CCSS Research Concept Proposal

Study Title: Impact of the COVID-19 Pandemic on Major Health Events and Death Among Survivors of Childhood Cancer

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1. Background and Rationale

Overall impact of the COVID-19 pandemic on the general population. The COVID-19 pandemic, declared in early 2020 and caused by the SARS-CoV-2 virus, placed a huge burden on the United States (U.S.) health care system. Substantial increases in overall and disease-specific mortality rates [1, 2], along with a decline in general health, including physical, mental, and emotional health [3, 4], were observed during this period, and some of these effects still persist to this day [5]. Globally, more than 7 million deaths have been attributed to COVID-19 [6], with over 1 million of these occurring in the U.S. [7]. In 2021, COVID-19 surpassed strokes to become the second leading cause of death worldwide, with age-adjusted mortality rates of 94 deaths per 100,000 population [8]. Non-Covid disease specific mortality rates, such as cardiovascular disease (CVD) mortality, have also increased since the pandemic. Recent evidence shows that, compared to the 2018–2019 period, overall excess CVD death rates rose by 6.7%, including a 2.5% increase in excess deaths due to myocardial infarction and 8.5% increase in excess deaths due to stroke during calendar years 2020–2021 [9]. Risk factors, including sociodemographic characteristics (older age, male sex [10], African-American or Hispanic descent [11]), and pre-existing comorbidities (obesity, diabetes, hypertension, and cardiovascular diseases [12]) are associated with an increased risk of COVID-19-related mortality.

Beyond mortality, the disruption to the U.S. health care system caused by the COVID-19 pandemic also significantly affected health outcomes, including the rates at which new chronic conditions and some cancers were diagnosed, and it led to a decline in many non-COVID-related chronic disease outcomes, as reported in the literature. For example, in a longitudinal study of a U.S.-based employer-sponsored program, a significant rise in both systolic and diastolic blood pressure values was observed during the pandemic compared to the pre-pandemic period, potentially increasing the risk for CVD [3]. Decreases in the incidence or diagnosis of new chronic conditions were also observed during this period [13]. This included a decline in non-fatal hospitalization for critical conditions such as stroke and heart attacks. In one study, authors found a 48% decrease in hospitalizations for acute myocardial infarction during the pandemic when compared to the same period in 2019 [14]. Similarly, among Medicare beneficiaries, Yang et al. reported a 22.3% decrease in non-fatal stroke hospitalization rates in the early phase of the pandemic compared to 2019, which narrowed to a 12.1% decrease in the later phases of the pandemic [15].

Similar trends in the reduction of overall cancer diagnoses in the period immediately during and after the COVID-19 pandemic were observed. For instance, Kava et al. reported a 13.6% decrease in new cases of lung cancer in 2020 compared to the same time period in the previous year [16]. Further, in a population-based cross-sectional study, authors found a 9.4% reduction in all-site cancer diagnosis rates compared to expected rates in 2020, and even in the following year (2021), cancer diagnosis rates remained 2.7% lower than expected [17]. Moreover, studies have also reported a higher proportion of late-stage cancer diagnoses during and after the COVID-19 pandemic [18]. Violante et al. found a significant rise in the incidence of metastatic colon cancer during the pandemic (12.9%) compared to the pre-pandemic period (4.5%). Similar trends were observed for rectal cancer, with rates increasing from 0.8% pre-pandemic to 2.2% during the pandemic [19].

Childhood cancer survivors are at increased risk for adverse health. As of 2020, approximately 496,000 childhood cancer survivors were living in the U.S. [20]. Although advancements in cancer treatment (chemotherapy, radiotherapy and supportive care) have improved 5-year survivorship, many continue to experience higher morbidity and mortality, often due to late effects of cancer treatment, compared to the general population [21-24]. Survivors are 3.3 times more likely to have chronic health conditions and 8.2 times more likely to develop severe or life-threatening conditions compared to their siblings [25]. More recently, using data from the Childhood Cancer Survivor Study (CCSS), authors found increased mortality due to health-related causes across the life-span with 131 excess deaths (95% CI: 111–163) per 10,000 person-years among survivors who were at least 40 years from childhood cancer diagnosis [22]. Other studies have also shown elevated risks for major adverse cardiovascular events among childhood cancer survivors. Hammoud et al. reported that by age 50, 17.7% of survivors had experienced at least one major cardiovascular event, compared to only 0.9% among community controls [26]. Survivors are also at increased risk of subsequent neoplasms, largely due to treatment exposures [27]. Previous studies have shown that they are 4.4 times more likely to be diagnosed with a subsequent neoplasm beyond age 40 compared to the general population [28].

