CCSS Analysis Concept Proposal

Title: Associations Between Body Mass Index at Diagnosis and Early Survivorship with Chronic Health Conditions and Late Mortality Among 5-Year Survivors of Childhood Cancer

Working groups: Chronic Disease (Primary), Epidemiology/Biostatistics (Secondary)

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Background and Rationale

Survivors of childhood cancer are at increased risk for developing chronic health conditions compared to the general population. Among survivors from the Childhood Cancer Survivor Study (CCSS), 73% of survivors experienced a chronic health condition (CHC) and 42% had severe or life-threatening conditions by 30-years post-diagnosis.[1] Compared to sibling controls, survivors had a three-fold increased risk for developing any type of CHC and an eight-fold increased risk for severe or life threatening conditions.[1] The St. Jude Lifetime Cohort Study has shown that at age 50, survivors experience an average of 17.1 CHCs, with 4.7 being severe or life threatening, approximately double what was observed in community controls.[2] These conditions not only cause increased health-related morbidity, but they also result in decreased quality of life and earlier mortality compared to matched peers from the general population.[1,3-6]

Survivors of childhood cancer are also at increased risk for late-mortality, with a CCSS investigation reporting a 40-year cumulative all-cause mortality among survivors of 23.3% compared with <5% expected mortality in the general population.[6] In this study, survivors had significantly higher risks of cause-specific mortality including mortality due to subsequent malignancy [standardized mortality ratio (SMR) 8.9, 95%CI 8.5–9.4], cardiac disease (SMR 4.3, 95%CI 3·9–4·7), cerebrovascular disease (SMR 5.1, 95%CI 4·2–6·2), and diabetes (SMR 1.7, 1.2–2.3).[6] Notably, leading a healthy lifestyle, inclusive of a healthy body mass index (BMI), was independently associated with a 20% reduction in health-related mortality among survivors in this study.[6] Despite efforts to minimize long-term treatment-related toxicities by risk-adapting therapeutic

exposures,[7,8] the prevalence of CHCs and risk for late-mortality remain high and a better understanding of modifiable risk factors for poor outcomes remains a priority.

Obesity is an established risk factor for many CHCs, including cardiovascular disease, diabetes, and certain malignancies.[9-16] In a recent CCSS investigation, obese BMI was associated with an increased risk for both benign and malignant subsequent neoplasm types, including solid organ (RR, 1.22; 95% CI, 1.01-1.46), CNS (RR, 1.47; 95% CI, 1.12-1.95), and skin (RR, 1.30; 95% CI,1.13-1.50) neoplasms.[17] Importantly, among survivors, excess weight gain has been shown to begin during childhood cancer treatment and persist into adulthood.[18,19] Patient and treatment factors associated with overweight/obesity in the survivorship period include genetic susceptibility, obesity and younger age at time of childhood cancer diagnosis, cranial radiation exposure, and older attained age.[18,20] Though limited, existing literature shows that overweight/obese children diagnosed with leukemia experience poor initial treatment response, higher rates of relapse, and have worse long-term survival than those without overweight/obesity.[21-23] Additionally, in a single-institution case-control study, Moke et al. observed that those who were obese both at childhood cancer diagnosis and at the end of treatment were at increased risk of subsequent malignancies compared to those who were not.[24]

However, there are limited data evaluating the trajectory of BMI beginning at childhood cancer diagnosis and into adulthood among childhood cancer survivors. The overarching purpose of this study is to characterize this trajectory in a multi-institutional cohort of survivors with longitudinal follow-up decades beyond their primary cancer and determine its relationship with the development of CHCs among survivors. The outcomes of this study will generate new information about the relationship between childhood weight status, late effects, and health-related late mortality following childhood cancer treatment; and may identify additional supporting evidence for obesity prevention and treatment in children undergoing pediatric cancer treatment.

Specific Aims

Aim 1a: Describe BMI trajectory among survivors from 1) start of cancer treatment through: 2) baseline CCSS questionnaire, and 3) duration of CCSS enrollment, based on demographics (age at diagnosis, race/ethnicity, sex), childhood cancer factors (diagnosis, treatment era and exposures), and socioeconomic status during survivorship.

Aim 1b. Evaluate the association between early treatment BMI and BMI trajectory during survivorship (CCSS baseline through most recent-follow-up).

