

Study title: Post-Traumatic Growth (PTG) and Life Satisfaction (LS) as Predictors of Long-Term Functioning in Childhood Cancer Survivors

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Background and rationale:

Despite improvements in cure rates over the last several decades,¹ a considerable proportion of childhood cancer survivors will experience long-term impairments in functioning. These can occur across cognitive, emotional, physical, and socioeconomic domains. Over 20% of survivors demonstrate cognitive impairment, with deficits in attention, processing speed, executive function, memory, and emotional regulation.²⁻⁴ Significant subsets of survivors experience increased risk of global distress, depression, anxiety, post-traumatic stress symptoms, and suicidal ideation relative to siblings and their peers.⁵⁻⁸ Survivors face elevated risks of cardiovascular disease,⁹ pulmonary disease,¹⁰ and musculoskeletal problems¹¹ compared to peers in the decades following cure, leading to limitations in performing physical activities of daily life.^{12,13} Survivors are less likely to attain a college degree (OR 0.79), be employed full-time (OR 0.39), or be married/partnered (OR 0.69), and are more likely to be unemployed (OR 1.89) and live with a parent (OR 3.34) compared to matched controls, with delayed psychosexual development, lower rates of marriage, and non-independent living also well documented.^{14,15}

Cognitive, emotional, physical, and adult social and economic outcomes in survivors may be influenced by both the direct toxic effects of cancer therapies and by disruptions to normal behavioral development when cancer occurs during childhood.¹⁶ The vast majority of survivorship research has focused on identifying risk factors for poor outcomes rather than factors that promote positive adaptation.¹⁴ However, emerging evidence highlights the importance of protective factors in considering long-term functioning outcomes in survivors, including self-esteem, social support, acceptance, courageous coping, hope, positive affectivity, and school connectedness.¹⁷⁻¹⁹ Importantly, survivors themselves express a desire for this type of research. They want more support and concrete resources for their emotional well-being as they navigate the transition to survivorship.²⁰⁻²² A recent 2025 international guideline from the European Youth Cancer Network (EU-CAYAS-NET) explicitly recommends that survivorship care "should adopt a strength-based approach, focusing on positive and feasible outcomes for young survivors rather than rigid pathways" to actively promote overall wellbeing.²³

Post-traumatic growth (PTG) and life satisfaction (LS) are two potentially important psychosocial resilience factors that have been understudied in childhood cancer survivors. PTG refers to positive psychological change that a person perceives to arise after a major life crisis.²⁴ One established measurement tool is the Posttraumatic Growth Inventory (PTGI), which assesses domains such as relating to others, new possibilities, personal strength, spiritual change, and appreciation of life.²⁵ LS, in contrast, reflects a person's self-evaluation of his or her life as a whole. One measurement tool frequently used is Cantril's Ladder, a three-item scale on which respondents place their current, past, and future lives on one of 10 ladder "rungs" from the "worst possible" (bottom rung) to the "best possible" (top rung).²⁶ Both PTG and LS have previously been assessed as part of Childhood Cancer Survivor Study (CCSS) analyses. Early work showed that most survivors report favorable life satisfaction and good overall psychological well-being.^{27,28} Subsequent analyses examined these constructs more in-depth: Klosky et al. evaluated PTG in relation to post-traumatic stress symptoms, demonstrating that growth and distress can coexist rather than representing opposite ends of a single continuum.²⁹ In CCSS participants diagnosed as adolescents, Weinstein et al. reported higher LS was associated with better perceived emotional and physical health, whereas PTG was closely linked to perceiving cancer as having had a positive impact on life.³⁰

Outside childhood cancer, the broader literature suggests that PTG is associated with higher positive well-being and lower negative well-being in trauma-exposed populations living with serious chronic disease.^{31,32} In population-based studies, higher LS has been linked to superior psychosocial, behavioral, and physical health outcomes in late adulthood.³³ Additionally, a population-based Canadian cohort (N=73,904) showed that low LS was an independent risk factor for developing chronic disease (HR 1.70; 95% CI: 1.16–2.51) and death (HR 1.59; 95% CI: 1.15–2.19), even after adjusting for sociodemographic, behavioral, and clinical confounders.³⁴ Although PTG and LS are both indicators of positive adaptation, they capture distinct psychological constructs. Considering these constructs jointly may identify complementary patterns of resilience that are not apparent when each is examined independently. Furthermore, neighborhood environments may shape long-term functioning by influencing opportunities for social engagement, physical activity, access to healthcare, and other health-promoting resources. These contextual factors may strengthen or weaken the ability of survivors with similar psychological resilience profiles to translate PTG and LS into favorable cognitive, emotional, physical, and socioeconomic outcomes.

The purpose of this study is to evaluate whether PTG and LS serve as meaningful predictors of long-term cognitive, emotional, physical, and individual-level adult social and economic outcomes in survivors of childhood cancer. Leveraging longitudinal data from the Childhood Cancer Survivor Study (CCSS), we will move beyond traditional variable-centered approaches by using cluster-based methods to identify distinct survivor profiles characterized by patterns of PTG and LS at Follow-Up 2 (FU2). We hypothesize that these multidimensional PTG/LS profiles will more strongly predict long-term functioning outcomes than either construct alone or when examined as isolated subcomponents. We will further examine demographic, disease- and treatment-related factors that may interact with these profiles to better understand their effects. Recognizing that survivorship outcomes are shaped by broader contextual influences, we will evaluate whether neighborhood-level characteristics modify associations between PTG/LS profiles and long-term functioning. Finally, we will assess whether modifiable health behaviors—including healthcare engagement, physical activity, sleep, and substance use—further influence these relationships. The goal of this study will be to identify potentially modifiable factors associated with resilience and favorable long-term functioning in survivors, thereby informing future interventions and survivorship care strategies that extend beyond risk mitigation to actively foster positive adaptation.

Specific aims/objectives/research hypotheses

Aim 1: Characterize long-term cognitive, emotional, physical, and individual-level adult social and economic outcomes (see definitions of each below in **Outcome(s) of interest**) in childhood cancer survivors from CCSS based on cluster profiles of PTG and LS at FU2 using responses from their modified PTGI and Cantril's Ladder questionnaires.

***Aim 1 Hypothesis:** Cluster profiles derived from jointly modeling PTG and/or LS at FU2 will better characterize our four long-term functioning outcomes (see below under "Outcome(s) of interest") than analyses considering PTG or LS measures separately.*

Aim 1.1: Determine which profiles of PTG and LS best characterize our four long-term functioning outcomes

Aim 1.1.1: Identify and characterize distinct cluster profiles of PTG and LS, both separately and combined. This will determine how/if PTG and LS are correlated.

Aim 1.1.2: Evaluate associations between said clusters with our four long-term functioning outcomes

Aim 1.1.3: Compare the explanatory value of PTG/LS cluster profiles with PTG and LS considered separately.

