CHILDHOOD CANCER SURVIVOR STUDY ANALYSIS PROPOSAL

STUDY TITLE: The Multifactorial Etiology of Obesity among CCSS Participants

Working Group: Chronic Diseases and Psychology

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Survivors of childhood cancer undergo treatments that place them at an increased risk for being both overweight and underweight. The odds ratio (OR) for obesity (body mass index (BMI) ≥ 30 kg/m^2) was 1.5 (95% confidence interval (CI), 1.2 to 1.8, p = 0.001) among adult female and was 1.2 (95% CI, 1.0 to 1.5, p = 0.02) among

adult male leukemia survivors in the Childhood Cancer Survivor Study (CCSS) compared to US normative data from the 1995 National Health Interview Survey. Underweight was more frequent in both male and female survivors of Hodgkin lymphoma (HL) and Wilms tumor, female survivors of bone cancer, and male survivors of brain tumors, non-Hodgkin lymphoma (NHL), soft tissue sarcoma and neuroblastoma [1].

The frequency of obesity was greater in adult survivors of childhood acute lymphoblastic leukemia (ALL) who participated in the CCSS than in their siblings. The age- and race-adjusted OR for being obese among survivors treated with a cranial radiation (CRT) dose ≥ 2000 cGy was 2.59 (95% CI, 1.88 to 3.55, $p < 0.001$) for females and was 1.86 (95% CI, 1.33 to 2.57, $p < 0.001$) for males compared to sibling participants in the CCSS, but was not increased among those who received a CRT dose of 1000 – 1999 cGy [2]. In a longitudinal evaluation of CCSS participants who completed both the baseline (1995 – 1996) and the follow-up (2002 – 2003) questionnaires, with a mean elapsed time between questionnaires of 7.8 years, women treated with CRT ≥ 1000 cGy had a mean BMI increase of 0.41 $kg/m^2/yr$ (95% CI, 0.37 to 0.45 $kg/m^2/yr$; $p < 0.01$), and men treated with CRT ≥ 1000 cGy had a mean BMI increase of 0.29 $kg/m^2/yr$ (95%CI, 0.26 to 0.32; $p < 0.01$) in comparison with same sex CCSS siblings [3].

The etiology of obesity in childhood cancer survivors is multi-factorial. Among CCSS male survivors, white, non-Hispanic race/ethnicity and brain radiation were associated with an increased OR of obesity, whereas black, non-Hispanic race/ethnicity and brain radiation increased the OR of obesity among CCSS female survivors [1]. In a

pilot study, the OR for obesity among females who had received ≥ 2000 cGy cranial irradiation and who were homozygous Arg/Arg for the Gln223Arg polymorphism in the leptin receptor gene was 6.1 (95% CI 2.1 to 22, p = 0.002) [4].

In the US population, declines in physical activity correlate strongly with excessive weight gain in children and adolescents. Using the Habitual Activity Questionnaire, Kim et al. reported that the respective median activity scores for 1213 black girls and 1166 white girls in the National Heart, Lung and Blood Institutes Growth and Health Study (NGHS) were 27.3 and 30.8 metabolic equivalent of task (MET) times per week at base line and declined to 0 and 11.0 by year 10 of the study (a 100 percent decline for black girls and a 64 percent decline for white girls, p < 0.001). By the age of 16 or 17 years, 56 percent of the black girls and 31 percent of the white girls reported no habitual leisure-time activity [5].

In the NGHS population, each decline in activity of 10 metabolic equivalent (MET)-times per week was associated with an increase in BMI of 0.14 kg/m^2 (standard error (SE) ± 0.03) and in sum of skinfold thickness of 0.62 mm (SE ± 0.17) for black girls, and of 0.09 kg/m^2 (SE ± 0.02) and 0.63 mm (SE ± 0.13) for white girls. At ages 18 or 19 years, BMI differences between active and inactive girls were 2.98 kg/m^2 (p < 0·0001) for black girls and 2.10 kg/m^2 (p < 0·0001) for white girls [6].

Berkey et al. reported larger increases in BMI from 1996 to 1997 among those female participants in the Growing Up Today Study (16,882 children born to participants in the Nurses' Health Study II) who reported higher caloric intakes (0.0061 ± 0.0026 kg/m^2 per 100 kcal/day)(β ± SE), less physical activity (- 0.0284 ± 0.0142 kg/m^2 per hour/day of physical activity) and more time with TV/videos/games (0.0372 ± 0.0106

kg/m^2 per hour/day of TV/videos/dames) during the year between the 2 BMI assessments. Larger BMI increases occurred in boys who reported more time with TV/videos/games (0.0384 ± 0.0101 kg/m^2) during the year. For both boys and girls, a larger rise in caloric intake from 1996 to 1997 predicted larger BMI increases (girls: 0.0059 ± 0.0027 kg/m^2 per increase of 100 kcal/day; boys: 0.0082 ± 0.0030 kg/m^2 per increase of 100 kcal/day) [7].