In order to build BMI trajectories during survivorship, participants are required to have ≥3 BMI data points from CCSS enrollment. If there are not enough participants meeting this requirement, for this aim and for those below, the evaluation of first CCSS BMI will be substituted for BMI trajectory during survivorship.

Aim 2: Examine the association between 1) early treatment BMI and 2) BMI trajectory during survivorship/first CCSS BMI and risk for CTCAE grade 1-5 CHCs, grade 3-5 CHCs, and occurrence of 2 or more severe (grade 3-5) CHCs.

- Evaluate the association between early treatment BMI and prevalence of CHCs (grades 1-5 and 3-5 CHCs overall and by specific organ system) at CCSS entry.
- Evaluate the association between early treatment BMI and BMI trajectory during survivorship/first CCSS BMI and cumulative incidence and cumulative burden[25] of grades 1-5 and 3-5 CHCs (overall and by specific organ system) at last CCSS follow-up.
- Perform multivariable analyses to assess associations between early treatment BMI, BMI trajectory during survivorship/first CCSS BMI, and grade 3-5 CHCs and then specific cardiometabolic CHCs (hypertension, dyslipidemia, diabetes, cardiovascular disease, stroke) and obesity-related (joint replacement, adiposity associated subsequent Malignant Neoplasms [SMNs]) CHCs. Fatty liver and

cirrhosis will be included as exploratory outcomes. For cardiometabolic CHCs we will first consider the distribution of any graded condition and then limit to grade 2+ hypertension, dyslipidemia, diabetes, grade 1 fatty liver and grade 3-5 cirrhosis in the absence of hepatitis.

- Evaluate the association between 1) early treatment BMI and 2) BMI trajectory during survivorship/first CCSS BMI and cumulative incidence of SMNs categorized as all SMNs, obesity-related SMNs (esophageal adenocarcinoma, breast, colorectal cancer, uterine, gallbladder, stomach, kidney, liver, ovarian, pancreatic, thyroid, meningioma, multiple myeloma), breast SMN, and colorectal SMN.
- Compare SMN incidence for the categories above among survivors with obesity at early treatment and then obesity at first CCSS BMI with expected incidence in the general population.

Aim 3: Describe late mortality according to 1) early treatment BMI, and 2) BMI trajectory during survivorship/first CCSS BMI.

- Estimate cumulative incidence of mortality and calculate standardized mortality ratios (SMRs), using U.S. population data, by early treatment BMI and BMI trajectory during survivorship/first CCSS BMI.
- Describe causes of death and estimate cumulative incidence of cause-specific death, by early treatment BMI and BMI trajectory during survivorship/first CCSS BMI.
- Use multivariable models (adjusting for other cancer treatment exposures and sociodemographic factors) to estimate the association of early treatment BMI and BMI trajectory during survivorship/first treatment BMI on SMRs.

Hypotheses

Aim 1: We hypothesize that survivors of certain childhood cancers, including hematologic malignancies, will have larger BMI increases from diagnosis to survivorship and that those with overweight or obese BMI at early treatment will be more likely to remain overweight or obese into survivorship compared to those with healthy or underweight BMI at early treatment.

Aim 2: We hypothesize that, compared to survivors with healthy BMI at early treatment, survivors with obesity will have a higher prevalence of any (grade 1-5) and severe (grade 3-5) CHCs at CCSS entry as well as a higher cumulative burden of any (grade 1-5) and severe (grade 3-5) CHCs at last CCSS follow-up. Additionally, compared to survivors with healthy BMI at early treatment and stably healthy BMI trajectory/healthy first CCSS BMI, survivors with obesity or increasing BMI trajectory will have a higher incidence of SMNs overall and obesity-related SMNs and that the incidence of both categories of SMNs will be higher among survivors with obesity than expected based on general population estimates.

Aim 3: We hypothesize that, compared to survivors with healthy BMI at early treatment and stably healthy BMI trajectory/healthy first CCSS, survivors with obesity or increasing BMI trajectory will have significantly higher rates of late mortality.

