

Concept Proposal Concept 26-12

Study title: Associations between Health Behaviors during Adolescence and Frailty in Adulthood among Childhood Cancer Survivors

Working group: Cancer Control (Primary), Psychology (Secondary), Chronic Disease (Secondary)

Investigators:

- Mary Claire McGlynn, MD (mmcglynn@wustl.edu)
- Ellen van der Plas, PhD (EVanderplas@uams.edu)
- Tara Brinkman, PhD (Tara.Brinkman@STJUDE.ORG)
- Sedigheh Mirzaei, PhD (Sedigheh.Mirzaei@STJUDE.ORG)
- Allison A. King, MD, PhD (king_a@wustl.edu)
- Kirsten K. Ness, PT, PhD, FAPTA (Kiri.Ness@STJUDE.ORG)
- Robert J. Hayashi, MD (hayashi_r@wustl.edu)
- AnnaLynn Williams, MD (Annalynn_Williams@URMC.Rochester.edu)
- Paul C. Nathan, MD, MSc (paul.nathan@sickkids.ca)
- Claire Snyder, MHS, PhD (csnyder@jhu.edu)
- Eric Chow, MD, MPH (ericchow@uw.edu)
- Kevin Oeffinger, MD (kevin.oeffinger@duke.edu)
- Kumar Srivastava, PhD (kumar.srivastava@stjude.org)
- Greg Armstrong, MD, MSCE (Greg.Armstrong@stjude.org)

Background and Rationale

Pediatric cancers are increasingly treatable and curable resulting in an estimated 500,000 pediatric cancer survivors living in the United States.[1, 2] Adult childhood cancer survivors experience long term health complications or late effects related to their malignancy and the treatments.[3] One such late effect is frailty. Frailty is a phenotype seen in 10% of individuals 65 years of age and older. It is associated with vulnerability to adverse health outcomes, precedes onset of chronic disease, and is a predictor of early mortality.[4, 5] Previous studies have demonstrated that the prevalence of frailty among young adult childhood cancer survivors is similar to that among adults ages 65 and older, suggesting childhood cancer survivors experience accelerated aging.[6, 7]

Childhood cancer survivors with frailty have lower health related quality of life (QOL) than non-frail childhood cancer survivors.[8, 9]. Childhood cancer survivors with frailty or prefrailty (several features of frailty but not yet reaching diagnostic threshold) have greater declines in cognitive domains associated with aging and dementia, are at increased risk of developing a chronic health condition, and are at increased risk of death compared to non-frail childhood cancer survivors.[6, 10, 11]

There are known risk factors for frailty, frailty progression, and premature aging among childhood cancer survivors that are related to childhood cancer survivors' cancer and related therapies. [12] Modifiable risk factors have been described such as growth hormone deficiency, smoking, lack of strength training, and sedentary lifestyle.[13, 14] Severity of frailty has also been demonstrated to be partially mediated by psychosocial factors.[12]

Despite knowledge of these modifiable risk factors, no studies have examined the longitudinal impact of *adolescent* health behaviors on the development of frailty in childhood cancer survivors, representing a critical knowledge gap for developing targeted interventions. Past studies of non- childhood cancer survivors have demonstrated that adolescence is a formative time for establishing healthy behaviors (e.g. increased physical activity and reduce alcohol and tobacco use) that correlate with healthy behaviors and favorable health outcomes in adulthood.[15-19] We propose that adolescence is a promising age to intervene in childhood cancer survivors as health behaviors established during this developmental period may have lasting effects on mitigating frailty risk.

This study is innovative because it is the first to examine longitudinal associations between modifiable adolescent health behaviors and frailty development in adult childhood cancer survivors using data *from the Childhood Cancer Survivor Study (CCSS)* across this critical developmental period.[20-23] ***Findings from this effort could*** identify the optimal timing and targets for behavioral interventions to prevent frailty, potentially leading to evidence-based recommendations for adolescent health promotion. ***Our long-term goal*** is to develop interventions establishing healthy behaviors in young childhood cancer survivors to mitigate the

onset of frailty as they advance into adulthood. We will achieve our objectives pursuing the following **specific aims**:

Study Aims

Specific Aim 1: To determine whether adolescent health behaviors (physical activity, tobacco use, and alcohol use) are associated with frailty in adult childhood cancer survivors.

Lifestyle factors/health behaviors will be determined from baseline, baseline expansion, or any follow-up surveys completed when the survivor was between the ages of 12-17 years old, and include physical activity, alcohol use, tobacco use, and a composite score. We will also construct a composite healthy lifestyle score (range 0–3), with one point assigned for each healthy behavior (physical activity, no alcohol use, no tobacco use during adolescence). [25] Frailty will be assessed in adulthood and evaluated using Deficit Accumulation Index (DAI) (continuous score with categorical thresholds).

- **Aim 1.1: To identify the association between adolescent health behaviors and frailty at the latest follow-up assessment.**
 - We hypothesize that survivors who engaged in poor health behaviors during adolescence will have a higher prevalence of frailty and higher DAI scores than survivors with healthy lifestyle behaviors.
- **Aim 1.2: To determine the association between adolescent health behaviors and incident of new onset frailty at follow-up 5 or 7.**
 - We hypothesize that survivors who engaged in poor health behaviors in adolescence will exhibit frailty symptoms prior to survivors who engaged in healthy lifestyle behaviors during adolescence.

Specific Aim 2: To identify patterns of health behaviors from adolescence into adulthood among survivors and determine if these patterns are associated with frailty outcomes.

We will characterize behavioral change groups from adolescence through adulthood (e.g., maintaining a healthy lifestyle (maintainers), not adopting a healthy lifestyle (non-adopters), declining health behaviors (decliners), improving health behaviors (adopters) and determine their relationship with frailty status and DAI at the latest follow-up. Health behaviors will be repeated measures with time points differing by cohort. The baseline cohort will have health behaviors assessed during adolescence (baseline), follow-up two and frailty at follow-up five. The expansion cohort will have health behaviors measured at baseline (during adolescence), follow-up five and frailty assessed at follow-up seven.

- **Aim 2.1: To determine if longitudinal patterns of health behaviors from adolescence into adulthood among survivors are associated with frailty outcomes.**
 - We hypothesize that maintainers will have the lowest DAI scores, lowest prevalence of medium/high DAI, and latest onset of medium/high DAI, followed by adopters, decliners, then non-adopters.

