**Impact of Diabetes Mellitus on neurocognitive outcomes in childhood cancer survivors: A Report from the Childhood Cancer Survivor Study**

## Working groups

Primary: Psychology

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**Background**

The childhood cancer survivor (CCS) population has increased substantially over recent decades due to advances in treatment and supportive care.[1] However, chronic health burden remains high, with endocrine conditions being predominant, particularly among survivors treated more recently.[2,3] Diabetes Mellitus (DM) is a disorder of the endocrine system characterized by elevated blood sugar for prolonged periods of time due to insufficient insulin secretion, insulin resistance, or both. Converging evidence from non-cancer populations shows that DM predisposes individuals to cognitive impairment, dementia, and Alzheimer's Disease (AD).[4] A recent meta-analysis estimated that 45% of patients with DM experienced mild cognitive impairment.[5,6] DM is also associated with physiological frailty, referring to a multidimensional condition associated with reserve loss and susceptibility to stressors.[7] The cumulative incidence of DM among CCS significantly increased over a 20-year period.[8] According to a recent study, the cumulative incidence of DM by age 45 was 6.6% in survivors who received radiation therapy,[9] which is roughly twice as high compared to similar-aged peers in the general population (CDC.gov). Younger age at diagnosis, total body irradiation, exposure to high doses of exogenous corticosteroids,[10] untreated hypogonadism, and abdominal adiposity[11] increase risk of DM in long-term CCS.[12-14] While some endocrine conditions have been identified as a prominent risk factor of poor neurocognitive function in CCS,[15-19] less is known about the specific role of DM, a relatively modifiable condition. Given evidence of accelerated age-related phenotypes and frailty in survivors, [20-23] the role of DM in neurocognitive impairment among CCS should be explored in the context of predictors of cognitive aging.

Links between DM and brain function are likely driven by a multitude of pathophysiological pathways that differently contribute to neurocognitive dysfunction.[24] Insulin receptors (IR) are expressed throughout the brain, but are particularly abundant in the hippocampus, cortex and thalamus.[25,26] The brain also contains high levels of IGF-1 receptors (IGF1R), which can act as a lower-affinity receptor for insulin. Viral-mediated deletion of

IR/IGFR1 in the hippocampus has been shown to impair learning and memory,[26] suggesting that these receptors play a role in normal brain function. Moreover, insulin/IGF1 signaling regulates tau expression and phosphorylation,[27] with hyper-phosphorylated intracellular tangles of the protein tau being a hallmark of AD pathology. Animal studies have also demonstrated an essential role of insulin in neurodegeneration.[28] Abnormal brain insulin signaling may also disrupt glucose metabolism. Glucose is the key substrate for energy production in adult brains, meaning that maintaining glucose homeostasis is critical for proper brain function. The family of sodium-independent facilitated glucose transporters (GLUTs) ensures that glucose is being transported into the cell. Insulin appears to be involved in GLUT4 translocation to the neuron cell membrane, and insulin-induced GLUT4 was shown to improve glucose flux into neurons during periods of high metabolic demand, such as learning.[29]

Hyperglycemia, a hallmark of DM, has been associated with overproduction of reactive oxygen species (ROS) and subsequent oxidative stress.[30] Long-term exposure to oxidative stress results in chronic inflammation, contributing to the development of cardiovascular disease.[30,31] Cardiovascular disease encompasses coronary heart disease, stroke, heart failure and other conditions affecting the heart and blood vessels, and has been associated with cognitive decline.[32] A recent analysis estimates that approximately one third of individuals with type 2 DM experience cardiovascular disease, highlighting cardiovascular disease as an important consideration when evaluating associations between DM and neurocognitive impairment.[33]

