

**CHILDHOOD CANCER SURVIVOR STUDY (CCSS)  
Analysis Concept Proposal**

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

**2. WORKING GROUP AND INVESTIGATORS:** This proposed study will be conducted in collaboration with the Neuropsychological/Psychosocial Working group and statistical center of the CCSS. Proposed investigators include:

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**3. BACKGROUND AND RATIONALE:**

*Pain prevalence*

Relatively little is known about the prevalence or etiology of pain in childhood cancer survivors. Estimates of pain prevalence among children receiving treatment or follow-up care have ranged from 13-26% for outpatients and 39%-54% for inpatients (Elliott et al., 1991; Miser et al., 1987). Few studies to date have examined pain prevalence in long-term survivors. Our preliminary work suggests that approximately 12% of survivors reported pain and 23% reported frequent headaches or migraines (Lu et al., 2003); over 16% of survivors reported having current or recent pain that they attributed to their cancer and over 82% reported having consistently used prescription analgesics (Owen et al., manuscript). These estimates of pain prevalence among survivors of childhood cancer suggest a clinically significant symptom burden in this population. Previous studies of pain among childhood cancer survivors have utilized small sample sizes and typically do not employ a control group. The proposed study will utilize data obtained from the CCSS- the largest and most comprehensively characterized epidemiological research cohort of childhood cancer survivors and matched siblings recruited from 25 sites in North America. In this proposal, we plan to compare survivors and siblings on the prevalence of pain and pain disability at follow-up 2 (approximately 7 years post-baseline). Because pain was assessed using a well established measure (SF-36), we will also be able to compare the level of pain in survivors with the general U.S. population.

*Sociodemographic and medical predictors of pain*

The relationship of pain to gender, ethnicity, age, and socioeconomic status has been largely unexplored in survivors of childhood cancer. In non-cancer populations, previous research has

extensively documented sex differences in the experience of pain (higher pain reported by females) and differences between ethnic groups (higher pain among African-Americans) in laboratory-based experiments (Chesterton et al., 2003; Edwards & Fillingim, 1999; Fillingim, 2000; Sarlani & Greenspan, 2002) and among patients with chronic disease (Faucett et al., 1994; Norrbrink et al., 2003; Riley et al., 2002). In surveys of cancer patients, non-white patients have been shown to be more likely to receive inadequate pain management therapy (Anderson et al., 2000; Cleeland et al., 1997) and may therefore experience higher levels of pain.

Our analysis of CCSS baseline data (Owen et al. manuscript) revealed that self-reported pain symptoms at baseline were associated with female gender, lower income, older age, cancer diagnosis (i.e., osteosarcoma and soft-tissue sarcoma), taking prescription analgesics, and attributing pain to cancer. These findings warrant further studies that examine the relationship between these factors and pain at a longer follow-up. It is also important to determine whether these sociodemographic and medical risk factors for pain at study entry (baseline) influence pain at a longer follow-up above and beyond initial baseline pain symptoms. For example, pain medication was positively associated with pain symptoms at baseline. These cross-sectional findings however, do not speak to the direction of the relationship between analgesics and pain symptoms. A longitudinal approach is therefore needed to examine how risk and protective factors at baseline may influence pain at a long-term follow-up. Based on preliminary data at baseline, we propose that pain and pain-related disability at the follow-up will be predicted by demographic factors (i.e., gender, race, age, and social economic status), medical factors (i.e., treatment type, cancer diagnosis, medical conditions) and use of pain medicine controlling for pain symptoms at study baseline (hypothesis 2.1).