Male and female CCSS survivors with all diagnoses are more likely to lead an inactive lifestyle compared to CCSS sibling participants. Only males with the diagnoses of other central nervous system (CNS) tumor or HL and females with the diagnoses of acute myeloid leukemia, other or unspecified leukemia, HL, kidney tumor or Ewing sarcoma meet the Centers for Disease Control physical activity guidelines [8]. CCSS ALL survivors were more likely to not meet CDC recommendations for physical activity (OR, 1.44; 95% CI), 1.32-1.57) and more likely to be inactive (OR, 1.74; 95% CI, 1.56-1.94) in comparison with the Behavior Risk Factor Surveillance System (BRFSS) general population. Survivors treated with >2000 cGy cranial radiotherapy were at particular risk. Compared with BRFSS participants and adjusted for age, race, and ethnicity, survivors were more likely to not meet CDC physical activity recommendations (females: OR, 2.07, 95% CI, 1.67 to 2.56; males: OR, 1.43, 95% CI, 1.16 to1.76) and more likely to be inactive (females: OR, 1.86; 95% CI, 1.50 to 2.31; males: OR, 1.84; 95% CI, 1.45 to 2.32) [9].

In a recent structural equation model, Cox et al. identified factors that predict, mediate, or modify physical activity in CCSS participants; self-reported health fears (P=0.01), baseline exercise frequency (P=<0.001), educational level (P=0.01), self-

reported physical function (P=0.01), cancer related pain (P=<0.001), fatigue (P=<0.001), cancer-related anxiety (P=<0.001), and discussion of subsequent cancer risk with a primary care provider (P=<0.001) directly or indirectly contributed to explaining 40% of the variance in male CCSS survivors' physical activity participation. Thirty-one percent of the variance in CCSS female survivors' physical activity participation was explained by fatigue (P=0.01), self-reported physical function (P=<0.001), baseline exercise frequency (P=0.01), cancer-related pain (P=<0.001), cancer-related anxiety (P=0.01), and recency of visits with a PCP (P=<0.001)[10]

Zebrack et al. evaluated psychological outcomes in CCSS survivors of ALL, HL and NHL using the Brief Symptom Inventory (BSI). Compared with siblings (3.4%), survivors were more likely to score symptomatic levels for depression (ALL (5.4%), HL (5.5%) and NHL (4.4%)). Female ALL and HL survivors were more likely than male survivors to report symptomatic levels for depression (ALL - relative risk (RR) 1.87, 95% CI 1.32 to 2.66, p < 0.001; HL - RR 1.96, 95% CI 1.25 to 3.06, p = 0.003). Those with a household income < $ 20,000 (ALL - RR 2.67, 95% CI 1.85 to 3.85, p < 0.001; HL - RR 2.49, 95% CI 1.52 to 4.06, p < 0.001), less than a high school education (ALL - RR 2.27, 95% CI 1.24 to 4.15, p = 0.008; HL - RR 2.56, 95% CI 1.20 to 5.43, p = 0.024; NHL - RR 5.15, 95% CI 1.67 to 15.90, p = 0.004) and who were not currently employed (ALL - RR 2.16, 95% CI 1.41 to 3.29, p < 0.001; HL - RR 3.46, 95% CI 2.03 to 5.91, p < 0.001) were more likely to report symptomatic levels of depression. Prior treatment with cranial irradiation did not increase the RR for reporting symptomatic depression (RR 0.91, 95% CI 0.64 to 1.32, p = 0.63) [11]. CCSS participants with solid tumors had significantly higher scores on the depression, somatic distress and anxiety subscales of the BSI than

both CCSS sibling participants. However 71 – 78% of survivors and 76 – 85% of siblings scored at or near the lowest scores on the three subscales, indicating most in both groups had few, if any, symptoms measured by the subscales [12].

Weight gain is a frequent side effect of the use of some of the newer anti-depressants, particularly paroxetine (Paxil) [13, 14], as well as antipsychotic drugs such as clozapine (Clozaril), olanzapine (Zyprexa), and risperidone (Risperdal) [15-26]. In general weight gain is not significant during treatment with bupropion (Wellbutrin), sertaline (Zoloft), fluoxetine (Prozac), ziprasidone (Zeodon), aripiprazole (Abilify) or haloperidol (Haldol) (Table 1). Weight gain has not been reported in randomized, double-blind, placebo-controlled evaluations of lithium carbonate [27, 28]. Among the drugs used for seizure control, weight gain is increased among patients treated with sodium valproate (Depakote) compared to carbamazepine (Tegretol) [29-31]. The use of antidepressants has increased dramatically in the age group 18 – 44 years during the period 1992 – 2002 along with a significant shift in prescribing from tricyclic antidepressants to selective serotonin reuptake inhibitors (SSRIs) [32]. In the CCSS cohort, the use of risperidone, paroxetine sertaline and fluoxetine was reported as follows: Baseline – risperidone – 10, paroxetine – 69, sertaline – 126, fluoxetine - 188; Follow-up 1 - risperidone – 34, paroxetine – 252, sertaline – 287, fluoxetine - 251; Follow-up 2 - risperidone – 41, paroxetine – 258, sertaline – 316, fluoxetine - 217.

