1. STUDY TITLE

Predictors and outcomes of personal strengths in young adult cancer survivors.

2. WORKING GROUP AND INVESTIGATORS

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3. BACKGROUND AND RATIONALE

Today, thanks to improvements in cancer treatment, the survival rate for childhood cancer is over 80% (Howlader et al., 2013). Cancer survivors have become more frequent in the population with roughly 330,000 Americans currently identified as a survivor of childhood cancer (Brown, 2006) Therefore, it is important to examine the long-term consequences of cancer and cancer therapy, and to identify factors associated with positive psychological outcomes.

Many studies have examined the patterns and predictors of morbidity in survivors of childhood cancer. Compared to siblings, more adverse health issues, activity limitations, and functional impairments are reported (Kazak et al, 2010; Mertens et al., 2014). Despite these adverse effects, many survivors view their life as generally posiitve (Zebrack et al., 2012). Several studies have found that most survivors remain psychologically healthy, report positive life satisfaction, and good emotional well-being (Bellizzi et al., 2012; Zeltzer et al., 2008), and that a relative minority report significant symptoms of distress over time (Brinkman et al., 2013).

Some studies have investigated how the experience of having cancer can promote positive changes in life perspective (Sundberg et al., 2010; Phipps, Steele, & Leigh, 2001). Many cancer survivors report positive quality of life when they experience a sense of purpose (Weaver et al., 2012; Zebrack et al., 2012). Findings from these studies raise the possibility that survivors may find personal strength to cope with the adverse circumstances of recovering from cancer. Such experiences can enable a reevaluation of one's goals and priorities, a better sense of self, an improved ability to find meaning in life, the development of better coping skills, and the enhancement of interpersonal relationships (Boals & Schuettler, 2011). However, the literature is not consistent in indicating which characteristics may lead a survivor toward these positive outcomes and specifically positive growth. Several researchers have highlighted the importance of examining environmental, health-related, and mental health variables as predictors of personal strengths. Younger age, marital status, employment status, higher income, lower education level, intensity and severity of the disease, perception of pain, and reduction in depression were considered by these researchers as predictors of positive growth (Bellizzi & Blank, 2006; Hart, Vella, & Mohr, 2008; Stanton et al., 2007). However, other researchers did not confirm those findings (Mols et al., 2009; Widows et al., 2005). A goal of the currently proposed work will be to better understand what predicts resilience and sense of purpose in response to stressful and life-threatening disease.

Personal strengths, such as courage, optimism, interpersonal skills, faith, and perseverance, may help prevent future illness and future psychological issues. Studies have found that posttraumatic growth, one component of personal strengths, was related to more well-being and less distress (Park & Fenster, 2004). Positive beliefs may influence the course of physical disease by reducing the impact of emotional stress on neuroendocrine and immune function (Diener & Chan, 2011; Dockray & Steptoe, 2010). Research has shown evidence that while negative feelings such as stress can suppress immune function (Miller, Chen & Parker, 2011; Vitlic, Lord & Philips, 2014), positive feelings may positively impact immune function. Futterman, Kemeny, Shapiro, and Fahey found that positive mood had an impact on immunological processes such as increased response to the mitogen PHA (1994) and Giltay et al. found that optimistic people had a lower frequency of cardiovascular disease (2004). Segerstrom, Taylor, Kemeny, and Fahey found that law school students in stressful situations showed relationships between optimism and high number of CD4 T cells that was mediated by positive mood (1998). Personal strength may also be connected to likelihood of physical disease by promoting better health behavior. Cancer survivors who have positive beliefs about the future may be more likely to practice good health habits and to use health services appropriately. This proposed study may provide insight on whether personal strengths are associated with the course of chronic health conditions in cancer survivors.

As health beliefs and behaviors are often established during adolescence and young adulthood (Lerner, Boyd, Kiely, Napolitano, & Schmidt, 2010; Steinberg & Morris, 2001), we propose targeting this age group. The overall goal of this study is to better understand what predicts personal strengths and sense of meaning after adversity, and whether these conditions lead to future positive outcomes such as improved overall well-being and better health conditions.

4. SPECIFIC AIMS AND RESEARCH HYPOTHESES

4.1. Aim 1: Among survivors who were adolescents at Baseline, to identify a latent construct representing personal strengths during young adulthood (i.e from data collected in the Follow-up 2 [2003] survey).