Secondary Aim: To assess whether the associations between adolescent health behaviors and the prevalence and severity of frailty in adult survivors are statistically explained by neurocognitive functioning in adulthood.

Lifestyle factors/health behaviors will be determined from baseline, baseline expansion, or any follow-up surveys completed when the survivor was between the ages of 12-17 years old, and include physical activity, alcohol use, tobacco use, and a composite score. Psychological factors will be assessed in adulthood and include results from the NCQ (memory, task efficiency, emotional regulation, and organization). Frailty will be assessed in adulthood and evaluated using the DAI (continuous score).

- **Secondary Aim 1.1: To evaluate whether psychological factors statistically account for the association between adolescent health behaviors and prevalence of frailty at most recent follow-up considering psychological factors in adulthood as measured in the NCQ.**
 - We hypothesize that adverse psychological health will partially explain (i.e., statistically decompose) the association between adolescent health behavior and frailty in adulthood.

Exploratory Aim: To examine the association between self-reported adolescent health behaviors (physical activity, alcohol use, tobacco use, marijuana use, and screen time use, and sedentary behaviors as measured as part of the Teen Health Ancillary Survey) and the prevalence of medium/high DAI, time to onset of medium/high DAI, and DAI severity in adulthood. Frailty will be assessed in adulthood and evaluated using the DAI (continuous score).

- **Exploratory Aim 1.1: To identify the association between adolescent health behaviors and frailty at the latest follow-up assessment.**
 - We hypothesize that survivors who engaged in poor health behaviors during adolescence will have a higher prevalence of frailty and higher DAI scores than survivors with healthy lifestyle behaviors.
- **Exploratory Aim 1.2: To determine the association between adolescent health behaviors and time to onset of frailty symptoms**
 - We hypothesize that survivors who engaged in poor health behaviors in adolescence will develop medium/high DAI at younger ages than survivors with healthy lifestyle behaviors.

Analysis Framework

Specific Aim 1 To determine whether adolescent health behaviors (physical activity, tobacco use, and alcohol use) are associated with frailty in adult childhood cancer survivors.

1. **Population:** The population will include 5-year survivors enrolled in the CCSS cohort, diagnosed between 1970 and 1999. We will include survivors whose caregivers completed the Baseline Questionnaire, Baseline Expansion Questionnaire, or at least one Follow-up Survey during the survivor's adolescence (ages 12-17). Preliminary analysis demonstrates baseline questionnaires were completed for 4,373 adolescents. Survivors will need to have completed at least one subsequent follow up survey to allow us to determine if the patient developed frailty. Estimates of the number of eligible patients are included in Figure 1.
Exclusion criteria: Survivors with incomplete data on primary outcomes (Frailty measures e.g., <80–90% of required items for DAI), those who died or were lost to follow-up before age 18, and those with missing covariate data on cancer diagnosis and treatment exposures that cannot be imputed.
2. **Exposure** Exposures will include health behaviors during adolescence only (ages 12–17 years). If multiple surveys are available for ages 12–17, we will summarize them considering the worst-risk value. This will be consistent across behaviors. Data from subsequent follow-up surveys will consider “age at first use” if reported for an adolescent survivor. The primary exposure of interest will be a composite healthy lifestyle score. Health behaviors will include:
 - a. physical activity (frequency and intensity)
 - b. Alcohol initiation prior to 18 (yes/no, number of years from age 12-17)
 - c. tobacco initiation prior to age 18 (yes/no, number of years from age 12-17)

These behaviors will include physical activity (frequency and intensity), tobacco use, and a composite healthy lifestyle score, (range 0-3, with higher scores indicating healthier behaviors).[25] Lifestyle factors, including smoking, alcohol use, and physical activity, will be assigned a score of 0 (unhealthy) or 1 (healthy) and combined to create a lifestyle score ranging from 0-3. This will be modified from prior CCSS. Because BMI is included in the DAI, we will not consider healthy weight as determined by BMI in the lifestyle score, although it has previously been published by the CCSS due to concerns for collinearity. We defined unhealthy as: ever smoked more than 100 cigarettes, heavy or risky drinking (>7 drinks/week or >3 drinks/day for women, >14 drinks/week or >4 drinks/day for men), and sedentary (0-3 MET-h/week of activity). For low physical activity (3-6 MET-h/week) a score of 0.5 will be assigned. (See reference Table 1)

The lifestyle score was categorized as

- a. unhealthy (0-1)
- b. moderately healthy (1.5-2)
- c. healthy (2.5-3).

Per preliminary analysis, health behavior data during adolescence are available for physical activity (99% via baseline survey), alcohol use (67% via baseline survey and 12% via age of first use per

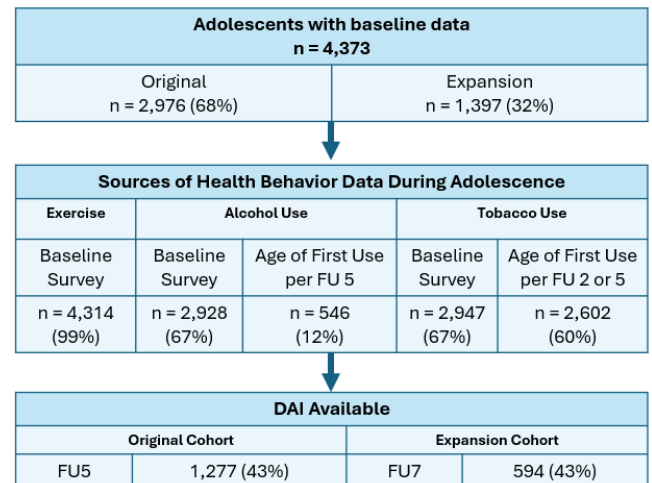


Figure 1. Adolescents with baseline data, health behavior data during adolescence, and frailty data

follow-up 5), and tobacco use (67% via baseline survey and 60% via age of first use per follow-up 2 or follow-up 5).

- **Outcome** Outcomes will include adult frailty measured at survivor's most recent adult follow-up (typically FU7) using the DAI.[11] The DAI is a validated index that has previously been reported in childhood cancer survivors. [11, 24] The CCSS DAI includes 30 aging-related constructs across multiple health domains. (See reference Table 2)

1. Each deficit is scored as present (range 0-1). Item responses will be summed and divided by the total number of items, resulting in a ratio ranging from 0 to 1, with higher ratios being more severe.
2. The DAI will be scored continuously and categorically. If sparse cell sizes are observed, medium and high DAI categories may be combined in sensitivity analyses
 1. Robust: DAI less than 0.2
 2. Medium DAI: DAI of 0.2 to less than 0.35
 3. High DAI: DAI of 0.35 or higher
3. Higher scores indicate greater frailty severity.

