1. WORKING STUDY TITLE: Body Mass Index Trajectories Among Adult Survivors of Childhood Central Nervous System Tumors (Proposal #20110422)

2. WORKING GROUP AND INVESTIGATORS:

2.1. Working Groups: Chronic Disease, Psychology

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3. BACKGROUND AND RATIONALE:

Second to leukemia, central nervous system tumors including brain and spinal cord tumors, are the most common cancer among children <20 years old in the United States.[1] With the increased five-year survival rate, emerging health problems related to their cancer treatment, months or even years later, are a growing concern.[2] Survivors of childhood central nervous system tumors (SCCNST) are at a higher risk for developing severe or life-threatening chronic health conditions, such as disturbances in endocrine function, in comparison to other childhood cancer survivors.[3-5]

One of the major physiological sequelae of childhood CNS tumors and cancer treatment is the development of obesity in subsets of survivors.[6-8] Morbidities related to obesity may be even greater among survivors of childhood CNS tumors due to toxicity introduced during cancer treatment and hypothalamic-pituitary injury.[9,10] For example, Adachi et al. found higher incidence of hyperlipidemia (58%) among obese (BMI>90th percentile) survivors and significantly higher levels of triglycerides and lower HDL-C compared to non-obese survivors.[10] Heikens et al. also found elevated total cholesterol/HDL cholesterol ratios, LDL cholesterol, and apo B among 26 long-term SCCNST in comparison to 29 healthy controls.[10]

Similar to cancer development itself, late effects experienced by SCCNST are not homogeneous. Although 50 to 80% of SCCNST developed obesity post-treatment in studies that included survivors diagnosed with craniopharyngioma and pituitary adenomas, [9,11,12] findings from the Childhood Cancer Survivor Study (CCSS) indicated no significant difference in BMI obtained in 1996 between survivors' (who were at least five years post diagnosis) and population norms for males and females of a similar age.[13] However, identifying potential factors related to changes in BMI over time is important for the development of lifestyle interventions that might mitigate the late effects discussed above among SCCNST. Current lifestyle interventions do not adequately address weight management needs due to the complexity of late effects experienced by SCCNST.[12,14]

To date, several additional contributing risk factors for obesity have been identified despite the heterogeneity of disease, treatment, and late effect experiences across various SCCNST.[15,16] Risk factors related to obesity development can be categorized as either biological or behavioral/psychological. Biological risk factors include female sex,[9,13] younger age at diagnosis (<10 years old),[13,17,18] and radiation or injury to the hypothalamic/pituitary region.[9,13,14,17,18] Lustig et al. found that increase in BMI was related to younger age at diagnosis, radiation dosage (>51 Gy), and presence of endocrinopathy, as well as tumor location, histology, and extent of surgery.[17] Lek et al. and Muller et al. also found that BMI at baseline was an indicator of risk for obesity.[9,18] However, these risk factors are currently limited in their ability to be modified and are not amenable to intervention.

In contrast to biological risk factors, behaviors are modifiable and physical activity (PA) is one of the behaviors that is frequently targeted within cancer-free populations for obesity prevention.[19] Recent work by Green et al. found that inactive lifestyle (no leisure-time PA in the past month) may have contributed to development of obesity among childhood cancer survivors.[20] Ness et al. also found that cancer survivors, in comparison to their siblings, were 1.2 times more likely to not meet the Centers for Disease Control and Prevention's PA guidelines during a typical week and 1.6 times more likely to report no PA during the previous month.[21] Risk factors associated with reporting of an inactive lifestyle and not meeting PA guidelines were: female sex, black race/ethnicity, older age, being underweight or obese, CNS tumors or bone cancer diagnoses, amputations, or treatment with cranial radiation.[21,22] Concurrently, evidence-based approaches for obesity management among SCCNST are gradually being developed. Adolescents who participated in a comprehensive care program (receiving intervention from a team of health providers) experienced significantly lower percentage weight gain (8.5%/year, range 3.4-14.0) than prior to participating in the program (21.4%/year, range 15.8-32.0).[23] With accumulating evidence among SSCNST indicating that being overweight or obese affects quality-of-life (QOL),[24,25] it is important to increase our understanding of the mechanisms involved in weight change.

Psychosocial distress such as anxiety and depression in the cancer-free adolescent population have also been found to be correlated with increased BMI.[26] Similarly, Green et al. also found an increased risk of obesity associated with BSI-18 somatic distress ≥63 among childhood cancer survivors.[20] Furthermore, risk of obesity development may be compounded by the use of antidepressant medications (i.e. paroxetine)[20], anti-epileptic drugs (i.e. valporate)[27] and associated decrease of physical activity while on antidepressant medications as indicated by Krull et al. after controlling for current depressive symptoms among childhood cancer survivors.[22]

Overall, common limitations of previous studies of SCCNST include retrospective study design, focus within one institution, limited number of survivors, and inclusion of only limited CNS tumor types.[7] Additionally, behavioral and psychological factors such as PA level, physical functioning ability or depression that may have affected health related QOL, were addressed in a limited number of studies. Lastly, the majority of the studies categorized BMI into normal, overweight, or obese. However, this categorization may not provide information on how these factors affect changes in BMI over time. This information is important for developing programs that would prevent SCCNST from reaching an unhealthy weight status. Thus, our primary goal is to investigate the influence of biological, behavioral, and psychological factors on the longitudinal development of BMI among adult SCCNST. We would like to use the data collected from 1996 to 2007 from the CCSS.[28] Our primary research will extend the work by Green et al.[20] by evaluating BMI trajectories instead of focusing on overweight/obesity status as the end point. With the assumption that we will find that BMI and PA are related to one another, our

secondary aim is to examine how BMI and PA "travel together" through time among SCCNST and their siblings.[29] Such comparison will provide a more detailed explanation of how BMI and PA are related to one another among SCCNST.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

We propose using data collected in 1996, 2003, and 2007 from the CCSS to address the following study aims.

The proposed study aims and hypotheses are:

1. We will first examine changes in BMI as a single outcome among survivors of childhood CNS tumors (SCCNST) as compared to cancer free siblings while examining the relation between BMI and the biological, behavior, and psychological factors.

   Hypothesis 1: We hypothesize that both the level and change in BMI will vary as a function of the time-invariant variables including survivor or sibling, gender, race/ethnicity, age at diagnosis, treatment era, treatment received, age at baseline, and self-reported GHD (verified and non-verified versions).

   Hypothesis 2: We hypothesize that the degree of BMI will vary as a function of each time-varying variables including report number of days of physical activity, BSI-18 subscales responses, use of CNS agents, educational level, and household income.

Based on the literature in the cancer-free population,[30,31] we assume that PA will be uniquely associated with changes in BMI above and beyond the other variables. Therefore, we propose the following sub aims to further examine how BMI and PA co-change over time, which is not achieved in Aim 1. The Aim 1 model will only examine whether or not PA is associated with BMI at each time point, not how PA co-changes with changes in BMI over time.

1a. We will examine the level and changes in BMI and the level and changes in physical activity (PA) as a combined outcome (bivariate outcome) among adult SCCNST while controlling for biological, behavioral, and psychological factors.

Hypothesis for aim 1a: We hypothesize that SCCNST who experience a lower PA at baseline and greater decrease in PA over time will have a greater level of BMI at baseline and greater degree of increase in BMI while controlling for biological, behavioral, and psychological factors.

1b. We will examine the level and changes in BMI and the level and changes in PA as a combined outcome (bivariate outcome) among siblings as compared to adult SCCNST while controlling for biological, behavioral, and psychological factors.