> We hypothesize that five positive parameters: life satisfaction, strengths, spiritual beliefs, relating to others, and finding new possibilities can be explained by a single latent construct representing personal strengths.

4.2. Aim 2: To examine predictors of this latent personal strength construct from adolescents' medical, demographic and behavioral factors (i.e. from data collected in the Baseline survey under 18).

> We hypothesize that younger age at disease onset, higher household income, positive health conditions, and a low level of mental illness during adolescence will be related to higher personal strengths in young adulthood.

4.3 Aim 3: Examine health and psychological outcomes of the latent personal strength construct (i.e. from adverse health conditions in the Follow-up 4 [2007] survey).

> We hypothesize that personal strengths measured during Follow-up 2 will be associated with improved mental and physical health conditions between Follow-up 2 and Follow-up 4.

5. ANALYSIS FRAMEWORK

5.1. Population

The sample will be comprised of survivors who completed at least one of the following three surveys over time: the Baseline survey while they were ages 12-17; the Follow-up 2 (2002-2005) survey; and the Follow-up 4 (2007-2010) survey. A sample of 3,280 survivors between the ages of 12 and 17 years are represented in the Baseline survey. Of these, 1,686 survivors completed the Follow-up 2 survey, which would be the target sample for Aims 1 and 2 above. 1,296 participants from these 1,686 survivors completed the Follow-up 4 survey. For those survivors who did not partially or fully complete one or both follow-up surveys, their responses will be estimated as described in the missing data section. Those respondents who die before completing a survey will not be included in this study.

5.2. Variables

5.2.1. Variables for Aim 1

- Post Traumatic Growth: measured with the Post Traumatic Growth Inventory, with questions H1 to H.21 (PTGI; Follow-up 2). PTGI total scores range from 0 to 105, with higher scores suggesting greater PTG.

  Previous studies using the CCSS dataset showed that Cronbach's alphas varied between .84 to .86 for subscales and total score (Klosky et al., 2014)

- Life satisfaction: measured with the Cantril Ladder of Life, with questions I1, I2, and I3 (Follow-up 2).

  No alpha level was found from previous articles. However, Cantril ladder of life was used in several studies using the CCSS dataset (Ganz et al., 2002; Hudson et al., 2003; Zeltzer et al., 2008; 2009).

5.2.2. Variables for Aim 2

- Socio-economic: income (< $19,999 or $20,000 - $60,000+), school (utilization of special education services- yes or no), (Baseline)

- Demographics: age at diagnosis, sex (male or female), race (White, Black, Asian, and Others), and religion (yes or no) (Follow-up 2)

- Physical Conditions: Physical Conditions: measured with the CTCAE, which includes hearing/vision/speech, urinary, hormonal, heart and circulatory, respiratory, digestive, surgical, brain and nervous system. The questions are from the medical conditions section in the survey (Baseline). The maximum score for each subscale along with the maximum score across all organ systems will be included. Yes will consist of "Yes and the condition is still present", and "Yes but the condition is no longer present". The severity of health conditions was scored related to the Common Terminology Criteria for Adverse Events. Health conditions did not include the conditions the child had before diagnosis.

  CTCAE was used in several studies using the CCSS dataset (Armstrong et al., 2013; Mody et al., 2008; Wasilewski-Masker et al., 2010).

- Mental Health: internalizing and externalizing problems measured with the Behavior Problem Index (BPI; Baseline), with questions J19, J20, and J21.

  The Cronbach's alpha level for depression and anxiety in a previous study using the same dataset was .87 (Schultz et al., 2007)

- Personal Strengths: measured with the Cantril Ladder of life with questions I1, I2, and I3 and PTGI with questions H1 to H.21 (Follow-up 2)

5.2.3. Variables for Aim 3

- Socio-economic: income (< $19,999 or $20,000 - $60,000+), school (utilization of special education services- yes or no) (Baseline)

- Demographics: age at diagnosis, sex (male or female), race (White, Black, Asian, and Others), and religion (yes or no) (Follow-up 2)

- Mental Health: internalizing and externalizing problems measured with the BPI with questions J19, J20, and J21 (Baseline); somatization, depression, and anxiety with the Brief Symptom Inventory with questions L1 to L18 (BSI-18; Follow-up 4).