Aim 1.2: Determine sociodemographic- and cancer-related factors (e.g., diagnosis and treatment-related variables) associated with PTG/LS cluster profiles.

Aim 2: Investigate how neighborhood-level characteristics—including social cohesion, green space, walkability, access to healthy food (grocery store/supermarket availability), availability of healthcare resources/facilities (composite variable), and overall neighborhood social

vulnerability as measured by the Social Vulnerability Index (SVI)—modify associations between PTG/LS cluster profiles and our four functioning outcomes.

Aim 2 Hypothesis: *Neighborhood-level characteristics are hypothesized to modify associations between PTG/LS cluster profiles and long-term functioning outcomes. Because characteristics such as green space, walkability, and social cohesion may not uniformly benefit all survivors and may operate differently across urban and rural settings, we do not assume in advance that higher levels of any given characteristic are protective; the direction and magnitude of each association will instead be treated as an empirical question, interpreted with reference to prior literature specific to each measure.*

Aim 3: Evaluate modifiable health behaviors (e.g., substance use, sleep, healthcare engagement, and physical activity) as moderators of the relationship between PTG/LS cluster profiles and our four long-term functioning outcomes. These models will include the same sociodemographic- and treatment-related covariates as **Aim 1** and will additionally adjust for neighborhood-level contextual variables examined in **Aim 2**.

Aim 3 Hypothesis: *Healthy behaviors—including greater healthcare engagement, regular physical activity, adequate sleep, and abstinence from substance use—will amplify positive associations between PTG/LS cluster profiles and our four long-term functional outcomes.*

Analysis framework

Outcome(s) of interest: Our four long-term functioning outcomes will be measured at the latest/most recent timepoint that a CCSS survivor has data. For example, the CCSS Neurocognitive Questionnaire was administered at FUs 5-8, and we will take the latest/most recent FU survey (e.g., FU8) that a survivor completed. Because our four functioning outcomes are measured at survivors' latest available FU survey (FU5-FU8), we will describe the distribution of baseline (FU2) status for each outcome where available and will conduct a sensitivity analysis restricting to survivors without the outcome present at FU2 (e.g., new-onset impairment) to address confounding by baseline functioning. Definitions and timepoints assessed are as follows:

- 1. Cognitive functioning:** Will measure using the CCSS Neurocognitive Questionnaire (FU5 Q1-33; FU6 long version G1-33; FU7 P1-33; FU8 long version C1-33). In keeping with prior studies, a total raw score will be calculated (range 8–24) for each of the four domains (emotional regulation, task efficiency, memory, and organization), then converted to a Z-score per scoring instructions, with higher Z-scores corresponding to worse neurocognitive scores.³⁵ Also consistent with previous studies, this variable will be dichotomized as “impairment” versus “no impairment”, with impairment defined as a Z-score >1.5 for the entire CCSS-NCQ (corresponding to the worst 10th percentile of scores based on healthy control age-adjusted norms).³⁵
- 2. Emotional functioning:** Will measure using the Brief Symptom Inventory, 18 item (BSI-18; FU5 L1-18; FU7 L1-18), a self-report questionnaire specifically designed to screen for psychological distress symptoms experienced in the previous seven days.³⁶ It has previously been validated for use in the CCSS cohort.^{28,37} In addition to subscale scores

for depression, anxiety, and somatic symptoms, the questionnaire provides a summary score, the Global Severity Index (GSI), which helps measure overall psychological distress.³⁶ For our study, we measure GSI, depression, and anxiety subscales. In keeping with prior CCSS studies, we will take the raw depression subscale, anxiety subscale, and total BSI-18 raw scores and transform them into T-scores based on sex-specific population norms. The T-scores will then be dichotomized, with a T-score ≥ 65 classifying a participant as being positive for emotional distress (GSI), depression (depression subscale), and/or anxiety (anxiety subscale) at the given FU survey.³⁷

3. **Physical functioning (frailty):** Will measure using the modified Fried frailty criteria³⁸ previously defined using CCSS questionnaires by Hayek et al (able to calculate from FU5 and FU7 survey variables).³⁹ These modified criteria include: 1) low lean muscle mass (defined by BMI or unintentional weight loss); 2) exhaustion (from the Short Form (SF)-36 vitality subscale); 3) low energy expenditure (by converting frequency and duration of low, moderate and vigorous physical activity levels into kilocalories); 4) slowness (limitations in walking uphill/upstairs, or limitation in walking one block); 5) weakness (“have you ever been told that you have, or have had weakness or inability to move arms”). Consistent with previous CCSS studies, survivors will be categorized as non-frail (0-1 frailty criteria met), pre-frail (2 frailty criteria met), and frail (3 or more frailty criteria met).
4. **Individual-level adult social and economic outcomes:** Within this domain, we will examine three separate outcomes measured at FU5 and/or FU7, rather than combining them into a single dichotomous composite, so that no single component determines an overall classification:
 - a. Employment status: Dichotomized as full-time employment (working full time; student; caring for family) vs. other
 - b. Independent living: Dichotomized as yes (live with spouse/partner, alone, with roommates) vs no
 - c. Insurance coverage: Because insurance status is influenced by employment, disability, age, state policy, and the healthcare system, and because all Canadian participants are automatically classified as insured, a simple insured/uninsured measure will not be used. Instead, we will characterize type and consistency of coverage (e.g., employer-sponsored, public, marketplace, or none; continuous vs. interrupted) within the U.S. subsample as the primary analysis, modeling country as a stratifying variable, with country-stratified sensitivity analyses reported separately rather than pooled

Employment status, independent living, and insurance coverage will be examined as three separate outcomes rather than combined into a single dichotomous functioning/non-functioning composite. These three domains were selected because each reflects a discrete and clinically meaningful dimension of adult role attainment that has been previously identified as a long-term survivorship concern, and together they capture distinct economic, residential, and healthcare access aspects of adult outcomes. Examining them separately avoids requiring a survivor to meet criteria across all three domains for a single overall classification, since one component (e.g., insurance coverage, which is shaped by factors such as state policy) could otherwise determine the overall classification independent of the other two domains.^{40,41} As a secondary, descriptive measure only, we will also report a count of how many of the three domains

each survivor meets (0-3); this count will not be dichotomized into an overall functioning classification or used as a primary outcome. We will report the proportion of survivors who meet criteria for each individual component and each combination of components, providing transparency about the distribution of attainment across the cohort.