### *Psychological predictors of pain*

Psychological distress, and its implications for emotional well-being, may have an important effect on mechanisms of pain processing that ultimately impact experience of pain. Moreover, psychological distress might potentially mediate the effects of sociodemographic and medical factors on pain. Zebrack et al. (2003) found that solid tumor survivors, compared to siblings had higher levels of overall psychological distress as indicated by Global Severity Index (GSI) composed of depression, anxiety and somatization subscales. Zebrack et al. also reported that female gender, lower educational and income attainment, perceived poor health status and reports of current health problems all were associated with reporting increased psychological distress symptoms for both survivors and siblings. Psychological distress and pain often co-exist. Moreover, psychological distress and pain seem to share similar risk factors. However, the relationship between psychological factors and pain has not been examined in childhood cancer survivors. Therefore, it is important to evaluate from both a cross-sectional and a longitudinal perspective the relationship between pain and psychological factors as well as the potential role of psychological factors which might mediate the effects of sociodemographic and medical factors on pain.

Facing a life-threatening trauma such as childhood cancer may result in distress as well as posttraumatic growth (PTG) (Barakat, Kunin-Batson, & Kazak, 2003). PTG has been defined as the cognitive process by which those who have experienced trauma apply positive interpretations to and find meaning in the traumatic event. This process results in restoration of pretrauma schema and positive changes in one's sense of self, relationships, and philosophy of life

(Calhoun & Tedeschi, 1999). Findings suggest that perceived benefits or PTG following a trauma are associated with lower levels of distress or PTSD over time (Davis, Nolen-Hoeksema, & Larson, 1998; Ullrich & Lutgendorf, 2002). It is likely that PTG is a protective factor for late effect of pain after cancer diagnosis and treatment and this possibility warrants further exploration, as we propose to do.

### *Health behaviors*

Engaging in fewer overall health behaviors (e.g., less physical activity, abstinence from alcohol, tobacco, and recreational drugs) may be associated with greater risk for further health complications, psychological distress, and pain. While these relationships have not been adequately explored in childhood cancer survivors, they have been well-studied in non-cancer populations. Physical activity is known to be protective against mood dysregulation (Thirlaway and Benton 1992; Lee, Goldberg et al. 2001) and chronic pain (Hayden, Mior et al. 2003), whereas use of tobacco may be associated with the onset of depressed mood in childhood and early adolescence (Wu and Anthony 1999) and chronic pain conditions in adults (Dobie, Kivlahan et al. 2004). In prior work using CCSS data, greater dependence on tobacco was associated with higher levels of psychological distress among survivors (Emmons, Butterfield et al. 2003). Alcohol use is likely to be associated with chronic pain conditions (Booker, Haig et al. 2003; Ohayon 2004; Brennan, Schutte et al. 2005; Latthe, Mignini et al. 2006), and in one CCSS study, survivors who reported pain were more likely to be heavy drinkers than those without pain (Lown and 2006). Based on these preliminary findings, we predict that those engaging in less exercise and more drinking and smoking behavior will report more pain and pain-related disability than those who exercise more, and drink and smoke less. One aim of the present study is to evaluate the relationship between health behaviors and pain as well as the potential role of health behaviors in mediating the effects of sociodemographic and medical factors on pain among childhood cancer survivors. These results of these analyses may help inform intervention efforts focused on changing health behaviors that may lead to subsequent reductions in long-term pain among childhood cancer survivors.

## **4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESIS**

The objectives of the study are to analyze pain and its predictors in a cohort of long-term survivors of childhood cancer and in their siblings, in order to characterize the prevalence of and identify risk factors for, pain and pain-related disability. The findings of this research may assist in the development of interventions aimed at reducing pain in childhood cancer survivors.

Aim 1: Use *cross-sectional analyses* to compare levels of pain and pain-related disability at long term follow-up among childhood cancer survivors with sibling controls and normative values in the United States (U.S.) general population, and to examine the associations between multiple factors and pain.

Hypothesis 1.1: Survivors will report higher levels of pain and pain-related disability at long term follow-up (time 2) compared with siblings and with normative values in the U. S. general population.

