CCSS Analysis Concept Proposal

Study Title: The changing pattern of late mortality as survivors age and the impact of modifiable risk factors and markers of biologic and cognitive impairment on late mortality among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study

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1. Background and Rationale

Although 5-year survival after childhood cancer diagnosis now exceeds 85%,[1] long-term survivors still experience excess mortality compared to the general population.[2-4] Prior studies using the Childhood Cancer Survivor Study (CCSS) cohort identified that although death due to relapse or progression of primary cancer accounted for most deaths in early survivorship, by 30 years from diagnosis, a larger proportion of survivors died due to health-related causes.[4] Studies since observed that survivors diagnosed in the 1990s experience a much lower 15-year recurrence/progression related cumulative mortality than those diagnosed in the 1970s or 1980s (15-year cumulative recurrence/progression mortality among 1990s: 3.4%, 1980s: 4.9%, 1970s: 7.1%). Although mortality due to health-related causes at 15-years was also lower among the 1990s group, the magnitude of difference between eras was only approximately one-third of that seen for mortality due to recurrence/progression (15-year cumulative health-related mortality among 1990s: 1.9%, 1980s: 2.4%, 1970s: 3.1%). The change in health-related mortality at 25-years from diagnosis remains unknown.[2] As survivors continue to age, advancing understanding about the contribution of specific causes of death to overall mortality is important as is identifying which risk factors, aside from treatment exposures, have the greatest impact on late-mortality risks over time. Prior studies identified that up to 30 years from diagnosis, the rate of death due to recurrence or progression of primary disease decreases. Death due to specific health-related causes initially increases slowly in a fairly linear fashion from years 5-20 from

diagnosis; however, between 20-30 years from diagnosis, health-related deaths increase exponentially.[4,5] This trend is true for health-related mortality overall but also evident for subsequent malignancies, cardiac, pulmonary and other health-related causes. The current expanded CCSS cohort with 2017 death data provides 15 additional years of mortality data compared to prior cause-specific mortality studies, with 45 years of follow-up among survivors diagnosed in the early 1970s. Further, with over 6,000 deaths in the eligible cohort including 4,000 deaths that occurred after completion of baseline questionnaire, of which almost 50% are anticipated to be due to health-related causes, this analysis will provide a novel opportunity to describe more detailed specific health-related causes of death than the broad categories of subsequent malignancy, cardiac causes, etc. and to describe changes in subsequent cancer type (leukemia, lymphoma, breast, colon, lung etc.) or cardiac condition (myocardial infarction, heart failure, etc.) causing death over time.

Modifiable cardiovascular risk factors including hypertension, diabetes, dyslipidemia and obesity have been demonstrated to potentiate treatment-associated risk for major cardiac events in survivors.[6] Other behavioral risk factors, such as smoking history, alcohol consumption and physical activity, may independently increase risk for mortality outcomes. Prior studies in the CCSS have demonstrated that low levels of physical activity are associated with increased mortality among survivors.[7,8] Additionally, a study by Cox et al. identified being underweight, compared to healthy weight, and no alcohol consumption, compared to ever consuming, as risk factors for health-related late mortality among survivors. However, they were unable to identify associations with obesity and smoking status and did not examine cause-specific mortality as there were only 445 health-related deaths among their population.[7] Studies from the general population have shown that behavioral factors or living a "healthy lifestyle", including low to moderate alcohol consumption, no tobacco exposure, remaining physically active, maintaining a normal BMI and eating a healthy diet reduce all-cause and both cancer-related and cardiac mortality.[9-11] Additionally, studies from the general population have demonstrated that approximately 40% of cancer cases and deaths in adults in the United States can be attributed to behavioral risk factors (cigarette smoking, excess body weight, alcohol intake, physical inactivity, sun exposure and dietary choices).[12] With regard to modifiable cardiovascular health conditions, within the NHANES cohort, adults in the general population with diabetes had a 68% increase in rate of death from any cause with an 81% increase in rate of death from cardiovascular disease compared to non-diabetics after adjustment for age, sex, BMI, smoking status and alcohol use.[13] Also from the NHANES cohort, adults in the general population with hypertension that was either untreated or undertreated/uncontrolled had a 62% increase in rate of death from any cause with a more than 2-fold increase in rate of death due to cardiovascular disease compared to normotensive adults.[14] The CCSS cohort has collected detailed treatment and mortality data as well as self-reported modifiable risk factors at multiple time-points including hypertension, diabetes, dyslipidemia, BMI, smoking status, alcohol intake and physical activity over 40 years of follow-up among the oldest survivors. This offers a unique opportunity to not only identify changing patterns of cause-specific late mortality as survivors age, but also the impact of modifiable risk factors on all-cause and cause-specific mortality.

Associations between other markers of aging and mortality have not been explored in the entire CCSS cohort. In the general population, cognitive decline, specifically in the domains of memory and processing speed, has been identified as a predictor of mortality.[15] Among older adults, the presence of mild cognitive impairment has also been associated with long-term mortality.[15] Another marker of aging described in the CCSS cohort is frailty. Frailty, most commonly described in elderly adults, is a decrease

in physiologic reserve that interferes with normal physical function and has been associated with multiple adverse health outcomes, including death.[16] The reported prevalence of frailty among adult survivors of childhood cancer in the CCSS was 3 times that of siblings.[17] Among survivors in the SJLIFE cohort, survivors with a median age in their 30s had a similar prevalence of frailty to general population adults in their 60s and beyond.[18] Further, in the SJLIFE cohort, the presence of frailty in survivors was associated with an increased risk for death compared to those who were not frail, even after adjusting for chronic conditions (HR 2.6, 95% CI 1.2 to 6.2). Associations between frailty and mortality have not been explored in the CCSS. Inclusion of frailty and cognitive impairment as markers of biologic aging will complement the analysis of chronologic aging and mortality.

2. Specific Aims

2.1. **Aim 1a:** Describe the impact of aging on cause-specific late-mortality among childhood cancer survivors comparing cumulative mortality (all-cause and cause-specific) and evaluating specific ICD-based causes of death conditioned on survival from diagnosis (5, 10, 15, 20, 25, 30, 35 and 40 years later) and then attained age to identify changes in patterns of mortality as survivors age.

2.2. **Aim 1b:** Examine the impact of original cancer treatment on late mortality conditioned on survival (attained age) as treatment-related risk may change over time.

2.3. **Aim 2:** Examine the association between modifiable risk factors, including lifestyle behaviors, and rates of late mortality (all-cause and cause-specific) and standardized mortality ratios (all-cause and cause-specific). We will examine each behavioral lifestyle factor (BMI, smoking, alcohol intake, physical activity) and cardiovascular risk factor (hypertension, diabetes, dyslipidemia) individually and also by a composite of a healthy lifestyle score that will include smoking, alcohol, physical activity and BMI. This will be presented overall, and by attained age in 10-year increments (5-15 years, 16-25 years, 26-35 years, 36-45 years, 45+ years). Of note, because many survivors are surveyed at multiple time points and these conditions and behaviors change, we will treat them as time-varying predictors and use each survey response in the analysis.

