Burden and Timing and Risk of Sensory, Motor, and Cognitive Impairments among Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study

Working Group:
Chronic Disease and Psychology (primary), Epidemiology/Biostatistics (secondary)

List of researchers: (final list TBD)
Cesia Cotache-Condor ccotach1@jhu.edu
Ellen van der Plas evanderplas@uams.edu
Tara Brinkman tara.brinkman@stjude.org
Eric Chow ericchow@uw.edu
Cindy Im imcindy@umn.edu
Wendy Leisenring wleisenr@fredhutch.org
Deo Kumar Srivastava kumar.srivastava@stjude.org
Greg Armstrong greg.armstrong@stjude.org
Chiara Papini chiara.papini@stjude.org
Rachel Peterson petersonr@kennedykrieger.org
Lennie Wong lenniewong@coh.org
Corinne Joshu cjoshu1@jhu.edu
Amber D'Souza gdsouza2@jhu.edu

About the research group: The following concept proposal was developed as part of the thesis dissertation requirements for Cesia Cotache-Condor, who is a PhD student in the Department of Epidemiology at Johns Hopkins University. She and her mentors, Drs. D'Souza and Joshu, have refined this proposal based on the feedback from the four assigned working groups, as well as the leading CCSS statistician, the CCSS PI, and other additional researchers with previous experience working with this data, as listed above. This proposal is composed of two aims related to sensory, motor, and cognitive impairments in childhood cancer survivors. Each aim intends to offer a different perspective on these impairments. Aim 1 proposes to measure the burden of multiple types of sensory impairments using DALYs. Aim 2 focuses specifically on hearing loss, exploring the full risk trajectory and associated factors specific to late hearing loss. Each aim is expected to be explored in a separate manuscript and will be part of Cesia's PhD thesis in Cancer Epidemiology.

SPECIFIC AIMS AND HYPOTHESES

Aim 1: To quantify and compare Disability-Adjusted Life Years (DALYs) related to sensory, motor, and cognitive impairments across demographic and clinical characteristics, and between survivors and sibling controls. We will explore differences in DALYs related to sensory, motor, and cognitive impairments across sex, race/ethnicity, cancer diagnosis, treatment modality, treatment exposure, age at cancer diagnosis, treatment era, and cancer status (all survivors versus all siblings as a comparison group).

Aim 2: To evaluate whether 5-year childhood cancer survivors experience an accelerated onset of hearing loss based on cumulative dose levels of cisplatin, carboplatin, and brain radiation treatment. We will use Acceleration Failure Time models to identify whether the onset of hearing loss is accelerated by cumulative dose levels of three cancer therapies: cisplatin (levels: none, <300mg/mg^2, ≥300mg/mg^2), carboplatin (levels: none, <1500mg/mg^2, ≥1500mg/mg^2), and brain radiotherapy (levels: none, <30 Gy^2, 30-49 Gy^2, ≥ 50 Gy^2). Each cancer treatment will be assessed independently

- Hypothesis: For each cancer treatment, survivors with higher levels of cumulative treatment dose will experience earlier onset of hearing loss.

A. BACKGROUND AND RATIONALE

High survival, high morbidity: The paradox of childhood cancer survivorship

Five-year childhood cancer survival has improved over time in North America, rising from 63% in the 1970s to 85% today, with these rates exceeding 95% for certain cancer types such as Hodgkin lymphoma (97.6%), retinoblastoma (95.6%), and thyroid carcinoma (99.8%).[1] The growing population of childhood cancer survivors was estimated to be around 500,000 as of 2020 in the US, and is expected to continue to grow due to ongoing improvements in treatment and care.[2,3]

Childhood cancer survivorship has increased, but survivors face significant risks of developing chronic, disabling, and fatal health conditions that emerge as a result of their cancer and its therapy.[4]
These health conditions are also called side effects (including acute toxicities, late effects, and long-term effects), and their prevalence is three times higher among survivors compared with the general population, especially among survivors from older treatment generations.[5,6]

Sensory, motor, and cognitive impairments are side effects of childhood cancer

Survivors with sensory, motor, and cognitive impairments experience limitations in their ability to perform activities and participate in society. They are less likely to live independently, graduate from high-school, attend college, or be employed, while being more likely to experience anxiety, depression, frailty, and limitations in language acquisition and speech, compared to the general population.[7-11] Furthermore, previous research has suggested that sensory, motor, and cognitive impairments can interplay with each other, magnifying their effect and underscoring the need to address them together to better understand their full impact.[12-14]

Even though significant progress in understanding these impairments has been made over the last decades, a systematic assessment of the burden, timing, and risk of sensory, motor, and cognitive impairments within the survivor population and comparisons across all cancer groups is still lacking. A major limitation to conducting such comprehensive evaluations is the scarcity of long-term survivorship data and small cohort sizes.[15,16] In this proposal, we will address these limitations by leveraging the data from the Childhood Cancer Survivor Study (CCSS), one of the largest, most heterogeneous, and with the longest follow-up worldwide.

We will build on the significant progress made from previous studies and will focus on two gaps that remain underexplored: 1) the burden of sensory, motor, and cognitive impairments beyond incidence and prevalence, and 2) the effect of cumulative dose of treatment on accelerated onset of hearing loss.

Gap 1: What is the full burden of sensory, motor, and cognitive impairments among childhood cancer survivors?

Previous studies have quantified the burden of sensory, motor, and cognitive impairments among childhood cancer survivors mainly using measures of incidence and prevalence.[6,11,17-20] However, these measures only provide a partial view of the burden of disease and can therefore underestimate the full burden, especially when rare outcomes are compared with common ones. Disability-Adjusted Life Years (DALY) is an established metric of disease burden that offers a policy-oriented perspective, integrating incidence, duration, and severity to estimate the magnitude of health lost and enabling head-to-head comparisons across all health conditions.[21] One DALY is equivalent to losing one year lived in full health, and higher DALYs indicate more cumulative loss of healthy life.[22]

Little progress has been made to apply DALYs to childhood cancer survivors, and this metric has only been assessed at a cancer type level (i.e., overall DALYs among Leukemia survivors). However, each cancer type encompasses a unique set and/or severity of late effects contributing to the overall burden of disease. Understanding the specific contribution of these late effects within each cancer type remains unexplored.[23]

The proposed research study will leverage the longitudinal data from the CCSS to quantify DALYs specific to sensor, motor, and cognitive impairments, thereby contributing to a more complete characterization of the burden of disease for these impairments among 5-year childhood cancer survivors (Aim 1). CCSS has the required data to calculate DALYs, including incidence, duration, and severity of sensory, motor, and cognitive impairments.

Gap 2: Does cumulative treatment dose accelerate the onset of hearing loss?