Increasing evidence suggests that neurocognitive function and physical health share neural systems that jointly regulate somatic physiology and cognition.[34] The presence of obesity has been shown to increase the risk of neurocognitive impairment in individuals with DM,[35] although there is some evidence to suggest that these links are specific to men.[36] Likewise, poor diet has been shown to increase risk for poorer neurocognitive performance. Xu et al identified dietary patterns in Chinese adults aged 55 years or older, and reported that a “protein-

rich" diet was associated with better global neurocognitive performance than a "starch-rich" diet.[37] In another study, Chen and colleagues showed that DM, smoking and physical inactivity increased an individual's risk of being on a trajectory of low neurocognitive function that declined overtime.[38] By contrast, healthy lifestyle behaviors, such as physical activity appear to have a positive impact on neurocognitive function. For example, Espeland et al reported improved global cognition and better delayed memory performance in DM patients (aged 70-89 years old) who participated in a physical activity intervention compared to patients who did not participate in the physical activity intervention.[39] Among CCS, vigorous exercise was linked with less psychological burden and neurocognitive impairment,[40] while exercise intolerance appeared to exacerbate neurocognitive impairment among survivors.[41]

Taken together, research in non-cancer DM populations have linked DM with neurocognitive decline, and demonstrated associations between neurocognitive function and health behaviors. The literature in CCS has indicated increased risk of DM,[2,3] accelerated aging phenotypes,[20-23] and neurocognitive impairment. However, neurocognitive decline in CCS has not been studied in the context of DM. The overarching goals of the present research are to characterize the role of DM on neurocognitive impairment and decline in CCS and to explore the potential mechanistic role of cardiovascular conditions and health behaviors on neurocognitive outcomes.

**Aims**

**Aim 1:** To examine the association of DM with neurocognitive outcomes in long-term survivors of childhood cancer.

Aim 1.1: Compare neurocognitive impairment in survivors with and without DM, adjusting for relevant demographic factors and cancer-treatment exposures.

*Hypothesis 1.1: After adjusting for relevant demographic variables and treatment exposures, survivors with DM will have poorer neurocognitive outcomes than survivors without DM.*

Aim 1.2: Identify the extent to which cardiovascular conditions (grade ≥3) and health risk behaviors mediate the relationship between DM status and neurocognitive impairment in CCS.

*Hypothesis 1.2: Cardiovascular conditions* (grade ≥3) *and risky health behaviors (e.g., smoking, limited exercise, and high BMI) will mediate risk of neurocognitive impairment.*

**Aim 2:** To assess longitudinal associations between DM duration, progression (expressed as an increase in CTCAE grade), and severity with decline in neurocognitive function among survivors with DM.

*Hypothesis 2: Increased duration and/or progression of severity of DM will increase risk of neurocognitive impairment in survivors of childhood cancer with DM.*

## Analysis Framework

### *Overview*

This proposal includes longitudinal and cross-sectional analysis using data from all survivors in the Childhood Cancer Survivor's Study (CCSS) cohort.

### *Study Population*

CCSS participants who have completed at least 2 survey evaluations (including health questionnaire and neurocognitive questionnaire [NCQ]) will be considered in longitudinal analysis. Participants will be excluded if they have a history of brain injury unrelated to cancer (e.g., traumatic brain injury), genetic syndromes associated with neurocognitive impairment, or other neurocognitive impairment unrelated to cancer diagnosis.

*Outcomes*

Neurocognitive Questionnaire (NCQ)

Neurocognitive outcomes in CCSS participants will be assessed with the NCQ. The NCQ outcomes are available at follow-up (FU) 2 (J1-25), FU5 (Q1-Q33), and FU6 (G1-G33) for the original cohort and baseline, FU5, and FU6 for the expansion. The NCQ was developed to determine neurocognitive outcomes in childhood cancer survivors.[42] Since inception, the NCQ has been optimized and validated against in-person direct neurocognitive assessment.[43] Neurocognitive domains assessed in the NCQ include attention and processing speed (task efficiency), emotional reactivity and frustration tolerance, organization and memory (long and short term). T-scores will be used to classify survivors as impaired vs non-impaired, with impairment defined as a T-score above the 90$^{th}$ percentile (T≥63) in Aims 1.1 and 3

*Predictors*

Diabetes Mellitus (DM)

