Exercise and QUality Diet after Leukemia: A Randomized Weight Loss Trial among Adult Survivors of Childhood Leukemia in the Childhood Cancer Survivor Study

Danielle N. Friedman[1,2], Joanne F. Chou[1], Jeanne M. Clark[3], Chaya S. Moskowitz[1,2], Jennifer S. Ford[4], Gregory T. Armstrong[5], Nidha Z. Mubdi[1], Aaron McDonald[5], Paul C. Nathan[6], Charles A. Sklar[1,2], Lakshmi V. Ramanathan[1,2], Leslie L. Robison[5], Kevin C. Oeffinger[7], and Emily S. Tonorezos[8]

ABSTRACT

Background: Obesity is prevalent in childhood cancer survivors and interacts with cancer treatments to potentiate risk for cardiovascular (CV) death. We tested a remote weight-loss intervention trial that was effective among adults with CV risk factors in a cohort of adult survivors of childhood acute lymphoblastic leukemia (ALL) with overweight/obesity.

Methods: In this phase III efficacy trial, survivors of ALL enrolled in the Childhood Cancer Survivor Study with a body mass index ≥25 kg/m^2 were randomized to a remotely delivered weight-loss intervention versus self-directed weight loss, stratified by history of cranial radiotherapy. The primary endpoint was the difference in weight loss at 24 months in an intent-to-treat analysis. Analyses were performed using linear mixed-effects models.

Results: Among 358 survivors (59% female; median attained age: 37 years; IQR: 33–43 years), the baseline mean (SD) weight was 98.6 kg (24.0) for the intervention group ($n = 181$) and 94.9 kg (20.3) for controls ($n = 177$). Adherence to the intervention was poor; 15% of individuals in the intervention group completed 24/30 planned coaching calls. Weight at 24 months was available for 274 (77%) participants. After controlling for cranial radiotherapy, sex, race/ethnicity, and age, the mean (SE) change in weight from baseline to 24 months was −0.4 kg (0.8) for the intervention group and 0.2 kg (0.6) for control participants ($P = 0.59$).

Conclusions: A remote weight-loss intervention that was successful among adults with CV conditions did not result in significant weight loss among adult survivors of childhood ALL.

Impact: Future interventions in this population must be tailored to the unique needs of survivors to encourage engagement and adherence.

Introduction

Improved survival of childhood acute lymphoblastic leukemia (ALL) is one of the great medical successes of the last century (1), with 5-year survival rates now exceeding 90% (2, 3). However, survivors of childhood ALL are at lifelong risk for developing a range of cardiometabolic complications (4, 5) or cardiovascular (CV) and metabolic diseases that interact, modify one another, and contribute to premature CV death (5–8). Conditional life expectancy for survivors of childhood ALL is 11.8% to 21.8% lower than that for the general population, depending on the treatment era (9). We have previously shown that adult survivors of childhood ALL are more likely to have obesity (7) and insulin resistance (6, 10) when compared with regional controls (6). Female sex, younger age at treatment, and exposure to cranial radiotherapy (CRT) are associated with particularly pronounced risk of cardiometabolic disease in a dose-dependent fashion in this population (11).

Although CRT is an important risk factor for cardiometabolic disease, contemporary leukemia protocols have sought to avoid the use of CRT whenever possible (3, 12). Nevertheless, recent data have shown that the prevalence of overweight/obesity increases during ALL therapy even among individuals not exposed to CRT (13, 14), with persistence of overweight/obese status into survivorship (13). This is particularly alarming given the exponential increase in rates of childhood obesity in the general population in the United States (15, 16), which will likely result in a growing cohort of children who are obese at diagnosis of ALL and will remain so during survivorship. Efficacious weight-loss interventions that are feasible and sustainable are thus critically needed among ALL survivors, regardless of whether therapeutic exposures include CRT.

To fill this gap, we conducted the two-arm, randomized Exercise and QUality diet After Leukemia (EQUAL) study (clinicaltrials.gov identifier: NCT02244411) among a nationwide population of adult survivors of childhood ALL enrolled in the Childhood Cancer Survivor Study (CCSS) who were overweight or obese. In this phase III trial, we sought to test the efficacy of a 24-month, remotely delivered weight-loss intervention, which had previously been shown to be effective among adults with CV risk factors recruited in primary care practices through the remotely delivered weight-loss intervention trial Practice-based Opportunities for Weight Reduction (POWER; herein, referred to as POWER trial; ref. 17).