Hypothesis 1.2 Higher levels of pain and pain-related disability at time 2 will be associated with health behaviors (i.e., more smoking and less physical exercise) and psychological factors (i.e., less posttraumatic growth, more posttraumatic stress, more pain and anxiety attribution to cancer, and more psychological distress indicated by depression, anxiety, and somatization) at time 2 controlling for baseline pain symptoms, demographic factors, cancer diagnosis and treatment, and health conditions. Differences in the associations between survivors and siblings will be explored.

Aim 2: To identify risk factors for pain and pain-related disability in survivors at long-term follow-up using *longitudinal* multivariate predictor models.

Hypothesis 2.1 Higher levels of pain and pain-related disability at the long-term follow-up (time 2) will be predicted by preexisting risk factors, such as demographic factors (i.e., female gender, non-caucasian race/ethnicity, age, and poorer social economic status) and medical factors (i.e., more aggressive treatment type and cancer diagnosis, poorer medical conditions) at study baseline (time 1) controlling for pain symptoms at time 1.

Hypothesis 2.2 Higher levels of pain and pain-related disability at time 2 will be predicted by modifiable risk factors, such as health behaviors (i.e., more smoking and more drinking and less physical excise), more psychological distress (i.e., depression, anxiety, and somatization), more pain attribution, and less pain medication use at time 1 controlling for pain symptoms as well as demographic and medical factors at time 1.

Aim 3: To identify behavioral and psychological pathways through which sociodemographic and medical factors influence long-term pain and pain-related disability in survivors using structural equation modeling (SEM).

Hypothesis 3: Health behaviors, psychological factors, pain attribution and pain medication will mediate the effects of sociodemographic and medical factors on pain and disability at time 2.

## 5. ANALYSIS FRAMEWORK

### 5.1 Subject population

Subjects will be survivors of childhood cancer and siblings in the CCSS cohort who responded to the 1<sup>st</sup> (1994) or the 2<sup>nd</sup> (2002) follow-up questionnaire. 9034 survivors responded to both time 1 and time 2 questionnaires. Average length between the 1<sup>st</sup> and the 2<sup>nd</sup> follow-up questionnaires was 7.73 years (SD=1.26), ranging from 0.025 to 11.87 years. Three sub data sets will be created. Data set 1, associated with aim 1 (cross-sectional analyses), includes survivors and siblings who responded to the 2<sup>nd</sup> follow-up questionnaire. Data set 2, associated with aim 2 and aim3 (longitudinal analyses), includes survivors who responded to both the 1<sup>st</sup> and 2<sup>nd</sup> follow-up questionnaire. Data set 3, associated with missing data analysis, includes survivors and siblings who responded to the 1<sup>st</sup> questionnaires with information regarding whether they responded to the 2<sup>nd</sup> questionnaire. One of the purposes of analyzing miss data is to examine how participants missing at time 2 follow-up differed from participants remaining in the study at time 2 follow-up.

### 5.2 Pain outcomes

*Pain and pain disability at the 2<sup>nd</sup> follow-up* Pain was assessed at follow-up 2 using the bodily pain scale of the Short-Form 36 (SF-36), a widely used and psychometrically sound instrument. It was indicated by the two scale items: (1) how much bodily pain have you had during the *past 4 weeks*? Responses ranged from ‘none’=1 to ‘very severe’=6. (2) ‘During the *past 4 weeks*, how much did pain interfere with your normal work (including work outside the house and housework)?’ Responses ranged from ‘Not at all’=1, to ‘extremely’=5. In order to compare survivors’ scores with normative values among general population in the U.S., a composite of a bodily pain variable will be created. The responses to the two items are summed and linearly transformed to produce a composite score ranging from 0 (lowest pain) to 100 (highest pain). In order to calculate relative risk for pain and disability, two dichotomous variables will be created. Responses to the pain item will be coded as “no pain” if it is 1 and coded as “having pain” if the responses range from 2 to 6. Responses to the disability item will be coded as “no disability” if it is 1 and coded “having disability” if the responses range from 2 to 5.

