PAIN TRAJECTORIES AND SYMPTOMS OF SOCIAL ISOLATION AND LONELINESS IN LONG-TERM SURVIVORS OF CHILDHOOD CANCER

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1. Background and Rationale

Childhood cancer survivors face a multitude of long-term functional and health consequences. Due to the toxic cancer-directed therapies received during childhood, survivors often develop severe and disabling chronic health conditions and are at an increased risk for adverse late effects in multiple domains that impact both physical and mental functioning, and contribute to higher mortality rates[1-4].

The adverse outcomes associated with survivorship extend into social domains, where childhood cancer survivors often struggle to achieve normal levels of overall social attainment, including reporting lower educational and vocational achievements and more difficulty forming friendships and romantic relationships [1, 5-10]. Cancer diagnosis and treatment during childhood can disrupt critical developmental milestones, leaving survivors vulnerable to isolation, loneliness, and reduced social engagement[10, 11]. Research shows that survivors experience significantly more loneliness compared to the general population[12, 13]. In turn, elevated loneliness in adult survivors has been linked to poor future emotional, behavioral, and physical health outcomes[14], with lonely survivors reporting increased symptoms of somatization, anxiety, and depression[13], alongside a higher risk for suicidal ideation[13, 15]. Beyond mental health, social isolation and loneliness pose significant health risks that affect overall well-being and survival. Extensive research in the general population has shown that social isolation and loneliness are strongly associated with poor health outcomes, including over a 25% increased risk of premature death[16, 17]. Moreover, the impact of social disconnection extends to impact even neurobiological and systemic function, and has been associated with worsened cardiovascular function, impaired immune response, increased inflammation, diminished overall well-being, and increased rates of suicide, particularly in populations already burdened with chronic illness[18-21].

A late effect commonly observed in childhood cancer survivors is pain, which not only contributes to significant physical and emotional distress but may also worsen social difficulties[22, 23]. Chronic pain has been reported in up to 40% of survivors[24-28], with evidence linking pain in this population to poorer emotional and neurocognitive functioning[29-37]. Longitudinally, data from CCSS has identified trajectories of pain and pain interference in survivors, demonstrating that survivors are at increased risk for worsening pain and pain interference over time compared to sibling controls[25]. This, in turn, places them at higher risk for anxiety and depression[25]. Additionally, survivors with chronic pain are more likely to experience co-occurring severe chronic health conditions, reinforcing a cycle of pain and functional limitations that negatively impact multiple domains of life[25, 38, 39].

While the emotional and cognitive consequences of pain in survivors have been well-documented, the social ramifications remain understudied. Emerging evidence suggests that pain in long-term survivors is associated with poorer social outcomes, including lower educational attainment, unemployment, and single or

unmarried status[28]. However, little is known about the mechanisms underlying these associations or the full scope of social disruptions caused by pain in survivorship.

The biopsychosocial model of pain emphasizes that, beyond psychological factors, social factors also play a critical role in shaping pain experiences[40]. Social isolation and loneliness are not only correlated with chronic pain but may also exacerbate its severity through shared affective-motivational regions and neural mechanisms. Specifically, brain regions such as the dorsal anterior cingulate cortex and anterior insula, which are involved in processing physical pain, also regulate responses to social rejection[41-43]. This suggests a deeply interconnected relationship between chronic pain and social disconnection. Increased social support has been shown to buffer the negative impact of chronic pain by mitigating functional limitations[44]. Conversely, lower perceived social support is linked to greater pain intensity, pain interference, pain catastrophizing, anxiety, depression, and diminished quality of life[45, 46]. Emotional distress, which is well documented in survivorship, may further mediate the relationship between social disconnection and chronic pain outcomes, amplifying pain-related suffering[47].

Despite these clear links, the role of social isolation and loneliness in shaping pain experiences in survivors remains insufficiently explored. Survivors with pain may be at increased risk for social isolation and loneliness, which could, in turn, contribute to heightened pain intensity and interference. Given the potential bidirectional nature of this relationship, further investigation is warranted. In the current study, we aim to (1) evaluate the associations between pain and symptoms of social isolation and loneliness in long-term childhood cancer survivors and (2) evaluate how longitudinal pain trajectories may be associated with symptoms of social isolation and loneliness in survivorship. Building on prior evidence that chronic pain in survivors often co-occurs with severe chronic health conditions that contribute to functional limitations and reduced quality of life[25, 38, 39], this study will use exploratory analyses to examine how chronic conditions may contribute to symptoms of social isolation and loneliness in survivors with pain. We will also explore whether social isolation and loneliness mediate the relationship between pain and negative affect—specifically symptoms of anxiety and depression—during survivorship. Understanding the multifaceted interactions between chronic pain, social isolation, and psychological and health outcomes in childhood cancer survivors is essential for developing interventions that address both physical and social challenges faced by this population.