> **Hypothesis for 1b: We hypothesize** that the relation of both the level and changes in BMI and both the level and changes in PA over time will be stronger in SCCNST than in the siblings.

Aim 1b is still of interest even if PA (aim 1) or changes in PA (aim 1a) are not found to be uniquely associated with changes in BMI above and beyond the other variables. This is

because the relation between changes in BMI and changes in PA may be different for siblings in comparison to SCCNST.

5. ANALYSIS FRAMEWORK/METHODS:

The following provides a detailed description of the analysis methods for each aim. We will achieve our overall purpose, which is to examine potential factors (biological, behavioral, and psychological factors) in relation to changes in BMI over time with the hope of informing the development of lifestyle interventions that may mitigate late treatment effects compounded by changes in BMI among survivors of childhood CNS tumors.

A. Target population:

The target population consists of SCCNST and sibling participants who completed the baseline (1996), 2003 follow-up, and/or 2007 follow-up questionnaires. We will include participants who responded to ≥1 questionnaire. An advantage of analyzing longitudinal data using mixed models is that we can incorporate all available data.[32,33] Laird (1988) indicated that fitting a multilevel model and including data that are missing completely at random, covariate dependent dropout, and missing at random still produce valid and generalizable results.[32,34] Even if a participant only has one data point, the data will be used to estimate variances, but not covariances. Therefore, the variance estimate will be less biased if all available data are incorporated into the analysis.

According to Robison et al[35], 67% of the participants were ≥20 years old and 32% were <20 years old at the time of response to the baseline questionnaire. For SCCNST that are <20 years old at baseline, we will include a variable categorized as <20 and ≥20 to control for the potential age related differences in BMI trajectory.

B. Variables considered:

All variables of interest and the accompanying questions at each survey time point (time1—1996 data collection, time 2—2003 data collection, and time 3—2007 data collection) are summarized in Table 1.

B.1. Primary outcome/dependent variable

Outcome of interest/dependent variable: Body Mass Index (kg/m^2) will be calculated based on self-reported height and weight at each time point. BMI will be treated as a continuous variable. BMI as an outcome is considered as a valid approximation of body fat mass and is the preferred method to screen and classify overweight and obesity status because of its low cost and ease of calculation. In addition, we will also adjust body weight if amputation of extremities was indicated. Adjustment used by the current proposal will follow the same adjustment made by Green et al.[20] The percentage adjustment for amputation of foot will be 1.5%, below the knee amputation will be 3.7%, knee disarticulation will be 5.7%, Van Ness rotationplasty will be 7.2%, above the knee amputation will be 11.0%, and hip disarticulation or hemipelvectomy will be 16.0%.[20]

B.2. Exploratory variables (independent variables):

We will examine predictors that would affect the level and change in BMI based on previously published literature.[9,13,14,17,18,20,21] Time invariant variables will be determined as being associated with changes in BMI over time while time varying variables will be determined as being associated with BMI at each time point.

Detailed information including question that is associated with each variable, the source of the questionnaire, and coding plans are presented in **Appendix A**. The following is a summary of the exploratory variables we will evaluate to build the final model.

B.2.1. Biological and treatment related variables

1. Gender
2. Race/ethnicity
3. Age at diagnosis (We will use the same categories as proposed by Brinkman et al. concept proposal #11-07. The age categories are 0-6, 7-10, 11-15, 16-20 yrs old.)
    a. We will also conduct an exploratory analysis to evaluate pre/post menarche with BMI among female participants.
4. Treatment era (We will use similar categories as presented by Kirchhoff et al[36]: 1970-1973, 1974-1997, 1978-1981 and 1982-1986)
5. Treatments received: Chemotherapy, Cranial radiation therapy (CRT), and surgery (Cranial radiation therapy dosage will be determined by using the region 2 variable, which included the maximum dose to at least 50% of segment 2. Based on the literature, radiation to the hypothalamic and pituitary regions seemed to affect changes in BMI among the subset of childhood tumor survivors therefore we will focus on using region 2 CRT dosage data. However, we will also request for maximum CRT dosage data for all other regions to explore the possible effects.
6. Self-report of growth hormone deficiency (GHD) at 1996 and 2007 and the externally validated GHD information at baseline in 1996.

    We will compare the self-report of GHD at 1996 to the externally validated GHD information collected at baseline in 1996. We wanted to examine whether or not the different measurement may affect the estimation of the relation between GHD and changes in BMI.

B.2.2. Behavioral variables

1. Physical function
2. Report of number of days of physical activity (vigorous and moderate combined)

B.2.3. Psychological variables

1. Psychological distress [Brief Symptom Inventory (BSI)-18 subscales—depression, somatic distress, and anxiety score of ≥63 vs. <63]
2. Use of specific central nervous system (CNS) agents.[37] Weight gain has been shown to be a side effect of the CNS agents listed below.[20,38-41]
    a. Anti-psychotic drugs: Olanzapine (Zyprexa), risperidone (Risperdal), auetiapine (Seroquel, Xeroquel, Ketipinor), clozapine (Clozaril), and aripiprazole (Abilify)[38,39]
    b. Anti-depressant drugs: Imipramine (Tofranil), amitriptyline (Elavil), SSRIs [fluoxetine (Prozac, Rapifux, Sarafem, Selfemra), sertraline (Zoloft), paroxetine (Paxil)], mirtazapine (Remeron, Aranza, Zispin), escitalopram (Lexapro),[42] and citalopram (Celexa)[38]
    c. Anti-convulsant drugs: Valproic acid (Depakene, Depacon, Stavzor, Valproic), carbamazepine (Tegretol, Equetro, Epitol), divalproex (Depakote), lamotrigine (Lamictal), gabapentine (Neurontin, Gralise, Fanatrex), lithium, and vigabatrin (Sabril).[38,40]

    A recent systematic review indicated that the risk of being overweight and obese is predicted by exposure to multiple antipsychotic medications,[39] therefore we planned

to create an ordered categorical variable to indicate the number of specific CNS agents used to simply the analysis. However, we will also conduct exploratory analysis using the each CNS agent listed above. We will include CNS agents that are used by more than 30 people in the analysis which is similar to the technique used by Green and colleagues.[20]

B.2.4. Other socioeconomic and time related variables

1. Education level
2. Household income
3. Age at baseline (yrs)

C. Analytic approach and example tables:

Baseline summary statistics will be evaluated between SCCNST and sibling controls using p-values obtained from the generalized linear models based on generalized estimating equations (GEE) that utilize robust variance estimates to account for intra-family correlation between survivors and siblings. Summary of baseline characteristics of study participants will be presented in Table 1. For descriptive purposes, the BMI at baseline, 2003 follow up and 2007 follow up will be presented as percentage of overweight and obesity (Table 2).

Table 1. Baseline (1996) characteristics of Survivors of childhood CNS tumors and Cancer-Free Sibling participated in CCSS.