### **5.3 Independent variables (Exploratory variables)**

All independent variables were measured at baseline except that health behaviors, the Brief Symptom Inventory -18 (BSI-18), anxiety and pain attribution were measured at both baseline and follow-up 2. Posttraumatic growth (PTGI) and posttraumatic stress (PTS) were only measured at follow-up 2.

#### *5.3.1. Sociodemographic variables:*

- i. Age at interview
- ii. Gender
- iii. Race/ethnicity
- iv. Household income
- v. Health insurance
- vi. Education
- vii. Marital status
- viii. Employment status

#### *5.3.2 Medical variables:*

##### (a) Disease variables:

- i. Age at diagnosis
- ii. Specific Diagnosis (ICD-9 codes): leukemia, non-Hodgkin’s lymphoma, Hodgkins lymphoma, CNS tumors, and solid tumor group including: Kidney, Neuroblastoma, Soft Tissue Sarcoma, Bone Tumor. Note that we will examine the outcome variables within each separate diagnosis subgroup, in order to determine whether the groups could be collapsed into broader categories.
- iii. Time since diagnosis (note, either age at diagnosis or time since diagnosis will be used in multivariate analysis because these two variables are essentially the same).

##### (b) Treatment variables:

- i. Chemotherapy yes/no and chemical agents
- i. Surgery yes/no
- ii. Radiation: yes/no; If yes, then yes/no for Brain, Spine, Chest, Pelvis, Extremity

(c) Health condition variable: To determine the severity of health conditions, scoring was based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3, a scoring system developed through the National Cancer Institute by a multi-disciplinary group. CTCAE v3 is intended for use in scoring both acute and chronic conditions for cancer patients and survivors of all ages. There are five grades: grade 1 - mild; grade 2 - moderate; grade 3 - severe; grade 4 - life-threatening or disabling; and grade 5 - death. This study will be using the code created by Oeffinger et al., (manuscript). A total of 137 health conditions will be scored. As per instructions in the CTCAE v3, when a particular condition was not specified in the scoring schema, it was entered in the 'Other, specify' by organ system affected. If there was not enough information provided to distinguish between grades, the lower score was selected. Adverse psychosocial outcomes, including depression and anxiety disorder, will not be included in this analysis. This coding has been used by Oeffinger et al.

### **5.3.3 Health behavior variables:**

<u>Smoking behavior</u>	Measured at time 1 and time 2.
<u>Alcohol consumption</u>	Measured at time 1.
<u>Physical exercise</u>	Measured at time 1 and time 2.

Six or seven questions were asked in each health behavior category. We plan to use all the items in this category first and then determine which item should be used in the final models by exploring the relationship between these items and pain outcomes.

### **5.3.4 Psychological variables**

Psychological distress. Measured by BSI-18 which includes three subscales measuring depression, somatization, and anxiety. The BSI-18 assessed depressive and anxiety symptoms and physical complaints in the past seven days. BSI-18 contains 18 items and each item is rated on a 5-point Likert scale from 0 (not at all) to 4 (always). The author reported a high level of internal consistency (0.80~0.84) and test-retest reliability (0.68~0.84) for the subscales (Derogatis, 2000). Psychological distress will be indicated by the total score of BSI-18 for regression analysis or a latent factor underlining the three subscales for structural equation modeling. The relationship between the BSI-18 subscales and pain will be explored.

Anxiety attribution. Survivors were also asked whether they "currently have anxiety/fears as a result of [their] cancer, leukemia, tumor or similar illness, or its treatment?". Response options were "no anxiety/fears", "small amount of anxiety/fears", "medium amount of anxiety/fears", "a lot of anxiety/fears", or "very many, extreme anxiety/fears."

Pain attribution to cancer. Survivors were also asked whether they "currently have pain as a result of [their] cancer, leukemia, tumor or similar illness, or its treatment?" Response options were "no pain", "small amount of pain", "medium amount of pain", "a lot of pain", or "very bad excruciating pain."

