Study Title

Longitudinal Predictors of Quality of Life in Adolescent Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study.

Working Group and Investigators

Working Group: Psychology

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Background and Rational

Each year, approximately 12,400 children are diagnosed with cancer, with one in 300 boys and one in 333 girls being diagnosed. Although childhood cancer remains the number one disease killer of children, recent medical advances have contributed to a higher rate of survivorship, with 80% of children reaching the five year survival mark.[1] As childhood cancer survival rates increase, the focus of psychological research has shifted from palliative care and grief in the 1970's, to pain management in the 80's and 90's, to issues of survivorship and quality of life in the past fifteen years.[2] Current estimates suggest that 1 in 900 adults between the ages of 15 and 45 are childhood cancer survivors, a prevalence that stress the need to study survivorship and optimal adjustment to cancer diagnosis and treatment.[3]

Quality of Life in Childhood Cancer Survivors

Although rates of survivorship have increased, the physical cost to surviving cancer can be high. Two-thirds of survivors experience secondary medical late effects as a result of treatment, including secondary cancers, cardiac and/or pulmonary morbidity, infertility, stunted growth and impaired cognitive ability.[4] The negative physical impact of being diagnosed and treated for cancer as a child is well-established, but the impact of cancer on future quality of life is less clear. Quality of life is a broad concept defined as a, "multidimensional construct including general health, and physical, emotional, and social functioning." [5] Quality of life has been examined as both a general construct in this population,[6,7] and as separate constructs including physical, psychological or social functioning. While several studies report poor quality of life outcomes for childhood cancer survivors,[8] including higher rates of anxiety,[9,10] depressive symptomatology, [9,11] suicidal ideation,[12] delay in reaching developmental milestones,[13] and social impairment,[14,15] other studies report that childhood cancer survivors do not substantially differ from the general population in regards to quality of life,[6] depression,[16] and anxiety.[17]

Moreover, some studies suggest increased functioning in survivors and report resiliency and improved adaptation.[7, 18, 19]

Such inconsistent findings are likely related to the varied methodological approaches. For example, where some studies focus on adult survivors of cancer, [11,12,13, 15] others focus on survivors who are still in childhood and adolescence.[5,9,20,21] Even within studies of child and adolescent survivors, there is variability, including those that examine parent-report of child symptoms,[5,9,20] those that discuss self-reported symptoms,[21,17] and those that examine both parent and child report.[22] Moreover, some studies examine only certain diagnoses, such as brain tumors [14,18] or leukemia,[20,23] while others are broad and include several cancer diagnoses.[5,9,13,15] Another area of variability is sample size, with some studies reporting large sample sizes across institutions,[9,11,17] and others a smaller number of subjects within one institution.[14,18,22] Comparison groups also vary, with some studies comparing survivors to established population norms,[10,12,20] others comparing outcomes to siblings,[9,11,15] and others comparing to groups of individuals who never had a cancer-related experience.[5,13,22] Finally, the wide range of outcomes chosen (e.g. depression, anxiety, posttraumatic stress, quality of life, developmental milestones, social relationships, employment, involvement in romantic relationships) makes it difficult to reach a general conclusion about the adaptation of childhood cancer survivors.

There is a great deal of disagreement in the literature about the overall psychological status of survivors, but studies agree that there is a wide-variety of functioning in important domains. Therefore, rather than continuing to examine outcomes of childhood cancer survivors in order to create blanket statements about their overall functioning, a shift should be made to identifying the predictors of such outcomes. While several studies have focused on demographic and treatment-related variables related to quality of life, very few studies have examined constructs that are malleable to change, such as perceptions of health or psychosocial functioning. Treatment-related and demographic variables help clinicians to better understand which populations may be at an increased risk for poor outcomes, but it is also important to identify variables that would allow for interventions designed to increase positive outcomes in all survivors.