DM status and severity will be based on existing CTCAE grading. First, all survivors will be categorized according to DM status (yes/no). DM survivors will be further categorized according to CTCAE Grade 1 (DM with no medication) Grade 2 (DM with oral medication), and Grade 3 (DM requiring insulin) (FU2, Q4-Q5[medication]; FU5, G5-G7). Type 1 and Type 2 DM have both been associated with altered cognitive outcomes.[24,44] Therefore, we will include cases with DM regardless of type. Further, DM type may not be distinguishable in childhood cancer survivors since treatment-associated DM may not fit into Type 1 or Type 2 categorization. However, the duration of DM may play a role in DM-associated cognitive impairment, we will use time since DM diagnosis as a covariate in the analyses. Time since DM diagnosis will be calculated by subtracting age at DM diagnosis from age at NCQ evaluation. Given potential concerns with self-reported Grade 1 DM, analyses will be considered with and without DM 1 included.

According to the publicly accessible CCSS tables from the January 2020 data freeze, N=330 CCS reported having DM that is managed with diet, N=266 manages DM with oral medication, and N=398 reported requiring insulin for DM management. In total, N=994 of CCS (3.87% of total cohort) reported having DM.

Demographic variables

Models will be adjusted for age at follow-up, sex (male vs. female), and race/ethnicity. Categorization of the latter will depend on the frequency distributions of the sample. Age at diagnosis will also be considered as a continuous variable.

Treatment variables

Previous research has identified total body irradiation, exposure to supraphysiologic doses of exogenous corticosteroids, and CNS-directed treatment as risk factors for DM.[10,13,141] Models will therefore be adjusted for exposure to radiation (pelvis, chest, abdomen, pancreatic tail), corticosteroids (yes/no), and CNS-directed treatment (i.e., IT MTX, neurosurgery, and/or cranial radiation). We will also explore the potential impact of growth hormone deficiency by self-reported receipt of injection for growth hormones.

We will explore the impact of chemotherapy agents expressed as binary yes/no variables, including high-dose IV methotrexate (HD MTX), high dose IV cytarabine, vincristine, anthracyclines, alkylating agents, platinum agents, and etoposide. The impact of hematopoietic stem cell transplant will likewise be explored.

Mediators: Health behaviors and Cardiovascular health conditions (≥ grade 3)

***Physical Activity*** *(Follow-up 2 [Baseline Cohort] or Follow-up 5 [Expansion Cohort])*

Physical activity will be ascertained from questions of the Behavioral Risk Factor Surveillance Survey, and one question on physical activity that states: “On how many of the past 7 days did you exercise or do sports for at least 20 minutes that made you sweat or breathe hard (e.g., dancing, jogging, basketball, etc.).”[45]

Quantity and intensity of physical activity will be expressed as metabolic equivalent (MET) hours per week, representing the frequency of sessions per week multiplied by session duration, and weighted by the standardized classification of energy expenditure (i.e., moderate and vigorous activity).[45,46] For analytical purposes, levels of activity are binarized using ≥9 MET-hours per week as the cutoff, constituting the minimal MET hours for meeting national exercise guidelines.[47]

***Tobacco*** *(Follow-up 2 [Baseline Cohort] or Follow-up 5 [Expansion Cohort])*

Smoking will be included in models as a categorical variable with two levels: current smoker vs. never/former smoker.

**BMI** (Follow-up 2 [Baseline Cohort] or Follow-up 5 [Expansion Cohort])Body mass index is calculated as follows: $\mathrm{BMI} = \frac{weight\ (kg)}{\mathrm{Height\ (m)}^2}$

BMI will be categorized as not obese and obese, where the latter is defined as BMI≥30.

Cardiovascular Conditions *(Follow-up 2 [Baseline Cohort] or Follow-up 5 [Expansion Cohort])*

We will include binary variables of cardiovascular conditions that indicate the presence of grade ≥3 cardiovascular conditions. Presence and severity of chronic health conditions will be derived from surveys about organ-based health conditions at follow-up.

***Alcohol Use.*** While heavy alcohol use may also be considered a potential health-behavior-related moderator, there is no data available on alcohol use for the Original Cohort at follow-up 2. This variable will therefore not be included.