Hearing loss is a sensory impairment caused by damage to the outer, middle, inner ear, auditory nerve, or central auditory system.[24,25] In childhood cancer survivors, hearing loss is a side effect that is often irreversible and has been mainly attributed to treatment exposures such as platinum-based chemotherapy agents and cranial radiation.[26-28]

The association between these treatment exposures and hearing loss has mainly been explored from the perspective of an increased risk of hearing loss occurrence. For instance, Moke et al. reported that higher cisplatin dose intensity was associated with a twofold increased risk of hearing loss compared with lower dose intensity.[27] Whelan et al also reported a twofold risk of hearing loss for survivors receiving platinum-based chemotherapy when compared to sibling controls, but at that time only had access to the CCSS original baseline cohort diagnosed between 1970 and 1989.[29]

These estimates inform the magnitude of risk and help identify survivors at the highest risk based on treatment exposure. However, risk magnitude alone provides only a partial picture for prioritizing screening and intervention.[30] Equally important, but less investigated, is whether certain survivors experience an accelerated onset of hearing loss based on treatment exposure.

Together, these dimensions provide a more complete understanding of which survivors are at greatest risk and which survivors may benefit from earlier screening and targeted interventions.
The proposed research study aims to complement previous risk stratification research based on treatment exposure by determining whether certain survivors experience an accelerated onset of hearing loss based on levels of cumulative dose of cisplatin, carboplatin, and brain radiotherapy. Each exposure will be modeled separately within a unified analytic framework to estimate independent associations with hearing loss in the same study population.

B. ANALYSIS FRAMEWORK

Overall strategy: The proposed study aims to improve the understanding of sensory, motor, and cognitive impairments among childhood cancer survivors in two ways (Fig 1).

First, we will characterize the full burden of sensory, motor, and cognitive impairments among childhood cancer survivors using DALYs, accounting for incidence, duration, and severity.

Second, we will focus on one specific sensory impairment,

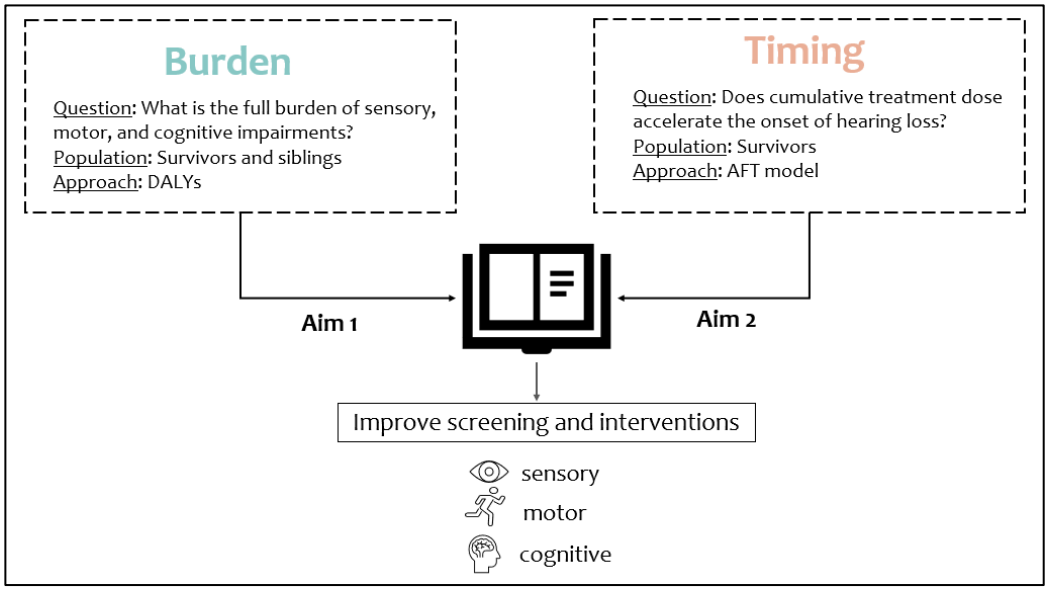

Figure 1. Simplified study framework.

hearing loss, and we will determine whether there is an accelerated onset of time to hearing loss based on cisplatin, carboplatin, and brain radiation cumulative treatment levels.

Data source: For both aims, we will use CCSS, a multicenter, retrospective cohort with prospective follow-up. Participants were eligible to enter the cohort if they were diagnosed with leukemia, CNS tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, or bone tumors before the age of 21 and between January 1, 1970 and December 31, 1999, and had survived at least 5 years from their primary cancer diagnosis. Nearest-age siblings from a randomly selected subset of survivors were also included in the study. The CCSS cohort has followed 25,735 survivors and 5,045 siblings retrospectively, with survivors followed from five years post-primary cancer diagnosis and siblings followed on the same dates as corresponding survivors.

Data collection scheme and ascertainment in CCSS: The follow-up and data collection scheme for sensory, motor, and cognitive impairments, cumulative treatment dose, and other covariates used across all aims are depicted in Figure 2. All impairments were ascertained by the participant's retrospective self-report of diagnoses. Participants reported whether they had been diagnosed with one or more impairments and provided the age at which this diagnosis first occurred.