In addition to shifting the focus from outcomes of survivors to identifying predictors of such outcomes, attention to specific subsets of childhood cancer survivors is warranted. Fewer studies of childhood cancer survivors have specifically focused on survivors in adolescence and their quality of life, with many studies including either a wide age-range of child survivors or focusing on adult survivors. Adolescence is a unique developmental time when emotional and physical late effects from cancer treatment can be particularly powerful.[24] It is important to understand functioning in adolescent survivors as it can be predictive of future functioning in areas such as relationships, education, and productivity in the work-force.[25,26] In addition to focusing on this unique developmental period, it is also important to assess quality of life from the adolescent's perspective. Studies consistently suggest that parent reports of their adolescent's symptoms are not always accurate, highlighting a need in the literature to increase our understanding of the adolescent cancer survivor's experience from their own point of view.[27] Finally, long-term adolescent survivors represent a unique group of survivors who were treated for cancer at a younger age. Intensive treatments during these critical years may impact development and future functioning in distinctive ways. Several studies have identified increased risk in this population, including a greater likelihood of experiencing neurocognitive late-effects, [28] increased utilization of special education services in school, and increased risk for

unemployment in adulthood.[15] Taken together, it is clear that focus on long-term adolescent survivors is necessary.

Quality of Life Model

A model to help guide our understanding of quality of life in childhood cancer survivors is now offered. The Wilson and Cleary model [29] is a guide for the examination of a variety of important variables that may impact quality of life. Wilson and Cleary assert that characteristics of the person and environment, biological variables, physical and psychological symptoms, health perceptions and functional status are important predictors of quality of life. While the model has been applied to quality of life in adults with angina,[30] heart-failure,[31] HIV,[32] and in older adults,[33] it has never been examined in childhood cancer survivors. Previous studies suggest that the variables outlined by Wilson and Cleary will likely be related to quality of life in adolescent survivors. Demographic variables such as younger age at diagnosis,[12,15,28] lower socioeconomic status,[11] and female gender [11,15] have been found to be negatively related to quality of life outcomes in childhood cancer survivors. Biological variables including diagnosis and treatment modality are also consistently linked to long-term functioning (e.g. exposure to Methotrexate and cranial radiation have been associated with negative quality of life in survivors) .[5,9,12]

Less information is available about the longitudinal relationship between psychological symptoms and quality of life in survivors. Several studies have concluded that early psychological adjustment in the course of cancer treatment, or during specific phases of treatment (e.g. stem cell transplant), predicts later psychological adjustment in parents [34, 35] and children.[36] Other studies have also reported that psychological functioning and quality of life are cross-sectionally related in children going through stem cell transplant.[37] However, no studies have examined the predictive power of psychological functioning on future quality of life in childhood cancer survivors. In children with asthma, one study found that parent-ratings of child psychological symptoms significantly predicted self-reported quality of life in the children.[38] These findings suggest that psychological functioning may be related to quality of life in children with chronic illness, but further research is needed to determine whether such relationships are evident in children with cancer. Physical symptoms such as pain, fatigue, and aches have also been found to be associated with quality of life in adolescent and young-adult cancer survivors.[39] Several studies have also examined the relationship between perceptions of health and quality of life in adult survivors of cancer and have found that perceptions of poor health are related to higher rates of posttraumatic stress,[10] and lower ratings of quality of life.[8] Finally, functional status has been found to be significantly related to quality of life in adult survivors of childhood cancer [8] but has not been examined in childhood cancer survivors.

Proposed Project

The purpose of the proposed study is to examine the longitudinal impact of parent-report of psychological and physical symptoms along with functional status and health perceptions on future self-rated quality of life in adolescent survivors of cancer using hierarchical regression. Select demographic and treatment-related variables will be controlled while identifying target variables for future interventions to increase positive quality of life in childhood cancer survivors. Examined variables will be chosen based on previous literature and guided by the Wilson and Cleary model which posits that demographic, disease variables, physical and psychological symptoms, perceptions of health, and functional status are related to quality of life.

