CHILDHOOD CANCER SURVIVOR STUDY (CCSS) Analysis Concept Proposal

STUDY TITLE: Predictors of Longitudinal Pain in Long-Term Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

WORKING GROUP AND INVESTIGATORS: This proposed study will be conducted through the Psychology Working group, with analyses conducted through the CCSS Statistical Center.

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BACKGROUND AND RATIONALE:

Epidemiology studies suggest that there are over 420,000 survivors of childhood cancer in the United States, of whom more than 82% are greater than 5 years after diagnosis.[1,2] Recent reports, including some from the Childhood Cancer Survivor Study, suggest that pain is a significant ongoing concern for long-term survivors of pediatric cancer.[3-6] Estimates of pain prevalence among childhood cancer survivors range from 13-57%.[4,7-9] Abdominal pain, neck and back pain, migraines, headaches and neuropathic pain are among the most common pain conditions in childhood cancer survivors[7-11]and these conditions occur at rates higher than sibling comparison group.[7] Moreover, greater than 16% of adult childhood cancer survivors report current use of prescription analgesics,[7,12] suggesting that clinically significant levels of pain persist into adulthood. As awareness increases of the persistence of pain in long-term childhood cancer survivors so does the awareness of disability related to persistent pain. Specifically, a subset of childhood cancer survivors report clinically significant morbidity and disability from pain, particularly as they get older. Pain in adolescent and adult childhood cancer survivors is associated with poor quality of life, fatigue, difficulty sleeping, depression, post-traumatic stress, and suicidal ideation.[4-6,13,14] In a study of survivors who recently completed treatment for pediatric leukemia, brain tumor, and solid tumor, the presence of pain was related to mild daily functional disability.[15] However, in survivors more than 5 years after diagnosis persisting pain (i.e., chronic pain) was linked to significant limitations in daily activity levels (i.e., pain-related disability).[16] Thus, efforts to understand predictors, and in turn potential means of mitigating, chronic pain and pain-related disability are a priority.

Cross-sectional research suggests that several demographic and medical variables may predict pain in childhood cancer survivors. For instance, higher rates of pain in long-term survivors are associated with female gender, minority racial status, and lower educational attainment.[1,7,9,17,18] Pain rates

tend to be highest in survivors of pediatric brain tumor with nearly one-third of survivors reporting persisting pain after treatment.[3,15,19,20] Those individuals diagnosed at a young age, and those with a history of non-Hodgkin lymphoma, Wilms tumor, or neuroblastoma (compared to leukemia) also have a greater risk for persisting pain after treatment.[7] In addition, the prevalence of pain symptoms is higher in survivors who are further out from diagnosis,[4] and greater time since diagnosis may be associated with new report of pain symptoms in adult childhood cancer survivors (i.e., late reported pain).[12] Finally, treatment variables including vincristine and platinum chemotherapy agents[21-24] and central nervous system radiation[25] are associated with increased rates of neuropathic and body pain, increased somatic symptoms, and poorer health-related quality of life in child and adult survivors of childhood cancer. These previously identified demographic and medical variables have yet to be examined as they relate to longitudinal patterns of late reported pain, chronic pain, and pain-related disability in long-term childhood cancer survivors.

In addition to demographic and medical variables, recent literature suggests that psychological variables such as emotional distress and fatigue may also play an important role in concurrent and chronic pain. Although the co-occurrence and relationship between pain and emotional distress has been studied to a greater extent in pediatric populations other than cancer,[e.g.,26,27] emotional distress is documented to be closely intertwined with pain in childhood cancer survivors.[12,28] For example, Brinkman and colleagues[12] found that persistent emotional distress in adult childhood cancer survivors was predicted by perceived worsening physical health and worsening pain over time. Prospective longitudinal studies in pediatric abdominal pain[29] and adult populations[30] further suggest that depressive symptoms may predict the onset and/or maintenance of chronic pain. Emotional distress and fatigue may share similar pathways and risk factors, as these psychological variables often correlate and are both associated with greater reports of pain in pediatric cancer populations.[9,31,32] Similar to cross-sectional studies examining pain, multiple pediatric oncology studies document high levels of fatigue in children both during and after cancer treatment.[20,33-37] **Despite documentation of these symptoms at individual time points, the longitudinal relationship between emotional distress and chronic pain in childhood cancer survivors has yet to be examined. Similarly, the impact of fatigue on emotional distress and pain has not yet been examined in childhood cancer survivors. This proposal aims to address these gaps in the literature through the following objectives and specific aims.**

