| | |
|---|---|
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# Project Requirements and Description

## Requirements to submit AOI (all answers must be "yes" to proceed)

| | |
|---|---|
| **A comprehensive review of previously published data has been completed** | Yes |
| **The specific aims are clear and focused** | Yes |
| **The investigator has appropriate experience and expertise to develop the concept proposal; if not, has identified a mentor or senior co-investigator.** | Yes |
| **The investigator agrees to develop an initial draft of the concept proposal within 6 weeks of approval of the AOI and to finalize the concept proposal within 6 months** | Yes |

**Project Title**

Associations between Health Behaviors during Adolescence and Frailty in Adulthood among Childhood Cancer Survivors.

## Planned research population (eligibility criteria)

o CCSS participants who completed either Baseline or Follow-Up Questionnaire between ages 12-18 and had subsequent Follow-up Questionnaires completed.
o Exploratory subgroup analysis of CCSS participants who completed the Teen Health Ancillary Survey

## Proposed specific aims

Specific Aim 1: Since adolescence is a formative time for establishing health behaviors (e.g., physical activity, BMI, alcohol, and tobacco use) and therefore a potential window for intervention, we aim to examine the association between adolescent health behaviors and the incidence, age of onset, and severity of frailty (as measured by the Fried Frailty Criteria and Deficit Accumulation Index (DAI)) in adult CCS after controlling for cancer diagnosis and treatment exposures.
Hypothesis: CCS with risky health behaviors during adolescence will have increased incidence of frailty, younger age of onset of frailty, and greater severity of frailty in adulthood. These associations will be observed even after controlling for the direct impact of childhood cancer treatment exposures.

Specific Aim 2: To determine if patterns of health behaviors from adolescence into adulthood are associated with frailty outcomes, accounting for treatment-related factors and chronic health conditions.
Hypothesis: Survivors who demonstrate persistently unhealthy, or increased risky health behaviors from adolescence to adulthood are more likely to be frail in adulthood compared to survivors who maintain a

healthy lifestyle.

Secondary Aim: To explore whether the associations between adolescent healthy lifestyle behaviors (including physical activity, BMI, tobacco use, and alcohol use) and the incidence, age of onset, and severity of frailty in adult CCS are partially mediated by interim psychosocial factors (anxiety, depression, employment, educational attainment etc.) and/or cognitive impairment (CCSS NCQ), after controlling for childhood cancer treatment exposures.
Hypothesis: CCS with lower healthy lifestyle scores during adolescence will have increased incidence of frailty, younger age of onset of frailty, and greater severity of frailty in adulthood. This association is expected to be partially mediated by the development of adverse psychosocial factors and cognitive impairments. These mediated effects are hypothesized to persist even after controlling for the direct impact of childhood cancer treatment exposures.

Exploratory Aim: Examine the association between self-reported adolescent health behaviors (physical activity, BMI, alcohol use, tobacco use, marijuana use, screen time, and sedentary behaviors) as measured as part of the Teen Health Ancillary Survey by early CCS and the incidence, age of onset, and severity of frailty in adulthood after controlling for cancer treatment exposures.
Hypothesis: CCS with lower physical activity, increased alcohol use, increased tobacco use, increased marijuana use, increased screen time, and increased sedentary behavior in adolescence will have increased incidence of frailty, younger age of onset of frailty, and greater severity of frailty in adulthood. These associations will persist even after controlling for the direct impact of childhood cancer treatment exposures.

**Will the project require non-CCSS funding to complete?** No

**If yes, what would be the anticipated source(s) and timeline(s) for securing funding?**

**Does this project require contact of CCSS study subjects for:**

| | |
|---|---|
| **Additional self-reported information** | No |
| **Biological samples** | No |
| **Medical record data** | No |

**If yes to any of the above, please briefly describe.**

**What CCSS Working Group(s) would likely be involved? (Select all that apply)**

| | Primary | Secondary |
|---|---|---|
| **Second Malignancy** | | |
| **Chronic Disease** | | ✓ |
| **Psychology/Neuropsychology** | | ✓ |
| **Genetics** | | |
| **Cancer Control** | ✓ | |
| **Epidemiology/Biostatistics** | | |

# Outcomes or Correlative Factors

| | Primary | Secondary | Correlative Factors |
|---|---|---|---|
| Late Mortality | | | |
| Second Malignancy | | | |

