

FORMAL PROPOSAL FOR THE CHILDHOOD CANCER SURVIVOR STUDY (CCSS ANCILLARY STUDY)

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Proposal Title: “Adverse Childhood Experiences (ACEs), Resilience, and Cardiovascular Outcomes in Adult Survivors of Childhood Cancer”

Working Groups: Chronic Disease (Primary); Psychology (Secondary); Cancer Control (Secondary)

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SPECIFIC AIMS

There are currently over 500,000 long-term survivors of childhood cancer living in the United States (US), and this number is growing due to treatment advances.¹ Unfortunately, childhood cancer survivors report chronic medical conditions in adulthood earlier and at higher rates compared to the general population, leading to premature mortality.² Specifically, cardiovascular disease is the most prevalent non-malignant cause of death for childhood cancer survivors, with a seven-fold higher risk compared to age-matched peers.³ Several treatment-related risk factors, especially anthracyclines and chest radiation therapy (RT) exposures, have well-documented cardiotoxicity and cardiac-related late effects; however, they remain essential therapies to achieve cure for many childhood cancers.^{4,5} To develop targeted interventions to prevent and mitigate adverse outcomes, it is critical to identify high-risk populations of childhood cancer survivors.

Adverse Childhood Experiences (ACEs) are traumatic events (e.g. experiencing abuse and/or neglect) that occur during childhood and can undermine a person's sense of safety, stability, and bonding.⁶ Over time, experiencing ACEs leads to development of toxic stress, defined as strong, frequent, or prolonged activation of the body's stress response systems in the absence of protective physiologic and psychologic corrections. ACEs have been associated with increased cardiovascular morbidity in adulthood for the general population, leading to premature death.⁶⁻⁸ Of note, perceived distress in adulthood has been associated with adverse cardiovascular outcomes among childhood cancer survivors.⁹ However, associations of ACEs with stress and cardiovascular outcomes have not previously been evaluated in childhood cancer survivors.

Possessing resilience, defined as the ability to harnesses resources to sustain psychological and/or physical well-being during adversity, can mitigate the development of toxic stress in children and potentially prevent poor long-term health outcomes caused by ACEs in the general population.^{10,11} While experiencing cancer as a child is not considered an ACE in the literature, resilience training has shown efficacy for childhood cancer patients in managing distress related to their cancer diagnosis and treatment.¹² Resilience can be cultivated, providing a potential target for intervention for those further impacted beyond their cancer diagnosis by ACEs.

We performed a pilot study examining ACEs and resilience in a convenience sample of childhood cancer patients undergoing active treatment at the University of Chicago Medical Center. Of our 52 participants, 26 (50%) reported at least one ACEs (mean 1.27±1.7; range 0-7), and overall participant resilience was above average. These pilot data show that investigation of ACEs and resilience was feasible in childhood cancer populations and provided rationale for studying these subjects in larger, nationally representative childhood cancer cohorts to better delineate their associations with long-term health outcomes.

The Childhood Cancer Survivor Study (CCSS) is a well-characterized, retrospective, North American cohort of over 25,000 long-term survivors of childhood cancer diagnosed from 1970-1999 and before 21 years old.¹³ Since its inception in 1994, the CCSS has published over 400 scientific manuscripts. Utilizing a nested case-control study design, we plan to recruit 92 cases with known cardiovascular disease and 276 controls matched using previously collected demographic data and treatment exposure from the larger CCSS cohort. With validated tools to measure ACEs and resilience, we aim to:

Primary Aim 1: Determine the odds of developing cardiovascular health conditions based on prior ACEs.

Hypothesis 1: Prior ACEs (defined as endorsing ≥ 1 ACE(s)) will be associated with increased occurrence of cardiovascular disease (defined as having ≥ 1 Grade 3 or 4 myocardial infarction (MI), congestive heart failure (CHF), or arrhythmia as per the Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE v4.03)¹⁴) after accounting for treatment exposures, such as anthracyclines and chest RT.^{4,5}

Primary Aim 2: Evaluate resilience as a mediator between exposure to ACEs and development of cardiovascular health conditions.

Hypothesis 2: Above-average resilience (calculated using the Connor-Davidson Resilience Scale¹⁵) will attenuate the odds of developing cardiovascular disease (defined as having ≥ 1 Grade 3 or 4 MI, CHF, or arrhythmia as per the CTCAE v4.03) for participants with prior ACEs (defined as endorsing ≥ 1 ACE(s)).