[1]Memorial Sloan Kettering Cancer Center, New York, New York. [2]Weill Cornell Medical College, New York, New York. [3]Johns Hopkins University Schools of Medicine and Public Health, Baltimore, Maryland. [4]Hunter College and The Graduate Center, City University of New York, New York, New York. [5]St. Jude Children's Research Hospital, Memphis, Tennessee. [6]The Hospital for Sick Children, Toronto, Canada. [7]Duke Cancer Institute, Duke University, Durham, North Carolina. [8]National Cancer Institute, National Institutes of Health, Rockville, Maryland.

Corresponding Author: Emily Tonorezos, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850. E-mail: Emily.tonorezos@nih.gov

Cancer Epidemiol Biomarkers Prev 2024;XX:XX–XX

doi: 10.1158/1055-9965.EPI-23-1601

Materials and Methods

Study population

Participants were recruited from the CCSS, a cohort of 25,665 five-year survivors of childhood cancer, diagnosed before age 21 years between 1970 and 1999 and treated at one of 31 North American institutions. The study design and methodology of CCSS have been described previously in detail (18, 19). Survivors were eligible to participate in the EQUAL study if they were 5-year survivors of ALL, age 18 or older, English-speaking, living in the United States, and with self-reported body mass index (BMI) ≥25 kg/m^2 on their most recent CCSS questionnaire, based on self-reported height and weight. ALL survivors with a history of total body irradiation were excluded. All participants provided signed written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Study groups

Participants were randomized 1:1 to the intervention or control group, stratified by history of CRT, as CRT is independently associated with obesity (20) with potentially distinct underlying mechanisms leading to obesity (21).

Intervention arm

Participants in the intervention group were assigned to a call center-directed weight-loss program grounded in social cognitive theory (22). Using telephone coaching and an intervention website, which had previously been shown to be effective in adults with CV risk factors in primary care (17), participants assigned to the intervention group were instructed to set a weight-loss goal of at least 5% (individually tailored), consume a low-calorie, low-salt diet with 7 to 12 daily servings of fruits and vegetables and low-fat dairy products, and increase levels of moderate to vigorous physical activity to ≥180 minutes per week, using an activity of their own choosing. Calorie goals were based upon weight at study entry and whether or not the weight-loss goal had been met. Details of the intervention protocol have been previously published (17); specifics are also included in Supplementary Methods S1.

During the first 6 months of the study, participants were offered contact via telephone or email with a personalized health coach every other week and encouraged to log on daily to the study website, which contained learning modules; options for logging and self-monitoring of weight, caloric intake, and physical activity; and feedback on progress in these key behaviors. As the study progressed, the frequency of participant contact with the health coach decreased, with participants offered monthly contact with their health coach during months 7 to 24 of the study. This approach was designed to allow participants to build self-efficacy and solve problems independently as the study progressed. All health coaches were trained and employed by the Healthways at Hopkins Program (17), which also provided the study website.

Control arm

Individuals enrolled in the control arm received mailed brochures on healthy living at months 1, 7, and 12 of the study (Supplementary Methods S1). They were encouraged to follow a self-directed weight-loss program without additional weight-loss support; they did not have access to the website or counselors, and a weight-loss goal was not specified. This approach was designed to mimic real-world conditions that survivors might experience in routine clinical care.

Assessment of study outcomes

The primary outcome was difference in weight loss between the two arms 24 months after randomization. Prespecified secondary outcomes included change in blood pressure, cholesterol, and triglycerides at 24 months. High-density lipoprotein (HDL) cholesterol and triglycerides were determined using the Abbott ARCHITECT c8000 Chemistry Analyzer. Low-density lipoprotein (LDL) cholesterol was calculated based on the Friedewald equation (23). Other secondary prespecified weight-loss outcomes were at or below baseline weight and achieving 5% or 10% weight loss. Anthropometric (height and weight), blood pressure, and blood-based biomarkers were collected in the fasting state via a home phlebotomy vendor, who was not informed of the group assignment, at 0, 12, and 24 months after randomization. Participants completed online questionnaires about perceived behavioral control (or self-efficacy), as outlined by Sallis (24), and perceived risk (25–30) of developing heart problems or diabetes in comparison with others of their age and sex at the three time points. These items were designed as 5-point Likert-type items (31–33), rated on a scale of 1 (strongly agree) to 5 (strongly disagree; refs. 25, 30, 31, 34–40).