Exposure(s) of interest: We will examine responses to FU2 questionnaires assessing PTG (PTGI) and LS (Cantril's Ladder). In addition to calculating global raw scores and reporting median/IQR/ranges for each of these questionnaires, we will calculate subscale scores for the PTGI and categorize survivors into LS subgroups as follows:

- PTG subscales⁴²
 - New possibilities (items 3, 7, 11, 14, 17)
 - Relating to others (items 6, 8, 9, 15, 16, 20, 21)
 - Personal strength (items 4, 10, 12, 19)
 - Spiritual change (items 5, 18)
 - Appreciation of life (items 1, 2, 13)
- LS subscales^{26,43-46}
 - Thriving (current LS rating of 7 or higher AND future LS rating of 8 or higher)
 - Suffering (current AND future LS rating of 4 or lower)
 - Struggling (everyone else not meeting “thriving” or “suffering” criteria)

Subject population to be included: We will include CCSS survivors from the original cohort who:

- Were ≥ 5 years old at cancer diagnosis: This will ensure autobiographical memory of their cancer experience, which is a prerequisite for valid measurement of PTG. See eligibility rationale below.
- Have PTGI and/or Cantril's Ladder data available at FU2.
- Have data available at ≥ 1 FU survey for our four long-term functioning outcomes of interest (see above)

A minimum age at diagnosis of five years is required to ensure that survivors retain autobiographical memory of their cancer experience, which is a necessary prerequisite for valid PTG measurement. Autobiographical memory develops gradually across the preschool years through processes of social interaction and cognitive development, with consolidation occurring by approximately age five.^{47,48} However, it is important to distinguish autobiographical recall from the higher-order cognitive processing that PTG requires. Tedeschi and Calhoun's foundational model posits that PTG emerges from significant cognitive engagement with threatened or disrupted belief structures,⁴⁹ and some authors have suggested that the cognitive capacities specifically relevant to PTG may not fully emerge until early adolescence.⁵⁰ Accordingly, while age 5 at diagnosis ensures that survivors can meaningfully recall their cancer experience, we acknowledge that full PTG-related cognitive processing capacity likely develops later. As a sensitivity analysis, we will examine whether PTG/LS cluster profiles and their associations with long-term functioning differ by age at diagnosis (e.g., diagnosed at age 5-10 versus 11 and older), which will allow us to assess whether younger age at diagnosis moderates the validity or predictive utility of PTG measurement in this cohort.⁵¹⁻⁵³

Exploratory variables: We have grouped these variables of interest according to our specific aims noted above. For fixed variables not expected to change with time (e.g., age at diagnosis, cancer diagnosis), the value will be taken from participants' Baseline survey. For those that could change over time (e.g., smoking), temporality will be assured by taking the value that occurred between FU2 and the next FU survey the participant completed (ex., measuring smoking at FU4 and frailty at FU5/7):

1. **Aim 1 – Sociodemographic- and cancer-related factors:**

- Age at diagnosis and FU2 completion (when PTG/LS assessed)
- Sex (female/male)
- Race/ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, other)
- Cancer diagnosis
- Cancer treatments: Radiation therapy (total body irradiation (TBI), head, neck, chest, abdomen, pelvis, legs, arms – yes/no; cumulative Gy), surgery (brain, thoracic, laparotomy, amputation, limb-sparing, splenectomy, nephrectomy – yes/no), hematopoietic stem cell transplant (yes/no), alkylating agents (yes/no; total cumulative Cyclophosphamide-equivalent mg/m² dose), anthracyclines (yes/no; total cumulative Doxorubicin-equivalent mg/m² dose), Platinum agents (yes/no, total cumulative mg/m² dose), epipodophyllotoxins (yes/no, total cumulative mg/m² dose), vinca alkaloids (yes/no, total cumulative mg/m² dose), and glucocorticoids (yes/no, total cumulative mg/m² dose)
- Chronic health conditions (Grade 3-4 only): To capture this potential confounder, we will include it as a dichotomous covariate in analysis (“Chronic health conditions – yes/no”)⁵⁴

2. **Aim 2 – Neighborhood-level characteristics:** Geocoded residential address data are available in CCSS only at baseline, FU5, and FU7 (not at FU2). Per consultation with the CCSS Data Coordinating Center, because these neighborhood characteristics are proposed as effect modifiers of the PTG/LS-outcome association (for which an earlier-measured exposure is preferable), the following constructs will be measured using the baseline residential address as a proxy for the FU2 exposure window, treating residential mobility between baseline and the outcome assessment as a potential mediator rather than an effect-modification concern. As a sensitivity analysis, we will repeat these analyses using the FU5/FU7 address closest to the outcome assessment window and will report the proportion of survivors who moved and the concordance between the two addresses:

- Social cohesion: Measured using the U.S. Joint Economic Committee (JEC) Social Capital Index (SCI), a county-level composite measure of neighborhood social cohesion that captures family unity, community health, institutional health, and collective efficacy. Higher SCI scores indicate greater neighborhood social connectedness and social capital.⁵⁵
- Green space: Measured using the Normalized Difference Vegetation Index (NDVI) derived from Landsat satellite imagery and linked to participants' residential census tract. NDVI ranges from -1 to 1, with higher values indicating greater neighborhood vegetation density.⁵⁶
- Walkability: Measured using the U.S. Environmental Protection Agency (EPA) National Walkability Index, a census block group-level measure based on intersection density, proximity to destinations, and employment mix. Higher

scores indicate neighborhoods that are more supportive of walking and physical activity.⁵⁷

- Access to healthy food (grocery store/supermarket availability): Measured using the USDA Food Access Research Atlas, which identifies census tracts with low supermarket access and low income. Variables describing proximity to supermarkets and food retailers will be used to characterize neighborhood food access.⁵⁸
- Availability of healthcare resources/facilities: Measured using the Area Health Resources Files (AHRF) maintained by the Health Resources and Services Administration (HRSA). Because primary care provider density, hospital availability, FQHC availability, and other healthcare resources may capture distinct aspects of access, we will first examine these indicators separately as standardized (z-scored) variables and will evaluate whether they share a common underlying access dimension using exploratory factor analysis, reporting loadings and internal consistency; a composite will be used in primary models only if the indicators demonstrate a coherent factor structure, and the individual indicators will otherwise be retained separately as distinct covariates/moderators. We will also ensure the selected AHRF indicators reflect a time frame consistent with our exposure assessment window, per consultation with the CCSS Data Coordinating Center. Wherever source data permit, these measures will be constructed at the census tract level using the National Neighborhood Data Archive (NaNDA), which provides tract-level facility- and provider-availability measures (drawing on sources such as HIFLD and CMS METs) available since 2000 and has been used in prior CCSS/SJLIFE projects; per consultation with the Data Coordinating Center, NaNDA will serve as our primary source for these measures. Network-based driving distance/time from each participant's address to the nearest relevant facility will be considered as a supplementary measure where point-level facility data are available; because this approach requires ArcGIS and point-of-interest data and is more resource-intensive, it will not be the primary analytic method. County-level measures will be retained only as a supplementary, broader-context variable.
- Neighborhood social vulnerability, measured by the Social Vulnerability Index (SVI): The CDC/ATSDR Social Vulnerability Index is a place-based index, database, and mapping application designed to identify and quantify communities experiencing social vulnerability. Social vulnerability refers to the demographic and socioeconomic factors -- such as poverty, lack of access to transportation, and crowded housing. The SVI organizes vulnerability factors into four core themes: Socioeconomic Status (income, poverty, unemployment, and educational attainment), along with household characteristics, racial and ethnic minority status, and housing type and transportation. Within each measure, communities are assigned a percentile ranking from 0 (least vulnerable) to 1 (most vulnerable). The relative vulnerability of each tract is scored at three levels: by each variable, by each theme, and as an overall score. The categories are: Very Low (0.0--0.19), Low (0.20--0.39), Moderate (0.40--0.59), High (0.60--0.79), and Very High (0.80--1.0).