4. OBJECTIVES

The objectives of the proposed study are to examine the longitudinal pattern of pain in long-term survivors of childhood cancer, identifying both demographic and medical predictors of chronic pain, late reported pain, and pain-related disability. This study also seeks to examine emotional distress as a predictor of chronic pain, late reported pain, and pain-related disability, as well as examine the cross-sectional relationship between emotional distress, pain, and fatigue. The findings of this research will assist in identifying childhood cancer survivors at high risk for chronic pain, late reported pain, and pain-related disability, as well as identifying modifiable targets for intervention development. Study time periods are defined as surveys completed at Baseline, Follow-up 2 (FU2) and Follow-up 4 (FU4) by survivors and siblings in the original cohort.

Specific Aims:

Aim 1: To estimate prevalence and identify demographic and medical predictors of late reported pain, chronic pain, and pain-related disability among adult survivors of childhood cancer.

Hypothesis 1.1: Cancer survivors will have a greater prevalence of late reported pain, chronic pain, and pain-related disability than their siblings.

Hypothesis 1.2: Late reported pain, chronic pain, and pain-related disability at long-term follow-up will be predicted by Baseline demographic (i.e., female gender, non-Caucasian race, and lower

income) and medical variables (e.g., younger age at diagnosis, greater time from diagnosis, cranial radiation).

Aim 2: To examine emotional distress as a predictor of late reported pain, chronic pain, and pain-related disability among adult survivors of childhood cancer.

Hypothesis 2: Late reported pain, chronic pain, and pain-related disability at long-term follow-up (FU2 and FU4) will be predicted by Baseline emotional distress.

Aim 3: To examine the associations between emotional distress, pain, and fatigue in adult survivors of childhood cancer.

Hypothesis 3: Fatigue will be associated with emotional distress and pain and will mediate the association between emotional distress and pain.

ANALYSIS FRAMEWORK

5.1 Participant population

Participants will be survivors of childhood cancer in the original CCSS cohort, and their siblings, who responded to the Baseline (1994, n = 14,054) and at least one of FU2 (2003, n = 7,123), or FU4 (2007, n = 7,021) questionnaires. For Aim 3, subjects will also have responded to the 2003 Fatigue/Sleep survey that was sent out as a separate mailing between 2002 and 2004 (n = 1,810).

Aims 1 and 2 will be addressed by examining outcomes in survivors and siblings who responded to the Baseline questionnaire and at least one of the follow-up questionnaires (FU2 or FU4). We will analyze data to examine how individuals with missing data at FU2 or FU4 differ from individuals who completed Baseline only and those who completed all three time points (Table 1). Missing data will generally be handled using full information maximum likelihood estimation to minimize bias. Aim 3 (mediation analyses), will be addressed by utilizing outcomes in survivors who responded to the Baseline questionnaire, the FU2 questionnaire, and the fatigue/sleep survey.

5.2 Pain outcomes:

Pain symptoms at Baseline. Participants were asked whether they "have or have had" any of the following pain conditions. Responses will be dichotomized and coded as “no” or "not sure" = *no pain* and “yes” = *pain*.