2. Specific Aims and Hypotheses

Aim 1. Examine associations between pain and symptoms of social isolation and loneliness (FU7) in adult survivors of childhood cancer.

Hypothesis 1: Survivors with pain will be at greater risk for symptoms of social isolation and loneliness compared to survivors without pain.

Aim 2. Examine how pain trajectories are associated with symptoms of social isolation and loneliness in adult survivors of pediatric cancer.

Hypothesis 2: Persistent or worsened pain and pain interference trajectories (FU4 to FU7; approximately 12 years) will be associated with greater risk of symptoms of social isolation and loneliness in survivors (FU7).

Exploratory Aims:

(1) Examine the impact of chronic health conditions on social isolation and loneliness in survivors across pain and pain interference trajectories.

(2) In survivors with persistent or worsened pain, evaluate whether social isolation and loneliness modify the association between pain and symptoms of depression and anxiety (FU7).

3. Analysis Framework

Inclusion criteria: This study will include CCSS study participants who completed FU7 for Aim 1, and Original Cohort participants who completed both FU4 and FU7 for the other aims.

1. Survivors must be at least 5 years from diagnosis and ≥ 18 years of age.

2. At FU7, survivors will need to have completed the PROMIS Social Isolation 4a questionnaire (L20) or the loneliness item from the BSI-18 (L6).
3. Survivors will need to provide data on at least one pain item (migraine [J3], headache [J4], cancer pain [L22], bodily pain [N7]) and pain interference (N8) from the SF-36 at FU7, and at FU4 for Aim 2.
4. For Exploratory Aim 2, survivors will also need to have completed the BSI-18 (L1-18).

Exclusion criteria:

1. Questionnaires completed by proxy-report will be excluded from this study.
2. Survivors reporting “None to mild” pain with “moderate to extreme” interference (as this likely indicates misclassification; see Proposal Table 1).

Predictors:

Cross-sectional analysis: Cross-sectional analysis of ***pain*** at FU7 will be determined via self-report by survivors indicating at least one of the following:

a. migraine (yes/no, where yes is defined as a response of “yes, and the condition is still present”) (J3)
b. other severe headaches (yes/no, where yes is defined as a response of “yes, and the condition is still present”) (J4)
c. cancer-related pain (yes/no, where no is defined as a report of “no pain” or “small amount of pain”, and yes is defined as a response of “medium amount of pain”, “a lot of pain”, or “very bad, excruciating pain”) (L22)
d. bodily pain via SF-36 Item 21 (yes/no, where no is defined as a report of “none”, “very mild” or “mild” pain and yes is defined as “moderate”, “severe”, or “very severe” pain) (N7)

Pain interference will be evaluated via self-report from the SF-36 Item 22 (N8) (“During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?”), where answers range on a 5-point Likert scale (“not at all”, “a little bit”, “moderately”, “quite a bit”, “extremely”). Pain interference will be defined as a report of moderate to extreme interference.

Cross-sectional pain status groups will be established based on responses to pain and pain interference. Pain status will be established based on responses to migraine (J3), headaches (J4), cancer-related pain (L22), and bodily pain (N7). Pain interference status will be established based on responses of pain interference levels over the past 4 weeks (N8). Final cross-sectional pain groupings will include (1) no pain, (2) pain without interference, (3) pain with interference, and (4) no pain with interference. The "no pain with interference" group will be excluded to reduce misclassification bias, as reports of pain interference without concurrent pain may reflect measurement or recall error, which could confound group comparisons. Pain and pain interference criteria for each of the pain status groups can be found in Proposal Table 1.

Proposal Table 1. Cross-sectional pain status groups based on pain criteria (migraine, headache, cancer-related pain, and bodily pain) and pain interference criteria.