In terms of utilization, childhood cancer survivors often require long-term follow-up care and utilize healthcare resources more frequently than the general population. In a self-reported U.S. survey, hospitalization rates were 1.6 times higher than age and sex-stratified controls [29], while ED visits were twice as high among survivors compared to their siblings [30]. A recently published Canadian study also found that survivors had higher rates of hospitalizations, surgeries, sub-specialist visits, and diagnostic imaging compared to their matched controls. However, no differences were observed in ED or primary care visits [31].

Impact of the pandemic on childhood cancer survivors: Long-term follow-up care is essential for survivors of childhood cancer to optimize health outcomes. However, delays or disruptions in the continuum of care have been widely reported as a result of the pandemic [32, 33]. Data from the French Childhood Cancer Survivor Study (FCCSS) cohort showed that 30% of respondents to an online self-reported survey reported forgoing medical care such as missing routine follow-up visits or other health consultations at least once in 2020 due to concerns about COVID-19 infection [34]. An international survey that gathered data from 178 long-term follow-up (LTFU) clinics across 37 countries found that 42% of survivorship clinics temporarily closed shortly after the outbreak, and restrictions led to a reduction in in-person visits [33]. These interruptions are concerning, especially given the potential for increased morbidity in the form of unmanaged late effects.

Therefore, this study aims to examine the impact of the COVID-19 pandemic on major health events and death among survivors of childhood cancer. This is crucial because the effect of the pandemic on childhood cancer survivors remains poorly understood. Understanding its impact on this vulnerable group can help identify gaps in care, support targeted interventions, and inform preparedness for future public health emergencies.

2. Specific Aims:

2.1 Describe the annual mortality rates during the 10 years prior to March 2020 and after March 1, 2020 among CCSS survivors overall and by specific-cause and then compare the relative mortality rates among survivors and the general population before and after March 2020.

- If the number of deaths during the first year (March 2020–March 2021) and the COVID recovery period (March 2021–NDI freeze) is sufficient, we will explore dynamic changes in mortality risk among survivors during both the acute phase of the COVID-19 pandemic (first year) and the subsequent recovery period.
- Compare overall and cause-specific mortality rates among survivors before and after March 2020 (cardiac, pulmonary, subsequent cancer and other health-related causes). We will explore if there are adequate deaths due to ischemic heart disease, heart failure, and then stroke to report individually. We can also explore the number of COVID-related deaths.
- Compare overall and cause-specific mortality rates among survivors before and after March 2020 to those in the general population using standardized mortality ratios (SMRs).

Hypothesis: We hypothesize that overall and cause-specific mortality rates increased among survivors after March 2020 and that survivors experienced a greater relative increase in overall and cause-specific mortality rates after March 2020 compared to the general population.

Hypothesis: We hypothesize that survivors with a two or more-grade 2+ CHC chronic health conditions had the largest increase in mortality rates after March 2020.

Hypothesis: We hypothesize that survivors residing in neighborhoods with higher social vulnerability will experience a greater increase in all-cause and cause-specific mortality risk after March 2020 compared to the general population, with the rate of increase being even higher than among those living in lower-vulnerability neighborhoods.

2.2 Describe the annual incidence of subsequent malignant neoplasms (SMNs) during the 10 years prior to March 2020 and after March 1, 2020, among CCSS survivors, and then compare the relative rate of subsequent malignancies between survivors and the general population before and after March 2020.

- If the number of cases is sufficient during the first year (March 2020–March 2021) and the COVID recovery period (March 2021– end of the FU8 adjudication period for SMN), we will examine temporal trends in SMNs among survivors, assessing dynamic changes during both the acute phase of the COVID-19 pandemic (first year) and the subsequent recovery period.
- Compare the relative rate of SMNs before and after March 2020 among survivors overall, and examine common neoplasms shared by survivors and the general population that were

known to be impacted by the COVID-19 pandemic (breast, colorectal, thyroid, and melanoma).

- Compare the rate of SMNs among survivors to the general population using standardized incidence ratio (SIRs) before and after March 2020.

Hypothesis: We hypothesize that the incidence of SMN initially declined but then rebounded post-COVID and consistently exceeded that in the general population.