- prolonged pain or abnormal sensation in arms, legs, or back (J13)
- migraine (J6)
- other frequent headaches (J7)

Pain at FU2 and FU4. Pain will be assessed using the bodily pain scale of the Short-Form 36 (SF-36)[38] at FU2 and FU4 (Note: although the entire SF-36 was not administered at FU4, the Pain subscale was included). Responses range from “None” to “Very Severe.” Given that this is a Likert rating scale, we will examine the distribution of pain responses and determine a cutpoint for dichotomizing the presence of pain based on the sibling distribution. Specifically, sibling scores at or above the third quartile (upper 25%) will be used as a cutpoint for dichotomizing the presence of pain.

- How much bodily pain have you had during the past 4 weeks? (FU2 = E21; FU4 = L21)

Pain-related disability at FU2 and FU4. Pain-related disability will be assessed using the bodily pain scale of the SF-36. Responses range from “Not at all” to “Extremely.” Given that this is a Likert rating scale, we will examine the natural distribution of pain disability and then dichotomize the pain disability based on the sibling distribution. Specifically, sibling scores at or above the third quartile (upper 25%) will be used as a cutpoint for dichotomizing the presence of pain-related disability.

- During the past 4 weeks, how much did pain interfere with your normal work (including work outside the house and housework)? (FU2 = E22; FU4 = L22)

Three dichotomous outcomes will be created from the pain variables listed above:
(1) **Late reported pain** will be defined as pain that emerges at FU2 or FU4, without being present at an earlier survey.
(2) **Chronic pain** will be defined as pain at baseline, as well as pain at FU2 and/or FU4.
(3) **Pain-related disability** will be defined as pain that interferes with normal work, based on the second item from SF-36 pain scale at FU2 and/or FU4.

	Baseline (Pain conditions: J6, J7, J13)	FU2 (SF-36 E21; E22)	FU4 (SF-36 L21; L22)
No Late reported or Chronic pain	-	-	-
Late reported pain	-	+	
Late reported pain	-	-	+
Chronic pain	+	+	-
Chronic pain	+	-	+
Chronic pain	+	+	+
Pain-related disability	NA	+	-
Pain-related disability	NA	-	+
Pain-related disability	NA	+	+

5.3 Independent predictor variables
5.3.1 Medical variables:
(a) Diagnosis variables:
i. Age at diagnosis (Baseline = P1)
ii. Specific Diagnosis (MRAF)
iii. Time since Diagnosis:
- At Baseline, FU2, FU4

(b) Treatment variables: Medical Chart Review[39]
i. Surgery yes/no
ii. Chemotherapy yes/no
- Platinum agents (Cisplatin, Carboplatin, Other)
- Vinca alkaloids (Vincristine, Other)

iii. Radiation: yes/no
- If yes, then yes/no for Cranial, Non-cranial
- If yes, then dose (Cranial RT < 20 Gy, Cranial RT ≥ 20 < 30 Gy, ≥ 30 Gy)

5.3.2. Demographic variables:
i. Age at interview (Baseline, FU2, FU4, Sleep Survey)
ii. Gender (Baseline = A2)
iii. Race (Baseline = A4 & A4a)

iv. Household income (Baseline = Q8; FU2 = S1; FU4 = A6)
vi. Education (Baseline = Q1; FU2 = 1; FU4 = A3)
vii. Marital status (Baseline = L2; FU2 = 2; FU4 = M2)

5.3.3 Psychological variables

(a) Emotional distress. The Brief Symptom Inventory-18 (BSI-18) was administered at Baseline, FU2, and FU4 and includes three subscales measuring depression, somatization, and anxiety. The total BSI-18 raw score will be converted to a T-score using sex-specific normative data from a sample of community dwelling adults in the United States[40] and used in analyses. Higher scores on the BSI-18 represent greater levels of distress.