Statistical analysis

Significant difference in weight loss between arms at 24 months was defined as a difference of 2.75 kg. This difference was based on preliminary data from the POWER trial, which utilized the same intervention and reached the mean weight reduction from baseline to 24 months of 4.6 kg in the call center-directed (intervention) group and 0.8 kg in the self-directed (control) group or a 3.8 kg difference between arms. In preparation for the EQUAL study, a baseline weight of 98.7 kg ($\sigma = 19$) was estimated with an anticipated weight loss of 0.8 kg among participants in the self-directed (control) arm. In order to have at least 87% power to detect a clinically meaningful weight-loss difference of 2.75 kg between groups at 24 months, using a two-sided 0.05-level test, target enrollment was set at 200 patients in each arm (17).

Sociodemographic characteristics were compared between participants and nonparticipants using the Fisher exact test and the Wilcoxon rank-sum test for categorical and continuous covariates, respectively. A linear mixed-effects model with robust SEs and an unstructured covariance matrix were fit (41). All participants had at least one measurement and were included in the models, consistent with an intent-to-treat approach. The estimation procedure uses a maximum likelihood approach that allows all patients to contribute information to the analysis even if they are missing a measurement. Weight measurements at each time point (0, 12, and 24 months after randomization) were modeled as a function of time, randomization arm, history of CRT, gender, age, and race/ethnicity together with an interaction term between time and randomization arm. The primary test of efficacy was conducted by specifying the appropriate linear contrasts to test the difference in the change between arms from baseline to 24 months. Secondary endpoints included the change in cholesterol (LDL, HDL, and triglycerides) and systolic and diastolic blood pressure from baseline to 24 months. These were also evaluated using linear mixed-effect models as described previously.

Adherence to the intervention was defined as completion of 24/30 (80%) scheduled coaching calls. We also examined the effectiveness of the intervention within different subgroups of participants based on baseline characteristics, including history of CRT, educational attainment, employment status, home living situation, marital status, self-efficacy for diet, self-efficacy for exercise, perceived risk for