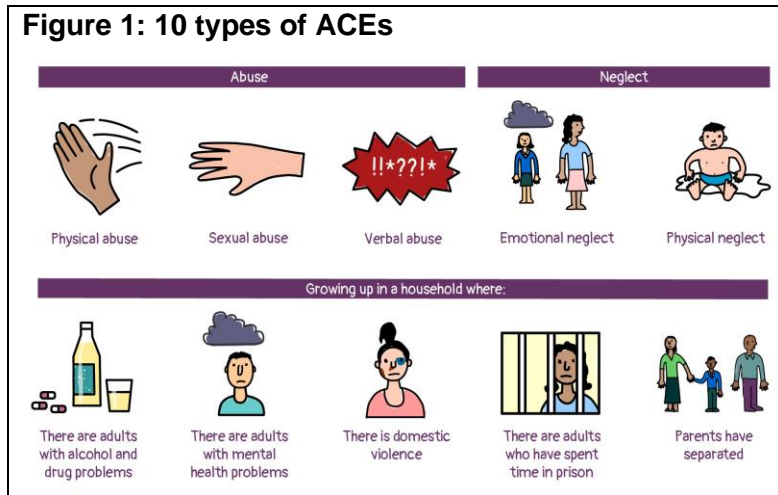
Exploratory Aim: Compare prevalence and demographics of those with ACEs to that of the 2010 Behavioral Risk Factor Surveillance System (BRFSS) survey cohort, a well-established survey that collects state-level data on health risks in the US.⁷

Data from this study will provide the grounds for larger examinations of the impact of ACEs on other types of chronic medical conditions experienced by childhood cancer survivors (e.g., lung disease, endocrinopathies).

Also, this study will provide data to support the development of targeted interventions strategies to improve clinical outcomes of this vulnerable population

SIGNIFICANCE

Due to continued advances in lifesaving treatments, over 85% of childhood cancer patients are now surviving well into adulthood.¹ Unfortunately, a great majority will also experience at least one severe chronic medical condition or late effect from their treatments, such as cardiotoxicity.^{2,16,17} These chronic diseases may result in long-term loss of productivity and compromised quality of life as well as premature mortality for childhood cancer survivors.³ Focused efforts to identify and prevent these outcomes in high-risk survivors are needed to reduce overall mortality in this population.



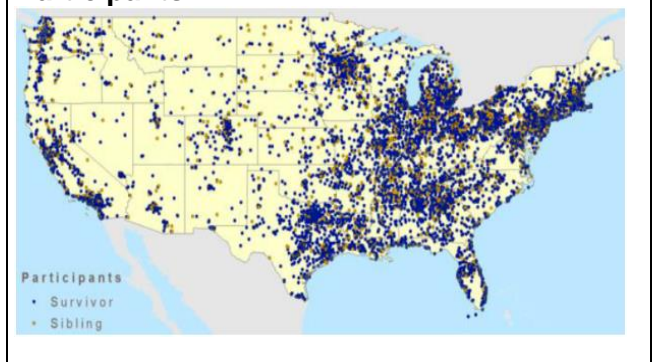
ACEs are classified into three main categories – abuse, neglect, and household dysfunction – and each category is then further subdivided (Figure 1). ACEs can contribute to long-term negative effects on health, well-being, educational attainment, and stable employment.^{6,7,18,19} In the general population, they have also been associated with increased development of chronic cardiovascular disease and risk of premature mortality.⁶ ACEs have not previously been described in nationally representative populations of childhood cancer survivors, despite their potential overlap with individuals who have experienced ACEs in developing significant cardiovascular morbidities.³

Not only can ACEs be deadly, they are also expensive: the economic and social costs to families and society from effects of ACEs, such as chronic disease, disability, and loss of employment, are estimated to total hundreds of billions of dollars each year in the US.^{8,20} In 2012, the American Academy of Pediatrics released a policy statement on Early Childhood Adversity and Toxic Stress, which called on healthcare providers to address ACEs as a public health crisis and integrate interventions to prevent ACEs and/or their long-term sequelae into existing clinical models.²¹

Research has long demonstrated that early adversity can be mitigated, or even overcome, through the promotion of resilience.^{22,23} Though studies into the exact neurobiological pathways connecting ACEs, resilience, and long-term health outcomes are ongoing,²⁴ research in the general population using “strength-based” therapeutic interventions (e.g. those that focus on the positive attributes of a person or a group rather than the negative) to cultivate resilience have shown promise in children and adolescents/young adults (AYAs) with ACEs in increasing health-promoting behaviors,²⁵⁻²⁷ with the ultimate goal of preventing poor long-term health outcomes influenced by ACEs.^{10,11}