5. **Analysis Structure** Frailty will be considered in a cross-sectional analysis examining the association between adolescent health behaviors and frailty at the most recent follow up and a longitudinal analysis considering adolescent behavior and time to onset across follow-ups.

1. Continuously (DAI)
2. Categorically (DAI: robust, medium DAI, high DAI)
3. Based upon age of onset (earliest time point across follow-up surveys at which robust/medium/high DAI are diagnosed).

Aim 1.1 (cross-sectional): We will model (a) DAI continuous using linear regression, and (b) DAI categories using ordinal logistic regression (Robust < Medium DAI < High DAI); if proportional odds is violated, we will use multinomial logistic regression.

Aim 1.2 (time-to-onset): We will use a Piecewise exponential regression model. Onset will be defined as the earliest follow-up survey at which medium or high DAI is first observed.

Specific Aim 2 To identify patterns of health behaviors from adolescence into adulthood among survivors and determine if these patterns are associated with frailty outcomes.

1. **Population:** The population will include 5-year survivors enrolled in the CCSS cohort, diagnosed between 1970 and 1999. We will include survivors whose caregivers completed the Baseline Questionnaire, Baseline Expansion Questionnaire, or at least one Follow-up Survey during the survivor's adolescence (ages 12-17). The baseline cohort will have health behaviors assessed during adolescence (baseline), follow-up two and frailty at follow-up five. The expansion cohort will have health behaviors measured at baseline (during adolescence), most recent follow-up. We will harmonize time points so that each participant contributes an adolescent behavior measure and at least one adult behavior measure prior to the frailty assessment. *Exclusion criteria:* Survivors with more than 10% incomplete data on primary outcomes (Frailty measures), those who died or were lost to follow-up before age 18, those without follow-up as described above, and those with missing covariate data on cancer diagnosis and treatment exposures that cannot be imputed. The exclusion criterion (>10% missingness in frailty measures) is intended to ensure reliable construction of the DAI and frailty phenotype, which require a minimum number of observed components. We will quantify missingness across variables and compare included versus excluded participants to assess potential selection bias; analyses will be restricted to participants with sufficiently complete data to ensure valid frailty classification.
2. **Exposure** Exposures will include repeated measures of health behaviors during adolescence (ages 12-17 years) and health behaviors at one subsequent follow-up (follow-up five for all participants, given the completeness of data). We will consider health behaviors individually and where feasible, as a composite healthy lifestyle score, (range 0-3, with higher scores indicating healthier behaviors) as above in Aim 1[25]

We will categorize survivors into trajectory groups of health behaviors from adolescence through adulthood into the following groups (Figure 2)

- a. Maintainers (childhood cancer survivors who are moderately healthy or healthy at timepoint one and remain moderately healthy or healthy at timepoint two) (Healthy Lifestyle Score ranging from 1.5 to 3 at both timepoint one and two)

	Trajectory Group	Timepoint One	Timepoint Two
d.	Maintainers Lifestyle Score	Moderately Healthy or Healthy 1.5-3	Moderately Healthy or Healthy 1.5-3
	Decliners Lifestyle Score	Moderately Healthy or Healthy 1.5-3	Unhealthy 0-1
	Non-adopters Lifestyle Score	Unhealthy 0-1	Unhealthy 0-1
	Adopters Lifestyle Score	Unhealthy 0-1	Moderately Healthy or Healthy 1.5-3

Figure 2. Healthy Lifestyle Score Trajectory Groups

- e. Non-adopters (childhood cancer survivors who are unhealthy at timepoint one and unhealthy at timepoint two) (i.e. Lifestyle score 0-1 at timepoint one and score 0-1 at timepoint two)
- f. Adopters (childhood cancer survivors with who are unhealthy at timepoint one and moderately healthy or healthy at timepoint two) (i.e. lifestyle score 0-1 at timepoint one and lifestyle score 1.5 to 3 at timepoint two)

4. **Outcome** We will quantify the number and percentage of patients who are maintainers, non-adopters, decliners, and adopters. We will assess the association between trajectory group and adult frailty measured at the most recent follow-up with the DAI (robust/medium/high DAI).[11] To score the DAI,
 - Each deficit is scored as present (range 0-1). Item responses will be summed and divided by the total number of items, resulting in a ratio ranging from 0 to 1, with higher ratios being more severe.
 - The DAI will be scored continuously and categorically.
 1. Robust: DAI less than 0.2
 2. Medium DAI: DAI of 0.2 to less than 0.35
 3. High DAI: DAI of 0.35 or higher
 - Higher scores indicate greater frailty severity.
4. **Analysis Structure** Frailty will be considered by examining the association between behavioral change groups and frailty at most recent follow-up. Frailty will be assessed
 - Continuously (DAI)
 - Categorically (DAI: robust, medium DAI, high DAI)
 Based upon onset (earliest time point across follow-up surveys at which medium/high DAI are diagnosed).

Models are the same as in Aim 1, with exposure defined as trajectory behavior.

Secondary Aim: To assess whether the associations between adolescent health behaviors and the prevalence and severity of frailty in adult survivors are correlated with psychological factors in adulthood.

1. **Population:** The population will include 5-year survivors enrolled in the CCSS cohort, diagnosed between 1970 and 1999. We will include survivors from Specific Aim 1
2. **Exposure** Exposures will be the same as Aim 1, Adolescent health behaviors (parent- reported during ages 12-17)
3. **Correlatives** Adult neuropsychological functioning from NCQ (memory, task efficiency, emotional regulation, organization), Neurocognitive functioning will be assessed prior to DAI measurement whenever possible (Original cohort: FU2 NCQ preceding FU5 DAI; Expansion cohort: FU5 NCQ preceding FU7 DAI), improving temporal ordering between neurocognitive functioning and frailty outcomes. However, because these are observational data, analyses will be interpreted as associational rather than causal. If earlier psychological measures are available, we will prioritize correlative measurement from the wave preceding frailty assessment (sensitivity analysis).
4. **Outcome** Outcomes will include adult frailty measured at the survivor's most recent adult follow-up using the DAI as in Aim 1.