  Cronbach alpha as a measure of internal reliability for the CCSS dataset were 0.88 for the depression subscale, 0.71 for somatization, and 0.80 for anxiety (Zebrack et al., 2007).

- Physical Conditions: measured with the CTCAE, which includes hearing/vision/speech, urinary, hormonal, heart and circulatory, respiratory, digestive, surgical, brain and nervous system. The questions are from the medical conditions section in the survey (Baseline and Follow-up 4). The maximum score for each subscale along with the maximum score across all organ systems will be included. Yes will consist of "Yes and the condition is still present", and "Yes but the condition is no longer present". The severity of health conditions was scored related to the Common Terminology Criteria for Adverse Events. Health conditions did not include the conditions the child had before diagnosis.

- Personal Strengths: measured with the Cantril Ladder of life with questions I1, I2, and I3 and PTGI with questions H1 to H.21 (Follow-up 2)

5.3. Plan of Analysis

5.3.1. Research Methods and Analysis

A longitudinal approach will allow for the examination of predictors of, and outcomes influenced by personal strengths over time and to test the direction of effects more rigorously than with purely cross-sectional data. The use of structural equation modeling (SEM) will enable us to estimate complex covariate structures over time, to test directional relationships among variables, and to determine if the hypothesized model will be a good fit for the data.

5.3.2 Statistical Analysis for Aim 1

Two Confirmatory Factor Analysis (CFA) models that represent personal strengths will be compared using the statistical software SAS. Previous research showed that the posttraumatic growth inventory (PTGI) could lead to one, three, and seven factors (Osei-Bonsu, Weaver, Eisen, & Vander Wal, 2011) or two factors (Levine, Laufer, Stein, & Solomon, 2008) as compared to the original five factors model (Tedeshi & Calhoun, 1996). In addition, positive relationships between PTGI and Cantril life satisfaction were found (Blix, Bang Hansen, Skogbrott Birkeland, Nissen, & Heir, 2013; Triplett, Tedeshi, Calhoun, & Reer, 2011). Therefore, we hypothesize that a simplified model of a one-factor solution that comprises subscales from the Cantril life satisfaction and the PTGI could represent personal strengths. This model will be compared to a two-factor solution with growth and life satisfaction as our latent constructs (see figures A1 and A2). The purpose is to see whether the variables load on one or two factors related to strengths. Our goal is to simplify the model to have only one latent construct that represents the positive outcomes. However, if the model cannot be simplified with one latent construct, the two-factor solution will be chosen and be kept to examine Aim 2 and Aim 3.

We will compare the fit of this nested model to the alternative two-factor nested model. A nested model is a model that uses the same variables as another model but specifies at least one additional parameter to be estimated. The model with more free parameters, which could be called a reduced model, is nested within the more restricted model, which could be called the full model. Therefore, we will compare two different models with the same variables but one more parameters added, which is comparing a one-factor to a two-factor model with the same variables, imposing equality constraints. To analyze a good fit of the one factor model compared to the two-factor model, a chi square difference will be performed. The chi-square test is the difference between the full model and the reduced model, using the difference in degrees of freedom as the degrees of freedom for the test. In SAS, we can use the Likelihood ratio, score, and wald test to compare chi-square difference, with a preference for the likelihood ratio test as the most reliable test.

5.3.3 Statistical Analysis for Aim 2

A structural regression model that specifies relationships among latent constructs will be identified using the statistical software SAS (PROC CALIS). The structural model will be tested and modified to obtain a good fit to the data by assessing the fit indices such as Chi-squares, AIC, GFI, RMSEA, SRMR, and CFI. Three latent constructs: socio-economic, health conditions, and mental health assessed with indicators variables, will be used to see whether these constructs, as measured when cancer survivors were adolescents Baseline questionnaire, can forecast the personal strengths latent construct when cancer survivors become young adults as measured on the Follow-up 2 survey (see figure B).

5.3.4 Statistical Analysis for Aim 3

A structural regression model that specifies relationships among latent constructs will be identified using the statistical software SAS (PROC CALIS). For this model, the latent construct personal strengths from Follow-up 2 will be assessed to see whether it predicts the health conditions and mental health constructs from Follow-up 4, controlling for health conditions and mental health ascertained at the Baseline survey (see figure C). The structural model will be tested and modified to obtain a good fit to the data by assessing the fit indices such as Chi-squares, AIC, GFI, RMSEA, SRMR, and CFI.