Pain Group	Description	Pain Criteria	Pain Interference Criteria
No Pain	None to mild pain with no to little interference	“None” to “mild” bodily pain AND no migraines AND no headaches AND no cancer-related pain	“None” or “a little”
Pain without Interference	Moderate to severe bodily pain, or report of migraines, headaches, cancer-related pain, with none to little interference	“Moderate” to “Very severe” bodily pain, OR yes migraines OR yes headaches OR yes cancer-related pain	“None” or “a little”
Pain with Interference	Moderate to severe bodily pain, or report of migraines, headaches, cancer-	“Moderate” to “Very severe” bodily pain, OR yes migraines OR	“Moderate” to “Extremely”

	related pain, with moderate to extreme interference	yes headaches OR yes cancer-related pain	
No Pain with Interference (excluded from analyses)	None to mild pain with moderate to extreme interference	"None" to "mild" bodily pain AND no migraines AND no headaches AND no cancer-related pain	"Moderate" to "Extremely"

Longitudinal analysis: Using past CCSS definitions/methods[25], *pain and pain interference trajectories* will be determined from FU4 to FU7 using severity grades of cross-sectional pain status groups (Proposal Table 1). Trajectories will be categorized as (1) None/Decreasing pain, which will include no pain, decreased pain with persistent no interference, decreased pain and interference, and persistent pain with decreased interference, (2) Persistent pain, which will include persistent pain with interference and persistent pain without interference, or (3) Increasing pain, which will include persistent pain with increased interference, increased pain and increased interference, or increased pain with persistent lack of interference. Survivors who indicate no pain with some grade of interference (no pain with interference group) will be excluded from the longitudinal analyses to reduce potential misclassification bias. Specific criteria for categorization of pain trajectories based on changes in cross-sectional pain status groups can be found in Proposal Table 2.

Proposal Table 2. Pain and pain interference trajectory criteria based on transitions in cross-sectional pain status groups from FU4 to FU7.

Pain Trajectory Group	**Description**	**Pain Status Transition** (FU4 → FU7)
None/Decreasing Pain	- Pain decreases from FU4 to FU7 - No pain at either FU4 or FU7	- Pain with interference → pain without interference or no pain - Pain without interference → no pain - No pain → no
Persistent Pain	- Pain remains the same from FU4 to FU7	- Pain with interference → pain with interference - Pain without interference → pain without interference
Increasing Pain	- Pain increases from FU4 to FU7	- No pain → Pain with interference - No pain → Pain without interference - Pain without interference → Pain with interference

Primary Outcomes

Social isolation will be assessed at FU7 and measured using the PROMIS Social Isolation 4a scale. Responses range on a 5-point Likert scale anchored by "Never" to "Always". Socially isolated will be defined as + 1 SD from the general population PROMIS normative sample mean (T-scores ≥ 60).

Loneliness will be assessed at FU7 and measured using a single item from the Brief Symptom Inventory-18 (L6) where responses range on a 5-point Likert scale ("not at all," "a little bit," "moderately," "quite a bit," and "extremely"). Participants who endorse moderate to extreme loneliness at FU7 will be considered to feel lonely.

Secondary Outcomes

Depression and *anxiety* will be assessed at FU7 using subscales from the BSI-18, where responses range on a 5-point Likert scale anchored by "Not at all" to "Extremely". The variable will be expressed as a categorical variable, where presence/absence emotional distress will be defined as + 1 SD from the general population BSI-18 normative sample mean (T-scores ≥ 60).

Covariates and Demographics

Data for the following sociodemographic, clinical, treatment, and health-related factors will be extracted. All models will be adjusted for age at FU7, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, chronic health conditions at FU7, and physical activity at FU7. Note: Diagnosis and treatment exposures will not be included as covariates in the same models due to their association, in order to reduce potential confounding effects.