2.4. **Aim 3:** Examine the association between frailty and subsequent late mortality. We will present these data overall and by attained age in 10-year increments (5-15 years, 16-25 years, 26-35 years, 36-45 years and 45+ years). Of note, because many survivors are surveyed at multiple time points and frailty status may change over time, we will treat it as a time-varying predictor and use each survey response in the analysis.

2.5. **Aim 4:** Examine the association between cognitive impairment associated with aging (memory and executive function) and mortality, We will present these data overall and by attained age in 10 year increments (5-15 years, 16-25 years, 26-35 years, 36-45 years and 45+ years). Of note, if any survivors contribute neurocognitive questionnaire responses at multiple timepoints (FU-2, FU-5, FU-6), we will consider treating this as a time-varying predictor and use each survey response in the analysis.

2.6. **Exploratory Aim:** Evaluate the above associations between modifiable risk factors and cumulative mortality by treatment era, using 5-year time blocks.

3. Hypotheses

Aim 1:

3.1. We hypothesize that the rate of late-mortality will be highest in years 5-9 from diagnosis due to risk of death from recurrent or progressive disease, which has been demonstrated in prior studies.[5] However, we also anticipate that the rate will be somewhat U-shaped for all-cause mortality, and begin to increase again 25-30 years from diagnosis (or in the 4th and 5th decades of life) as survivors accumulate a larger burden of chronic disease related to treatment, lifestyle factors and/or aging.

3.2. We hypothesize that cause-specific mortality will change significantly by survival time. We will build on the knowledge that there is a progressive decrease in rate of recurrence/progression-related mortality over time and an increase in the rate of subsequent malignancy and cardiac deaths as survivors age into middle and late adulthood by describing changes in patterns of specific causes of death based on ICD codes.

3.3. When compared to the general population (matched for age, sex, race/ethnicity and calendar-year), we anticipate that across attained ages, the rate of death among survivors for all causes of death (except external causes) will be higher than the US population. Although the rate for death due to recurrence/progression will continually decrease over time, we anticipate that while the SMRs for death due to specific health-related causes will decrease over time, they will remain higher relative to the general population (SMR>1.0) as survivors age.

Aim 2:

3.4. We hypothesize that survivors with modifiable risk factors including both lifestyle factors and preventable/modifiable chronic health conditions will have an increased risk for mortality compared to survivors without these conditions. Additionally, when compared to the general population overall (age-, sex-, race/ethnicity- and calendar-year matched), we hypothesize that survivors with modifiable risk factors will have higher SMRs for both all-cause and health-related causes of death than survivors without modifiable risk factors, although we expect both groups to have higher rates of death than the general population (SMR >1.0).

3.5. We hypothesize that when compared to survivors with a favorable healthy lifestyle composite score, those with a worse score (more risk factors) will have higher rates of death. Further, we hypothesize that an unfavorable healthy lifestyle score will further increase risk of death among individuals with preventable/modifiable chronic health conditions, compared to individuals with the condition who live a “healthy lifestyle”.

Aim 3:

3.6. We hypothesize that survivors with frailty will have increased all-cause and health-related mortality when compared to both survivors without frailty and the general population matched for age, sex, race and calendar year.

Aim 4:

3.7. We hypothesize that survivors with impairment in memory and/or executive function will have increased all-cause and health-related mortality when compared to survivors without

impairment. Further, we anticipate that survivors with impairment in both memory and executive function will have higher risk for mortality than those without impairment or with impairment in only single domain. Finally, we expect those with more severe impairment will be at highest risk.

Exploratory Aim:

3.8. We hypothesize that the addition of treatment era may attenuate some of the observed associations due to changes in combinations of treatment exposures and intensity of treatment overtime.

4. Methods

4.1. **Study Population:** All 5-year survivors in the overall CCSS cohort (diagnosed between 1970 and 1999). For Aim 1, all eligible subjects will be included. For subsequent aims, the subset of eligible CCSS participants who completed a baseline or follow-up survey that includes the measures of interest will be included. For aims 2-4, Canadian survivors will be excluded because cause of death is unknown. For aim 3, frailty will only be assessed among participants who were 18 or older at the time of survey completion (proxy report is allowed). For aim 4, neurocognitive outcomes will only be assessed among participants who were 18 or older at the time of survey completion (proxy reports will be excluded).

4.2. **Outcome Measure:** Mortality data will be obtained from the US National Death Index (NDI) through 2017. Deaths that predated the NDI (those occurring in 1975-1978) have been obtained using death certificates from the states where deaths occurred. Mortality will be evaluated as a time-to-event outcomes and all relevant information will be collected from all questionnaires. For aim 1 only, cause of death among Canadian participants will be imputed, as has been performed in prior CCSS analyses.[6]

We will use vital status (alive/dead) to estimate a) cumulative mortality b) mortality rates and c) standardized mortality ratios (SMR). SMRs will be calculated using age- sex-, race- and calendar year-specific mortality rates for the U.S. population from the National Center for Health Statistics as per the method established by Mertens et al for previous CCSS publications.[19] Underlying cause of death has been determined from death certificates and will be grouped into three mutually exclusive categories as[2]:

4.2.1. Recurrence/progression of primary childhood malignancy
4.2.2. External cause (e.g. accidents, injuries, suicides)
4.2.3. Non-recurrence/non-external cause (attributable to chronic health conditions) sub-classified as subsequent neoplasms, cardiac, pulmonary and all other causes.

We will also describe causes of death by specific ICD-based causes of death for health-related causes of death by survival.

4.3. **Explanatory variables:**

Sociodemographic variables:

4.3.1. Age at cancer diagnosis
4.3.2. Age at follow-up
4.3.3. Sex

4.3.4. Race and ethnic group
4.3.5. Treatment era (1970-74, 1975-79, 1980-84, 1985-89, 1990-94, 1995-99)
4.3.6. Education attainment (high school or less vs some college) at each time-point surveyed (treat as time-varying covariate)
4.3.7. Insurance status at each time-point surveyed (treat as time-varying covariate)
4.3.8. Marital status at each time-point surveyed (treat as time-varying covariate)
4.3.9. Household Income at each-time-point surveyed (treat as time-varying covariate)

Prior to analyses, we will examine the missingness of education, insurance, marital status and household income at each survey collected.

Modifiable lifestyle/behavior risk factors recorded at each survey returned and treated as time-varying covariates in analyses:
For the below covariates, smoking status and alcohol consumption will include only self-report from participants 18+ at the time of survey completion. Prior to analyses, we will explore the missingness of the below variables at each survey collected.

