robison, L. L., & Zeltzer, L. (2010). Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *28*(4), 655–661. https://doi.org/https://dx.doi.org/10.1200/JCO.2009.22.8635

Reinherz, H. Z., Paradis, A. D., Giaconia, R. M., Stashwick, C. K., & Fitzmaurice, G. (2003). Childhood and adolescent predictors of major depression in the transition to adulthood. *American Journal of Psychiatry*, *160*(12), 2141–2147. https://doi.org/10.1176/appi.ajp.160.12.2141

Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: Family social environments and the mental and physical health of offspring. *Psychological Bulletin*, *128*(2), 330–366. https://doi.org/10.1037//0033-2909.128.2.330

Richter, L. M. (2006). Studying adolescence. *Science*, *312*(5782), 1902–1905. https://doi.org/10.1126/science.1127489

Ritchie, J., & Lweis, J. (2003). *Qualitative research practice: a guide for social science students and researchers*. London: SAGE Publications Ltd.

Roadmap: Europe's beating cancer plan. (2020). Brussels, Belgium. Retrieved from https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12154-Europe-s-Beating-Cancer-Plan

Robinaugh, D. J., Millner, A. J., & Mcnally, R. J. (2016). Identifying Highly Influential Nodes in the Complicated Grief Network. *Journal of Abnormal Psychology*, *125*(6), 747–757. https://doi.org/10.1037/abn0000181.supp

Robinson, K. E., Gerhardt, C. A., Vannatta, K., & Noll, R. B. (2007). Parent and family factors associated with child adjustment to pediatric cancer. *Journal of Pediatric Psychology*, *32*(4), 400–410. https://doi.org/https://dx.doi.org/10.1093/jpepsy/jsl038

Robison, L. L., Armstrong, G. T., Boice, J. D., Chow, E. J., Davies, S. M., Donaldson, S. S., … Zeltzer, L. K. (2009). The childhood cancer survivor study: A national cancer institute-supported resource for outcome and intervention research. *Journal*

of Clinical Oncology, *27*(14), 2308–2318. https://doi.org/10.1200/JCO.2009.22.3339

Rokitka, D. A., Curtin, C., Heffler, J. E., Zevon, M. A., Attwood, K., & Mahoney, M. C. (2017). Patterns of Loss to Follow-Up Care Among Childhood Cancer Survivors. *Journal of Adolescent and Young Adult Oncology*, *6*(1), 67–73. https://doi.org/10.1089/jayao.2016.0023

Rooij, B. H. De, Thong, M. S. Y., Roij, J. Van, Bonhof, C. S., Husson, O., & Ezendam, P. M. (2018). Optimistic, Realistic, and Pessimistic Illness Perceptions; Quality of Life; and Survival Among 2457 Cancer Survivors: The Population-Based PROFILES Registry. *Cancer*, *0*, 1–9. https://doi.org/10.1002/cncr.31634

Roscoe, J. A., Kaufman, M. E., Matteson-Rusby, S. E., Palesh, O. G., Ryan, J. L., Kohli, S., … Morrow, G. R. (2007). Cancer-Related Fatigue and Sleep Disorders. *The Oncologist*, *12*(S1), 35–42. https://doi.org/10.1634/theoncologist.12-s1-35

Rose, S. R., Horne, V. E., Howell, J., Lawson, S. A., Rutter, M. M., Trotman, G. E., & Corathers, S. D. (2016). Late endocrine effects of childhood cancer. *Nature Reviews Endocrinology*, *12*(6), 319–336. https://doi.org/10.1038/nrendo.2016.45

Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software*, *48*(2), 1–93.

Rothan, H. A., & Byrareddy, S. N. (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *Journal of Autoimmunity*, *109*(February), 102433. https://doi.org/10.1016/j.jaut.2020.102433

Ruggeri, M., Pagan, E., Bagnardi, V., Bianco, N., Gallerani, E., Buser, K., … Pagani, O. (2019). Fertility concerns, preservation strategies and quality of life in young women with breast cancer: Baseline results from an ongoing prospective cohort study in selected European Centers. *Breast*, *47*, 85–92. https://doi.org/10.1016/j.breast.2019.07.001

Rutter, M. (2006). Families count: Effects on child and adolescent development. The Jacobs Foundation series on adolescence. In A. Clarke-Stewart & J. Dunn (Eds.), *The promotion of resilience in the face of adversity* (pp. 26–52). New York, NY, US: Cambridge University Press.

Rutter, Michael. (2006). Implications of resilience concepts for scientific understanding. *Annals of the New York Academy of Sciences*, *1094*, 1–12. https://doi.org/10.1196/annals.1376.002

Rutter, Michael. (2012). Resilience as a dynamic concept. *Development and Psychopathology*, *24*(2), 335–344. https://doi.org/10.1017/S0954579412000028

Sansom-Daly, U. M., & Wakefield, C. E. (2013). Distress and adjustment among adolescents and young adults with cancer: an empirical and conceptual review. *Translational Pediatrics*, *2*(4), 167–197. https://doi.org/10.3978/j.issn.2224-4336.2013.10.06

Sansom-Daly, U. M., Wakefield, C. E., Bryant, R. A., Patterson, P., Anazodo, A., Butow, P., … Cohn, R. J. (2019). Feasibility, acceptability, and safety of the Recapture Life videoconferencing intervention for adolescent and young adult cancer survivors. *Psycho-Oncology*, *28*(2), 284–292. https://doi.org/10.1002/pon.4938

Sansom-Daly, U. M., Wakefield, C. E., Robertson, E. G., McGill, B. C., Wilson, H. L., & Bryant, R. A. (2018). Adolescent and young adult cancer survivors' memory and future thinking processes place them at risk for poor mental health. *Psycho-Oncology*, (January), 1–8. https://doi.org/10.1002/pon.4856

Sanson-Fisher, R., Mackenzie, L., Butow, P., Rankin, N., & Paul, C. (2012). Advancing the evidence base in cancer: Psychosocial multicenter trials. *Trials*, *13*(171), 1–8.

https://doi.org/10.1186/1745-6215-13-171

Saunders, J. M. (2010). Understanding Random Effects in Group-Based Trajectory Modeling: *Journal of Drug Issues*, *40*(1), 195–220. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf

Scheier, M. F., & Carver, C. S. (1985). Optimism, coping, and health: assessment and implications of generalized outcome expectancies. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *4*(3), 219–247. https://doi.org/10.1037/0278-6133.4.3.219

Schellekens, M. P. J., Wolvers, M. D. J., Schroevers, M. J., Bootsma, T. I., Cramer, A. O. J., & van der Lee, M. L. (2019). Exploring the interconnectedness of fatigue, depression, anxiety and potential risk and protective factors in cancer patients: a network approach. *Journal of Behavioral Medicine*. https://doi.org/10.1007/s10865-019-00084-7

Schrag, D., Hershman, D. L., & Basch, E. (2020). Oncology Practice During the COVID-19 Pandemic. *JAMA, published*. https://doi.org/doi:10.1001/jama.2020.6236

Schrag, N. M., McKeown, R. E., Jackson, K. L., Cuffe, S. P., & Neuberg, R. W. (2008). Stress-related mental disorders in childhood cancer survivors. *Pediatric Blood and Cancer*, *50*(1), 98–103. https://doi.org/https://dx.doi.org/10.1002/pbc.21285

Schwartz, L. A., & Brumley, L. D. (2017). What a Pain: The Impact of Physical Symptoms and Health Management on Pursuit of Personal Goals among Adolescents with Cancer. *Journal of Adolescent and Young Adult Oncology*, *6*(1), 142–149. https://doi.org/10.1089/jayao.2016.0031

Scott, J. A., Lasch, K. E., Barsevick, A. M., & Piault-Louis, E. (2011). Patients' experiences with cancer-related fatigue: A review and Synthesis of qualitative research. *Oncology Nursing Forum*, *38*(3), 191–203. https://doi.org/10.1188/11.ONF.E191-E203

Seale, C. (2001). Sporting cancer: Struggle language in news reports of people with cancer. *Sociology of Health and Illness*, *23*(3), 308–329. https://doi.org/10.1111/1467-9566.00254

Sellick, S., & Crooks, D. (1999). Depression and cancer: An appraisal of the literature for prevalence, detection, and practice guideline development for psychological interventions. *Psycho-Oncology*, *8*, 315–333.

Sender, L., & Zabokrtsky, K. B. (2015). Adolescent and young adult patients with cancer: A milieu of unique features. *Nature Reviews Clinical Oncology*, *12*(8), 465–480. https://doi.org/10.1038/nrclinonc.2015.92

Servitzoglou, M., Papadatou, D., Tsiantis, I., & Vasilatou-Kosmidis, H. (2008). Psychosocial functioning of young adolescent and adult survivors of childhood cancer. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer*, *16*(1), 29–36. https://doi.org/https://dx.doi.org/10.1007/s00520-007-0278-z

Shapiro, C. L. (2018). Cancer survivorship. *New England Journal of Medicine*, *379*(25), 2438–2450. https://doi.org/10.1056/NEJMra1712502

Shaw, J. W., Johnson, J. A., & Coons, S. J. (2005). US valuation of the EQ-5D health states: Development and testing of the D1 valuation model. *Medical Care*, *43*(3), 203–220. https://doi.org/10.1097/00005650-200503000-00003

Simard, S., & Savard, J. (2015). Screening and comorbidity of clinical levels of fear of cancer recurrence. *Journal of Cancer Survivorship*, *9*(3), 481–491. https://doi.org/10.1007/s11764-015-0424-4

Simard, S., Thewes, B., Humphris, G., Dixon, M., Hayden, C., Mireskandari, S., &

Ozakinci, G. (2013). Fear of cancer recurrence in adult cancer survivors: A systematic review of quantitative studies. *Journal of Cancer Survivorship*, *7*(3), 300–322. https://doi.org/10.1007/s11764-013-0272-z

Singer, S., Kuhnt, S., Zwerenz, R., Eckert, K., Hofmeister, D., Dietz, A., … Brown, A. (2011). Age-and sex-standardised prevalence rates of fatigue in a large hospital-based sample of cancer patients. *British Journal of Cancer*, *105*(3), 445–451. https://doi.org/10.1038/bjc.2011.251

Skinner, R., Wallace, W. H. B., & Levitt, G. A. (2006). Long-term follow-up of people who have survived cancer during childhood. *Lancet Oncology*, *7*(6), 489–498. https://doi.org/10.1016/S1470-2045(06)70724-0

Smith, A. W., Bellizzi, K. M., Keegan, T. H. M., Zebrack, B., Chen, V. W., Neale, A. V., … Lynch, C. F. (2013). Health-related quality of life of adolescent and young adult patients with cancer in the United States: The adolescent and young adult health outcomes and patient experience study. *Journal of Clinical Oncology*, *31*(17), 2136–2145. https://doi.org/10.1200/JCO.2012.47.3173

Smith, A. W., Parsons, H. M., Kent, E. E., Bellizzi, K., Zebrack, B. J., Keel, G., … Link, M. (2013). Unmet support service needs and health-related quality of life among adolescents and young adults with cancer: The AYA HOPE study. *Frontiers in Oncology*, *3 APR*(April), 1–11. https://doi.org/10.3389/fonc.2013.00075

Smith, H. R. (2015). Depression in cancer patients: Pathogenesis, implications and treatment (review). *Oncology Letters*, *9*(4), 1509–1514. https://doi.org/10.3892/ol.2015.2944

Smith, M. (2004). Parental mental health: disruptions to parenting and outcomes for children. *Child and Family Social Work*, *9*, 3–11. https://doi.org/10.1111/j.1365-2206.2004.00312.x

Smits-Seemann, R. R., Kaul, S., Zamora, E. R., Wu, Y. P., & Kirchhoff, A. C. (2017). Barriers to follow-up care among survivors of adolescent and young adult cancer. *Journal of Cancer Survivorship*, *11*(1), 126–132. https://doi.org/10.1007/s11764-016-0570-3