Table 1

Weight gain after treatment in randomized trials conducted in non-cancer populations with selected anti-depressants or anti-psychotics

Drug	Number of patients	Duration of study	> 7% Weight	Weight gain	p-value

		(weeks)	gain		
Paroxetine[13]	47	26 - 32	25.5% (12)		
Sertaline	48	26 - 32	4.2% (2)		p = 0.003[a]
Fluoxetine	44	26 - 32	6.8% (3)		p = 0.016[b]
Sertaline[14]	176	24		2.9 lb	NS
Paroxetine	177	24		1.3 lb	
Olanzapine[15]	35	6	77.1% (27)		
Risperidone	33	6	63.6% (21)		p < 0.001
Haloperidol	31	6	22.6% (7)		
Olanzapine[18]	1059	6		2.24 ± 3.31 kg	p < 0.001
Haloperidol	310	6		0.01 ± 2.97 kg	
Olanzapine[18]	133	6		2.66 ± 3.42 kg	p = 0.081
Risperidone	135	6		1.99 ± 2.77 kg	
Clozapine[19]	19	52		11.7 ± 7.0 lb	-
Halperidol	20	52		1.5 ± 6.0 lb	
Olanzapine[17]	172	28		4.1 ± 5.9 kg	p = 0.015
Risperidone	167	28		2.3 ± 4.8 kg	
Aripiprazole[21]	156	26		(1.37 kg)	p < 0.001
Olanzapine	161	26		4.23 kg	
Olanzapine[22]	202	24		2.53 ± 4.91 kg	p < 0.001
Ziprasidone	192	24		(1.65 ± 4.16) kg	
Placebo[23]	91	6		0 (median)	
Ziprasidone (80 mg/day)	104	6		1.0 (median)	
Ziprasidone (160 mg/day)	103	6		0 (median)	
Placebo[24]	71	52		(3.6 kg)	
Ziprasidone (40 mg/day)	72	52		(2.7 kg)	
Ziprasidone (80 mg/day)	68	52		(3.2 kg)	
Ziprasidone (160 mg/day)	67	52		(2.9 kg)	
Placebo[25]	96	4	5%		
Quetiapine (750 mg/day)	94	4	25%		
Quetiapine (250 mg/day)	96	4	16%		
Placebo[26]	19	6	6%	(0.8 kg)	
Quetiapine (75 mg/day)	19	6	11%	0.9 kg	
Quetiapine (150 mg/day)	25	6	17%	2.9 kg	

Quetiapine (300 mg/day)	31	6	10%	2.0 kg	
Quetiapine (600 mg/day)	28	6	16%	2.6 kg	
Quetiapine (750 mg/day)	28	6	13%	2.3 kg	
Haloperidol (12 mg/day)	24	6	4%	0.3 kg	

[a] – Pairwise comparison of sertaline vs paroxetine; [b] – Pairwise comparison of fluoxetine vs paroxetine

In a preliminary analysis, we evaluated the relationship between the use of paroxetine, risperidone, sertaline or fluoxetine, cranial radiation dose ≤ 2000 cGy or > 2000 cGy and overweight and obesity. The data suggest that there may be an independent effect of the use of these agents on the risk of overweight and obesity in CCSS participants.

Table 2

Relationship between use of specific antidepressant and antipsychotic drugs, cranial irradiation, and the frequency of overweight or obesity in CCSS participants

	≤2000 cGy		**>2000 cGy**		**Pooled estimate**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR_{CMH} (95% CI)	P value
Risperidone						
Overweight	--	0.05*	2.2 (0.6, 7.8)	0.22	3.4 (1.0, 11.7)	0.04
Obese	2.5 (0.5, 12.3)	0.24*	3.2 (1.1, 9.3)	0.04*	3.0 (1.2, 7.2)	0.01
Paroxetine						
Overweight	1.9 (0.9, 4.4)	0.10	1.3, (0.8, 2.1)	0.36	1.4 (0.9, 2.2)	0.10
Obese	1.5 (0.7, 3.1)	0.28	2.1 (1.3, 3.4)	0.001	1.9 (1.3, 2.8)	0.0009
Zoloft						
Overweight	2.1 (1.0, 4.2)	0.03	1.8 (1.1, 3.0)	0.01	1.9 (1.3, 2.9)	0.001
Obese	2.2 (1.2, 4.0)	0.01	1.9 (1.2, 2.9)	0.005	2.0 (1.4, 2.8)	0.0002
Prozac						
Overweight	1.3 (0.7, 2.7)	0.44	2.3 (1.3, 4.1)	0.004	1.9 (1.2, 2.9)	0.005
Obese	1.3 (0.7, 2.7)	0.41	2.1 (1.3, 3.4)	0.002	1.8 (1.2, 2.7)	0.003

-- Zero cell - OR not calculated
* Fisher's exact p value

Krull et al. recently examined the association between adolescent behavior problems and adult BMI and physical activity in CCSS survivors. For this study,

behavioral problems and use of anti-depressant medications were identified in 1,656 adolescent survivors whose parents completed the Baseline CCSS survey. These adolescents then completed the Follow-up 2003 survey to report BMI and physical activity levels. Although adolescent depression was not associated with adult BMI in this subset of CCSS survivors, those adolescents who were taking anti-depressants were more likely not to meet CDC recommendations for physical activity as adults (OR, 3.2; 95% CI, 1.2-8.2).