I. Analysis Framework

Population: This study includes 5-year survivors enrolled in the CCSS cohort, diagnosed between 1970 and 1999, who have BMI data (height and weight) available near the time of childhood cancer diagnosis and at least one time point during CCSS follow-up. BMI at early treatment will only be available for those who received chemotherapy as part of their treatment regimen, as body surface area calculations were reported for chemotherapy dosing. Survivors who received radiation or surgery will be included if they also had chemotherapy, but early treatment BMI is unavailable for survivors treated with surgery or radiation

alone. For participants that were pregnant during the study time period, if a BMI time point was measured during pregnancy or up to 6 months post-partum these time points will be censored.

We'll describe the population's characteristics in Table 1 for survivors (participants, non-participants). Descriptive statistics include the distribution summary of treatment exposures and medical history as predictors and some sociodemographic covariates (e.g., sex, race, age at evaluation, age at diagnosis, and year of diagnosis). We'll compare the distribution of socioeconomics variables for participants and non-participants using a Chi-square/Exact Fisher test, two-sample t-tests, or their corresponding non-parametric tests (whichever applies).

Outcome Measures:

Chronic health conditions

- Chronic health conditions overall and by system (cardiovascular, pulmonary, renal, hepatic, gastrointestinal, endocrine, musculoskeletal, neurologic, hematologic, infectious, other)
    - Any grade (1-5) Common Terminology Criteria for Adverse Events (CTCAE, version 4)
    - Severe or life-threatening (grades 3-5)
- Cardiometabolic and obesity-related conditions will be considered separately
    - Hypertension
    - Dyslipidemia
    - Major adverse cardiovascular events (heart failure CTCAE grade 2+, coronary artery disease CTCAE grade 3+, stroke CTCAE grade 4+)
    - Diabetes
    - Cirrhosis in absence of hepatitis (exploratory outcome)
    - Polycystic ovary syndrome
    - Fertility impairment (among those with who answer "yes" to ever sexually active, those who answer "yes" to "Was there ever a period in your life when you and a partner tried for one year or more to become pregnant, without success?")
    - Joint replacement surgery (exclude surgeries related to cancer treatment)

Subsequent malignant neoplasms: SMNs will be identified via self- or proxy-reported surveys confirmed by pathological report consistent with previous CCSS methodology. If pathology report is unavailable, death certificate or medical records will be used for verification. SNs are coded by histology using the International Classification of Diseases for Oncology (ICD-O). Of interest for this study are adiposity associated invasive neoplasms (thyroid, breast, liver, gallbladder, stomach, pancreas, colon/rectum, uterine, ovary, kidney, multiple myeloma, esophageal, meningioma) as classified by ICD-O, 3rd Edition, behavior code 3,[26] as well as ductal carcinoma in situ (DCIS) of the breast and meningiomas. All other nonmalignant neoplasms will be excluded from the analysis.

Mortality

- Vital status (alive/dead), based on most recent National Death Index update
    - Age at death
    - Underlying cause of death, based on death certificates. Will use categories which mirror those used by Armstrong et al.[7]

Recurrence/progression of primary childhood malignancy
External causes (i.e. accidents, injuries, suicide)
Non-recurrence, non-external cause (attributable to chronic health conditions)
Subsequent neoplasm cause

Cardiac cause
Pulmonary cause
Other causes

Predictor Variables:

- Body mass index
    - BMI at the start of treatment (within 6 weeks of initiating chemotherapy) will be calculated from the heights, weights, and body surface area (BSA) measures reported in the medical record abstraction form (MRAF), section D1 - D10. Dates of first chemotherapy initiation, completion of all chemotherapy, as well as the start and last dose of each individual chemotherapy are outlined in the MRAF.
    - BMI and BMI category during the survivorship period will be calculated from self-reported heights and weights for survivors at each available CCSS survey follow-up time point. Height and weight data correspond to A.10 - A.11 in the Baseline survey, 7 - 8 in follow-up survey 2, and A.1 - A.2 in follow-up surveys 4, 5, 6, and 7. BMI categories will be determined by CDC guidelines.[27]

        Underweight, < 18 years old: ≤ 5th percentile; ≥ 18 years old: BMI < 18.5 kg/m^2
        Normal, < 18 years old: 6th - 84th percentile; ≥ 18 years old: BMI 18.5-24.9 kg/m^2
        Overweight, < 18 years old: 85 - 94th percentile; ≥ 18 years old: BMI 25-29.9 kg/m^2
        Obese, < 18 years old: ≥95th percentile; ≥ 18 years old: BMI ≥ 30 kg/m^2
        Severely Obese, < 18 years old: ≥120% of the 95th percentile; ≥ 18 years old: BMI ≥ 35 kg/m^2