This model has been examined in other populations but has not been used as a theoretical guide to examining outcomes in childhood cancer survivors. Studies have consistently shown that parent-report of child symptoms are valid, especially in children younger than 11 years old. [40,41] Furthermore, using parent-report of symptoms to examine associations with future quality of life will help to make this study generalizable to clinic settings where information gathered on child functioning is more likely to be based on parent-ratings. The proposed study addresses current gaps in the pediatric psycho-oncology literature by utilizing longitudinal data and focusing on the identification of predictors of quality of life that can be targeted with future interventions.

Specific Aims/Research Hypotheses

Specific Aims:

1. To explain variance in positive adolescent quality of life (satisfaction with health, achievement, resilience), as rated by survivors on the CHIP-AE, using individual baseline characteristics such as child behavior, anxieties/fears, perceptions of health, pain, functional status, diagnosis, cancer therapy, and demographic factors.

2. To identify explain variance in negative adolescent quality of life (discomfort, risk, disorders), as rated by survivors on the CHIP-AE, using individual baseline characteristics such as child behavior, anxieties/fears, perceptions of health, pain, functional status, diagnosis, cancer therapy, and demographic factors.

Hypotheses:

1. Psychological and physical symptoms, functional status and health perceptions as rated by parents at baseline will predict variance in quality of life as rated by adolescents at follow-up after adjusting for select demographic and treatment-related variables.

2. For each block in the hierarchical regression, given previous literature, it is predicted that the following relationships will be found:

    a. Demographics: Male gender, older age at diagnosis, and higher socioeconomic status at baseline will significantly predict positive quality of life as rated by adolescent cancer survivors at follow-up.

    b. Treatment: Exposure to Methotrexate and/or cranial radiation will significantly predict negative quality of life outcomes as rated by adolescent cancer survivors at follow-up.

    c. Symptoms: Fewer psychological symptoms and fewer physical symptoms as rated by the parent at baseline will significantly predict positive quality of life outcomes as rated by adolescent cancer survivors at follow-up.

    d. Functional status: Lower functional status as rated by the parent at baseline will significantly predict negative quality of life as rated the adolescent cancer survivors at follow-up.

e. Health Perceptions: Negative health perceptions as reported by the parent at baseline will predict negative quality of life outcomes as rated by adolescent cancer survivors at follow-up.

Analysis Framework

Population: Cancer survivors with Baseline parent-report information who also completed the Teen Survey.

Diagnosis information for CCSS patients who were included in the Baseline survey at age less than 18 and who then completed the Teen survey

Diagnosis	Baseline <18 yrs (N=3960)	Teen Survey (N=307)	Both Baseline <18 yrs and Teen Survey (N=307)
Leukemia	1771 (44.7)	95 (30.9)	95 (30.9)
CNS tumor	551 (13.9)	40 (13.0)	40 (13.0)
Hodgkin Lymphoma	50 (1.3)	-	-
NHL	154 (3.9)	4 (1.3)	4 (1.3)
Wilms tumor	585 (14.8)	56 (18.2)	56 (18.2)
Neuroblastoma	538 (13.6)	90 (29.3)	90 (29.3)
Soft tissue sarcoma	255 (6.4)	19 (6.2)	19 (6.2)
Bone tumor	56 (1.4)	3 (1.0)	3 (1.0)
Total	3960	307	307

Outcome of interest: The primary outcome of interest is the Child Health and Illness Profile – Adolescent Edition (CHIP-AE).[42] The CHIP-AE is a measure of quality of life that assesses 20 subdomains that map onto six primary domains: satisfaction with health, discomfort, achievement, risk, resilience, and disorders. The CHIP-AE is an adolescent self-report of quality of life that has been normed in the general population. Each domain has a standard score of 20 and a standard deviation of 5 and will be analyzed as continuous variables. The CHIP-AE was collected as part of the Teen Survey in the Childhood Cancer Survivor Study.