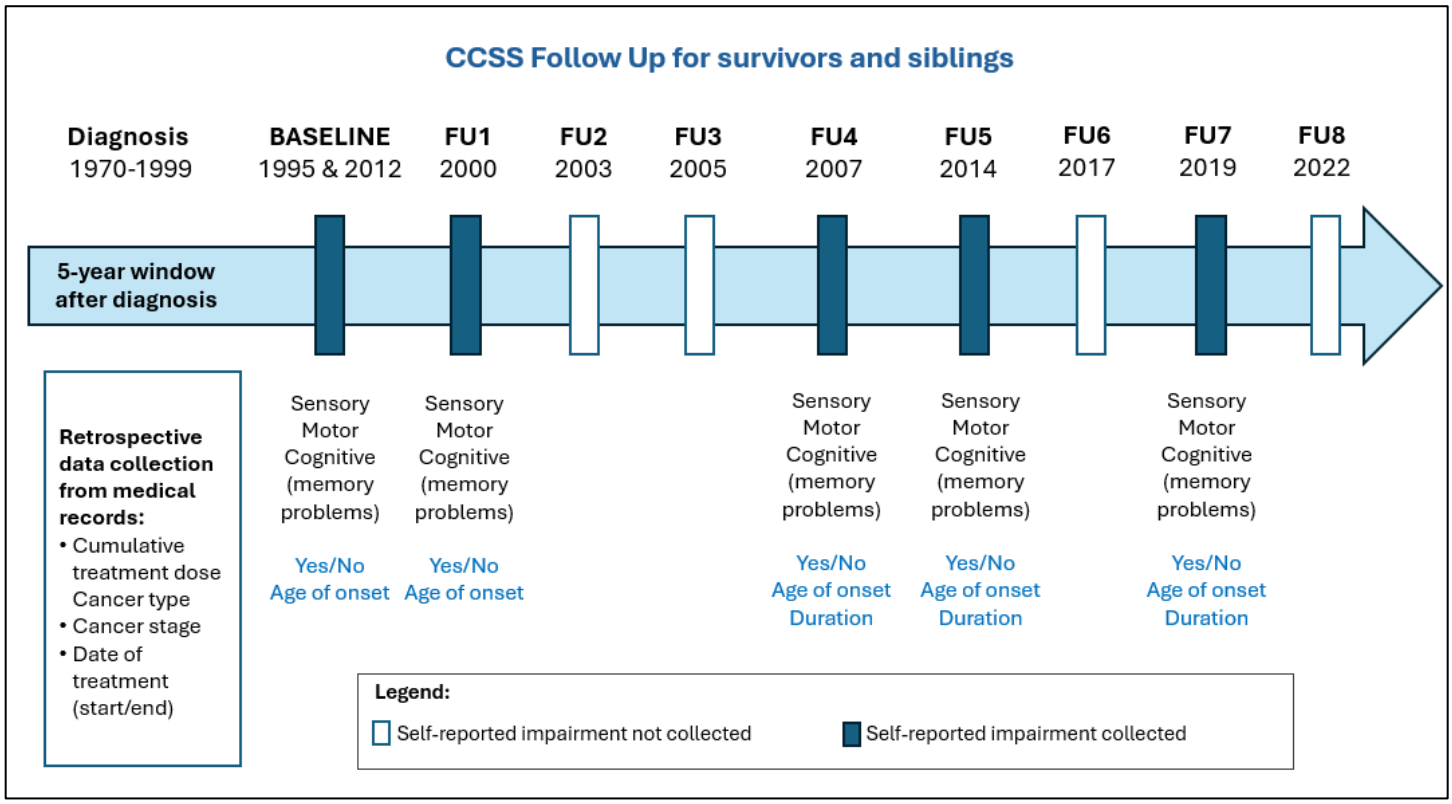

Figure 2. CCSS design and data collection scheme.

To improve completeness of ascertainment, sensory, motor, and cognitive impairments were assessed repeatedly at baseline and follow-up surveys (FU1, FU4, FU5, and FU7). Together, the *retrospective* and *repetitive* nature of data collection for age at onset of sensory, motor, and cognitive impairments facilitates the self-reported ascertainment of events occurring before and after the CCSS cohort entry. Therefore, in this study, sensory, motor, and cognitive impairments refer to self-reported diagnosis of impairment as captured through CCSS study questionnaires. This definition will be used consistently across all aims.

The complete list of covariates that will be used across all aims is outlined in Table 1. Sex and race/ethnicity variables were collected at baseline. Data on treatment exposure for methotrexate, prednisone, and dexamethasone will be included as binary variables (yes/no). Treatment exposures to cisplatin, carboplatin, brain radiotherapy, and vincristine will be included as cumulative dose categories. Cancer type and treatments

were collected retrospectively from medical records. Treatment exposure data covers the first five years after the first cancer diagnosis. Mortality was ascertained using the National Death Index, with data available through December 31, 2021.

Aim 1: To quantify and compare DALYs related to hearing loss among 5-year childhood cancer survivors across demographic and clinical characteristics, and between survivors and sibling controls.

Overview: First, we will calculate DALYs for sensory, motor, and cognitive impairments using the Global Burden of Disease methodology, a standardized framework developed by the Institute for Health Metrics and Evaluation. This methodology is widely used to ensure comparability of disease burden estimates across a wide range of health conditions and populations. We will calculate DALYs as: incidence multiplied by duration, multiplied by disability weight (0 to 1 scale, representing the severity of health loss).[31] Then, we will compare DALYs across demographic and clinical characteristics to determine whether the burden of impairments is disproportionate among certain groups of childhood cancer survivors.

Population: Childhood cancer survivors and their siblings who answered whether they had sensory, motor, or learning/memory conditions will be included. We will use the original and expansion baselines, and all available follow-ups addressing these questions (FU1, FU4, FU5, and FU7). All survivors diagnosed between 1970 and 1999 will be included. We will assess the inclusion of prevalent cases (events occurring before diagnosis) during the analysis.

Outcome definition: DALYs attributable to sensory, motor, and cognitive impairments. A detailed list of impairments from CCSS dataset is included in Table 2.

Table 1. Covariates used across all aims

Covariates	Levels
Cancer type	Acute lymphoblastic leukemia, Acute myeloid leukemia, Other leukemias, Central Nervous system, Hodgkin lymphoma, Non-Hodgkin lymphoma, Wilms tumor, Neuroblastoma, Soft tissue sarcoma, Osteosarcoma, Ewing sarcoma
Age at diagnosis	0-4 years, 5-9 years, 10-14 years, 15-20 years (or continuous)
Second malignancy	Yes, No
Cancer stage	Varies by cancer type
Treatment era	1970-1979, 1980-1989, 1990-1999
Treatment date	Start and end by treatment type
Chemotherapy	Yes, No
Radiotherapy	Yes, No
Surgery	Yes, No
Methotrexate all routes (including IM, IT/Ommaya, IV, PO)	Yes, No
Prednisone	Yes, No
Dexamethasone	Yes, No
Cumulative dose of platinum-based chemotherapy	None, <350 mg/m2, >= 350 mg/m2
Cumulative dose of cisplatin	None, <300 mg/m2, >= 300 mg/m2
Cumulative dose of carboplatin	None, <1500 mg/m2, >= 1500 mg/m2
Cumulative dose of brain radiation	None, <30 Gy2, 30-49Gy2, >=50 Gy2
Vincristine	None, <39 mg/m2, >= 39 mg/m2

Variables needed for calculation of DALYs: DALYs are not calculated yet in the CCSS dataset. The data below will be used to calculate them.

- *Incidence of impairment:* We will include impairments with any grade of severity, as specified in the CCSS Chronic Conditions Matrix Common Terminology for Adverse Events (CTCAE). The main analysis will be restricted to impairments with grade 3+ severity for severe/life-threatening events to reduce recall bias and misclassification, and secondary analysis will include milder grades to account for disabilities that might be otherwise underestimated, since mild impairments can still contribute to DALYs (Figure 3). All sensory, motor, and cognitive impairments will be defined as incident if reported after cancer diagnosis.
- *Duration:* Data for each impairment comes from the question about whether “disease is still present”.