3. **Aim 3 – Modifiable health behaviors:** These will include:
- Healthcare engagement (FU4–FU7): Consistent with prior CCSS work,⁵⁹ participants will be categorized as receiving no healthcare, general health care (doctor’s office), survivor-focused care (oncology cancer center), and long-term survivorship care (long-term follow-up clinic) over the past two years. Emergency room care will also be coded dichotomously (yes vs. no emergency care).
 - Physical activity (FU5): Will be coded dichotomously as whether or not the participant met the CDC-recommended ≥ 150 minutes/week of moderate to vigorous physical activity (yes/no)
 - Sleep quality (FU6): This will be assessed using the one question on FU6 from the Pittsburgh Sleep Quality Index
 - Substance use (FU4, FU5, FU7)
 - Smoking (never, former, current): If data are available at multiple time points, the variable will represent whether participants were former or current smokers at any point during the study period.
 - Alcohol use (current, risky, heavy): If data are available at multiple time points, the variable will represent whether participants were current, risky, or heavy drinkers at any point during the study period.

Methods/Statistical analyses: Analyses will be limited to CCSS survivors who meet eligibility criteria and have PTGI and/or Cantril’s Ladder data at FU2 and at least one subsequent FU assessment of a functioning outcome. PTG and LS will first be summarized descriptively using medians, interquartile ranges, and score distributions. Covariates considered across aims will include sociodemographic variables, cancer diagnosis, treatment exposures, and Grade 3–4 chronic health conditions. Missing covariate data will be described, and multiple imputation may be considered if missingness is substantial and judged to be missing at random.

1. **Aim 1:** To identify survivor cluster profiles, we will use a person-centered clustering approach based on FU2 PTG and LS measures, considering PTGI total score, PTGI subscales, and LS subgroup/global LS measures. Candidate cluster solutions will be compared using model fit indices, parsimony, and interpretability, and the final profile structure will be selected accordingly. Associations between PTG/LS profiles and each long-term functioning outcome will be evaluated using regression models matched to outcome type: logistic regression for dichotomous outcomes, multinomial or ordinal logistic regression for frailty, and linear regression if continuous summary scores are analyzed. Predictive utility of PTG/LS profiles will be compared with models using PTG subscales or LS categories alone. We will then compare baseline sociodemographic- and cancer-related characteristics across PTG/LS profiles using chi-square tests for categorical variables and ANOVA or Kruskal-Wallis tests for continuous variables, as appropriate. Although both PTG and LS show individual-level variability, longitudinal evidence supports their relative stability over time in cancer survivors,^{60,61} justifying their use as predictors of long-term functioning from a single FU2 assessment. We acknowledge this as a limitation and will describe the distribution of time between FU2 and outcome assessment. This comparison is intended to evaluate explanatory value rather than to develop or validate a clinical prediction model; external validation is beyond the scope of this concept.

2. **Aim 2:** To evaluate neighborhood-level modification, we will fit multivariable regression models for each functioning outcome that include PTG/LS profile, each neighborhood-level characteristic, and a multiplicative interaction term between profile and the characteristic of interest. Significant interactions will be probed by estimating stratum-specific associations or plotting adjusted predicted probabilities/outcomes across levels of the characteristic. Because these variables may be correlated, we will assess collinearity and consider separate models for individual neighborhood measures and/or a composite neighborhood opportunity index. Given the number of possible neighborhood characteristic-by-outcome combinations, we will designate the characteristic with the strongest a priori and empirical support as the primary moderator and one outcome as the primary outcome for confirmatory interaction testing; remaining combinations will be treated as secondary, hypothesis-generating analyses, with a false discovery rate correction applied across the full set of secondary interaction tests.
3. **Aim 3:** To evaluate modifiable health behaviors as moderators, we will use the same interaction-based framework as detailed for *Aim 2*, modeling each functioning outcome as a function of PTG/LS profile, the health behavior of interest, and their interaction. For each analysis, temporal ordering will be enforced as FU2 PTG/LS assessment, followed by the health behavior moderator measured at the earliest eligible follow-up occurring after FU2 and before the outcome assessment window, followed by the later outcome (FU5-FU8); survivors for whom this ordering cannot be established will be excluded from that specific analysis. Significant interactions will be followed by estimation of adjusted effects within behavior strata to determine whether healthier behaviors strengthen the association between favorable PTG/LS profiles and better long-term functioning. Given the number of possible health behavior-by-outcome combinations, we will designate a primary moderator (the behavior with the most consistent prior association with adult outcomes in the survivorship literature) and a primary outcome for confirmatory interaction testing, with remaining combinations treated as secondary, hypothesis-generating analyses; a false discovery rate correction will be applied across the full set of secondary interaction tests, and the power analysis will be built around the primary interaction term.

Sample size and power considerations:

Because eligibility for the Aim 3 interaction analyses is now conditioned on the availability of an FU2 PTG/LS assessment, an eligible health behavior moderator assessed between FU2 and the outcome window, and an eligible outcome assessment at FU5-FU8, we will report the resulting analytic sample size for each interaction analysis alongside the number of survivors excluded at each stage of this eligibility sequence. Power for the primary confirmatory interaction (primary health behavior moderator by primary outcome) will be calculated based on this analytic sample size, assuming a two-sided alpha of 0.05, and will report the minimum detectable interaction effect size (e.g., minimum detectable odds ratio for the moderator-by-cluster interaction term) given the available sample. Sample sizes and detectable effect sizes for the secondary interaction analyses (Aim 2 and remaining Aim 3 combinations) will be reported descriptively alongside the false discovery rate-corrected results. [Placeholder: exact CCSS analytic sample sizes and minimum detectable effect sizes will be calculated once the FU2/moderator/outcome eligibility sequence has been applied to the CCSS dataset and the primary moderator and outcome have been designated.]