Snyder, C. F., Jensen, R., Segal, J., & Wu, A. W. (2013). Patient-reported outcomes (PROs): Putting the patient perspective in patient-centered outcomes research. *Medical Care*, *51*(8), S73–S79. https://doi.org/10.1097/MLR.0b013e31829b1d84.PATIENT-REPORTED

Sodergren, S. C., Husson, O., Robinson, J., Rohde, G. E., Tomaszewska, I. M., Vivat, B., … Darlington, A. S. (2017). Systematic review of the health-related quality of life issues facing adolescents and young adults with cancer. *Quality of Life Research*, *26*(7), 1659–1672. https://doi.org/10.1007/s11136-017-1520-x

Sodergren, S. C., Husson, O., Rohde, G. E., Tomasewska, I. M., Vivat, B., Yarom, N., … Darlington, A. S. (2018). A Life Put on Pause: An Exploration of the Health-Related Quality of Life Issues Relevant to Adolescents and Young Adults with Cancer. *Journal of Adolescent and Young Adult Oncology*, *7*(4), 453–464. https://doi.org/10.1089/jayao.2017.0110

Sørensen, K., Makaroff, L. E., Myers, L., Robinson, P., Henning, G. J., Gunther, C. E., & Roediger, A. E. (2020). The call for a strategic framework to improve cancer literacy in Europe. *Archives of Public Health*, *78*(1), 1–4. https://doi.org/10.1186/s13690-020-00441-y

Spathis, A., Hatcher, H., Booth, S., Gibson, F., Stone, P., Abbas, L., … Barclay, S. (2017). Cancer-Related Fatigue in Adolescents and Young Adults After Cancer Treatment: Persistent and Poorly Managed. *Journal of Adolescent and Young*

Adult Oncology, *6*(3), 489–493. https://doi.org/10.1089/jayao.2017.0037

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, *166*(10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092

Stiller, C. A., Bielack, S. S., Jundt, G., Steliarova-Foucher, E., Petrovich, S. V., Budanov, O., … McDonald, A. (2006). Bone tumours in European children and adolescents, 1978-1997. Report from the Automated Childhood Cancer Information System project. *European Journal of Cancer*, *42*(13), 2124–2135. https://doi.org/10.1016/j.ejca.2006.05.015

Stone, D. S., Ganz, P. A., Pavlish, C., & Robbins, W. A. (2017). Young adult cancer survivors and work: a systematic review. *Journal of Cancer Survivorship*, *11*(6), 765–781. https://doi.org/10.1007/s11764-017-0614-3

Storey, L., Fern, L. A., Martins, A., Wells, M., Bennister, L., Gerrand, C., … Taylor, R. M. (2019). A Critical Review of the Impact of Sarcoma on Psychosocial Wellbeing. *Sarcoma*, *2019*. https://doi.org/10.1155/2019/9730867

Sulkers, E., Fleer, J., Brinksma, A., Roodbol, P. F., Kamps, W. A., Tissing, W. J. E., & Sanderman, R. (2013). Dispositional optimism in adolescents with cancer: Differential associations of optimism and pessimism with positive and negative aspects of well-being. *British Journal of Health Psychology*, *18*(3), 474–489. https://doi.org/10.1111/j.2044-8287.2012.02096.x

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *American Journal of Psychiatry*, *157*(10), 1552–1562. https://doi.org/10.1176/appi.ajp.157.10.1552

Suris, J. C., Michaud, P. A., & Viner, R. (2004). The adolescent with a chronic condition. Part I: Developmental issues. *Archives of Disease in Childhood*, *89*(10), 938–942. https://doi.org/10.1136/adc.2003.045369

Tai, E., Buchanan, N., Townsend, J., Fairley, T., Moore, A., & Richardson, L. C. (2012). Health status of adolescent and young adult cancer survivors. *Cancer*, *118*(19), 4884–4891. https://doi.org/10.1002/cncr.27445

Team, R. C. (2020). R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from https://www.r-project.org/.

Teenage Cancer Trust. (2019). Retrieved March 21, 2019, from https://www.teenagecancertrust.org/about-usv

Thewes, B., Kaal, S. E. J., Custers, J. A. E., Manten-Horst, E., Jansen, R., Servaes, P., … Husson, O. (2018). Prevalence and correlates of high fear of cancer recurrence in late adolescents and young adults consulting a specialist adolescent and young adult (AYA) cancer service. *Supportive Care in Cancer*, *26*(5), 1479–1487. https://doi.org/10.1007/s00520-017-3975-2

Thomas, D. M., Albritton, K. H., & Ferrari, A. (2010). Adolescent and young adult oncology: An emerging field. *Journal of Clinical Oncology*, *28*(32), 4781–4782. https://doi.org/10.1200/JCO.2010.30.5128

Thompson, A. L., Long, K. A., & Marsland, A. L. (2013). Impact of childhood cancer on emerging adult survivors' romantic relationships: a qualitative account. *The Journal of Sexual Medicine*, *10 Suppl 1*(SUPPL.), 65–73. https://doi.org/https://dx.doi.org/10.1111/j.1743-6109.2012.02950.x

Tinsley, A., MacKlin, E. A., Korzenik, J. R., & Sands, B. E. (2011). Validation of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) in patients with inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics*, *34*(11–12), 1328–1336. https://doi.org/10.1111/j.1365-2036.2011.04871.x

Tolman, D. L., & Mcclelland, S. I. (2011). Normative sexuality development in adolescence: A decade in review, 2000-2009. *Journal of Research on Adolescence*, *21*(1), 242–255. https://doi.org/10.1111/j.1532-7795.2010.00726.x

Tomasetti, C., Li, L., & Vogelstein, B. (2017). Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science*, *355*, 1330–1334. https://doi.org/10.1126/science.aaf9011

Tong, A., Sainsbury, P., & Craig, J. (2007). Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*, *19*(6), 349–357. https://doi.org/10.1093/intqhc/mzm042

Treynor, W., Gonzales, R., & Nolen-Hoeksema, S. (2003). Rumination reconsidered: A psychometric analysis. *Cognitive Therapy and Research*, *27*(3), 247–259. https://doi.org/10.1023/A:1023910315561

Tschudin, S., & Bitzer, J. (2009). Psychological aspects of fertility preservation in men and women affected by cancer and other life-threatening diseases. *Human Reproduction Update*, *15*(5), 587–597. https://doi.org/10.1093/humupd/dmp015

Tuckett, A. G., & Stewart, D. E. (2004). Collecting qualitative data: part I: Journal as a method: experience, rationale and limitations. *Contemporary Nurse : A Journal for the Australian Nursing Profession*, *16*(1–2), 104–113. https://doi.org/10.5172/conu.16.1-2.104

Turner-Sack, A. M., Menna, R., & Setchell, S. R. (2012). Posttraumatic Growth, Coping Strategies, and Psychological Distress in Adolescent Survivors of Cancer. *Journal of Pediatric Oncology Nursing*, *29*(2), 70–79. https://doi.org/10.1177/1043454212439472

Twisk, J., & de Vente, W. (2002). Attrition in longitudinal studies. *Journal of Clinical Epidemiology*, *55*(4), 329–337. https://doi.org/10.1016/s0895-4356(01)00476-0

Twombly, R. (2004). What ' s in a Name : Who Is a Cancer Survivor ? *Journal of the National Cancer Institute*, *96*(19), 1414–1415.

Ungar, M. (2018). Systemic resilience: principles and processes for a science of change in contexts of adversity. *Ecology and Society*, *23*(4). https://doi.org/10.5751/ES-10385-230434

van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software*, *45*(3), 1–67. https://doi.org/10.18637/jss.v045.i03

van de Haar, J., Hoes, L. R., Coles, C. E., Seamon, K., Fröhling, S., Jäger, D., … Voest, E. E. (2020). Caring for patients with cancer in the COVID-19 era. *Nature Medicine*. https://doi.org/10.1038/s41591-020-0874-8

Vehling, S., Malfitano, C., Shnall, J., Watt, S., Panday, T., Chiu, A., … Lo, C. (2017). A concept map of death-related anxieties in patients with advanced cancer. *BMJ Supportive and Palliative Care*, *7*(4), 427–434. https://doi.org/10.1136/bmjspcare-2016-001287

Vetsch, J., Wakefield, C. E., McGill, B. C., Cohn, R. J., Ellis, S. J., Stefanic, N., … Sansom-Daly, U. M. (2018). Educational and vocational goal disruption in adolescent and young adult cancer survivors. *Psycho-Oncology*, *27*(2), 532–538. https://doi.org/10.1002/pon.4525

Walker, E., Martins, A., Aldiss, S., Gibson, F., & Taylor, R. M. (2016). Psychosocial interventions for adolescents and young adults diagnosed with cancer during adolescence: A critical review. *Journal of Adolescent and Young Adult Oncology*, *5*(4), 310–321. https://doi.org/http://dx.doi.org/10.1089/jayao.2016.0025

Wang, J., & Wang, X. (2012). *Structural equation modeling: Applications using Mplus.*

New York, NY: John Wiley & Sons.

Wang, R., Syed, I. A., Nathan, P. C., Barr, R. D., Rosenberg-Yunger, Z. R. S., & Klassen, A. F. (2015). Exploring Cancer Worry in Adolescent and Young Adult Survivors of Childhood Cancers. *Journal of Adolescent and Young Adult Oncology*, *4*(4), 192–199. https://doi.org/10.1089/jayao.2015.0029

War on Cancer. (2020). Retrieved September 18, 2020, from https://waroncancer.com/

Waterman, A. S. (1982). Identity development from adolescence to adulthood: An extension of theory and a review of research. *Developmental Psychology*, *18*(3), 341–358. https://doi.org/0012-1649/82/1803-0341J00.75

Watkins, E. R. (2008). Constructive and Unconstructive Repetitive Thought, *134*(2), 163–206. https://doi.org/10.1037/0033-2909.134.2.163

Webster, K., Cella, D., & Yost, K. (2003). The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: Properties, applications, and interpretation. *Health and Quality of Life Outcomes*, *1*, 1–7. https://doi.org/10.1186/1477-7525-1-79

Weinberg, R. A. (1996). Special issue: What you need to know about cancer. *Scientific American*, *275*(3), 62–70. Retrieved from https://www.jstor.org/stable/10.2307/24993349

Weitz, J., Antonescu, C. R., & Brennan, M. F. (2003). Localized extremity soft tissue sarcoma: Improved knowledge with unchanged survival over time. *Journal of Clinical Oncology*, *21*(14), 2719–2725. https://doi.org/10.1200/JCO.2003.02.026

Wengenroth, L., Rueegg, C. S., Michel, G., Gianinazzi, M. E., Essig, S., von der Weid, N. X., … Swiss Paediatric Oncology Group, S. (2015). Concentration, working speed and memory: cognitive problems in young childhood cancer survivors and their siblings. *Pediatr Blood Cancer*, *62*(5), 875–882. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med8&AN=25645276

Wettergren, L., Kent, E. E., Mitchell, S. A., Zebrack, B., Lynch, C. F., Rubenstein, M. B., … Smith, A. W. (2017). Cancer negatively impacts on sexual function in adolescents and young adults: The AYA HOPE study. *Psycho-Oncology*, *26*(10), 1632–1639. https://doi.org/10.1002/pon.4181

WHO. (2002). Towards a Common Language for Functioning, Disability and Health ICF. *World Health Organization*, 1–22. Retrieved from http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf

WHO. (2018). The top 10 causes of death. Retrieved September 15, 2020, from https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

WHO. (2019). *International Statistical Classification of Diseases and Related Health Problems* (11th Editi). World Health Organisation.

WHO. (2020). Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: interim guidance. Retrieved May 11, 2020, from https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

Widaman, K. F., Ferrer, E., & Conger, R. D. (2010). Factorial Invariance within Longitudinal Structural Equation Models : Measuring the Same Construct across Time. *Child Dev Perspect.*, *4*(1), 10–18. https://doi.org/doi:10.1111/j.1750-8606.2009.00110.x.