(b) Fatigue. Vitality and Fatigue scales were administered at FU2 and during the Sleep Survey. We will use data gathered for this proposal to inform our choice of fatigue scale. If the Vitality scale is highly correlated ($r \geq 0.8$) with the Fatigue scale in the smaller subset of survivors who completed both FU2 and the Sleep Survey, then we will use the Vitality scale from FU2, which provides a larger sample size. We will also examine the associations with emotional distress and pain for both the Vitality and Fatigue scales to ensure corresponding patterns. If the correlation between Vitality and Fatigue is not highly correlated ($r < 0.8$), then we will use the smaller sample size who completed the Fatigue scale. Note: This applies only to Aim 3.

(i) Vitality scale. Four items on the SF-36 comprise the Vitality scale.[38] Items are rated on a six-point Likert scale and measure the degree of feeling energetic and full of life versus feeling tired and worn out. The subscale score is converted to a T-score that will be used in analyses, with lower scores equaling poor vitality.

- FU2 = F1, F5, F7, F9

(ii) Fatigue scale. The total score of the Fatigue subscale of the Functional Assessment of Chronic Illness Therapy-Fatigue will be examined.[41] The 13-items comprising this measure are scored on a reverse five-point Likert scale. Greater fatigue is represented by lower scores.

- 2003 Fatigue/Sleep Survey = 14a-m

Participant demographic and psychological characteristics will be presented across time in Table 2.

5.3.4 Covariates:

Medications. Medications will be classified using the American Hospital Formulary Service Drug Information database (AHFS). A list of the AHFS drug classes and codes is provided in AHFS Online resource.[42] Responses will be coded “no” or "not sure" = no use and “yes” = use.

(a) Use of antidepressant medications. Participants were asked whether they had used prescription antidepressant medications either consistently for more than one month or for a total of 30 days in one year for the 2-year period. We will examine the association of antidepressant use with pain and emotional distress and adjust statistical models accordingly

- Baseline = 15
- FU2 = Q8
- FU4=C8.9

(b) Use of analgesic medications. Participants were asked whether they had used prescription pain medications (baseline) or other prescription medications (FU2 and FU4) either consistently for more than one month or for a total of 30 days in one year for the 2-year period. We will examine the association of analgesic medication use with pain and emotional distress and adjust statistical models accordingly

- Baseline = 9
- FU2 = Q9 (other prescription medication = analgesic medication)

- FU4=C8.10 (other prescription medication = analgesic medication)

(c) Chronic medical conditions: We will select categories of chronic medical conditions graded according to Common Terminology Criteria for Adverse Events, version 4.03.[43] Potential conditions include endocrine (e.g., osteoporosis), respiratory, cardiac, gastrointestinal, renal, musculoskeletal, and neurologic (e.g., neuropathy). Participant chronic medical grade will be presented across time in Table 2.

5.4 Analysis approach, examples of tables and figures:

Analytic approach for hypothesis 1.1: Prevalence ratios for pain outcomes at each time point will be calculated, comparing adult survivors to siblings with 95% Confidence Intervals. Prevalence ratios will be estimated using generalized linear models with a log-link function and Poisson error structure with robust variances to account for intra-family correlations between survivors and siblings. Prevalence ratios will be adjusted for age at survey response, gender, and chronic medical condition grade. Additional psychological and demographic variables will be compared between survivors and siblings using similar methods, but with the appropriate link function for the outcome of interest (linear for continuous, logit for rare binary, etc). See Table 3.

(a) Baseline pain
(b) Late reported pain at FU2 and/or FU4
(c) Chronic pain at Baseline, FU2, and/or FU4
(d) Pain-related disability at FU2 and/or FU4

Analytic approach for hypothesis 1.2:

Descriptives: The prevalence of pain outcomes by diagnosis and treatment will be calculated using descriptive statistics (Table 4).