Special considerations: We envision many potential future directions for this work. PTG and LS can be understood as downstream outcomes of modifiable upstream processes—coping skill cultivation, social support, cognitive reappraisal, and resilience. An intervention arising from this work, therefore, would not be as simple as "prescribing PTG and LS", but rather targeting the modifiable mechanisms that foster it. Examples that already target these mechanisms include:

1. Cognitive behavioral therapy (CBT): The International Late Effects of Childhood Cancer Guideline Harmonization Group gives a strong recommendation (Level B evidence) for CBT to treat anxiety, depression, and post-traumatic stress symptoms in childhood/AYA cancer survivors.⁶² The NCCN Survivorship Guidelines list CBT as a Category 1 recommendation for distress, fear of recurrence, and trauma symptoms. While these trials primarily target distress reduction, reducing PTSD symptoms and improving coping are mechanistically linked to PTG.⁶³
2. Mindfulness: Recommended by NCCN for survivorship distress and are Category 1 for fatigue management.⁶³
3. Existential therapy: This technique focuses on values, meaning, and purpose in life, and is specifically listed in the NCCN Survivorship Guidelines as a nonpharmacologic intervention for adjustment disorder and distress.⁶³ Its addressed domains directly map onto PTG.
4. Modern and third-wave CBT approaches represent particularly promising intervention frameworks for promoting PTG and life satisfaction in childhood cancer survivors, because they target the upstream psychological processes most mechanistically linked to these constructs. Unlike traditional CBT, which primarily focuses on symptom reduction, third-wave approaches explicitly address values clarification, acceptance of distress, meaning-making, and behavioral activation -- processes that map directly onto the cognitive engagement and life reassessment that characterize PTG.⁵¹ Acceptance and Commitment Therapy (ACT), through its emphasis on psychological flexibility and committed action toward individually defined values, aligns closely with PTGI domains including personal strength, new possibilities, and appreciation of life.^{64,65} Recovery-oriented cognitive therapy (CT-R) shifts the therapeutic target from reducing psychopathology to strengthening positive beliefs and fostering engagement in meaningful activity, directly reflecting the strength-based orientation motivating this study and the EU-CAYAS-NET recommendation to prioritize positive outcomes in young survivors.⁶⁶ Findings from this study identifying which PTG and LS profiles predict better long-term outcomes, and which modifiable behaviors amplify those associations, will directly inform how these frameworks can be tailored and scaled to actively foster resilience and positive adaptation in survivors.
5. Another burgeoning program is PRISM (Promoting Resilience in Stress Management).^{67,68} This is a brief, skills-based positive psychology program designed specifically for AYA cancer patients that addresses stress management, goal-setting, cognitive reappraisal, and meaning-making. A phase 2 RCT demonstrated improvements in cancer-related quality of life, hope, and resilience while reducing psychological distress at 6 months. Notably, PRISM was designed to target life satisfaction, positive affect, and absence of negative affect—recognizing that prior interventions had failed to durably improve AYA well-being because they did not address all three.

Ultimately, we envision that this work within CCSS will directly inform and support the design, tailoring, and implementation of scalable programming that actively promotes long-term resilience, life satisfaction, and function in our survivors.

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Draft Tables/Figures

Table 1. Cohort Characteristics by PTG/LS Cluster Profile

Characteristic	Overall (N=)	Cluster 1 (n=)	Cluster 2 (n=)	Cluster 3 (n=)	Cluster 4 (n=)	p-value
Age at diagnosis, mean (SD)						
Age at FU2, mean (SD)						
Sex, n (%)						
Female						
Male						
Race/Ethnicity, n (%)						
NH White						
NH Black						
Hispanic						
Other						

Characteristic	Overall (N=)	Cluster 1 (n=)	Cluster 2 (n=)	Cluster 3 (n=)	Cluster 4 (n=)	p-value
Diagnosis, n (%)						
Leukemia						
CNS tumor						
And so on...						
Treatment exposures						
Radiation (any)						
Chemotherapy (yes/no)						
HSCT (yes/no)						
Chronic conditions (Grade 3–4)						
Yes						

Table 2. Predictive Model Comparison

Model	AUC (95% CI)	BIC	ΔAUC vs Cluster Model
PTG subscales only			
LS subgroup only			
PTG + LS (separate)			
PTG/LS clusters (primary)			Reference

Note. This comparison is intended to evaluate explanatory value rather than to develop or validate a clinical prediction model.

Supplementary Table 1. PTG and LS Characteristics by Cluster Profile

Measure	Cluster 1	Cluster 2	Cluster 3	Cluster 4	p-value
PTGI total score, median (IQR)					

Measure	Cluster 1	Cluster 2	Cluster 3	Cluster 4	p-value
New possibilities					
Relating to others					
Personal strength					
Spiritual change					
Appreciation of life					
LS current score, mean (SD)					
LS past score, mean (SD)					
LS future score, mean (SD)					
LS subgroup, n (%)					
Thriving					
Struggling					
Suffering					

Supplementary Table 2. Associations Between PTG/LS Clusters and Outcomes

Cluster Profile	Poor cognitive functioning OR (95% CI)	Poor emotional functioning OR (95% CI)	Poor physical functioning (pre-frail or frail) OR (95% CI)	Poor adult social/economic outcomes (any of 3) OR (95% CI)
Cluster 1 (ref)	1.00	1.00	1.00	1.00
Cluster 2				
Cluster 3				
Cluster 4				
And so on... if >4 clusters				

***Adjust for age, sex, diagnosis, treatment exposures, CHC?*

Supplementary Table 3. Effect Modification by Neighborhood Characteristics

Cluster	Low Walkability OR (95% CI)	High Walkability OR (95% CI)	Interaction p-value
Cluster 1 (ref)	1.00	1.00	
Cluster 2			
Cluster 3			
Cluster 4			

Supplementary Table 4. Moderation by Health Behaviors

Cluster	Inactive OR (95% CI)	Active OR (95% CI)	Interaction p-value
Cluster 1 (ref)	1.00	1.00	
Cluster 2			
Cluster 3			
Cluster 4			