The proposed analysis will evaluate, using multivariable and structural equation modeling, the relationship of gender, race/ethnicity, education level, age at diagnosis, age at questionnaire, family income, health insurance, physical activity, inactivity, hypothalamic/pituitary radiation dose, BSI depression, BSI somatic distress, BSI anxiety, the use of specific anti-depressant and anti-psychotic drugs to the frequency of overweight and obesity in CCSS survivors. Overweight will be defined as BMI ≥ 25 kg/m^2 and < 30 kg/m^2 and obesity as BMI ≥30 kg/m^2 for those ≥ 18 years of age [33]. Obesity will be further subdivided into Class I (BMI ≥ 30 kg/m^2 and < 35 kg/m^2), Class II (BMI ≥ 35 kg/m^2 and < 40 kg/m^2) and Class III (BMI ≥ 40 kg/m^2) [33]

SPECIFIC AIMS

Primary Aims

The purpose of this proposal is to study the etiology of overweight and obesity in CCSS survivors, to determine which factors contribute independently to an increased risk for obesity in CCSS participants and to compare the impact of various risk factors on the frequency of overweight, obesity and the combination of overweight and obesity in CCSS participants compared to CCSS siblings.

Aim 1: To test in univariable models the effect of age at diagnosis, age at questionnaire, sex, race/ethnicity, educational level, family income, health insurance, physical activity (not meet CDC recommendations), inactive (no leisure time physical activity in the month preceding completion of the questionnaire), hypothalamic/pituitary radiation dose (none, < 2000 cGy, 2000 to 3000 cGy, > 3000 cGy), BSI depression, BSI somatic distress, BSI anxiety, specific anti-depressant and anti-psychotic drug use including sertaline (Zoloft), paroxetine (Paxil), fluoxetine (Prozac), citalopram (Celexa), escitalopram (Lexapro), buproprion (Wellbutrin), nefazodone (Serzone), venlafaxine (Effexor), amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan), desipramine (Norpramin), notrtiptyline (Pamelor), olanzapine (Zyprexa), aripiprazole (Abilify), ziprasidone (Zeodon), thioridazine (Mellaril), quetiapine (Seroquel), clozapine (Cloxaril), risperidone (Risperdal) and valproate (Depakote) on the frequency of overweight and obesity among CCSS participants.

Aim 2: To develop multivariable models based on the results of the univariable analyses in **Aim 1** to determine which factors independently increase the risk of overweight or obesity in CCSS participants. Factors entered into the multivariable model will be those significant at the $p < 0.1$ in the univariable models.

Aim 3: To compare in univariable models the effect of age at questionnaire, sex, race/ethnicity, educational level, family income, health insurance, physical activity, inactivity, hypothalamic/pituitary radiation dose (none, < 2000 cGy, 2000 to 3000 cGy, > 3000 cGy), BSI depression, BSI somatic distress, BSI anxiety, specific anti-depressant and anti-psychotic drug use including sertaline (Zoloft), paroxetine (Paxil), fluoxetine (Prozac), citalopram (Celexa), escitalopram (Lexapro), buproprion (Wellbutrin),

nefazodone (Serzone), venlafaxine (Effexor), amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan), desipramine (Norpramin), notrtiptyline (Pamelor), olanzapine (Zyprexa), aripiprazole (Abilify), ziprasidone (Zeodon), thioridazine (Mellaril), quetiapine (Seroquel), clozapine (Cloxaril), risperidone (Risperdal) and valproate (Depakote) the frequency of overweight and obesity among CCSS participants and CCSS siblings.

AIM 4: To compare in two separate structural equation models (survivor and sibling) the antecedents, mediators and moderators of obesity.

Analysis framework:

Sample

Survivor and sibling participants who completed the baseline and second follow-up questionnaire are eligible for these analyses.

Outcomes of interest

Overweight and obesity (Follow-up 2 → Height, weight → BMI)

- Overweight:
    - Age≥18, BMI ≥25 kg/m^2 and <30 kg/m^2
- Obesity:
    - Age≥18, BMI ≥30 kg/m^2
        - Class I - BMI ≥ 30 kg/m^2 and < 35 kg/m^2
        - Class II - BMI ≥ 35 kg/m^2 and < 40 kg/m^2
        - Class III - BMI ≥ 40 kg/m^2