- *Disability weights:* We will use the Global Burden of Disease (GBD) Study 2023 disability weight list to match disability weights to our sensory, motor, and cognitive impairment data.[32]

The CCSS health conditions will be grouped together into three impairment domains (sensory, motor, and cognitive), see Table 3. Within these domains, we will classify impairment subdomains related to body functions (seeing, hearing, vestibular, other sensory, muscle, movement, and memory) based on the International Classification of Functioning, Disability and Health (ICF) framework.[33,34] Thus, outcomes will be considered in several different ways, including: 1) as impairment domains, 2) as impairment subdomains, 3) as combinations of domains (sensory+motor, sensory+cognitive, motor+cognitive, and sensory+motor+cognitive), and 4) as the cumulative number of impairment subdomains by body function (1 impairment, 2-3 impairments, and 4+ impairments).

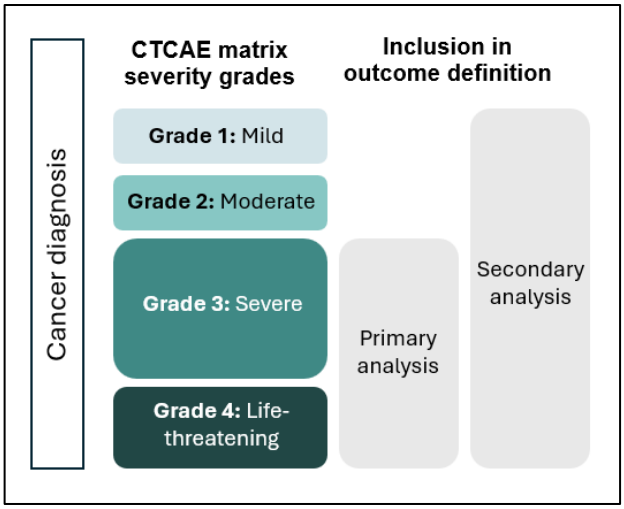

Figure 3. Inclusion of impairments by severity grade for Aim 1.

Table 2. Sensory, motor, and cognitive impairments by severity grade

Outcomes for primary analysis: Grade 3+ impairments	Outcomes for secondary analysis: All grades of impairment
• Blindness, Grade 3-4 • Cataracts, Grade 3 • Loss of hearing, Grades 3-4 • Balance problems, Grades 3-4 • Paralysis, Grades 3-4 • Memory problems, Grades 3-4	• Blindness, Grade 1-4 • Cataracts, Grade 1,3 • Crossed eye, Grade 1 • Double vision, Grade 2 • Glaucoma, Grade 1 • Other vision problem, Grade 1-2 • Loss of hearing, Grades 1-4 • Other hearing condition, 1-2 • Vertigo, Grade 1 • Balance problems, Grades 1-4 • Sensory neuropathy, Grade 1 • Abnormal taste, Grade 1 • Tremors, Grade 1 • Paralysis, Grades 1-4 • Weakness in arm, Grade 1 • Weakness in leg, Grades 1-2 • Memory problems, Grades 1-4

Table 3. Grouping of impairments by domain and subdomain for outcomes

CCSS Health condition	Impairment Domain	Impairment Subdomain: Body Function
Blindness	Sensory	Seeing
Cataracts	Sensory	Seeing
Crossed eye	Sensory	Seeing
Double vision	Sensory	Seeing
Glaucoma	Sensory	Seeing
Other vision problem	Sensory	Seeing
Loss of hearing	Sensory	Hearing
Other hearing condition	Sensory	Hearing
Vertigo	Sensory	Vestibular

Balance problems	Sensory	Vestibular
Abnormal taste	Sensory	Other sensory
Tremors	Motor	Movement
Paralysis	Motor	Muscle/Movement
Weakness in arm	Motor	Muscle/Movement
Weakness in leg	Motor	Muscle/Movement
Learning/memory problems	Cognitive	Memory

Covariates: Other relevant variables used to facilitate DALY comparisons will include cancer type, age at diagnosis, treatment era, treatment modality (chemotherapy, radiotherapy, and surgery), treatment exposure to cisplatin, carboplatin, brain radiotherapy, vincristine, methotrexate, prednisone, and dexamethasone, as well as sex, race, and cancer status (survivor versus siblings as a comparison group).

Analytical approach: We will use the incidence-based Global Burden of Disease approach to calculate DALYs.[31] For conditions that can impact mortality, DALYs are calculated by adding Years of Life Lost (YLL) and Years Lived with Disability (YLD). Since the sensory, motor, and cognitive impairments included in this study are not identified as causes of death by the Global Burden of Disease, DALYs for this analysis will be based only on Years Lived with Disability. Years Lived with Disability, and therefore DALYs, will be calculated as the product of incidence (I), duration (D), and disability weight (DW), as summarized below:

$$YLD = I \times D \times DW \quad \rightarrow \quad DALY = YLD$$

The incidence of these impairments is well documented in the CCSS dataset. Data on impairment duration is measured within CCSS by reports of recovery or ongoing impairment at follow-up visits, but the exact time of recovery is not precise, given the long follow-up windows (4 and 7 years). Therefore, when recovery is reported, we will refine its estimation by using a single-random point imputation approach to randomly determine recovery time between the last time reporting hearing loss and the first time reporting recovery.[35] This methodology is consistent with previous literature.[35] When recovery is not reported (i.e., the participant indicates that the impairment is still present at the most recent follow-up), the date of the last follow-up will be used as the end point for the DALY calculation. Of note, recovery from sensory, motor, or cognitive impairments grade 3+ might be unlikely and therefore not relevant in the calculation of DALYs for most survivors. However, because a subset of survivors may still report recovery and the exact recovery date is not available due to the long intervals between follow-up questionnaires, we believe it is important to retain this approach to estimate duration as accurately as possible for those individuals.

DALYs will first be calculated at the individual survivor level. Group-specific DALY rates will then be estimated by summing individual DALYs within each subgroup and dividing by the total accumulated person-years contributed by survivors in that subgroup. These rates will be expressed per 100,000 person-years. Our results will include descriptive and inferential statistical analysis. For the descriptive analysis, we will provide a comprehensive overview of the distribution of the study participants classified into impairment domains (sensory, motor, and cognitive) and subdomains (seeing, hearing, vestibular, other sensory, muscle, movement, and memory) and across demographic and clinical characteristics, as outlined in Table 4.