    *If at any pediatric age the BMI exceeds the absolute threshold for the adult class, the adult cut-point will be used (i.e. a 17.5-year-old male with a BMI of 25 kg/m^2 (83rd percentile) should be categorized as overweight (adult cut-off) and not normal weight as percentile would suggest)

- Sociodemographic variables
    - Attained age
    - Sex
    - Race and ethnicity
    - Insurance status
    - Education attainment
    - Household income
- Cancer history and treatment
    - Treatment era (1970-79, 1980-89, 1990-99)
    - Age at diagnosis
    - Cancer type
    - Radiation y/n
        - Age at radiation
        - Maximum dose to exposed region (Gy)
        - TBI y/n, dose (Gy)
        - Chest y/n, dose (Gy)
        - Neck y/n, dose (Gy)
        - Abdomen/pelvis y/n, dose (Gy)
        - Extremity y/n, dose (Gy)

        - Spinal y/n, dose (Gy)
        - Cranial y/n, dose (Gy)
            - Brain segment 1 (infratentorial region) (yes/no)
            - Brain segment 2 (surrogate for pituitary) (yes/no)
            - Brain segment 3 (frontal supratentorial region) (yes/no)
            - Brain segment 4 (posterior supratentorial region) (yes/no)
    - Chemotherapy y/n
        - Alkylating agents y/n, cyclophosphamide equivalent dose[28]
        - Anthracyclines y/n, doxorubicin equivalent dose[29]
        - Epipodophyllotoxins y/n, cumulative dose
        - Platinating agents y/n, cumulative dose
        - Corticosteroids y/n, cumulative dose
    - Hematopoietic stem cell transplant y/n
        - Autologous y/n
        - Allogeneic y/n
    - Surgery y/n
        - Cranial surgery y/n
        - Limb amputation y/n
- Health behaviors:
    - Physical activity level: Presented as average number of minutes per day (or week) of vigorous physical activity. Data are available on Baseline and follow-up questionnaires and corresponds to N9 in the Baseline questionnaire, D1 - D7 in follow-up survey 2, N15 - N21 in follow-up survey 4, N15 - N24 in follow-up survey 5, D1 - D10 in follow-up survey 6, and M15 - M29 in follow-up survey 7. Using published CCSS methodology by Scott et al. physical activity time will be calculated into metabolic hours per week (MET-h/week) and categorized as 0, 3-6, 9-12 and 15-21 MET-h/wk.[30] Adequate physical activity (Y/N) will be defined as survivors achieving at least 9 MET-h/wk.
    - Smoking status (yes [ever smoked at least 100 cigarettes in entire life]/no): Corresponds to N1 - N2 in the Baseline survey, L1 - L6 in follow-up survey 2, N7 - N14 in follow-up surveys 4 / 5, and M7 - M14 in follow-up survey 7.
    - Alcohol use (never/moderate/moderate-high/high-risk): Corresponds to question N3 - N8 in the Baseline survey, N1 - N6 in follow-up surveys 4 / 5, and M1 - M6 in follow-up survey 7. Alcohol use categories will be defined as per the U.S. Department of Health and Human Services and U.S. Department of Agriculture.[31] For each individual the highest reported alcohol use category will be used for analysis.

        Moderate, women: up to 1 drink per day; men: up to 2 drinks per day.
        Moderate-high, women: 2-3 drinks per day; men: 3-4 drinks per day.
        High-risk use, women: $\geq$ 4 drinks per day; men: $\geq$ 5 drinks per day.

Analytic Approach

Aim 1a: Summary statistics for demographic variables (e.g., age at diagnosis, race/ethnicity, sex), childhood cancer factors (e.g., diagnosis, treatment era, therapeutic exposures), and socioeconomic status will be reported for survivors included in the analysis. These will be stratified by BMI at key time points: at cancer treatment, at CCSS baseline completion, at each follow-up, and through the last follow-up. Median BMI percentiles and proportions of survivors falling into each weight status category will be calculated by childhood cancer diagnosis. Using a chi-squared test, BMI distributions will also be compared across treatment-related

variables, including diagnosis groups and specific therapeutic exposures. We'll check descriptive changes in BMI over time to track transitions from therapy initiation through follow-up periods.
If needed, we will compare the prevalence of obesity in survivor groups to that of the general population. These comparisons will leverage temporally matched, age—and sex-adjusted NHANES survey data (1971–present) to contextualize obesity risk across different childhood cancer diagnoses.