Hypothesis: We hypothesize that survivors may have been less likely to forgo cancer screening after March 2020, and therefore, the relative change in the rate of cancer diagnoses during this period may have been lower in survivors than in the general population.

2.3 Describe changes in self-reported unplanned health care utilization (non-obstetric hospitalizations and emergency department use) and insurance status among survivors before and after March 2020. If there are significant differences, we will consider exploring the degree to which health-care utilization change accounts for differences in cardiovascular disease or mortality before and after March 2020.

- If the number of cases is sufficient during the first year (March 2020–March 2021) and the COVID recovery period (March 2021–end of the FU8 adjudication period), we will examine temporal trends in self-reported unplanned healthcare utilization (non-obstetric hospitalizations, emergency department visits and insurance status) among survivors, assessing dynamic changes during both the acute phase of the COVID-19 pandemic (first year) and the subsequent recovery period.

  Hypothesis: We hypothesize that survivors' self-reported health care utilization rates were higher after March 2020 compared to period before March 2020

2.4 Exploratory: Describe changes in the use of preventive care services such as visits to the primary care physician, echocardiograms, and cancer screenings (including colorectal, cervical and breast cancer screening) among survivors before and after March 2020. If there are significant differences, we will consider exploring the extent to which changes in the use of preventive care services account for differences in SMN incidence.

Hypothesis: We hypothesize that the use of preventive care services among survivors was lower after March 2020 compared to the period before March 2020.

2.5 Exploratory: Describe changes in the prevalence of modifiable lifestyle risk factors (overweight/obesity and physical activity) among survivors before and after March 2020. If there are significant differences, we will consider exploring the degree to which lifestyle change accounts for differences in cardiovascular disease, SMN or mortality before and after March 2020.

Hypothesis: We hypothesize that survivors experienced significant changes in the pattern of modifiable lifestyle risk factors after March 2020 compared period before March 2020.

Note: Alcohol and tobacco use was not included in FU8 and therefore not considered in modifiable risk factors for this aim but will be considered as covariates in analyses for those whose use was reported in prior surveys.

3. Analysis Framework:

3.1 Study Population: This study will include adult (age 18 or older at the time of any survey) five-year survivors of childhood cancer enrolled in the overall CCSS cohort (diagnosed between 1970 and 1999). A detailed description of the cohort design and methodology has been published elsewhere [35, 36]. For all aims, responses from Follow-up Surveys 5, 6, and 7 will serve as the period before March 2020 (CY 2014 -February 2020), and some responses from Follow-up Survey 7 (March 1, 2020- Dec 2021) and 8 (March 2022 -2024) will serve as the period after March 2020. For the mortality aim, all eligible participants will be included, and the date of death will be categorized as occurring before or after March 2020.

3.2 Outcomes: The outcomes of interest will be assessed using self-reported surveys from CCSS and siblings' control (follow-up surveys 5, 6, 7, and 8), the U.S. National Death Index (NDI), and data from the National Center for Health Statistics.

1) **Overall and cause-specific mortality:** Date and cause of death for eligible CCSS survey respondents will utilize data from prior NDI linkages to CCSS and include deaths occurring between calendar year 2010 – the most recent NDI linkage. Overall and cause specific mortality will be assessed before and after March 2020.
   Cause-specific death will be identified using ICD-10 and categorized as either recurrence or progression of the original cancer; death due to external causes, such as accidents or injuries; or death related to a health condition, such as cardiac disease, pulmonary disease, or SMNs, and excludes deaths directly attributable to the original cancer diagnosis.

2) **SMNs:** New diagnosis of SMN will be defined as subsequent neoplasm (that occurred ≥ 5 years after initial childhood cancer) reported by a survey respondent or a next of kin proxy and confirmed through pathology results. If pathological results are unavailable, death certificate or medical reports would be used to confirm a new SMN diagnosis. Cancers included will be those classified in the International Classification of Diseases for Oncology (ICD-O) with a 5th digit code of 3 [37]. SMNs reported before March 2020 will be classified as those before March 2020, and those reported after this date will be classified as occurring after March 2020.

3) **Health care utilization**: We will define unplanned urgent/emergent health care utilization as any self-reported non-obstetric hospitalizations and emergency department use in the last 12 months. This is because all CCSS surveys 5 through 8 asked about these types of visits in the prior 12 months. We will utilize date of visit, reported in the survey, to determine if the visit occurred before or after March 2020. We will consider unplanned

urgent/emergent health care utilization for each participant as a dichotomous variable (yes/no) and as a count.

