Childhood Cancer Survivor Study

Analysis Concept Proposal

1. **Project Title:**

   Accelerated Aging as an Accumulation of Deficits in Survivors of Childhood Cancer and its Association with Mortality, Cognitive, and Sleep Outcomes.

2. **Working group:**

   Psychology/Neuropsychology (primary)

   Chronic Disease Working Group (secondary)

   Epidemiology/Biostatistics (secondary)

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4. **Background:**

   Cancer survivors experience significant premature mortality and age-related health conditions, such as cognitive decline and sleep disturbance. In the general population, age is the most significant risk factor for mortality, cognitive decline, and sleep disturbance. Yet we know that among individuals of the same chronological age there is great variability in physical and psychosocial health, suggesting differences in biological

aging. This underlying variability in biological aging may be exacerbated in childhood cancer survivors whose cancer treatment exposures may cause molecular damage, including changes to DNA structure, cellular function, signaling, and tissue integrity. These treatment exposures happen during key developmental stages and may alter growth and maturation and subsequently set them on a unique physiologic, biologic, and cognitive aging trajectory. Further, early molecular damage may make survivors more vulnerable to social and environmental insults as they age (e.g. socioeconomic factors, smoking, low physical activity).[1] This accumulation of damage may result in multimorbidity and physiologic frailty which can contribute to cognitive decline, sleep disturbance, and early mortality.

At a mean age of 33 years, 8% of childhood cancer survivors have a physiologic frailty phenotype; a prevalence similar to that of adults at an age of 65 years.[1] Ninety-five percent of childhood cancer survivors have at least one chronic health condition and 68% have at least one serious, life-threatening, or disabling condition.[2] These data suggest that childhood cancer survivors may experience premature aging and an accumulation of aging-related deficits. In the general population, aging is associated with changes in sleep architecture and circadian rhythm including an increased risk for obstructive sleep apnea and insomnia.[3] In childhood cancer survivors, BMI and various chronic health conditions, both of which increase with age, were associated with an increased risk of disordered sleeping and daytime sleepiness.[4] Additionally, in non-cancer populations, various chronic health conditions such as cardiovascular conditions are associated with cognitive decline and shorter lifespan.[5-8] We have also demonstrated that specific health conditions (e.g., hypertension) and physiologic frailty are associated with cognitive impairment and decline in childhood cancer survivors (Williams et al., manuscript under review).[9] However, these individual factors have not been examined using an integrative approach that allows us to evaluate an accumulation of multiple types of deficits in relation to age, as well as their impact on cognitive or sleep outcomes.

We propose to evaluate an age-related deficit accumulation index (DAI) as an indication of the changes in health status associated with biologic aging and physiologic dysregulation in childhood cancer survivors (Figure 1), and assess its association with mortality, cognitive, and sleep outcomes.[10] Deficit accumulation indexes are composed of 30 or more aging-related conditions, with a ratio created of the proportion of those potential conditions that an individual has, to conceptualize aging as a process of accumulation of deficits. Items included in the DAI must 1) be associated with health status, 2) have an increasing prevalence with age, and 3) not saturate in the population too early (see section 6b).[11] The proposed CCSS DAI covers a diverse group of aging-related factors, such as hearing loss and cardiovascular morbidity (Table 1). DAI scores can range from 0 to 1 with a higher score indicating more deficits. Deficit accumulation indices have predicted hospitalization and mortality in non-cancer populations and have been used to characterize aging and functional and cognitive decline in breast cancer survivors and other cancers.[12-16] Moreover, meaningful clinical differences in changes in the DAI have been established.[17] However, this framework has not yet been applied to childhood cancer survivors. This approach allows us to integrate large and small effects, using information that on its own may only weakly correlate with an outcome, but when combined together will contribute to significant effects. In fact, these indexes have

predicted dementia when individual risk factors do not.[18] An integrated approach to measuring individual aging is important because the components that contribute to aging are not independent.

This will be the first study to use the accumulation of deficits to characterize accelerated aging using longitudinal data from survivors as well as siblings. The aims and hypotheses below focus on two approaches: 1) the change in DAI between two time points and 2) the trajectory of the DAI across three or more time points. Currently, only the original cohort in the CCSS has survey items necessary to compute the DAI at three or more time points. We can only measure the DAI at two time points in the expansion cohort. Because the expansion and original cohorts differ on key treatment factors it is important to include both cohorts. Therefore, our primary analyses will focus on the change in DAI between baseline and FU2 or FU5 surveys, respectively. Additional exploratory analyses will examine the trajectory of the DAI over three or more time points in the original cohort.

The results from this study will provide important data on the accelerated accumulation of age-related deficits in childhood cancer survivors relative to siblings and which treatment, clinical, and social factors are associated with a greater increase in aging-related deficit accumulation over time. It will also inform on aging-related trajectories and their influence on functional outcomes such as cognition and sleep and ability to predict mortality. This study also aims to inform a clinically feasible method to comprehensively evaluate aging and aging-related risks in childhood cancer survivors as all items used to generate the index are readily available in the medical record or easily collected via questionnaire.

5. Specific Aims:

Aim 1: Assess the change (e.g., from baseline to follow-up) in aging-related deficit accumulation index (DAI) and the trajectories of the DAI over time (e.g., ≥3 time points in the original cohort) in childhood cancer survivors using siblings' DAI data as age-sex-specific normative data.

Hypothesis 1.1: Compared with siblings, survivors will have a greater change in DAI between baseline and follow-up.

Hypothesis 1.2: The trajectory of DAI over time will differ in survivors relative to siblings, with survivors experiencing a faster accumulation of deficits with time.

Aim 2: Among survivors, examine associations between treatment/clinical factors with change and trajectories of the aging-related DAI over time.