Sociodemographic features**:**

- Race/ethnicity (White/non-Hispanic, Black/non-Hispanic, Hispanic, others)
- Sex
- Household income (< $20,000, $20,000 - $60,000, > $60,000)
- Marital status (Marital history [married, living as married, widowed, divorced, separated] vs. single never married)
- Education at FU7 (College graduate [college graduate/post graduate level] vs. high school graduate [completed high school, training after high school, some college] vs. less than high school [1-8 years, 9-12 years but did not graduate]).
- Employment at FU7 (full-time [working full-time, student, caring for family] vs. other)
- Insurance at FU7 (none, public, private)

- Clinical features:
  - Age at diagnosis
  - Age at evaluation
  - Time since diagnosis
  - Diagnosis (acute lymphoblastic leukemia, acute myeloid leukemia, other leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, CNS tumor, bone cancer or sarcoma, neuroblastoma, Wilms tumor, other embryonal non-CNS solid tumor)
- Treatment exposures:
  - Surgery (yes vs. no)
  - Radiation: We will consider binary (yes/no) as well as dose category (none, <30 Gy, or ≥ 30 Gy) for cranial and non-cranial
  - Chemotherapy: We will consider cumulative dose, dichotomous variables, and dose categories as available and appropriate: vincristine, methotrexate, anthracyclines, alkylating agents, corticosteroids, platinum agents
- Health-related factors
  - Physical activity at FU7 (Met CDC guidelines [< 150 weekly minutes of moderate-intensity aerobic activity or < 75 weekly minutes of vigorous-intensity aerobic activity] vs. did not meet CDC guidelines)
  - Heavy/risky drinking (≥ 5 drinks per day or 14 drinks per week for men; ≥ 4 drinks per day or 7 drinks per week for women)
  - Smoking status (current, ever, never)
  - Illicit drug use (current ["past week", "past month" = use within the past month], former ["past tear", "more than a year ago" = previous, but not current use], "never" = never used)
  - Chronic health conditions by FU7 (presence of CTCAE grade 3-4 in any organ system [yes/no])

Statistical Analysis

Frequency distributions will be generated to categorize relevant outcome variables, predictors and covariates according to a prior and/or reasonable grouping based on observed distributions. Descriptive statistics

including means, standard deviation, medians, ranges, frequencies, and percentages will be calculated for all outcomes, predictors and covariates. Given the longitudinal aims, participation at FU's will be examined for the potential need of inverse probability weighting. As a sensitivity analysis, the analyses below will be replicated using inverse probability weighting to adjust for the selective participation of FU7 (Aim 1) or FU4 and FU7 (Aim 2 and Exploratory Aims). The propensity scores will be estimated using multivariable logistic regression models in all CCAA cancer survivor participants (for Aim 1) and CCSS Original Cohort cancer survivor participants (for the other aims), adjusting for sex, treatment era, age at baseline survey, and cancer diagnosis.

Aim 1. Examine associations between pain and symptoms of social isolation and loneliness (FU7) in adult survivors of childhood cancer. For this analysis, survivor data from FU7 only will be considered. Multivariable logistic regression will be used to examine the association between pain and symptoms of social isolation and loneliness while adjusting for age at FU7, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, chronic health conditions at FU7, and health behaviors at FU7.
a. Predictor: Pain at FU7

b. Outcomes: Social isolation at FU7 (yes/no), loneliness at FU7 (yes/no)

c. Covariates: age at FU7, time since diagnosis, sex, race/ethnicity, diagnosis and/or treatment exposures (separate models), presence of CTCAE grade 3-4 chronic health conditions at FU7 (yes/no), and health behaviors at FU7

Aim 2. Examine how pain trajectories are associated with symptoms of social isolation and loneliness in adult survivors of pediatric cancer. For this analysis, survivors' pain trajectories will be determined by evaluating changes in pain and pain interference reports from FU4 to FU7. Symptoms of social isolation and loneliness will be considered from FU7. To evaluate the association between longitudinal pain trajectories (FU4 to FU7) and symptoms of social isolation and loneliness (FU7) a multivariable logistic regression will be used, while adjusting for age at FU7, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, chronic health conditions at FU7, and health behaviors at FU7.

a. Predictor: Pain trajectory (Pain and pain interference from FU4 to FU7: None/decreasing pain, persistent pain, increasing pain [see Proposal Table 2])
b. Outcomes: Social isolation at FU7, loneliness at FU7
c. Covariates: age at FU7, time since diagnosis, sex, race/ethnicity, diagnosis and/or treatment exposures (separate models), chronic health conditions at FU7, and health behaviors at FU7

Exploratory Aims:

1. In survivors with persistent or worsened pain, examine the impact of chronic health conditions on social isolation and loneliness. In subgroups of survivors with persistent and increasing pain, multivariable linear regression models will be used to examine the association between CTCAE grades of CHCs and social isolation and loneliness, adjusting for age at FU7, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, chronic health conditions at FU4, and health behaviors at FU7 (Table 5). Chronic health conditions will be evaluated categorically (none, grades 1-2, grades 3-4) for each of the following systems: endocrine, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological.