Independent (exploratory) variables

A. Demographic and personal factors

1. Gender (Baseline→ baseA→ sex)

2. Race/ethnicity (Baseline → baseA→race)
    - Non-Hispanic white
    - Non-Hispanic black
    - Hispanic
    - Other
3. Educational level (Follow-up 2→ f2main→ educatn, educ_oth)
    - No high school or GED
    - High school or GED
    - Some college no bachelor's degree
    - Bachelor's degree or higher
4. Age at diagnosis
    - 0 - 4
    - 5 - 9
    - 10 - 14
    - 15 - 20
5. Age at questionnaire (a_fu2)
    - 5-15
    - 16-25
    - 26-35
    - 36-45
    - 46-55
    - >=55
6. Family income (Follow-up 2 → f2main→ hincome)

- <$ 20,000/year
- ≥ $ 20,000 and < $ 30,000
- ≥ $ 30,000 and < $ 40,000
- >=$40,000/year

7. Health insurance (Follow-up 2 → f2main→ hinsnow)
    - Yes or Canadian
    - No
8. Vigorous physical activity (Follow-up 2→ f2main → vigact, d_vigact, t_vigact)
    - It is a binary variable for whether or not subjects meet the nationally recommended guideline for vigorous physical activity (30 minutes of vigorous physical activity on 3 or more days of the week).
9. Inactive (Follow-up 2 → physical)
    - It is a binary variable for whether or not subjects reported leisure time physical activity in the month preceding the completion of the questionnaire.
10. Physical function (Follow-up2→e6→climbing several flights of stairs→climbsev; e7→climbing one flight of stairs→climbone; e9→walking more than a mile→wmiles; e10→walking several blocks→wsevblks; e11→walking one block→woneblk)
    - Yes, limited a lot
    - Yes, limited a little
    - No, not limited at all

B. Diagnosis and treatment variables

1. Hypothalamic/pituitary radiation dose
    - None
    - <2000 cGy
    - 2000 – 3000 cGy
    - >3000 cGy
2. Specific anti-depressant and anti-psychotic medications including paroxetine, olanzapine, clozapine, quetiapine, thioridazine, risperidone, valproate (Follow-up 2, f2drug→drugname)
3. Psychological distress (Follow-up 2→f2psycho→ BSI questionnaire;)
    - Yes: Depression T score ≥ 63
    - No: Depression T score <63
    - Yes: Somatic distress score ≥ 63
    - No: Somatic distress score < 63
    - Yes: Anxiety score ≥ 63
    - No: Anxiety score < 63
4. Feelings about previous illness (Follow-up 2→K1-17→PTS)
    - ●Not at all or only one time
    - ●Once in a while
    - ●Half the time
    - ●Almost always
5. Cancer anxiety (Follow-up2→g20→cancranx)

- No anxiety/fears
- Small amount of anxiety/fears
- Medium amount of anxiety/fears
- A lot of anxiety/fears
- Very many, extreme anxiety/fears

6. Cancer pain (Follow-up 2→g20→cancerpn)
    - No pain
    - Small amount of pain
    - Medium amount of pain
    - A lot of pain
    - Very bad, excruciating pain

7. Medical care source (Follow-up 2 →a1which of the following health care providers did you see or talk to for medical care→nohcare, physcn, nurse, chiro, physther;)

8. Medical care site (Follow-up 2→a2 where did you receive your health care→docoff, oncclin, othclin, hospital, emroom;)

9. How many times did you see a physician (visphys; Follow-up 2→a3)
    - 0 times
    - 1-2 times
    - 3-4 times
    - 5-6 times
    - 7-10 times
    - 11-20 times

- More than 20 times

10. How many of these visits were related to your previous cancer or similar illness (CAphys; Follow-up 2→A5)

- 0 times
- 1-2 times
- 3-4 times
- 5-6 times
- 7-10 times
- 11-20 times
- More than 20 times

11. Discuss with physician or primary health care provider (Follow-up2→a6→hrtdis, osteodis, cncerdis)

Note: Here we only list independent variables for survivor group. Independent variables for sibling group will be found in baseline and follow-up 2 similarly.

Statistics

Aim 1: To test in univariable models the effect of age at diagnosis, age at questionnaire, sex, race/ethnicity, educational level, family income, health insurance, physical activity, inactivity, hypothalamic/pituitary radiation dose (none, < 2000 cGy, 2000 to 3000 cGy, > 3000 cGy), BSI depression, BSI somatic distress, BSI anxiety, and specific anti-depressant and anti-psychotic drug use including sertaline (Zoloft), paroxetine (Paxil), fluoxetine (Prozac), citalopram (Celexa), escitalopram (Lexapro), buproprion (Wellbutrin), nefazodone (Serzone), venlafaxine (Effexor), amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan), desipramine (Norpramin),

notrtiptyline (Pamelor), olanzapine (Zyprexa), aripiprazole (Abilify), ziprasidone (Zeodon), thioridazine (Mellaril), quetiapine (Seroquel), clozapine (Cloxaril), risperidone (Risperdal) and valproate (Depakote) on the frequency of overweight and obesity among CCSS participants (Table 4).

The primary outcome is the status of being overweight or obese or not, which is a binary variable measured at follow-up 2. We will do univariate logistic regression analysis to test the significance of each demographic/diagnostic/treatment variable on the risk of overweight, obesity or overweight and obesity combined. The model will include sex, age at questionnaire and race/ ethnicity each time for adjustment.