Hypothesis 2: Survivors of central nervous system tumors, those that received craniospinal irradiation and those further from diagnosis will have a larger change and worse trajectories of the aging-related DAI.

Aim 3: Among survivors, characterize the association between trajectory/change in aging-related DAI and subsequent cognition, sleep, and mortality.

Hypothesis 3.1: A positive change in the aging-related DAI between baseline and follow-up survey will be associated with an increased risk of subsequent neurocognitive impairment (at FU5), poor sleep (at FU6), and mortality.

Hypothesis 3.2: A worsening trajectory of the aging-related DAI over time will be associated with an increased risk of subsequent neurocognitive impairment (at FU5), poor sleep (at FU6), and mortality.

Note: FU7 anticipated completion is Fall of 2021 with data freeze available Summer of 2022. Therefore, if FU7 data become available during our analyses, we will incorporate FU7 data into these analyses. Specifically, the Expansion Cohort will be included in the trajectory analysis: without FU7, the Expansion Cohort has only two surveys.

6. Analysis Framework:

a. Study Population: All survivors of childhood cancer and siblings enrolled in the CCSS cohort who were ≥ 18 years attained age at the required follow-up survey. All items for the DAI are available on questionnaires from the original/expansion baseline surveys, FU2, FU4 and FU5. For Hypothesis 1.1 we will calculate change in DAI between two time points. For the original cohort this will be done in participants who completed baseline and FU2 surveys, for the expansion, this will be done in participants who completed baseline and FU5 surveys. For hypothesis 2.2 we will calculate trajectories of the DAI over time which requires at least three time points. Therefore, only participants from the original cohort with data from at least three follow up time points will be included (e.g. baseline, FU2, FU4, or FU5). However, should data from FU7 become available, participants form the expansion cohort with data from three or more time points will be included. Aims 2 and 3 will use these same groups. For Aim 3, neurocognitive outcomes will be taken from FU5, sleep outcomes from FU6, and mortality from the most recent National Death Index inquiry.

b. Outcome Variables:

i. Aging-related Deficit Accumulation Index (DAI): We will use the methods of Searle and colleagues[11] to design an aging-related deficits accumulation index (DAI) using data available from CCSS questionnaires. The index consists of 30 items that are: 1) associated with health status, 2) have an increasing prevalence with age, and 3) do not saturate in the population too early.[11] The entire index covers a diverse group of aging-related factors, such as hearing loss and cardiovascular morbidity (Table 1). The items included are non-specific in that they do not necessarily predict risk of decreased life expectancy, but rather correlate with age. This allows us to integrate large and small effects, using information that on its own may only weakly correlate with an outcome, but when combined together may contribute more significant effects.

Rockwood and colleagues have demonstrated that the total number of items or the specific items included in an index do not need to be identical across studies to see similar associations with mortality and the rate of deficit accumulation.[11] This suggests that age-related accumulation of deficits can be measured in a variety of ways, across a variety of studies, or clinical settings. Therefore, we have carefully evaluated the data available from CCSS for a total of 30 total items.

The index will be calculated by summing the number of items a participant has and dividing by the total number of items (30). Items may be individually weighted as 1 for yes and 0 for no for dichotomous items. Items may also be weighted on a scale from 0 to 1 for categorical items. As an example: for questions on a Likert scale with 5 response options, 0 would be assigned if the participant indicates “none of the time”, 0.2 if they indicate “a little of the time”, 0.4 if they indicate “some of the time” and so on. We will examine the grade distribution of conditions and determine if the grading should be incorporated into the weighting of that item. We will also examine frequencies and determine if these should be weighted by the frequency of conditions as well. Based on published guidance, participants will have to have complete data for ≥90% of the items for the DAI to be calculated.[11] Prior to analyses we will check the frequency of each item, including its missingness, and the proportion of participants missing >10% of items (Table 1).

Once the index is calculated we will examine its distribution and determine if any clear thresholds or cut points emerge. We will also explore using the siblings to define a level of “impairment/aging” that is meaningful (e.g. top 10th percentile of DAI in siblings).

ii. Neurocognitive Outcomes: Neurocognitive impairment will be assessed using the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ; FU2: J1-J25, FU5: Q1-Q33). The CCSS-NCQ was developed and validated for use in cancer survivors and assesses four specific domains: task efficiency, emotional regulation, organization, and memory. Scores for each of the four domains will be operationalized as binary variables (impaired vs not) for each of the Aims (unless otherwise noted). Participants will be considered impaired if their score is ≥ the 90th percentile based on values obtained in the sibling cohort.

iii. Sleep

1. Sleep will be assessed using the Pittsburg Sleep Quality index (PSQI, FU6) which asks participants to describe their sleep habits over the past month. Higher scores indicate worse sleep. The overall score as well as score from the following 7 sub-domains will be examined: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime sleepiness. Norms are available for total PSQI score and each subdomain with a specific focus on domains related to aging: snoring, sleep efficiency, and daytime sleepiness. Scores will be calculated and converted to T-scores. A higher T-score indicates worse sleep. A T-score >90th percentile will be used to define impairment.

iv. Mortality

1. The primary mortality end point will be all-cause mortality. If the data allow, we will examine cause-specific mortality (e.g. cardiovascular)

c. Covariates:

i. Aim 1
    1. Survivor or sibling control
    2. Age at evaluation
    3. Sex
    4. Race and ethnicity
    5. Smoking status at baseline (never a smoker, >100 cig/lifetime but not currently smoking, >100 cigs/lifetime and current smoker)

ii. Aim 2:

    1. Age at diagnosis
    2. Time since diagnosis
    3. Diagnosis (separate analyses)
    4. HSCT recipient (allogeneic, autologous, none)
        a. Will examine with and without total body irradiation
    5. Radiation Exposures (y/n, can also look at cumulative dose defined cut points depending on numbers)
        a. Craniospinal
        b. Chest
        c. Abdominal/Pelvic
    6. Chemotherapy Exposures (y/n or can also look at cumulative dose defined cut points depending on numbers)
        a. Anthracycline /Alkylating agents (CED and doxorubicin equivalents)
        b. Vincristine
        c. Cyclophosphamide
        d. Corticosteroid/glucocorticoids (prednisone equivalents)
        e. Platinum agents (y/n)
        f. Intrathecal chemotherapy (methotrexate and/or cytarabine)
        g. High-dose IV methotrexate
        h. High-dose IV cytarabine
    7. Surgery
        a. Neurosurgery
        b. Amputation

7. Statistical Analysis

Aim 1: Assess the change (e.g., from baseline to follow-up) in aging-related deficit accumulation index (DAI) and the trajectories of the DAI over time (e.g., ≥3 time points in the original cohort) in childhood cancer survivors using siblings' DAI data as age-sex-specific normative data.

Hypothesis 1.1: Compared to siblings, survivors will have a greater change in DAI between two time points.

Baseline descriptive characteristics will be reported (Table 2) including the mean DAI in survivors and siblings at their baseline survey (mean and 95%CI) and each follow up survey. The aging-related DAI will be calculated for both CCSS survivors and siblings using data from their baseline surveys and FU2 for the original cohort and FU5 for the expansion cohort so that the time between surveys is comparable. We will examine the mean time between surveys to determine if another time point is more appropriate (e.g.

FU4 for original cohort). There may be significant attrition from baseline to follow-up surveys, therefore, survivors who completed both time points will be compared to survivors who were eligible but did not complete both time points (Table 3). If they differ on key factors and the potential for selection bias exists, we will use inverse probability weighting for all analyses moving forward.

Due to the difference in time between baseline and FU2 for the original cohort and baseline and FU5 for the expansion cohort we will standardize the DAI with respect to age and sex according to the sibling distribution. We will first take the DAI calculated at all time points for the sibling cohort accounting for within-subject correlation and estimate age-sex-specific means and standard deviations of siblings. With these, we will calculate age-sex-specific Z-scores (or T-scores) for the survivors at each relevant time point according to their age, sex, and DAI. Change in DAI will then be calculated as their Z-score from time 2 minus the Z-score at time 1. A primary advantage of this approach is that it provides an estimate of the change in DAI relative to what is expected among a general (sibling) population for a given age and sex (as the change in DAI likely increases with age and could differ by sex). Our primary model will be a linear regression of changes in the DAI Z-score with time, adjusting for the baseline DAI Z-score and age/sex (age/sex is need to estimate potential differential increases of DAI Z-score by baseline age/sex among survivors). The mean change and its 95%CI from baseline to time 2 will be reported.

In exploratory analyses, we will examine differences in the change in aging related DAI between survivors and siblings stratified by sex (Table 4). For example, the difference in change in DAI in survivors vs. siblings may be greater among females than among males.

Hypothesis 1.2: The trajectory of DAI over time will differ between survivors and siblings, with survivors experiencing a faster accumulation of deficits with time.

Currently only survivors and siblings from the original cohort who have complete data at three or more time points will be eligible for these analyses (the expansion cohort only has two time points, unless FU7 becomes available). Because the original and expansion cohorts differ on key factors likely related to the DAI (e.g. amount of radiation exposure) our primary analyses will focus on change between two time points where we can use both cohorts, and trajectory analyses will remain exploratory. There has been significant attrition in the group of original cohort members completing three or more surveys that include DAI items, therefore, those who completed three or more surveys will be compared to those who were eligible but did not complete three or more surveys (Table 5). If the potential for selection bias exists, we will use inverse probability weighting in all longitudinal analyses. Using the same methods described above, we calculate age and sex specific Z-scores for each time point available for the survivors. We will use the SAS Proc Traj package (downloadable here: http://www.andrew.cmu.edu/user/bjones/) [19] to identify group-based trajectories of the aging-related DAI. This method assumes the population is composed of distinct groups with distinct trajectories. It is an extension of mixture modeling and uses maximum likelihood methods to estimate membership probabilities for multiple trajectories.[20] The Bayesian Information Criterion (BIC) will be used to select the number of trajectory groups (e.g. lowest BIC). Once the aging-related DAI trajectories are identified, they will be plotted in survivors and siblings (Figure 1). Then logistic regression (or multinomial logistic through the GEE framework to account for the correlation between siblings and

siblings) will be used to compare the trajectories of survivors and siblings adjusting for current age, sex, and race/ethnicity (Table 6).

Note on availability of FU7 data: If FU7 data become available, participants in the expansion cohort who completed both FU5 and FU7 will be included in analyses described above for Hypothesis 1.2.

Aim 2: Among survivors, examine associations between treatment/clinical factors with change and trajectories of the aging-related DAI over time.

Hypothesis 2: Survivors of central nervous system tumors, those that received craniospinal irradiation or HSCT, and those further from diagnosis will have a larger change and worse trajectories of the aging-related DAI.

Analyses performed for Aim 1 will be repeated for each diagnosis group (provided there are sufficient numbers) with a focus on acute lymphoblastic leukemia, Hodgkin lymphoma, and CNS tumor survivors (Table 7). Distributions of treatment and sociodemographic variables will be examined to determine how to parametrize them (e.g. continuous, yes/no, categorical). Linear regression will be used to identify sociodemographic and treatment factors (noted above) associated with change in the aging-related DAI. Marginal adjusted means for the change in DAI Z-score will be reported according to treatment era, and treatment exposures (Table 7). Univariate analyses will be run for each predictor, then multivariable models will be generated that account for all marginally significant predictors ($p<0.20$).