Primary Predictors: The primary predictors are outlined in five categories (demographics/environment, biological, symptoms, functional status, and general health perceptions) based on the guiding model for the proposed project.[29]

Demographics/Environment

- Sex
  - Male
  - Female
- Race
  - White
  - Non-White
- Income

    - < $19,999
    - $20,000 - $60,000+
- Age at diagnosis, months
    - Continuous
- School (Baseline, O.4)
    - Utilization of special education services (yes or no)

Biological

- Diagnosis (descriptive purposes only)
    - Leukemia
    - CNS tumors
    - Hodgkin's Disease
    - Non-Hodgkin's Lymphoma
    - Wilms tumor
    - Neuroblastoma
    - Soft tissue sarcoma
    - Bone tumors
- Treatment modalities (categorical)
    - Chemotherapy
        - Methotrexate
    - Radiation
        - Cranial (yes/no direct exposure)
        - Other bodily (yes/no)
        - None
    - Surgery (yes/no)

Symptoms

- Psychological
    - Behavior problems index (Baseline, J. 16 – 21)
        - Total score
        - Internalizing score
        - Externalizing score
    - Social competence (Baseline, J. 16 – 18)
    - Anxieties/Fears (Baseline, J.24)
- Physical
    - Deformities (Baseline, B.9)
    - Pain (Baseline, J.23)

General Health Perceptions (Baseline, N.11, R.1,3)
Functional status (Baseline, N.6,7,8,10)

Statistical Analyses: Linear analyses will be used to analyze the data with Statistical Analysis Software (SAS) version 9.3. All data will be inspected for conformance to the assumptions of the General Linear Model (GLM).[43] Normality of distribution of all continuous variables will be examined by checking the skewness and kurtosis of each value. Skewness and kurtosis values greater than +/- 1 will be transformed. Univariate outliers will also be determined by examining

the standardized values of each variable, with standardized values greater than 3.29 being deleted. Linearity will be determined by examining a scatterplot of the predictor and outcome variables. Necessary adjustments will be made to ensure that the analyzed data is normally distributed.

In order to reduce redundancy and inflated standard errors, multicollinearity will be examined. All continuous predictors and outcomes will be entered into a correlation matrix and highly correlated variables ($r > .70$) will be identified and decisions about dropping variables will be guided by the literature. The variance inflation factor (VIF) will also be examined to identify multicollinearity. Mahalanobis distances will be examined to determine the presence of multivariate outliers, with the critical cut-off value being determined based on the number of independent variables and the degrees of freedom with an alpha level of .001. The residual scatterplot will be examined to check for normality, linearity, and homoscedasticity. The normal probability plot of residuals will also be examined to assure that the expected normal values for residuals and the actual values have a linear relationship.

Descriptive statistics, including means, standard deviations, ranges, medians, and frequencies, will be calculated for the primary outcome of interest as well as the selected predictors.

Hierarchical regression will be used to test whether psychological and physical symptoms along with functional status and health perceptions will account for additional variance in quality of life over and above the variance accounted for by demographic and treatment-related variables. With hierarchical regression, independent variables are entered into the regression model in a pre-specified order based on theoretical grounds. Variables are entered in blocks with each independent variable being assessed for how much variance it adds to the model after the previous variables have been controlled for.[43] Six separate hierarchical regressions will be built for each of the six quality of life domains.

As guided by the Wilson and Cleary model,[29] the blocks entered into the regression will include demographics/environment, biological (treatment) variables, psychological and physical symptoms, functional status, and health perceptions. Given that demographic and treatment-related variables have been examined more often in the literature and are consistently linked with quality of life outcomes in cross-sectional studies, these blocks will be entered first, with block 1 being demographic variables and block 2 being treatment-related variables. Thus, the first blocks entered into the model will assess for the impact of factors that are not malleable to change and will be controlled for moving forward. Next, in line with previous literature,[12] the symptom block of predictors will be added, starting with the psychological variables followed by the physical variables, to assess for the additional impact of these constructs on quality of life. The final two blocks of predictors will be functional status and perceptions of health. After each block is entered, independent contributions of each variable along with interactions will be examined, and those no longer significant at the $p < .05$ will be dropped. Adjusted R^2 will be examined and to inform decisions about which predictors to retain in the model. Alternative models will be tested using different combinations of predictors, and the goal will be to develop the most parsimonious model that explains the most variance in quality of life.