Relative Risk (RR): Multivariable regression will be used to estimate Relative Risks for late reported pain, chronic pain, and pain-related disability.[45] A generalized linear model with a log link, using a modified Poisson regression model and robust standard errors will be used to directly model RRs for late reported pain, chronic pain, and pain-related disability. Variables that demonstrate univariate association with the outcome (determined by a p-value of <0.10) will be evaluated in multivariable models in a stepwise fashion. Multivariable models will examine demographic variable (i.e., gender, race, age at time of survey, and household income), diagnosis variables (i.e., age at diagnosis, diagnosis, time since diagnosis), treatment variables (i.e., chemotherapy, radiation, antidepressant medication, analgesic medication), and chronic medical conditions at each time point as predictors of RR. See Table 5.

Analytic approach for hypothesis 2: As emotional distress is associated with pain, and both are expected to be associated with treatment exposures, we will use structural equation modeling (SEM) to address Aim 2. SEM longitudinal modeling will be used to examine the relationship between emotional distress, late reported pain, chronic pain, and pain-related disability.

SEM Step 1: SEM Step 1 will be a cross-sectional SEM model analysis at Baseline, FU2, and FU4 to establish the significant relationships between emotional distress, pain, and pain-related disability (FU2 and FU4). The first set of predictors will be significant demographic factors (i.e., age at time of survey, gender, race, household income). The second set of predictors will be significant diagnosis variables (i.e., age at diagnosis, diagnosis, time since diagnosis). The third set of predictors will be significant treatment variables (i.e., chemotherapy, radiation). The fourth set of predictors will be emotional distress. Covariates will include antidepressant and analgesic medication use, as well as chronic medical condition grade, at each time of survey. See Table 6.

SEM Step 2: SEM Step 2 will be a longitudinal SEM model analysis of baseline emotional distress influence on late reported pain, chronic pain, and pain-related disability. The first set of predictors will be significant baseline demographic factors (i.e., age at time of survey, gender, race, and household income). The second set of predictors will be significant diagnosis variables (i.e., age at diagnosis, diagnosis, time since diagnosis). The third set of predictors will be significant treatment variables (i.e.,

chemotherapy, radiation). The fourth set of predictors will be baseline emotional distress. Covariates will include antidepressant and analgesic use, as well as chronic medical condition grade. See Table 7.

Analytic approach for hypothesis 3: Cross-sectional bootstrap mediation analyses will be conducted to examine the direct and indirect effects (through FU2 fatigue) of FU2 emotional distress on FU2 pain (E21) in adult survivors of childhood cancer. Covariates will include FU2 demographics (age at survey, gender, race, household income), FU2 antidepressant and analgesic medication use, and FU2 chronic medical condition grade. See Figure 1.

Table 1. Participant demographics and medical characteristics

		Survivors Baseline only N = *n* (%)	Survivors 2 surveys N = *n* (%)	Survivors all 3 surveys N = *n* (%)	$t/\chi 2^{*}$	*p*
Age at diagnosis (M± SD)						
Time since diagnosis (M± SD)						
Baseline age (M± SD)						
Martial status						
Education						
Gender	Female					
	Male					
Ethnicity	Caucasian					
	Hispanic					
	African American					
	Other					
Annual household Income	<$19,999					
	$20K-$59,999					
	$60,000					
Diagnosis	Leukemia					
	CNS tumour					
	Hodgkin lymphoma					
	Non-Hodgkin's lym					
	Wilms tumour					
	Neuroblastoma					
	Other Cancer					
Surgery	Yes					
Chemotherapy						
	Platin agents					
	Vinca alkaloids					
Radiation Therapy	Non-cranial					
	Cranial RT					
	Cranial RT <20 Gy					
	Cranial RT ≥20 <30 Gy					
	Cranial RT ≥30 Gy					

*Denote two-group differences using [a,b,c] with explanation in Notes

Table 2. Participant characteristics across time

	Baseline N= (M±SD)	Baseline Sibling N= (M±SD)	t/χ^2	p	2003 FU2 N= (M±SD)	2003 FU2 Sibling N= (M±SD)	t/χ^2	p	2007 FU4 N= (M±SD)	2007 FU4 Sibling N= (M±SD)	t/χ^2	p
Age												
Married *n*(%)												
Annual Income (*Med*)												
Chronic Medical Condition Grade *n*(%)												
Depression												
Anxiety												
Somatization												
Total Emotional Distress												
Fatigue/Vitality												