	CNS tumors		**Sibling**		p
	N	**%**	**N**	**%**	
Biological					
Gender Male Female					
Race/Ethnicity White Black American Indian or Alaskan Native Asian or Pacific Islander Other Hispanic					
Age at dx 0-6 7-10 11-15 16-20			N/A	N/A	N/A
Treatment era 1970-1973 1974-1977 1978-1981 1982-1986			N/A	N/A	N/A
Surgery only Yes No			N/A	N/A	N/A

Chemotherapy None Any Anthracycline Alkylating Agents Antimetabolites & Corticosteroids Vinca Alkaloids & Heavy Metal			N/A	N/A	N/A
Accumulated CRT No CRT <29.9 Gy 30-39.9 Gy 40-49.9 Gy 50-49.9 Gy ≥60 Gy			N/A	N/A	N/A
GHD (self-report) Yes No			N/A	N/A	N/A
Externally validated GHD Yes No			N/A	N/A	N/A
Behavioral					
Physical Function Limitation Yes No					
PA levels of at least 20 minutes 0 day 1 day 2 day 3 day 4 day 5 day 6 day 7 day					
Psychological					
BSI-18 Anxiety T ≥ 63 T < 63					
BSI-18 Depression T ≥ 63 T < 63					
BSI-18 Somatization T ≥ 63 T < 63					
BSI-18 GSI T ≥ 63 T < 63					
Use of specific CNS agents 0 1			N/A	N/A	N/A

2 3+					
Other socioeconomic related variables					
Education level No HS or GED HS or GED Some college College and higher					
Family Income <$9,999K $10K-$19K $20K-$39K $40K-$59K >$60K					
Age at baseline (mean, SD)					
Pre-menarche					
Post-menarche					

Table 2. Mean BMI and Prevalence of Overweight and Obesity among survivors of childhood CNS tumors and sibling controls at baseline, 2003 and 2007 follow-up.

	Baseline					2003 Follow-up					2007 Follow-up				
Characteristics	N	Mean BMI	SD	Overweight (%)	Obese (%)	N	Mean BMI	SD	Overweight (%)	Obese (%)	N	Mean BMI	SD	Overweight (%)	Obese (%)
Female															
Survivor															
Sibling															
Male															
Survivor															
Control															

We will build a univariate three-level growth model of BMI for aim 1 and a bivariate three-level growth model of BMI and PA for aim 1b. The three-level growth model will allow us to account for the fact that SCCNST and their siblings are nested within a family. In order to conduct the three-level analysis, we are assuming that the ages of the siblings are not far apart from the ages of the SCCNST in order to ensure that the growth trajectories are comparable.

Prior to conducting the analyses to address the aims, we will evaluate whether or not the age of siblings of SCCNST and SCCNST are similar in range. If the age between siblings of SCCNST and SCCNST is too far apart, then an independent sample of sibling controls that are matched on age, gender, and race/ethnicity will be used. These sibling controls will be selected such that they do not include the siblings of SCCNST to simplify the analysis methodology. If we use an independent sample of sibling controls, then we will conduct a univariate two-level growth model of BMI for aim 1 and a bivariate two-level growth model of BMI and PA for aim 1b. Analytical strategy for two-level growth model of BMI and PA with non-sibling controls will be similar to the strategies presented below.

C.1. Specific Aim 1 We will first examine changes in BMI as a single outcome among survivors of childhood CNS tumors (SCCNST) as compared to cancer free siblings while examining the relation between BMI and the biological, behavior, and psychological factors.

Hypothesis 1: We hypothesize that both the level and change in BMI will vary as a function of time-invariant variables including survivor or sibling, gender, race/ethnicity, age at diagnosis, treatment era, treatment received, age at baseline, and self-reported GHD (verified and non-verified versions).

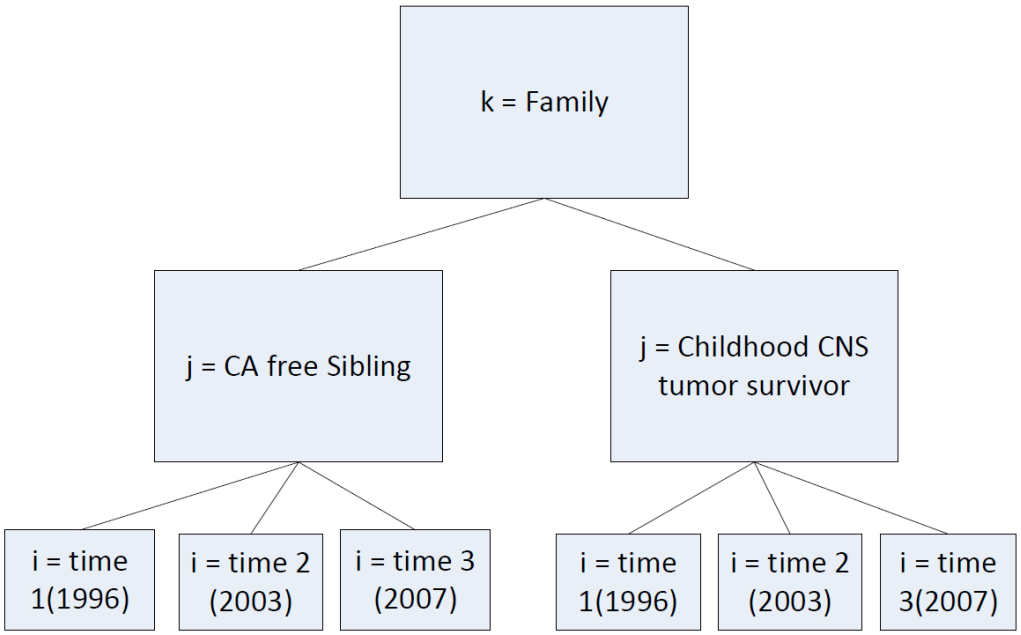
Hypothesis 2: We hypothesize that the degree of BMI will vary as a function of each time-varying variables including report number of days of physical activity, BSI-18 subscales responses, use of CNS agents, educational level, and household income.

Prior to building the multilevel model (MLM) to address aim 1, the data will be restructured from a wide format (person-level) to a long format (person-period).[29,43] The wide format is the usual format where each person has a single record with multiple variables, while the long format will consist of multiple records per individual, one for each assessment time period (Example presented in Appendix B1).

We will use the SAS statistical software (Cary, NC) to explore and build the MLM that will identify risk factors that influence the main outcome of interest. We chose MLM as our analytical method to evaluate the changes in BMI because the method considers the repeated measurements on an individual in a hierarchical structure, where the measurements are considered as nested within an individual.[29,43] In other words, the MLM method will allow us to examine the individual variability (within-person changes over time) and person-to-person variability (between-person changes over time) so we can understand the changes in BMI on a continuum within and between persons.[29,43] The goal is to build a parsimonious model that would explain the observed variability within and between individual changes in BMI. Thus, for variable selections, we will use a backward selection method where the full conditional model will be evaluated. The full conditional model will include all the variables we would like to examine. Second, we will remove variables one-at-a-time.

We will assume simple linear trajectory for modeling the changes in BMI based on previous literature.[14,17] With the assumption that the age of siblings of SCCNST and SCCNST are similar in range, the following is a schematic of the three-level data structure (Figure 1). The three levels represented as time nested within individual (sibling or survivor) and individual nested within family. We followed the notations as presented by Raudenbush and Bryk (2002)[44] and Curran et al. (2012)[29] for general growth model representations presented below.

Figure 1. Schematic of three-level data structure assuming that the age of siblings of SCCNST and SCCNST are similar in range.