a. Predictor: Presence of CTCAE grade 3-4 chronic health conditions at FU7 among survivors with persistent/increasing pain

b. Outcomes: Social isolation at FU7, loneliness at FU7

c. Covariates: age at FU7, time since diagnosis, sex, race/ethnicity, diagnosis and/or treatment exposures (separate models), chronic health conditions at FU4, and health behaviors at FU7

2. In survivors with persistent or worsened pain, evaluate the mediating effects of social isolation and loneliness on symptoms of depression and anxiety (FU7). In subgroups of survivors with persistent and increasing pain, mediation analysis using structural equation modeling will be used to assess whether social isolation and loneliness mediate the relationship between pain trajectories and anxiety and depression, adjusting for age at FU7, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, chronic health conditions at FU4, and health behaviors at FU7 (Table 6). Only significant associations between pain trajectories and social isolation and loneliness will be included in the mediation analyses (Figure 1). Separate

models will be used for each mediator (social isolation and loneliness) and outcome (depression and anxiety). Because the loneliness item from the BSI-18 contributes to the depression subscale, that item will be treated as missing, and the imputation approach described in the BSI-18 manual will be used to derive the depression scale score (Derogatis, L. R. (2001). *BSI 18, Brief Symptom Inventory 18: Administration, scoring and procedures manual*. NCS Pearson, Incorporated.).

a. Predictor: Persistent/increasing pain trajectory (FU4 to FU7)

b. Outcomes: BSI-18 anxiety and depression (FU7)

c. Mediators: Social isolation at FU7 and loneliness at FU7 (if significantly associated with persistent/increasing pain trajectory)

d. Covariates: age at FU7, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, chronic health conditions at FU4, and health behaviors at FU7

Suggested Tables

Table 1. Demographic, clinical, chronic health conditions, and health behavior factors of survivors across pain and pain interference status.

	Pain with interference (n =)	**Pain without interference (n =)**	**No Pain (n =)**	**Overall (N =)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age at diagnosis (years)				
Age at FU7 evaluation (years)				
Time since diagnosis (years)				
	n (%)	**n (%)**	**n (%)**	**N (%)**
Sex				
Male				
Female				
Race/ethnicity				
White, non-Hispanic				
Black, non-Hispanic				
Hispanic				
Other				
Marital Status				
Single/never married				
Ever married				
Employment Status				
Full-time				
Part-time/unemployed				
Educational Attainment				
< High school				
High school graduate				
≥ College graduate				
Health Insurance				
None				
Public				
Private				
Diagnosis				
Leukemia				
CNS tumor				
Lymphomas (HL, NHL)				
Wilms, neuroblastoma, soft tissue sarcoma				
Ewing sarcoma or osteosarcoma				
Surgery				
None				
Amputation				
Limb-sparing				
Other				
Radiation Site				
None				
Head				

Neck	
Chest	
Abdomen	
Pelvis	
Limb	
Other	
Chemotherapy	
None	
Vinca alkaloids	
Platinum	
IV methotrexate ≥ mg/m^2	
IT methotrexate	
Anthracyclines	
Corticosteroids	
Chronic Health Conditions (CTCAE grade 3-4)	
Yes	
No	
Heavy/risky Drinking	
Yes	
No	
Smoking	
Never	
Former	
Current	
Physical Activity	
Did not meet CDC guidelines	
Met CDC guidelines	

Abbreviations: SD, standard deviation"

Note: Pain defined as “moderate to severe” bodily pain; pain interference defined as “moderate to extreme” interference.

Table 2. Prevalence of social isolation, loneliness, depression, and anxiety in survivors with and without pain at follow up.

	Pain with interference (N =)	**Pain without interference (N =)**	**No pain (N =)**
	N (%)	**N (%)**	**N(%)**
Socially isolated			
Yes			
No			
Lonely			
Yes			
No			
Depression			
Yes			
No			
Anxiety			
Yes			
No			

Note: Pain defined as “moderate to severe” bodily pain; pain interference defined as “moderate to extreme” interference

Table 3. Prevalence of social isolation and loneliness in survivors across pain trajectories from FU4 to FU7.