The CCSS cohort provides the ideal population to study the impact of ACEs on long-term outcomes in childhood cancer survivors. The CCSS is a multi-institutional cohort established in 1994 to evaluate the outcomes of childhood cancer survivors and currently includes 25,583 survivors located across the US (Figure 2).¹³ Based on data from the Surveillance, Epidemiology and End Results (SEER), CCSS participants are “similar in terms of gender, race, and cancer type by time interval since diagnosis to those reported in SEER, indicating that the CCSS is representative of the larger US population of childhood cancer survivors”.²⁸ Furthermore, the CCSS has a well-established infrastructure of statisticians, program coordinators, and

Figure 2: US Distribution of CCSS Participants



oversight committees, ensuring the feasibility of carrying out large data studies.

INNOVATION

This study is innovative because:

1. To date, no literature has described the impact of ACEs on the development of chronic health conditions, specifically cardiovascular health conditions, in childhood cancer survivors.
2. It will examine the association between ACEs and resilience – a potential mitigating factor against long-term unfavorable health outcomes caused by ACEs – which has not previously been explored in childhood cancer survivors.
3. It includes participants from the nationally representative and well characterized CCSS cohort, which possesses the infrastructure to ensure that analyses examining ACEs, resilience, and long-term health outcomes can be undertaken successfully.

Ultimately, data from this study will provide the basis for a more extensive investigation of associations between ACEs and other chronic health conditions commonly experienced by adult survivors of childhood cancer, such as chronic pulmonary disease and endocrinopathies. This would lead to the development of interventions tailored to childhood cancer survivors who have experienced ACEs, thereby potentially reducing additional morbidity and premature mortality for this high-risk population.

APPROACH

Study Overview: We have developed this nested case-control study, “Adverse Childhood Experiences (ACEs), Resilience, and Cardiovascular Outcomes in Adult Survivors of Childhood Cancer,” which will include 92 cases with chronic cardiovascular disease and 276 controls matched on sex, race, age at diagnosis, treatment era, and anthracyclines and chest RT exposure from the nationally-representative CCSS cohort. We hypothesize that ACEs (**Exposure**) will be independently associated with increased occurrence of chronic cardiovascular disease (**Primary Outcome**), even after accounting for high-risk treatment exposures, and that resilience will mitigate this association. We will survey approximately 800 survivors in the CCSS cohort, with the goal of approximately 50% completion to reach our target accrual of 92 cases and 276 controls. In order to reduce the “noise” from treatment effects, we will oversample among survivors who did not receive anthracycline exposure ≥ 250 mg/m² or chest radiation (including cardiac exposure) ≥ 15 Gray (Gy) to obtain about 50% cases and controls without these exposures.

Preliminary Studies: We developed a pilot study in collaboration with Chapin Hall, a child welfare research institute affiliated with the University of Chicago, to examine the relationship between ACEs, resilience, chronic medical conditions, mental health issues, and substance misuse in a diverse cohort of childhood cancer patients undergoing active treatment at the University of Chicago Medical Center. We also assessed the feasibility and acceptability of assessing ACEs and resilience in this patient population, given the sensitive nature of the subject matter.

Patients ≤ 25 years old actively receiving cancer treatments at the University of Chicago were approached. Participants ≤ 17 years old completed the study with a parent/caregiver. Demographic, health, and behavioral variables were collected through self-report questionnaires, which included endorsement/denial of chronic medical conditions, mental illness, and substance use. Age-stratified ACEs questionnaires, provided by the Department of Health Care Services (DHCS)/Office of the California Surgeon General (CA-OSG) and adapted from the measurement tool used by Felitti et al., were used.^{6,29} Positive endorsements were summed to create the final ACE score. Resilience was assessed using age-stratified measures from the Resilience Research Centre,³⁰ categorizing resilience based on a summed score as “Low” (≤ 62), “Moderate” (63-70), “High” (71-76), and “Exceptional” (≥ 77). All participants also completed feasibility/acceptability questionnaires. All questionnaires were completed electronically during previously scheduled clinic visits for treatment or follow up. Descriptive statistics characterized demographic, health, and behavioral variables as well as study feasibility/acceptability. Two-sample *t*-tests and chi-squared tests evaluated differences in demographics, health behaviors, health outcomes, and resilience based on ACEs exposure.