Because some of the demographic (e.g. SES, gender) and treatment variables (e.g. cranial radiation, intrathecal methotrexate) have been found to be related to quality of life as well as some of the examined predictors in these models (e.g. behavioral problems index)[9], efforts will be made to reduce the risk of causing instability in the parameter estimates and their standard errors due to multicollinearity. While studies have established that cranial radiation and intrathecal methotrexate are related to the BPI scores in this sample, no published data is available about the r-value for these relationships. Therefore, decisions about excluding demographic and treatment variables will be made after examining the correlation matrix. If treatment and demographic variables are found to be highly correlated with other predictors ($r > .70$), several steps will be taken to reduce the risk of instability due to potential multicollinearity. To begin, the model will be built as planned, with demographic variables entered first, followed by treatment variables, psychological symptoms, physical symptoms, functional status, and perceptions of health. Next, the model will be built without the demographic or treatment variables highly correlated with the other predictors to see if significant changes in R^2, signs of parameter estimates or significance of the estimates occur in the model when these variables are removed. After examining the differences between these models, decisions about a final model will be made and will include variables predicting variance in quality of life and that help minimize the Variance Inflation Factors (VIF) for the covariates that remain in the model.

Tables:

Table 1. Descriptive Statistics of Survivors

	N	%
Sex		
Male		
Female		
Race		
White		
Non-White		
Income		
<$19,999 - $39,999		
>$40,000		
Age (M, SD)		
Use of Special Education		
Yes		
No		
Diagnosis		
Leukemia		
CNS tumors		
Hodgkin's Disease		
Non-Hodgkin's Lymphoma		
Wilms Tumor		
Neuroblastoma		
Soft tissue sarcoma		
Bone tumor		
Treatment		
Chemotherapy		
Methotrexate		
Radiation		
Cranial		
Other bodily		
None		
Surgery		

Table 2. Average CHIP-AE Scores by Domain

Domain Score	Mean	Std Deviation
Satisfaction with Health		
Resilience		
Achievement		
Risk		
Disorders		
Discomfort		

Table 3. Model Summary

Model	R-Square	Adjusted R-Square	St. Error of Estimate	F change	Sig F change
1. Demographics & Biological 2. Model 1 + Symptoms 3. Model 2 + Functional Status 4. Model 3 + Health Perceptions					

Table 4. Coefficient Table

Model	B	St. Error	t	Sig.
1 **Demographic** Sex Race Income Age at diagnosis Special Education **Biological** Chemotherapy Radiation Cranial Other bodily None Surgery				
2 *Demographic* *Sex* *Race* *Income* *Age at diagnosis* *Special Education* *Biological* *Chemotherapy* *Radiation* *Cranial* *Other bodily* *None* *Surgery* **Symptoms** **Psychological** Behavior Problems Index Total Score Internalizing Score Externalizing Score Social Competence Anxieties/Fears **Physical** Deformities Pain				
3 *Demographic* *Sex* *Race* *Income* *Age at diagnosis* *Special Education* *Biological* *Chemotherapy*				

Radiation *Cranial* *Other bodily* *None* *Surgery* *Symptoms* *Psychological* *Behavior Problems Index* *Total Score* *Internalizing Score* *Externalizing Score* *Social Competence* *Anxieties/Fears* *Physical* *Deformities* *Pain* **Health Perceptions**				
4 *Demographic* *Sex* *Race* *Income* *Age at diagnosis* *Special Education* *Biological* *Chemotherapy* *Radiation* *Cranial* *Other bodily* *None* *Surgery* *Symptoms* *Psychological* *Behavior Problems Index* *Total Score* *Internalizing Score* *Externalizing Score* *Social Competence* *Anxieties/Fears* *Physical* *Deformities* *Pain* *Health Perceptions* **Functional Status**				

Figure 1. Baseline Factors Impacting Positive Quality of Life in Adolescent Cancer Survivors