4.3.10. Smoking status ever (Ever/Never based on the response to question N7, "have you smoked at least 100 cigarettes since you last provided us the information?" ever being yes)
4.3.11. Smoking status current (Current, Former or Never) based on ever having smoked at least 100 cigarettes and whether or not they currently reported smoking[20]
4.3.12. Alcohol consumption, drinks/week and heavy alcohol consumption (Y/N: 7+/week female, 14+/week male)
4.3.13. Risky drinking as yes to the answer "ever consuming in excess of 3 (F) or 4 (M) drinks per day
4.3.14. Physical activity (MET-h/week) calculated using the methods from the prior analysis by Scott et al. to categorize as 0, 3 to 6, 9 to 12 and 15-21 MET-h/wk.[8] Adequate physical activity (Y/N) will be defined as survivors achieving at least 9 MET-h/wk. This information is available on baseline and follow-up questionnaires whereas the necessary questions to calculate minutes/wk of moderate to vigorous physical activity are not available at baseline.
4.3.15. BMI in kg/m^2 and healthy weight (Y/N) as BMI 18.5 to <25 for adults and BMI 5^{th}%ile to <85^{th}%ile for children
4.3.16. Healthy Lifestyle Score: Will be calculated for each survey returned as a composite of the above variables with 0 being an unhealthy lifestyle and 4 being a healthy lifestyle. We will examine the distribution of the above variables prior to finalizing the below proposed scoring.
    1) Smoking: Ever = 0 and Never = 1; however, we will examine the distribution of pack-years and consider a 0.5 point for survivors who report very low lifestyle tobacco use.
    2) Alcohol consumption: Heavy or Risky drinking = 0, no heavy or risking drinking = 1
    3) Physical activity: 0 Met-h/wk = 0, 3 to 6 MET-h/wk = 0.5 and 9 to 12, or 15-21 MET-h/wk = 1, based on findings from the analysis of Scott et al.[8]
    4) BMI: Healthy weight (N) = 0, Healthy weight (Y) = 1; however, we will examine the distribution of BMI and consider a score of 0.5 for survivors with a BMI of 25-<30

Modifiable chronic health conditions as risk factors recorded at each survey returned and treated as time-varying covariates in analyses:

4.3.17. Hypertension (Y/N: defined as CTCAE grade ≥2) and CTCAE grade: grade 2 (medications) and grade 3 (hypertensive heart or chronic kidney disease). We will explore the number of participants with CTCAE grade 1 (hypertension, not on medications) prior to analysis.
4.3.18. Diabetes (Y/N: defined as CTCAE grade ≥2) and CTCAE grade: grade 2 (oral medications only) and grade 3 (requiring insulin). We will explore the number of participants with CTCAE grade 1 (diabetes not on medications) prior to analysis.
4.3.19. Dyslipidemia (Y/N: defined as CTCAE grade 2 for either high cholesterol or high triglycerides requiring medication). We will explore the number of participants with CTCAE grade 1 (other and unspecified hyperlipidemia) prior to analysis.

Modified Fried frailty criteria among adults (≥18 years at survey) [16,17,21], recorded at each survey returned and treated as time-varying covariate in analysis:

4.3.20. Low lean muscle mass: BMI <18.5 kg/m^2
4.3.21. Self-reported exhaustion: score of ≤40 on the Vitality subscale of the Medical Outcomes Survey Short Form-36[22]
4.3.22. Low energy expenditure: < 383 kcal/wk males and < 270 kcal/wk females from conversion of frequency and duration of low, moderate, and vigorous activities[23,24]
4.3.23. Walking limitations: "limited for more than 3 months" in response to the question "Over the last 2 years, how long has your health limited you in walking uphill or climbing a few flights of stairs?" or "Over the last 2 years, how long has your health limited you in walking on block?"
4.3.24. Weakness: "Yes, and the condition is still present" to the question "have you ever been told by a doctor or other health care professional that you have, or have had, weakness or inability to move your arms?"

Cognitive impairment including memory and task efficiency recorded at each survey containing the NCQ (FU-2, FU-5 and FU-6 long):

Cognitive impairment in survivors will be assessed using the CCSS-NCQ which was developed for use and validated within the CCSS cohort using 4 factors; Task Efficiency, Emotional Regulation, Organization, and Memory. Raw scores referenced to the sibling cohort, with scores ≥90th percentile of siblings classified as impairment has been the threshold used in the validation studies of the CCSS-NCQ and prior CCSS studies.[25] As task efficiency or processing speed and memory are the measures assessed typically associated with aging, we will focus our analysis to impairments in these domains. Additionally, we will grade the degree of neurocognitive impairment modelling the grading scale after studies using the St. Jude Lifetime Cohort[26] where impairment will be defined as ≥1 and < 2 standard deviations (SDs) (Grade 1, mildly impaired), ≥ 2and <3 SD (Grade 2, moderately impaired), and ≥ 3 SD (Grade 3, severely impaired) below the mean age-adjusted population normative score on any one measure. Moderate impairment (scores below the lowest 3rd percentile for population norms) would be expected to impact instrumental activities of daily living, while severe impairment (scores below the lowest 0.3 percentile for population norms) would be expected to impact self-care activities of daily living. Of note, this analysis will exclude those <18 year or with proxy reports.

4.3.25. Memory Impairment (Y/N) and grade
4.3.26. Task Efficiency Impairment (Y/N) and grade

4.3.27. Category of Impairment: mutually exclusive as 1) no impairment in either task efficiency or memory 2) memory impairment alone 3) task efficiency impairment alone and 4) both memory and task efficiency impairment
4.3.28. Grade of impairment (recorded as the maximum grade of Memory and Task Efficiency)

Treatment-related variables:
4.3.29. Cancer Diagnosis
4.3.30. Cranial irradiation (Y/N) and dose
4.3.31. Total body irradiation, TBI (Y/N)
4.3.32. BMT, hematopoietic cell transplant within 5 years from diagnosis (Y/N)
4.3.33. Chest irradiation (Y/N) and dose
4.3.34. Anthracycline (Y/N) and cumulative anthracycline in doxorubicin equivalent dose[27]
4.3.35. Alkylators (Y/N) and cumulative alkylators in cyclophosphamide equivalent dose[28]
4.3.36. Epipodophyllotoxins (Y/N) and cumulative dose by summing the doses of etoposide and teniposide as done in prior analyses[5,29]
4.3.37. Bleomycin (Y/N) and cumulative dose
4.3.38. Platinum (Y/N) and cumulative dose as the sum of the carboplatin dose divided by 4 and the cisplatin dose as done in prior analyses[29,30]
4.3.39. Methotrexate (Y/N) and cumulative dose
4.3.40. SMN status: (Y/N) occurring 5 or more years from diagnosis. This variable will be collected only to explore use as a surrogate for survivors who would have received additional treatment not included in their MRAF

4.4. **Statistical Analysis Framework:**

4.4.1. **Aim 1: Describe the impact of aging on causes of late mortality among childhood cancer survivors.**

Since mortality data are available for all CCSS eligible subjects (except Canadians) from the National Death Index (NDI), we will use the eligible cohort (rather than participants only) for aim 1 using methods consistent with previous CCSS mortality publications including imputation of treatment information for non-participants with missing treatment information.[2]

We will estimate:

1) Cumulative mortality with 95% confidence intervals (CI) for all-cause and cause-specific mortality for the entire CCSS eligible cohort by gender, diagnosis and conditional survival time in 5-year (and/or 10 year) intervals after cohort entry at 5-years from diagnosis.