Aim 2: To develop multivariable models based on the results of the univariable analyses in **Aim 1** to determine which factors independently increase the risk of overweight or obesity in CCSS participants.

Those variables with p value < 0.1 from **Aim 1** will be included in the multiple logistic regression models. We will use three separate multiple logistic regression models to test the effects of the significant univariate predictors on the risk of overweight, obesity and the combined group with overweight or obesity (Table 5) (variables included in Table are for example only). The model will include sex, age at questionnaire and race/ ethnicity each time for adjustment regardless of their significance in the univariable model. Also, the correlations among the independent variables will be examined and variables with high correlation (p>0.70) will be identified. A decision will be made to either combine variables or choose one variable. (Table 5) (variables included in Table are for example only).

Aim 3: To compare the risk of overweight and/or obesity for CCSS participants versus CCSS siblings in the subgroups of age at questionnaire, sex, race/ethnicity, educational level, family income, health insurance, physical activity, inactivity, hypothalamic/pituitary radiation dose (none, < 2000 cGy, 2000 to 3000 cGy, > 3000 cGy), BSI depression, BSI somatic distress, BSI anxiety, specific anti-depressant and anti-psychotic drug use including sertaline (Zoloft), paroxetine (Paxil), fluoxetine (Prozac), citalopram (Celexa), escitalopram (Lexapro), buproprion (Wellbutrin), nefazodone (Serzone), venlafaxine (Effexor), amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan), desipramine (Norpramin), notrtiptyline (Pamelor), olanzapine (Zyprexa), aripiprazole (Abilify), ziprasidone (Zeodon), thioridazine (Mellaril), quetiapine (Seroquel), clozapine (Cloxaril), risperidone (Risperdal) and valproate (Depakote).

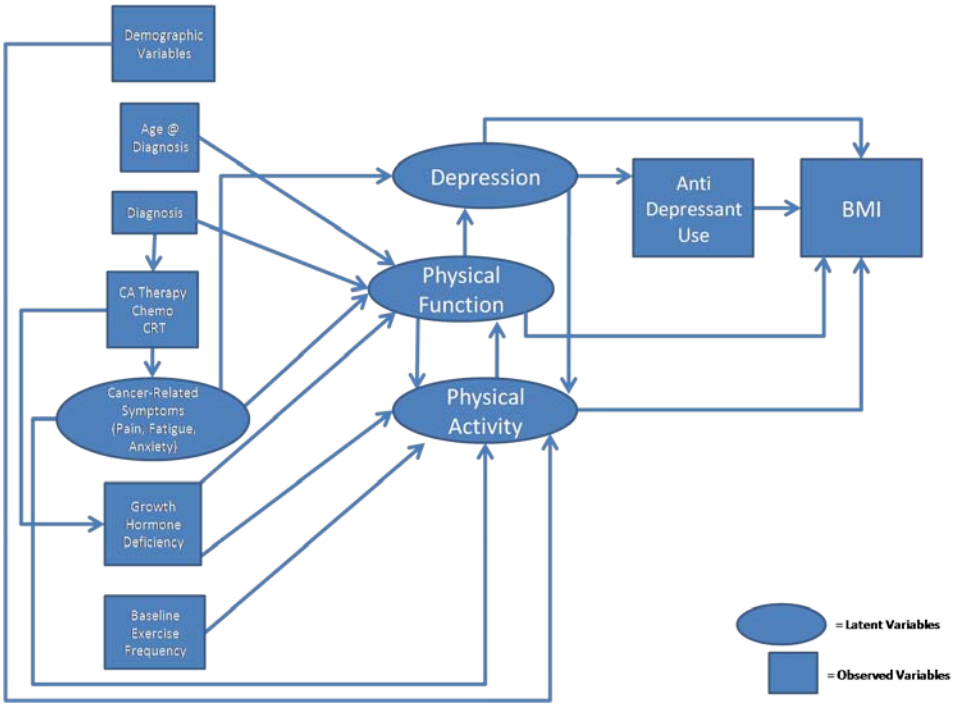
We will use univariate logistic regression analysis to compare the risk of overweight, obesity or overweight and obesity combined, for survivors versus siblings in the subgroups of each demographic/diagnostic/treatment variable such as the subgroups of sex (female, male). The model will include sex, age at questionnaire and race/ ethnicity each time for adjustment. If the prevalence<10%, odds ratio of overweight, obesity or overweight and obesity combined for survivors versus siblings will be reported in Table 6. Otherwise, relative risk will be reported. Proc Genmod (and/or macro if needed) will be applied to get relative risk.

Aim 4: To compare in two separate structural equation models (survivor and sibling) the antecedents, mediators and moderators of obesity.

The first three aims will identify those factors that independently and collectively predict obesity in survivors. Integral to the development of intervention strategies,

however, is an understanding of how these predictors may be related to one another and to what extent variables identified as direct predictors may mediate or modify other predictors in the models. Structural equation modeling (SEM) offers a simultaneous evaluation of the total structure of a multivariable model using a combination of directly observed variables and higher-order latent variables (not directly observed).