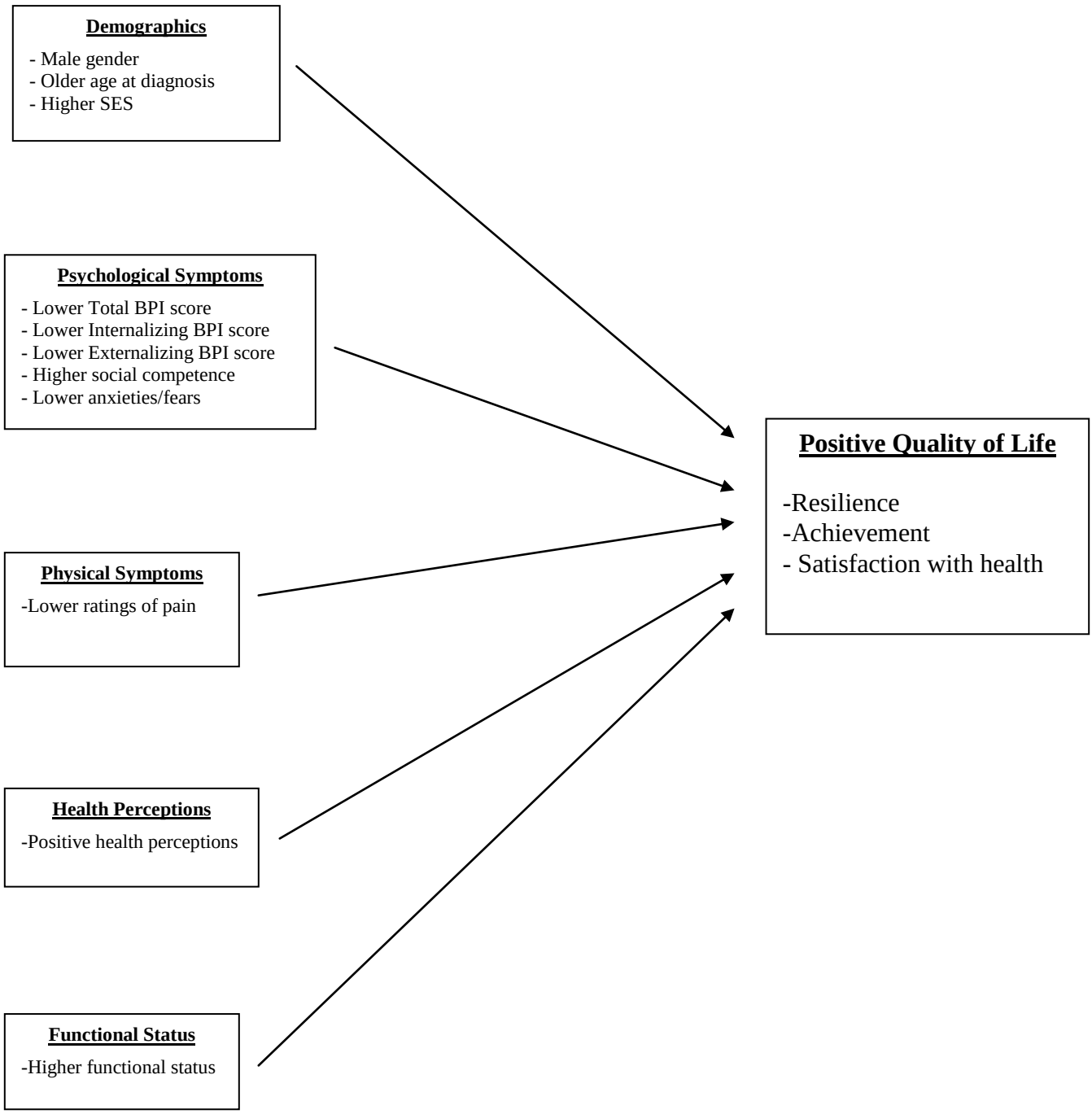


Figure 2. Baseline Factors Impacting Negative Quality of Life in Adolescent Cancer Survivors