2) Rates of death (all-cause and cause-specific) per 1,000 person-years with 95% CI by gender, diagnosis and conditional survival in 5-year intervals beginning at 5-years from diagnosis. (Table 5)

3) Standardized mortality ratios (SMR) and absolute excess risk (AER) with 95% CI using age-, sex- and calendar year- specific U.S. mortality rates from the NDI by gender, diagnosis and survival time in 5-year intervals beginning at 5-years from diagnosis for all-cause and cause-specific mortality. We will also present the SMR in 5-year intervals by chronologic age beginning at age 5-9 years old. (Table 6)

4) Relative rates (RR) and 95% confidence intervals (CI) of death due overall health-related causes of death and then due to specific health-related causes (cardiac,

pulmonary, infection, etc.) by survival time, relative to a reference survival time (will explore use of 5-9 years vs intermediate survival time) and then by chronologic age (will explore use of 5-9 years vs a more intermediate time-point), using multivariable piecewise exponential models adjusting for sex, race/ethnicity and age at diagnosis. The model will also adjust for specific therapeutic exposures which will require multiple imputation of therapeutic exposures for eligible survivors who did not MRAF data collected. (Table 7)

5) Descriptive analysis including graphic presentations of specific ICD-coded causes of death by survival time. Figures would visually display the causes of health-related mortality by ICD-code (or code groups) for survivors who died in the 5-9 year period, 10-14 year period etc. and then for survivors by chronologic age who died between ages 5-9 years, 10-14 years old etc. Depending on the number of deaths in each category we may choose to present this data in 10-year periods and 10-year age blocks.

4.4.2. **Aim 2: Examine the association between modifiable risk factors (both lifestyle/behavioral and modifiable chronic conditions) and health-related mortality rates and compare to the general population using standardized mortality ratios.**

This analysis will include only CCSS participants who have completed a survey that includes the modifiable and lifestyle factors at age 18 or greater. To estimate the association between overall and cause-specific mortality and modifiable risk factors including lifestyle/behavioral factors (smoking, alcohol intake, physical activity and BMI) and modifiable chronic conditions (hypertension, diabetes, and dyslipidemia) we will first dichotomize each risk factor as above. Importantly, all risk factors will be treated as time-varying covariates as survivors may be diagnosed with hypertension, diabetes or dyslipidemia at some time after baseline and we will have the age of diagnosis. For lifestyle/behavioral factors these may change at each survey time-point which will be important to account for in analyses.

We will estimate:

1) Rates of death (all-cause and cause-specific) per 1,000 person-years with 95% CI by individual modifiable risk factor and also a composite healthy lifestyle score by number of low-risk lifestyle factors (0, 1, 2, 3, 4). We will present these rates overall and by attained age in 10-year increments (5-14 yrs, 15-24 yrs, 25-34 yrs, 35-44 yrs, 45+ years). (Table 8)
2) Standardized mortality ratios (SMR) and absolute excess risk (AER) with 95% confidence intervals (CI) using age-, sex- and calendar year- specific U.S. mortality rates from the NDI by individual modifiable risk factor and also a composite healthy lifestyle score by number of low-risk lifestyle factors for all-cause and cause-specific mortality. We will present these rates overall and by attained age in 10-year increments (5-14 yrs, 15-24 yrs, 25-34 yrs, 35-44 yrs, 45+ years). (Table 9)
3) Hazard ratios (HR) with 95% CI for all-cause, overall health-related causes of death and then due to specific health related causes (cardiac, pulmonary, infection, etc.) using piecewise exponential models for each individual modifiable risk factor and then a composite healthy lifestyle score. We will then go on to estimate the HR for combinations of modifiable risk factors and healthy lifestyle score. This will be presented overall, and by attained age in 10-year increments (5-14 yrs, 15-24 yrs,

25-34 years, 35-44 years, 45+ years). These analyses will adjust for sociodemographic factors known to impact chronic conditions, lifestyle and mortality such as education, income, and insurance status in addition to age, sex and race/ethnicity. (Table 10)

4) Depending on the significance and magnitude of the above hazard ratios, we will consider presenting proportion of deaths attributable to each modifiable risk factors will be estimated considering the mortality rate among the survivors with the risk factor of interest and comparing to the those without the risk factor of interest for all-cause and health-related specific causes of death (subsequent malignancy, cardiac, pulmonary and other health-related cause).

4.4.3. **Examine the association between frailty and late mortality.** This analysis will include only CCSS participants who have completed a survey that includes the modified Fried frailty criteria at age 18 or greater.[16] Similar to a recent analysis by Hayek et al., frailty status will be categorized as not frail for those endorsing 0-1 of 5 measures, prefrail for those endorsing 2 of 5 measures and frail for those endorsing 3 or more of the 5 measures listed in outcome variables.[17] However, we will use data from all surveys that include frailty questions (original baseline, expansion baseline, follow-up 2 and follow-up 5). We will examine missingness of data needed for categorization prior to analysis. Frailty status may change at each survey time-point, which will be important to account for in analyses as a time-varying predictor.

We will estimate:

1) Rates of death per 1,000 person-years with 95% CI by frailty status (not frail, prefrail and frail). We will present these rates overall and by attained age in 10-year increments (18-24 yrs, 25-34 yrs, 35-44 yrs, 45+ years). (Table 11)
2) Standardized mortality ratios (SMR) and absolute excess risk (AER) with 95% confidence intervals (CI) using age-, sex- and calendar year- specific U.S. mortality rates from the NDI for the general population to compare to survivors by frailty status (not frail, prefrail and frail) for all-cause and cause-specific mortality. We will present these rates overall and by attained age in 10-year increments (18-24 yrs, 25-34 yrs, 35-44 yrs, 45+ years). (Table 12)
3) Hazard ratios (HR) with 95% CI for all-cause mortality, overall health-related mortality and specific health-related causes (SMN, cardiac, pulmonary other) using piecewise exponential models for frailty status. This will be presented overall, and by attained age in 10-year increments (18-24 yrs, 25-34 yrs, 35-44 yrs, 45+ years). These analyses will adjust for sociodemographic factors known to impact chronic conditions, lifestyle and mortality such as education, income, and insurance status in addition to age at diagnosis, sex and race/ethnicity. (Table 13)

4.4.4. **Examine the association between memory impairment as a marker of cognitive age and late mortality.** This analysis will include only CCSS participants who have completed a survey that includes the NCQ (FU-2 or FU-5) at the age of 18 or greater and will exclude proxy reports. Because only the original cohort would have the potential to contribute multiple time-points of NCQ data, we will use only the first time point for analysis.