Wilder, J. M. (2020). The Disproportionate Impact of COVID-19 on Racial and Ethnic Minorities in the United States. *Clinical Infectious Diseases*, 1–17. https://doi.org/doi:10.1093/cid/ciaa959

Wilkins, K. L., D'Agostino, N., Penney, A. M., Barr, R. D., & Nathan, P. C. (2014). Supporting Adolescents and Young Adults with cancer through transitions: Position statement from the Canadian Task Force on Adolescents and Young Adults with cancer. *Journal of Pediatric Hematology/Oncology*, *36*(7), 545–551. https://doi.org/10.1097/MPH.0000000000000103

Williams, V., Boylan, A. M., & Nunan, D. (2020). Critical appraisal of qualitative research: Necessity, partialities and the issue of bias. *BMJ Evidence-Based Medicine*, *25*(1), 9–11. https://doi.org/10.1136/bmjebm-2018-111132

Wilson, I. B., & Cleary, P. D. (1995). Health-Related Quality of Life. *JAMA*, *273*(1), 59–65. https://doi.org/10.1007/978-1-4419-1005-9_753

Winnette, R., Hess, L. M., Nicol, S. J., Fritz, D., & Copley-merriman, C. (2017). The Patient Experience with Soft Tissue Sarcoma : A Systematic Review of the Literature. *The Patient - Patient-Centered Outcomes Research*, *10*(2), 153–162. https://doi.org/10.1007/s40271-016-0200-1

Winskill, P., Whittaker, C., Walker, P., Watson, O., Laydon, D., Imai, N., … Ghani, A. (2020). *Equity in response to the COVID-19 pandemic: an assessment of the direct and indirect impacts on disadvantaged and vulnerable populations in low- and lower middle-income countries*. https://doi.org/doi:10.1093/cid/ciaa959

Wolf, E. J., Harrington, K. M., Clark, S. L., & Miller, M. W. (2013). Sample Size Requirements for Structural Equation Models: An Evaluation of Power, Bias, and Solution Propriety. *Educational and Psychological Measurement*, *73*(6), 913–934. https://doi.org/10.1177/0013164413495237

World Health Organization. (2013). *Health Literacy: The Solid Facts*. (I. Kickbusch, J. M. Pelikan, F. Apfel, & A. D. Tsouros, Eds.). Copenhagen: WHO Regional Office for Europe. https://doi.org/10.1016/j.socscimed.2008.09.050

Yallop, K., McDowell, H., Koziol-McLain, J., & Reed, P. W. (2013). Self-reported psychosocial wellbeing of adolescent childhood cancer survivors. *European Journal of Oncology Nursing : The Official Journal of European Oncology Nursing Society*, *17*(6), 711–719. https://doi.org/https://dx.doi.org/10.1016/j.ejon.2013.06.007

YCE. (2020). YCE: Policy work.

Yeh, J. M., Ward, Z. J., Chaudhry, A., Liu, Q., Yasui, Y., Armstrong, G. T., … Diller, L. (2019). Life Expectancy of Adult Survivors of Childhood Cancer over 3 Decades. *JAMA Oncology*, *02115*, 1–8. https://doi.org/10.1001/jamaoncol.2019.5582

Zebrack, B. J., Block, R., Hayes-Lattin, B., Embry, L., Aguilar, C., Meeske, K. A., … Cole, S. (2013). Psychosocial service use and unmet need among recently diagnosed adolescent and young adult cancer patients. *Cancer*, *119*(1), 201–214. https://doi.org/10.1002/cncr.27713

Zebrack, B., Mathews-Bradshaw, B., & Siegel, S. (2010). Quality cancer care for adolescents and young adults: A position statement. *Journal of Clinical Oncology*, *28*(32), 4862–4867. https://doi.org/10.1200/JCO.2010.30.5417

Zebrack, Brad J. (2011). Psychological, social, and behavioral issues for young adults with cancer. *Cancer*, *117*(SUPPL. 10), 2289–2294. https://doi.org/10.1002/cncr.26056

Zebrack, Brad J., Corbett, V., Embry, L., Aguilar, C., Meeske, K. A., Hayes-Lattin, B., … Cole, S. (2014). Psychological distress and unsatisfied need for psychosocial support in adolescent and young adult cancer patients during the first year following diagnosis. *Psycho-Oncology*, *23*(11), 1267–1275. https://doi.org/https://dx.doi.org/10.1002/pon.3533

Zebrack, Brad J., Gurney, J. G., Oeffinger, K., Whitton, J., Packer, R. J., Mertens, A., … Zeltzer, L. K. (2004). Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *22*(6), 999–1006. https://doi.org/https://dx.doi.org/10.1200/JCO.2004.06.148

Zebrack, Brad, Kent, E. E., Keegan, T. H. M., Kato, I., & Smith, A. W. (2014). "Cancer sucks," and other ponderings by adolescent and young adult cancer survivors. *Journal of Psychosocial Oncology*, *32*(1), 1–15. https://doi.org/10.1080/07347332.2013.855959

Zeltzer, L. K., Recklitis, C., Buchbinder, D., Zebrack, B., Casillas, J., Tsao, J. C. I. I., … Krull, K. (2009). Psychological status in childhood cancer survivors: A report from the childhood cancer survivor study. *Journal of Clinical Oncology*, *27*(14), 2396–2404. https://doi.org/10.1200/JCO.2008.21.1433

Zlotnick, C., Franklin, C. L., & Zimmerman, M. (2002). Does "subthreshold" posttraumatic stress disorder have any clinical relevance? *Comprehensive Psychiatry*, *43*(6), 413–419. https://doi.org/10.1053/comp.2002.35900

APPENDIX A: Selected quality indicators (Chapter 3)

Adapted from Downs & Black, (1998).

[1] Is the hypothesis/aim/objective of the study clearly described?	Yes = 1	No = 0
[2] Are the main outcomes to be measured clearly described in the Introduction or Methods section? *(If the main outcomes are first mentioned in the Results section, then NO)*	Yes = 1	No = 0
[3] Are the characteristics of the patients included in the study clearly described? *(In cohort studies and trials, inclusion/exclusion should be given. Incase-control studies, a case-definition and the source for controls should be given.)*	Yes = 1	No = 0
[4] Are the main findings of the study clearly described? *(Simple outcome data – denominators/numerators – should be reported for all major analyses and conclusions. – Excluding Stat tests)*	Yes = 1	No = 0
[5] Have actual probability values been reported from the main outcomes except where the probability value is less than 0.001?	Yes = 1	No = 0
[6] Were the subjects asked to participate in the study representative of the entire population from which they were recruited? *(The study must identify the source population for the patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.)*	Yes = 1	No/Unable to determine = 0
[7] Were those subjects who were prepared to participate representative of the entire population from which they were recruited? *(The proportion of those asked who agreed should be stated. Validation that the sample was representative would indicate demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.)*	Yes = 1	No/Unable to determine = 0
[8] If any of the results of the study were based on "data dredging," was this made clear? *(Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.)*	Yes = 1	No/Unable to determine = 0
[9] Were the main outcome measures used accurate (valid and reliable)? *(For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered yes.)*	Yes = 1	No/Unable to determine = 0

APPENDIX B: Complete tables included in the systematic review (Chapter 3)

Table B.0.1: Measures for Posttraumatic Stress Disorder.

Measure name	Measure description	Used in
Kiddie-Schedule for Affective Disorders and Schizophrenia-Epidemiologic Version-5 (K-SADS-E-5; Orvaschel, 1995)	Semi-structured diagnostic interview	Robinson et al. (2007)
Impact of Event Scale - Revised (IES-R; Weiss & Marmar, 1997)	22-item self-report questionnaire	Kazak et al. (2004); Ozono et al. (2010)
Child PTSD Symptom Scale (CPSS; Foa, Johnson, Feeny, & Treadwell, 2001)	17-item self-report questionnaire	Cousino et al. (2017)
University of California at Los Angeles Post-Traumatic Stress Disorder Reaction Index (UCLA-RI; Pynoos et al., 1998)	22-item self-report questionnaire	Michel et al. (2009)
Structured Clinical Interview for DSM-IV (SCID) – non-patient edition of the SCID (First, Spitzer, Gibbon, & Williams, 1995)	Structured diagnostic interview	Kazak et al. (2004); Alderfer et al. (2009); Pelcovitz et al. (1998)
Posttraumatic Stress Disorder Reaction Index (PTSD-RI; Pynoos, Fred- erick, Nader, & Arroyo, 1987)	20-item self-report questionnaire	Kazak et al. (2004); Brown et al. (2003)
Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA; Newman et al., 2004)	Semi-structured diagnostic interview	Erickson et al. (2008)
Child Posttraumatic Stress Reaction Index Revision 2 (CPTS-RI Revision 2; Steinberg & Pynoos, 2001)	30-item self-report questionnaire	Erickson et al. (2008)
Trauma Symptom Checklist for Children - Alternate version (TSCC-A; Briere, 1996)*	44-item self-report questionnaire	Erickson et al. (2008)

Note. *The measure also assessed depression and anxiety in addition to trauma symptoms (i.e. dissociation).

Table B.0.2: Measures for Depression and Anxiety.

Measure name	**Measure description**	**Used by**
Child Depression Inventory (CDI; Kovacs, 1985)	27-item self-report questionnaire	Ozono et al. (2010)
Brief Symptom Inventory - 18 (BSI-18; Derogatis, 2001)	18-item self-report questionnaire	Gianinazzi et al. (2013)
Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983)	53-item self-repot questionnaire	Turner-Sack et al. (2012)
Children's Depression Rating Scale (CDRS; Poznanski et al., 1984)	16-item clinician administered scale	Fritz & Williams (1988)
Behavior Assessment System for Children - 2nd Edition Self-Report (BASC-2; Reynolds & Kamphaus, 2004)	Self-report measure	Cousino et al. (2017); Carpentieri et al. (2003)
Reynolds Adolescent Depression Scale - Short Form (RADS2-SF; Reynolds, 2002)	10-item self-report questionnaire	Yallop et al. (2013)
Center for epidemiologic studies depression (CES-D; Radloff, 1977)	20-item self-report questionnaire	Bitsko et al. (2008)
Clinical interview based on DSM-IV-TR (APA, 2000)	Semi-structured interview	Liptak et al. (2012)
State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970)	40-item self-report questionnaire	Ozono et al. (2010); Servitzoglou et al. (2008); Bauld et al. (1998)
Multidimensional Anxiety Scale for Childrene short form (MASC-10; March et al., 1997)	10-item self-report questionnaire	Yallop et al. (2013)
Social Anxiety Scale for Children-Revised (SASC-R; La Greca, 1992)	22-item self-report questionnaire	Pendley et al. (1997)
The Beck Youth Inventories-II (BYI-II; Beck et al., 2005)	20-item self-report questionnaire	Liptak et al. (2012)

Table B.0.3: Included studies (Complete table for Chapter 3, results section).

Reference	**Country**	**Quality rating**	**Aims of the study/Psychopathology measured**	**N**	**Age at the time of the study** M(SD) [range]	**Age at diagnosis** M(SD) [range]	**Time off treatment** M(SD) [range]	**Cancer specifics**	**Main findings**
Alderfer et al. (2009)	USA	8	To investigate the relationship between family functioning and PTSD in adolescent survivors	144	14.6 (2.4) [11 - 19 years]	7.8 years (4.3) [3 months - 16.4 years]	5.3 (2.9) [1-12 years]	Leukemia (31%), solid tumor (22%), lymphoma (22%), bone tumors (8%), other (17%)	8.3% of survivors met PTSD criteria and did not differ in cancer diagnosis or age at diagnosis from those without PTSD. Survivors with PTSD were 5x more likely to emerge from families with poor functioning.
Bauld et al. (1998)	Australia	6	To assess psychosocial functioning (anxiety) in adolescent cancer survivors and compare it to healthy peers	32	14.9 (1.6) [12 - 17 years]	7.5 years	8 years	Brain tumors excluded, predominantly ALL	Survivors reported higher state anxiety than healthy controls, but were overall less anxious. Survivors employed more maladaptive coping mechanisms such as wishful thinking and avoidance.
Bitsko et al. (2008)	USA	7	To test whether happiness and time perspective mediate positive psychosocial adjustment (depression) to adolescent cancer survivorship	50	20.2 [10 - 21 years]	13.7 [10 - 21 years]	53.9 months (30.5)	Leukemia (26%), lymphoma (38%), other (36%)	Happiness is a stronger predictor of depression than intensity of treatment. Thinking negatively about one's past is stronger predictors about depression than female gender.