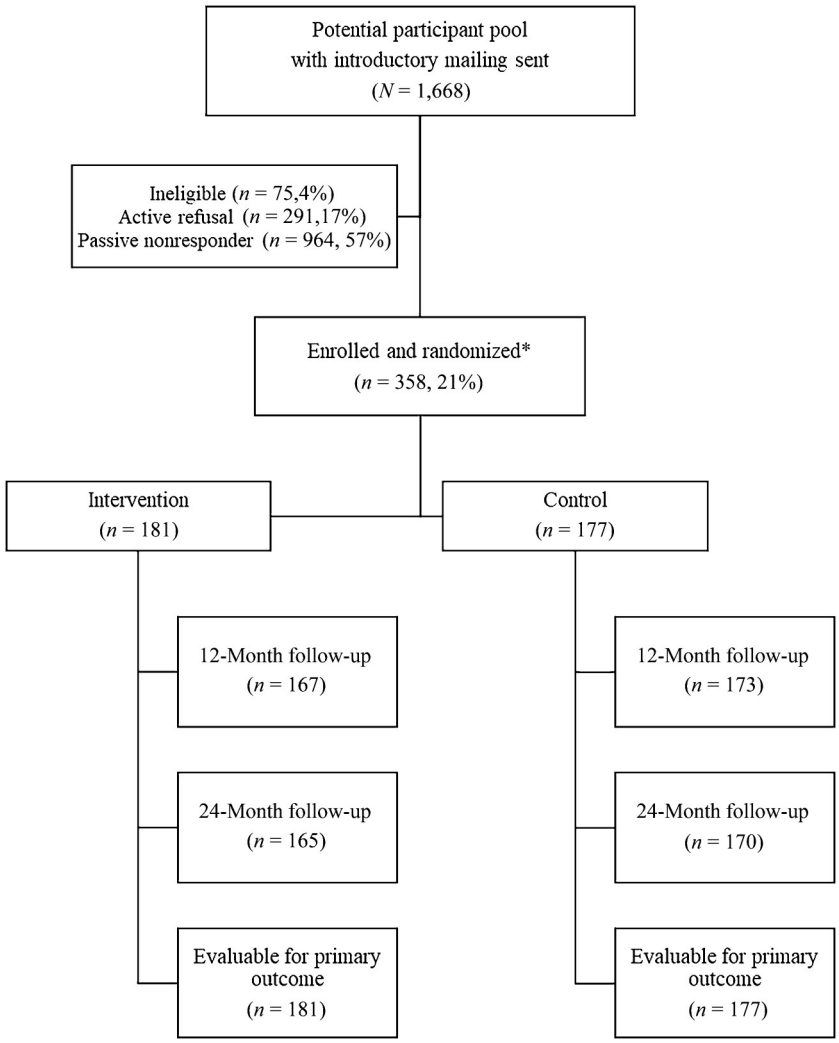

Figure 1.
CONSORT diagram for EQUAL: the EQUAL study, an ancillary study of the CCSS.

diabetes, and perceived risk for heart disease. This was evaluated using the linear mixed-effects model described previously. To generate scores for self-efficacy for diet and exercise separately, as well as perceived risk of diabetes and heart disease, we summed item responses from a 5-point Likert scale and linearly rescaled the resulting scores to range from 0 to 100, with higher scores indicating higher levels of self-efficacy and perception of risk (42).

All statistical analyses were performed using SAS (SAS/STAT User's Guide; SAS Institute, Cary, NC) or StataSE 15.0 for Windows (STATA, College Station, TX; Computing Resource Center, Santa Monica, CA) using two-sided tests and a significance level of $P \leq 0.05$. Enrollment was terminated after $N = 358$ (90% of the target goal). Approval was obtained from the institutional review boards of the participating institutions. CONSORT reporting guidelines were used (43). The study was registered at clinicaltrials.gov (NCT02244411).

Data availability

The CCSS is a US NCI-funded resource (U24 CA55727) to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence. CCSS data are publicly available on dbGaP at https://www.ncbi.nlm.nih.gov/gap/ through its accession number phs001327.v2.p1 and on the St Jude Survivorship Portal within the St. Jude Cloud at https://survivorship.stjude.cloud/. Full analytical data sets associated with CCSS publications since January 2023 are also available on the St. Jude Survivorship Portal at https://viz.stjude.cloud/community/cancer-survivorship-community~4/publications.

Results

Among 1,688 ALL survivors who self-reported being overweight or obese living in the United States who were eligible for this study and were sent an introductory study packet, 358 (21.2%) consented to the study (**Fig. 1**). Nonparticipants were more likely to be male than participants but otherwise similar in terms of attained age [37.2 (SD 7.4) years for nonparticipants; 38.2 (SD 7.6) years for participants] and prior exposure to CRT (Supplementary Table S1).

Baseline characteristics for all participants by their random assignment group are shown in **Table 1**. Among the 358 participants who were randomized, 274 individuals provided a final weight at 24 months (76.5%). A total of 181 participants were randomized to

Table 1. Baseline characteristics of survivors of childhood ALL in the EQUAL study according to the randomization arm.

Characteristic	Intervention (*N* = 181)	Control (*N* = 177)
Female	108 (60%)	102 (58%)
Age at randomization (years), median (range)	37 (21–57)	38 (22–57)
BMI (kg/m^2), mean (SD)	34.8 (7.67)	34.1 (6.17)
Baseline weight (kg), mean (SD)	98.7 (24.07)	95.0 (20.31)
Race/ethnicity, number (%)		
Other racial and ethnic groups	12 (6.9%)	5 (3.0%)
White, non-Hispanic	162 (93%)	164 (97%)
CRT, number (%)	105 (58%)	102 (58%)
Health insurance, number (%)		
No	11 (7.5%)	8 (5.4%)
Yes	135 (92%)	141 (95%)
Living with parents, number (%)		
No	139 (77%)	149 (86%)
Yes	41 (23%)	25 (14%)
Marital status, number (%)		
Never married	47 (32%)	47 (31%)
Married or living like married	81 (55%)	86 (57%)
Widowed/divorced/separated	19 (13%)	17 (11%)
Employment status, number (%)[a]		
Full/part-time	115 (79%)	124 (83%)
Others	31 (21%)	25 (17%)
Education, number (%)		
Post high school, not college or lower	13 (8.8%)	22 (15%)
College or additional schooling	134 (91%)	128 (85%)
Household income, number (%)		
Less than $19,999	31 (20%)	22 (14%)
$20,000–$39,999	33 (21%)	35 (22%)
$40,000–$59,999	25 (16%)	26 (16%)
More than $60,000	68 (43%)	78 (48%)
Years from diagnosis to randomization, median (range)	30 (16–46)	32 (15–45)

[a]Other employment status included care home ($n = 15$), looking for work ($n = 10$), unable to work ($n = 22$), retired ($n = 2$), and student ($n = 7$).

the intervention group, of which 27 (14.9%) completed at least 24 of 30 scheduled coaching calls over the 24-month intervention. Among those were not adherent to the intervention, the median number of coaching calls was 5 (range, 0–23).