4) **Use of each of the below preventive care services (yes/no) will be defined as:**
    - Any visit to the primary care physician within the past 2 years
    - An echocardiogram within the last 5 years
    - A mammogram or other breast cancer screenings within the last 2 years
    - Any colorectal cancer screening, either DNA stool testing within the past 2 years or a colonoscopy within the last 5 years
    - A Pap smear and/or cervical HPV test within the last 5 years

    Among survivors before and after March 2020. This corresponds to question C1 in FU-5, FU-6, and FU-7, and question F in FU-8.

5) **Modifiable lifestyle risk factors:**
    - Overweight/obesity (yes/no) will be defined as a BMI ≥ 25 kg/m^2.
    - Physical activity meeting recommendations (yes/no) will be defined as engaging in at least 9 metabolic equivalent task (MET) hours per week, as described by Scott et al [38]. Exercise exposure ranged from 0 to 21 MET-h/week and is categorized as 0, 3–6, 9–12, and 15–21 MET-h/week.

    Changes in the pattern of modifiable lifestyle risk factors listed above will be assessed both before and after March 2020.

3.3 Covariates

Sociodemographic variables:

- Sex
- Race and ethnic group
- Age at cancer diagnosis
- Age at follow-up
- Education attainment (high school or less vs some college)
- Marital status
- Household income
- Insurance status (yes/no) will be defined as "Yes" if the answer to the question "Do you currently have health insurance coverage?" is positive. This corresponds to question A10 on FU-5 and question A16 on FU-7, where the question was phrased as "Do you currently have health insurance that covers outpatient care and hospital care?"
- Cancer diagnosis
- Social Vulnerability Index (SVI)

Modifiable lifestyle risk factors (treated as time-varying covariates):

- Smoking status will be defined as never or ever based on the question "Have you smoked at least 100 cigarettes since you last provided us this information?". This corresponds to question N7 on FU-5 and question M7 on FU-7.

- Alcohol consumption: Heavy or risky drinking (yes/no): "Yes" response will be defined as 7+ drinks per week for females and 14+ drinks per week for males.
- BMI (kg/m²) classification: Adults: Underweight (BMI <18.5), Healthy weight (BMI 18.5 to <25), Overweight (BMI ≥25 to <30) or Obese (BMI ≥30).
- Physical activity (yes/no) will be defined as engaging in at least 9 MET hours per week, as described by Scott et al (38). Exercise exposure ranged from 0 to 21 MET-h/week and is categorized as 0, 3–6, 9–12, and 15–21 MET-h/week.

Modifiable CHC (treated as time-varying covariates):

- Hypertension (yes/no) defined as CTCAE grade ≥ 2
- Diabetes (yes/no) defined as CTCAE grade ≥ 2
- Dyslipidemia (yes/no) defined as CTCAE grade ≥ 2

Treatment-related covariates

- Any radiation (yes/no) with maximum dose
- Cranial irradiation (yes/no) and dose
- Total body irradiation, TBI (yes/no)
- Chest directed radiation (yes/no) and dose
- Neck directed radiation (yes/no) and dose
- Abdominal directed radiation (yes/no) and dose
- BMT, hematopoietic cell transplant within 5 years from diagnosis (yes/no)
- Anthracycline (yes/no) and cumulative anthracycline in doxorubicin equivalent dose [39]
- Alkylating agents (yes/no) and cumulative alkylators in cyclophosphamide equivalent dose [40]
- Platinum (yes/no) and cumulative dose as the sum of the carboplatin dose divided by 4 and the cisplatin dose similar to previous studies [41]
- Epipodophyllotoxins (yes/no) and cumulative dose by summing the doses of etoposide and teniposide similar to previous studies [42]
- SMN status: (yes/no) occurring 5 or more years from diagnosis and treated as a time dependent covariate.