5. **Analysis Structure** We will use a mediation-based framework to decompose the association between adolescent health behaviors and the prevalence of frailty at the most recent follow-up
 1. Primary mediators will include the four NCQ domains (memory, task efficiency, emotional regulation, and organization). Each NCQ domain will first be evaluated separately to estimate its contribution to the association between adolescent health behaviors and adult DAI. Because the NCQ domains are correlated, simultaneous mediator models may be explored in secondary analyses. Mediation results will be interpreted as a statistical decomposition of observed associations rather than evidence of causal pathways.
6. (Figure 1). We will examine if psychological factors statistically account for the association between adolescent health behaviors and DAI severity at the most recent follow-up.
 1. Continuously (DAI)
 2. Categorically (DAI: robust, medium DAI, high DAI)

Separate mediation models will be fit for each NCQ domain. For continuous DAI outcomes, linear regression-based mediation models will be used. For categorical DAI outcomes (Robust, Medium DAI, High DAI), generalized mediation models will be used. , All adjusted for the same confounders used in Aim 1.

Preliminary analyses indicate approximately 900 to 950 survivors in the original cohort have data available for adolescent health behavior exposure, NCQ assessment, and subsequent DAI assessment, supporting the feasibility of the proposed analyses.

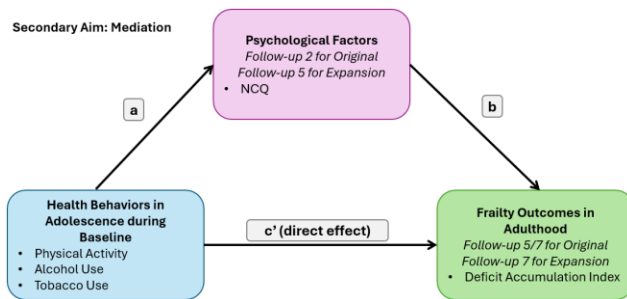


Figure 3 Secondary Aim

Exploratory Aim: To examine the association between self-reported adolescent health behaviors (physical activity, alcohol use, tobacco use, marijuana use, and screen time use, and sedentary behaviors as measured as part of the Teen Health Ancillary Survey) and the prevalence, time to onset, and severity of frailty in adulthood. Frailty will be assessed in adulthood and evaluated using the DAI (continuous score and categorical score).

1. **Population:** The population will include 5-year survivors enrolled in the CCSS cohort, diagnosed between 1970 and 1999 who completed the Teen Ancillary Study and at least one subsequent follow-up study. The Teen Ancillary Study includes 303 childhood cancer survivors who were diagnosed with cancer at a very young age and completed a self-report questionnaire, the Teen Health Survey, between the ages of 15-19 during the years 2001 to 2003. The exposure window in this exploratory aim (15-19) differs from the primary aims (12–17). Analyses will be presented separately and not pooled with the primary aims. While this sample has a higher proportion of survivors with Wilms tumor or neuroblastoma (47%), it provides valuable self-reported health behavior data from adolescent childhood cancer survivors that may be more accurate than parent-report as research demonstrates that parents underestimate risky health behaviors adolescents engage in. Additionally, the Teen Ancillary Study collected health behavior habits that were not addressed in the CCSS Baseline or Follow-up Questionnaires.[22, 23] We will exclude survivors with more than 10% incomplete data on primary outcomes (Frailty measures), those who died or were lost to follow-up before age 18, and those with missing covariate data on cancer diagnosis and treatment exposures that cannot be imputed.
2. **Exposure** Exposures will be self-reported adolescent health behaviors from the Teen Ancillary Survey, including Physical activity (details frequency, duration, and type), Alcohol use, Tobacco use, Marijuana, Screen time use, Sedentary behaviors
3. **Outcome** Outcomes will include adult frailty measured at survivor's most recent adult follow-up (typically FU7) using the Deficit Accumulation Index (DAI) as in Aim 1.

4. **Analysis Structure** We will examine the association between self-reported adolescent health behaviors and frailty at most recent follow up and time to frailty onset across follow-ups.
1. Continuously (DAI)
 2. Categorically (DAI: robust, medium DAI, high DAI)
 3. Based upon age of onset (earliest time point across follow-up surveys at which medium/high DAI are diagnosed).

Because this is an exploratory analysis, findings will be interpreted as hypothesis-generating.

Control Variables Our models will be controlled for:

- *Treatment exposures:*
 - Cancer diagnosis
 - Age at diagnosis
 - Treatment exposures.
 - Chemotherapy and cumulative doses
 - Radiation exposure and field
 - Surgery and surgical procedures
- *Sociodemographic factors:*
 - Sex
 - Race
 - Education
 - Educational attainment
 - Utilization of special education services
 - Social competence
 - Employment
 - Annual household income
 - Health insurance status

Confounders will be selected a priori based on a conceptual model.

Expected outcomes and Impact: Upon completion of this study, we expect to demonstrate that risky health behaviors in adolescence are associated with increased prevalence, earlier onset, and greater severity of frailty in adult childhood cancer survivors. We anticipate identifying critical periods for intervention, with survivors who maintain healthy behaviors throughout adolescence and adulthood having the lowest frailty risk, while those with persistently unhealthy or declining behaviors will have higher risk. We expect to find that neuropsychological factors are correlative with adolescent health behaviors and adult frailty, highlighting opportunities for multi-level interventions.

- Tables (see sample tables below)
 - Table 1 Baseline characteristics of the study population
 - Table 2 Association between adolescent health behaviors and frailty outcomes (Specific Aim 1)
 - Table 3 Health Behavior Trajectory Groups (Specific Aim 2)
 - Table 4 Health behavior trajectory groups and frailty risk (Specific Aim 2)
 - Table 5 Correlative analysis results (Secondary Aim 1)
 - Table 6 Association between adolescent health behaviors and frailty outcomes Teen health survey (exploratory aim)
- Figures
 - CONSORT diagram
 - Kaplan-Meier curves for frailty-free survival (Specific Aim 1)
 - Y axis, Frailty-free survival
 - X axis, time
 - Curves: Categorical Healthy Lifestyle Scores
 - Forest plot of health behavior associations (Specific Aim 1)
 - Health behavior trajectory visualization (Specific Aim 2)
 - Correlation pathway diagram (Secondary Aim 1)
 - Forest plot of association between adolescent health behaviors and frailty outcomes Teen Survey (exploratory aim)

These findings will directly inform clinical practice by (1) identifying adolescence as a critical window for prevention of frailty in childhood cancer survivors; (2) establishing evidence-based targets for health behavior

interventions in survivorship care; (3) Demonstrating the potential for lifestyle modifications to mitigate frailty even among high-risk survivors; (4) informing the development of tailored interventions that address both behavioral and psychosocial risk factors. *This work will provide the foundation for future randomized controlled trials* testing behavioral interventions to prevent frailty in adolescent and young adult childhood cancer survivors, with the ultimate goal of reducing premature aging and improving long-term quality of life for the growing population of cancer survivors.