We will estimate:

1) Rates of death per 1,000 person-years with 95% CI by cognitive impairment (memory impairment (Y/N), task efficiency impairment (Y/N)) and then by category of impairment (no impairment, task efficiency impairment alone, memory impairment alone, both memory and task efficiency impaired). We will present these rates overall and by attained age in 10-year increments (18-24 yrs, 25-34 yrs, 35-44 yrs, 45+ years). (Tables 14, 15)
2) Standardized mortality ratios (SMR) and absolute excess risk (AER) with 95% confidence intervals (CI) using age-, sex- and calendar year- specific U.S. mortality rates from the NDI for the general population to compare to survivors by cognitive impairment for all-cause and cause-specific mortality. We will present these rates overall and by attained age in 10-year increments (18-24 yrs, 25-34 yrs, 35-44 yrs, 45+ years). (Table 16)
3) Hazard ratios (HR) with 95% CI for all-cause mortality, overall health-related mortality and specific health-related causes (SMN, cardiac, pulmonary other) using piecewise exponential models for frailty status. This will be presented overall, and by attained age in 10-year increments (18-24 yrs, 25-34 yrs, 35-44 yrs, 45+ years). These analyses will adjust for sociodemographic factors known to impact chronic conditions, lifestyle and mortality such as education, income, and insurance status in addition to age at diagnosis, sex and race/ethnicity. If neurocognitive impairment is found to be associated with mortality, we will perform an additional analysis that adjusts for alcohol intake, physical activity, smoking status and BMI as these are known to impact neurocognitive status and may attenuate the association. (Table 17)

4.4.5. **Exploratory Aim:** As an exploratory outcome, we will evaluate the above associations between modifiable risk factors and mortality by treatment era adding a variable for treatment era in 5-year time blocks to the models generated for hazard ratios.

References

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Mock Tables

Table 1. Demographic and diagnosis characteristics of 5-year survivors of childhood cancer by vital status

	All eligible survivors (N=_)			**CCSS participants (N=)**		
	Total n (%)	**Alive n (%)**	**Dead n (%)**	**Total n (%)**	**Alive n (%)**	**Dead n (%)**
All Survivors						
Sex						
Male						
Female						
Race/ethnicity						
Non-Hispanic white						
Non-Hispanic black						
Hispanic						
Other						
Unknown						
Age at diagnosis (years)						
Median, range, IQR						
0-4						
5-9						
10-14						
15-21						
Age at last follow-up (years)						
5-14						
15-24						
25-34						
35-44						
45-54						
≥55						
Survival after diagnosis (years)						
5-14						
15-24						
25-34						
35-44						
≥45						
Decade of diagnosis						
1970-79						
1980-89						
1990-99						
Diagnosis						
Leukemia						
Acute lymphoblastic leukemia						
Acute myeloid leukemia						
Other leukemia						
Hodgkin lymphoma						
Non-Hodgkin lymphoma						
CNS tumor						

Astrocytoma						
Medulloblastoma, PNET						
Other CNS						
Wilms (kidney) tumor						
Neuroblastoma						
Soft tissue sarcoma						
Bone tumors						
Ewing sarcoma						
Osteosarcoma						
Other bone tumors						
Educational attainment						
Less than high school graduate						
High school graduate or GED						
Some college						
College graduate or more						
Marital status						
Married/living as married						
Separated/divorced						
Widowed						
Never married/lived as married						
Insurance status						
Uninsured						
Private						
Public						
Household income, 2016 dollars						
<20,000						
20-40,000						
40-80,000						
>80,000						

Reported percentages were weighted to account for under-sampling of ALL survivors in the latter recruitment era (1897-1999) with a weight of 1.21 for ALL age 0 or 11-20 years at diagnosis and a weight of 3.63 for those age 1-10 years at diagnosis.

Table 2. Treatment characteristics of 5-year survivors of childhood cancer

	All eligible survivors, n (%)	CCSS participants, n (%)
Radiation exposure		
Any radiation		
Cranial radiation (Gy)[a]		
Any exposure		
Median dose (IQR)		
Chest radiation (Gy)[a]		
Any exposure		
Median dose (IQR)		
TBI		
Yes		
No		
Chemotherapy		
Anthracycline (mg/m^2)[b]		
Any exposure		
Median dose (IQR)		
Alkylating agents (mg/m^2)[c]		
Any exposure		
Median dose (IQR)		
Bleomycin (mg/m^2)		
Any exposure		
Median dose (IQR)		
Epipodophyllotoxin (mg/m^2) d		
Any exposure		
Median dose (IQR)		
Platinum[e]		
Any exposure		
Median dose (IQR)		
Methotrexate (mg/m^2)[f]		
Any exposure		
Median dose (IQR)		

TBI = Total body irradiation

Reported percentages were weighted to account for under-sampling of ALL survivors in the latter recruitment era (1897-1999) with a weight of 1.21 for ALL age 0 or 11-20 years at diagnosis and a weight of 3.63 for those age 1-10 years at diagnosis.

[a] Cranial radiation and chest radiation are all excluding body site scatter. Cranial radiation is maxTD (maximum target dose), taken as the sum of the prescribed dose for all overlapping brain fields. Cumulative dose median and IQR are among participants who received the agent of interest.

[b] Anthracycline dose reported as doxorubicin equivalent dose where conversions are idarubicin x 3, daunorubicin x 0.5, mitoxantrone x 10 and epirubicin x 0.67.[27]

[c] Alkylator dose reported as cyclophosphamide equivalent dose were conversions are ifosfamide x 0.244, procarbazine x 0.857, BCNU x 15, CCNU x 16, melphalan x 40, Thio-TEPA x 50, nitrogen mustard x 100 and Busulfan and 8.823.[28]

[d] Epipodophyllotoxin dose is the sum of teniposide and etoposide cumulative doses.

[e] Platinum dose is the sum of the cumulative carboplatin dose divided by 4 and the cisplatin dose.

[f] Methotrexate include all systemic methotrexate (IV, IM, PO, SubQ)

Table 3. Proportion of survivors with each predictor of interest at most recent survey

	CCSS participants, n (%) N=	**CCSS participants ≥18 years, n (%) N=**	**CCSS participants ≥18 years no proxy, n (%) N=**
Behavioral/lifestyle risk factors			
None			
Ever smoker			
Heavy drinker			
Unhealthy weight			
Low physical activity			
Modifiable chronic conditions			
None			
Diabetes			
Dyslipidemia			
Hypertension			
Frailty status			
Not frail			
Prefrail			
Frail			
Cognitive impairment			
None			
Memory impairment alone			
Task efficiency impairment alone			
Combined memory and task efficiency impairment			

Table 4. Frequency of deaths by cause in the Childhood Cancer Survivor Study (all eligible)