Level 1: i = 1, 2,..., n_{jk} survey times within individuals j in families k;
Level 2: j = 1, 2,…, J_k individuals in families k; and
Level 3: k = 1, 2,…,k families

Conditional Models

General Level 1 Model: Within each survey time, we will model the individual's BMI as a function of the individual-level exploratory predictors with a random individual-level error (time-varying covariates):

$y_{ijk} = \pi_{0jk} + \pi_{1jk}\alpha_{1jk} + \pi_{2jk}\alpha_{2jk} + \ldots + \pi_{pjk}\alpha_{pjk} + e_{ijk}$, where

$\mathbf{y_{ijk}}$: the BMI of individuals at each time point (i) for each individual (j) and family (k);
$\boldsymbol{\pi_{0jk}}$: the random intercept for individual (j) in family (k);
$\boldsymbol{\alpha_{pjk}}$: p = 1,...,P individual behaviors and time-varying characteristics that predict BMI;
$\boldsymbol{\pi_{pjk}}$: p = 0,...,P are the corresponding level-1 coefficients that indicate the direction and strength of association between each individual behavior and time-varying characteristics at each time point, α_p, and the outcome for individuals jk; and
$\boldsymbol{e_{ijk}}$: level-1 random effect that indicated the deviation of individual ijk's BMI from the predicted BMI based on the individual-level model. These residual are assumed to be normally distributed with a mean of 0 and variance σ^2 .

General Level 2 Model: Each of the regression coefficients in the time-related level, which includes the intercept, can be viewed as fixed, non-randomly varying, or random. The following general level 2 model represents the model to account for variation between individuals within families. For each individual behavior and time-varying characteristic effect, π_{pjk},

$\pi_{pjk} = \beta_{p0k} + \sum_{q=1}^{Q_p} \beta_{pqk} X_{qjk} + r_{pjk}$, where

p=0,…,P

$\boldsymbol{\beta_{p0k}}$: the intercept for family k in modelling the individual effect π_{pjk};

$\boldsymbol{X_{qjk}}$: individual characteristics that are time-invariant used as a predictor of the individual effect π_{pjk} (each π_p may have a unique set of these level-2 predictors X_{qjk} , q = 1, …, Q_p);

$\boldsymbol{r_{pjk}}$: level-2 random effect that indicated the deviation of individual jk's level 1 coefficient, π_{pjk}, from tis predicted value base on the individual-level model. Furthermore, the random effects are assumed to be correlated, multivariate normally distributed with a mean of 0 and with variance-covariance matrix $\boldsymbol{T}$, $Var \begin{matrix} u_{oi} \\ u_{1i} \end{matrix} = \begin{matrix} \tau_{00} & \tau_{01} \\ \tau_{10} & \tau_{11} \end{matrix} = \boldsymbol{T}$.

General Level 3 Model: Similar modeling process is repeated at the family level. Each level-3 "outcome" (each of the β_{pq} coefficient) may be predicted by the family-level characteristic and can be viewed as fixed, no-randomly varying, or random,

$\beta_{pqk} = \gamma_{pq0} + \sum_{s=1}^{S_{pq}} \gamma_{pqs} W_{sk} + u_{pqk}$, where

$\boldsymbol{\gamma_{pq0}}$: the intercept in the family-level model for β_{pqk};

$\boldsymbol{W_{sk}}$: family characteristics used as a predictor for the family effect, β_{pqk} (each β_{pq} may have a unique set of level-3 predictors, W_{sk}, s = 1,…, S_{pq};

$\boldsymbol{\gamma_{pqs}}$: corresponding level-3 coefficient that represents the direction and strength of association between family characteristic W_{sk} and β_{pqk} ; and there are $\sum_{p=0}^{p}(Q_p+1)$ equations in the level-3 model.

$\boldsymbol{u_{pqk}}$: level-3 random effect that indicated the deviation of family k's level-2 coefficient, β_{pqk}, from the its predicted value based on the family-level model. Furthermore, the residuals (random effects) are assumed to be multivariate normally distributed with a mean of zero, some variance, and covariance among all pairs of elements.

The following is a summary table (Table 3) that clarifies how each variable of interest will be used to address aim 1 and hypotheses 1 and 2.

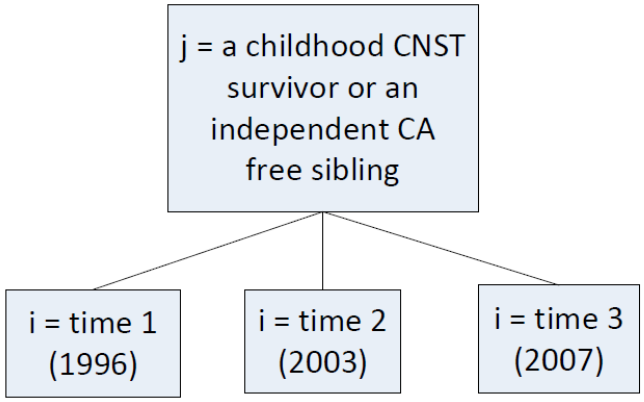
Table 3. Summary of how each parameters will address hypotheses 1 and 2 of aim 1.

	Exploratory Variables	Hypothesis 1 for Aim 1	Hypothesis 2 for Aim 1
Time-varying (aka: time specific) covariates (Relate to the BMI at each time point)			
Physical function	X		X
Report # of days of physical activity			X
BSI-18 subscales	X		X
Use of specific CNS agents	X		X
Education level	X		X
Household income	X		X
Time-invariant covariates (Affects the intercept, the level of BMI at baseline)			
Survivor and Cancer Free Sibling of Survivor		X	
Gender		X	
Race/ethnicity		X	
Age at diagnosis		X	
Treatment era		X	
Treatments received		X	
Self-reported GHD		X	
GHD diagnosis (externally validated data)		X	
Time-invariant * Time variables (Affects the slope, the change in BMI)			
Survivor and Cancer Free Sibling of Survivor*Time		X	
Gender*Time		X	
Race/ethnicity*Time		X	
Age at diagnosis*Time		X	
Treatment era*Time		X	
Treatments received*Time		X	
Self-reported GHD*Time		X	
GHD diagnosis (externally validated data)*Time		X	

We will use the three common criterion of goodness of fit used in multilevel models (deviance, Akaike's Information Criterion, and Bayesian Information Criterion) to assess the appropriateness of the functional form, optimal error structure for the residuals, or the existence of quadratic components.[29,45]

If our assumption is incorrect regarding the closeness of age range between siblings of SCCNST and SCCNST after the data evaluation, then we will build a two-level growth model using an independent sample of sibling controls that are matched on age, gender, and race/ethnicity (Figure 2). The two levels represented as time nested within individual (independent sample of sibling or survivor).

Figure 2. Schematic of two-level data structure.



Level 1: i = 1, 2,..., n_j survey times within individuals j;and
Level 2: j = 1, 2,…, J individuals (survivors of independent sample of cancer free sibling)

Conditional Models

General Level 1 Model: Within each survey time, we will model the individual's BMI as a function of the individual-level exploratory predictors with a random individual-level error (time-varying covariates):

$y_{ij} = \pi_{0j} + \pi_{1j}\alpha_{1j} + \pi_{2j}\alpha_{2j} + \ldots + \pi_{pj}\alpha_{pj} + e_{ij}$, where

$\mathbf{y_{ij}}$: the BMI of individuals at each time point (i) for each individual (j);
$\boldsymbol{\pi_{0j}}$: the random intercept for individual (j);
$\boldsymbol{\alpha_{pj}}$: p = 1,...,P individual behaviors and time-varying characteristics that predict BMI;
$\boldsymbol{\pi_{pj}}$: p = 0,...,P are the corresponding level-1 coefficients that indicate the direction and strength of association between each individual behavior and time-varying characteristics at each time point, α_p, and the outcome for individuals j; and
$\boldsymbol{e_{ij}}$: level-1 random effect that indicated the deviation of individual ij's BMI from the predicted BMI based on the individual-level model. These residual are assumed to be normally distributed with a mean of 0 and variance σ^2 .