3.4 Statistical Analyses Plan:

We will report the descriptive characteristics of all eligible CCSS participants and sibling controls, including sociodemographic characteristics, lifestyle risk factors, therapeutic exposures, and preexisting chronic conditions **(Table 1).**

Aim 1: Describe the annual mortality rates during the 10 years prior to March 2020 and after March 1, 2020 among CCSS survivors overall and by specific-cause and then compare the relative mortality rates among survivors and the general population before and after March 2020.

a. Compare overall and cause-specific mortality rates among survivors before and after March 2020 **(Table 2).**

b. Compare overall and cause-specific mortality rates among survivors before and after March 2020 with those in the general population using standardized mortality ratios (SMRs) **(Table 3)**.
c. Plot mortality curves among survivors before and after March 2020.
d. Adjust for sociodemographic variables (sex, race/ethnicity, age at diagnosis, age during follow-up, educational attainment, marital status, household income, SVI and insurance status); modifiable lifestyle risk factors (smoking status, alcohol consumption, BMI, and physical activity); modifiable chronic health conditions (hypertension, diabetes, and dyslipidemia); and treatment-related covariates (cranial irradiation, chest radiation, total body irradiation [TBI], neck-directed radiation, abdominal-directed radiation, anthracyclines, alkylating agents, epipodophyllotoxins, and platinum-based agents).

Aims 1a and 1b: The mortality rates and SMR will be calculated (1) among survivors at risk between January 1, 2010, and February 29, 2020; (2) among survivors at risk between March 1, 2020, and the date of the most recent NDI freeze (December 31, 2023). Sex/age-specific morality rates and SMR will also be calculated. Mortality rates and SMR will also be calculated for both time periods stratified by sociodemographic variables, cancer treatment exposure, and history of modifiable CHC, measured at the beginning of either time period, for the survivors with the information available. The analysis will be repeated for cause-specific mortality rates and SMR.

To account for the potential temporal population trend of mortality and SMR, we consider the following alternative methods. (1) We use Weibull proportional hazard distribution to study the mortality using calendar time as the time scale, with January 1, 2010, as the time origin and a time-varying covariate for time before or after March 1, 2020. That is, according to the model, the population mortality hazard will follow a temporal trend indicated by the Weibull distribution before March 1, 2020; the hazard will have a multiplicative change after March 1, 2020. Both overall analysis and stratified analysis by sociodemographic variables, cancer treatment exposure, and history of modifiable CHC on January 1, 2020, will be performed. The analysis will be repeated using cause-specific Weibull proportional hazard distribution. (2) We will use inverse variance weighted linear regression to describe the linear trend of SMR between 2010 and 2019. The fitted linear trend will be extrapolated to 2020 and 2021 and compared to the actual SMRs. The difference between the forecasted and observed SMR will be calculated, and the 95% confidence intervals will be obtained using nonparametric bootstrap. The quadratic temporal trend of SMR will also be considered. Stratification by the same variables, evaluated at the beginning of each year, will also be performed.

Aim 1c and 1d: Kaplan-Meier estimators will be used to calculate the cumulative incidence functions from January 1, 2020 to December 31, 2023 (or the most recent NDI freeze) as well as their annual increments (annual incidences of deaths). Stratified Kaplan-Meier estimators will be used to calculate the cumulative incidence functions and annual incidences in each subgroup, where the strata are defined similar to Aim 1c. Unstratified and stratified cause-specific mortality will also be estimated using Aalen-Johansen estimators.

Aim2: Describe the annual incidence of SMNs during the 10 years prior to March 2020 and after March 1, 2020, among CCSS survivors, and then compare the relative rate of subsequent malignancies between survivors and the general population before and after March 2020.

a. Compare the relative rate of SMN among survivors before and after March 2020 (**Table 4**).
b. Compare the rate of SMN among survivors with that of the general population using standardized incidence ratio (SIRs) before and after March 2020 **(Table 5).**
c. Plot the cumulative incidence curve and its annual increments of SMNs from January 1, 2020 to the end of the adjudication period for FU8 SMN data.
d. Adjust for all covariates except from SMN status.

Aim 2a and 2b: The incidence rates of SMN and SIR will be calculated (1) among survivors at risk between January 1, 2010, and February 29, 2020; (2) among survivors at risk between March 1, 2020, and the end of the FU8 adjudication period for SMN. Besides overall summaries, sex/age-specific incidence rates and SIR will also be calculated. Incidence rates and SIR will also be calculated for both time periods stratified by sociodemographic variables, cancer treatment exposure, and history of modifiable CHC, measured at the beginning of either time period, for the survivors with the information available. Sociodemographic variables for the period before March 2020 will come from FU4 questionnaire for the original cohort and Baseline questionnaire for the expansion cohort; those for the period after March 2020 will come from FU7 questionnaire.