		Total Deaths		Male		Female	
Specific Cause of Death	**ICD-9 Code**	**N**	**%**	**N**	**%**	**N**	**%**
Total known							
Recurrence/progressive disease							
Medical causes of death							
Subsequent neoplasm	140-239						
Lip, oral cavity, pharynx	140-149						
Digestive organs and peritoneum	150-159						
Respiratory and intrathoracic organs	160-165						
Bone, connective tissue, skin	170-173						
Breast	174-175						
Genitourinary organs	179-189						
Brain and nervous system	191-192						
Lymphatic and hematopoietic	200-208						
Other subsequent cancer							
Endocrine, nutritional, and metabolic diseases	240-279						
Diseases of blood and blood-forming organs	280-289						
Mental health disorders	290-319						
Diseases of the nervous system and sensory organs	320-389						
Diseases of the circulatory system	390-459						
Ischemic heart disease	410-414						
Cardiomyopathy	425						
Heart failure	428						
Cerebrovascular diseases	430-438						
Other cardiac							
Diseases of the respiratory system	460-519						
Pneumonia	480-486						
Pulmonary fibrosis	515						
Other pulmonary							
Diseases of the digestive system	520-579						
Diseases of the genitourinary system	580-629						
Infectious diseases	001-139						
Complications of the puerperium	670-676						
Diseases of the musculoskeletal system and connective tissues	710-739						
Congenital anomalies	740-759						
Symptoms, signs, and ill-defined conditions	780-799						

External causes of injury and/or poisoning	E800-E999						
Motor vehicle accidents	E810-E825						
Other accidents	E826-E929						
Suicide	E950-E959						
Homicide	E960-E978						
Other injury	E980-E999						
Unknown cause of death							

Table 5. Mortality rates (deaths/1,000 person-years) by cause of death in all eligible survivors

	All cause			Recurrence/Progression			External cause (accident/injury)			Health-related cause		
	No. of deaths*	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**
All survivors												
Sex												
Male												
Female												
Diagnosis												
Acute lymphoblastic leukemia												
Acute myeloid leukemia												
Other leukemia												
Hodgkin lymphoma												
Non-Hodgkin lymphoma												
Astrocytoma												
Medulloblastoma, PNET												
Other CNS												
Wilms (kidney) tumor												
Neuroblastoma												
Soft tissue sarcoma												
Ewing sarcoma												
Osteosarcoma												
Other bone tumors												
Survival after diagnosis (years)												
5-9												
10-14												
15-19												
20-24												
25-29												
30-34												
35-44												
≥45												
Attained age (years)												
5-9												
10-14												
15-19												

20-24												
25-29												
30-34												
35-44												
45-49												
50-54												
≥55												

	Health-related causes of death											
	Subsequent malignant neoplasm			**Cardiac**			**Pulmonary**			**Other**		
	No. of deaths*	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**
All survivors												
Sex												
Male												
Female												
Diagnosis												
Acute lymphoblastic leukemia												
Acute myeloid leukemia												
Other leukemia												
Hodgkin lymphoma												
Non-Hodgkin lymphoma												
Astrocytoma												
Medulloblastoma, PNET												
Other CNS												
Wilms (kidney) tumor												
Neuroblastoma												
Soft tissue sarcoma												
Ewing sarcoma												
Osteosarcoma												
Other bone tumors												
Survival after diagnosis (years)												
5-9												
10-14												
15-19												

20-24												
25-29												
30-34												
35-44												
≥45												
Attained age (years)												
5-9												
10-14												
15-19												
20-24												
25-29												
30-34												
35-44												
45-49												
50-54												
≥55												

*Number of deaths are unweighted; however, rate and 95% CI take weight into account.

† per 1000 person year

Mortality analyses exclude Canadian participants as National Death Index data is limited to U.S. participants

Table 6. Standardized mortality ratios (SMR) and 95% confidence intervals by cause of death in all eligible survivors, excluding death due to recurrence

	All cause			External Cause (Accident/Injury)			Health-related cause		
	No. of deaths*	**SMR**	**95% CI**	**No. of deaths***	**SMR**	**95% CI**	**No. of deaths***	**SMR**	**95% CI**
All survivors									
Sex									
Male									
Female									
Diagnosis									
Acute lymphoblastic leukemia									
Acute myeloid leukemia									
Other leukemia									
Hodgkin lymphoma									
Non-Hodgkin lymphoma									
Astrocytoma									
Medulloblastoma, PNET									
Other CNS									
Wilms (kidney) tumor									
Neuroblastoma									
Soft tissue sarcoma									
Ewing sarcoma									
Osteosarcoma									
Other bone tumors									
Survival after diagnosis (years)									
5-9									
10-14									
15-19									
20-24									
25-29									
30-34									
35-44									
≥45									
Attained age (years)									
5-9									
10-14									

15-19									
20-24									
25-29									
30-34									
35-44									
45-49									
50-54									
≥55									

	Health-related causes of death											
	Subsequent malignant neoplasm			**Cardiac**			**Pulmonary**			**Other**		
	No. of deaths*	**SMR**	**95% CI**	**No. of deaths***	**SMR**	**95% CI**	**No. of deaths***	**SMR**	**95% CI**	**No. of deaths***	**SMR**	**95% CI**
All survivors												
Sex												
Male												
Female												
Diagnosis												
Acute lymphoblastic leukemia												
Acute myeloid leukemia												
Other leukemia												
Hodgkin lymphoma												
Non-Hodgkin lymphoma												
Astrocytoma												
Medulloblastoma, PNET												
Other CNS												
Wilms (kidney) tumor												
Neuroblastoma												
Soft tissue sarcoma												
Ewing sarcoma												
Osteosarcoma												
Other bone tumors												
Survival after diagnosis (years)												
5-9												
10-14												

15-19												
20-24												
25-29												
30-34												
35-44												
≥45												
Attained age (years)												
5-9												
10-14												
15-19												
20-24												
25-29												
30-34												
35-44												
45-49												
50-54												
≥55												

*Number of deaths are unweighted; however, SMR and 95% CI take weight into account.

Mortality analyses exclude Canadian participants as National Death Index data is limited to U.S. participants

Table 7. Risk of mortality due to specific causes of death in all eligible survivors

	All cause			Recurrence/progression			External Cause (Accident/Injury)			Health-related cause		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Sex												
Male	1.0											
Female												
Race/ethnicity												
Non-Hispanic white	1.0											
Non-Hispanic black												
Hispanic												
Other												
Age at diagnosis (years)												
0-4												
5-9	1.0											
10-14												
15-21												
Treatment exposures												
Cranial radiation per 5 Gy												
Chest radiation per 5 Gy												
TBI exposure, reference to No												
Anthracycline per 50 mg/m^2												
Alkylator per 1000 mg/m^2												
Bleomycin per 10 mg/m^2												
Epipodophyllotoxin per 500 mg/m^2												
Platinum per 100 mg/m^2												
Methotrexate per 1000 mg/m^2												
Survival after diagnosis (years)												
5-9	1.0											
10-14												
15-19												
20-24												
25-29												
30-34												
35-44												
≥45												

	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Sex												
Male	1.0											
Female												
Race/ethnicity												
Non-Hispanic white	1.0											
Non-Hispanic black												
Hispanic												
Other												
Age at diagnosis (years)												
0-4												
5-9	1.0											
10-14												
15-21												
Treatment exposures												
Cranial radiation per 5 Gy												
Chest radiation per 5 Gy												
TBI exposure, reference to No												
Anthracycline per 50 mg/m^2												
Alkylator per 1000 mg/m^2												
Bleomycin per 10 mg/m^2												
Epipodophyllotoxin per 500 mg/m^2												
Platinum per 100 mg/m^2												
Methotrexate per 1000 mg/m^2												
Survival after diagnosis (years)												
5-9	1.0											
10-14												
15-19												
20-24												
25-29												
30-34												
35-44												
≥45												