Table 4. Distribution of childhood survivors' demographic and clinical characteristics by domain and subdomain impairments. Note: RT= Radiation therapy

Characteristics	n (%)							
	All	Sensory				Motor		Cognitive
		Seeing	Hearing	Vestibular	Other	Muscle	Movement	Memory
Sex								
Male								
Female								

Race/ethnicity								
White not Hispanic								
Black not Hispanic								
American Indian/Alaska Native								
Asian or Pacific Islander								
Hispanic								
Other								
Age at diagnosis								
0-4								
5-9								
10-14								
15 to 20								
Diagnosis								
Acute lymphoblastic leukemia								
Acute myeloid leukemia								
Other leukemias								
Central nervous system								
Hodgkin lymphoma								
Non-Hodgkin lymphoma								
Wilms tumor								
Neuroblastoma								
Soft tissue sarcoma								
Treatment								
Chemo only								
Surgery only								
Chemo + RT								
Chemo + surgery								
RT + surgery								
Surgery + RT								
Chemo + RT + surgery								
Cumulative dose of platinum-based chemotherapy								
None								
<300 mg/m²								
≥ 300 mg/m²								
Cumulative dose of brain radiation								
None								
<30 Gy2								
30-49 Gy2								
≥ 50 Gy2								
Treatment era								
1970-79								
1980-89								
1990-99								

Our inferential analysis will be presented in Tables 5-13. For all these tables, we will compare DALYs per 100,000 person-years across impairment domains/subdomains and sex (Table 5), race/ethnicity (Table 6), cancer diagnosis (Table 7) treatment modality (Table 8), treatment exposure (Tables 9-10) age at cancer diagnosis (Table 10), treatment era (Table 11), and cancer status (Table 12). Of note, Tables 5-13 will be used to fully understand the distribution of DALYs across all impairment domains/subdomains and covariates. However, the final display of this information will be done through figures (i.e., combined bars and charts), appropriate for the descriptive nature of Aim 1 and the tables will be included as part of the supplementary data in our final paper.

Impairment categories will not be treated as restrictive, and participants will be able to contribute to one or more of the listed categories. For instance, there are seven categories for the impairment subdomain. Participants with both sensory and motor impairments will be able to contribute to both categories. We will also report the accumulation of impairments across impairment domain (sensory+motor, sensory+cognitive, motor+cognitive, sensory+motor+cognitive), and subdomain (0, 1, 2-3, 4+). We will compare DALY rates within specific impairment domains and subdomains across demographic and cancer-related characteristics using bootstrap resampling methods. Bootstrap-derived 95% confidence intervals will be calculated for each aggregate DALY rate estimate, and p-values will be obtained for comparisons between groups. Statistical significance will be defined as a two-sided p-value < 0.05.

Finally, we will explore the contribution of a secondary malignancy to the burden of sensory, motor, and cognitive impairments by comparing DALYs between survivors with and without a secondary malignancy.

Table 5. Distribution of childhood cancer survivors' standardized DALY rates by sex.

Impairment group definition	DALYs per 100,000 person-years 95% CI		
	Male	Female	p-value*
Domain †			
No impairment			
Any Sensory			
Any Motor			
Any Cognitive			
Any Sensory, Motor or Cognitive			
Combined Domain			
sensory+motor			
sensory+cognitive			
motor+cognitive			
sensory+motor+cognitive			
Impairment Subdomains by Body Function †			
Any Seeing			
Any Hearing			
Any Vestibular			
Any Other sensory			
Any Muscle			
Any Movement			
Any Memory			
No impairment			
Cumulative Number of Impairment Subdomains by Body Function			
0			
1			

2-3			
4+			

† Categories are not mutually exclusive, participants can contribute to each of these categories in which they have an impairment.
*p-values will be calculated for each variable level (i.e., each row)
Note: Groups with small sample sizes may be combined as needed following data exploration.

Table 6. Distribution of childhood cancer survivors' DALY rates by race/ethnicity.

Impairment group definition	DALYs per 100,000 person-years 95% CI					
	White not Hispanic	Black not Hispanic	American Indian/Alaska Native	Asian or Pacific Islander	Hispanic any race	p-value*
Domain †						
No impairment						
Any Sensory						
Any Motor						
Any Cognitive						
Any Sensory, Motor or Cognitive						
Combined Domain						
sensory+motor						
sensory+cognitive						
motor+cognitive						
sensory+motor+cognitive						
Impairment Subdomains by Body Function †						
Any Seeing						
Any Hearing						
Any Vestibular						
Any Other sensory						
Any Muscle						
Any Movement						
Any Memory						
No impairment						
Cumulative Number of Impairment Subdomains by Body Function						
0						
1						
2-3						
4+						

† Categories are not mutually exclusive, participants can contribute to each of these categories in which they have an impairment.
*p-values will be calculated for each variable level (i.e., each row)
Note: Groups with small sample sizes may be combined as needed following data exploration.

Table 7. Distribution of childhood cancer survivors' DALY rates by diagnosis group.

Impairment group definition	DALYs per 100,000 person-years 95% CI									
	ALL	AML	Other leukemia	CNS	HL	NHL	Wilms tumor	Neuro blastoma	Soft tissue sarcoma	p-value*
Domain †										
No impairment										
Any Sensory										
Any Motor										
Any Cognitive										
Any Sensory, Motor or Cognitive										
Combined Domain										
sensory+motor										
sensory+cognitive										
motor+cognitive										
sensory+motor+cognitive										
Impairment Subdomains by Body Function †										
Any Seeing										
Any Hearing										
Any Vestibular										
Any Other sensory										
Any Muscle										
Any Movement										
Any Memory										
No impairment										
Cumulative Number of Impairment Subdomains by Body Function										
0										
1										
2-3										
4+										

† Categories are not mutually exclusive, participants can contribute to each of these categories in which they have an impairment.
*p-values will be calculated for each variable level (i.e., each row)
Note: Groups with small sample sizes may be combined as needed following data exploration.

Table 8. Distribution of childhood cancer survivors' DALY rates by treatment modality.

Impairment group definition	DALYs per 100,000 person-years 95% CI							
	Chemo only	Surgery only	Chemo + RT	Chemo + surgery	RT + surgery	Surgery + RT	Chemo + RT + surgery	p-value*
Domain †								

No impairment								
Any Sensory								
Any Motor								
Any Cognitive								
Any Sensory, Motor or Cognitive								
Combined Domain								
sensory+motor								
sensory+cognitive								
motor+cognitive								
sensory+motor+cognitive								
Impairment Subdomains by Body Function †								
Any Seeing								
Any Hearing								
Any Vestibular								
Any Other sensory								
Any Muscle								
Any Movement								
Any Memory								
No impairment								
Cumulative Number of Impairment Subdomains by Body Function								
0								
1								
2-3								
4+								

† Categories are not mutually exclusive, participants can contribute to each of these categories in which they have an impairment.
*p-values will be calculated for each variable level (i.e., each row)
Note: Groups with small sample sizes may be combined as needed following data exploration.

Table 9. Distribution of childhood cancer survivors' DALY rates by cumulative treatment dose.