**Statistical Analysis**

Frequency distributions will be generated to categorize relevant outcome variables, predictors and covariates according to reasonable groupings. Descriptive statistics including means, standard deviation, medians, ranges, frequencies, and percentages will be calculated for outcomes of interest, as well as predictors and covariates. **Tables 1 and 2** provide examples of demographics and treatment tables that will be generated.

*Aim 1.1: Examine the impact of DM on neurocognitive outcomes in long-term survivors of childhood cancer.*

Multivariable logistic regression models will be used to assess the association between DM status (i.e., CCS with and without DM) and neurocognitive impairment risk in CCSS participants (**Table 3**). Models will be adjusted for age, sex, race/ethnicity, and age at diagnosis CNS-targeted treatment (IT MTX, cranial radiation, neurosurgery), radiation (pelvis/chest/abdomen), and corticosteroid exposures.

*Aim 1.2: To identify if the presence of cardiovascular conditions (≥ grade 3) and health risk behaviors mediate the relationship between DM status and neurocognitive outcomes in CCS*

Structural equation modeling will be used to examine the direct and indirect effects of health behaviors and presence of (≥ grade 3) cardiovascular conditions that developed after the onset of DM and at, or before, follow-up 2 (original cohort) or follow-up 5 (expansion cohort) on neurocognitive impairment among CCS with DM (Figure 1a). A conceptual model highlighting the timing of onset of DM with cardiovascular conditions is also presented in Figure 1b. Both health behaviors and cardiovascular conditions will be considered simultaneously in the overall model; however given the timing and limitations of the assessment approach multiple mediation models will not be explored (e.g., links between DM and cardiovascular conditions via health behaviors). Overall model fit will be explored across a variety of fit indices including, the Comparative Fit Index (CFI), chi-square goodness of fit ($X^2$), and the Root Mean Square Error of Approximation (RMSEA).CFI values greater than 0.95 are considered to reflect good model fit, whereas $X^2$ tests should be non-significant. RMSEA values of 0.08 or less indicate acceptable fit to the data. We will use the bootstrap method to determine the significance of the indirect mediation effect, where 95% CI that do not include zero are considered significant at the $p < .05$

level (**Table 4**). Should sample size preclude these analyses (e.g., insufficient number of participants with ≥ grade 3 cardiovascular chronic health conditions after diagnosis of DM and present at or before follow-up 2/follow-up 5), we will use multivariable logistic regression models to estimate associations between risky health behaviors (i.e., smoking, alcohol intake, physical inactivity, BMI) and cardiovascular conditions (i.e., grade≥3 cardiovascular conditions) on neurocognitive impairment (expressed as a binary variable) assessed using the NCQ at follow-up 2 (original) or follow up 5 (expansion) among survivors with DM (**Supplementary Table 1**).

*Figure 2a. Proposed mediation model to assess if associations between DM and neurocognitive outcomes (NCQ) are mediated through cardiovascular (CV) conditions and health behaviors.*

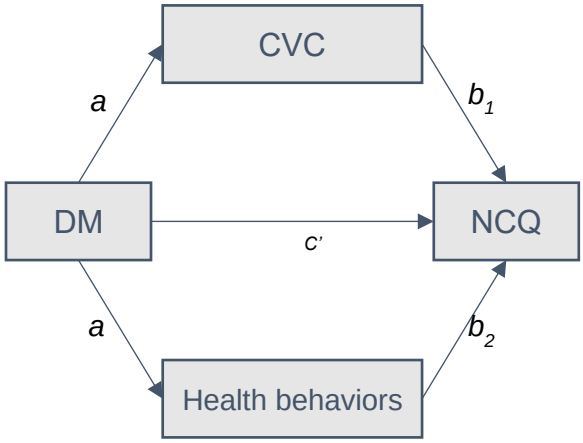
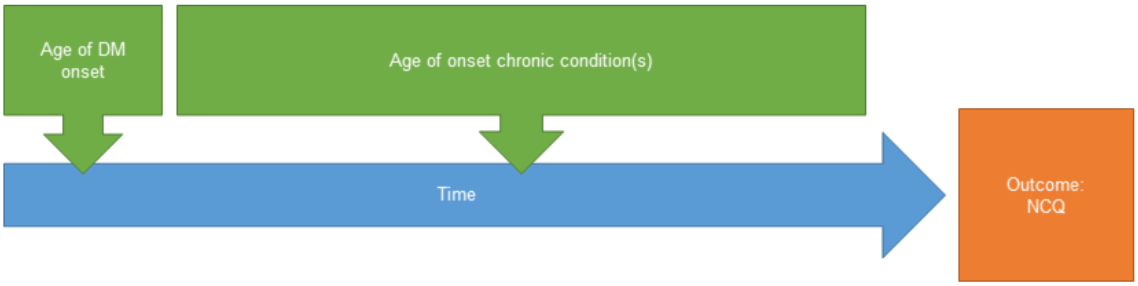