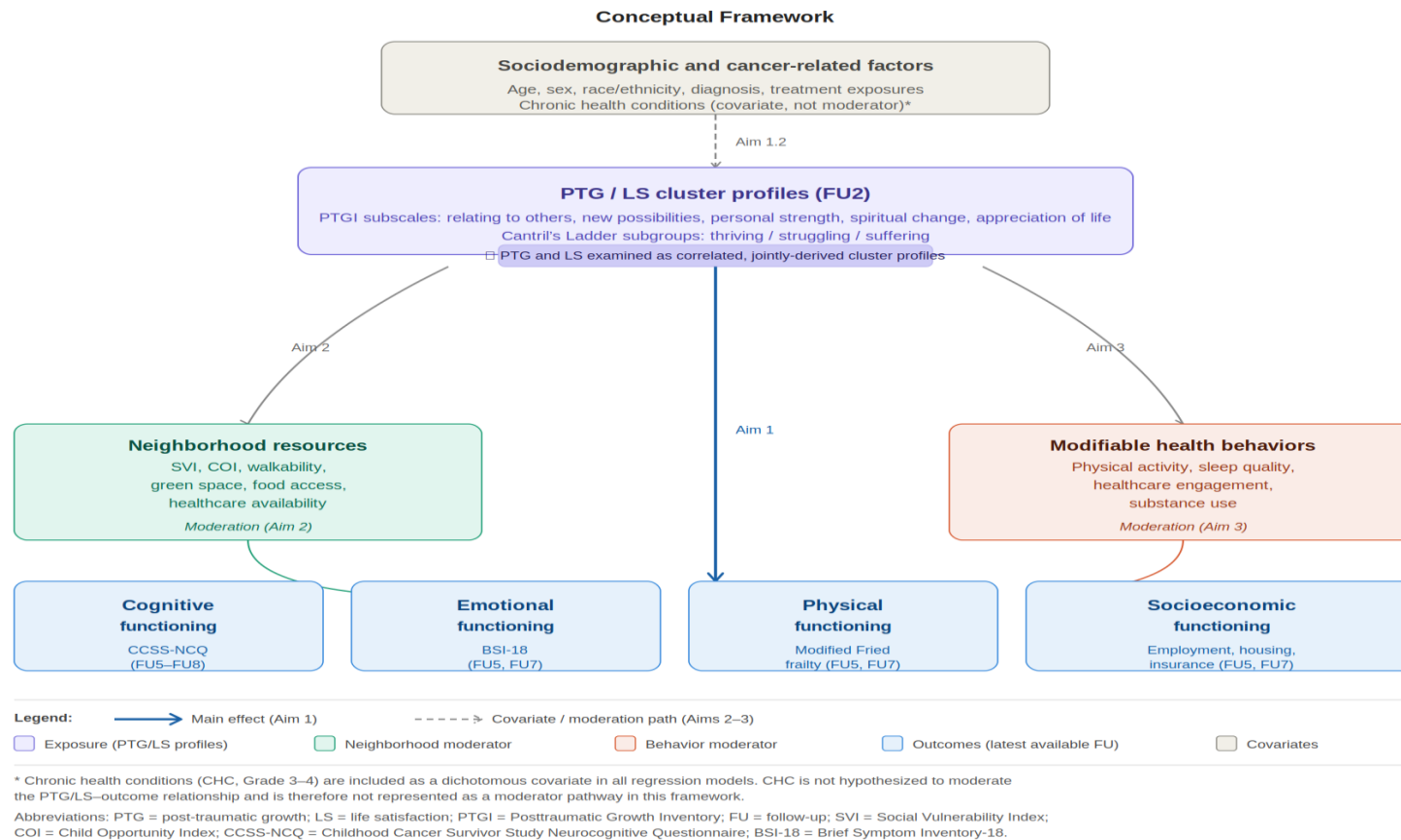
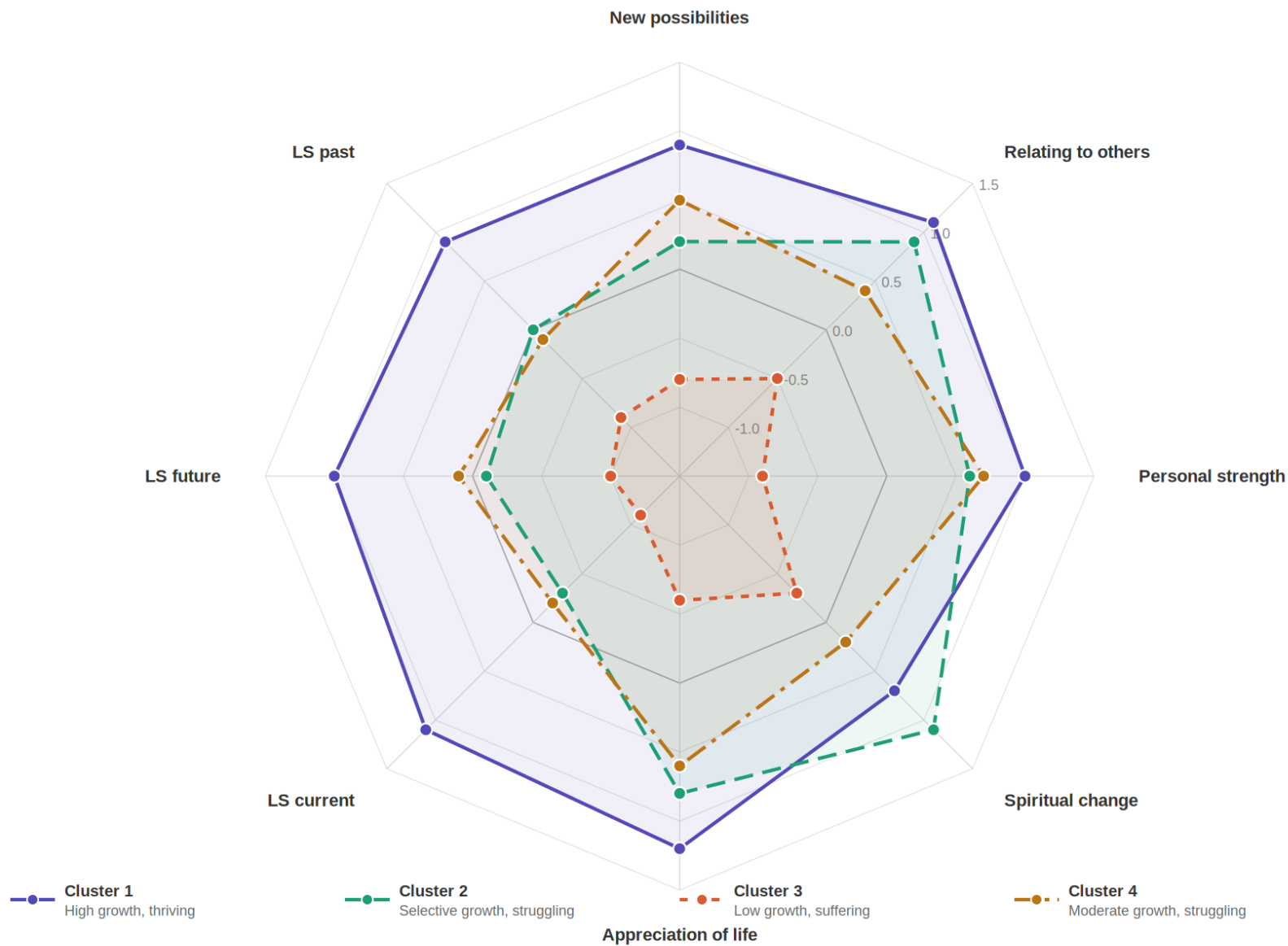


Figure 1. Conceptual framework. PTG/LS cluster profiles at FU2 are the primary exposure (Aim 1). Neighborhood-level characteristics (Aim 2) and modifiable health behaviors (Aim 3) are hypothesized moderators. Four functioning domains are outcomes. PTG and LS are examined as correlated constructs within jointly-derived profiles. CHC is adjusted for as a covariate. Solid arrow = main effect; dashed arrows = covariate and moderation pathways. Abbreviations: PTG = post-traumatic growth; LS = life satisfaction; FU = follow-up; SVI = Social Vulnerability Index; CCSS-NCQ = Childhood Cancer Survivor Study Neurocognitive Questionnaire; BSI-18 = Brief Symptom Inventory-18. **Purpose:** Maps the primary exposure (PTG/LS cluster profiles at FU2) to four long-term functioning outcomes, with neighborhood characteristics (Aim 2) and modifiable health behaviors (Aim 3) as moderators and sociodemographic/cancer-related factors as covariates.