Polytomous logistic regression will be used to identify if any sociodemographic, clinical, and treatment factors are associated with specific trajectories of the DAI over time. These models will be adjusted for age at DAI evaluation, sex, race, and baseline DAI. The ORs and 95% confidence intervals will be reported. Univariate analyses will be run for each predictor, then multivariable models will be generated that account for all marginally significant predictors ($p<0.20$).

Based on our findings here, sensitivity analyses will be done, repeating the analyses for Aim3 below independently among survivors of certain tumors or treatment exposures (e.g. CNS tumors, Hodgkin lymphoma, and Wilm's tumors).

Aim 3: Among survivors, characterize the association between trajectory/change in aging-related DAI and subsequent cognition, sleep, and mortality.

Hypothesis 3.1: A positive change in the aging-related DAI between first and last survey will be associated with an increased risk of neurocognitive impairment (at FU5), poor sleep (at FU6), and mortality.

Logistic regression will be used to estimate the association between change in DAI Z-score and the risk of neurocognitive impairment (FU5) and sleep impairment(FU6), adjusted for the baseline DAI Z-score (Table 8, adjusted for the same variables identified in Aim 2) and stratified by history of CNS-directed therapy (cranial radiation, intrathecal chemotherapy, and neurosurgery). Unfortunately baseline neurocognitive and sleep data are unavailable, therefore, results will be interpreted cautiously as we cannot truly determine temporality.

Cox proportional hazards models will be used to estimate the risk of death associated with change in DAI Z-score from baseline to FU2 (original cohort) or FU5 (expansion)

starting from FU2/FU5. We will also consider the use of a joint longitudinal-survival analysis (e.g. frailty model analysis) if the data fit. This will allow us to examine if the baseline DAI or the change in DAI has a higher influence on mortality risk. Additionally because this analysis inherently conditions that the survivor must have made it to FU2 or FU5, and those with the highest DAI are likely most at risk for mortality, we may underestimate the association between DAI and mortality. Therefore we will conduct additional Cox proportional hazards models using just the baseline DAI which will allow us to use the entire cohort.

As the change in DAI may differ depending on the baseline DAI, we will conduct sensitivity analyses stratified by baseline DAI using cut points widely used in the DAI literature to define robustness (e.g. 0.0 to 0.2).[11] We will also conduct sensitivity analyses to examine how the change in DAI Z-score is associated with change in neurocognition. Linear regression will estimate if the change in DAI Z-score is associated with change in each subdomain of the NCQ.

Hypothesis 3.2: A worsening trajectory of the aging-related DAI overtime will be associated with an increased risk of neurocognitive impairment (at FU5), poor sleep (at FU6), and mortality.

Logistic regression will be used to estimate the association between DAI Z-score trajectory groups and the risk of neurocognitive impairment (FU5) and sleep impairment(FU6), adjusted for the baseline DAI Z-score (Table 9, adjusted for the same variables identified in Aim 2). Cox proportional hazards models will be used to estimate the risk of death associated with DAI trajectory groups.

References:

1. Ness KK, Kirkland JL, Gramatges MM, Wang Z, Kundu M, McCastlain K, et al. Premature Physiologic Aging as a Paradigm for Understanding Increased Risk of Adverse Health Across the Lifespan of Survivors of Childhood Cancer. J Clin Oncol. 2018;36(21):2206-15.
2. Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). The Lancet. 2017;390(10112):2569-82.
3. Miner B, Kryger MH. Sleep in the Aging Population. Sleep Med Clin. 2017;12(1):31-8.
4. Mulrooney DA, Ness KK, Neglia JP, Whitton JA, Green DM, Zeltzer LK, et al. Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the childhood cancer survivor study (CCSS). Sleep. 2008;31(2):271-81.
5. Lee JH, Choi Y, Jun C, Hong YS, Cho HB, Kim JE, et al. Neurocognitive changes and their neural correlates in patients with type 2 diabetes mellitus. Endocrinology and metabolism (Seoul, Korea). 2014;29(2):112-21.
6. Crews WD, Jefferson AL, Bolduc T, Elliott JB, Ferro NM, Broshek DK, et al. Neuropsychological dysfunction in patients suffering from end-stage chronic obstructive pulmonary disease. Arch Clin Neuropsychol. 2001;16(7):643-52.
7. Vogels RL, Oosterman JM, van Harten B, Gouw AA, Schroeder-Tanka JM, Scheltens P, et al. Neuroimaging and correlates of cognitive function among patients with heart failure. Dement Geriatr Cogn Disord. 2007;24(6):418-23.

8. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. NCHS Data Brief. 2018(328):1-8.
9. Cheung YT, Brinkman TM, Li C, Mzayek Y, Srivastava D, Ness KK, et al. Chronic Health Conditions and Neurocognitive Function in Aging Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2018;110(4):411-9.
10. Rockwood K, Howlett SE. Age-related deficit accumulation and the diseases of ageing. Mech Ageing Dev. 2019;180:107-16.
11. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24.
12. Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc. 2006;54(6):975-9.
13. Mandelblatt JS, Clapp JD, Luta G, Faul LA, Tallarico MD, McClendon TD, et al. Long-term trajectories of self-reported cognitive function in a cohort of older survivors of breast cancer: CALGB 369901 (Alliance). Cancer. 2016;122(22):3555-63.
14. Mandelblatt JS, Zhou X, Small BJ, Ahn J, Zhai W, Ahles T, et al. Deficit Accumulation Frailty Trajectories of Older Breast Cancer Survivors and Non-Cancer Controls: The Thinking and Living With Cancer Study. JNCI: Journal of the National Cancer Institute. 2021.
15. Cohen HJ, Smith D, Sun CL, Tew W, Mohile SG, Owusu C, et al. Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. Cancer. 2016;122(24):3865-72.
16. Starkman R, Alibhai S, Wells RA, Geddes M, Zhu N, Keating MM, et al. An MDS-specific frailty index based on cumulative deficits adds independent prognostic information to clinical prognostic scoring. Leukemia. 2020;34(5):1394-406.
17. Jang IY, Jung HW, Lee HY, Park H, Lee E, Kim DH. Evaluation of Clinically Meaningful Changes in Measures of Frailty. J Gerontol A Biol Sci Med Sci. 2020;75(6):1143-7.
18. Song X, Mitnitski A, Rockwood K. Nontraditional risk factors combine to predict Alzheimer disease and dementia. Neurology. 2011;77(3):227-34.
19. Jones BL, Nagin DS. Advances in Group-Based Trajectory Modeling and an SAS Procedure for Estimating Them. Sociological Methods & Research. 2007;35(4):542-71.
20. JONES BL, NAGIN DS, ROEDER K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. Sociological Methods & Research. 2001;29(3):374-93.