General Level 2 Model: Each of the regression coefficients in the time-related level, which includes the intercept, can be viewed as fixed, non-randomly varying, or random. The following general level 2 model represents the model to account for variation between individuals. For each individual behavior and time-varying characteristic effect, π_{pj},

$\pi_{pj} = \beta_{p0} + \sum_{q=1}^{Q_p} \beta_{pq} X_{qj} + r_{pj}$, where

p=0,…,P
$\boldsymbol{\beta_{p0}}$: the intercept for the individual effect π_{pj};
$\boldsymbol{X_{qj}}$: individual characteristics that are time-invariant used as a predictor of the individual effect π_{pj} (each π_p may have a unique set of these level-2 predictors X_{qj} , q = 1, …, Q_p);

$\boldsymbol{r_{pj}}$: level-2 random effect that indicated the deviation of individual j's level 1 coefficient, π_{pj}, from is predicted value base on the individual-level model. Furthermore, the random effects are assumed to be correlated, multivariate normally distributed with a mean of 0 and with variance-covariance matrix T, $Var \begin{matrix} u_{oi} \\ u_{1i} \end{matrix} = \begin{matrix} \tau_{00} & \tau_{01} \\ \tau_{10} & \tau_{11} \end{matrix} = T$.

The following is a summary table (Table 4) that clarifies how each variable of interest will be used to address aim 1 and hypotheses 1 and 2 if we are using an independent sample of cancer-free sibling controls.

Table 4. Summary of how each parameters will address hypotheses 1 and 2 of aim 1 if we are using an independent sample of cancer-free sibling controls.

	Exploratory Variables	Hypothesis 1 for Aim 1	Hypothesis 2 for Aim 1
Time-varying (aka: time specific) covariates (Relate to the BMI at each time point)			
Physical function	X		X
Report # of days of physical activity			X
BSI-18 subscales	X		X
Use of specific CNS agents	X		X
Education level	X		X
Household income	X		X
Time-invariant covariates (Affects the intercept, the level of BMI at baseline)			
Survivor and Not Matched/independent Cancer Free Sibling		X	
Gender		X	
Race/ethnicity		X	
Age at diagnosis		X	
Treatment era		X	
Treatments received		X	
Self-reported GHD		X	
GHD diagnosis (externally validated data)		X	
Time-invariant * Time variables (Affects the slope, the change in BMI)			
Survivor and Not Matched/independent Cancer Free Sibling *Time		X	
Gender*Time		X	
Race/ethnicity*Time		X	
Age at diagnosis*Time		X	
Treatment era*Time		X	
Treatments received*Time		X	
Self-reported GHD*Time		X	
GHD diagnosis (externally validated data)*Time		X	

C.2. Specific Aim 1a: We will examine the level and changes in BMI and the level and changes in physical activity (PA) as a combined outcome (bivariate outcome) among adult SCCNST while controlling for biological, behavioral, and psychological factors.

> **Hypothesis for aim 1a:** We hypothesize that SCCNST who experience a lower PA at baseline and greater decrease in PA over time will have a greater level of BMI at baseline and greater degree of increase in BMI while controlling for biological, behavioral, and psychological factors.

To address secondary Aim 1a, we will conduct a bivariate two-level growth model of BMI and PA. The Aim 1a model is an expansion of the univariate model that was conducted in Aim 1 to the multivariate setting. In Aim 1a we will be able to evaluate how changes in BMI are related to changes in PA simultaneously within individuals and across individuals.

Prior to model building, we will need to add three key elements into the data. The first is the addition of three new variables.[29,46] These include dv_{ti}, δ_y and δ_z.[29]

dv_{ti} = the synthesized criterion variable that includes the BMI (y) and PA (z) outcomes for each individual at each time point.
δ_y and δ_z = indicator variables that would indicate either element of dv_{ti} for outcome **y** (BMI) or outcome **z** (PA). Essentially these indicator variables would allow for each outcome to move in and out of the equation. For example, when $\delta_y = 0$ and $\delta_z = 1$, this represent the outcome of z (PA). An example of how the data will be structured is presented in the **Appendix B2**.

For both aim 1a and 1b, our plan is conduct exploratory analyses. However, if we are able to find interesting findings, we will be cautious in the interpretations and discussion of the inference (confidence intervals, p-values) of the point estimates we will obtain on the variance-covariance for random coefficients based on the Wald tests. As indicated by Stram and Lee (1994), there may be issues with restricted parameter space.[47] If needed, we will bootstrap the model, taking 5000 sample of size n with replacement and estimate the variances of and the covariances between the slopes (or intercepts) using mixed for each replication. If it the siblings are independent from the childhood CNSTS, then the sample will be on the individual level. If the siblings are related to the childhood CNSTS, then the sample will be based on the family level. Furthermore, we will then form a 95% confidence interval about the variance and covariance parameters based on those 5000 estimates. If the cancer free siblings are not independent from the childhood CNSTS, joint confidence interval about the variance and covariance parameters will be formed. If the CI does not contain zero, we can say the variance or covariance differs from zero. We can use the mean or median, depending on the distributional form of the 5000 estimates, to obtain our expected variance or covariance.

The following is a summary table (Table 5) that clarifies how each variable of interest will be used to address our aim 1a and hypothesis for aim 1a. The random slope and random intercept are of interest.

Table 5. Summary of how each parameter will address the scientific questions for hypothesis for aim 1a.

	Controlled Variables	Hypothesis aim 1a
Assess the random intercept and random slope and the correlations		
BMI intercept variance	X	
BMI slope variance	X	
PA intercept variance	X	
PA slope variance	X	
Covariance of BMI intercept and PA intercept		X
Covariance of BMI slope and PA slope		X
Covariance of BMI intercept and PA slope	X	
Covariance of BMI slope and PA intercept	X	
Time-varying Variables		
Physical function	X	
BSI-18 subscales	X	
Use of specific CNS agents	X	
Education level	X	
Household income	X	
Time-invariant variables (Affects the intercept, the level of BMI and PA)		
Gender	X	
Race/ethnicity	X	
Age at diagnosis	X	
Treatment era	X	
Treatments received	X	
Self-reported GHD	X	
GHD diagnosis (externally validated data)	X	
Time-invariant * Time (Affects the slope, the changes of BMI and PA)		
Gender*Time	X	
Race/ethnicity*Time	X	
Age at diagnosis*Time	X	
Treatment era*Time	X	
Treatments received*Time	X	
Self-reported GHD*Time	X	
GHD diagnosis (externally validated data)*Time	X	

Below are the general forms of conditional bivariate two-level growth models using notations as presented by Raudenbush and Bryk (2002) and Curran et al. (2012).[29,44]

Level 1: t = 1, 2,..., n_{ti} survey times within individuals i; and
Level 2: i= 1, 2,…, I individuals (survivors only)
K=1 and 2 (k represent the outcomes of interest)

Bivariate Conditional Models

General Level 1 Models for BMI (k = 1 also shown as y) and PA (k = 2, also shown as z): Within each survey time, we will model the individual's BMI and PA as a function of individual-level exploratory predictors with a random individual-level error (time-varying covariates):

$y_{ti}^{k} = \pi_{oi}^{k} + \pi_{1i}^{k}\alpha_{1i}^{k} + \pi_{2i}^{k}\alpha_{2i}^{k} + \ldots + \pi_{pi}^{k}\alpha_{pi}^{k} + e_{ti}^{k}$, where

y_{ti}^{k} : the BMI and PA of individuals at each time point (t) for each individual (i);
π_{oi}^{k} : the random intercept for individual (i);
α_{1i}^{k} : p = 1,..., P individual behaviors and time-varying characteristics that predict BMI and PA;
π_{pi}^{k} : p= 0,..., P are corresponding level-1 coefficients that indicate the direction and strength of association between each individual behaviors and time-varying characteristics at each time point, α_{p}^{k}, and the outcome for individuals j; and
e_{ti}^{k} : level-1 random effect that indicated the deviation of individual ij's BMI from the predicted BMI based on the individual-level model.