Posttraumatic growth. Measured by Posttraumatic Growth Inventory (PTGI) (Tedeschi & Calhoun, 1996). The PTGI lists 21 positive changes and instructs respondents to indicate on a 6-point Likert-type scale (0 to 5) the degree to which the listed changes occurred in their lives following childhood cancer or similar illness. The PTGI yields a total score as well as scores on five subscales and has good reliability and validity: The full scale alpha for a sample of undergraduate students was .90, and the subscales' coefficients ranged from .67 to .85 (Tedeschi & Calhoun, 1996).

Posttraumatic stress. Measured by PTSD Symptom Scale-Self-Report version with 17 items (PSS-SR) (Foa, Riggs, Dancu, & Rothbaum, 1993). Subscale scores are calculated by summing symptoms in the re-experiencing (4 items), avoidance (7 items), and arousal (6 items) clusters. The total score alpha was .91 and subscale alphas (for re-experiencing, avoidance, and arousal) ranged from .78 to .82. In addition, one-month test-retest reliability for the total score was .74, while test-retest reliability for subscales ranged from .56 to .71 (Foa, Riggs, Dancu, & Rothbaum, 1993). The relationships among PSS subscales, PTGI subscales, and pain will be explored.

### **5.3.5 Pain variables:**

Use of medications for pain at time 1. All participants were asked whether they had used specific types of prescription pain medications either consistently for more than one month or for a total of 30 days in one year for the 2-year period preceding the administration of the baseline questionnaire. Examples of certain types of prescription pain medications were provided, and use of over the counter medications was not assessed. Response options included yes, no, and not sure. Missing or “not sure” responses will be collapsed with “no” responses.

Pain symptoms at time 1. On the baseline questionnaire, participants were asked whether they had “ever been told by a doctor or other health care professional” they “have or have had” any of the following pain conditions: “prolonged pain or abnormal sensation in arms, legs, or back,” “migraine,” or “other frequent headaches.” Participants were given response options of yes, no, or not sure. Non-response or “not sure” responses on these items are considered to indicate a lack of pain and will be collapsed together with “no” responses.

### **5.3.6 Health-related Quality of life**

At baseline, health related quality of life was indicated by one item N15 “state of health”. At follow-up 2, quality of life was measured by SF-36 items (item E1 to E 22). SF-36 is a widely used generic questionnaire to assess health-related quality of life (HRQoL). The SF-36 questionnaire is a self-administered, 36-item questionnaire that measures HRQoL across eight dimensions: physical functioning (PF), role limitations-physical (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations-emotional (RE), and mental health (MH). According to the originators of the SF-36, these eight dimensions can be grouped into two health subscales: the physical subscales (PF, RP, BP, GH) and the mental subscales (VT, SF, RE, MH). The responses to items within each dimension are summed and linearly transformed to produce dimension scores ranging from 0 (lowest well-being) to 100 (highest well-being). and two superordinate physical and mental health composite scores normed with a mean of 50 and a standard deviation (SD) of 10.

### **(5.4) Analysis approach, examples of tables and figures:**

Analytic approach for hypothesis 1.1: Initially, missing data analysis will be conducted to examine whether there are differences in pain as well as demographic and medical variables between those who returned follow-up 2 survey and those who did not. Since survivors and siblings were nested within families, mixed modeling will be used to compare pain between survivors and siblings in the CCSS cohort. In addition, we will also compare pain between survivors and siblings controlling for demographic and medical variables. The means obtained in

survivors for the sample as well as the means within gender and age groups will also be compared with U.S. normative values provided by Sf-36 manual using T-tests. Odds ratio will be calculated to capture the relative risk for survivors vs. siblings, for having pain and/or disability.

Analytic approach for hypothesis 1.2: Hierarchical regression will be used to examine the association between pain at time 2 and multiple factors at time 2 controlling for baseline pain symptoms, cancer diagnosis and treatment at time 1. Sequences of the sets of independent variables will be: Step 1 - baseline self-reported pain symptoms, cancer diagnosis and treatment, Step 2 - time 2 variables including demographic variables and health conditions, Step 3- time 2 variables including health behaviors and psychological factors. Whether the associations differ by survivor/sibling status will be explored by examining the interaction effect of survivor/sibling status and these multiple factors on pain.