*Figure 1b. Proposed conceptual model exploring highlighting timing of onset of DM and CVC.*



*Aim 2: Assess longitudinal associations between DM and neurocognitive function in childhood cancer survivors.*

Initial multinomial logistic regression models will be used to estimate associations between duration and/or progression of DM and cognitive change. Cognitive change will be based on NCQ scores assessed at follow-up 2 (original) and follow-up 5 (expansions) and follow-up 6 (both cohorts), and change will be expressed as three categories: (1) remain unimpaired (i.e., scores remain T-score <90$^{th}$ percentile throughout assessments); (2) become impaired (i.e., scores change from unimpaired to impaired); (3) remain impaired (i.e., T-scores remain ≥90$^{th}$ percentile throughout assessments). The predictor of interest will be time since DM diagnosis, defined as the difference between age at follow-up and age at reported DM diagnosis. Progression of DM will be defined as a binary variable with two levels: no grade change vs. worsening in grade from baseline to follow-up assessment (**Table 5**). To account for potential confounders related to chronic health conditions,[15,16,48] we will include binary variables in the models indicating the presence of grade ≥3 cardiovascular and/or neurological conditions. If the sample size is not sufficient for categorical analysis, linear regression models will be used to estimate the relationship between duration and progression of DM and change in T-scores on the NCQ, using baseline NCQ T-score as a covariate (**Table 6**). Baseline visit is defined as initial evaluation where DM is present. The subsequent evaluation will be considered as follow-up.

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## Proposed Tables

*Table 1 Sample characteristics*

| Variable | Levels | CCS without DM | CCS with DM | *P** |
|---|---|---|---|---|
| **Sex** | Males N (%) | | | |
| | Females N (%) | | | |
| **Age at assessment** | Median (Range) | | | |
| | Mean (SD) | | | |
| **Age at diagnosis** | Median (Range | | | |
| | Mean (SD) | | | |
| **Time since treatment** | Median (Range | | | |
| | Mean (SD) | | | |
| **Race/Ethnicity** | White, non-Hispanic N (%) | | | |
| | Black, non-Hispanic N (%) | | | |
| | Hispanic N (%) | | | |
| | Other N (%) | | | |
| | Unknown N (%) | | | |
| **Education** | <High School N (%) | | | |
| | High school N (%) | | | |
| | Some College N (%) | | | |
| | College/Post Grad N (%) | | | |
| **Marital status** | Single N (%) | | | |
| | Married/Common law N (%) | | | |
| | Divorced/Widowed N (%) | | | |
| **Employment status** | Employed N (%) | | | |
| | Unemployed N (%) | | | |
| | Unable to work N (%) | | | |
| | Student N (%) | | | |
| | Homemaker N (%) | | | |
| **Household income** | <$20,000 N (%) | | | |
| | $20,000-39,999 N (%) | | | |
| | $40,000-59,999 N (%) | | | |
| | ≥$60,000 N (%) | | | |
| **Smoking*** | Yes N (%) | | | |
| | No N (%) | | | |
| **≥9 MET hours/week**** | Yes N (%) | | | |
| | No N (%) | | | |
| **Obesity Status** | Yes N (%) | | | |
| | No N (%) | | | |
| **Grade≥3 cardiovascular disease** | Yes N (%) | | | |
| | No N (%) | | | |

| | | | |
|---|---|---|---|
| | | | |

**No represents a combination of never and former smoker.*
*** Quantity and intensity of physical activity were expressed as metabolic equivalent (MET) hours per week, representing the frequency of sessions per week multiplied by session duration, and weighted by the standardized classification of energy expenditure (i.e., moderate and vigorous activity). ≥9 MET hours/week represents minimum MET hours for meeting national exercise guidelines.*