References

1. Siegel, D.A., et al., *Pediatric cancer mortality and survival in the United States, 2001-2016*. Cancer, 2020. **126**(19): p. 4379-4389.
2. Robison, L.L. and M.M. Hudson, *Survivors of childhood and adolescent cancer: life-long risks and responsibilities*. Nat Rev Cancer, 2014. **14**(1): p. 61-70.
3. Oeffinger, K.C., et al., *Chronic Health Conditions in Adult Survivors of Childhood Cancer*. New England Journal of Medicine, 2006. **355**(15): p. 1572-1582.
4. Hogan, D.B., C. MacKnight, and H. Bergman, *Models, definitions, and criteria of frailty*. Aging Clin Exp Res, 2003. **15**(3 Suppl): p. 1-29.
5. Fried, L.P., et al., *Frailty in Older Adults: Evidence for a Phenotype*. The Journals of Gerontology: Series A, 2001. **56**(3): p. M146-M157.
6. Ness, K.K., et al., *Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime cohort study*. J Clin Oncol, 2013. **31**(36): p. 4496-503.
7. Yeh, J.M., et al., *Accelerated Aging in Survivors of Childhood Cancer—Early Onset and Excess Risk of Chronic Conditions*. JAMA Oncology, 2025. **11**(5): p. 535-543.
8. Pranikoff, S., et al., *Frail young adult cancer survivors experience poor health-related quality of life*. Cancer, 2022. **128**(12): p. 2375-2383.
9. Daniel, L.C., et al., *Frailty and Sleep in Adult Survivors of Childhood Cancer: A Childhood Cancer Survivor Study Report*. Psychooncology, 2025. **34**(2): p. e70098.
10. Williams, A.M., et al., *Physiologic Frailty and Neurocognitive Decline Among Young-Adult Childhood Cancer Survivors: A Prospective Study From the St Jude Lifetime Cohort*. J Clin Oncol, 2021. **39**(31): p. 3485-3495.
11. Williams, A.M., et al., *Premature aging as an accumulation of deficits in young adult survivors of pediatric cancer*. J Natl Cancer Inst, 2023. **115**(2): p. 200-207.
12. Hayek, S., et al., *Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study*. J Clin Oncol, 2020. **38**(3): p. 232-247.
13. Wilson, C.L., et al., *Modifiable Factors Associated With Aging Phenotypes Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia*. J Clin Oncol, 2016. **34**(21): p. 2509-15.
14. Delaney, A., et al., *Progression of Frailty in Survivors of Childhood Cancer: A St. Jude Lifetime Cohort Report*. J Natl Cancer Inst, 2021. **113**(10): p. 1415-1421.
15. Burdette, A.M., et al., *Health Lifestyles in Adolescence and Self-rated Health into Adulthood*. J Health Soc Behav, 2017. **58**(4): p. 520-536.
16. Akasaki, M., et al., *The clustering of risk behaviours in adolescence and health consequences in middle age*. J Adolesc, 2019. **77**: p. 188-197.
17. Engeland, A., et al., *Obesity in adolescence and adulthood and the risk of adult mortality*. Epidemiology, 2004. **15**(1): p. 79-85.
18. Telama, R., et al., *Physical activity from childhood to adulthood: a 21-year tracking study*. Am J Prev Med, 2005. **28**(3): p. 267-73.
19. Kongsvald, A., et al., *Associations of sport and exercise participation in adolescence with body composition and device-measured physical activity in adulthood: longitudinal data from the Norwegian HUNT study*. Int J Behav Nutr Phys Act, 2025. **22**(1): p. 29.
20. Leisenring, W.M., et al., *Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study*. J Clin Oncol, 2009. **27**(14): p. 2319-27.

21. Robison, L.L., et al., *The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research*. J Clin Oncol, 2009. **27**(14): p. 2308-18.
22. Devine, K.A., et al., *Factors associated with physical activity among adolescent and young adult survivors of early childhood cancer: A report from the childhood cancer survivor study (CCSS)*. Psychooncology, 2018. **27**(2): p. 613-619.
23. Mertens, A.C., et al., *Health and well-being in adolescent survivors of early childhood cancer: a report from the Childhood Cancer Survivor Study*. Psychooncology, 2014. **23**(3): p. 266-75.
24. Williams, A.M., et al., *Deficit Accumulation Index and Biological Markers of Aging in Survivors of Childhood Cancer*. JAMA Netw Open, 2023. **6**(11): p. e2344015.
25. Dixon, S.B., et al., *Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort*. Lancet, 2023. **401**(10386): p. 1447-1457.

Example Tables

Example Table 1. Baseline Characteristics of Childhood Cancer Survivors by Adult Frailty Status

Characteristic	Overall	DAI					
		Frail (n) %	P- value	Robust	Medium DAI	High DAI	p-value
Demographics							
Age at assessment, years (mean $\pm$ SD)							
Female sex, n (%)							
Race/Ethnicity, n (%)							
Other							
Educational attainment, n (%)							
High school or less							
Some college							
College graduate or higher							
Utilized special education services, n (%)							
Currently employed, n (%)							
Annual household income $\geq$ \$60,000, n (%)							
Has health insurance, n (%)							
Cancer Diagnosis and Treatment							
Age at diagnosis, years (mean $\pm$ SD)							
Cancer diagnosis, n (%)							
Leukemia							
CNS tumor							
Hodgkin lymphoma							
Non-Hodgkin lymphoma							
Wilms tumor							
Neuroblastoma							
Bone tumor							
Soft tissue sarcoma							
Chemotherapy exposure, n (%)							
Anthracycline exposure, n (%)							
Alkylating agent exposure, n (%)							
Radiation exposure, n (%)							
Cranial radiation $\geq$ 20 Gy, n (%)							
Chest radiation, n (%)							
Abdominal/pelvic radiation, n (%)							

