Exercise and QUality diet After Leukemia: The EQUAL Study
An Ancillary Study of the Childhood Cancer Survivor Study
Funding: R01CA187397; PI: Tonorezos

1. Investigators and Working Groups:
Emily S. Tonorezos, MD MPH;
Gregory T. Armstrong, MD MS:
Joanne F. Chou, MPH;
Eric Chow, MD, MPH
Jeanne M. Clark, MD MS;
Jennifer S. Ford, PhD;
Aaron McDonald, PhD;
Carly Miron, BS;
Chaya S. Moskowitz, PhD;
Nidha Mubdi, MPH;
Paul Nathan, MD;
Danielle Novetsky Friedman, MD MS;
Kevin C. Oeffinger, MD;
Lakshmi Ramanathan, PhD;
Leslie L. Robison, PhD;
Charles A. Sklar, MD;

Primary: Cancer Control Working Group
Secondary: Chronic Conditions Working Group

2. Background and Rationale:
Childhood acute lymphoblastic leukemia (ALL) is the most common childhood cancer, accounting for almost one-quarter of childhood cancer survivors. We and others have demonstrated that ALL survivors develop a deleterious cardiometabolic phenotype following cancer therapy including: obesity (and sarcopenia), insulin resistance, chronically elevated c-reactive protein levels, dyslipidemia (especially increases in small, dense highly atherogenic LDL), hypertension, stroke, and ultimately an increased risk for cardiovascular death. Furthermore, we reported an association between unhealthy dietary habits and increased visceral adiposity, higher systolic and diastolic blood pressure, greater waist circumference, and increased body mass index.

The recognized causes of this adverse cardiometabolic profile include an unhealthy diet, a sedentary lifestyle, reduced cardiorespiratory fitness, altered leptin/adiponectin metabolism, and decreased muscle strength and coordination directly and indirectly attributable to the cancer therapy. While those treated with cranial radiotherapy (CRT) are at the highest risk, all leukemia survivors have an excess risk compared with same age individuals without a history or cancer. Prior work by our investigators suggests that ALL survivors do not adhere to dietary guidelines, perhaps due to faulty risk perception, and that small improvements in diet and physical activity are metabolically beneficial.

In sum, ALL survivors have an increased risk of deleterious cardiometabolic changes that leads to accelerated aging and premature, but preventable, death. Methods to enhance weight loss and increase levels of physical activity are urgently needed to mitigate the progression of this deleterious cardiometabolic phenotype. A landmark study by Appel, Clark, and colleagues demonstrated that significant weight loss could be achieved entirely through phone- and web-based support, compared to self-directed weight loss via printed materials and a general

information web page, among obese community-dwelling adults. Importantly, the vast majority of long-term ALL survivors are not followed at a cancer center, thus necessitating an intervention that can be delivered via distance medicine.

Therefore, we will test the effectiveness of a remotely-delivered diet and physical activity intervention, compared to self-directed controls, on weight loss and metabolic biomarkers among long-term ALL survivors. As CRT is an important risk factor which may also alter the metabolic pathways to cardiometabolic disease, the diet and physical activity intervention will be tested separately in those with and without a history of CRT. Participants (200 with a history of CRT and 200 without) will be a nationwide sample of ALL survivors enrolled in the Childhood Cancer Survivor Study, a cohort of long-term cancer survivors that includes a large population of ALL survivors and is currently undergoing expansion.

3. Specific Aims / Objectives

Specific Aim 1:   Determine the effectiveness of a 24-month remotely-delivered diet and physical activity intervention, compared to self-directed weight loss, among a nationwide sample of obese and overweight adult survivors of childhood acute lymphoblastic leukemia (ALL).
Hypothesis 1:   *ALL survivors randomized to the call-center directed intervention will lose on average 2.75kg more than those engaged in self-directed weight loss.*

Specific Aim 2:   Calculate the effect of the diet and physical activity intervention, compared to self-directed weight loss, on lipid profiles and hypertension.
Hypothesis 2:   *Improvements in biomarkers will be greater among participants in the intervention group.*

Specific Aim 3:   Calculate the relative contribution of diet and physical activity to weight loss, lipid profiles, and hypertension.
Hypothesis 3:   *A diet rich in fruits and vegetables and with little meat consumption will result in the greatest benefit.*

Specific Aim 4:   Assess the roles of self-efficacy and risk perception on weight loss, activity and diet goals.
Hypothesis 4:   *Subjects with high self-efficacy and enhanced risk perception will be more likely to lose weight and make behavioral and nutritional changes.*

4. Intervention
Briefly, the participants enrolled in the intervention arm of the EQUAL study will be assigned an individual diet and physical activity counselor through *Healthways at Hopkins*. This counselor will stay with the participant for the 24 month duration of the intervention.
Diet: Participants will be encouraged to consume a low-calorie, low-salt diet with 7-12 daily servings of fruits and vegetables and low-fat dairy products. Calorie goals are based upon weight at study entry and whether or not the weight loss goal has been met.
Physical Activity: Participants will gradually build to ≥ 180 minutes of moderate to vigorous physical activity per week, using the activity of their own choosing and gradually adding bouts of ≥ 10 minutes in length.