Impairment group definition	DALYs per 100,000 person-years 95% CI												
	Platinum-based chemotherapy				Brain radiotherapy					Vincristine			
	None	< 350 mg/m²	≥ 350 mg/m²	p*	None	< 30 Gy^2	30-49 Gy^2	≥ 50 Gy^2	p*	None	<39 mg/m²	≥ 39 mg/m²	p*
Domain †													
No impairment													
Any Sensory													
Any Motor													
Any Cognitive													
Any Sensory, Motor or Cognitive													
Combined Domain													

sensory+motor													
sensory+cognitive													
motor+cognitive													
sensory+motor+cognitive													
Impairment Subdomains by Body Function †													
Any Seeing													
Any Hearing													
Any Vestibular													
Any Other sensory													
Any Muscle													
Any Movement													
Any Memory													
No impairment													
Cumulative Number of Impairment Subdomains by Body Function													
0													
1													
2-3													
4+													

† Categories are not mutually exclusive, participants can contribute to each of these categories in which they have an impairment.
*p-values will be calculated for each variable level (i.e., each row)
Note: Groups with small sample sizes may be combined as needed following data exploration.

Table 10. Distribution of childhood cancer survivors' DALY rates by other treatment exposures.

Impairment group definition	DALYs per 100,000 person-years 95% CI								
	Methotrexate all routes			Prednisone			Dexamethasone		
	Yes	No	p-value*	Yes	No	p-value*	Yes	No	p-value*
Domain †									
No impairment									
Any Sensory									
Any Motor									
Any Cognitive									
Any Sensory, Motor or Cognitive									
Combined Domain									
sensory+motor									
sensory+cognitive									
motor+cognitive									
sensory+motor+cognitive									
Impairment Subdomains by Body Function †									
Any Seeing									

Any Hearing									
Any Vestibular									
Any Other sensory									
Any Muscle									
Any Movement									
Any Memory									
No impairment									
Cumulative Number of Impairment Subdomains by Body Function									
0									
1									
2-3									
4+									

† Categories are not mutually exclusive, participants can contribute to each of these categories in which they have an impairment.
*p-values will be calculated for each variable level (i.e., each row)
Note: Groups with small sample sizes may be combined as needed following data exploration.

Table 11. Distribution of childhood cancer survivors' DALY rates by age at cancer diagnosis.

Impairment group definition	DALYs per 100,000 person-years 95% CI				
	0-4 yrs	5-9 yrs	10-14 yrs	15-20 yrs	p-value*
Domain †					
No impairment					
Any Sensory					
Any Motor					
Any Cognitive					
Any Sensory, Motor or Cognitive					
Combined Domain					
sensory+motor					
sensory+cognitive					
motor+cognitive					
sensory+motor+cognitive					
Impairment Subdomains by Body Function †					
Any Seeing					
Any Hearing					
Any Vestibular					
Any Other sensory					
Any Muscle					
Any Movement					
Any Memory					
No impairment					
Cumulative Number of Impairment Subdomains by Body Function					

0					
1					
2-3					
4+					

† Categories are not mutually exclusive, participants can contribute to each of these categories in which they have an impairment.
*p-values will be calculated for each variable level (i.e., each row)
Note: Groups with small sample sizes may be combined as needed following data exploration.

Table 12. Distribution of childhood cancer survivors' DALY rates by treatment era.

Impairment group definition	DALYs per 100,000 person-years 95% CI			
	1970-1979	1980-1989	1990-1999	p-value*
Domain †				
No impairment				
Any Sensory				
Any Motor				
Any Cognitive				
Any Sensory, Motor or Cognitive				
Combined Domain				
sensory+motor				
sensory+cognitive				
motor+cognitive				
sensory+motor+cognitive				
Impairment Subdomains by Body Function †				
Any Seeing				
Any Hearing				
Any Vestibular				
Any Other sensory				
Any Muscle				
Any Movement				
Any Memory				
No impairment				
Cumulative Number of Impairment Subdomains by Body Function				
0				
1				
2-3				
4+				

† Categories are not mutually exclusive, participants can contribute to each of these categories in which they have an impairment.
*p-values will be calculated for each variable level (i.e., each row)
Note: Groups with small sample sizes may be combined as needed following data exploration.

Table 13. Distribution of DALYs rates by cancer status.

Impairment group definition	DALYs per 100,000 person-years 95% CI		
	Childhood cancer survivors	Sibling controls	p-value*
Domain †			
No impairment			
Any Sensory			
Any Motor			
Any Cognitive			
Any Sensory, Motor or Cognitive			
Combined Domain			
sensory+motor			
sensory+cognitive			
motor+cognitive			
sensory+motor+cognitive			
Impairment Subdomains by Body Function †			
Any Seeing			
Any Hearing			
Any Vestibular			
Any Other sensory			
Any Muscle			
Any Movement			
Any Memory			
No impairment			
Cumulative Number of Impairment Subdomains by Body Function			
0			
1			
2-3			
4+			

† Categories are not mutually exclusive, participants can contribute to each of these categories in which they have an impairment.
*p-values will be calculated for each variable level (i.e., each row)
Note: Groups with small sample sizes may be combined as needed following data exploration.

Potential challenges and mitigation strategies:

- *GBD disability weights are derived from population-based assessments and may not fully capture the lived experience of childhood cancer survivors*: We will acknowledge this limitation and emphasize that, despite its shortcomings, the GBD methodology provides the only global, standardized, and comprehensive set of disability weights for estimating DALYs. Therefore, it represents the most appropriate approach to achieve our primary goal of facilitating head-to-head comparisons between sensory, motor, and cognitive impairments in childhood cancer survivors and other health conditions.
- *Covariate missingness*: We will assess the pattern of missingness and apply multiple imputations by chain equations accordingly.

- The outcome will be defined as any sensory, motor, or cognitive impairment occurring after five years of survival if there are issues that systematically affect the availability, report, or ascertainment of events occurring before the 5-year survival mark, even when the questionnaires do not indicate such issues.

Aim 2: To evaluate whether 5-year childhood cancer survivors experience an accelerated onset of hearing loss based on cumulative dose levels of cisplatin, carboplatin, and brain radiation treatment.

Overview: We will examine the association of three main cancer treatment exposures: cumulative dose of cisplatin, cumulative dose of carboplatin, and cumulative dose of brain radiation with time to hearing loss among participants. For each treatment, time at risk will start at the end of the treatment. Therefore, we will the events occurring after treatment completion. For the analysis, first, we will characterize the time to hearing loss in our population across cumulative treatment exposures by using the Cummulative Incidence Funcion plots accounting for the competing risk of death. Second, we will use Acceleration Failure Time models to determine whether survivors with certain levels of cumulative treatment experience earlier onset of hearing loss compared to others.

Inclusion criteria: Our analysis will include childhood cancer survivors who provided information on hearing loss at baseline and/or follow-up surveys and had complete data on cumulative treatment doses. Since age at hearing loss onset is reported without a specific day or month, hearing loss onset may occur in the same calendar year as treatment completion, limiting the ability to establish temporal ordering. Consequently, we will also exclude from the analytical sample participants for whom the temporal relationship between exposure and outcome cannot be ascertained.