Table 1: CCSS Aging-related deficit accumulation index.

DAI Construct	CCSS Item	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	Value/Criteria	DAI Item Score
1. Can take bath/shower (IADL)	O3-J: Does your health now limit you in these activities? If so how much? J: Bathing or dressing yourself	N14 F	E12	N26F	O20 F (asked over 2 years)	N29E	Yes limited a lot	1
							Yes, limited a little	0.5
							No Not limited at all	0
2. Can walk (IADL)	O3-I: Does your health now limit you in these activities? If so how much? I: Walking 100 yards (or walking one block)	N14E	E11	N26E	O20 E (Asked over 2 years)	N29E	Yes limited a lot	1
							Yes, limited a little	0.5
							No Not limited at all	0
3. Health limited moderate activities (SF-12)	Does your physical health not 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	Yes limited a lot	1
							Yes, limited a little	0.5
							No Not limited at all	0
4. 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)	Yes limited a lot	1
							Yes, limited a little	0.5
							No Not limited at all	0
5. Mobility	Does your health now limit you in these activities? If so how much? Bending lifting or stooping	N14D	E8	N26D	O20D	N29D	Yes limited a lot	1
							Yes, limited a little	0.5
							No Not limited at all	0

DAI Construct	CCSS Item	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	Value/Criteria	DAI Item Score
6. Health limited climbing stairs	O3-D: Does your health now limit you in these activities? If so how much? D: Climbing one Flights of Stairs	N14 C	E7	N26C	O20 C (asked over 2 years)	N29C	Yes limited a lot	1
							Yes, limited a little	0.5
							No Not limited at all	0
7. Pain	O7: 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	FU5: O7	Very Severe	1
							Severe	0.8
							Moderate	0.6
							Mild	0.4
							Very Mild	0.2
							None	0
8. General Health (SF-12)	O1: In general, how would you say your health is	N15	E1	L19	O21	FU5: O1	Poor	1
							Fair	0.75
							Good	0.5
							Very Good	0.25
							Excellent	0
9. Marital status	M2: Current marital status	L1 and 2	Question 2	M2	M3	FU5: M2	Not Married	0
							Formerly Married (divorced/widowed)	0.5
							Married/Living as	1
10. Weight/BMI	A1: Current weight; A2 height	A10 height, A11 weight	Questions 7 and 8	A1 and A2	A3 and A4	FU 1 A1 and 2	Obese BMI >=30	1
							Underweight BMI <18.5	1
							Normal/Overweight	0
							BMI >=18.5 and <30	

DAI Construct	CCSS Item	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	Value/Criteria	DAI Item Score
11. Poly-pharmacy	C2: Please indicate all medicines/drugs you took regularly during the two year period between:	B8	Section Q	C8	B8	FU 5 C2	>= 5 Prescription Meds	1
							<5 Prescription Meds	0
12. Depression	BSI	BSI	BSI	BSI	BSI	BSI	T-Score >=63	1
							T-Score <63	0
13. Anxiety	BSI	BSI	BSI	BSI	BSI	BSI	T-Score >=63	1
							T-Score <63	0
14. Hearing Problems	D1-D7 (hearing loss requiring hearing aid, deafness, tinnitus etc.)	C1-C7	hearing loss identified on FU4 or earlier	hearing loss identified on FU4 or earlier	C1-7	D1-D7 (hearing loss requiring hearing aid, deafness, tinnitus etc.)	Any “yes, and the condition is still present”	1
							No or Yes, but the condition is no longer present	0
15. Balance Problems	K5 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 Problems with balance, equilibrium or ability to reach for or manipulate objects?	Any “yes, and the condition is still present”	1
							No or Yes, but the condition is no longer present	0
16. Weakness	Weakness or inability to move arms or legs?	J10 or J11	use FU4 answer and age at onset	K11 or K12 (have age at occurrence)	J11 or J12	K11 or K12	Any “yes, and the condition is still present”	1
							No or Yes, but the condition is no longer present	0

DAI Construct	CCSS Item	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	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	Any “yes, and the condition is still present”	1
							No or Yes, but the condition is no longer present	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)	J17	K7	Any “yes, and the condition is still present”	1
							No or Yes, but the condition is no longer present	0
19. Smell and taste problems	D21: Abnormal sense of taste or D22: Loss of taste or smell lasting for 3 months or more	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	D21 and D22 (have age at occurrence)	C21 or C22	D21: Abnormal sense of taste or D22: Loss of taste or smell lasting for 3 months or more	Any “yes, and the condition is still present”	1
							No or Yes, but the condition is no longer present	0
20. Can eat (IADL)	N25: 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	FU5: N25	Yes	1
							No	0
21. Heart Disease Comorbidity	F2: Myocardial Infarction; F3: Arrhythmia?; F4 Coronary Artery Disease?: F6: Angina pectoris? F7:	Use CTCAE Grading and date of onset for all time points					≥ 1 Grade 3 or 4 Condition	1
							≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5