General Level 2 Models: Each of the regression coefficients in the time-related level, which includes the intercept, can be viewed as fixed, non-randomly varying, or random. The following general level 2 model represents the model to account for variation between individuals within families. For each individual behavior and time-varying characteristic effect, π_{pi}^{k},

$\pi_{pi}^{k} = \beta_{p0}^{k} + \sum_{q=1}^{Q_p^k} \beta_{pq}^{k} X_{qi}^{k} + r_{pi}^{k}$, where

β_{p0}^{k} : the intercept for the individual effect π_{pi}^{k} ;
X_{qi}: individual characteristics that are time-invariant used as a predictor of the individual effect π_{pi}^{k} (each π_{p}^{k} may have a unique set of these level-2 predictors X_{qi}^{k} , q = 1, …, Q_p^k);
r_{pi}^{k}: level-2 random effect that indicated the deviation of individual i's level 1 coefficient, π_{pi}^{k} , from is predicted value base on the individual-level model.

General expression for a two-level conditional multivariate model:

$\boldsymbol{dv_{ti}} = \sum_{k=1}^{k} \delta_k [(\beta_{p0}^{k} + \sum_{q=1}^{Q_p^k} \beta_{pq}^{k} X_{qi}^{k}) + (r_{pi}^{k} + e_{ti}^{k})]$

C3. Specific Aim 1b: We will examine the level and changes in BMI and the level and changes in PA as a combined outcome (bivariate outcome) among siblings as compared to adult SCCNST while controlling for biological, behavioral, and psychological factors.

> **Hypothesis for 1b:** We hypothesize that the relation of both the level and changes in BMI and both the level and changes in PA over time will be stronger in SCCNST than in the siblings.

With the assumption that the ages of the siblings are not far apart from the ages of the SCCNST, an additional variable "j" will be added that indicate the group membership (survivor or sibling) to the bivariate three-level growth model of BMI and PA. Other key elements will be similar to what was presented in aim 1a.

dv_{tij} = the synthesized criterion variable that includes the BMI (y) and PA (z) outcomes for each individual at each time point.
$\delta_y \; and \; \delta_z$ = indicator variables that would indicate either element of dv_{tij} for outcome **y** (BMI) or outcome **z** (PA). Essentially these indicator variables would allow for each outcome to move in and out of the equation. For example, when $\delta_y = 0$ and $\delta_z = 1$, this represent the outcome of PA (z_{tij}).

The following is a summary table (Table 6) that clarifies how each variable of interest will be used to address our aim 1b and hypothesis for 1b. The random slope and random intercept are of interest.

Table 6. Summary of how each parameters will address the scientific questions for hypothesis for aim 1b.

	Controlled Variables	Hypothesis aim 1b
Assess the random intercept and random slope and the correlations		
BMI intercept variance	X	
BMI slope variance	X	
PA intercept variance	X	
PA slope variance	X	
Covariance of BMI intercept and PA intercept		X
Covariance of BMI slope and PA slope		X
Covariance of BMI intercept and PA slope	X	
Covariance of BMI slope and PA intercept	X	
Time-varying Variables		
Physical function	X	
BSI-18 subscales	X	
Use of specific CNS agents	X	
Education level	X	
Household income	X	
Time-invariant variables (Affects the intercept, the level of BMI and PA)		
Survivor and Matched/not matched cancer free sibling		X
Gender	X	
Race/ethnicity	X	
Age at diagnosis	X	
Treatment era	X	
Treatments received	X	
Self-reported GHD	X	
GHD diagnosis (externally validated data)	X	
Time-invariant * Time (Affects the slope, the changes of BMI)		
Survivor and Matched or Not Matched Cancer Free Sibling*Time		X
Gender*Time	X	
Race/ethnicity*Time	X	
Age at diagnosis*Time	X	
Treatment era*Time	X	
Treatments received*Time	X	
Self-reported GHD*Time	X	
GHD diagnosis (externally validated data)*Time	X	

Below is the general form of conditional bivariate three-level growth models using notations as presented by Raudenbush and Bryk (2002) and Curran et al. (2012).[29,44]

Level 1: t = 1, 2,..., n_{ti} survey times within individuals I in families j; and
Level 2: i = 1, 2,…, i individuals in families k; and
Level 3: j = 1, 2,…, families

K=1 and 2 (k represent the outcomes of interest)

Bivariate Conditional Models

General Level 1 Models for BMI (k = 1 also shown as y)and PA (k = 2, also shown as z): Within each survey time, we will model the individual's BMI and PA as a function of individual-level exploratory predictors with a random individual-level error:

$y^{k}_{tij} = \pi^{k}_{oij} + \pi^{k}_{1ij}\alpha^{k}_{1ij} + \pi^{k}_{2ij}\alpha^{k}_{2ij} + \ldots + \pi^{k}_{pij}\alpha^{k}_{pij} + e^{k}_{tij}$, where

y^{k}_{tij} : the BMI and PA of individuals at each time point (t) for each individual (i);
π^{k}_{oij} : the intercept for individual (i);
α^{k}_{1ij}: p = 1,..., P individual behaviors and time-varying characteristics that predict BMI and PA;
π^{k}_{pij} :p = 0,..., P are the corresponding level-1 coefficients that indicate the direction and strength of association between each individual behaviors and time-varying characteristics at each time point,π^{k}_{p}, and the outcome for individuals j; and
e^{k}_{tij} : level-1 random effect that indicated the deviation of individual ij's BMI from the predicted BMI based on the individual-level model.

General Level 2 Model: Each of the regression coefficients in the time-related level, which includes the intercept, can be viewed as fixed, non-randomly varying, or random. The following general level 2 model represents the model to account for variation between individuals within families. For each individual behavior and time-varying characteristic effect, π^{k}_{pij},

$\pi^{k}_{pij} = \beta^{k}_{p0j} + \sum_{q=1}^{Q^{k}_{p}} \beta^{k}_{pqj} X^{k}_{qij} + r^{k}_{pij}$, where

p = 0,..., P
β^{k}_{p0j} : the intercept for the individual effect π^{k}_{pij} ;
X^{k}_{qij} : individual characteristics that are time-invariant used as a predictor of the individual effect π^{k}_{pij} (each π^{k}_{p} may have a unique set of these level-2 predictors X^{k}_{qij} , q = 1, …, Q^{k}_{p});
r^{k}_{pij}: level-2 random effect that indicated the deviation of individual jk's level 1 coefficient, π^{k}_{pi} , from is predicted value base on the individual-level model.