Outcome definition: Time to hearing loss will be defined as incident hearing loss after treatment completion. The definition of hearing loss is restricted to grades 3 or higher to capture more disruptive and clinically meaningful hearing loss. Our primary outcome will include events after five years post-diagnosis. Our secondary outcome will include all events after treatment completion; however, if there are issues with the availability, reporting, or ascertainment of events occurring between the end of treatment and five years of survival, or issues with the availability of treatment dates, the secondary outcome may only be descriptive. Of note, deafness in both ears that is not completely corrected by a hearing aid was classified as grade 4 by the CCSS CTCAE matrix, though it is not technically a life-threatening impairment. Therefore, we will discuss our results focusing on the severity of grades 3 and 4 impairments rather than treating them as life-threatening.

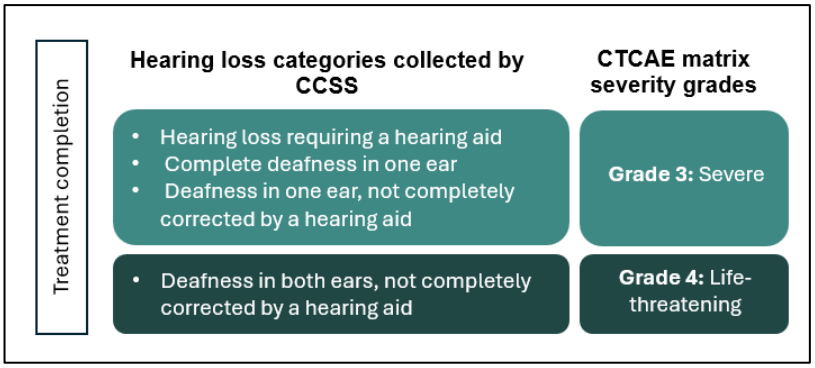

Figure 4. Definition of outcome for Aim 2.

Exposure definition: Three treatment exposures will be assessed independently in relation to the outcome.

- Cumulative dose of cisplatin (None, <300 mg/m², ≥ 300 mg/m²)
- Cumulative dose of carboplatin (None, 1500 mg/m^2, ≥ 1500 mg/m^2)
- Cumulative dose of brain radiation (None, <30 Gy^2, 30-49 Gy^2, ≥ 50 Gy^2)

Each exposure will be defined as a time-fixed variable quantifying the total cumulative dose received from cancer diagnosis through the end date of the corresponding therapy.

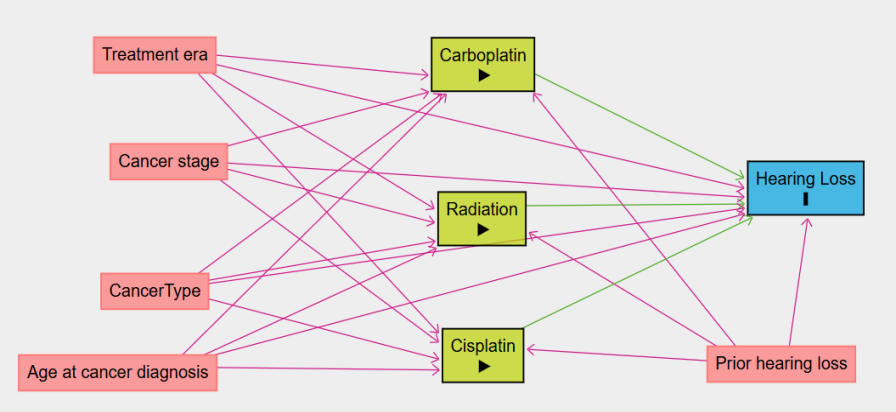

Figure 5. Combined version of three directed acyclic graphs that assess 3 independent associations or cumulative dose of treatment and hearing loss for Aim 2. Green box: Exposures. Blue box: Outcome. Red box: Minimal adjustment set.

Confounder adjustment: Confounders will be selected based on the minimal adjustment set suggested by directed acyclic graphs designed for each exposure-outcome association. Figure 6 is a combined version of three directed acyclic graphs assessing the association of cumulative dose of cisplatin, carboplatin, and brain radiation with hearing loss independently.

For each exposure-outcome association, we will include treatment era, cancer type, age at cancer diagnosis, and prior hearing loss as confounders (hearing loss grades 1 or 2, reported before the end of treatment completion) in the main model. We will perform sensitivity analysis, including cancer stage to a model restricted to participants with stage data to assess whether cancer stage influences the exposure-outcome association and whether its omission would likely result in unmeasured confounding.

For aim 2, prior hearing loss will be defined as self-reported grades 1 and 2 of hearing loss, since these participants are still at risk of experiencing grades 3+ of hearing loss after treatment completion. Any participant with grades 3+ before treatment completion will be excluded from the analytical sample. Because of sample size constraints, we will explore including a more condensed version of the cancer type variable during the modeling process (Table 14).

Table 14. Compact definition and rationale of cancer type

Grouped cancer type	Definition	Rationale
Leukemias	Acute lymphoblastic leukemia, Acute myeloid leukemia, and other leukemias	Hematological malignancies that often require multi-agent chemotherapy and sometimes cranial radiation.
Lymphomas	Hodgkin lymphoma and Non-Hodgkin lymphoma	Hematological malignancies treated with multimodal approaches that included both chemotherapy and radiotherapy. In Hodgkin lymphoma, radiotherapy played a dominant role in earlier treatment eras before treatment shifted toward greater use of multiagent chemotherapy. In contrast, non-Hodgkin lymphoma was treated primarily with chemotherapy, with radiotherapy used more selectively.
Central Nervous System tumors	Central Nervous System tumors	Solid tumors requiring cranial radiation, cranial surgery, and cisplatin-based chemotherapy.
Other solid tumors	Wilms tumor, Neuroblastoma, Soft tissue sarcoma, Osteosarcoma, and Ewing sarcoma	Solid tumors less likely to require cranial radiation or cisplatin-based chemotherapy compared to the previous categories.

Cohort design: For each exposure–outcome association, study entry will be defined as the date of completion of the corresponding therapy. Study exit will be defined at the earliest of hearing loss onset, death, or loss to follow-up. Finally, we will define the time scale as years since treatment completion.