Hypotheses that are tested by structural equation modeling fall into two separate groups: measurement hypotheses, which relate observed variables to the unobserved latent factors, and structural hypotheses, which specify the causal pathways between exogenous and endogenous directly observed and latent variables. We will use Mplus 5.2[34] to: a) assess the relationship between the potential latent variables and their indicators; b) assess the fit of the hypothesized structural model by examining the relations among the latent and directly observed variables. Figure 1 illustrates a potential SEM to be tested; ultimately the SEM will be largely informed by the findings from the univariate and multivariable analyses. The following information will be



evaluated for each structural equation model: a) a non-significant X^2 test statistic measures the absolute fit of the model to the data[35] ; b) all parameters and their standard errors, a complete correlation matrix and any associated discrepancies; and, c) goodness of fit indices (CFI, TLI root mean squared error). The Comparative Fit Index (CFI) and Tucker Lewis Index (TLI) test the proportionate improvement in fit by comparing the target model to an independent base model; a value of 0.90 is minimally acceptable[36], values approximating 0.95 indicate a good fit, and values at or close to 1.000 indicate an excellent fit[37]. The Root Mean Square of Approximation (RMSEA) represents closeness of fit, and values approximating 0.06 and 0.00 demonstrate close and exact fit of the model respectively[37, 38]. For binary dependent measures, the weighted root mean square residual will also be examined; acceptable values = ≤ 0.80. In sum, goodness of fit of the model and significant parameter estimates for each path will provide support for the relationships tested.

C. Tables

Table 3. Characteristics of CCSS Survivors and Siblings

	Survivors, N=		Siblings, N=	
Variable	**No.**	**%**	**No.**	**%**
Gender				
Male				
Female				
Race/Ethnicity				
Non-Hispanic White				
Hispanic				
Non-Hispanic Black				
Other				
Education Level				
No High School or GED				
High School or GED				
Some college no bachelor's degree				
Bachelor's degree or higher				
Age at Diagnosis in years				
0 – 4				
5 – 9				
10 – 14				
15 - 20				
Age at Questionnaire in years				
5 – 15				
16 – 25				
26 – 35				
36 – 45				
46 – 55				
> 55				
Family income				
< $ 20,000/year				
≥ $ 20,000/year				
Health insurance				
No				
Yes or Canadian				
Physical activity				
No				
Yes				
Inactive				
No				
Yes				
Treatment Exposure				
Hypothalamic/pituitary radiation dose				
None				
< 2000 cGy				
2000 – 3000 cGy				
> 3000 cGy				
BSI-18 Depression Score				
< 63				
≥ 63				
BSI-18 Somatic Distress Score				
< 63				
≥ 63				
BSI-18 Anxiety Score				
< 63				

≥ 63				
Fluoxetine				
No				
Yes				
Sertraline				
No				
Yes				
Paroxetine				
No				
Yes				
Citalopram				
No				
Yes				
Escitalopram				
No				
Yes				
Bupropion				
No				
Yes				
Nefazodone				
No				
Yes				
Venlafaxine				
No				
Yes				
Amitriptyline				
No				
Yes				
Imipramine				
No				
Yes				
Doxepin				
No				
Yes				
Desipramine				
No				
Yes				
Nortriptyline				
No				
Yes				
Olanzipine				
No				
Yes				
Aripiprazole				
No				
Yes				
Ziprasidone				
No				
Yes				
Thioridazine				
No				
Yes				
Quetiapine				
No				
Yes				
Clozapine				
No				
Yes				
Risperidone				

No				
Yes				
Valproate				
No				
Yes				

Table 4: Relative Risk of Overweight or Obesity among Childhood Cancer Survivors

Variable	Overweight				Obese				Overweight or Obese			
	No.	%	RR*	CI	No.	%	RR*	CI	No.	%	RR*	CI
Gender												
Male			1.00				1.00				1.00	
Female												
Race/Ethnicity												
Non-Hispanic White			1.00				1.00				1.00	
Hispanic												
Non-Hispanic Black												
Other												
Education Level												
No High School or GED			1.00				1.00				1.00	
High School or GED												
Some college no bachelor's degree												
Bachelor's degree or higher												
Age at Diagnosis in years												
0 – 4			1.00				1.00				1.00	
5 – 9												
10 – 14												
15 - 20												
Age at Questionnaire in years												
5 – 15			1.00				1.00				1.00	
16 – 25												
26 – 35												
36 – 45												
46 – 55												
> 55												
Family income												
< $ 20,000/year			1.00				1.00				1.00	
≥ $ 20,000/year												
Health insurance												
No			1.00				1.00				1.00	
Yes or Canadian												
Physical activity												
No			1.00				1.00				1.00	
Yes												
Inactive												
No												
Yes												
Treatment Exposure												
Hypothalamic/pituitary radiation dose												
None			1.00				1.00				1.00	
< 2000 cGy												
2000 – 3000 cGy												
> 3000 cGy												
BSI-18 Depression Score												
< 63			1.00				1.00				1.00	
≥ 63												
BSI-18 Somatic Distress Score												
< 63			1.00				1.00				1.00	
≥ 63												
BSI-18 Anxiety Score												
< 63			1.00				1.00				1.00	
≥ 63												
Fluoxetine												
No			1.00				1.00				1.00	
Yes												
Sertraline												
No			1.00				1.00				1.00	
Yes												
Paroxetine												
No			1.00				1.00				1.00	