Table 3. Pain variables across time (Hypothesis 1.1)

	Baseline N= (M±SD)	Baseline Sibling N= (M±SD)	t/χ^2	p	Prevalence Ratio*	2003 FU2 N= (M±SD)	2003 FU2 Sibling N= (M±SD)	t/χ^2	p	Prevalence Ratio*	2007 FU4 N= (M±SD)	2007 FU4 Sibling N= (M±SD)	t/χ^2	p	Prevalence Ratio*
Antidepressant Medication *n*(%)															
Analgesic Medication *n*(%)															
Baseline Pain *n*(%)															
Late reported pain															
Chronic Pain *n*(%)															
Pain-related disability *n*(%)															

Note: *Adjusted for age at survey response, gender, and chronic medical condition grade.

Table 4. Prevalence of Adult Survivor Pain by Diagnosis and Treatment (Hypothesis 1.2)

	No Pain *n* (%)	Baseline Pain *n* (%)	Late Reported Pain *n* (%)	Chronic Pain *n* (%)	Pain-related Disability *n* (%)
Diagnosis					
Leukemia					
CNS tumor					
Hodgkin lymphoma					
Non-Hodgkin lymphoma					
Wilms tumor					
Neuroblastoma					
Other Cancer					
Surgery Only					
Chemotherapy					
Cisplatin					
Carboplatin					
Vincristine					
Radiation					
Non-cranial					
Cranial RT <20 Gy					
Cranial RT ≥20 <30 Gy					
Cranial RT ≥30 Gy					

Table 5: Relative risk of pain and pain-related disability: Multivariable predictors (Hypothesis 1.2)

Conceptual Model: Demographic variables and medical variables influence on pain and pain-related disability.

	Baseline Pain			Late reported pain			Chronic pain			Pain-related disability		
Independent Variable	RR	95% CI	*p*	RR	95% CI	*p*	RR	95% CI	*p*	RR	95% CI	*p*
Age at survey												
35-39 (referent)												
40-49												
50+												
Sex												
Male (referent)												
Female												
Race												
Minority (referent)												
White, non-Hispanic												
Household income												
<$40,000												
$40,000-$79,999												
$80,000+												
Age at diagnosis												
≤10 (referent)												
>10												
Diagnosis												
Leukemia (referent)												
CNS tumor												
Other Cancer												
Time since diagnosis												

<10 years (referent)												
10-19 years												
≥20 years												
Chemotherapy												
No (referent)												
Yes												
Radiation												
No (referent)												
Yes												
Antidepressant use												
No (referent)												
Yes												
Analgesic use												
No (referent)												
Yes												
Chronic medical condition grade												

Table 6: Cross-sectional influence of emotional distress on pain and pain-related disability. (Hypothesis 2—Step 1)

Conceptual Model: Significant demographic variables (identified with hypothesis 2), significant medical variables (identified with hypothesis 2), and emotional distress influence on concurrent pain and concurrent pain-related disability. Controlling for antidepressant and analgesic medication use, as well as chronic medical condition grade, at each time point.