Analytic approach for hypothesis 2.1: Hierarchical regression will be used to predict pain outcomes at time 2 from multiple factors at time 1 controlling for baseline pain symptoms. The first set of predictors will be baseline self-reported pain symptoms, the second set of predictors will be demographic variables, and the third set of predictors will be medical factors. Time interval between baseline and follow-up questionnaires will be controlled for as a covariate.

Analytic approach for hypothesis 2.2: Hierarchical regression will be used to predict pain outcomes at time 2 from multiple factors at time 1 controlling for baseline pain symptoms, demographic and medical variables. The first set of predictors will be baseline self-reported pain symptoms, the second set of predictors will be demographic variables, the third set of predictors will be medical factors, the fourth set of predictors will be use of pain medicine, the fifth set of predictors will be health behaviors and the last set of predictors will be psychological variables. Hypothesis 2.2 will be built on hypothesis 2.1 such that the testing of hypothesis 2.1 informs hypothesis 2.2 regarding which demographic and medical factors at time 1 should be controlled for.

Analysis approach for hypothesis 3: The hypothesized model is a mediational model in which the effects of medical and demographic variables on pain are mediated by the effects of health behaviors and psychological variables. In other words, the relationship between medical factors and pain at follow-up 2 and the relationship between demographic variables and pain at follow-up 2 are hypothesized to be at least partially explained by the effects of these variables on health behaviors and psychological factors at baseline, which in turn, have direct effects or indirect effects on pain via corresponding health behaviors and psychological factors at follow-up 2. The hypothesized model (see Figure 1) will be evaluated by structural equation modeling (SEM) using EQS 6.1 (Multivariate Software, Inc., 2003). The model will include a measurement model for the following latent factors: health behavior (i.e., extracting the latent factor from physical activity, tobacco use, and alcohol use), psychological distress (i.e., from depression, anxiety, and somatic distress), posttraumatic stress (i.e., from avoidance, arousal, and re-experiencing), pain symptoms at baseline (i.e., from pain/abnormal sensation, and headache), and pain at follow-up 2 (pain and disability). Dr. Qian Lu has training and experience in conducting SEM using EQS 6.1 (Tsao et al., 2006; Tsao et al. in press). These analyses will be performed by Qian Lu, with oversight provided by Wendy Leisenring at the Statistical Coordinating Center.





Table 2

Comparison of Bodily Pain (the total of Pain and Pain Disability) among Survivors, Siblings, and Normative Values