Fifty-two participants were recruited (51.9% female, 48.1% white, and mean age 13.8±7.2 years old). Twenty-six participants (50%) reported prior ACEs (mean 1.27±1.7; range 0-7). The most common ACEs endorsed were emotional abuse ($n = 12$) and caregiver separation/divorce ($n = 11$). Compared to participants without ACEs, those with ACEs were older, $t(46.77)=-2.07, p=0.04$) and had a higher likelihood of mental health issues ($X^2(1, N=52)=4.59, p=0.03$) and substance misuse, $X^2(1, N=52)=5.2, p=0.02$. Participants with ACEs had lower resilience scores compared to those without ACEs, $X^2(3, N=52)=9.39, p=0.02$. Regarding study feasibility/acceptability, participants rated their overall study experience favorably; they reported comfort when answering sensitive questions and felt they had enough privacy to do so.

This preliminary study was significant in that half of this cohort endorsed ACEs, similar to larger local and national general population cohorts.^{6,7} Given the sensitive subject matter, it was also reassuring that our patients and their families undergoing childhood cancer treatment were accepting of the study and reported favorable study experiences. Of note, the University of Chicago serves one of the most demographically and socioeconomically diverse childhood cancer populations in the US, and these results provided the groundwork and rationale for investigating ACEs and resilience in larger, nationally representative cohorts of childhood cancer patients and survivors in order to better delineate associations with long-term health outcomes.

Methods: For this nested case-control study, we plan to recruit and match three controls for every case using the following criteria:

- 1) Cases must have reported Grade 3 or 4 MI, CHF, and/or arrhythmia cardiovascular outcome(s), as per the CTCAE v4.03 that occurred after age 18.
- 2) Controls must be free of any Grade 3 or 4 cardiovascular outcome, as per the CTCAE v4.03, at the time post-diagnosis that the case developed their condition after age 18.
- 3) Additional matching criteria will include sex, race (white versus non-white), age at diagnosis, treatment era, anthracycline exposure ≥ 250 mg/m², and chest radiation (including cardiac exposure) ≥ 15 Gray (Gy).^{4,5} Given the potential confounding effect of treatment exposures, we will recruit both cases and controls with and without these exposures, oversampling those without exposures to make up approximately half the sample

ACEs will be assessed via the original measurement tool used by Felitti et al (see Appendix 1).⁶ This tool has been used in over cited in over 134 scientific studies and validated for use in large local and national population cohorts in the US.³¹⁻³⁴ Lastly, ACE factors were tested for measurement invariance using multiple group factor analysis. It uses a simple scoring system that attributes one point for each “yes” answer. There are 10 questions in total that each cover a different subcategory of childhood abuse, neglect, and/or household dysfunction and refer to experiences that occurred prior to the age of 18. Scores are summed at the end to form an ACE score, with higher scores indicating increased exposure to childhood trauma. Ford et al. used exploratory factor analysis (EFA) and then confirmatory factor analysis (CFA) with ACEs data from the 2010 BRFSS to validate the ACE measurement tool and its scoring algorithm.³⁴

Resilience will be assessed using the Connor-Davidson Resilience Scale 10 item version (CD-RISC-10), which has previously been used and validated in studies of childhood cancer survivors (see Appendix 2).¹⁵ Each item in the scale is scored from 0-4, and there are 10 items. Scoring is based on summing the total of all items; therefore scores can range from 0 to 50, with higher scores reflecting greater resilience. For the US general population, the median score is 41; therefore, we will define “above-average resilience” as having a score >41 .

Eligibility Requirements: Participants will be adult survivors of childhood cancer greater than 18 years old currently enrolled in the CCSS. Of the 25,583 participants enrolled in the CCSS study, $n = 21,192$ are still living. After removing hard refusals (as of August 2020), there are $n = 19,054$ eligible for recruitment. 839 of these have previously reported Grade 3 or 4 MI, CHF, and/or arrhythmia cardiovascular outcome(s) and will be approached as potential cases for this study. The 17,340 participants without a history of a Grade 3 or 4 cardiovascular outcome could be approached as potential controls. Additional matching criteria will be considered in assigning controls to cases, including participant demographic and cancer diagnosis/treatment data as noted above. Table 1 shows characteristics of current enrolled participants in the CCSS.