The incidence rates will be calculated as: Number of new cases / Number of person-years at risk * 100,000.

To account for the potential temporal population trend of incidence rates of SMN and SIR, we consider the following alternative methods. (1) We will use a mixed-effects Poisson regression model to study the incidence rates of SMN for each survivor in each year between 2010 and 2021, with individual-specific random intercept and using the follow-up time in each year as the offset (the follow-up time is less than 1 year if the survivor is censored by the year end). The calendar time since January 1, 2010 as months will be included in the model as linear or quadratic effects. The year 2020 will be split into on or before February 29, 2020, and on or after March 1, 2020. An additional effect will be added to the time periods between March 1, 2020 and December 31, 2021 for all individuals. Both overall analysis and stratified analysis by sociodemographic variables, cancer treatment exposure, and history of modifiable CHC at the beginning of each time period will be performed. (2) We will use the same method in Aim 1a and 1b to compare the forecasted SIR in 2020 and 2021 vs. the actual SIR.

Aim 2c: Aalen-Johansen estimators will be used to calculate the cumulative incidence functions of SMN from January 1, 2020 to December 31, 2021, as well as the annual increments of the cumulative incidence functions, treating death due to non-SMN causes as competing risks. The CIF curves and incidence curves will be plotted for descriptive purposes.

Aim 2d: Stratified Aalen-Johansen estimator similar to Aim 1c will be used to calculate CIFs of SMN, where the strata are defined by age at time origin. Further stratification will be performed using treatment exposure variables, modifiable CHC, sociodemographic variables measured near the time origin, and modifiable lifestyle factors near the time origin.

Aim 3: Describe changes in self-reported unplanned health care utilization (non-obstetric hospitalizations and emergency department use) and insurance status among survivors before and after March 2020. If there are significant differences, we will consider exploring the degree to which health-care utilization change accounts for differences in cardiovascular disease or mortality before and after March 2020.

a. Estimate the prevalence of self-reported health care utilization and insurance status among survivors before and after March 2020 **(Table 6).**
b. Estimate the prevalence ratios of self-reported health care utilization and insurance status among survivors compared with sibling controls, before and after March 2020 **(Table 7).**

For this aim, the last survey at or before February 29, 2020, and the first survey at or after March 1, 2020, will be used. The analysis will be similar to Aim 4, using self-reported health care utilization or insurance status as the outcomes.

Aim 4 (Exploratory): Describe changes in the use of preventive care services such as visits to the primary care physician, echocardiograms, and cancer screenings (including colorectal, cervical and breast cancer screening) among survivors before and after March 2020. If there are significant differences, we will consider exploring the extent to which changes in the use of preventive care services account for differences in SMN incidence.

a. Estimate the prevalence of any and then each specific (PCP, individual cancer screening, echocardiogram) self-reported use of preventive care services among survivors before and after March 2020 **(Table 8).**
b. Estimate prevalence ratios of self-reported preventive care services among survivors compared with sibling controls for primary care and cancer screenings, before and after March 2020 **(Table 9).**

For analysis in Aim 3-5, the last survey at or before February 29, 2020 and the first survey at or after March 1, 2020 will be used. The use of care services of each category at the time of each questionnaire will be dichotomized as Yes/No. Prevalence of any and then each specific (PCP, individual cancer screening, echocardiogram) self-reported use of preventive care services among survivors before and after March 2020 will be estimated. Stratification will also be performed by the covariates.

Prevalence ratio of survivor/sibling status for each preventive care service will be evaluated using Mixed-effects logistic regression model with individual-specific random intercepts for before and after March 2020 outcomes, adjusting for time period (before/after March 2020), age at survey completion, age at diagnosis, treatment exposure, sociodemographic variables, modifiable CHCs, lifestyle factors, and an interaction term for survivor/sibling status and time period. A preliminary variable selection will be performed using repeated 10-fold cross-validated elastic net logistic regression overlooking correlation of outcomes belonging to the same individual. Finally, in cancer survivors, SMN incidences and SIR will be calculated similar to Aim1 stratified by survivors' use of each preventive care service.