*Table 2 Cancer and treatment characteristics*

| Variable | Levels | CCS Without DM N (%) | CCS With DM N (%) | p |
|---|---|---|---|---|
| **Diagnosis** | Leukemia | | | |
| | CNS Tumor | | | |
| | Hodgkin's Lymphoma | | | |
| | Non-Hodgkin's Lymphoma | | | |
| | Neuroblastoma | | | |
| | Wilms tumor | | | |
| | Soft tissue sarcoma | | | |
| | Bone Tumor | | | |
| **CNS-Directed Treatment*** | Yes | | | |
| | No | | | |
| **Radiation Treatment** | Yes | | | |
| | No | | | |
| Head/neck | Yes | | | |
| | No | | | |
| Chest | Yes | | | |
| | No | | | |
| Abdomen | Yes | | | |
| | No | | | |
| Tail of Pancreas | Yes | | | |
| | No | | | |
| Pelvis | Yes | | | |
| | No | | | |
| **Chemotherapy** | Yes | | | |
| | No | | | |
| Alkylating agents | Yes | | | |
| | No | | | |
| Anthracycline | Yes | | | |
| | No | | | |
| Platinum agents | Yes | | | |
| | No | | | |
| Vinca alkaloids | Yes | | | |

| | | |
|---|---|---|
| | No | |
| Retinoic acid | Yes | |
| | No | |
| High-Dose IV Methotrexate | Yes | |
| | No | |
| Standard dose IV methotrexate | Yes | |
| | No | |
| Intrathecal methotrexate | Yes | |
| | No | |
| Corticosteroids | Yes | |
| | No | |
| **Neurosurgery** | Yes | |
| | No | |

*CNS directed treatment is defined as IT-MTX, neurosurgery, and/or cranial radiation*

*Table 3 Proposed table for Aim 1.1: Impact of DM on neurocognitive impairment in CCS*

| | | | Outcome variables | | | |
|---|---|---|---|---|---|---|
| | | | **Task Efficiency** | **Emotional Regulation** | **Organization** | **Memory** |
| **Predictors** | **Levels** | | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** |
| **DM status** | | CCS without DM | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | CCS with DM | | | | |
| **Age at assessment** | | | | | | |
| **Sex** | | Male | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Female | | | | |
| **Race** | | White | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Non-white | | | | |
| **Ethnicity** | | Non-Hispanic | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Hispanic | | | | |
| **Age at diagnosis** | | | | | | |
| **CNS-directed treatment*** | | No | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Yes | | | | |
| Radiation | Pelvis | No | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Yes | | | | |
| | Abdomen | No | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Yes | | | | |
| | Chest | No | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Yes | | | | |
| | Tail of pancreas | No | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Yes | | | | |

Outcome variables are defined as impaired vs. not impaired.*CNS-directed treatment defined as having been exposed (yes/no) to IT-MTX, neurosurgery and/or CRT.

*Table 4 Proposed table for Aim 1.2: To identify the extent to which cardiovascular conditions and health risk behaviors mediate neurocognitive outcomes in CCS with DM*

| Mediator | | Effect of DM on Mediator (a) | Effect of Mediator on Neurocognitive Outcome (b) | Indirect Effect (ab) | 95% Bootstrapped Confidence Interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Neurocognitive outcome: Task Efficiency** | | | | | | |
| **Health behaviors*** | Smoking status (never/former vs. current) | | | | | |
| | BMI (non-obese vs obese) | | | | | |
| | ≥9 MET Hours (yes/no) | | | | | |
| **Cardiovascular conditions** | Grade≥3 (yes/no) | | | | | |
| **Neurocognitive Outcome: Emotion Regulation** | | | | | | |
| **Health behaviors** | Smoking status (never/former vs. current) | | | | | |
| | BMI (non-obese vs obese) | | | | | |
| | ≥9 MET Hours (yes/no) | | | | | |
| **Cardiovascular conditions** | Grade≥3 (yes/no) | | | | | |
| **Neurocognitive Outcome: Organization** | | | | | | |
| **Health behaviors** | Smoking status (never/former vs. current) | | | | | |
| | BMI (non-obese vs obese) | | | | | |
| | ≥9 MET Hours (yes/no) | | | | | |
| **Cardiovascular conditions** | Grade≥3 (yes/no) | | | | | |
| **Neurocognitive Outcome: Memory** | | | | | | |
| **Health behaviors** | Smoking status (never/former vs. current) | | | | | |
| | BMI (non-obese vs obese) | | | | | |
| | ≥9 MET Hours (yes/no) | | | | | |
| **Cardiovascular conditions** | Grade≥3 (yes/no) | | | | | |