Brown et al. (2003)	USA	6	To examine PTSD in adolescent survivors and their mothers and compare it to healthy controls, and to assess contribution of family functioning to PTSD levels	52	17 (3.4) [13 - 23 years]	9.4 (4.9) [1.1 - 18.5 years]	11.4 (4.6) [3.1 - 19.5 years]	Brain tumors excluded, leukemia (51.9%), other solid tumors (48.1%)	None of the survivors met full-PTSD criteria, 36% endorsed sub-clinical levels; 25% of survivors' mothers met PTSD criteria. Late effects contributed to survivors' PTSD symptomatology.
Carpentieri et al. (2003)	USA	8	To describe the psychosocial and behavioral functioning in adolescent survivors via self-report, as well as parent and teacher report (using BASC)	31	14.5 [12 - 18 years]	8.8 (median = 10) [2 - 15 years]	4.1 (median = 3) [1.5 - 12 years]	Only brain tumor cases	6.5% and 3.2% of adolescent brain survivors reported depression and anxiety, respectively. Parents of these survivors reported problems with attention and leadership, while teachers reported problems in learning.
Cousino et al. (2017)	USA	8	To examine associations between survivor's late effects, illness specific family burden and emotional and behavioral outcomes (BASC and PTSD)	65	14.1 (2.1) [10 - 17 years]	6.2 (3.5) years	6.2 (2.8) years	ALL (36.9%), AML (6.2%), brain/CNS tumor (26.2%), neuroblastoma (4.5%), Hodgkin's lymphoma (1.5%) soft tissue (6.2%), bone cancer (3.1%), non-malignant brain tumor (12.3%)	33.8% of survivors endorsed clinically significant levels of PTSD. PTSD reported greater late effects.
Erickson et al. (2008)	USA	6	To examine the repressive adaptive style and its influence on psychosocial adaptation in adolescent cancer survivors	29	15.3 (1.82) [12 - 18 years]	6.2 (4.4) years	Minimum 1 year, not further specified	Brain tumors excluded, leukemia (31%), lymphoma (21%), solid tumor (24%), sarcoma (14%), other (10%)	13.8% of all survivors qualified for PTSD diagnosis, all were non-repressors. Non-repressors reported poorer QOL, higher anxiety and depression, more variability in PTSD, and heightened total problems. The differences were non-sig.

Fritz & Williams (1988)	USA	4	To assess the psychological adjustment (depression) in adolescent cancer survivors	41	17.3 (3.1) [13 - 21 years]	11 (3.6) years	2 - 8 years	Brain tumors excluded, leukemia (34%), Hodgkin's disease (21%), Non-Hodgkin's lymphoma (22%), bone sarcoma (10%), other (13%)	7% of survivors reported clinical depression and 12% were in sub-clinical levels. 50% of the sample was preoccupied with their body, 27% were counter-phobic, and 26% were hypochondrical.
Gianinazzi et al. (2013)	Switzerland	9	To examine psychological distress (BSI-18) and its risk factors in adolescent cancer survivors and compare it to siblings, norm and psychotherapy patients	407	17.9 (1.5) [16 - 19 years]	5.7 (3.9) years	>5 years	Leukemia & lymphoma (46%), CNS (17%), other (37%)	13% of survivors reported clinical distress compared to 11% of siblings. Higher distress in survivors was associated with female gender, somatic and psychological late-effects and low perceived parental support.
Kazak et al. (2004)	USA	6	To describe rates of PTSD and PTSS in adolescent cancer survivors as well as their mothers and fathers	150	14.7 (2.4) [11 - 19 years]	7.9 (4.3) [3 months - 16 years]	5.3 (2.9) years	Excluded any case with relapse of illness, leukemia (30.5%), solid tumors (35.1%), lymphoma (21.2%), other (13.2%)	8% of survivors met criteria for PTSD since diagnosis, and 4.7% for current PTSD. Survivors reported high levels of arousal (41%), and re-experiencing (73%).
Liptak et al. (2012)	USA	7	To assess self-reported brain tumor survivors' psychological wellbeing (depression, anxiety, and self-concept) and compare it the outcomes of clinical interviews	84	15.7 (1.9) [12 - 18 years]	9.1 (4.9) years	>1 year	Only brain tumor cases	17% of adolescent survivors reported clinical levels of depression and anxiety. The concordance between self-report and clinician ratings was low, with clinicians reporting higher distress than adolescents.

Michel et al. (2009)	UK	8	To establish the contribution of medical and demographic factors to benefit finding and PTG I adolescent survivors and parents	41	13.7 (1.1) [12 - 16 years]	5 (3.0) [0 - 12 years]	6.6 (2.9) [3 - 14 years]	Leukemia (50%), CNS (17%), solid tumor (33%)	PTSD symptomatology was not sig. associated with benefit finding in adolescent survivors. Diagnosis of leukemia, greater optimism, and illness impact were associated with higher levels of benefit finding in survivors.
Ozono et al. (2010)	Japan	9	To identify types of family clusters with cancer survivors, and assess the relationships between psychological distress (anxiety, depression, PTSD) and family functioning.	88	16.2 (2.2) [12- 20 years]	5.4 (3.8) years	>1 year	Brain tumors excluded, ALL (52%), other leukemia (16%), malignant lymphoma (10%), infant neuroblastoma (12%), other solid tumors (10%)	Adolescent survivors from conflictive families had higher levels of PTSD symptomatology, depression, and anxiety. Survivors who experienced a relapse had scored higher on PTSS.
Pelcovitz et al. (1998)	USA	7	To examine PTSD and family functioning in survivors and their mother and compare it to physically abused adolescents and healthy controls	23	17.6 (3.1) [15 - 19 years]	10.5 [2 - 18 years]	3.3 [0 - 11 years]	Leukemia (52%), lymphoma (30%), carcinoma (13%), Wilm's tumor (4%)	34.8% of survivors met lifetime, and 17.4% met current PTSD criteria, rates higher than in abused and healthy controls. Survivors reporting PTSD described their families as more chaotic, and 83% had mothers with PTSD.
Pendley et al. (1997)	USA	6	To describe psychosocial (social anxiety) and body image difficulties in adolescent survivors and compare them to healthy controls	21	11 - 21 years	12.2 (2.69) years	17 (8.65) months	Leukemia (38.1%), lymphoma (42.9%), other solid tumors (19%)	Survivors did not report higher social anxiety than peers. Those who were off treatment for more than a year reported lower self-worth, more social anxiety and more negative body image perceptions.

Robinson et al. (2007)	USA	7	To assess PTSS and PTSD in young adult survivors of childhood cancer and compare them to healthy peers	56	18.6 (0.8) years	8 - 15 years	>1 year	Brain tumors excluded, lymphoma (39%), leukemia (37%), solid tumors (24%)	3% of survivors met current or past PTSD criteria compared to 6% of comparison. Late effects were associated with more PTSD symptomatology. Only 31% of survivors described cancer as a traumatic event.
Servitzoglou et al. (2008)	Greece	8	To describe psychological wellbeing (of AYA cancer survivors and compare them to healthy peers	45	19.8 [15 - 29 years, analyses split for adolescents	8.8 [1 - 15 years]	>2 years	Leukemia (49.5%), sarcoma (17.5%), non-Hodgkin lymphoma (12.6%), Hodgkin's disease (8.7%), Wilms tumor (2.9%), other (6.9%)	Survivors reported higher state and trait anxiety than controls. Survivors with younger age at diagnosis had higher levels of anxiety.
Turner-Sack et al. (2012)	Canada	6	To examine survivors' psychological distress (via BSI) and assess demographic, disease-variables, and coping strategies in relationship to PTG	31	15.7 (2.25) years	7.45 (4.75) [2 - 17 years]	6.5 (2.7) [2 - 10 years]	Brain tumors excluded; ALL (58%), Hodgkin's lymphoma (13%), AML (10%), Other (19%)	Younger age at diagnosis and less avoidant coping predicted lower psychological distress. Distress went down with time passed since diagnosis.

Yallop et al. (2013)	New Zealand	8	To describe psychological wellbeing (depression and anxiety) of adolescent survivors of childhood cancer and compare it to healthy controls	107	15.3 [12 - 18 years]	5.6 [0 - 15 years]	>2 years	Leukemia & Lymphoma (49%), CNS (13%), Other (38%)	6% and 7% of survivors reported depression and anxiety, respectively. Survivors were sig. less likely to report abnormal psychological functioning, however, those with CNS tumors, older individuals, older at the time of diagnosis and from lower SES reported more psychosocial difficulties.

NOTE: *N* = Survivor sample size. Abbreviations: ALL = Acute Lymphoblastic Leukemia, AML = Acute Myeloid Leukemia, CNS = Central Nervous System, PTG = Posttraumatic Growth, AYA = Adolescent and Young Adult, SES = Socio-Economic Status

APPENDIX C: Sampling matrix with criteria (Chapter 4)

Table C.0.1: Sampling matrix used for the recruitment in the qualitative study with sarcoma.

	Cancer Type	Stage	Metastases	Recurrence	Surgery	Duration of Illness	Type of Treatment	Clinical Trial
Socio demographic variables: Age (<25; 25-40; 41-65; >65) Gender Race Income Level Education Level — — — — **Place of care** (specialist centre) **&** **Geography** (distance from follow up appointments)	**Bone**					(Years)		
	Limb	1-4	Size	Yes/No	Amputation Limb preservation/ other None or RT	<2; 2-5; >5	Chemo for relapse Chemo for cure	Yes/No
	Pelvis/spine							
	Craniofacial							
	GIST							
	Surgery or adjuvant	1-4	Size	Yes/No	Yes/No	<2; 2-5; >5		Yes/No
	Advanced							
	Soft Tissue Sarcoma							
	Extremity	1-4	Size	Yes/No	Yes/No	<2; 2-5; >5	RT/ Chemo	Yes/No
	Retroperitoneal							
	Head and Neck							

NOTE: *Bone* = bone sarcoma; *GIST* = Gastrointestinal stromal tumor; *RT* = Radiation therapy.

APPENDIX D: Supporting material (Chapter 5)

Content:

- Description of deviation from the pre-registered protocol
- Questionnaire details
- Sensitivity analyses
- Multiple imputation by chained equations (MICE) for missing data

Description of deviations from the pre-registered protocol

Table D.0.1: Deviations from the pre-registered protocol and analysis.