Yes												
Citalopram												
No			1.00				1.00				1.00	
Yes												
Escitalopram												
No			1.00				1.00				1.00	
Yes												
Bupropion												
No			1.00				1.00				1.00	
Yes												
Nefazodone												
No			1.00				1.00				1.00	
Yes												
Venlafaxine												
No			1.00				1.00				1.00	
Yes												
Amitriptyline												
No			1.00				1.00				1.00	
Yes												
Imipramine												
No			1.00				1.00				1.00	
Yes												
Doxepin												
No			1.00				1.00				1.00	
Yes												
Desipramine												
No			1.00				1.00				1.00	
Yes												
Nortriptyline												
No			1.00				1.00				1.00	
Yes												
Olanzipine												
No			1.00				1.00				1.00	
Yes												
Aripiprazole												
No			1.00				1.00				1.00	
Yes												
Ziprasidone												
No			1.00				1.00				1.00	
Yes												
Thioridazine												
No			1.00				1.00				1.00	
Yes												
Quetiapine												
No			1.00				1.00				1.00	
Yes												
Clozapine												
No			1.00				1.00				1.00	
Yes												
Risperidone												
No			1.00				1.00				1.00	
Yes												
Valproate												
No												
Yes												

Table 5. Multivariable Model of Relative Risk of Overweight or Obesity among Childhood Cancer Survivors

	Overweight				Obesity				Overweight or Obesity			
Characteristic	No.	%	RR	CI	No.	%	RR	CI	No.	%	RR	CI
Gender												
Male												
Female												
Race/Ethnicity												
Non-Hispanic White												
Hispanic												
Non-Hispanic Black												
Other												
Education Level												
No High School or GED												
High School or GED												
Some college no bachelor's degree												
Bachelor's degree or higher												
Age at Diagnosis in years												
0 – 4												
5 – 9												
10 – 14												
15 – 20												
Age at Questionnaire in years												
5 – 15												
16 – 25												
26 – 35												
36 – 45												
46 – 55												
> 55												
Family income												
< $ 20,000/year												
≥ $ 20,000/year												
Heath insurance												
No												
Yes or Canadian												
Physical activity												
No												
Yes												
Inactive												
No												
Yes												
Treatment Exposure												
Hypothalamic/pituitary radiation dose												
None												
< 2000 cGy												
2000 – 3000 cGy												
> 3000 cGy												
BSI-18 Depression Score												
< 63												
≥ 63												
BSI-18 Somatic Distress Score												
< 63												
≥ 63												
BSI-18 Anxiety Score												
< 63												
≥ 63												
Drug Exposure												
Paroxetine												
No												
Yes												

Table 6. Relative Risk of Overweight, Obesity or Overweight and Obesity in Childhood Cancer Survivors Compared to Siblings

	Overweight				Obesity				Overweight or Obesity			
Characteristic	No.	%	RR	CI	No.	%	RR	CI	No.	%	RR	CI
Overall												
Gender												
Male												
Female												
Race/Ethnicity												
Non-Hispanic White												
Hispanic												
Non-Hispanic Black												
Other												
Education Level												
No High School or GED												
High School or GED												
Some college no bachelor's degree												
Bachelor's degree or higher												
Age at Questionnaire in years												
5 – 15												
16 – 25												
26 – 35												
36 – 45												
46 – 55												
> 55												
Family income												
< $ 20,000/year												
≥ $ 20,000/year												
Heath insurance												
No												
Yes or Canadian												
Physical activity												
No												
Yes												
Inactive												
No												
Yes												
BSI-18 Depression Score												
< 63												
≥ 63												
BSI-18 Somatic Distress Score												
< 63												
≥ 63												
BSI-18 Anxiety Score												
< 63												
≥ 63												
Fluoxetine												
No												
Yes												
Sertraline												
No												
Yes												
Paroxetine												
No												
Yes												
Citalopram												
No												
Yes												
Escitalopram												
No												
Yes												
Bupropion												

No												
Yes												
Nefazodone												
No												
Yes												
Venlafaxine												
No												
Yes												
Amitriptyline												
No												
Yes												
Imipramine												
No												
Yes												
Doxepin												
No												
Yes												
Desipramine												
No												
Yes												
Nortriptyline												
No												
Yes												
Olanzipine												
No												
Yes												
Aripiprazole												
No												
Yes												
Ziprasidone												
No												
Yes												
Thioridazine												
No												
Yes												
Quetiapine												
No												
Yes												
Clozapine												
No												
Yes												
Risperidone												
No												
Yes												
Valproate												
No												
Yes												

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