Dependent Variable	Independent Variable	Standardized path coefficient	t-statistic	p-value	Variance explained
Baseline Pain	*Set 1:* Baseline Demographics				
	Age at survey				
	Gender				
	Race				
	Household income				
	Set 2: Diagnosis				
	Age at diagnosis				
	Diagnosis				
	Time since diagnosis				
	Set 3: Treatment				
	Chemotherapy				
	Radiation				
	Set 4: Baseline Emotional distress				
	Covariates:				
	Baseline Antidepressant use				
	Baseline Analgesic use				
	Baseline: Chronic medical condition grade				
Baseline Pain-related disability	*Set 1:* Baseline Demographics				
	Age at survey				
	Gender				
	Race				
	Household income				
	Set 2: Diagnosis				
	Age at diagnosis				
	Diagnosis				
	Time since diagnosis				
	Set 3: Treatment				
	Chemotherapy				
	Radiation				
	Set 4: Emotional distress				
	Covariates:				
	Baseline Antidepressant use				
	Baseline Analgesic use				

	Baseline: Chronic medical condition grade				
FU2 Pain	*Set 1:* FU2 Demographics				
	Age at survey				
	Gender				
	Race				
	Household income				
	Set 2: Diagnosis				
	Age at diagnosis				
	Diagnosis				
	Time since diagnosis				
	Set 3: Treatment				
	Chemotherapy				
	Radiation				
	Set 4: FU2 Emotional distress				
	Covariates:				
	FU2 Antidepressant use				
	FU2 Analgesic use				
	FU2: Chronic medical condition grade				
FU2 Pain-related disability	*Set 1:* FU2 Demographics				
	Age at survey				
	Gender				
	Race				
	Household income				
	Set 2: Diagnosis				
	Age at diagnosis				
	Diagnosis				
	Time since diagnosis				
	Set 3: Treatment				
	Chemotherapy				
	Radiation				
	Set 4: FU2 Emotional distress				
	Covariates:				
	FU2 Antidepressant use				
	FU2 Analgesic use				
	FU2: Chronic medical condition grade				
FU4 Pain	*Set 1:* FU4 Demographics				
	Age at survey				
	Gender				
	Race				
	Household income				
	Set 2: Diagnosis				
	Age at diagnosis				

	Diagnosis				
	Time since diagnosis				
	Set 3: Treatment				
	Chemotherapy				
	Radiation				
	Set 4: FU4 Emotional distress				
	Covariates:				
	FU4 Antidepressant use				
	FU4 Analgesic use				
	FU4: Chronic medical condition grade				
FU4 Pain-related disability	*Set 1:* FU4 Demographics				
	Age at survey				
	Gender				
	Race				
	Household income				
	Set 2: Diagnosis				
	Age at diagnosis				
	Diagnosis				
	Time since diagnosis				
	Set 3: Treatment				
	Chemotherapy				
	Radiation				
	Set 4: FU4 Emotional distress				
	Covariates:				
	FU4 Antidepressant use				
	FU4 Analgesic use				
	FU4: Chronic medical condition grade				

Fit indices for models	**Chi-square**	**df**	**NFI**	**NNFI**	**CFI**	**PR**	**PNFI**	**RNFI**	**RPR**	**RPFI**
Null model										
Uncorrelated factors										
Measurement model										
Final Theoretical Model										
Chi-squared difference										
Critical value of Chi-squared										

Table 7: Longitudinal SEM model of emotional distress influence on late reported pain, chronic pain, and pain-related disability. (Hypothesis 2—Step 2)

Conceptual Model: Significant baseline demographic variables (identified with hypothesis 2), significant medical variables (identified with hypothesis 2), and baseline emotional distress influence on late reported pain, chronic pain, and pain-related disability. Controlling for antidepressant and analgesic medication use, as well as chronic medical condition grade.