* Obesity is defined as BMI≥30. ≥9 MET hours/week represents minimum MET hours for meeting national exercise guidelines for cancer survivors.[47]

*Table 5 Proposed table for Aim 2: Impact of duration and progression of DM on cognitive change*

| | | | Non-impaired-Non-impaired | | | | Non-Impaired to Impaired | | | | Impaired-Impaired | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | TE | ER | OD | MD | TE | ER | OD | MD | TE | ER | OD | MD |
| **Predictor** | **Levels** | | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** |
| DM duration* | Years | | | | | | | | | | | | | |
| DM progression* | Stable (reference) | | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| | Worsened | | | | | | | | | | | | | |
| Cardiovascular conditions | Grade≥3 | No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| | | Yes | | | | | | | | | | | | |

Outcomes variables are expressed as a binary variable indicating whether a CCS changed or maintained impairment status (e.g., unimpaired to impaired) between follow-ups. *DM duration is defined age at F/U minus age at DM diagnosis and progression of DM is defined as a binary variable with two levels: no grade change vs. worsening in grade from baseline to follow-up assessment. Note. TE= Task Efficiency; ER = Emotion Regulation; OD=Organization Decline; MD= Memory Decline

*Table 6 Proposed table for Aim 2: Impact of duration and progression of DM on cognitive change using linear regression models*

| | | | Outcome variables | | | |
|---|---|---|---|---|---|---|
| | | | Task Efficiency | Emotional Regulation | Organization | Memory |
| **Predictor** | **Levels** | | **Estimate (95%)** | **OR (95%)** | **OR (95%)** | **OR (95%)** |
| Baseline score | | T-Scores | | | | |
| DM duration | | Years | | | | |
| DM progression worsened* | | No | | | | |
| | | Yes | | | | |
| Cardiovascular conditions | Grade≥3 | No | | | | |
| | | Yes | | | | |
| Neurological conditions | Grade≥3 | No | | | | |
| | | Yes | | | | |

For this table, change is expressed as a continuous variable, where T-score obtained at the last survey is subtracted from the T-score at the penultimate survey. Estimates are adjusted for baseline neurocognitive scores. DM progression is defined as no progression vs. worsening of grade. *DM progression is defined as no progression vs. worsening of grade. **Expressed as binary variables that indicate whether CCS had grade≥3 neurological and/or cardiovascular condition.

*Proposed Supplemental Table 1 for Aim 1.2: Logistic regression to assess cardiovascular conditions and health risk behaviors associations with neurocognitive impairment in CCS with DM*

| Predictor | | Levels* | Task Efficiency OR (95%) | Emotional Regulation OR (95%) | Organization OR (95%) | Memory OR (95%) |
|---|---|---|---|---|---|---|
| **Health behaviors*** | Smoking status | Never/Former | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Past | | | | |
| | BMI | Not Obese | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Obese | | | | |
| | ≥9 MET Hours | Yes | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | No | | | | |
| **Treatment** | CNS treatment | No | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Yes | | | | |
| **Cardiovascular conditions** | Grade≥3 | No | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| | | Yes | | | | |

* Obesity is defined as BMI≥30. ≥9 MET hours/week represents minimum MET hours for meeting national exercise guidelines for cancer survivors.[47] CNS-directed treatment is defined as IT MTX, neurosurgery and/or cranial radiation.