	Socially isolated (N =)	**Lonely (N =)**
	N (%)	**N(%)**
Pain trajectory		
None/decreasing		
Persistent		

Increasing	

Table 4. Associations between cross-sectional pain reports and longitudinal pain trajectories and symptoms of social isolation and loneliness.

Variable	Social Isolation		Loneliness	
	OR	**95% CI**	**OR**	**95% CI**
Pain				
No pain	Ref.	Ref.	Ref.	Ref.
Pain without interference				
Pain with interference				
Changes in pain				
None/Decreasing	Ref.	Ref.	Ref.	Ref.
Persistent pain				
Increasing pain				

Abbreviations: CI, confidence interval; OR, odds ratio. Multivariable logistic regression models adjusted for age at follow-up, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, chronic health conditions at follow-up, and health behaviors at follow up. Bold font indicates statistically significant results. Pain defined as “moderate to severe” bodily pain; pain interference defined as “moderate to extreme” interference.

Table 5. Associations between chronic health conditions and symptoms of social isolation and loneliness in survivors with persistent or increasing pain.

	Social Isolation		Loneliness	
	OR	**p-value**	**OR**	**p-value**
Persistent pain				
Grades 3-4				
Yes				
No				
Increasing pain				
Grades 3-4				
Yes				
No				

Multivariable logistic regression models adjusted for age at follow-up, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, and health behaviors at follow up. Bold font indicates statistically significant results.

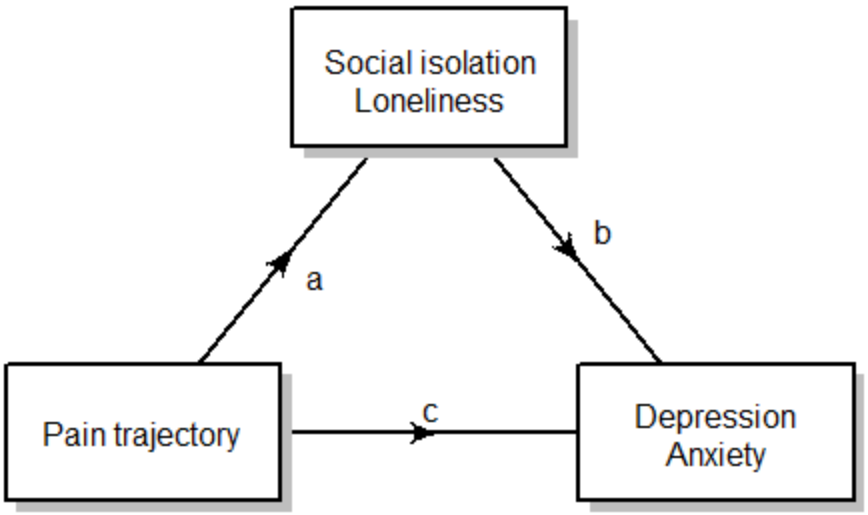

Figure 1. Proposed associations for each mediation model. Each analysis will be run as a separate model (e.g., Pain trajectory, social isolation, depression), and significant associations between pain trajectories and symptoms of social isolation and loneliness will inform which will be included as mediators. All models will be adjusted for age at follow-up, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, chronic health conditions at follow-up and health behaviors at follow-up.

Table 6. Social isolation, loneliness, and chronic health conditions as mediators of the relationship between pain trajectories and anxiety and depression in survivors.

		Direct Effect		Indirect Effect		Total Effect	
Outcome Measure	**Predictor**	**Coefficient (SE)**	**P-value**	**Coefficient (SE)**	**P-value**	**Coefficient (SE)**	**P-value**
Mediator: Social isolation							
Depression	Persistent pain						
	Increased pain						
Anxiety	Persistent pain						
	Increased pain						
Mediator: Loneliness							
Depression	Persistent pain						
	Increased pain						
Anxiety	Persistent pain						
	Increased pain						
Mediator: Chronic health conditions (grade 3-4)							
Depression	Persistent pain						
	Increased pain						
Anxiety	Persistent pain						
	Increased pain						

Abbreviations: SE, standard error. Mediation models adjusted for age at follow-up, time since diagnosis, sex, race/ethnicity, diagnosis, treatment exposures, chronic health conditions at follow-up, and health behaviors at follow-up. Bold font indicates statistically significant results.

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