Axes show standardized mean scores (z-scores). Values are illustrative pending cluster derivation. PTGI = Posttraumatic Growth Inventory; LS = life satisfaction (Cantril's Ladder).

FIGURES 2-4 illustrate the anticipated presentation of results, Data shown are illustrative using plausible hypothetical z-scores.

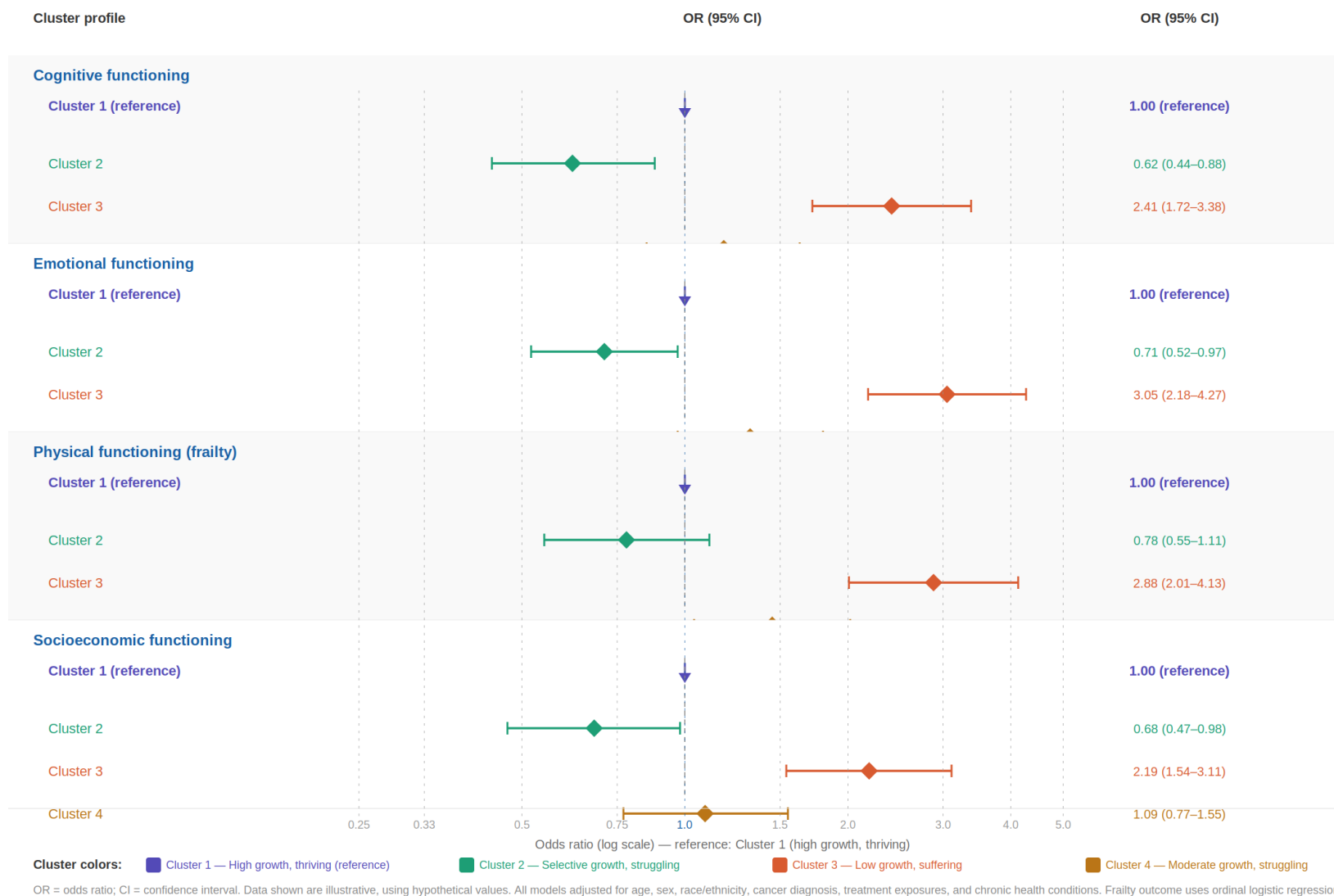


Figure 3. Forest plot of cluster–outcome associations. Odds ratios (ORs) and 95% confidence intervals for associations between PTG/LS cluster profiles and four long-term functioning outcomes (cognitive, emotional, physical, adult social/economic), with Cluster 1 (high growth, thriving) as the reference group. Diamond = point estimate; horizontal line = 95% CI; dashed vertical line = OR 1.00 (null). Log scale. Data are illustrative pending analyses. All models adjusted for age, sex, race/ethnicity, cancer diagnosis, treatment exposures, and chronic health conditions (Grade 3–4). Frailty outcome analyzed using ordinal logistic regression. Abbreviations: OR = odds ratio; CI = confidence interval; CHC = chronic health conditions. Direction, magnitude, and precision of cluster–outcome associations across all four domains in a single figure, allowing immediate visual comparison of which clusters drive risk or protection for each outcome. This figure replaces Table 3 in the main manuscript; Table 3 is retained as a supplementary table with precise estimates.

Interaction plots: moderator x PTG/LS cluster profile on predicted probability of poor functioning