Table 1: Characteristics of Enrolled CCSS Participants (N = 25,583)		
Characteristic	n	%
Current age in years (median; range)	31.5; 5.6–65.9	
Years since diagnosis (median; range)	23.0; 5.0–46.7	
Sex (Female)	11,905	46.5
Race		
White	21,637	83.8
Black	1,685	6.7
Other	2,261	9.5
Ethnicity		
Hispanic	2,028	8.7
Primary Cancer Diagnosis		
Leukemia	9,958	38.9
Lymphoma	3,104	12.1
CNS tumors	4,467	17.5
Neuroblastoma	1,939	7.6
Bone/Soft tissue sarcomas	3,846	15.0
Kidney tumors	2,269	8.9
Grade 3 or 4 cardiovascular outcome	1,714	6.7
MI	289	1.1
CHF	391	1.5
Arrhythmia	159	0.6

Participants will complete the study through their My LTFU Connect portal (see below). To date, over 11,000 CCSS cancer survivors are actively using this online portal. This will allow our study team to approach potential participants regarding study interest via the platform’s text notification capability. The CCSS coordinating center will also recruit eligible participants not yet using the portal, inviting them to activate their My LTFU Connect portal to initiate the study.

Participant Recruitment: We will sample eligible CCSS participants based on our matching criteria, assigning three controls for every case. We will plan to oversample cases without histories of high-risk cardiotoxic treatments, such as anthracycline and chest-directed RT. Those identified for study participation will be sent an invitation letter, the study consent, the ACE questionnaire, and Connor-Davidson Resilience scale via My LTFU Connect (see below) by a trained Clinical Research Associate (CRA). If identified participants do not currently have an active My LTFU Connect account, an email will be sent regarding study participation with an invitation to set up the My LTFU Connect portal by the CRA. After four weeks, a second notification will be sent to non-responders by the CRA. A text message will be sent to potentially eligible cohort members who fail to respond to two invitation letters. By the CRA, which will invite them to participate. We will continue attempting to accrue subjects from the eligibility list until 92 cases and 276 controls have been recruited into the study. The CCSS has a strong track record of longitudinal survey contact of the cohort since the study’s inception in 1994. While accrual for prior CCSS studies has averaged approximately 50% using this online platform, in the event we are not reaching our goals, we will contact survivors via telephone with the support of trained interviewers from the CCSS Coordinating Center. This is a successful approach that has been previously utilized by the CCSS to ensure high participation rates. In a recent study regarding the impact of COVID-19 pandemic on childhood cancer survivors and their siblings in the CCSS, which involved similar recruitment methods and survey administration, 4,148 survivors (56.3%) and 571 siblings (60.4%) submitted responses.³⁵ Therefore, expecting similar participation rates, in order to accrue 92 cases and 276 controls, we expect to contact approximately 200 cases and 600 controls for a total of 800 potential participants. With over 800 potentially eligible cases and over 17,000 potentially eligible controls, we believe we have a sufficient pool of potential participants. Participants that complete the study in full will receive a \$25 gift card.

My LTFU Connect: This online platform was established by the CCSS to facilitate mobile health (mHealth) approaches for intervention-based research. The platform provides: (1) A flexible, mobile, and responsive participant portal to remotely collect self-report and sensor-based data using a participant's smartphone; (2) Scalable and adaptable system architecture to reliably curate large quantities of data and automate study processes; (3) A study coordinator portal, allowing a readily accessible interface and dashboard for a study team, clinicians, and investigators; and, (4) Dynamic infrastructure to allow data analytics, visualizations, and interoperability with external systems and mobile devices. The My LTFU Connect platform was designed using the DatStat Connect application system. The DatStat Connect Data Capture Platform is enterprise software designed to make it easy for researchers and health care providers to get the information they need directly from participants, through participant-facing digital applications that can be used both at point of contact and outside a traditional setting. It is cloud based and accessible anywhere by web browser. DatStat Connect's friendly user interface allows research staff to self-configure versatile custom cloud based systems quicker than sourcing programmers to hard-code from scratch. This also allows for faster re-design as platforms need to change and grow. Users can create systems that include complex participant management, electronic consent (eConsent), electronic data capture (EDC), electronic patient reported outcomes (ePRO), secure messaging and electronic communications, clinical trial and study automations, and sophisticated surveys, assessments, and measures that include logic, scoring, piping, and more. DatStat Connect's systems are securely housed on the Microsoft Azure Cloud Computing Platform. The system is Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant and fully validated for 21 CFR Part 11.

The My LTFU Connect participant portal is accessible by computer, tablet, or smartphone and allows use for data entry and task completions, education, and self-management of participants' long-term follow up (LTFU) participation. Alerts and notifications, to-do lists, updated materials, real-time scoring, and automatic delivery of incentives keep participants engaged. The study invitation letter, consent form, ACEs questionnaire, and Connor-Davidson Resilience scale will be distributed electronically to participants via My LTFU Connect. Survey responses would then be matched to participant demographics, cancer diagnosis and treatment variables, and other health history and behavior data previously collected by the CCSS. The portal also has the capability to facilitate participants' direct interaction with the study team through secure chat should questions related to the study arise.