Original specification	**Change and justification**
Describe how cancer-specific worry, anxiety, and depressive symptoms relate to cognitive and psycho-social factors, such as mental defeat, cancer identity, and satisfaction with cancer care. Estimate one network with and one without the covariates, and subtract the networks in order to estimate the robustness of anxiety and depression. Inspect the delta network in order to estimate the weight of the covariates in the network.	We did not estimate the delta network of change. Despite the nonparanormal transformation of skewed variables, the network with covariates showed suboptimal stability (0.28).
Compare participants in treatment to those off treatment on levels of anxiety and depression. In case of significant differences, and adequate sample size we will estimate separate networks between the 2 groups.	We estimated network 1 on the complete dataset, and network 2 on individuals off treatment only. Due do unequal sample sizes and an underpowered sample overall, we made no further comparisons.
Inspect and describe any bridge symptoms between clusters of symptoms.	We did not estimate bridge symptoms and instead focused on predictability of each node. Rather than assessing comorbidity between anxiety, depression, and cancer worry clusters, we wanted to focus on overall symptomatology. Node predictability, which describes the shared variance with the surrounding nodes, quantifies the level of influence we can exert on particular node by intervening on the surrounding nodes (Fried et al., 2018).
Use “goldbricker” function to examine correlation between nodes (items) and exclude them to achieve more stable networks.	We obtained a stable network and included all the nodes. Reducing nodes did not improve stability of the network with covariates. We inspected item-to-item correlation of each respective scale and estimated networks with fewer nodes. The results did not change. The details are described in Appendix E.
If possible, compare the networks of symptoms across time (the original study protocol was designed to be longitudinal).	We only estimated cross-sectional networks on baseline data. High attrition rate (60%) on an initially small sample (*N*=233) would make

	comparison across time difficult, not only due to the lack of power, but also because it is hard to make meaningful comparisons between networks that are estimated on significantly different sample size (Epskamp, Waldorp, Mõttus, & Borsboom, 2013). Moreover, the interim impact of COVID-19, which we have shown to increase the levels of psychological distress (Košir, Loades, et al., 2020), would likely bias our estimation.
Report node strength, as well as expected influence.	We only report expected influence. Expected influence provides the absolute sum of edge weights, unlike node strength, it accounts for the negative edges. Because our networks showed uniformly positive correlations the values for node strength and expected influence were the same.

NOTE: The original and complete pre-registration protocol can be viewed online at: https://osf.io/gu52d/.

Questionnaire details

CANCER-SPECIFIC WORRY QUESTIONNAIRE (Klassen et al., 2015)

Please read the following statements and indicate **to what extent they apply to you**.

	Strongly disagree	Disagree	Agree	Strongly agree
I worry about my cancer/tumor every day.	○	○	○	○
Cancer/tumor is always at the back of my mind.	○	○	○	○
I worry my cancer/tumor will come back (i.e. relapse).	○	○	○	○
I worry about getting a new type of cancer/tumor.	○	○	○	○
I worry about late effects that might happen to me. (*Note: late effects are health problems caused by cancer treatments, e.g. heart problems, hearing loss, learning problems*).	○	○	○	○
I worry it might be difficult to have children in the future.	○	○	○	○

NOTE: This questionnaire was administered only to those who were off treatment at the time of the study. The questionnaire was developed for AYAs in remission and surveillance phase, and the level of worry may be inflated if administered to individuals currently undergoing cancer treatment.

MENTAL DEFEAT QUESTIONNAIRE (MDQ)
Adapted from Dunmore, Clark, & Ehlers (2001)

Please rate whether the following statements applied to you **at any time** during your illness experience.

	Not at all	A little	Moderately	Strongly	Very Strongly
I lost any will-power.	○	○	○	○	○
I didn't care what happened to me anymore.	○	○	○	○	○
I felt completely defeated.	○	○	○	○	○
I no longer felt like a human being.	○	○	○	○	○
In my mind, I gave up.	○	○	○	○	○
I felt destroyed as a person.	○	○	○	○	○
I wanted to die.	○	○	○	○	○
I lost any inner resistance.	○	○	○	○	○
I felt like an object.	○	○	○	○	○
I felt completely at the mercy of other people or the situation.	○	○	○	○	○
I felt completely humiliated and lost any sense of inner dignity.	○	○	○	○	○

QUESTIONS ABOUT THE SATISFACTION WITH CARE:

Please answer to the following 3 questions by dragging the slider
(***0*** *indicates no satisfaction or no agreement, and* ***100*** *indicates satisfaction or strong agreement*).

	0 10 20 30 40 50 60 70 80 90 100
How satisfied are you about the way you found out your diagnosis?	
How good is your relationship with your cancer medical team?	
To what extent are/were your needs as a patient met?	

OPEN-ENDED QUESTIONS:

Please tell us how you heard about your cancer diagnosis and whether the experience was positive or negative.

_____

_____

As part of our work we are striving to improve cancer care for young patients.

Please use the space below to tell us what you wish **could have been done better** in your care.

We would also be happy to hear about **anything that worked really well for you**!

_____

_____

Sensitivity analyses

Table D0.2: Comparison between the Slovenian and English-speaking participants.

	Slovenian participants (N=74)		**English-speaking participants (N=159)**		**Test Statistic**
	N	**M (SD) Range**	**N**	**M (SD) Range**	
Gender					p=0.394
Male	68		136		
Female	6		21		
Other			2		
Age at study		31.4 (5.85)		29.4 (5.66)	**p=0.017**
Age at diagnosis		26.7 (7.9)		24.7 (7.33)	p=0.057
Treatment status					p=0.986
On treatment	30 (33%)		44 (30%)		
Off treatment	61 (67%)	50.2 (59.3)	102 (70%)	50.1 (57.9) [1 – 248]	
Relationship Status					p=0.987
Single	26 (29%)		49 (34%)		
In a relationship	22 (24%)		40 (27%)		
Married/Cohabiting	39 (43%)		51 (35%)		
Separated/Divorced	4 (4%)		6 (4%)		
Children					p=0.382
Yes	30 (33%)		40 (27%)		
No	61 (67%)		106 (73%)		
Education					p=0.859
Elementary school	1 (1%)		1 (<1%)		
High school/higher degree below university	34 (37%)		58 (39%)		
Bachelor's					
Master's	31 (34%)		53 (36%)		
PhD/Doctorate	20 (22%)		24 (16%)		
Prefer not to answer	4 (4%)		6 (4%)		
	1 (1%)		4 (2%)		
Cancer type					p=0.589
Hematologic cancers	31 (34%)		50 (34%)		
Breast	24 (26%)		26 (18%)		
Sarcomas	8 (9%)		21 (14%)		
CNS	5 (5%)		14 (10%)		
Reproductive organs	7 (8%)		11 (7%)		
Colorectal cancers	7 (8%)		7 (6%)		
Thyroid	3 (3%)		5 (3%)		
Other	6 (7%)		7 (6%)		
Multiple cancers					**p=0.031**
Yes	5 (5%)		1 (<1%)		
No	86 (95%)		146 (99%)		

Metastasis Yes No Don't know	 27 (30%) 56 (61%) 8 (9%)	 42 (30%) 89 (60%) 15 (10%)	p=0.958
Relapse* Yes No	 9 (11%) 71 (89%)	 16 (14%) 98 (86%)	p=0.665
Mental Health diagnosis Yes No Prefer not to answer	 26 (29%) 65 (71%) 0	 53 (36%) 89 (61%) 4 (3%)	p=0.115
Anxiety	7.88 (5.54) [0 – 20]	8.28 (5.21) [0 – 21]	p=0.585
Depression	5.91 (5.06)	9.91 (6.25)	p<0.001
Cancer worry	10.8 (4.31) [1 – 18]	11.4 (4.22) [0 – 18]	p=0.421
Satisfaction with receiving diagnosis	53.6 (36.7) [0 – 100]	48.7 (35.3) [0 – 100]	p=0.325
Relationship with the medical team	83.9 (20.1) [19 – 100]	80.9 (25.1) [0 – 100]	p=0.333
Extent of needs met	79.1 (22.1) [8 – 100]	72.7 (25.2) [0 – 100]	**p=0.049**

NOTE: Anxiety was measured using GAD-7, Depression was measured using PHQ-9. See section 5.3.2 and section "Questionnaire details" for more description of the questionnaires.
*The question about experiencing a relapse was only asked to the individuals who were off treatment at the time of the study.

Multiple imputation using chained equations (MICE) for missing data

Table D.0.3: Level of missingness.

Imputed variable(s)	Level of missingness (%)
GAD-7	6.9%
PHQ-9	7.3%
Cancer worries	9%

NOTE: *GAD-7* = Generalized anxiety disorder questionnaire (Spitzer, Kroenke, Williams, & Löwe, 2006); *PHQ-9* = Patient Health Questionnaire ((Kroenke et al., 2001).

Table D.0.4: Description of variables used in MICE.

Variables used to impute	Description of variables
GAD-7 Items, PHQ-9 Items, CES Items, MDQ Items, Cancer-related Worry Items	Ordered categorical variables
Having children, Treatment status, Relapse	Dichotomous variables
Gender, Relationship status, Education level, Metastasis*	Unordered categorical variables
Satisfaction with care	Continuous

NOTE: *CES* – Centrality of Events Scale, a 7-item scale that asks individuals to what extent a stressful or traumatic event affects their sense of being and identity. The scores range from 0 to 28, and higher scores mean that the event serves as a stronger reference point in one's life (D. Bernstein & Rubin, 2006); *MDQ* – Mental Defeat Questionnaire, an 11-item questionnaire about individuals' perceptions of their mental state during a traumatic event (i.e. cancer). Higher scores indicate higher level of mental defeat during illness (Dunmore et al., 2001); Satisfaction with care contained 3 questions: "How satisfied are you with learning your diagnosis?", "How good is your relationship with your cancer medical team?" and "To what extent are/were your needs as a patient met?" The rating ranged from 0 (least satisfied/ worst) to 100 (most satisfied/ best).
*metastasis responses were coded as yes/no/don't know (3 levels)

APPENDIX E: Supplementary material for network analysis (Chapter 5)

Content:

- All items included in the network analysis
- Item-to-item correlations and post hoc network sensitivity
- Node predictability
- Centrality indices for the estimated networks

All items included in the network analysis

Table E.0.1: Item (node) description and their assigned labels.

Construct	Item	Item label	Description
Anxiety	1	GAD1	Feeling nervous, down or on edge
	2	GAD2	Not being able to stop or control worrying
	3	GAD3	Worrying too much about different things
	4	GAD4	Trouble relaxing
	5	GAD5	Being so restless that it is hard to sit still
	6	GAD6	Becoming easily annoyed or irritable
	7	GAD7	Feeling afraid as if something awful might happen
Depression	1	PHQ1	Little interest or pleasure in doing things Feeling down, depressed, or hopeless Trouble falling or staying asleep, or sleeping too much
	2	PHQ2	Feeling down, depressed, or hopeless
	3	PHQ3	Trouble falling or staying asleep, or sleeping too much
	4	PHQ4	Feeling tired or having little energy
	5	PHQ5	Poor appetite or overeating
	6	PHQ6	Feeling bad about yourself - or that you are a failure or have let yourself or your family down
	7	PHQ7	Trouble concentrating on things, such as reading the newspaper or watching television
	8	PHQ8	Moving so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual
	9	PHQ9	Thoughts that you would be better off dead or of hurting yourself in some way
Cancer worry	1	W1	I worry it might be difficult to have children in the future.
	2	W2	I worry about late effects that might happen to me.
	3	W3	I worry about getting a new type of cancer/tumor.
	4	W4	I worry my cancer/tumor will come back (i.e. relapse).
	5	W5	Cancer/tumor is always at the back of my mind.
	6	W6	I worry about my cancer/tumor every day.

NOTE: *GAD* = Generalized anxiety disorder, items from GAD-7 questionnaire; *PHQ* = Patient health questionnaire, items from PHQ-9 questionnaire; *W* = worry, items from Cancer-specific worry questionnaire.