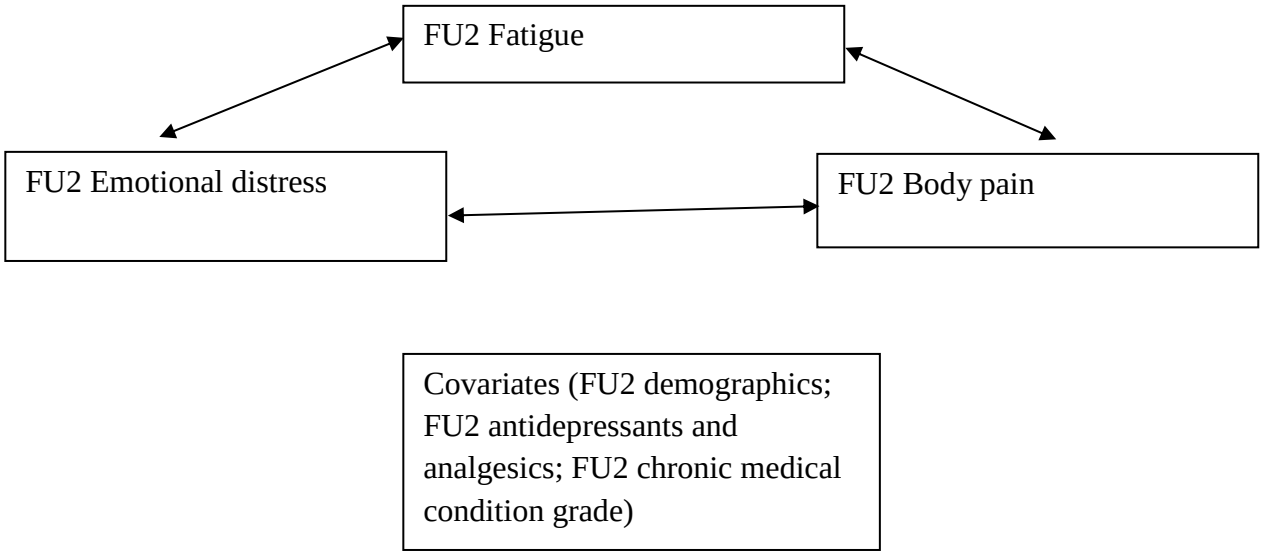
Dependent Variable	Independent Variable	Standardized path coefficient	t-statistic	p-value	Variance explained
Late reported Pain	*Set 1:* Baseline Demographics				
	Age at survey				
	Gender				
	Race				
	Household income				
	Set 2: Diagnosis				
	Age at diagnosis				
	Diagnosis				
	Time since diagnosis				
	Set 3: Treatment				
	Chemotherapy				
	Radiation				
	Set 4: Baseline Emotional distress				
	Covariates:				
	Antidepressant use				
	Analgesic use				
	Chronic medical condition grade				
Chronic Pain	*Set 1:* Baseline Demographics				
	Age at survey				
	Gender				
	Race				
	Household income				
	Set 2: Diagnosis				
	Age at diagnosis				
	Diagnosis				
	Time since diagnosis				
	Set 3: Treatment				
	Chemotherapy				
	Radiation				
	Set 4: Baseline Emotional distress				
	Covariates:				
	Antidepressant use				
	Analgesic use				
	Chronic medical condition grade				

Pain-related disability	*Set 1:* Baseline Demographics				
	Age at survey				
	Gender				
	Race				
	Household income				
	Set 2: Diagnosis				
	Age at diagnosis				
	Diagnosis				
	Time since diagnosis				
	Set 3: Treatment				
	Chemotherapy				
	Radiation				
	Set 4: Baseline Emotional distress				
	Covariates:				
	Antidepressant use				
	Analgesic use				
	Chronic medical condition grade				

Fit indices for models	**Chi-square**	**df**	**NFI**	**NNFI**	**CFI**	**PR**	**PNFI**	**RNFI**	**RPR**	**RPFI**
Null model										
Uncorrelated factors										
Measurement model										
Final Theoretical Model										
Chi-squared difference										
Critical value of Chi-squared										

Figure 1: Mediation Model of pain at FU2. (Hypothesis 3)

Conceptual Model: Fatigue at FU2 will explain the relationship between FU2 emotional distress and FU2 body pain, controlling for FU2 demographic variables and FU2 antidepressants and analgesic medication use.



Demographic Variables = gender, race, age at time of survey, household income

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