General Level 3 Model: Similar modeling process is repeated at the family level. Each level-3 "outcome" (each of the β^{k}_{pqj} coefficient) may be predicted by the family-level characteristic and can be viewed as fixed, no-randomly varying, or random,

$\beta^{k}_{pqj} = \gamma^{k}_{pq0} + \sum_{s=1}^{S^{k}_{pq}} \gamma^{k}_{pqs} W^{k}_{sj} + u^{k}_{pqj}$, where

γ_{pq0}^{k}: the intercept in the family-level model for β_{pqj}^{k};

W_{sj}^{k} : family characteristics used as a predictor for the family effect, β_{pqj}^{k} (each β_{pq}^{k} may have a unique set of level-3 predictors, W_{sj}^{k} , s = 1,..., S_{pq}^{k};

γ_{pq0}^{k} : corresponding level-3 coefficient that represents the direction and strength of association between family characteristic W_{sj}^{k} and β_{pqj}^{k}; and there are $\sum_{p=0}^{p^k}(Q_p^k+1)$ equations in the level-3 model.

u_{pqj}^{k}: level-3 random effect that indicated the deviation of family j's level-2 coefficient, β_{pqj}^{k}, from the its predicted value based on the family-level model.

General expression for a three-level conditional multivariate growth model:

$$\boldsymbol{dv_{tij}} = \sum_{k=1}^{k} \delta_k[(\gamma_{pq0}^{k} + \sum_{s=1}^{S_{pq}^{k}} \gamma_{pqs}^{k} W_{sj}^{k}) + (u_{pqj}^{k} + r_{pi}^{k} + e_{ti}^{k})]$$

C.4. Anticipated Sample Size

According to Harrell,[48] we will need approximately 300 participants (# participants = 15x # independent variables) for multivariable regression models. We anticipate that we will have a large enough sample size to conduct the analyses based on the number of survivors who completed the BSI-18 at each time point. According to Brinkman et al., there are approximately 403 CNS tumor survivors who are at least 18 years of age at baseline and completed BSI-18 at baseline, 2003, and 2007 (Brinkman et al. Concept proposal #11-07).

6. SPECIAL CONSIDERATIONS:

6.1. Dr. Wenyaw Chan at the University of Texas, School of Public Health has agreed to oversee the statistical analyses performed by Maria Chang. Dr. Wendy Leisenring, from CCSS, will also supervise the statistical analyses, review analyses, and methods prior to manuscript submission to the publication committee.

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8. Appendices:

Appendix A. Variables of interest (dependent and independent) and the accompanying questions at each time point

Variables/Questionnaire	Baseline (<18 years old)	Baseline (>18 years old)	2003 FU	2007 FU	Coding Plan
DOB	A.1. What is your child's date of birth?	A.1. What is your date of birth?	N/A	N/A	Use to calculate age at baseline
Gender	A.2 What is his/her sex?	A.2 What is your sex?	N/A	N/A	Male/Female
Race/ethnicity	A.4 To which one of the following groups does he/she belong? A.4 a Is he/she Hispanic?	A.4 To which one of the following groups do you belong? A.4a Are you Hispanic?	N/A	N/A	White, Black, American Indian or Alaskan Native, Asian or Pacific Islander, Other, Hispanic
Education level	O.1 What is the highest grade or level of schooling that your child has completed? O.2 If your child completed HS, did he/she receive a regular HS diploma or receive a HS equivalence certificate, also called a GED?	O.1 what is the highest grade or level of schooling that you have completed? O.2 If you have completed HS, did you receive a regular HS diploma or did you receive a HS equivalence certificate, also called a GED?	1. What is the highest grade or level of schooling you have now completed?	A3. What is the highest grade or level of schooling you have now completed?	Categorical responses, but will be treated as a continuous variable (1-8 yr=0, 9-12 yr=1, completed HS=2, training after HS, other than college=3, some college=4, College graduate=5, Post graduate level=6, Other=7)
Age at diagnosis	P.1 Age of Onset (yrs) & Medical Record	P.1 Age of Onset (yrs) & Medical Record	N/A	N/A	Categorized as: 0-6, 7-10, 11-15, and 16-20.
Pre/post menarche	E.16 FEMALES—Has she ever had a menstrual periods?	E.16 FEMALES—Has you ever had a menstrual periods?	N/A	F.13 FEMALES—Have you had a menstrual period naturally, that is, without needing hormones or medication?	Categorize as either pre/post menarche based on the response of Yes/No
Today's date	(month/day/year) when participant completed the questionnaire	(month/day/year) when participant completed the questionnaire	(month/day/year) when participant completed the questionnaire	(month/day/year) when participant completed the questionnaire	Use to calculate age at baseline
Household income	Q8. Over the last year, what is the total income of the household your child lives in?	Q8. Over the last year, what is the total income of the household you live in?	S.1 over the last year, what was the total income of the household you live in?	A6. Over the last year, what was the total income of the household you live in?	Categorical responses, but will be treated as a continuous variable (<$9,999K=0, $10K-$19K=1,

					$20K-$39K=2, $40K-$59K=3, >$60K=4)
Cancer diagnosis	P.1 Medical History of cancer	P.1 Medical History of cancer	N/A	N/A	Indicating CNS tumor survivor/cancer-free sibling
Height (ht)	A.10. What is his/her current ht without shoes?	A.10 What is your current ht without shoes?	7. What is your current height without shoes?	A1. What is your current height without shoes?	Use for BMI calculation
Weight (wt)	A.11 What is his/her current wt without shoes?	A.11 What is your current weight without shoes?	8. What is your current weight without shoes?	A. What is your current weight without shoes?	Use for BMI calculation
Amputation status	I.1 Amputation of an arm, leg, hard, 8foot, finger or toe? If yes, specify.	I.1 Amputation of an arm, leg, hard, foot, finger or toe? If yes, specify.	N/A	N/A	Use for weight adjustment
Physical Activity levels (PA)	N.5 On how many of the past 7 days did your child exercise or do sports for at least 20 min that made him/her sweat or breathe hard (e.g. dancing, jogging, basketball, etc.)	N.9 On how many of the past 7 days did you exercise or do sports for at least 20 min that made you sweat or breathe hard (e.g. dancing, jogging, basketball, etc.)	D.2-7 D2. Now thinking about the vigorous physical activities you do in a usual week, do you do vigorous activities for at least 10 min at a time, such as running, aerobics, wheelchair basketball, heavy yard work, or anything else that causes large increases in breathing or heart rate? D3. How many days per week do you do these vigorous activities for at least 10 min at a time? D4. On days when you do vigorous activities for at least 10 min at a time, how much total time per day do you	N.16-21 (same questions as the 2003 follow up questions)	Will be treated as continuous variable (0 to 7 days) Note: Will recode 2003 and 2007 responses to match up with the information collected @ baseline

			spend doing these activities? D5. Now, thinking about the moderate physical activities you do in a usual week, do you do moderate activities for at least 10 min at a time, such as brisk walking, bicycling, vacuuming, gardening, manual operation of a wheelchair, or anything else that causes small increases in breathing or heart rate? D6. How many days per week do you do these moderate activities for at least 10 min at a time? D7. On days when you do moderate activities for at least 10 min at a time, how much total time per day do you spend doing these activities?		
Physical function	N.10 Over the last 2 years, how long (if at all) has your child's health limited them in each of the following activities? a. The kinds or amounts of vigorous activities he/she can do, like lifting heavy objects, running or	N.14 Over the last 2 years, how long (if at all) has your health limited you in each of the following activities? a. The kinds or amounts of vigorous activities he/she can do, like lifting heavy objects, running	E. The following items are about activities you might do during a typical day. Does your physical health now limit you in these activities? If so how much? 3. Vigorous activities, such as running, lifting heavy	N. 26 a to f (same questions as the baseline questions)	Categorical responses that were different between baseline and follow up questionnaires. Responses will be recoded to a dichotomous responses (Yes=if responded as limited for 3