Primary outcome

There was no significant difference in the mean weight change between participants in the intervention and control groups at 24 months [−0.5 kg, 95% confidence interval (CI), −2.5, 1.5], after adjusting for CRT, age, gender, and race (**Fig. 2**). The results were similar in unadjusted analyses (−0.8 kg, 95% CI, −1.8, 1.2). When analyzing the groups by history of CRT, significant weight loss was not noted at 24 months in either group (no CRT: +1.9 kg, 95% CI, −1.5, 5.2; history of CRT: −2.1 kg, 95% CI, −4.6, 0.3).

Among all participants in the intervention group, 24.2% ($n = 31$) of participants were at least 5% below their baseline weight at 24 months, compared with 17.1% ($n = 25$) of controls. Similarly, 10.9% ($n = 14$) of intervention participants were at least 10% below their baseline weight at 24 months, compared with 10.3% ($n = 15$) of controls (Supplementary Table S2).

Secondary outcomes

When comparing participants in the intervention and control groups, there was no difference in the estimated average systolic (**Fig. 3A**) or diastolic (**Fig. 3B**) blood pressure between groups, after adjusting for age, CRT, race, gender, and BMI. Similarly, there was no change in cholesterol parameters, including LDL, triglycerides, or HDL (**Fig. 4A–C**).

Factors moderating the efficacy of the intervention

We explored a variety of potential factors that might moderate the efficacy of the intervention (**Fig. 5**). Educational attainment was the only factor significantly associated with weight change between intervention and control groups at 24 months. The difference in the mean weight change between participants in the intervention and control groups who had completed college or a higher degree was −2.2 kg at 24 months (95% CI, −4.1, −0.2). In contrast, the mean change in weight between groups among participants who had completed high school alone was +8.1 kg (95% CI, 2.8, 13.5); this observation, however, is limited by small numbers of participants; only 13 participants in the intervention group and 22 controls had completed high school alone. None of the other factors of interest, including self-efficacy or perceived risk (25–30), which have been strongly implicated in behavior change in other studies, were significantly associated with change in weight between groups.

We also explored weight loss among participants who were adherent to the intervention, which was defined as completion of 80% of coaching calls. The average difference in weight change from baseline to 24 months between participants in the intervention arm who were adherent ($n = 27$) and those who were not ($n = 154$) was