Aim 5 (Exploratory): Describe changes in the prevalence of modifiable lifestyle risk factors (overweight/obesity and physical activity) among survivors before and after March 2020. If there are significant differences, we will consider exploring the degree to which lifestyle

change accounts for differences in cardiovascular disease, SMN or mortality before and after March 2020.

a. Estimate the prevalence of overweight/obese survivors before and after March 2020 **(Table 10).**
b. Estimate the prevalence of inadequate physical activity among survivors before and after March 2020 **(Table 10).**
c. Estimate the prevalence ratios of overweight/obese survivors compared with sibling controls, before and after March 2020 **(Table 11).**
d. Estimate the prevalence ratios for inadequate physical activity among survivors compared with sibling controls, before and after March 2020 **(Table 11).**

Modifiable lifestyle risk factors (overweight/obesity and low physical activity) will be dichotomized. Overall and stratified prevalences of modifiable lifestyle risk among survivors before and after March 2020 will be estimated similarly to Aim 4.

Prevalence ratio of survivor/sibling status for each modifiable risk factor will be evaluated using Mixed-effects logistic regression model similar to the analysis in Aim 4.

Finally, in cancer survivors, SMN incidences and SIR will be calculated similar to Aim1 stratified by survivors' modifiable risk factors.

Mock Tables

Table 1. Overall characteristics of 5-year childhood cancer survivors and sibling controls

	All eligible participants (N=_)	CCSS participants (N=)	Siblings (N=)
Sociodemographic factors			
Sex			
▪ Male			
▪ Female			
Race/ethnicity			
▪ Non-Hispanic white			
▪ Non-Hispanic black			
▪ Hispanic			
▪ Other			
▪ Unknown			
Age at cancer diagnosis (years)			NA
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			
Educational attainment			
▪ ≤ 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			
▪ Yes			
Household income, US dollars			
▪ <20,000			
▪ 20-39,000			
▪ 40-79,000			
▪ ≥80,000			
Social vulnerability index			
▪ Quartile 1			
▪ Quartile 2			
▪ Quartile 3			
▪ Quartile 4			
Primary Cancer Diagnosis			NA
▪ Acute lymphoblastic leukemia			
▪ Acute myeloid leukemia			
▪ Other leukemia			
▪ Hodgkin lymphoma			
▪ Non-Hodgkin lymphoma			
▪ Astrocytoma			
▪ Medulloblastoma, PNET			
▪ Other CNS tumor			
▪ Wilms (kidney) tumor			
▪ Neuroblastoma			
▪ Soft tissue sarcoma			
▪ Ewing sarcoma			
▪ Osteosarcoma			
▪ Other bone tumors			
Lifestyle risk factors			
Smoking status			
▪ Never			

▪ Ever			
Heavy or risky drinking			
▪ Yes			
▪ No			
BMI			
▪ <18·5			
▪ 18.5 - 24.9			
▪ ≥25 - <30			
▪ ≥30			
Physical activity (MET hours/week)			
▪ 0			
▪ 3 - 6			
▪ 9-12			
▪ 15-21			
Modifiable chronic conditions			
Diabetes			
▪ Grade 0 (No)			
▪ Grade 1			
▪ Grade ≥ 2			
Hypertension			
▪ Grade 0 (No)			
▪ Grade 1			
▪ Grade ≥ 2			
Dyslipidemia			
▪ Grade 0 (No)			
▪ Grade 1			
▪ Grade ≥ 2			
Treatment-related covariates			
Any radiation			NA
Cranial radiation (Gy)			NA
▪ Any exposure			
▪ Median dose (IQR)			NA
Total body irradiation			NA
Chest directed radiation (Gy)			NA
▪ Any exposure			
▪ Median dose (IQR)			
Neck directed radiation (Gy)			
▪ Any exposure			
▪ Median dose (IQR)			
Abdominal directed radiation (Gy)			
▪ Any exposure			
▪ Median dose (IQR)			
BMT, hematopoietic cell transplant (Yes)			
Chemotherapy			NA

Anthracycline (mg/m^2)			NA
▪ Any exposure			
▪ Median dose (IQR)			
Alkylating agents (mg/m^2)			NA
▪ Any exposure			
▪ Median dose (IQR)			
Platinum			NA
▪ Any exposure			
▪ Median dose (IQR)			
Epipodophyllotoxin (mg/m^2)			NA
▪ Any exposure			
▪ Median dose (IQR)			
Bleomycin (mg/m^2)			NA
▪ Any exposure			
▪ Median dose (IQR)			
Methotrexate (mg/m^2)			NA
▪ Any exposure			
▪ Median dose (IQR)			

Table 2. Mortality rates (death/1000 person - years) among survivors overall and by specific cause before and after March 2020.