Aim 1b. We will check the association between early treatment BMI and BMI trajectory during survivorship, provided we have distinct BMI classes. If there won't be enough survivors with three or more BMI data available, we will independently use ordinal logistic regression to check the association of BMI at treatment with BMI at the CCSS baseline and the most recent follow-up.

For **Aim 2**, we will apply several regression analyses/cumulative incidences.

- We'll provide the distribution (e.g., median [range]) of CHCs (grades 1-5 and 3-5 CHCs overall and by specific organ system) by treatment BMI status. Also, we'll estimate the prevalences of grades 1-5 and 3-5 CHCs at the baseline.
- We'll use an ordinal logistic regression to evaluate the association between early treatment BMI and first CCSS BMI. We will estimate the twenty-year cumulative incidence and the cumulative burden of grades 1-5 and 3-5 conditions (overall and by organ system) by BMI status at diagnosis, beginning five years from initial diagnosis. Deaths due to causes other than CHCs should be considered as competing risks.
- We'll perform multivariable regression analyses to assess associations between early treatment BMI and the cumulative burden of grades 1-5 and 3-5 CHCs (overall and by specific organ system) at last CCSS follow-up. We'll also check the association between early treatment BMI and specific cardiometabolic CHCs (hypertension, dyslipidemia, diabetes, cardiovascular disease, stroke) and obesity-related (e.g., joint replacement) CHCs. Fatty liver and cirrhosis will be included as exploratory outcomes. For cardiometabolic CHCs, we will first consider the distribution of any graded condition and then limit to grade 2+ hypertension, dyslipidemia, diabetes, grade 1 fatty liver, and grade 3-5 cirrhosis in the absence of hepatitis. If in previous aims, we were able to create distinct classes of BMI trajectory, we will repeat the analysis with BMI trajectory as an exposure. Otherwise, we can consider the survivorship BMI (from baseline to the last follow-up) as a time-varying covariate. For the time-to-event analysis, we'll use a piecewise exponential model to check the association of the risk of BMI at treatment and BMI trajectory (in separate models) with late CHCs. For these models, a death due to causes other than a specific CHC (of outcome) will be considered as a competing risk. Models will be adjusted for demographics, treatment variables, and lifestyle factors (smoking, alcohol use, vigorous physical activity).
- We'll repeat a similar analysis as above with all SMNs, obesity-related SMNs (esophageal adenocarcinoma, breast, colorectal cancer, uterine, gallbladder, stomach, kidney, liver, ovarian, pancreatic, thyroid, meningioma, multiple myeloma), breast SMN, and colorectal SMN as the outcome. Each outcome is considered independently.
- We'll apply the Fine-Gray test to compare the SMN incidence curve for the categories above among survivors with obesity at early treatment and obesity at first CCSS BMI.

Aim 3: We'll describe vital status (alive/dead) based on the most recent National Death Index updates. The distribution of age at death and cause of death will be stratified by 1) early treatment BMI and 2) first CCSS BMI. The cumulative incidence of mortality will be estimated based on weight status. Cumulative incidence will be estimated for each of the mortality categories: 1) recurrence/progression, 2) external causes, 3) non-recurrence, non-external causes [subsequent malignancy, cardiac cause, pulmonary cause, other], accounting for competing risk of death from other causes.

The standardized mortality ratio (SMR) will be calculated using the U.S. population for age, race, calendar year, and sex-matched sample by early treatment BMI and/or first CCSS BMI. Piecewise exponential regression will be performed to examine the impact of demographic factors, treatment exposures, health behaviors, and follow-up/adulthood weight status on mortality (all-cause and cause-specific).

In our study, we will explore how obesity at diagnosis can change the effect of treatment on the late effect by adding interaction terms in our models for Aims 2 and 3 wherever applicable. In time-to-event analysis, we might consider additive interaction if the multiplicative interaction is not interpretable.