Item-to-item correlations and post hoc networks sensitivity

Table E.0.2: Zero-order correlations between items of psychological questionnaires.

	gad_1	gad_2	gad_3	gad_4	gad_5	gad_6
gad 1	—					
gad 2	**0.668**	—				
gad 3	0.549	**0.683**	—			
gad 4	0.638	0.637	0.609	—		
gad 5	0.445	0.470	0.373	0.549	—	
gad 6	0.600	0.557	0.479	0.615	0.475	—
gad 7	0.444	0.538	0.504	0.498	0.381	0.394

	worry_1	worry_2	worry_3	worry_4	worry_5
worry_1	—				
worry_2	**0.760**	—			
worry_3	0.627	0.619	—		
worry_4	0.536	0.586	0.586	—	
worry_5	0.405	0.386	0.378	0.500	—
worry_6	0.079	0.135	0.188	0.212	0.367

	phq_1	phq_2	phq_3	phq_4	phq_5	phq_6	phq_7	phq_8
phq_1	—							
phq_2	**0.644**	—						
phq_3	0.475	0.504	—					
phq_4	0.484	0.418	0.587	—				
phq_5	0.351	0.376	0.503	0.440	—			
phq_6	0.508	0.560	0.466	0.401	0.379	—		
phq_7	0.434	0.442	0.525	0.476	0.453	0.460	—	
phq_8	0.302	0.324	0.442	0.373	0.436	0.339	0.538	—
phq_9	0.458	0.495	0.341	0.319	0.294	0.366	0.326	0.406

NOTE: gad_1 – gad_7 are items on Generalized Anxiety Disorder questionnaire (Spitzer et al., 2006); worry_1 – worry_6 are items on cancer-specific worry questionnaire (Klassen et al., 2015); phq_1 – phq_9 are items on Patient Health Questionnaire (Kroenke et al., 2001). Emboldened values represent very high correlation.

Post Hoc sensitivity analysis

Because of the high correlation between some items (nodes; see in bold in Table E.2) we re-estimated the 2 networks and excluded items with >0.65 correlation and based on the topological overlap. As a result, we excluded GAD 2 (chronic worry) and worry 1 (fertility concern).

The stability of Network 1 and network 2 was 0.51 and 0.36, respectively. GAD 4 (trouble relaxing) and PHQ2 (low mood) remained the most central symptoms.

Node predictability

Table E.0.3: Predictability of each node in the network.

			Predictability values	
	Label	**Description**	**Network 1**	**Network 2**
Anxiety	GAD1	On edge	0.594	0.653
	GAD2	Chronic worry	0.631	0.634
	GAD3	Worry > 1 thing	0.569	0.661
	GAD4	Trouble relaxing	0.657	0.680
	GAD5	Restlessness	0.433	0.500
	GAD6	Irritability	0.520	0.592
	GAD7	Afraid	0.361	0.445
Depression	PHQ1	Anhedonia	0.558	0.572
	PHQ1	Low mood	0.606	0.640
	PHQ3	Sleep disturbance	0.518	0.573
	PHQ4	Fatigue	0.472	0.487
	PHQ5	Appetite disturbance	0.390	0.430
	PHQ6	Worthlessness	0.457	0.540
	PHQ7	Concentration problems	0.488	0.473
	PHQ8	Psychomotor disturbance	0.504	0.594
	PHQ9	Suicidality	0.379	0.441
Cancer worry	W1	Fertility concern	N/A	0.607
	W2	Late effects		0.634
	W3	New cancer		0.496
	W4	Relapse		0.518
	W5	Cancer on mind		0.373
	W6	Cancer every day		0.160

NOTE: *GAD* = Generalized anxiety disorder, items from GAD-7 questionnaire; *PHQ* = Patient health questionnaire, items from PHQ-9 questionnaire; *W* = worry, items from Cancer-specific worry questionnaire.
Node predictability describes the shared variance with the surrounding nodes. The value provides an absolute value of interconnectedness and quantifies the level of influence we can exert on that particular node by intervening on the surrounding nodes (Fried et al., 2018).

Centrality indices for the two estimated networks

Table E0.4: Network 1 centrality indices, standardized z-scores.

Node	Betweenness	Closeness	Expected influence
GAD1	-0.056	0.803	0.796
GAD2	-0.500	-0.754	1.167
GAD3	0.537	0.581	-0.123
GAD4	3.055	1.907	1.938
GAD5	0.241	0.390	-0.904
GAD6	-0.648	0.224	-0.032
GAD7	-0.944	-2.116	-1.541
PHQ1	-0.056	0.312	0.302
PHQ2	0.093	0.788	1.253
PHQ3	-0.796	-0.573	0.647
PHQ4	1.129	0.622	-0.546
PHQ5	-0.944	-1.853	-1.009
PHQ6	-0.648	-0.412	-0.532
PHQ7	-0.352	0.072	0.199
PHQ8	0.389	0.223	-0.094
PHQ9	-0.500	-0.214	-1.521

NOTE: *GAD* = Generalized anxiety disorder, items from GAD-7 questionnaire; *PHQ* = Patient health questionnaire, items from PHQ-9 questionnaire; *W* = worry, items from Cancer-specific worry questionnaire. Node description can be seen in Table E.0.1.

Node centrality refers to the importance of each node in the network and it is based on node strength, betweenness, closeness (Opsahl et al., 2010), and expected influence (Robinaugh et al., 2016). Node strength is the sum of absolute edge weights connected to each node, betweenness refers to how often one node is in the shortest paths between other nodes, and closeness is the inverse sum of distances from one node to all other nodes in the network. Expected influence provides the sum of edge weights, but unlike node strength, it accounts for the negative edges. Due to no negative edges in our networks, we only report expected influence, which is the same as node strength.

Table E0.5: Network 2 centrality indices, standardized z-scores.

Node	Betweenness	Closeness	Expected influence
GAD1	0.922	1.474	1.159
GAD2	-0.871	0.183	0.555
GAD3	-0.311	0.711	0.107
GAD4	2.266	1.929	1.854
GAD5	-0.647	0.299	-0.634
GAD6	-1.431	-0.169	0.337
GAD7	0.698	-0.037	-0.639
PHQ1	-0.199	0.045	0.054
PHQ2	0.810	0.499	1.212
PHQ3	1.146	0.735	0.928
PHQ4	-0.423	1.031	-0.520
PHQ5	0.698	0.518	-0.365
PHQ6	-0.423	0.434	0.080
PHQ7	-0.871	0.063	-0.288
PHQ8	0.585	0.463	0.580
PHQ9	-1.095	-0.520	-1.227
W1	-1.207	-1.868	0.263
W2	0.361	-1.654	0.704
W3	-1.543	-1.873	-0.718
W4	0.922	-0.998	0.198
W5	1.034	-0.392	-0.688
W6	-0.423	-0.874	-2.952

NOTE: *GAD* = Generalized anxiety disorder, items from GAD-7 questionnaire; *PHQ* = Patient health questionnaire, items from PHQ-9 questionnaire; *W* = worry, items from Cancer-specific worry questionnaire. Node description can be seen in Table E.0.1.

Node centrality refers to the importance of each node in the network and it is based on node strength, betweenness, closeness (Opsahl et al., 2010), and expected influence (Robinaugh et al., 2016). Node strength is the sum of absolute edge weights connected to each node, betweenness refers to how often one node is in the shortest paths between other nodes, and closeness is the inverse sum of distances from one node to all other nodes in the network. Expected influence provides the sum of edge weights, but unlike node strength, it accounts for the negative edges. Due to no negative edges in our networks, we only report expected influence, which is the same as node strength.

APPENDIX F: Abridged version of the online COVID-19 impact Survey (Chapter 6)

Q1 Over **the last 2 weeks,** how often have you been bothered by the following problems?

	Not at all (0)	Several days (1)	More than half of the days (2)	Nearly every day (3)
Feeling nervous, anxious or on edge (1)	○	○	○	○
Not being able to stop or control worrying (2)	○	○	○	○
Little interest or pleasure in doing things (3)	○	○	○	○
Feeling down, depressed, or hopeless (4)	○	○	○	○

Q2 **Did COVID-19 pandemic have an impact on your treatment protocol or follow up appointments?**

- ○ Yes (1)
- ○ No (2)
- ○ Not yet, but I worry it will (3)

Q2.1 **If yes, please briefly describe what was the impact (e.g. my chemo was postponed):**

_____

Q3 **Does COVID-19 pandemic and associated events (lockdown) have an impact on your psychological well-being?**

- ○ I am feeling better than before (1)
- ○ I am feeling the same way as before (2)
- ○ I am feeling more anxious and stressed than before (3)

Q3.1 **Can you briefly describe any concerns related to COVID-19 and your current health status?**

_____

Q4 **Does COVID-19 pandemic contribute to your feelings of isolation?**

- ○ I feel less isolated than before (1)
- ○ I feel the same way as before (2)
- ○ I feel more isolated than before (3)

Q4.1 **Can you please briefly describe how COVID-19 influences your feelings of isolation?**

_____

Q5 Did you receive any special instructions or additional information from your oncologist or the medical team on how to cope with the COVID-19 pandemic as a cancer patient?

- ○ Yes (1)
- ○ No (2)

Q5.1 Can you briefly describe what you were told:

_____

Q6 **Where do you get your information about the COVID-19 pandemic? (mark all that apply)**

- ☐ Medical professionals (including nurses, pharmacists, doctors) (1)
- ☐ Social media (2)
- ☐ Support groups/Patient Organizations (3)
- ☐ Relatives and friends (4)
- ☐ News websites, newspapers (5)
- ☐ Specialized internet websites that are not news sources or social media (6)
- ☐ Other (please specify): (7) _____

Q7 **How satisfied are you with the information about the COVID-19 pandemic you receive?**

	Extremely disatisfied									Extremely satisfied
	0	1	2	3	4	5	6	7	8	9	10
Drag the slider: ()											

Q8 **To what extent do you trust the information you receive about COVID-19?**

	Entirely mistrust									Entirely trust
	0	1	2	3	4	5	6	7	8	9	10
Drag the slider: ()											

Q9 **As a cancer patient, would you prefer to have more information on how to best cope and manage your health during a pandemic outbreak?**

- ○ Yes (1)
- ○ No (2)
- ○ Not sure (3)

Q9.1 **Please briefly elaborate on your answer:**

_____

APPENDIX G: Supplementary tables (Chapter 6)

The following tables show breakdown of the results by the time passed since treatment.

Table G0.1: : Table showing the proportion of individuals feeling more anxious or distressed now, compared to the time prior to the pandemic, stratified by treatment phase.

	Better than before N (%)	**Same as before N (%)**	**More anxious than before N (%)**
Undergoing treatment (n = 57)	7 (12%)	14 (25%)	36 (63%)
Completed within 6 months (n = 24)	2 (8%)	9 (38%)	13 (54%)
Completed more than 6 months ago (n = 96)	7 (7%)	29 (30%)	60 (63%)

Table G0.2: Table showing the proportion of individuals who received direct communication about COVID-19 from the health care team by treatment phase.

	Received info about COVID-19 N (%)	**Did not receive info about COVID-19 N (%)**
Undergoing treatment (n = 57)	27 (47%)	30 (53%)
Completed within 6 months (n = 23)	4 (17%)	19 (83%)
Completed more than 6 months ago (n = 91)	11 (10%)	82 (90%)

Table G0.3: Table showing the proportion of individuals who would have wanted more information about COVID-19, stratified by treatment phase.

	Want more information N (%)	**Don't want more information N (%)**	**Not sure N (%)**
Undergoing treatment (n = 56)	33 (59%)	13 (23%)	10 (18%)
Completed within 6 months (n = 23)	13 (57%)	4 (17%)	6 (26%)
Completed more than 6 months ago (n = 91)	50 (55%)	16 (18%)	25 (27%)

Table G0.4: Table showing the most commonly used information resources for COVID-19, and reported satisfaction and perceived trustworthiness of these resources, stratified by treatment.

	COVID-19 Information sources	**Satisfaction (mean)**	**Trustworthiness (mean)**
Undergoing treatment (n = 57)	General news (n = 44) Medical Professionals (n = 43) Social Media (n = 37)	6/10	5.8/10
Completed within 6 months (n = 23)	General news (n = 22) Medical Professionals (n = 14) Social Media (n = 12)	6.3/10	6.5/10
Completed more than 6 months ago (n = 91)	General news (n = 69) Social Media (n = 60) Medical Professionals (n = 44)	6.3/10	6.2/10

NOTE: Satisfaction and trustworthiness are rated on a scale from 0 (least satisfied/trustworthy) to 10 (most satisfied/trustworthy).