Monitoring and Counselor Contacts: For the first three months of the intervention, participants are encouraged to log into the web hub on a daily basis to record weight, food intake, and physical activity. Contacts with the counselor, who can view the web hub data and give direct

feedback to the participant, are initially weekly. Prior studies have demonstrated that personal contacts with an interventionist can improve physical activity and promote self-monitoring, which is relevant for initial weight loss and maintenance[50,51]. As the trial proceeds and the weight loss goal is achieved, contacts are reduced in frequency. Participants are sent reminder emails and/or called by telephone if they have not logged into the web hub on schedule.

5. Analysis Framework

Aim 1: The primary endpoint will be evaluated in an intent-to-treat analysis with a linear mixed effects model with robust standard errors and an unstructured covariance matrix using weight at each time point as the outcome modeled as a function of time, randomization arm, gender, age, and race together with interaction terms between time and randomization arm. By using an unstructured covariance matrix with data where measurements are taken at fixed time points, our model essentially reduces to the classical multivariable regression model and eliminates the need to specifically model random effects. The test of the difference in weight loss between the two arms at 24 months will be evaluated by specifying the appropriate contrasts after the model has been fit. We will evaluate the fitted mixed effects model to ensure whether the underlying distributional assumptions, including whether the random error is normally distributed and whether the within-group errors are independent and identically distributed, are satisfied. Diagnostic plots such as individual boxplots for each participant, plots of standardized residuals and observed versus fitted values of weight from the model will assessed.

Aims 2, 3, 4: Mixed effects models (linear models for Aims 2 and 3 and non-linear models for Aim 4) as described above will be used to analyze these aims as well. Each outcome will be modeled separately as a function of relevant covariates.

Missing data: Despite our efforts to encourage all participants to remain in the study, it is likely that some will drop out of the study at different points in time. It is for this reason that the primary analytic method we will use is a mixed effects model. The mixed effects model produces valid estimates of the treatment effect as long as data are missing at random (that is, missing data are independent of unobserved measurements conditional on the observed data), allows participants with incomplete data to contribute information to the estimated treatment effect, and is consistent with the intent-to-treat principle[73]. We will evaluate the missing data mechanism by modeling the drop out process and the data simultaneously and testing whether the dropout depends on unobserved weight measurements.

Sample size justification

Aim 1: In the most recent data available on the CCSS participants who will be eligible for this study, the mean weight was 98.7 kg with a standard deviation (σ) of approximately 19. Based on prior studies, we assume the correlation

Table 1. Power calculations for main and subgroup comparison

Difference in average weight loss between arms (kg)	Power for overall comparison	Power for CRT subgroup comparison
2.50	79%	39%
2.75	87%	45%
3.00	91%	55%
3.25	94%	60%
3.50	97%	69%
3.75	98%	75%
4.00	99%	81%
4.25	>99%	85%

between longitudinal measurements of BMI will be 0.85[33,34]. In the POWER trial, the average weight loss in the SD arm from baseline to the 24 month assessment was 0.8 kg. Assuming a

baseline weight of 98.7 kg (σ =19) in both arms of our proposed study and that we observe a similar weight loss of 0.8 in the SD arm, with 200 participants in each arm we will have 87% power to detect a clinically meaningful difference in weight loss of 2.75 kg between the two groups at 24 months (corresponding to approximate 24 month measurements of 97.9 kg vs. 95.1 kg) using a two-sided 0.05 level test (**Table 1**). The tested intervention (CCD) in this trial is run by *Healthways at Hopkins* and was previously tested in the POWER trial. Among obese participants in POWER, the mean weight reduction from baseline to 24 months was 4.6kg in the CCD group and 0.8kg in the control (SD) group, and other behavioral intervention studies have met or exceeded this level of weight loss.

Aim 2: In our preliminary work among 118 ALL survivors (**Table 2**), we found standard deviations of 10.2 for fasting insulin, 2.0 for the leptin:adiponectin ratio, and 20.0 for small dense LDL across all participants. Assuming similar variation in our data, using two-sided 0.0125 level tests for each of the 4 outcomes, we have 90% power to detect a difference between the intervention and control groups for each outcome separately.

Table 2. Hormone and fat measures in 118 childhood ALL survivors

	All N=118		CRT N=39		No CRT N=77	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Leptin:adiponectin	1.7	2.0	2.6	2.5	1.2	1.5
Insulin	18.5	10.2	22.1	12.4	16.7	8.4
Glucose	97.4	14.9	95.7	23.0	89.3	7.3
HOMA-IR	4.2	2.6	5.3	3.3	3.7	2.0
HsCRP	3.6	4.4	5.1	4.4	2.8	4.2
Weight (kg)	77.1	19.2	78.5	22.5	76.4	17
Height (cm)	166.5	10.3	161.2	11.2	169.3	8.7
BMI	27.9	7.0	30.2	8.2	26.7	5.9
Small dense LDL_{3+4}	50.9	20.0	57.7	19.8	48.0	19.4

Aim 3: Assuming the same standard deviations for the four metabolic parameters as listed above, using a two-sided 0.0125 level test there is a 90% probability that we will detect an association between each independent variable, the dietary characteristics and physical activity.

Aim 4: There is an 80% probability that the study will detect a relationship between the self-efficacy or perceived risk and dietary intake at a two-sided 0.05 significance level if the true change in the dietary intake is 0.141 standard deviations per one standard deviation change in self-efficacy or perceived risk. We have the same probability of finding a relationship between these independent variables and physical activity goals.