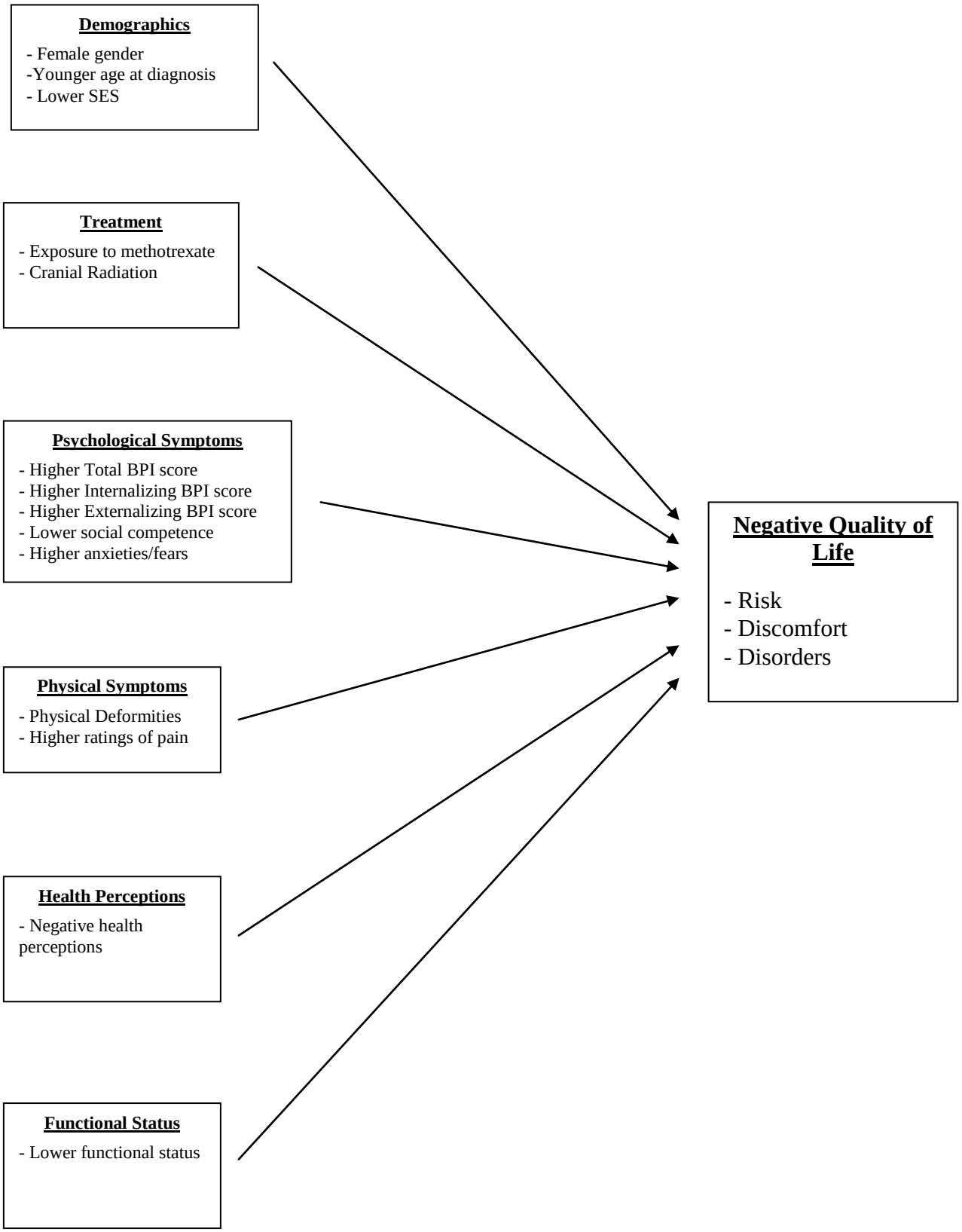
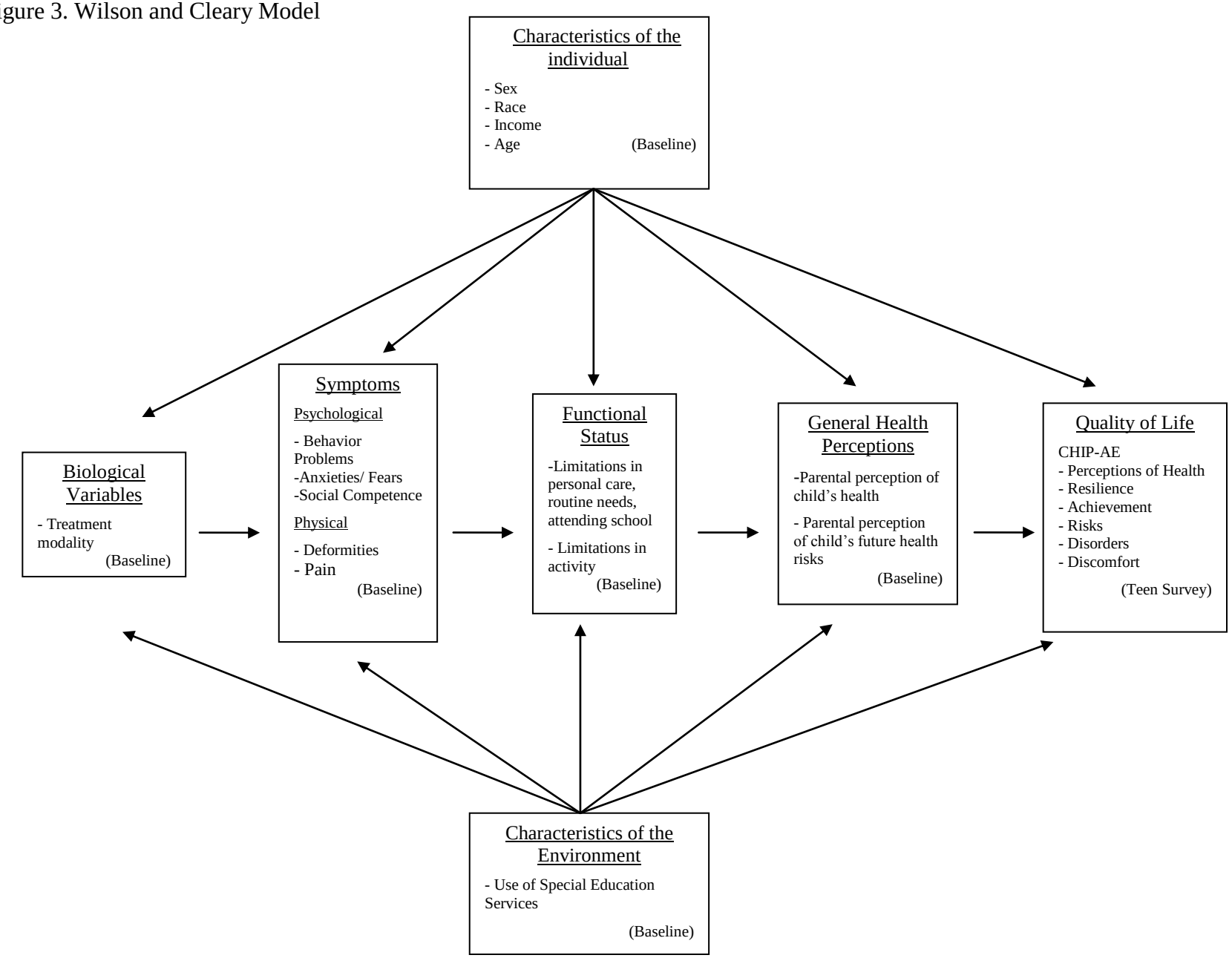


Figure 3. Wilson and Cleary Model



Special Considerations

The proposed project will fulfill the dissertation requirement for Claire Russell and will be advised by Marilyn Stern, Ph.D. Leroy Thacker, Ph.D. is serving as the statistical consultant on this project.

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