APPENDIX H: Supplementary material and tables (Chapter 7)

Content:

- Details of the measures and questionnaires
- Abbreviation of the FACIT questionnaire
- Multiple imputation by chained equation (MICE) for missing data and sensitivity analyses
- Complete tables with group-based trajectory modelling (GBTM) indices for classes 1 through 6

Details of the measures and questionnaires

Table H0.1: Questionnaires from the IHRT Biobank used in Chapter 7.

Measure name	Time points administered
Outcome expectations	BL
EQ-5D	BL, 12m, 24m, 36m
FACIT-fatigue	BL, 12m, 24m, 36m
TESS	BL, 3m, 6m, 12m, 24m, 36m

NOTE: IHRT = Interdisciplinary Health Research Team, BL = baseline (Pre-operative); m = months post treatment; EQ-5D = European Quality of Life Questionnaire, self-reported measure for quality of life; FACIT = Functional Assessment of Chronic Illness Therapy; TESS = Toronto Extremity Salvage Score.

- - - - - - -

OUTCOME EXPECTATIONS
Please read the following statements and circle the most suitable answer for what you expect.

1) How long do you think it will take you to recover from your treatment for your arm or leg problem?
    a. 3 months
    b. 6 months
    c. 12 months
    d. 24 months
    e. I don't expect to recover
    f. I don't know what to expect

2) Do you expect to experience any complications from your treatment?
    a. No
    b. Yes
    c. I don't know what to expect

3) In general, how difficult do you expect your daily activities to be once you recover from the treatment for your arm or leg problem?
    a. Not at all difficult
    b. Somewhat difficult
    c. Extremely difficult
    d. I don't know what to expect

LIFE ORIENTATION TEST (LOT)

Please answer the following questions about yourself by indicating the extent of your agreement. Be as honest as you can, and try to not let your responses to one question influence your response to other questions. There are no right or wrong answers.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
In uncertain times I usually expect the best.*					
It's easy for me to relax.					
If something can go wrong for me, it will.					
I always look on the bright side of things.					
I'm always optimistic about my future.*					
I enjoy my friends a lot.					
It's important for me to keep busy.					
I hardly ever expect things to go my way.					
Things never work out the way I want them to.					
I don't get upset too easily.					
I'm a believer that "every cloud has a silver lining".*					
I rarely count on good things happening to me.					

*items used to calculate the optimism score

European Quality of Life Questionnaire (EQ-5D)

*The following questions are about your health **today**. By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.*

Do not tick more than one box in each group.

Mobility

- ☐ 1 I have no problems in walking about
- ☐ 2 I have some problems in walking about
- ☐ 3 I am confined to bed

Self-Care

- ☐ 1 I have no problems with self-care
- ☐ 2 I have some problems washing or dressing myself
- ☐ 3 I am unable to wash or dress myself

Usual activities (e.g. Work, study, housework, family or leisure activities)

- ☐ 1 I have no problems with performing my usual activities
- ☐ 2 I have some problems with performing my usual activities
- ☐ 3 I am unable to perform my usual activities

Pain/Discomfort

- ☐ 1 I have no pain or discomfort
- ☐ 2 I have moderate pain or discomfort
- ☐ 3 I have extreme pain or discomfort

Anxiety/Depression

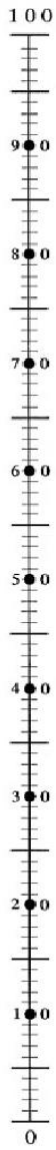
- ☐ 1 I am not anxious or depressed
- ☐ 2 I am moderately anxious or depressed
- ☐ 3 I am extremely anxious or depressed

To help people say how good or bad their health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.

Best Imaginable Health State

Your own health state today:



Worst Imaginable Health State

Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue

Below is a list of statements that other people with your illness have said are important. ***By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.***

	Not at all	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
I feel fatigued	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I feel listless ("washed out")	0	1	2	3	4
I feel tired	0	1	2	3	4
I have trouble starting things because I am tired	0	1	2	3	4
I have trouble finishing things because I am tired	0	1	2	3	4
I have energy	0	1	2	3	4
I am able to do my usual activities	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I am too tired to eat	0	1	2	3	4
I need help doing my usual activities	0	1	2	3	4
I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
I have to limit my social activity because I am tired	0	1	2	3	4

Toronto Extremity Salvage Score (TESS)

The following questions ask about your ability to perform activities that are common to every day life. Considering the amount of difficulty you have performing the activity due to the current problem you are having with your arm, please answer the questions by choosing the answer that best describes your ability to do the activity ***over the past week.***

Site: ☐ **Bone** ☐ **Soft tissue** **Side of lesion:** ☐ **Right** ☐ **Left** **Are you:** ☐ **Right handed** ☐ **Left handed**

		Impossible to do	Extremely difficult	Moderately difficult	A little bit difficult	Not at all difficult	Not applicable for me
1	Putting on a pair of pants is	1	2	3	4	5	6
2	Tying shoe laces is	1	2	3	4	5	6
3	Putting on socks or stockings is	1	2	3	4	5	6
4	Showering is	1	2	3	4	5	6
5	Dressing my arms and upper body is	1	2	3	4	5	6
6	Buttoning a shirt is	1	2	3	4	5	6
7	Tying a tie or a bow at the neck of a blouse is	1	2	3	4	5	6
8	Putting on make-up or shaving is	1	2	3	4	5	6
9	Brushing your teeth is	1	2	3	4	5	6
10	Brushing your hair is	1	2	3	4	5	6
11	Doing light household chores is	1	2	3	4	5	6
12	Gardening or yard work is	1	2	3	4	5	6
13	Preparing and serving meals is	1	2	3	4	5	6
14	Cutting food while eating is	1	2	3	4	5	6
15	Drinking from a glass is	1	2	3	4	5	6
16	Performing heavy household chores is	1	2	3	4	5	6
17	Going shopping is	1	2	3	4	5	6
18	Giving or receiving change (i.e. coins or bills) is	1	2	3	4	5	6
19	Carrying a shopping bag or briefcase is	1	2	3	4	5	6
20	Lifting a box to an overhead shelf is	1	2	3	4	5	6

		Impossible to do	Extremely difficult	Moderately difficult	A little bit difficult	Not at all difficult	Not applicable for me
21	Turning a key in a lock is	1	2	3	4	5	6
22	Pushing or pulling open a door is	1	2	3	4	5	6
23	Writing is	1	2	3	4	5	6
24	Picking up small items is	1	2	3	4	5	6
25	Completing my usual duties at work is (work includes both outside the home and as a homemaker)	1	2	3	4	5	6
26	Working my usual number of hours is (work includes both outside the home and as a homemaker)	1	2	3	4	5	6
27	Participating in my usual leisure activities is	1	2	3	4	5	6
28	Socializing with friends and family is	1	2	3	4	5	6
29	Participating in my usual sporting activities is	1	2	3	4	5	6

		Impossible to do	**Extremely difficult**	**Moderately difficult**	**A little bit difficult**	**Not at all difficult**	**Not applicable for me**
1	Considering all the activities in which I participate in daily life, I would rate my ability to perform these activities during the past week as:	1	2	3	4	5	6
		Completely disabled	**Severely disabled**	**Moderately disabled**	**Mildly disabled**	**Not at all disabled**	
2	I would rate myself as being:	1	2	3	4	5	

Abbreviation of the FACIT questionnaire

Description

Fatigue was assessed with Functional Assessment of Chronic Illness Therapy (FACIT) – fatigue scale, which is a 13-item scale that asks about fatigue, tiredness, weakness, listlessness, lack of energy, and the impact of these on social activities, as well as functioning (i.e. sleeping). The scale was originally developed to assess cancer-related fatigue and has shown good reliability and validity in a sample of cancer patients (Webster et al., 2003). Items 7 (I have energy) and 8 (I am able to do my usual activities) are reverse coded and the scale was treated as a continuous variable.

The complete scale can be viewed above in section "Details of the measures and questionnaires."

Measurement invariance

When modeling individual scores of fatigue across time, we assume that the measure we are using is equivalent between different time points (time-invariant). This allows to attribute any change we observed to the real change in the construct (i.e. fatigue) and not be caused by errors in measurement (Meredith, 1993). Model fit was evaluated by comparative fit index (CFI), root mean square error of approximation (RMSEA), where values of CFI ≥ 0.95 and RMSEA ≤ 0.06 indicated acceptable model fit (Hu & Bentler, 1999). All of the analyses were done using package *lavaan* (Rosseel, 2012).

Because fatigue was the primary outcome of interest, we checked the reliability of FACIT measure using longitudinal confirmatory factor analysis. The original scale showed a poor model fit, CFI = 0.85 and RMSEA = 0.15.

Subsequently, we decided to abbreviate the scale and removed items based on 2 criteria: a) poor factor loading (<0.60) and b) lavaan's modification indices. The latter entailed examining pairs of items that demonstrated great overlap. We made the decision to exclude an item based on the overlap in semantic meaning. For example, item *I have trouble starting things because I am tired* showed almost identical correlation pattern with other items as *I have trouble finishing things because I am tired*. As a result, we decided to keep only *I have trouble starting things because I am tired* because if one expresses agreement with this statement, it is likely that they will also express agreement with *I have trouble finishing things because I am tired*. If one cannot start the activity, it is likely that they will not manage to *finish* it either.

The revised and abbreviated measure was tested by fitting a series of measurement models, each adding a constraint in order to simulate measurement invariance (MI) over time (Liu et al., 2017; Widaman et al., 2010). Four models were specified sequentially: a) configural invariance model, testing whether the same general pattern of factor loadings is consistent across time and fixes factor means; b) metric or weak invariance model, constraining all factor loadings as well as means to be identical across time; c) scalar or strong invariance model, further constraining thresholds going from one response category to the next to be equal across time for each indicator (i.e. factor intercepts are equal across time); and d) residual or strict invariance model, further constraining all unique factor variances and covariances to be equal across time (Curtis & Mackinnon, 2020; Liu et al., 2017).

Results

The abbreviated scale that we used in the longitudinal analyses is described below in Table H0.2 and the corresponding model fit is described in Table H0.3. All four models demonstrated acceptable fit, which allowed us to determine that the revised measure did not violate the assumption of MI. The adapted scale showed nearly perfect correlation with the old measure ($r = 0.98$, $p < 0.001$). Figure H0.1 shows the correlation between the old and new FACIT scales.

Table H0.2: Abbreviated version of the FACIT scale.

Original item	Not at all	A little bit	Somewhat	Quite a bit	Very much
F4 I feel fatigued					
F5 I feel weak all over					
F8 I have trouble starting things because I am tired					
F10 I have energy					
F12 I need to sleep during the day					
F13 I am too tired to eat					
F16 I have to limit my social activity because I am tired					

Table H0.3: Model fit indices for testing measurement invariance of abbreviated FACIT scale.

Model fit	**CFI**	**RMSEA**
Configural model fit	0.962	0.058
Metric or weak model fit	0.957	0.06
Scalar or strong model fit	0.956	0.058
Residual or strict model fit	0.955	0.057

NOTE: *CFI* = comparative fit index, *RMSEA* = root mean square error of approximation.