Relative rates are adjusted for all covariates displayed

Table 8. Mortality rates (deaths/1,000 person-years) by cause of death among CCSS participants by modifiable risk factors

	All cause			Recurrence/progression			External Cause (Accident/Injury)			Health-related cause		
	No. of deaths*	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**
Individual risk factors												
None												
Ever smoker alone												
Heavy drinker alone												
Unhealthy weight alone												
Low physical activity alone												
Hypertension alone												
Diabetes alone												
Dyslipidemia alone												
Healthy lifestyle score												
0												
1												
2												
3												
4												
Combination of factors												
Hypertension + Diabetes												
Hypertension + Dyslipidemia												
Diabetes + Dyslipidemia												
All three conditions												
Modifiable risk + lifestyle												
No conditions unhealthy (0-1)												
No conditions moderate (2)												
No conditions healthy (3-4)												
Hypertension unhealthy												
Hypertension moderate												
Hypertension healthy												
Diabetes unhealthy												
Diabetes moderate												
Diabetes healthy												
Dyslipidemia unhealthy												
Dyslipidemia moderate												
Dyslipidemia healthy												

	Health-related causes of death											
	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI
Individual risk factors												
None												
Ever smoker alone												
Heavy drinker alone												
Unhealthy weight alone												
Low physical activity alone												
Hypertension alone												
Diabetes alone												
Dyslipidemia alone												
Healthy lifestyle score												
0												
1												
2												
3												
4												
Combination of factors												
Hypertension + Diabetes												
Hypertension + Dyslipidemia												
Diabetes + Dyslipidemia												
All three conditions												
Modifiable risk + lifestyle score												
No conditions unhealthy (0-1)												
No conditions moderate (2)												
No conditions healthy (3-4)												
Hypertension unhealthy												
Hypertension moderate												
Hypertension healthy												
Diabetes unhealthy												
Diabetes moderate												
Diabetes healthy												
Dyslipidemia unhealthy												
Dyslipidemia moderate												
Dyslipidemia healthy												

*Number of deaths are unweighted; however, rate and 95% CI take weight into account.
† per 1000 person year. Mortality analyses exclude Canadian participants as National Death Index data is limited to U.S. participants

Table 9. Standardized mortality ratios (SMR) and 95% confidence intervals by cause of death among CCSS participants by modifiable risk factors, excluding death due to recurrence

	All cause			External Cause			Health-related cause		
	No. of deaths*	**SMR**	**95% CI**	**No. of deaths***	**SMR**	**95% CI**	**No. of deaths***	**SMR**	**95% CI**
Individual risk factors									
None									
Ever smoker alone									
Heavy drinker alone									
Unhealthy weight alone									
Low physical activity alone									
Hypertension alone									
Diabetes alone									
Dyslipidemia alone									
Healthy lifestyle score									
0									
1									
2									
3									
4									
Combination of factors									
Hypertension + Diabetes									
Hypertension + Dyslipidemia									
Diabetes + Dyslipidemia									
All three conditions									
Modifiable risk + lifestyle score									
No conditions unhealthy (0-1)									
No conditions moderate (2)									
No conditions healthy (3-4)									
Hypertension unhealthy									
Hypertension moderate									
Hypertension healthy									
Diabetes unhealthy									
Diabetes moderate									
Diabetes healthy									
Dyslipidemia unhealthy									
Dyslipidemia moderate									
Dyslipidemia healthy									

	Health-related causes of death											
	SMN			Cardiac			Pulmonary			Other		
	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI
Individual risk factors												
None												
Ever smoker alone												
Heavy drinker alone												
Unhealthy weight alone												
Low physical activity alone												
Hypertension alone												
Diabetes alone												
Dyslipidemia alone												
Healthy lifestyle score												
0												
1												
2												
3												
4												
Combination of factors												
Hypertension + Diabetes												
Hypertension + Dyslipidemia												
Diabetes + Dyslipidemia												
All three conditions												
Modifiable risk + lifestyle score												
No conditions unhealthy (0-1)												
No conditions moderate (2)												
No conditions healthy (3-4)												
Hypertension unhealthy												
Hypertension moderate												
Hypertension healthy												
Diabetes unhealthy												
Diabetes moderate												
Diabetes healthy												
Dyslipidemia unhealthy												
Dyslipidemia moderate												
Dyslipidemia healthy												

*Number of deaths are unweighted; however, SMR and 95% CI take weight into account.

Mortality analyses exclude Canadian participants as National Death Index data is limited to U.S. participants

Table 10. Risk of mortality due to specific causes of death by modifiable risk factors among CCSS participants by modifiable risk factors

	All cause			Recurrence/progression			External Cause (Accident/Injury)			Health-related cause		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Individual risk factors												
None	**1.0**											
Ever smoker alone												
Heavy drinker alone												
Unhealthy weight alone												
Low physical activity alone												
Hypertension alone												
Diabetes alone												
Dyslipidemia alone												
Healthy lifestyle score												
0												
1												
2												
3												
4	**1.0**											
Combination of factors												
No modifiable risk	**1.0**											
Hypertension + Diabetes												
Hypertension + Dyslipidemia												
Diabetes + Dyslipidemia												
All three conditions												
Modifiable risk + lifestyle score												
No conditions unhealthy (0-1)												
No conditions moderate (2)												
No conditions healthy (3-4)	**1.0**											
Hypertension unhealthy												
Hypertension moderate												
Hypertension healthy												
Diabetes unhealthy												
Diabetes moderate												
Diabetes healthy												
Dyslipidemia unhealthy												
Dyslipidemia moderate												
Dyslipidemia healthy												

	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Individual risk factors												
None	**1.0**											
Ever smoker alone												
Heavy drinker alone												
Unhealthy weight alone												
Low physical activity alone												
Hypertension alone												
Diabetes alone												
Dyslipidemia alone												
Healthy lifestyle score												
0												
1												
2												
3												
4	**1.0**											
Combination of factors												
No modifiable risk	**1.0**											
Hypertension + Diabetes												
Hypertension + Dyslipidemia												
Diabetes + Dyslipidemia												
All three conditions												
Modifiable risk + lifestyle												
No conditions unhealthy (0-1)												
No conditions moderate (2)												
No conditions healthy (3-4)	**1.0**											
Hypertension unhealthy												
Hypertension moderate												
Hypertension healthy												
Diabetes unhealthy												
Diabetes moderate												
Diabetes healthy												
Dyslipidemia unhealthy												
Dyslipidemia moderate												
Dyslipidemia healthy												

Hazard ratios are adjusted for age at diagnosis, race/ethnicity, sex, and attained age, education, income and insurance status as time-dependent variables.