Surgical procedures, n (%)							
Amputation, n (%)							
Nephrectomy, n (%)							
Adolescent Health Behaviors							
Physical activity frequency, n (%)							
Sedentary (0-3 MET-h/week of activity)							
Low physical activity (3-6 MET-h/week)							
Physically active ≥ 6 MET-h/week							
Tobacco use, n (%)							
Ever smoked more than 100 Cigarettes							
Have not smoke more than 100 cigarettes							
Alcohol use, n (%)							
Heavy or risky drinking (>7 drinks/week or >3 drinks/day for women, >14 drinks/week or >4 drinks/day for men)							
No heavy or risking drinking							
Composite healthy lifestyle score (mean $\pm$ SD)							
Healthy lifestyle score (categorical)							
unhealthy (0-1)							
moderately healthy (1.5-2)							
healthy (2.5-3)							
Deficit Accumulation Index (mean $\pm$ SD)							
DAI Categorical							

Example Table 2. Associations Between Adolescent Health Behaviors and Adult Frailty Outcomes (Specific Aim 1)

Health Behavior	High DAI		Frailty Severity (Deficit Accumulation Index)	
	OR (95% CI)	P-value	β (95% CI)	P-value
Physical activity frequency, n (%)				

Sedentary (0-3 MET-h/week of activity)				
Low physical activity (3-6 MET-h/week)				
Physically active ≥ 6 MET-h/week				
<i>P for trend</i>				
Tobacco Use (ever smoked more than 100 cigarettes)				
Onset after 18 or never (ref)				
Onset prior to 18				
Heavy or risky alcohol use (>7 drinks/week or >3 drinks/day for women, >14 drinks/week or >4 drinks/day for men)				
Onset after 18 or never (ref)				
Onset prior to 18				
Composite Healthy Lifestyle Score Continuous				
Per 1-point increase				
Composite Healthy Lifestyle Score (categorical)				
unhealthy (0-1)				
moderately healthy (1.5-2)				
healthy (2.5-3)				

Example Table 3. Health Behavior Trajectory Groups and Frailty Outcomes (Specific Aim 2)

	Cohort	DAI				
Trajectory Group	N (%)	Frailty Prevalence n (%)	Mean Age at Frailty Onset (years $\pm$ SD)	OR (95% CI)	HR (95% CI)	Mean DAI (mean $\pm$ SD)
Maintainers (Healthy throughout lifespan)						

Adopters (Improving over time)						
Decliners (Worsening over time)						
Non-adopters (Persistently unhealthy)						
<i>P for trend</i>						

Example Table 4. Mediation Analysis: Role of Neurocognitive Factors on Frailty (Secondary Aim 1)

Correlative Variable	Total Effect β (95% CI)	Direct Effect β (95% CI)	Indirect Effect β (95% CI)	% Correlated (95% CI)	P-value
Neurocognitive Function (NCQ)					
Memory impairment					
Task efficiency impairment					
Emotional regulation impairment					
Organization impairment					

Example Table 5 Associations Between Self-Reported Adolescent Health Behaviors and Adult Frailty (Exploratory Aim 1)

Self-Reported Health Behavior	Cohort	DAI		Frailty Severity (DAI)	
		OR (95% CI)	P-value	β (95% CI)	P-value
Physical Activity Frequency					
0-2 days/week (ref)					
3-4 days/week					
5-7 days/week					
<i>P for trend</i>					
Screen Time					
<2 hours/day (ref)					
2-4 hours/day					
≥ 4 hours/day					
<i>P for trend</i>					
Total Sedentary Time					
Per 2-hour increase					
Tobacco Use					
Never tried (ref)					
Tried/occasional use					
Alcohol Use					
Never tried (ref)					
Tried/occasional use					
Marijuana Use					
Never tried (ref)					
Tried/occasional use					

Reference Tables

Reference Table 1

Lifestyle factors, including smoking, alcohol use, and physical activity, will be assigned a score of 0 (unhealthy) or 1 (healthy) and combined to create a lifestyle score ranging from 0-3. This will be modified from prior CCSS. Because BMI is included in the DAI, we will not consider healthy weight as determined by BMI in the lifestyle score, although it has previously been published by the CCSS due to concerns for collinearity. We defined unhealthy as: ever smoked more than 100 cigarettes, heavy or risky drinking (>7 drinks/week or >3 drinks/day for women, >14 drinks/week or >4 drinks/day for men), and sedentary (0-3 MET-h/week of activity). For low physical activity (3-6 MET-h/week) a score of 0.5 will be assigned. The lifestyle score was categorized as unhealthy (0-1), moderately healthy (1.5-2), and healthy (2.5-3).

Health Behaviors	Under 18 Baseline	Under 18 Baseline Expansion	FU1	FU2	FU3	FU4	FU 5	FU 6	FU 7	FU8
Physical Activity	N5	O1	Na	D1-D7	na	N15-N21	N15-N24	D1-D10	M15-M24	B4-B13
Alcohol Use	N3, N4	na	Na	na	na	N1, N2 Age started	N1, N2 (age started)	na	M1, M2 (age started)	na
Tobacco Use	N1, N1a, N2	Na	na	L1, L2 (age start)	na	N7, N8 (age start)	N7, N8 (age start)	na	M7, M8 (age started)	na

Reference Table 2

The DAI will be scored continuously and categorically.

- Robust: DAI less than 0.2
- Medium DAI: DAI of 0.2 to less than 0.35
- High DAI: DAI of 0.35 or higher

DAI Construct	CCSS Item (s)	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	FU7	Value/Criteria	DAI Item Score
1. Can take bath/shower (IADL)	Does your health now limit you in these activities? If so how much? Bathing or dressing yourself	N14 F	E12	N26F	O20 F (asked over 2 years)	N29E	N3J	Yes limited a lot	1
								Yes, limited a little	0.5
								No Not limited at all	0

DAI Construct	CCSS Item (s)	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	FU7	Value/Criteria	DAI Item Score
2. Can walk (IADL)	Does your health now limit you in these activities? If so how much? Walking 100 yards (or walking one block)	N14E	E11	N26E	O20 E (Asked over 2 years)	N29E	N3I	Yes limited a lot	1
								Yes, limited a little	0.5
								No Not limited at all	0
3. Health limited moderate activities	Does your physical health now or over the past two years limit you in these activities? Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf	N14B	E4	N26B	O20B	N29B	M29B	Yes limited a lot	1
								Yes, limited a little	0.5
								No Not limited at all	0
4. Health Limited Vigorous Activity	Does your physical health not or over the past two years limit you in these activities? Vigorous activities such as running, lifting heavy objects, participating in strenuous sports	N14a (over 2 years)	E3	N26A	O20A (over years)	N29 A (over 2 years)	M29A	Yes limited a lot	1
								Yes, limited a little	0.5
								No Not limited at all	0
5. Health limited Mobility	Does your health now limit you in these activities? If so how much? Bending lifting or stooping	N14D	E8	N26D	O20D	N29D	N3F	Yes limited a lot	1
								Yes, limited a little	0.5
								No Not limited at all	0
6. Health limited climbing stairs	Does your health now limit you in these activities? If so how much?	N14 C	E7	N26C	O20 C (asked over 2 years)	N29C	N3E	Yes limited a lot	1
								Yes, limited a little	0.5