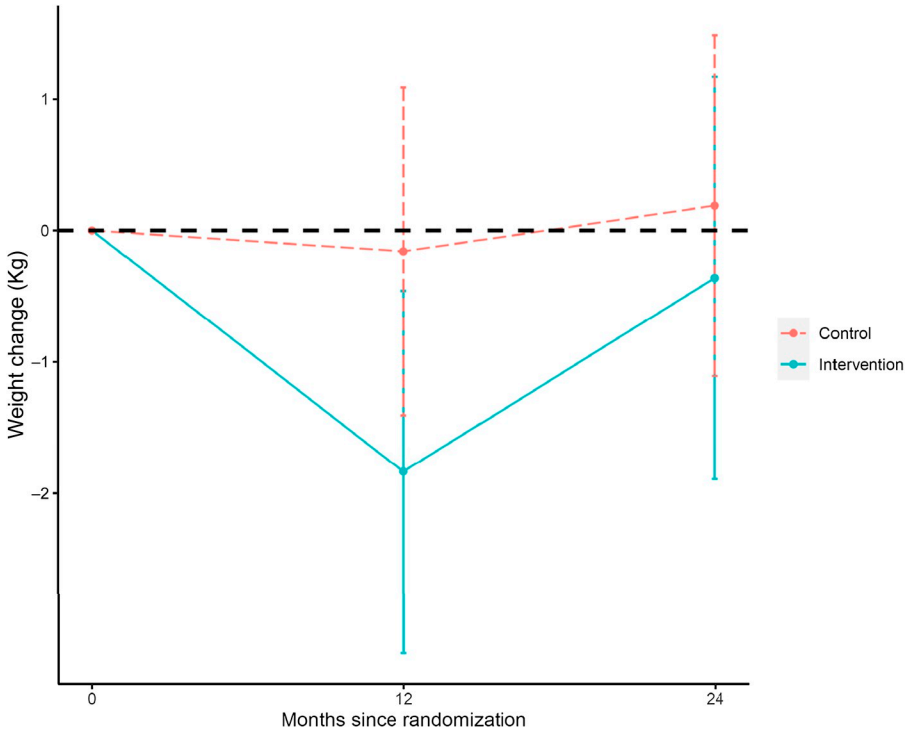

Figure 2.
Adjusted mean weight change (kg) among participants in the EQUAL study according to randomization groups.

−5.7 kg (95% CI, −9.35, −2.07), after adjusting for CRT, age, sex, and race. No harms were reported.

Discussion

In this large, randomized, controlled phase III efficacy trial, we utilized a remote weight-loss intervention which had previously been shown to be effective among adults with CV risk factors in primary care practices and applied it to a nationwide sample of adult ALL survivors in the CCSS. No difference in weight loss at 24 months was observed among individuals enrolled in the intervention group compared with controls. Additionally, there was no difference in other CV risk factors, such as blood pressure or cholesterol parameters, between groups. Apart from college-educated participants, we were also unable to identify a subgroup of participants for whom the intervention was efficacious. These findings suggest that interventions for childhood cancer survivors must be tailored to their unique needs; "off-the-shelf" interventions that have been effective in other populations seem to be suboptimal in this cohort.

Exposure to CRT, which was a key component of historical leukemia regimens, is strongly associated with the development of obesity in childhood cancer survivors, and among survivors of ALL

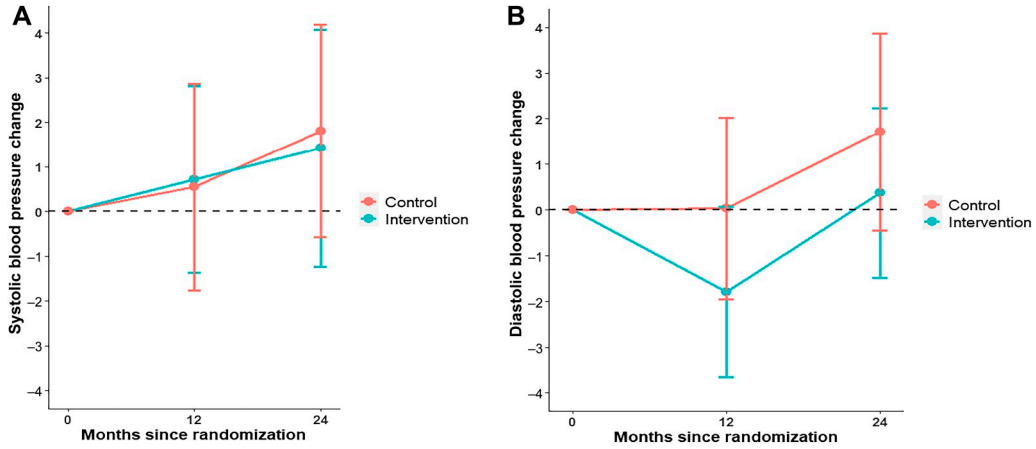

Figure 3.
Adjusted mean change in systolic (**A**) and diastolic (**B**) blood pressure among participants in the EQUAL study according to the randomization group. Estimated average blood pressure change adjusted for age, CRT, race, sex, and BMI.