DAI Construct	CCSS Item	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	Value/Criteria	DAI Item Score
	Pericarditis?; F8: Pericardial constriction?; F9: Stiff or leaking heart valves?; F10: Blood clot in head, lung, arm, leg, or pelvis? F12: High cholesterol?						None or Only Grade 1 Conditions	0
22. Diabetes Comorbidity	G5-G7: Diabetes controlled with diet, pills, or insulin shots?	Use CTCAE Grading and date of onset for all time points					≥ 1 Grade 3 or 4 Condition	1
							≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
							None or Only Grade 1 Conditions	0
23. Respiratory Comorbidity	H1: Asthma? H2: chronic cough or SOB? H3: need extra oxygen? H5: emphysema or other COPD? H6: problems with breathing that lasted >3 months?	Use CTCAE Grading and date of onset for all time points					≥ 1 Grade 3 or 4 Condition	1
							≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
							None or Only Grade 1 Conditions	0
24. Chronic Liver, Kidney, or GI Comorbidity	I1: hepatitis, I2: cirrhosis, I3: any other liver trouble; E1: kidney stones? E3 dialysis? E4/5: blood or protein in urine? I5: esophageal strictures, I7: rectal or anal fistula?, I8: rectal or anal stricture? I9: any other digestive or stomach trouble?	Use CTCAE Grading and date of onset for all time points					≥ 1 Grade 3 or 4 Condition	1
							≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
							None or Only Grade 1 Conditions	0
25. Other Cancer/Leukemia Comorbidity:	CCSS confirmed second malignancies (exclude	Use CTCAE Grading and					≥ 1 Grade 3 or 4 Condition	1

DAI Construct	CCSS Item	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	Value/Criteria	DAI Item Score
	Non-Melanoma skin cancer)	date of onset for all time points					≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
							None or Only Grade 1 Conditions	0
26. Glaucoma, Cataracts, or decreased vision Comorbidity:	D11: glaucoma? D10: cataracts? D8/9 legal blindness D12: problems with double vision?	Use CTCAE Grading and date of onset for all time points					≥ 1 Grade 3 or 4 Condition	1
							≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
							None or Only Grade 1 Conditions	0
27. Blood Pressure Comorbidity:	F5 Hypertension	Use CTCAE Grading and date of onset for all time points					≥ 1 Grade 3 or 4 Condition	1
							≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
							None or Only Grade 1 Conditions	0
28. Cerebrovascular disease	K14: Stroke?	Use CTCAE Grading and date of onset for all time points					≥ 1 Grade 3 or 4 Condition	1
							≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
							None or Only Grade 1 Conditions	0
29. Osteoporosis Comorbidity	G10: Osteoporosis or osteopenia?	Use CTCAE Grading and date of onset for all time points					≥ 1 Grade 3 or 4 Condition	1
							≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
							None or Only Grade 1 Conditions	0

DAI Construct	CCSS Item	Original Cohort Baseline Survey	FU 2	FU4	Expansion Cohort Baseline Survey	FU 5	Value/Criteria	DAI Item Score
30. Thyroid Comorbidity:	G1 through G4: Hypo-hyper- thyroidism; thyroid nodules, swollen or enlarged thyroid.	Use CTCAE Grading and date of onset for all time points					≥ 1 Grade 3 or 4 Condition	1
							≥ 1 Grade 2 Condition (but no grade 3 or 4)	0.5
							None or Only Grade 1 Conditions	0

Table 2: Characteristics of Study Population (N(%) unless otherwise specified)

	Survivors	**Siblings**	**p-value**
	N (%)	N (%)	
Sex			
Male			
Female			
Race			
White			
Black			
Other			
Ethnicity			
Hispanic			
Non-Hispanic			
Smoking Status			
Never			
Former (>100 cigs and no current smoking)			
Current (>100 cigs and current smoking)			
Age at Follow Up (Years)			
Mean (sd)			
Median (range)			
Age at Diagnosis (Years)		-	-
Mean (sd)		-	-
Median (range)		-	-
Time Since Diagnosis (Years)		-	-
Mean (sd)		-	-
Median (range)		-	-
Treatment Decade		-	-
1970-1979		-	-
1980-1989		-	-
1990-1999		-	-
Diagnosis		-	-
Acute lymphoblastic leukemia		-	-
CNS tumor		-	-
Hodgkin lymphoma		-	-
Neuroblastoma		-	-
Non-Hodgkin lymphoma		-	-
Osteosarcoma		-	-
Other Leukemia		-	-
Retinoblastoma		-	-
Ewing sarcoma		-	-
Soft tissue sarcoma		-	-
Others		-	-
Hematopoietic Stem Cell Transplant		-	-
Yes		-	-
No		-	-
Radiation		-	-

No radiation treatment		-	-
Any radiation treatment		-	-
Cranial radiation		-	-
Mean (SD)		-	-
Yes		-	-
No		-	-
		-	-
Chest		-	-
Mean (SD)		-	-
Yes		-	-
No		-	-
Abdomen/Pelvic		-	-
Mean (SD)		-	-
Yes		-	-
No		-	-
		-	-
Chemotherapy		-	-
High-dose IV cytarabine (N%)		-	-
Mean (SD)		-	-
Standard-dose IV cytarabine (N%)		-	-
Mean (SD)		-	-
High-dose IV methotrexate (N%)		-	-
Mean (SD)		-	-
Standard-dose IV methotrexate (N%)		-	-
Mean (SD)		-	-
Intrathecal methotrexate (N%)		-	-
Mean (SD)		-	-
IV Vincristine (N%)		-	-
Mean (SD)		-	-
Anthracycline Equivalent dose (N%)		-	-
Mean (SD)		-	-
Cyclophosphamide Equivalent dose (N%)		-	-
Mean (SD)		-	-
Any Platinum Agent (N%)		-	-
Mean (SD)		-	-
Cisplatin (N%)		-	-
Mean (SD)		-	-
Corticosteroid (All) (N%)		-	-
Mean (SD)		-	-
Surgery		-	-
Neurosurgery		-	-
Amputation		-	-
Major surgery (other than neurosurgery)		-	-
Minor Surgery		-	-

Table 3: Example potential for attrition to influence selection bias.