Analytical approach: During the data exploration process, we will use Kaplan Meier curves to visually examine time to hearing loss across levels of each exposure. Then, we will fit accelerated failure time models to estimate time ratios.[36] These time ratios will quantify whether the onset of hearing loss is accelerated and the magnitude of this acceleration across treatment exposure levels. Several AFT models will be considered based on the underlying distribution of our data. Candidate models may include Weibull, log-normal, and generalized gamma distributions.[37] We will use the Kaplan Meier curves generated during the data exploration process to visually assess the model fit against the observed data. The Akaike Information Criterion will be used to select the best-fitting model for each exposure–outcome association. Of note, the Kaplan Meier curves will be used only for data exploration and AFT model fit evaluation, and not for the display of time to hearing loss in the manuscript.

The competing risk of death will be addressed using a cause-specific hazard approach, in which death will be treated as a censoring event when modeling time to hearing loss. A separate cause-specific hazard model will be fit with death as the outcome and hearing loss treated as the competing event. We will use both models to estimate the cumulative incidence function and describe the cumulative probability of hearing loss over time while appropriately accounting for the competing risk of death.
We will adjust for confounding by incorporating the minimal adjustment set using inverse probability weighting (IPW). Propensity scores for each treatment exposure will be estimated using multinomial logistic regression and including the minimal sufficient adjustment set as the covariates. Finally, we will use the estimated propensity scores to derive Inverse probability weights that will be applied in the final models. The use of IPW in survival for covariate adjustment in accelerated failure time models is a well-established approach.[38,39] We will use a weighting-based approach for confounder adjustment rather than direct adjustment to address the limitation of having a small number of events in Aim 2. Direct adjustment would require including a larger number of parameters in the model relative to the number of observed events, which may reduce model stability. In contrast, IPW allows confounder adjustment while preserving a parsimonious accelerated failure time model. Although IPW is commonly used for causal inference, we aim to estimate associations rather than causal effects.

Exploration of cancer type during modelling: Although cancer type is adjusted for in the pooled model to control for confounding, the pooled estimate may mask relevant heterogeneity effects across diagnostic groups. Therefore, in addition to the primary pooled analysis, we will assess effect measure modification by cancer type using interaction terms between treatment exposures and cancer type to evaluate heterogeneity in treatment effects in the pooled model. We will also assess effect measure modification by fitting stratified models for each cancer type, based on the availability of exposure and outcome data. Given the limited number of events within some cancer types, we will perform stratified analyses using the combined cancer type categories defined in Table 14 and explore hierarchical mixed-effects models as sensitivity analyses to improve estimation stability by borrowing strength across groups. The proposed hierarchical mixed-effects model will allow us to account for clustering by cancer type and explore potential heterogeneity across diagnostic groups without requiring multiple interaction terms or cancer-specific models, which may not be feasible given the limited number of hearing loss events. This exploratory analysis aims to assess whether the association between treatment exposures and hearing loss is consistent across cancer types.

Our results will include a descriptive distribution of hearing loss status (no hearing loss, grade 1 hearing loss, grade 2 hearing loss, grade 3 hearing loss, and grade 4 hearing loss) across sex, age at diagnosis, race/ethnicity, diagnosis type, cumulative dose of cisplatin, cumulative dose of carboplatin, cumulative brain radiation, and treatment era as outlined in Table 15. Cumulative incidence functions will be displayed to the cumulative probability of hearing loss over time while appropriately accounting for the competing risk of death. across the three treatment exposure variables.

Table 15. Distribution of hearing loss status among childhood cancer survivors across demographic and clinical characteristics.

Characteristics	n(%)				
	No Hearing Loss	Grade 1 Hearing Loss	Grade 2 Hearing Loss	Grade 3 Hearing Loss	Grade 4 Hearing Loss
Sex					
Male					
Female					
Race/ethnicity					
White non-Hispanic					
Other					
Age at diagnosis (continuous)					
Age at diagnosis					
0-4					
5-9					
10-14					
15-20					
Diagnosis					
Acute lymphoblastic leukemia					
Acute myeloid leukemia					
Other leukemias					
Central nervous system					
Hodgkin lymphoma					
Non-Hodgkin lymphoma					
Neuroblastoma					
Soft tissue sarcoma					
Osteosarcoma					
Ewing sarcoma					
Cumulative dose of cisplatin					
None					
< 300 mg/m²					
≥ 300 mg/m²					
Cumulative dose of carboplatin					
None					
< 400 mg/m²					
≥ 400-600 mg/m²					
> 600 mg/m²					
Cumulative dose of brain radiation					
None					
<30 Gy^2					
30-49 Gy^2					
≥ 50 Gy^2					
Treatment era					
1970-1979					
1980-1989					
1990-1999					

The time ratios resulting from fitting the final Acceleration Failure Time models will be summarized in Table 16. Results will be presented for each treatment exposure variable.

Table 16. Time ratios obtained from Acceleration Failure Time models for each treatment exposure variable.

Exposures*	Cause-specific Multivariable AFT Model for Hearing Loss Time Ratio (95% CI)
Cumulative dose of cisplatin	
None	
< 300 mg/m²	
≥ 300 mg/m²	
Cumulative dose of carboplatin	
None	
< 400 mg/m²	
≥ 400-600 mg/m²	
> 600 mg/m²	
Cumulative brain radiation	
None	
<30 Gy^2	
30-49 Gy^2	
≥ 50 Gy^2	

*Each exposure will be evaluated independently in a multivariable model. All multivariable models will be adjusted for age at diagnosis, prior hearing loss, cancer diagnosis, and cancer stage.
**The cause-specific model for death will be reported in the appendix.

Potential challenges and mitigation strategies:

- We will only include events between treatment completion and five years post-diagnosis in our secondary outcome definition. If there are issues with the availability, reporting, or ascertainment of events occurring between the end of treatment and five years of survival, or issues with the availability of treatment dates, the secondary outcome might be only descriptive.
- *Covariate missingness*: We will assess the pattern of missingness and apply multiple imputations by chain equations accordingly.
- *Cumulative dose of treatment is only available for the first five years after primary cancer diagnosis*: We will use data on subsequent malignant neoplasms in an exploratory analysis as a proxy indicator of additional cancer-directed therapies received later in survivorship. We will conduct a sensitivity analysis where survivors are followed until hearing loss, death, loss to follow-up, or secondary malignancy diagnosis, whichever comes first. This approach may provide information about the extent to which unmeasured treatment exposures after the first five years may influence the observed associations between treatment dose and hearing loss.
- *Small number of events*: We will use the grouped definition of cancer type outlined in Table 14 to improve model stability and reduce overfitting. In addition, we will explore hierarchical models that allow for accounting of between-cancer-type heterogeneity in treatment effects. This approach will allow us to borrow strength across related cancer types while preserving clinically meaningful variation by treatment exposure.
- *Exclusion from the analytical sample participants for whom the temporal relationship between exposure and outcome cannot be ascertained:* We will perform sensitivity analysis, including these participants,

to assess the robustness of our findings and evaluate the potential impact of misclassification of exposure-outcome timing on the estimated associations.

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