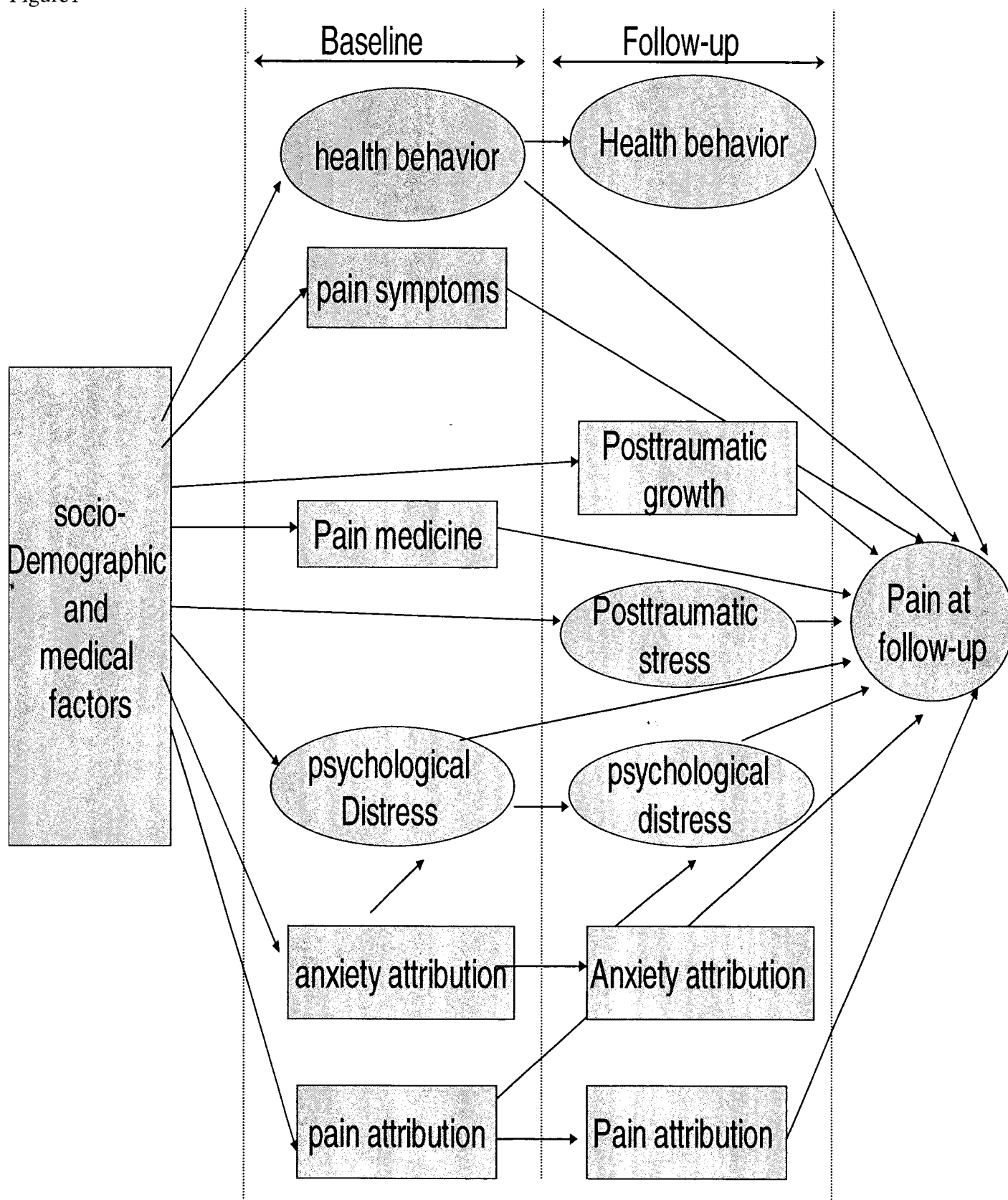
	Survivors (M± SD)	Sibling (M ± SD)	T	P	Normative value (M ± SD)	T	P
Total sample					75.15± 23.69		
Men					76.88± 22.97		
Women					73.59± 24.25		
Age 18-24					80.82± 21.33		
Age 25-34					81.35± 19.72		
Age 35-44					77.06± 22.11		
Age 45-54					73.12± 24.04		
Age 55-64					67.51± 25.63		
Age 65-74					68.49± 26.42		

Figure 1 · Conceptual Model: Sociodemographic and medical factors influence pain at long term follow-up via pain medicine, health behavior, psychological factors, and pain attribution

Note: For the simplicity of the figure, only one link is presented from sociodemographic factors/medical factors to outcome of interest. When SEM model is conducted, separate path coefficient of each factor (i.e., sex, ethnicity, age, income) will be estimated. Latent factors are in oval and measured variables are in square. Latent factors and indicators are:

Latent factor	Indicator
Pain at follow-up	Pain experience, and pain disability
Baseline health behavior	Smoking behavior, alcohol consumption, and physical exercise
Health behavior at follow-up	Smoking behavior, and physical exercise
Psychological distress	Depression, anxiety, and somatization
Posttraumatic stress	Avoidance, arousal, and re-experiencing

Figure 1





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