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Table 1. Participant Characteristics

Characteristic	Participants, n (%)
Sex	
Male	
Female	
Race and ethnicity	
Hispanic	
Non-Hispanic Black	
Non-Hispanic White	
Other	
Unknown	
Educational attainment	
<High school	
Completed high school	
Some college	
College graduate	
Household income	
Less than $19,000	
$20,000-39,000	
$40,000-60,000	
≥$60,000	
Age at primary cancer diagnosis, median (IQR)	
0-4 years	
5-9 years	
>10 years	
Age at last follow-up, median (IQR)	
Decade of diagnosis	
1970-79	
1980-89	
1990-99	
Primary cancer diagnosis	
ALL	
AML	
Other leukemia	
Hodgkin lymphoma	
Non-Hodgkin lymphoma	
CNS tumor	
Bone tumor	
Soft tissue sarcoma	
Kidney tumors	
Neuroblastoma	
Radiation exposure	
Any radiation	
TBI	
Yes	
No	
Cranial radiation	
Any exposure	
< 20 Gy	
≥ 20 Gy	

Abdominal/Pelvic radiation	
Any exposure	
< 10 Gy	
≥ 10 Gy	
Chest radiation	
Any exposure	
< 15 Gy	
15 - < 30 Gy	
≥ 30 Gy	
Any exposure	
Anthracycline exposure (mg/m^2)*	
Any exposure	
Median dose (IQR)	
< 250 mg/m^2	
≥ 250 mg/m^2	
Steroid exposure (mg/m^2)	
Any exposure	
Median prescribed prednisone equivalent dose (IQR)	
Alkylating agents (mg/m2)^	
Any exposure	
Median dose (IQR)	
Epipodophyllotoxins (mg/m^2)	
Any exposure	
Median dose (IQR)	
Platinating agents (mg/m^2)	
Any exposure	
Median dose (IQR)	
History of HSCT	
Yes	
No	
Limb amputation	
Yes	
No	
Chronic health conditions	
Any, grade 1-5	
Severe, grade 3-5	

*Doxorubicin equivalent dose; ^Cyclophosphamide equivalent dose

Potential figure. BMI trajectories overall and by and stratified by cancer diagnosis groups (hematologic malignancies, CNS tumors, non-CNS solid tumors), sex, race and ethnicity, presence of baseline obesity, decade of diagnosis, and treatment exposures

Table 2. Model adjusted odds of chronic conditions in survivors with overweight and obese BMI at early treatment compared to survivors with healthy BMI at early treatment

	BMI Category Early Treatment			
	Overweight		**Obese**	
Outcome	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Chronic conditions				
Any grade 1-5 chronic condition				
Any severe grade 3-5 chronic condition				
≥2 grade 3-5 chronic conditions				
Chronic conditions by system				
Cardiovascular				
Pulmonary				
Renal				
Gastrointestinal				
Endocrinologic				
Musculoskeletal				
Neurologic				
Hematologic				
Infectious				
Cardiometabolic and obesity related conditions				
Hypertension				
Dyslipidemia				
Diabetes				
Major adverse cardiovascular events				
Joint replacement				
Obesity associated SMNs				

Potential figures: Cumulative incidence of CHCs overall (grades 1-5) and severe CHCs (grades 3-5) at last CCSS follow-up by BMI category at diagnosis and separately by BMI category at CCSS entry. Sub-figures focused specifically on CHCs by organ system, cardiometabolic CHCs, and SMNs (categorized by SMNs overall, obesity-related SMNs, colorectal cancer, breast cancer).

Potential figures: Cumulative incidence of mortality and cause-specific mortality (recurrence/progression, external causes, non-recurrence/non-progression) by BMI category at diagnosis and CCSS entry

Table 3. Standardized mortality ratios among survivors by BMI category at early diagnosis and BMI trajectory classes during survivorship/ first CCSS BMI

Parameter	Overall Mortality			SMN Mortality			Cardiac Mortality			Pulmonary Mortality		
BMI Category at Diagnosis	SMR	No. of Deaths	95% CI	SMR	No. of Deaths	95% CI	SMR	No. of Deaths	95% CI	SMR	No. of Deaths	95% CI
Healthy												
Overweight												
Obese												
BMI Category at first CCSS (*Or BMI trajectory classes)												
Healthy												
Overweight												
Obese												