In the study coordinator portal, researchers will be able to view population analytics and insights or drill down into participant records to view data, status of assignments, share files, and communicate directly with participants.

This study's research team will work with Chris Vukadinovich, Director of Databases and Systems, specifically the My LTFU Connect platform, at St. Jude Children's Research Hospital. We will determine technical requirements to develop and maintain a unique series of modules for this study and incorporate them into the larger My LTFU Connect platform. Mr. Vukadinovich will also assist with data cleaning and freezing.

Statistical Plan: Based on previous data from the 2010 BRFSS – the US's premier health-related telephone survey that collect data on citizens' health-related risk behaviors, chronic health conditions, and use of preventive services – of 53,998 respondents from 14 states, approximately 40.6% of participants had zero ACEs, 44.1% had one to three ACEs, and 15.3% had four or more prior to their 18th birthday.⁸ These frequencies are similar to the original ACEs study by Felitti et al published in the late 1990s.⁶ If we assume the prevalence of one or more ACE among controls in our sample is slightly lower at 50%, in order to detect a minimum odds ratio of 2, using a two-sided hypothesis test with a significance level of 0.05, we will plan to recruit 92 cases and 276 controls from the larger CCSS cohort.

Descriptive statistics will be used to characterize the study population for all variables of interest, including demographic, clinical, and health behavior variables. The survey tools for ACEs and resilience will be scored, after which the prevalence of ACEs for our study population will be compared with data from the BRFSS using chi-square tests. Demographic data for our population with ACEs will be compared to data from the BRFSS using logistic regression, controlling for age, race/ethnicity, and sex. The prevalence of at least one ACE will be compared between cases and controls in our sample using logistic regression analysis, adjusting for the potential confounding effects, though we expect that by matching we will eliminate most confounding factors. We will also

examine the associations of the numeric ACE score with case status. The same process will then be repeated, substituting resilience scores for ACEs. Regression analyses will also be utilized to evaluate both ACEs and resilience in the same model, checking for possible correlation and interaction relationships between ACEs, resilience, and cardiovascular outcomes in our sample. We will also examine associations within stratum defined by exposures to treatments that are high risk for cardiovascular conditions.

This study's research team will work closely with the senior CCSS Statistician during all preliminary and final data analysis.

Limitations and Potential Problems, Pitfalls and Solutions: We chose a case-control study design in order to explicitly investigate if our exposure (ACEs) is associated with our primary outcome (development of cardiovascular morbidity). Study participation requires access of the mHealth platform through the use of an electronic device, such as smartphone or tablet with texting capability. It is possible that some eligible participants may not be able to participate in the study because of this. However, over 90% of individuals in our target age group use a smartphone with text-messaging capabilities.³⁶ Third, there is the possibility of retrospective underreporting of ACEs that could potentially bias our results. This is a common concern in research that encompasses sensitive subject matter, such as the abuse and neglect of children. Indeed, prior studies have shown even in well-documented cases of serious childhood abuse or neglect, retrospective reports are likely to provide underestimates of their incidence.^{37,38} However, certain survey methodology choices, such as the utilization of anonymous surveys and the creation of perceived confidential environments to disclose ACEs, both of which our study will apply through use of an mHealth portal, have been shown to improve accuracy of reports.^{32,39} Furthermore, in several studies looking at potential underreporting of ACEs due to recall bias, it was found to be not sufficient enough to invalidate study findings, as ACEs are major adversities of an easily defined nature.^{37,38} Lastly, regarding generalizability of this study, based upon SEER data, the CCSS is highly representative of the US population of childhood cancer survivors with respect to cancer type, age, as well as race and ethnicity.^{1,13}