DAI Construct	CCSS Item (s)	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	FU7	Value/Criteria	DAI Item Score
	Climbing one Flights of Stairs							No Not limited at all	0
7. Pain	How much bodily pain have you had during the past 4 weeks	J36: Do you currently have pain as a results of leukemia, tumor or similar illness or its treatment?	E21	L21	K21	O7	N7	Very Severe, very bad excruciating pain	1
								Severe, A lot of pain	0.75
								Moderate, Medium amount	0.5
								Mild Very Mild, Mild, Small Amount	0.25
								None/No Pain	0
8. General Health (SF-12)	In general, how would you say your health is	N15	E1	L19	O21	O1	N1	Poor	1
								Fair	0.75
								Good	0.5
								Very Good	0.25
								Excellent	0
9. Marital status	Current marital status	L1 and 2	Question 2	M2	M3	M2	A10	Not Married	1
								Formerly Married (divorced/widowed)	0.5
								Married/Living as	0
10. Weight/BMI	Current weight & height	A10 and A11	Questions 7 and 8	A1 and A2	A3 and A4	A1 and 2	A1 and A2	Obese BMI >=30	1
								Underweight BMI <18.5	1
								Normal/Overweight BMI >=18.5 and <30	0

DAI Construct	CCSS Item (s)	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	FU7	Value/Criteria	DAI Item Score
11. Poly-pharmacy	Please indicate all medicines/drugs you took regularly during the two year period Omit antibiotics and chemotherapy	B8	Section Q	C8	B8	C2	C2	>= 5 Prescription Meds	1
								<5 Prescription Meds	0
12. Depression	BSI	BSI	BSI	BSI	BSI	BSI	BSI	T-Score >=63	1
								T-Score <63	0
13. Anxiety	BSI	BSI	BSI	BSI	BSI	BSI	BSI	T-Score >=63	1
								T-Score <63	0
14. Hearing Problems	Hearing loss requiring hearing aid, deafness, tinnitus etc.	Yes to any: C1-C7	Use FU4 and age of onset	Yes to any: D1 through D7 (have age at onset)	Yes to any: C1-7	Yes to any: D1-D7	Yes to any: D1-7	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present or not sure	0
15. Balance Problems	Problems with balance, equilibrium or ability to reach for or manipulate objects?	J8 Problems with balance, equilibrium or ability to reach for or manipulate objects?	use FU4 answer and age at onset	K5 (have age at occurrence)	J5	K5	J5	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present or not sure	0
16. Weakness	Weakness or inability to move arms or legs?	Yes to any: J10 or J11	use FU4 answer and age at onset	Yes to any: K11 or K12 (have age at occurrence)	Yes to any: J11 or J12	Yes to any: K11 or K12	Yes to any: J11 or J12	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present or not sure	0

DAI Construct	CCSS Item (s)	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	FU7	Value/Criteria	DAI Item Score
17. Loss of sense of touch	Decreased sense of touch or feeling in hands, fingers, arms or legs	J12	use FU4 answer and age at onset	K8 (have age at occurrence)	J8	K8	J8	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present or not sure	0
18. Problems chewing and swallowing	Problems chewing or swallowing solids or liquids?	J14	use FU4 answer and age at onset	K7 (have age at occurrence)	J7	K7	J7	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present or not sure	0
19. Smell and taste problems	Abnormal sense of taste or Loss of taste or smell lasting for 3 months or more	Yes to any: C18: Abnormal sense of taste or C19: Loss of taste or smell lasting for 3 months or more	use FU4 answer and age at onset	Yes to any: D21 and D22 (have age at occurrence)	Yes to any: C21 or C22	Yes to any: D21 or D22	Yes to any: D21 or D22	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present or not sure	0
20. Can eat (IADL)	Because of any impairment of health problems, do you need the help of other persons with personal care needs, such as eating, bathing dressing or getting around your home?	N10	use FU4 answer and age at onset	N22 (have age at occurrence)	O16	N25	M25	Yes	1
								No	0

DAI Construct	CCSS Item (s)	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	FU7	Value/Criteria	DAI Item Score
21. Heart Disease Comorbidity	- Myocardial Infarction - Arrhythmia - Coronary Artery Disease - Angina pectoris - Pericarditis - Pericardial constriction - Stiff or leaking heart valves - Blood clot in head, lung, arm, leg, or pelvis - High cholesterol	If Yes to any of these: F3 Arrhythmia F5 Myocardial infarction F6 Coronary Heart Disease F10 Angina Pectoris F11 Pericarditis F12 Pericardial Constriction F13 Stiff/leaky valve F16 Blood clot High Cholesterol from FU4 with age of onset F4 congestive heart failure	use FU4 answer and age at onset	Yes to any: G3: Arrhythmia G2: MI G4: coronary heart disease G6: Angina pectoris G7: pericarditis G8: Pericardial constriction G9: Stiff leaky valves G10 blood clot G12 high cholesterol G1 congestive heart failure	Yes to any: F3: Arrhythmia F2: M I F4 Coronary heart disease F6: angina pectoris F7 Pericarditis F8 Pericardial constriction F9: Stiff or leaky valves F10 blood clot F12 high cholesterol F1 congestive heart failure	Yes to any: F3 Arrhythmia F2: M I F4 Coronary heart disease F6: angina pectoris F7 Pericarditis F8 Pericardial constriction F9: Stiff or leaky valves F10 blood clot F12 high cholesterol F1 congestive heart failure	Yes to any: F3 Arrhythmia F2: M I F4 Coronary heart disease F6: angina pectoris F7 Pericarditis F8 Pericardial constriction F9: Stiff or leaky valves F10 blood clot F12 high cholesterol F1 congestive heart failure	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present (or not sure)	0
22. Diabetes Comorbidity	Diabetes controlled with diet, pills, or insulin shots?	Yes to any: E5, E6, E7	use FU4 answer and age at onset	Yes to any: F5, F6, F7	Yes to any E5, E6, E7	Yes to any G5, G6, G7	Yes to any G5, G6, G7	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present (or not sure)	0
23. Respiratory Comorbidity	- Asthma - chronic cough or SOB - need extra oxygen	Yes to any: G6: Asthma G8: Chronic cough SOB G9: extra O2	use FU4 answer and age at onset	Yes to any: H1: Asthma H2: Chronic cough H3 extra O2	Yes to any: G1: Asthma G2: Chronic cough G3 extra O2	Yes to any: H1: Asthma H2: Chronic cough H3 extra O2	Yes to any: H1: Asthma H2: Chronic cough H3 extra O2	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer	0