We are seeking the unique effect of personal strengths on mental health and health conditions controlling for the previous effect of mental health and health conditions in Baseline. Thus, by controlling for the effect of physical health in Baseline over physical health in Follow-up 4, and mental health in Baseline over mental health in Follow-up 4, we can better understand the unique effect of personal strength in Follow-up 2 on physical and mental health in Follow-up 4. The estimation of the model will be done by the maximum likelihood method. The maximum likelihood method is an iterative estimation procedure, which produces estimates for the population parameters that maximize the probability of the data given the model. The health condition construct will be assessed with eight indicators variables (endocrine, cardiac, neurologic, disorder of hearing, speech, and vision, pulmonary, renal, gastrointestinal, and musculoskeletal). The mental health construct will be assessed with three indicators variables in Baseline (internalizing problems, externalizing problems, fear/anxiety) and three other indicators in Follow-up 4 (anxiety, depression, and somatization).

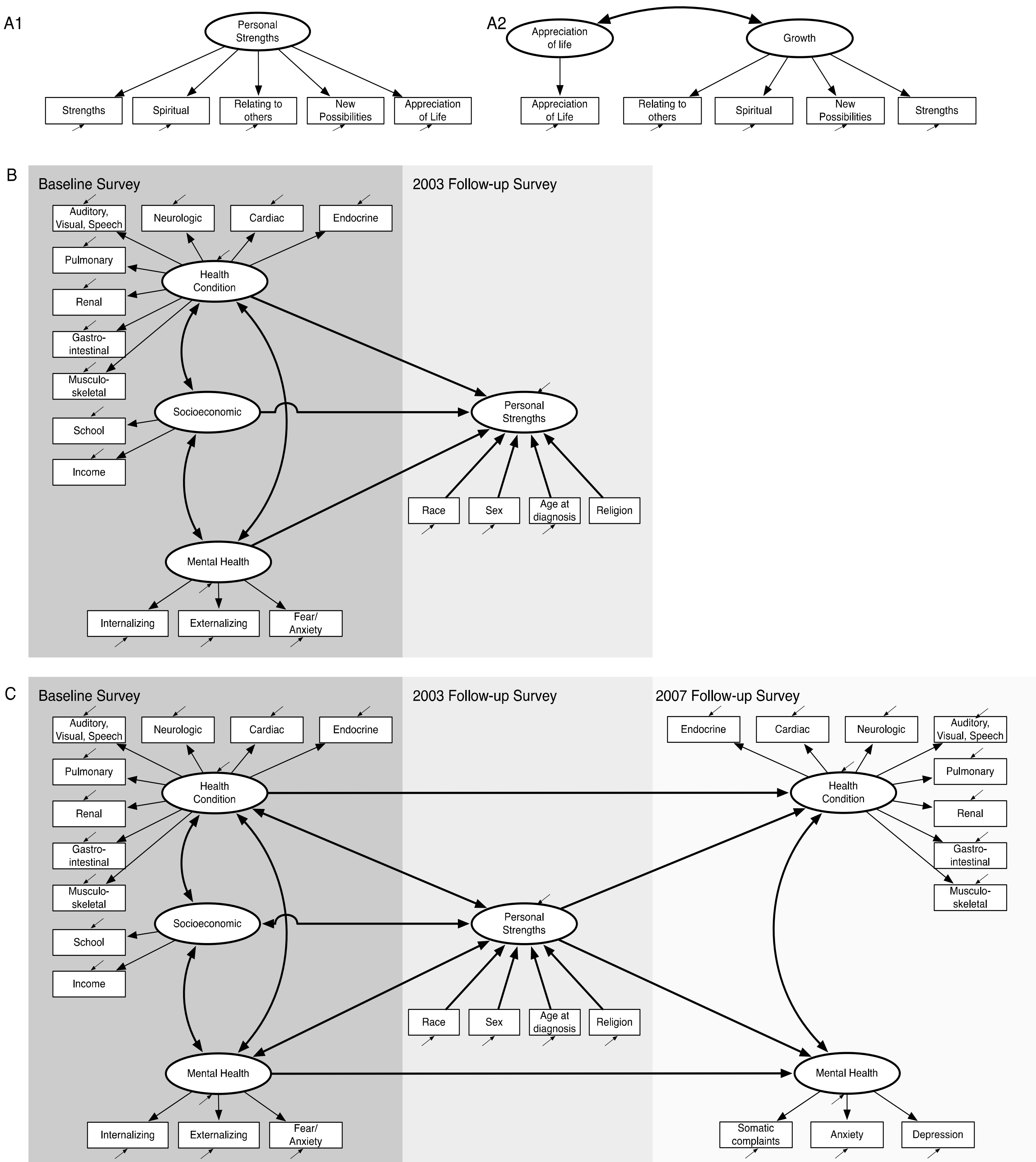
5.4. Missing data

An important challenge that will take significant care is mitigating missing data between the three-time periods. In particular for Aim 2 and Aim 3, one possibility is to remove all cohorts that have not completed all three surveys, however this may lead to biased results. An alternative choice is to use Inverse probability weighting (IPW) as one of the several methods that can reduce this bias. In this method, complete cases are weighted by the inverse of their probability of being a complete case. Some of the reasons preferred to use IPW is to correct for unequal sampling fractions as well as when data are missing in many variables such as this situation (Seaman & White, 2013).

The GEE procedure, introduced in SAS/STAT 13.2, provides a weighted generalized estimating equations (GEE) method for analyzing longitudinal data that have missing observations. The GEE procedure implements the inverse probability-weighted method to account for dropouts under the missing at random (MAR) assumption.

The analysis will carefully assess differences between respondents who answered the survey and respondents who did not, and then apply the IPW analysis that accounts for differences in subjects who were eligible and alive.