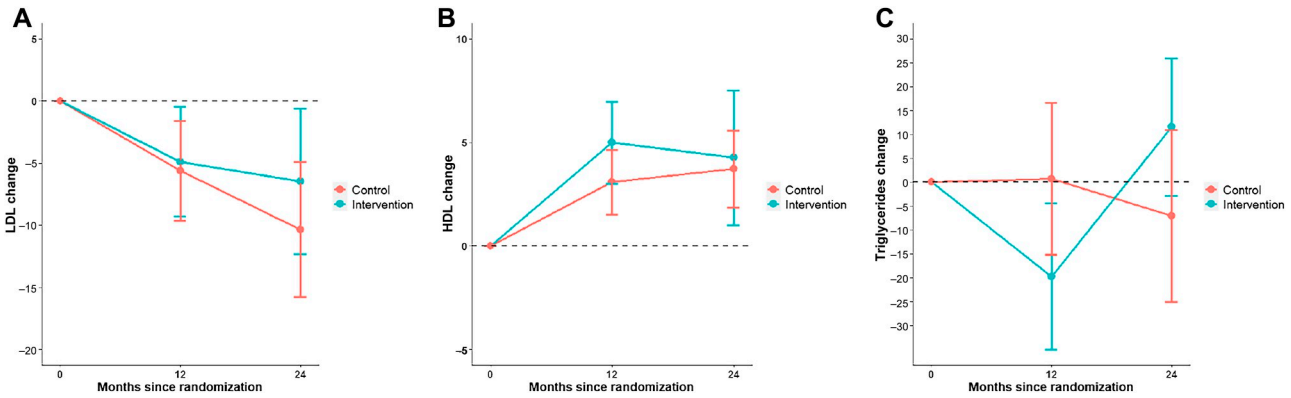

Figure 4.
Mean change in LDL (**A**), HDL (**B**), and triglycerides (mg/dL; **C**) among survivors of ALL enrolled in the EQUAL study according to randomization groups.

specifically (6, 20, 44, 45). The current intervention had previously been shown to be effective in primary care patients with obesity and at least one CV risk factor in the Baltimore area in the POWER trial (17) and thus seemed to provide a promising strategy for weight reduction in high-risk ALL survivors as well. However, despite employing the same intervention materials and trained coaches and ensuring integrity to the protocol and clinical trial strategy throughout study proceedings, we did not detect a significant difference in weight loss between groups. Notably, those who were adherent experienced significant weight loss, as expected. However, overall engagement and adherence were low in the overall cohort of participants. EQUAL participants likely differed in important ways from participants in the POWER trial, who were older with existing CV risk factors. Psychosocial outcomes of cancer treatment and prevalent health outcomes in ALL survivors (46, 47), such as low bone mineral density (48–50) and pain (51, 52), were not addressed by this untailored intervention. These issues could have impacted the ability of participants to engage in regular physical activity and should be addressed in future lifestyle modification interventions in this population.

Additionally, differences in the underlying mechanism for obesity or overweight among ALL survivors compared with the general population may have contributed to null findings or differences in adherence to the program. This may be particularly true among survivors of ALL treated with CRT, which was a key component of historical leukemia regimens and is no longer used routinely in most ALL treatment regimens (6, 20, 44, 45). Because the current study was not adequately powered to detect a difference in non-CRT–treated cases versus controls, the null findings may not indicate that the EQUAL intervention is futile in all survivors of ALL and may warrant additional exploration. Importantly, the POWER trial also recruited participants via referral from a primary care provider, who then received and reviewed a progress report on their patients who had been assigned to an intervention group, to guide and re-engage their patients. This study element may have been especially beneficial for some participants (53). The lack of primary care involvement in EQUAL could have been a critical factor missing for survivors. Future behavioral intervention studies among survivors may wish to involve clinicians, whether in primary care or in oncology, or include more personal connections to improve engagement among participants.

Other factors likely contributed to reduced adherence to the intervention among study participants in our trial. The duration of the EQUAL study was 24 months, a commitment which may have seemed daunting to some participants, especially as the study continued. Weight loss at 12 months was greater among intervention participants compared with control participants, a finding which had attenuated by the end of the trial. Weight-loss interventions often generate early rapid weight loss followed by regain (54). Importantly, achieving long-term sustained weight loss was the purpose of the EQUAL study. Planning or conducting a shorter study may have resulted in findings which would have misrepresented the long-term impact of the intervention.

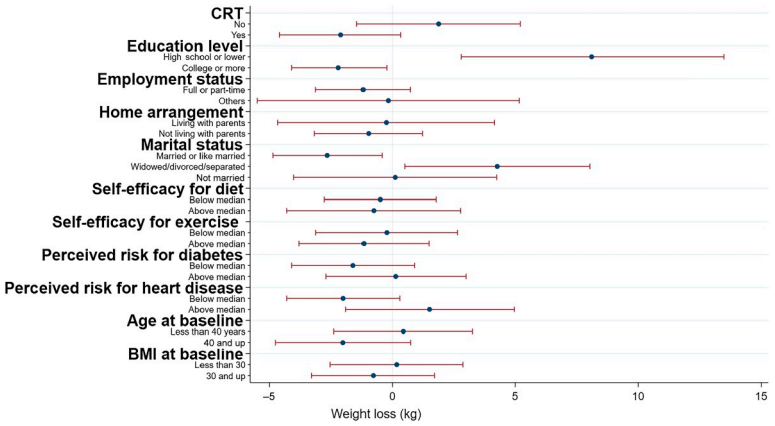

Figure 5.
Difference in weight loss between intervention and control groups, by demographic and treatment characteristics, among 358 ALL survivors in the EQUAL study. Points to the left of zero favor the intervention group, whereas points to the right of zero favor the control group.