	Survivors		**Siblings**		**p-value**
	Completed baseline and FU2/FU5	**Eligible for FU2/FU5 but did not complete**	**Completed baseline and FU2/FU5**	**Eligible for FU2/FU5 but did not complete**	
	N (%)	N(%)	N(%)	N (%)	
Sex					
Male					
Female					
Race					
White					
Black					
Other					
Ethnicity					
Hispanic					
Non-Hispanic					
Smoking Status					
Never					
Former (>100 cigs and no current smoking)					
Current (>100 cigs and current smoking)					
Age at Follow Up (Years)					
Mean (sd)					
Median (range)					
Age at Diagnosis (Years)				-	-
Mean (sd)				-	-
Median (range)				-	-
Time Since Diagnosis (Years)				-	-
Mean (sd)				-	-
Median (range)				-	-
Treatment Decade				-	-
1970-1979				-	-
1980-1989				-	-
1990-1999				-	-
Diagnosis				-	-

Acute lymphoblastic leukemia				-	-
CNS tumor				-	-
Hodgkin lymphoma				-	-
Neuroblastoma				-	-
Non-Hodgkin lymphoma				-	-
Osteosarcoma				-	-
Other Leukemia				-	-
Retinoblastoma				-	-
Ewing sarcoma				-	-
Soft tissue sarcoma				-	-
Others				-	-
Hematopoietic Stem Cell Transplant				-	-
Yes				-	-
No				-	-
Radiation				-	-
No radiation treatment				-	-
Any radiation treatment				-	-
Cranial radiation				-	-
Mean (SD)				-	-
Yes				-	-
No				-	-
				-	-
Chest				-	-
Mean (SD)				-	-
Yes				-	-
No				-	-
Abdomen/Pelvic				-	-
Mean (SD)				-	-
Yes				-	-
No				-	-
				-	-
Chemotherapy				-	-
High-dose IV cytarabine (N%)				-	-
Mean (SD)				-	-

Standard-dose IV cytarabine (N%)				-	-
Mean (SD)				-	-
High-dose IV methotrexate (N%)				-	-
Mean (SD)				-	-
Standard-dose IV methotrexate (N%)				-	-
Mean (SD)				-	-
Intrathecal methotrexate (N%)				-	-
Mean (SD)				-	-
IV Vincristine (N%)				-	-
Mean (SD)				-	-
Anthracycline Equivalent dose (N%)				-	-
Mean (SD)				-	-
Cyclophosphamide Equivalent dose (N%)				-	-
Mean (SD)				-	-
Any Platinum Agent (N%)				-	-
Mean (SD)				-	-
Cisplatin (N%)				-	-
Mean (SD)				-	-
Corticosteroid (All) (N%)				-	-
Mean (SD)				-	-
Surgery				-	-
Neurosurgery				-	-
Amputation				-	-
Major surgery (other than neurosurgery)				-	-
Minor Surgery				-	-

Table 4: Mean change in aging-related DAI.

	Marginal Adjusted Mean Change in DAI Z-score (95%CI)	p-value
In the entire cohort: [1]		
Survivors		
Among Females:		
Survivors		
Among Males:		
Survivors		

Table 5: Differences in original cohort participants who completed three or more assessments compared to those who did not.

	Survivors			Siblings		
	Completed ≥3 Assessments	Eligible but did not Complete ≥3 Assessments	p-value	Completed ≥3 Assessments	Eligible but did not Complete ≥3 Assessments	p-value
	N (%)	N (%)		N (%)	N (%)	
Sex						
Male						
Female						
Race						
White						
Black						
Other						
Ethnicity						
Hispanic						
Non-Hispanic						
Smoking Status						
Never						
Former (>100 cigs and no current smoking)						
Current (>100 cigs and current smoking)						
Age at Follow Up (Years)						
Mean (sd)						
Median (range)						
Age at Diagnosis (Years)						
Mean (sd)						
Median (range)						
Time Since Diagnosis (Years)						
Mean (sd)						
Median (range)						
Treatment Decade						
1970-1979						
1980-1989						
1990-1999						
Diagnosis						
Acute lymphoblastic leukemia						
CNS tumor						
Hodgkin lymphoma						
Neuroblastoma						
Non-Hodgkin lymphoma						
Osteosarcoma						

Other Leukemia				
Retinoblastoma				
Ewing sarcoma				
Soft tissue sarcoma				
Others				
Hematopoietic Stem Cell Transplant				
Yes				
No				
Radiation				
No radiation treatment				
Any radiation treatment				
Cranial radiation (n=387)				
Mean (SD)				
Yes				
No				
Chest				
Mean (SD)				
Yes				
No				
Abdomen/Pelvic				
Mean (SD)				
Yes				
No				
Chemotherapy				
High-dose IV cytarabine (N%)				
Mean (SD)				
Standard-dose IV cytarabine (N%)				
Mean (SD)				
High-dose IV methotrexate (N%)				
Mean (SD)				
Standard-dose IV methotrexate (N%)				
Mean (SD)				
Intrathecal methotrexate (N%)				
Mean (SD)				
IV Vincristine (N%)				
Mean (SD)				
Anthracycline Equivalent dose (N%)				
Mean (SD)				
Cyclophosphamide Equivalent dose (N%)				

Mean (SD)				[redacted]
Any Platinum Agent (N%)				
Mean (SD)				
Cisplatin (N%)				
Mean (SD)				
Corticosteroid (All) (N%)				
Mean (SD)				
Surgery				
Neurosurgery				
Amputation				
Major surgery (other than neurosurgery)				
Minor Surgery				

Figure 1: Trajectories of the DAI among survivors and siblings.