IMPACT

Understanding the relationship between ACEs and resilience could impact how clinicians approach not only their patients' cancer treatments but also their supportive and psychosocial care in order to improve long-term patient outcomes. Finding associations between cardiovascular morbidity and ACEs in childhood cancer survivors would highlight the need for early intervention to mitigate the potential lasting, negative effects of ACEs on health and well-being. Given the relationship between ACEs and development of toxic stress,^{6-8,11} future research could examine childhood cancer survivors' biologic response to distress through the use of epigenetic data currently being collected from CCSS participants.¹³ Furthermore, finding a mitigating effect in resilience could provide a target for intervention. Programming to cultivate resilience could be tailored to childhood cancer patients and survivors who have experienced ACEs in order to address and/or alleviate toxic stress, lessen the burden of ACE and cancer treatment exposures, and ultimately decreasing the development of chronic morbidity as well as the risk of premature mortality in this population. An example of such tailored programming is Promoting Resilience in Stress Management (PRISM), which uses cognitive-behavioral therapy (CBT) principles paired with skills-based training sessions to develop resilience in participants.¹² It was previously shown to be effective in increasing resilience in active therapy AYA cancer patients who reported experiencing "traumatic events" prior to their cancer diagnosis,⁴⁰ and its principles could be adapted to fit the needs of childhood cancer survivors who previously experienced ACEs. Cancer patients are well placed not only for identification of ACEs but also to receive related interventions due to frequent, necessary interactions with the healthcare system and its supportive services during treatment and afterwards as survivors. An integrated care model that provides cancer treatment, follow up care, as well as interventions to address ACEs would satisfy not only Center for Disease Control and Prevention (CDC) recommendations for how to support those with ACE exposures but also Institute of Medicine (IOM) and American Cancer Society (ACS) recommendations for comprehensive care of childhood and AYA cancer patients/survivors and their families.^{41,42} Lastly, this research aligns with the National Cancer Institute (NCI) Division of Cancer Control and Population Sciences (DCCPS) interest in research that addresses factors that contribute to disparities in health outcomes among childhood cancer survivors (<https://grants.nih.gov/grants/guide/notice-files/NOT-CA-22-029.html>).

TIMELINE

06/2022 - 07/2022	08/2022 - 11/2022	12/2022	01/2023 - 03/2023
IRB submission, preparation of electronic study materials for participant completion	Patient recruitment and data collection	Data preparation and cleaning	Data analysis and presentation

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INFORMATION REGARDING HUMAN SUBJECTS

Human Subjects Involvement and Characteristics: Participants will be male and female adult members of the Childhood Cancer Survivor Study (CCSS) cohort.

The CCSS is a North American, multi-institutional, retrospective cohort of over 25,000 childhood cancer survivors treated at 31 institutions in the United States (US) and Canada (<https://ccss.stjude.org>).¹³ The CCSS was founded in 1994 by the National Institutes of Health (NIH) and has been continuously funded since that time (U24 CA055727: Armstrong). To be eligible for the CCSS cohort study, survivors have to be diagnosed before the age of 21 years old, survived at least five years from their initial cancer diagnosis, with diagnosis dates between January 1, 1970 and December 31, 1999. To our knowledge, the CCSS has the largest minority population of any cohort of childhood cancer survivors.⁴³ The institutional review board (IRB) at each participating center reviewed and approved the CCSS protocol, and all study participants provided informed consent. For participants under the age of 18 years, a parent or proxy provided consent. Upon reaching the age of majority, the participant had to sign their own consent. Thus, all active participants have consented as adults to the CCSS. Once consented, all participants fall under the St. Jude Children's Research Hospital IRB as the IRB of record. A baseline survey was sent to all enrolled participants. Since baseline, there have been four follow-up questionnaires (Follow-Up 2000, Follow-Up 2003, Follow-Up 2005, Follow-Up 2007). Newsletters are sent to all participants every four months with information regarding current open research studies. All eligible participants are included in a search for matching death records in the National Death Index in order to have updated mortality data.

All CCSS and study specific materials will be available in English. All data collected will be used solely for the purpose of the present research study and will be treated with full confidentiality.

Potential Risks: Participants of the CCSS research cohort have a personal history of cancer, and therefore are potentially at risk for recurrent or additional cancers or health conditions associated with the participant's individual treatment exposures. The potential risks of participating in the proposed research include loss of confidentiality and distress related to re-opening previous discussions and experiences regarding their personal history of cancer and potential prior Adverse Childhood Experiences (ACEs).

Attempts will be made to minimize these risks at the time of consent. Study staff will be available to discuss these risks with participants through My LFTU Connect at any point during the study. Given the sensitive and potentially distressing nature of questions regarding ACEs, should a participant need to access a primary care physician or a specialist for psychological care, our study team will work with any participant in need of this support.

Adequacy of Protection Against Risks: As described above, potential risks include loss of confidentiality and emotional distress. Extensive efforts will be taken to minimize these potential risks and protect participants from these risks.

Psychological Distress: Side effects from aspects of the study might include emotional distress associated with discussion of prior cancer diagnosis and potential prior ACEs. Every effort will be made to support participants regarding potential prior ACEs and should a participant need to access a primary care physician or a specialist for psychological care, our team will facilitate this support.