## Health Behaviors

| | Primary | Secondary | Correlative Factors |
|---|---|---|---|
| Tobacco | ✓ | | |
| Alcohol | ✓ | | |
| Physical Activity | ✓ | | |
| Medical Screening | | | |
| Other | ✓ | | |

### If other, please specify

BMI for a healthy lifestyle score based on prior work by Dixon et al.  PMID: 37030315

## Psychosocial

| | Primary | Secondary | Correlative Factors |
|---|---|---|---|
| Insurance | | ✓ | |
| Marriage | | ✓ | |
| Education | | ✓ | |

| | Primary | Secondary | Correlative Factors |
|---|---|---|---|
| Employment | | | |
| Other | | | |

### If other, please specify

## Medical Conditions

| | Primary | Secondary | Correlative Factors |
|---|---|---|---|
| Hearing/Vision/Speech | | | |
| Hormonal Systems | | | |

| | | | |
|---|---|---|---|
| **Heart and Vascular** | | | ✓ |
| **Respiratory** | | | |
| **Digestive** | | | |
| **Surgical Procedures** | | | |
| **Brain and Nervous System** | | | |
| **Other** | | | |

### If other, please specify

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# Medications

### Describe medications

### Psychologic/Quality of Life

| | Primary | Secondary | Correlative Factors |
|---|---|---|---|
| **BSI-18** | | ✓ | |
| **SF-36** | ✓ | ✓ | |
| **CCSS-NCQ** | | ✓ | |
| **PTS** | | | |
| **PTG** | | | |
| **Other** | | | |

### If other, please specify

SF-36 as psychological/quality of life secondary outcome and components of SF-36 to be used to calculate a frailty score

## Other

| | Primary | Secondary | Correlative Factors |
|---|---|---|---|
| Pregnancy and Offspring | | | |
| Family History | | | |
| Chronic Conditions (CTCAE v3) | | | ✓ |
| Health Status | | | ✓ |

## Demographic

| | Primary | Secondary | Correlative Factors |
|---|---|---|---|
| Age | | | ✓ |
| Race | | | ✓ |
| Sex | | | ✓ |
| Other | | | |

## If other, please specify

## Cancer Treatment

| | Correlative Factors |
|---|---|
| Chemotherapy | ✓ |
| Radiation Therapy | ✓ |
| Surgery | ✓ |

## Anticipated Sources of Statistical Support

| | |
|---|---|
| CCSS Statistical Center | Yes |
| Local Institutional Statistician | No |

## If local, please provide the name(s) and contact information of the statistician(s) to be involved.

**Will this project utilize CCSS biologic samples?** No

**If yes, which of the following?**

**If other, please explain**

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# Other General Comments

This project was developed with mentorship/collaboration from Dr. Ellen van der Plas, Dr. Tara Brinkman, Dr. Kirsten Ness, and Dr. Robert Hayashi.

• If available, for exploratory aim, we would like to utilize the Ancillary Teen Health Study and access data on physical activity, body mass index, TV/video use and the following: 17. Smoked cigarettes?18. Chewed or dipped tobacco, usedsnuff?19. Drank beer, wine, or wine coolers?20. Drank hard liquor or mixed drinks? 22. Used marijuana?

Regarding Frailty, we will use 2 definitions previously utilized by the CCSS
- Frailty defined as Modified Fried Frailty Criteria as defined by Hayak et al. 2020
o Criteria
1) low lean muscle mass (defined by BMI or unintentional weight loss);
2) exhaustion (SF-36 vitality subscale);
3) low energy expenditure (convert frequency and duration of low, moderate, and vigorous physical activity levels into kilocalories);
4) slowness (limitations in walking uphill/upstairs, or limitation in walking one block);
5) weakness (“have you ever been told that you have, or have had weakness or inability to move arms”).
o The frailty phenotype will be defined accordingly (consistent with previous analyses in CCSS):
1) non-frail (less two components of frailty);
2) pre-frail (two components of frailty);
3) frail (three components of frailty).
- Frailty defined as Deficit Accumulation Index as defined by Williams et al: https://ccss.stjude.org/content/dam/en_US/shared/ccss/documents/concept-prop/concept-proposal-21-09.pdf#page=10.45
- Childhood Cancer Survivor Study Analysis Concept Proposal1. Project Title: Accelerated Aging as an Accumulation of Deficits in Survivors of Childhood Cancer and its Association with Mortality, Cognitive, and Sleep Outcomes.

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