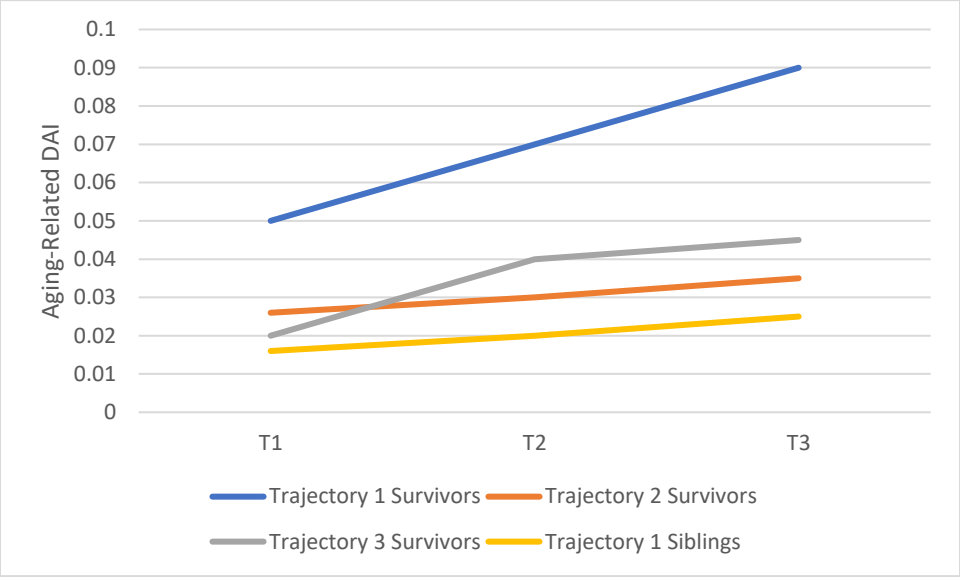

Table 6: Risk of being in each trajectory of the aging-related DAI in survivors compared to siblings.

	N(%)	Mean Difference (95%CI)	p-value
Trajectory 1			
Survivors			
Siblings		1.0 (ref)	
Trajectory 2			
Survivors			
Siblings		1.0 (ref)	
Trajectory 3			
Survivors			
Siblings		1.0 (ref)	
Etc.			

Table 7: The mean change in the aging-related DAI Z-score from FU2 to FU5 by demographic, clinical, and treatment factors.

	Change in DAI Mean (SD)	Mean Difference in Change in DAI (95%CI)	p-value
Diagnosis [1]			
Acute lymphoblastic leukemia			
CNS tumor			
Hodgkin lymphoma			
Neuroblastoma			
Non-Hodgkin lymphoma			
Osteosarcoma			
Other Leukemia			
Retinoblastoma			
Ewing sarcoma			
Soft tissue sarcoma			
Others			
Siblings		1.0 (ref)	
Age at Diagnosis (Years)	-		
Time Since Diagnosis (Years)	-		
Treatment Decade			
1970-1979			
1980-1989			
1990-1999		1.0 (ref)	
Hematopoietic Stem Cell Transplant			
Yes			
No		1.0 (ref)	
Radiation			
No radiation treatment		1.0(ref)	
Any radiation treatment			
Cranial radiation			
None		1.0 (ref)	
Any			
Chest			
None		1.0 (ref)	
Any			
Abdomen/Pelvic			
None		1.0 (ref)	
Any			
Chemotherapy			
High-dose IV cytarabine			
No		1.0 (ref)	
Yes			
Standard-dose IV cytarabine			
No		1.0 (ref)	
Yes			
High-dose IV methotrexate			

No		1.0 (ref)	
Yes			
Standard-dose IV methotrexate			
No		1.0 (ref)	
Yes			
Intrathecal methotrexate			
No		1.0 (ref)	
Yes			
IV Vincristine			
No		1.0 (ref)	
Yes			
Anthracycline Equivalent dose			
No		1.0 (ref)	
Yes			
Cyclophosphamide Equivalent dose			
No		1.0 (ref)	
Yes			
Any Platinum Agent			
No		1.0 (ref)	
Yes			
Cisplatin			
No		1.0 (ref)	
Yes			
Corticosteroid (All)			
No		1.0 (ref)	
Yes			
Surgery			
Neurosurgery			
No		1.0 (ref)	
Yes			
Amputation			
No		1.0 (ref)	
Yes			
Major surgery (other than neurosurgery)			
No		1.0 (ref)	
Yes			
[1] For each diagnosis group we will estimate the mean difference in change in DAI compared to siblings in a model separate from the treatment factors.			

Table 8: Associations between 1 unit increase in DAI Z-score and the risk of neurocognitive and sleep impairments.

	N(%)	Change in DAI Mean (SD)	t-test p-value	RR(95%CI)	p-value
NCQ at FU5					
Task Efficiency					
Impaired					
Unimpaired			-	1.0 (ref)	
Organization					
Impaired					
Unimpaired			-	1.0 (ref)	
Memory					
Impaired					
Unimpaired			-	1.0 (ref)	
Emotional Regulation					
Impaired					
Unimpaired			-	1.0 (ref)	
PSQI total score FU6					
Impaired					
Unimpaired			-	1.0 (ref)	

Table 9: Associations between DAI trajectories and the risk of neurocognitive and sleep impairments.

	N(%)	Task Efficiency	Organization	Memory	Emotional Regulation	Sleep impairment
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Trajectory 1						
Trajectory 2						
Trajectory 3		1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)