				Cause-specific mortality		
			All-cause mortality	**Recurrence/ progression**	**External cause**	**Health-related cause**
	Number of deaths	Total Person-time at risk	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
All Survivors before March 2020						
All Survivors after March 2020						

Table 3. Standardized mortality ratios (SMR) overall and by specific cause before and after March 2020.

				Cause-specific mortality

	Observed deaths	Expected deaths	All-cause mortality	Recurrence /progression	External cause	Health-related cause
			SMR (95% CI)	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)
All Survivors before March 2020						
All Survivors after March 2020						

Table 4. Incidence of subsequent malignant neoplasms (SMNs) before and after March 2020.

SMN	Number of new cases of SMN	Number of survivors at risk	Cumulative incidence % (95% CI)
All Survivors before March 2020			
All Survivors after March 2020			

Table 5. Standardized incidence ratios of subsequent malignant neoplasms (SMNs) among survivors, before and after March 2020.

SMN	Number Observed	Number Expected	SIR (95% CI)
All Survivors before March 2020			
All Survivors after March 2020			

Table 6. Prevalence of self-reported unplanned health care utilization and insurance status among survivors before and after March 2020.

	All Survivors before	Prevalence %	All Survivors after	Prevalence %	Absolute Change (pp)	Relative Change (%)

	March 2020 (N =)		March 2020 (N =)			
Non-obstetric hospitalizations						
Emergency department use						
Insurance status						

Table 7: Prevalence ratios of self-reported health care utilization and insurance status among survivors compared with sibling controls, before and after March 2020.

	Survivors before March 2020 %	Siblings before March 2020 %	Crude PR (95% CI	Adjusted PR (95% CI)	Survivors after March 2020 %	Siblings after March 2020 %	Crude PR (95% CI	Adjusted PR (95% CI)
Non-obstetric hospitalizations								
Emergency department use								
Insurance status								

Table 8. Prevalence of self-reported preventive care services among survivors before and after March 2020.

Preventive Care Service	All Survivors before March 2020 (N =)	Prevalence %	All Survivors after March 2020 (N =)	Prevalence %	Absolute Change (pp)	Relative Change (%)
Primary care visit						
Echocardiogram						
Colorectal cancer screening						
Cervical cancer screening						
Breast cancer screening						

Table 9: Prevalence ratios of self-reported preventive care services among survivors compared with sibling controls, before and after March 2020.

Preventive Care Service	Survivors before	Siblings before	Crude PR	Adjusted PR (95% CI)	Survivors after	Siblings after	Crude PR	Adjusted PR (95% CI)

	March 2020 %	March 2020 %	(95% CI)		March 2020 %	March 2020 %	(95% CI)	
Primary care visit								
Echocardiogram								
Colorectal cancer screening								
Cervical cancer screening								
Breast cancer screening								

Table 10. Prevalence of modifiable lifestyle risk factors among survivors before and after March 2020.

	All Survivors before March 2020 (N =)	Prevalence %	All Survivors after March 2020 (N =)	Prevalence %	Absolute Change (pp)	Relative Change (%)
Overweight/obese						
Inadequate Physical activity						

Table 11: Prevalence ratios of modifiable lifestyle risk factors among survivors compared with sibling controls, before and after March 2020.

	Survivors before March 2020 %	Siblings before March 2020 %	Crude PR (95% CI	Adjusted PR (95% CI)	Survivors after March 2020 %	Siblings after March 2020 %	Crude PR (95% CI	Adjusted PR (95% CI)
Overweight/obese								

Inadequate Physical activity								

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Supplementary

Outcomes	**FU-5**	**FU-6**	**FU-7**	**FU-8**
SMNs	X	X	X	X
Overall and cause-specific mortality	-	-	-	-
MACE	X	Was not asked	X	X
Overweight/obesity	X	X	X	X
Smoking status	X	Was not asked	X	Was not asked
Physical activity	X	X	X	X
Heavy or risky drinking	X	Was not asked	X	Was not asked
Health care utilization	X	X	X	X
Insurance status	X	Was not asked	X	Was not asked
Use of preventive care services	X	X	X	X

X – indicates that the question was asked or the variable is available in the survey.

- We would consider these changes by the period of the pandemic (early phase March 2020-March 2021 and then recovery phase (March 2021 --- censor time unless this is long and then we could consider a 3rd phase)