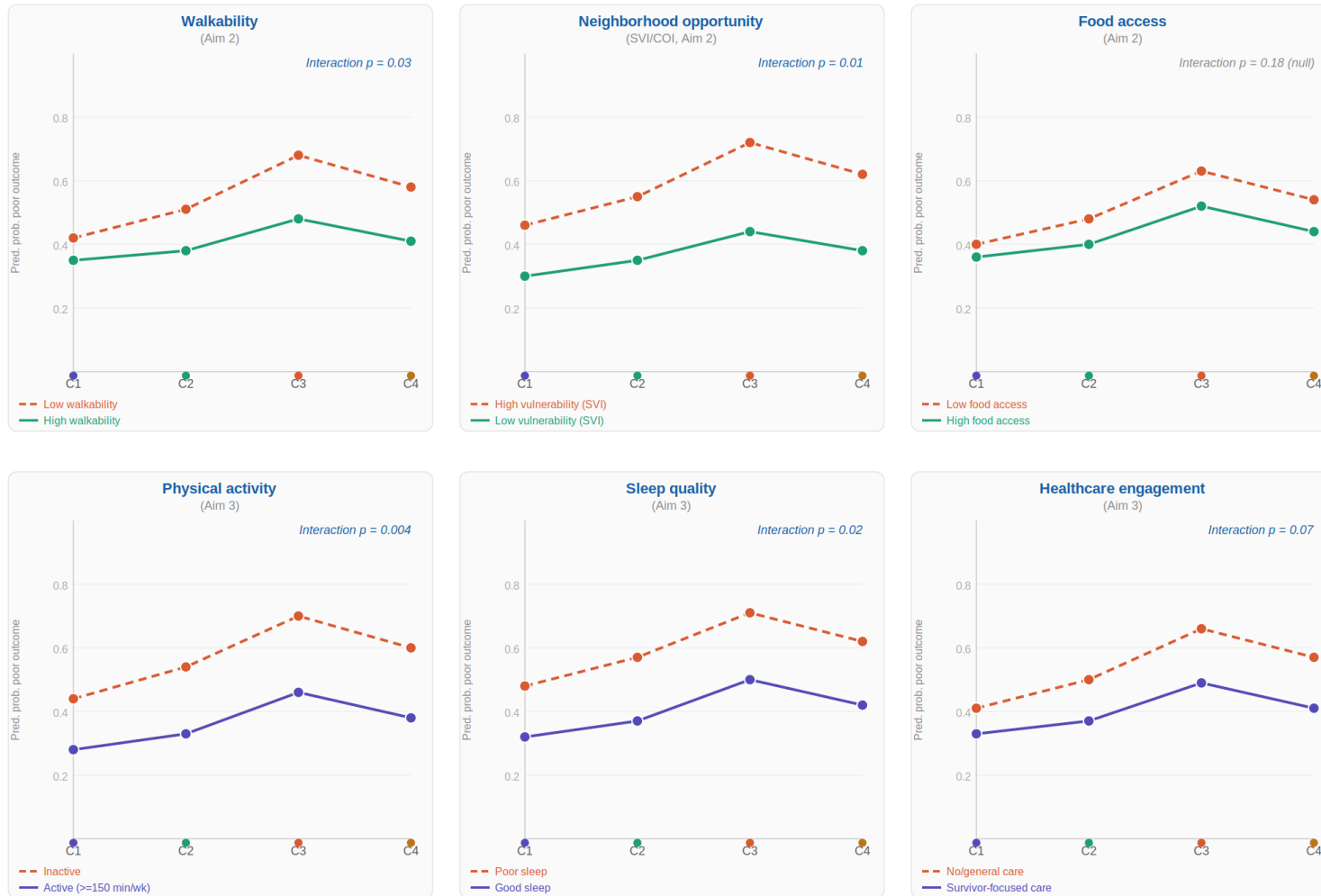


Figure 4. Interaction plots: moderation of PTG/LS cluster–outcome associations. Predicted probability of poor emotional functioning (BSI-18 T-score ≥ 63) by PTG/LS cluster profile, stratified by moderator level. Top row: neighborhood-level moderators (Aim 2). Bottom row: health behavior moderators (Aim 3). Solid lines = high/favorable moderator level; dashed lines = low/unfavorable level. Diverging lines indicate significant effect modification; parallel lines indicate null interaction. C1–C4 = Clusters 1–4. Data are illustrative pending analyses. Interaction p-values shown within each panel. Analogous figures for cognitive, physical, and adult social/economic outcomes and additional moderators are included in supplementary materials.

C1–C4 = Clusters 1–4. Solid lines = high/favorable moderator level; dashed lines = low/unfavorable level. Diverging lines indicate significant effect modification; parallel lines indicate null interaction. Data shown are illustrative using hypothetical predicted probabilities. Outcome: poor emotional functioning (BSI-18). Final values will replace these once analyses are complete.

Figure 5. Timeline of Aim 3 moderator and outcome assessment windows

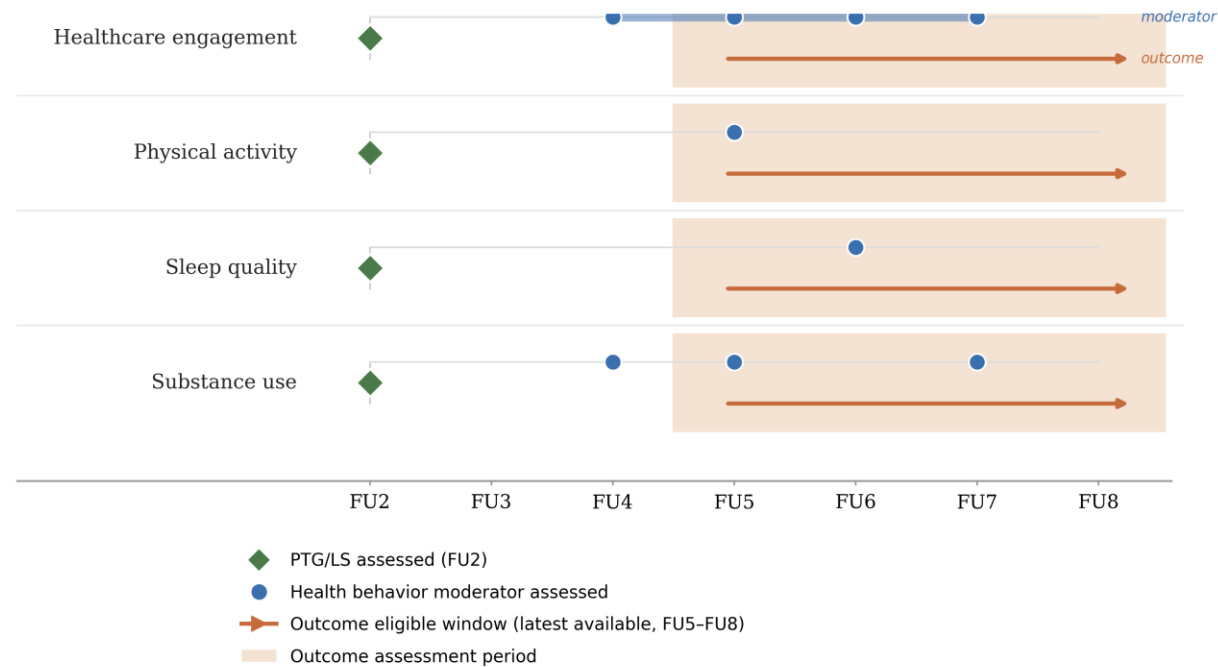


Figure 5. Timeline of Aim 3 moderator and outcome assessment windows. Depicts the temporal sequence enforced for each Aim 3 interaction analysis: PTG/LS assessed at FU2, followed by the health behavior moderator of interest measured at the earliest eligible follow-up survey occurring after FU2 and before the outcome assessment window, followed by the long-term functioning outcome measured at the latest available follow-up within FU5-FU8. A separate timeline row is shown for each of the four health behaviors examined (healthcare engagement, physical activity, sleep quality, and substance use), reflecting that each behavior is assessed at a different follow-up survey (FU4-FU7, FU5, FU6, and FU4/FU5/FU7, respectively) and that the eligible assessment window therefore differs by behavior. Survivors lacking an eligible moderator assessment between FU2 and their outcome window are excluded from that behavior's analysis, consistent with the eligibility sequence described under Aim 3 methods and Sample size and power considerations. *[Placeholder: final figure to be rendered once the primary moderator and outcome have been designated.]*