Confidentiality: The St. Jude and University of Chicago IRBs' and HIPAA regulations concerning confidentiality and information availability will be strictly enforced. A series of security procedures will be undertaken to ensure subject privacy and HIPAA compliance. Several steps will be taken to mitigate the risk of breach of confidentiality. All clinical data will be stored in a locked file or password protected database. All interviews, surveys, and data forms derived from medical records and clinical examinations will be coded with a study

number. The code numbers and data forms will be kept in separate locations. Each database will be password protected, with the password known only to the study coordinator, analyst, and the principal investigators. Only the principal investigators will have passwords to both databases.

Extensive efforts will be taken to minimize these potential risks and protect participants from these risks.

Potential Benefits of the Proposed Research to the Subjects and Others: Participants that complete this study will be provided a \$25 gift card. They otherwise may or may not experience direct benefits through participation in this study.

Dissemination of Results: CCSS participants can learn about study results and updates via summaries written in lay language that are included in quarterly participant newsletters and the participant website. In addition, participants may access personalized updates and resources related to their study participation on My LTFU Connect and pose questions related to the study to staff at any time through this online portal.

Appendix 1: Adverse Childhood Experience (ACE) Questionnaire

Our relationships and experiences—even those in childhood—can affect our health and well-being. Difficult childhood experiences are very common. Please tell us whether you have had any of the experiences listed below.

While you were growing up, during your first 18 years of life:

- | | Yes | No |
|---|--------------------------|--------------------------|
| 1. Did a parent or other adult in the household often or very often: | <input type="checkbox"/> | <input type="checkbox"/> |
| • Push, grab, slap, or throw something at you? | | |
| OR | | |
| • Hit, beat, kick, or physically hurt you so hard that you had marks or were injured in any way? | | |
| 2. Did a parent or other adult in your household: | <input type="checkbox"/> | <input type="checkbox"/> |
| • Often or very often swear at you, insult you, or put you down? | | |
| OR | | |
| • Act in a way that made you afraid that you might be physically hurt? | | |
| 3. Did an adult or person at least 5 years older ever: | <input type="checkbox"/> | <input type="checkbox"/> |
| • Touch or fondle you in a sexual way? | | |
| OR | | |
| • Have you touch their body in a sexual way? | | |
| OR | | |
| • Attempt oral, anal, or vaginal intercourse with you? | | |
| OR | | |
| • Actually have oral, anal, or vaginal intercourse with you? | | |
| 4. Did you often or very often feel that: | <input type="checkbox"/> | <input type="checkbox"/> |
| • You didn't have enough to eat, had to wear dirty clothes, or had no one to protect you? | | |
| OR | | |
| • Your parents (or other adults in your household) were too drunk or high to take care of you or take you to the doctor if you needed it? | | |
| 5. Did you often or very often feel that: | <input type="checkbox"/> | <input type="checkbox"/> |
| • No one in your family loved you or thought you were important or special? | | |
| OR | | |
| • Your family didn't look out for each other, feel close to each other, or support each other? | | |
| 6. Did you live with anyone who: | <input type="checkbox"/> | <input type="checkbox"/> |
| • Was a problem drinker or alcoholic? | | |
| OR | | |
| • Used street drugs? | | |
| OR | | |
| • Used prescription drugs inappropriately? | | |

7. Was a household member depressed or mentally ill?
OR
Did a household member attempt suicide?
8. Did your parents or adults in your home ever:
• Push, grab, slap, or throw things at each other?
OR
• Kick, bite, hit each other with a fist, or hit each other with something hard?
OR
• Repeatedly hit each other over at least a few minutes?
OR
• Threaten with or hurt each other with a knife or gun?
9. Did a household member go to jail or prison?
10. Were your parents ever separated or divorced?

Appendix 2: Connor-Davidson Resilience Scale 10 (CD-RISC-10) ©

*For each item, please mark an “x” in the box below that best indicates how much you agree with the following statements as they apply to you over the last **month**. If a particular situation has not occurred recently, answer according to how you think you would have felt.*

	Not true at all (0)	Rarely true (1)	Sometimes true (2)	Often true (3)	True nearly all the time (4)
1. I am able to adapt when changes occur.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I can deal with whatever comes my way.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I try to see the humorous side of things when I am faced with problems.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Having to cope with stress can make me stronger.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I tend to bounce back after illness, injury, or other hardships.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I believe I can achieve my goals, even if there are obstacles.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Under pressure, I stay focused and think clearly.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I am not easily discouraged by failure.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. I think of myself as a strong person when dealing with life’s challenges and difficulties.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I am able to handle unpleasant or painful feelings like sadness, fear, and anger.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>