	participating in strenuous sports b. The kinds or amounts of moderate activities he/she can do, like moving a table, carrying groceries or bowling c. Walking uphill or climbing a few flights or stairs d. Bending, lifting or stooping e. Walking one block f. Eating, dressing, bathing, or using the toilet	or participating in strenuous sports b. The kinds or amounts of moderate activities he/she can do, like moving a table, carrying groceries or bowling c. Walking uphill or climbing a few flights or stairs d. Bending, lifting or stooping e. Walking one block f. Eating, dressing, bathing, or using the toilet	objects, participating in strenuous sports 4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf 5. Lifting or carrying groceries 6. Climbing several flights of stairs 7. Bending, kneeling, or stopping 8. Walking one block 9.Bathing or dressing yourself		months or less and for more than 3 months as well as limited a little to limited a lot. No=Not limited at all)
Treatment era	Medical Record	Medical Record			Categorized as: 1970-1973 1974-1977 1978-1981 1982-1986
Chemotherapy	Medical Record	Medical Record	N/A	N/A	Categorized as: Any Anthracycline Alkylating Agents Antimetabolites & Corticosteroids Vinca Alkaloids & Heavy Metal None (Followed categories indicated in concept proposal #11-07)
Cranial radiation	Medical Record	Medical Record	N/A	N/A	Dosages categorized as: No CRT, <29.9 gray (Gy), 30-30.9 Gy, 40-49.9 Gy, 50-59.9 Gy, and ≥60 Gy
Surgery	Medical Record	Medical Record	N/A	N/A	Yes/No
BSI-18	N/A	J.16-J.35 (except	G.1-18 (same	L.1-18 (same	Follow the BSI-

		J.25 and J.28) J.16 nervousness or shaking inside J.17 Faintness or dizziness J. 18 Pains in heart or chest J.19 Thoughts of ending your life J.20 Suddenly scared for no reason J.21 Feeling lonely J.22 Feeling blue J.23 Feeling no interest in things J.24 Feeling fearful J.26 Nausea or upset stomach J.27 Trouble getting your breath J.29 Numbness or tingling in parts of your body J.30 feeling hopeless about the future J.31 Feeling weak in parts of your body J.32 Feeling tense or keyed up J.33 Spells of terror or panic J.34 Feeling so restless you couldn't sit still J.35 Feelings of worthlessness	questions as the baseline)	questions as the baseline and 2003 follow up)	18 scoring guide. Will use J.16-J.24, J.26, J.27, and J. 29-J.35 We examine the scores for somatization, depression, and anxiety as well as the composite Global Severity Index score as continuous variables.
Central Nervous System agent (Anti-epileptic drugs use)	B.8.11. Anti-Epileptic (Anti-Seizure) Drugs such as dilantin, Phenobarbital, depakane, Tegretol (Carbamazepine), Klonipen, Primidone (Mysoline), Zarontin or others	B.8.11. Anti-Epileptic (Anti-Seizure) Drugs such as dilantin, Phenobarbital, depakane, Tegretol (Carbamazepine), Klonipen, Primidone (Mysoline), Zarontin or others	Q9. Other prescribed drugs (specify)	C8.10. Other prescribed drugs (specify)	Use of CNS agents will be categorized into: 0, 1, 2, 3+, but will explore using specific CNS agents.
Central Nervous System agent (Psychoactive	B.8.15. Antidepressants or	B.8.15. Antidepressants	Q.8. Medications for	C.8.9. Medications for	

medications)	other prescribed drugs for depression or other mood disorders such as Elavil, Prozac, Paxil, Zoloft, Navane, Ritalin or others	or other prescribed drugs for depression or other mood disorders such as Elavil, Prozac, Paxil, Zoloft, Navane, Ritalin or others	Depression, such as Prozac, Serzone, Celexa, Zoloft, Wellbutrin, Effexor, Desyrel, or Vivactil (specify)	Depression, such as Prozac, Serzone, Celexa, Zoloft, Wellbutrin, Effexor, Desyrel, or Vivactil (specify)	
Deficiency of growth hormone (GHD)	E.8 Deficiency of growth hormone? And validated with medical record	E.8 Deficiency of growth hormone? And validated with medical record	No Question available (assumed diagnosis will not change over time)	N/A	Yes/No (self-report data)
Externally validated GHD Yes No	Medical record	Medical record	N/A	N/A	Yes/No (externally validated)

Appendix B. Data Structure Examples

Appendix B1. Examples of wide format and the long format data structure[29]

Appendix B1-1. Example of wide format

Obs.	Study ID	BMI96	BMI2003	BMI2007	PA96	PA2003	PA2007	Gender
1	1	25	26	30	3	3	2	F
2	2	35	40	48	0	1	4	M
3	3	22	24	18	1	1	1	M

Appendix B1-2. Example of long format

Obs.	Study ID	Time	BMI at each time point	PA at each time point	Gender
1	1	1	25	3	F
2	1	2	26	3	F
3	1	3	30	2	F
4	2	1	35	0	M
5	2	2	40	1	M
6	2	3	48	4	M
7	3	1	22	1	M
8	3	2	24	1	M
9	3	3	18	1	M

Appendix B2. Example of modified data structure for a 3-time-point 2-level bivariate longitudinal change model [29]

Obs.	Study ID (i)	Time	dv_{ti}	δ_y	δ_z	Gender
1	1	1	25 (Y_{11})	1	0	F
2	1	1	3 (Z_{11})	0	1	F
3	1	2	26 (Y_{21})	1	0	F
4	1	2	3 (Z_{21})	0	1	F
5	1	3	30 (Y_{31})	1	0	F
6	1	3	2 (Z_{31})	0	1	F
7	2	1	35 (Y_{12})	1	0	M
8	2	1	0 (Z_{12})	0	1	M
9	2	2	40 (Y_{22})	1	0	M
10	2	2	1 (Z_{22})	0	1	M
11	2	3	48 (Y_{32})	1	0	M
12	2	3	4 (Z_{32})	0	1	M
13	3	1	22 (Y_{13})	1	0	M
14	3	1	1 (Z_{13})	0	1	M
15	3	2	24 (Y_{23})	1	0	M
16	3	2	1 (Z_{23})	0	1	M
17	3	3	18 (Y_{33})	1	0	M
18	3	3	1 (Z_{33})	0	1	M

Appendix B3. Example of modified data structure for a 3-time-point 3-level bivariate longitudinal change model

Obs.	Group (j)	Study ID (i)	Time	dv_{tij}	δ_y	δ_z	Gender
1	1	1	1	25 (Y_{111})	1	0	F
2	1	1	1	3 (Z_{111})	0	1	F
3	1	1	2	26 (Y_{211})	1	0	F
4	1	1	2	3 (Z_{211})	0	1	F
5	1	1	3	30 (Y_{311})	1	0	F
6	1	1	3	2 (Z_{311})	0	1	F
7	1	2	1	35 (Y_{121})	1	0	M
8	1	2	1	0 (Z_{121})	0	1	M
9	1	2	2	40 (Y_{221})	1	0	M
10	1	2	2	1 (Z_{221})	0	1	M
11	1	2	3	48 (Y_{321})	1	0	M
12	1	2	3	4 (Z_{321})	0	1	M
13	2	3	1	22 (Y_{132})	1	0	M
14	2	3	1	1 (Z_{132})	0	1	M
15	2	3	2	24 (Y_{232})	1	0	M
16	2	3	2	1 (Z_{232})	0	1	M
17	2	3	3	18 (Y_{332})	1	0	M
18	2	3	3	1 (Z_{332})	0	1	M