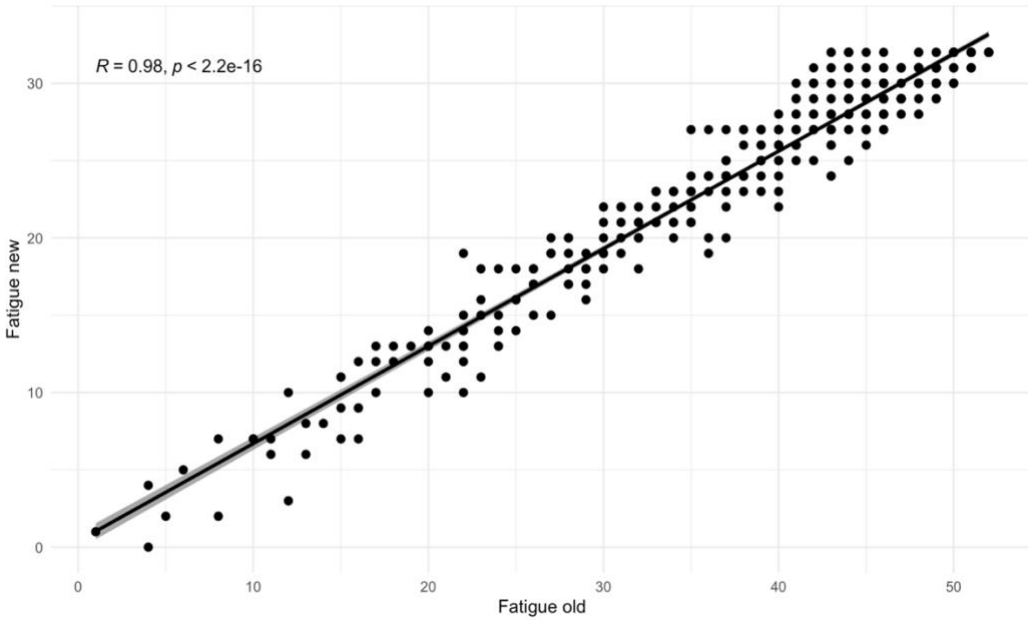


Figure H0.1: Correlation between old and new FACIT scales.
NOTE: X-axis demonstrates the values form the old FACIT scale and Y-axis demonstrates the values on the new FACIT scale. The correlation (R in top left corner) is very high (0.98), and p-value is highly significant, indicating that the abbreviated scale retained the same pattern of response, but in addition also met the criteria for the measurement invariance.

Multiple imputation by chained equation (MICE) for missing data and sensitivity analyses

In order to minimize data loss, we imputed missing variables using chained equations using *mice* package (van Buuren & Groothuis-Oudshoorn, 2011) and pooled the data using *sjmisc* package (Lüdecke, 2018). In line with recommendations for the level of missingness, we imputed 30 data sets (Little & Rubin, 2014).

Because imputations rely on the assumption that data is missing at random (MAR) (van Buuren & Groothuis-Oudshoorn, 2011), we performed sensitivity analyses before imputing data. We first compared individuals with completed baseline assessments to those who had baseline and 6-month assessment but were missing the 3-month data point. We wanted to make sure that individuals missing at 3 months were not worse off.

Table H0.4 shows the results, we found no significant differences. To further assess if the individuals who dropped out differed on any important variables, we compared individuals with complete data to those who dropped out at 2 years. Again, we observed no significant difference between complete cases and those who dropped out at 2 years (see Table H0.5).

Further consultation with the Principal Investigator of the study (Dr. Robert Turcotte) and research personal at McGill University Health Centre, we were assured that data missingness was also due to personnel errors (e.g. loss of questionnaires or consent form), as well as a server error, which caused some data loss in 2016. Thus we assumed MAR and conducted our analysis on the imputed data.

Table H0.4: Table comparing complete cases with those who are missing 3-month appointment.

Variable	**BL & 3M** **M(SD) or N**	**BL & 6M** **M(SD) or N**	**Test Statistic (p)**
Age at bl/dx	52.6 (18.3)	52.9 (18.0)	p = 0.872
BL Quality of life	73.4 (18.3)	74.4 (17.4)	p = 0.469
BL TESS	74.6 (19.3)	74.6 (19.5)	p = 0.972
Optimism	6.2 (2.04)	6.26 (2.01)	p = 0.873[a]
Mood			
Not worried (1)	203	215	
Moderately (2)	134	140	p = 0.794[b]
Extremely (3)	15	12	
Gender			
Female	159	164	p = 0.942 [b]
Male	219	230	
Site			
Upper	94	101	p = 0.80 [b]
Lower	286	294	
Type of cancer			
Bone	65	76	p = 0.798 [b]
Ewing	7	5	
Osteo	16	15	
Soft tissue	182	185	

NOTE: *BL* = baseline, *3M* = 3-month appointment, *6M* = 6-month appointment.
[a] – Mann-Whitney test
[b] – Fisher's exact test

Table H0.5: Table comparing baseline characteristics of complete cases with those who dropped out at 24 months.

Variable	**Baseline**	**24 months**	**Test Statistic (p)**
Age at diagnosis	51.8 (18.5)	53.4 (19.6)	p = 0.333
BL Quality of life	73.9 (18.1)	71.7 (18.9)	p = 0.167
BL FACIT (abb.)	6.87 (5.94)	6.34 (1.98)	p = 0.335
BL TESS	75.3 (19.0)	73.7 (19.1)	p = 0.323
LOT – Optimism	6.23 (1.99)	6.11 (1.81)	p = 0.510
Mood			
Not worried (1)	263	113	
Moderately (2)	173	73	p = 0.926
Extremely (3)	16	8	
Gender			
Female	206	80	p = 0.399
Male	280	126	
Site			
Upper	130	60	p = 0.578
Lower	359	149	
Type of cancer			
Soft tissue	228	111	p = 0.767
Other	115	60	

NOTE: *BL* = baseline, *LOT* = Life Orientation Test, *EQ-5D* = European Quality of Life Questionnaire, self-reported measure for quality of life; *FACIT (abb.)* = Functional Assessment of Chronic Illness Therapy, abbreviated version in our study; *TESS* = Toronto Extremity Salvage Score, VAS = Visual Analog Scale.

Table H0.6: Level of missingness for the main variables to be imputed.

Imputed variable(s)	**Level of missingness at baseline (%)**	**Level of missingness at 12m (%)**	**Level of missingness at 24m (%)**
FACIT	6.7%	6.9%	43.1%
TESS	0%	23.7%	42.7%
EQ-5D	7.1%	25.3%	43.5%

NOTE: *m* = months since treatment.

Table H0.7: Description of variables used in MICE.

Variables used to impute	**Description of variables**
EQ-5D Items without VAS, Expectations about recovery	Ordered categorical variables
Gender (M/F), Other chronic illness (Yes/No), tumor site (Upper/Lower), pain medication (Yes/No)	Dichotomous variables
Tumor type, Relationship status, Education level	Unordered categorical variables
Satisfaction with surgical outcomes, FACIT score, EQ-5D VAS score, age at diagnosis	Continuous

NOTE: *LOT* = Life Orientation Test, *EQ-5D* = European Quality of Life Questionnaire, self-reported measure for quality of life; *FACIT* = Functional Assessment of Chronic Illness Therapy; *TESS* = Toronto Extremity Salvage Score, VAS = Visual Analog Scale, *M* = male, *F* = female. Tumor type was either classified as bone sarcoma, soft tissue sarcoma, or Ewing's sarcoma.

Satisfaction with surgical outcomes: The 10-item scale measures overall satisfaction with outcomes. Items such as *How satisfied are you with the ability to perform self-care such as washing and dressing?* and *How satisfied are you with the appearance of your arm/leg?* Are rated on a 5-point Likert scale from Extremely satisfied to Extremely dissatisfied. Scores range from 10 to 50, with higher scores indicating higher level of dissatisfaction.

Complete tables with Group-based trajectory modelling (GBTM) indices for classes 1 through 6

Table H0.8: Model enumeration comparisons with linear terms, classes 1 - 6.

No variance	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**Class 6**
M1	3	440.80	449.77	440.28	1	100%					
M2	6	340.98	358.92	339.94	0.77	60.54%	39.56%				
M3	**9**	**337.76**	**364.67**	**336.19**	**0.73**	**55.8%**	**8.2%**	**36%**			
M4	12	340.46	376.35	338.37	0.59	11.6%	31.3%	13.6%	43.5%		
M5	15	340.53	385.39	337.92	0.89	21.1%	6.8%	6.1%	24.5%	41.5%	
M6	18	344.91	398.74	341.78	0.63	40.8%	6.8%	26.5%	14.9%	2.8%	8.2%
Random intercept, fixed slope	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**Class 6**
M1	4	350.41	362.37	349.71	1	100%					
M2	7	334.81	355.74	333.59	0.66	37.4%	62.6%				
M3	**10**	**337.23**	**367.14**	**335.49**	**0.74**	**2.7%**	**63.3%**	**34%**			
M4	13	339.12	378.00	336.86	0.73	32.6%	56.5%	3.4%	7.5%		
M5	16	342.53	390.38	339.74	0.68	44.2%	3.4%	31.3%	13.6%	7.5%	
M6	19	346.91	403.73	343.60	0.63	14.9%	2.8%	40.8%	8.2%	26.5%	6.8%
Random intercept, random slope	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**Class 6**
M1	6	346.72	364.66	345.67	1	100%					
M2	**9**	**334.83**	**361.74**	**333.26**	**0.69**	**36.7%**	**63.3%**				
M3	12	340.83	376.71	338.74	0.41	0%	57.8%	42.2%			
M4	15	341.50	386.36	338.89	0.74	55.1%	2.7%	34.7%	7.5%		
M5	18	346.53	400.36	343.39	0.68	7.5%	44.2%	12.6%	3.4%	31.3%	
M6	21	350.91	413.71	347.25	0.63	14.9%	40.8%	2.8%	6.8%	26.5%	8.2%

NOTE: The table presents the results from the most to least restrictive models with linear terms. M1 – 6 stands for number of classes specified. The emboldened line presents the best model fit in each category. NPM – Number of parameters, AIC – Akaike Information Criterion, BIC – Bayesian Information Criterion, SABIC – sample-size-adjusted BIC; Class 1 – 6 give the proportion of the sample in that specific class for each specified model.

Table H0.9: Model enumeration comparisons with quadratic terms, classes 1 - 6.

No variance	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**Class 6**
M1	4	440.94	452.90	440.25	1	100%					
M2	8	339.41	363.34	338.02	0.77	59.9%	40.1%				
M3	**12**	**335.47**	**371.35**	**333.38**	**0.71**	**10.9%**	**35.4%**	**53.7%**			
M4	16	332.36	380.21	329.57	0.72	12.9%	35.4%	42.2%	9.5%		
M5	20	324.61	384.42	321.13	0.72	16.3%	27.2%	12.9%	27.2%	16.4%	
M6	24	319.96	391.73	315.78	0.75	16.3%	6.1%	25.2%	14.3%	12.2%	25.9%
Random intercept, fixed slope	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**Class 6**
M1	5	348.84	363.79	347.97	1	100%					
M2	9	331.67	358.58	330.10	0.65	63.3%	36.7%				
M3	**13**	**331.09**	**369.97**	**328.83**	**0.67**	**8.8%**	**37.4%**	**53.8%**			
M4	17	326.17	377.00	323.21	0.66	39.5%	20.4%	29.9%	10.2%		
M5	21	315.40	378.20	311.75	0.71	16.3%	12.9%	24.5%	14.9%	31.4%	
M6	25	314.23	388.99	309.87	0.75	17%	11.6%	25.2%	27.9%	3.4%	14.9%
Random intercept, random slope	**NPM**	**AIC**	**BIC**	**SABIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**Class 6**
M1	10	345.84	363.79	347.97	1	100%					
M2	14	324.43	366.29	321.99	0.80	61.9%	38.1%				
M3	**18**	**314.98**	**368.81**	**311.85**	**0.84**	**35.4%**	**49.7%**	**14.9%**			
M4	22	297.66	363.45	293.83	0.92	6.8%	46.9%	24.5%	21.8%		
M5	26	291.25	369.00	286.72	0.89	21.1%	6.8%	6.1%	24.5%	41.5%	
M6	30	291.45	381.17	286.23	0.87	36.1%	6.8%	6.1%	6.8%	20.4%	23.8%

NOTE: The table presents the results from the most to least restrictive models with quadratic terms. M1 – 6 stands for number of classes specified. The emboldened line presents the best model fit in each category. NPM – Number of parameters, AIC – Akaike Information Criterion, BIC – Bayesian Information Criterion, SABIC – sample-size-adjusted BIC; Class 1 – 6 give the proportion of the sample in that specific class for each specified model.