Table 11. Mortality rates (deaths/1,000 person-years) by cause of death among CCSS participants by frailty status

	All cause			Recurrence/progression			External Cause (Accident/Injury)			Health-related cause		
	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI
Frailty Status												
Not frail												
Pre-frail												
Frail												
Attained age												
18-24 years												
Not frail												
Pre-frail												
Frail												
25-34 years												
Not frail												
Pre-frail												
Frail												
35-44 years												
Not frail												
Pre-frail												
Frail												
45+ years												
Not frail												
Pre-frail												
Frail												

	Health-related causes of death											
	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI
Frailty Status												
Not frail												
Pre-frail												
Frail												
Attained age												
18-24 years												

Not frail												
Pre-frail												
Frail												
25-34 years												
Not frail												
Pre-frail												
Frail												
35-44 years												
Not frail												
Pre-frail												
Frail												
45+ years												
Not frail												
Pre-frail												
Frail												

*Number of deaths are unweighted; however, rate and 95% CI take weight into account.

† per 1000 person year. Mortality analyses exclude Canadian participants as National Death Index data is limited to U.S. participants

Table 12. Standardized mortality ratios (SMR) and 95% confidence intervals by cause of death among CCSS participants by frailty status, excluding death due to recurrence

	All cause			External Cause (Accident/Injury)			Health-related cause		
	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI
Frailty Status									
Not frail									
Pre-frail									
Frail									
Attained age									
18-24 years									
Not frail									
Pre-frail									
Frail									
25-34 years									
Not frail									
Pre-frail									
Frail									
35-44 years									
Not frail									
Pre-frail									
Frail									
45+ years									
Not frail									
Pre-frail									
Frail									

	Health-related causes of death											
	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI
Frailty Status												
Not frail												
Pre-frail												
Frail												
Attained age												

18-24 years												
Not frail												
Pre-frail												
Frail												
25-34 years												
Not frail												
Pre-frail												
Frail												
35-44 years												
Not frail												
Pre-frail												
Frail												
45+ years												
Not frail												
Pre-frail												
Frail												

*Number of deaths are unweighted; however, SMR and 95% CI take weight into account.

Mortality analyses exclude Canadian participants as National Death Index data is limited to U.S. participants

Table 13. Risk of mortality due to specific causes of death by frailty status among CCSS participants

	All cause			Recurrence/progression			External Cause (Accident/Injury)			Health-related cause		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Frailty Status												
Not frail												
Pre-frail												
Frail												

	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Frailty Status												
Not frail												
Pre-frail												
Frail												

Hazard ratios are adjusted for age at diagnosis, race/ethnicity, sex, and attained age, education, income and insurance status as time-dependent variables.

Table 14. Mortality rates (deaths/1,000 person-years) by cause of death among CCSS participants by cognitive impairment

	All cause			Recurrence/progression			External Cause (Accident/Injury)			Health-related cause		
	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI
Cognitive impairment												
Memory impairment												
Yes												
No												
Memory impairment Grade												
0												
1												
2												
3												
Task efficiency impairment												
Yes												
No												
Task efficiency Grade												
0												
1												
2												
3												

	Health-related causes of death											
	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI
Cognitive impairment												
Memory impairment												
Yes												
No												
Memory impairment Grade												
0												
1												
2												
3												
Task efficiency impairment												

Yes												
No												
Task efficiency Grade												
0												
1												
2												
3												

*Number of deaths are unweighted; however, rate and 95% CI take weight into account.

† per 1000 person year. Mortality analyses exclude Canadian participants as National Death Index data is limited to U.S. participants

Table 15. Alternative to above Mortality rates (deaths/1,000 person-years) by cause of death among CCSS participants by cognitive impairment category

	All cause			Recurrence/progression			External Cause (Accident/Injury)			Health-related cause		
	No. of deaths*	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**	**No. of deaths***	**Rate†**	**95% CI**
Cognitive impairment												
Neither												
Memory alone												
Task efficiency alone												
Both												
Attained age												
18-24 years												
Neither												
Memory alone												
Task efficiency alone												
Both												
25-34 years												
Neither												
Memory alone												
Task efficiency alone												
Both												
35-44 years												
Neither												
Memory alone												
Task efficiency alone												
Both												
45+ years												
Neither												
Memory alone												
Task efficiency alone												
Both												

	Health-related causes of death											
	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI	No. of deaths*	Rate†	95% CI
Cognitive impairment												
Neither												
Memory alone												
Task efficiency alone												
Both												
Attained age												
18-24 years												
Neither												
Memory alone												
Task efficiency alone												
Both												
25-34 years												
Neither												
Memory alone												
Task efficiency alone												
Both												
35-44 years												
Neither												
Memory alone												
Task efficiency alone												
Both												
45+ years												
Neither												
Memory alone												
Task efficiency alone												
Both												

*Number of deaths are unweighted; however, rate and 95% CI take weight into account.
† per 1000 person year. Mortality analyses exclude Canadian participants as National Death Index data is limited to U.S. participants

Table 16. Standardized mortality ratios (SMR) and 95% confidence intervals by cause of death among CCSS participants by cognitive impairment, excluding death due to recurrence

	All cause			External Cause (Accident/Injury)			Health-related cause		
	No. of deaths*	**SMR**	**95% CI**	**No. of deaths***	**SMR**	**95% CI**	**No. of deaths***	**SMR**	**95% CI**
Cognitive impairment									
Neither									
Memory alone									
Task efficiency alone									
Both									
Attained age									
18-24 years									
Neither									
Memory alone									
Task efficiency alone									
Both									
25-34 years									
Neither									
Memory alone									
Task efficiency alone									
Both									
35-44 years									
Neither									
Memory alone									
Task efficiency alone									
Both									
45+ years									
Neither									
Memory alone									
Task efficiency alone									
Both									

	Health-related causes of death											
	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI	No. of deaths*	SMR	95% CI
Cognitive impairment												
Neither												
Memory alone												
Task efficiency alone												
Both												
Attained age												
18-24 years												
Neither												
Memory alone												
Task efficiency alone												
Both												
25-34 years												
Neither												
Memory alone												
Task efficiency alone												
Both												
35-44 years												
Neither												
Memory alone												
Task efficiency alone												
Both												
45+ years												
Neither												
Memory alone												
Task efficiency alone												
Both												

*Number of deaths are unweighted; however, SMR and 95% CI take weight into account.

Mortality analyses exclude Canadian participants as National Death Index data is limited to U.S. participants

Table 17. Risk of mortality due to specific causes of death by cognitive impairment among CCSS participants

	All cause			Recurrence/progression			External Cause (Accident/Injury)			Health-related cause		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Cognitive impairment												
Neither												
Memory alone												
Task efficiency alone												
Both												

	Subsequent malignant neoplasm			Cardiac			Pulmonary			Other		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Cognitive impairment												
Neither												
Memory alone												
Task efficiency alone												
Both												

Hazard ratios are adjusted for age at diagnosis, race/ethnicity, sex, and attained age, education, income and insurance status as time-dependent variables.

- If results are significant a secondary analysis will be performed to identify if addition of lifestyle factors known to impact cognitive impairment attenuate the observed outcomes (smoking, alcohol, BMI and physical activity).