6. Figures



A1
Personal Strengths
Strengths
Spiritual
Relating to others
New Possibilities
Appreciation of Life
A2
Appreciation of life
Growth
Appreciation of Life
Relating to others
Spiritual
New Possibilities
Strengths
B
Baseline Survey
2003 Follow-up Survey
Auditory, Visual, Speech
Neurologic
Cardiac
Endocrine
Pulmonary
Health Condition
Renal
Gastro-intestinal
Musculo-skeletal
Socioeconomic
School
Income
Personal Strengths
Race
Sex
Age at diagnosis
Religion
Mental Health
Internalizing
Externalizing
Fear/ Anxiety
C
Baseline Survey
2003 Follow-up Survey
2007 Follow-up Survey
Auditory, Visual, Speech
Neurologic
Cardiac
Endocrine
Pulmonary
Health Condition
Renal
Gastro-intestinal
Musculo-skeletal
Socioeconomic
School
Income
Personal Strengths
Race
Sex
Age at diagnosis
Religion
Mental Health
Internalizing
Externalizing
Fear/ Anxiety
Endocrine
Cardiac
Neurologic
Auditory, Visual, Speech
Pulmonary
Health Condition
Renal
Gastro-intestinal
Musculo-skeletal
Mental Health
Somatic complaints
Anxiety
Depression

Figure 1: The three models for this proposal. Aim 1 will test between the CFA models depicted in Figure A1 and A2. Aim 2 will evaluate the goodness of fit of the structural model depicted in Figure B. Aim 3 will evaluate the goodness of fit for the structural model depicted in Figure C.

7. Tables

Table 1

Diagnosis information for CCSS patients who were included in the Baseline survey at age less than 18 and who then completed the 2003 follow-up and 2007 follow-up surveys.

Population	Baseline survey (N=3,280)	Both Baseline under 18 years old and 2003 Follow-up survey (N=1,686)	Baseline under 18 years old and both 2003 and 2007 follow-up surveys (N=1,296)
Leukemia			
CNS tumor			
Hodgkin Lymphoma			
NHL			
Wilms tumor			
Neuroblastoma			
Soft tissue sarcoma			
Bone tumor			
Total			

Table 2

Descriptive Statistics of Survivors

	N	**%**
Sex		
Male		
Female		
Race		
White		
Non-White		
Income		
<$19,999 - $39,999		
>$40,000		
Age (Mean, 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		
Radiation		

Surgery		

Table 3

Fit Statistics for the one factor model, and the two-factor model.

Models	$\chi 2$	df	RMSEA	CI	SRMR	CFI
1						
2						

Table 4

Fit Statistics for the Aim2 model.

Models	$\chi 2$	df	RMSEA	CI	SRMR	CFI

Table 5

Fit Statistics for the Aim3 model.

Models	$\chi 2$	df	RMSEA	CI	SRMR	CFI

Reference

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