DAI Construct	CCSS Item (s)	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	FU7	Value/Criteria	DAI Item Score
	• emphysema or other COPD • lung fibrosis	G11 Emphysema G12 lung fibrosis		H5: Emphysema H6 Lung fibrosis	G5: Emphysema G6 Lung fibrosis	H5: Emphysema H6 Lung fibrosis	H5: Emphysema H6 Lung fibrosis	present (or not sure)	
24. Chronic Liver, Kidney, or GI Comorbidity	• Hepatitis • cirrhosis • any other liver trouble • kidney stones • dialysis • blood or protein in urine • esophageal strictures • rectal or anal fistula • rectal or anal stricture	Yes to any: H4: Hepatitis H3: Cirrhosis H6: any other liver D1: Kidney stones D4: Dialysis D2 or D3 repeated infections H17 Rectal/anal fistula H18 Rectal/anal stricture H8: any disease of esophagus	use FU4 answer and age at onset	Yes to any: I1: Hepatitis (any type) I2: Cirrhosis I3: any other liver E1: Kidney stones E3: Dialysis E2: repeated infections I7 Recta/ or anal fistula I8 rectal or anal stricture I6 Esophageal stricture	Yes to any: H1: Hepatitis (any type) H2: Cirrhosis H3: any other liver D1: Kidney stones D3: Dialysis D2: repeated infections H7 Recta/ or anal fistula H18 rectal or anal stricture H6 Esophageal stricture	Yes to any: I1: Hepatitis (any type) I2: Cirrhosis I4: any other liver E1: Kidney stones E3: Dialysis E2: repeated infections I7 Recta/ or anal fistula I8 rectal or anal stricture I6 Esophageal stricture	Yes to any: I1: Hepatitis (any type) I2: Cirrhosis I4: any other liver E1: Kidney stones E3: Dialysis E2: repeated infections I7 Recta/ or anal fistula I8 rectal or anal stricture I6 Esophageal stricture	Any “yes, and the condition is still present” No or Yes, but the condition is no longer present (or not sure)	1 0
25. Other Cancer/Leukemia Comorbidity:	Self Reported second malignancies (exclude Non-Melanoma skin cancer)	K1 and K5 if not a relapse or recurrence	R1 and R2, exclude recurrence or relapse	P1: exclude recurrence or relapse	L1 and L6: exclude recurrence or relapse	S1 and S6 exclude recurrence or relapse	R1 and R6 exclude recurrence or relapse	Yes and not relapse/recurrence (we may need to review these responses) No	1 0

DAI Construct	CCSS Item (s)	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	FU7	Value/Criteria	DAI Item Score
26. Glaucoma, Cataracts, or decreased vision Comorbidity:	- glaucoma - cataracts - legal blindness - problems with double vision?	Yes to any: C10 Glaucoma C8 legal blindness C11 double vision C9 Cataracts C12 detached retina C14 very dry eyes	use FU4 answer and age at onset	Yes to any: D11 Glaucoma D9: legal blindness D12: double vision D10 Cataracts D13 detached retina D17 dry eyes	Yes to any: C11 Glaucoma C9: legal blindness C12: double vision C10 Cataracts C13 detached retina C17 dry eyes	Yes to any: D11 Glaucoma D9: legal blindness D12: double vision D10 Cataracts D13 detached retina D17 dry eyes	Yes to any: D11 Glaucoma D9: legal blindness D12: double vision D10 Cataracts D13 detached retina D17 dry eyes	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present (or not sure)	0
27. Blood Pressure Comorbidity:	Hypertension	F8 (w/ medication)	use FU4 answer and age at onset	G5 with medication	G5 with medication	F5 with medication	F5 with medication	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present (or not sure)	0
28. Cerebrovascular disease	Stroke	F9	use FU4 answer and age at onset	K14	J14	K14	J14	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present (or not sure)	0
29. Osteoporosis Comorbidity	Osteoporosis or osteopenia?	E10	P1	F10	E10	G10	G10	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer	0

DAI Construct	CCSS Item (s)	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	FU7	Value/Criteria	DAI Item Score
								present (or not sure)	
30. Thyroid Comorbidity:	- through - Hypo-hyper-thyroidism; - thyroid nodules, - swollen or enlarged thyroid.	Yes to any: E1: hyperthyroid D2 hypothyroid E3 nodules E4: other thyroid enlargements	use FU4 answer and age at onset	Yes to any: F1 hyperthyroid F2 hypothyroid F3 nodules F4 swollen or enlarged thyroid	Yes to any: E1 hyperthyroid E2 hypothyroid E3 nodules E4 swollen or enlarged thyroid	Yes to any: G1 hyperthyroid G2 hypothyroid G3 nodules G4 swollen or enlarged thyroid	Yes to any: G1 hyperthyroid G2 hypothyroid G3 nodules G4 swollen or enlarged thyroid	Any “yes, and the condition is still present”	1
								No or Yes, but the condition is no longer present (or not sure)	0
								No or Yes, but the condition is no longer present (or not sure)	0

Reference Table 3

Control Variables: Cancer/Treatment
Age at diagnosis
Primary Cancer Diagnosis
Chemotherapy
Alkylating agent
Anthracycline (doxorubicin)
Platinum agent (cisplatin)
Platinum agent (carboplatin)
Antimetabolites (6-mercaptopurine)
Antimetabolites (6-thioguanine)
Antimetabolites -Methotrexate
Antimetabolites- Oral Methotrexates
Microtubule targeting drugs
Radiation
Radiation Cranial
Radiation chest
Radiation Abdomen/Pelvis
Surgery
Surgery Nephrectomy

Surgery cystectomy
Surgery Thoracotomy
Surgery Craniotomy
Surgery Amputation
Hematopoietic stem cell transplantation (yes/no)

Teen Ancillary Survey

Physical Activity
BMI
Alcohol use
Tobacco use
Marijuana Use
Screen time
Sedentary behavior