This study population carries a very high burden of chronic health conditions (55), which could interfere with their ability to maintain engagement. Among 181 individuals randomized to the 24-month intervention, 25% never completed a single coaching call after consent and enrollment, and only a small proportion completed 80% or more of planned coaching calls (the preplanned measure of adherence). It is possible that a lower burden of intervention activities may have been better suited to this relatively young cohort. Additionally, the incorporation of a run-in period may have excluded participants with low interest in a remotely delivered weight-loss intervention. Many weight-loss intervention studies utilize a run-in period, although the practice has been criticized (56, 57). The EQUAL study was designed without a run-in period with the goal of preserving the intention to test efficacy of the original POWER intervention and maximizing the generalizability and fidelity of the trial.

Interestingly, more than 70% of the participants completed all study requirements, including questionnaires and home phlebotomy visits, despite very low completion of coaching calls or online modules. Participants were remunerated with gift cards for completing questionnaires and home phlebotomy visits but not for completion of elements of the weight-loss intervention. It is possible that inclusion of financial incentives after completion of coaching calls would have improved participant engagement (58), but this would have substantially altered the study design.

The EQUAL study has several strengths, including being the largest and longest randomized, controlled trial completed to date testing a weight-loss intervention in ALL survivors who were overweight or obese; using a theoretically grounded approach for an intervention that had previously been effective in community-dwelling adults; and enrolling a geographically diverse group of ALL survivors exposed to disparate therapies but all at increased risk for cardiometabolic disease. A number of limitations must also be considered when interpreting the results of this study. Participants in this study are part of the larger CCSS cohort and thus may not be generalizable to other leukemia survivors in this country. EQUAL participants were also mostly White, non-Hispanic, which may limit its generalizability to racially and ethnically diverse populations, but this too was largely related to the cohort from which eligible participants were recruited. Fewer participants were enrolled than originally planned. Given that participation in the intervention among invited survivors was lower than expected, the findings of this study underscore the need to identify tailored strategies of engagement and retention in future behavioral weight-loss studies among childhood cancer survivors.

The EQUAL study thus raises a number of critical questions about the design, dissemination, and implementation of future studies to reduce risk in survivors of ALL and other survivors with treatment-related cardiometabolic disease. This study showed that a distance intervention with only remote elements may not be adequate for engaging survivors in weight loss. Furthermore, recruitment in a primary care or other clinical settings may be more effective. The null findings of the EQUAL study underscore this important lesson that can be integrated into all future lifestyle trials in this population. Effective interventions (59, 60), with consideration for the lessons learned herein, are urgently needed in this cohort with both modifiable and non-modifiable risks for CV disease and early mortality. Future interventions should consider clinician involvement and tailoring survivor-specific methods to increase engagement and facilitate weight loss.

Authors' Disclosures

D.N. Friedman reports grants from Meg Berté Owen Fund, NCI, and American Cancer Society during the conduct of the study, as well as UpToDate royalties. J.M. Clark reports grants from NIH/NCI during the conduct of the study and that Johns Hopkins had a consulting agreement with Healthways from 2013 to 2017. Johns Hopkins also worked with Healthways Corporation to try to commercialize POWER in a sell-to-employer model, the weight-loss intervention tested in this study. Modest royalties were received, which were divided across several units/programs at Johns Hopkins and not dispersed to individuals. C.S. Moskowitz reports grants from NCI during the conduct of the study. G.T. Armstrong reports grants from NIH during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

D.N. Friedman: Writing–original draft. **J.F. Chou:** Formal analysis, writing–review and editing. **J.M. Clark:** Conceptualization, resources, software, funding acquisition, methodology, writing–original draft, writing–review and editing. **C.S. Moskowitz:** Formal analysis, supervision, funding acquisition, writing–review and editing. **J.S. Ford:** Funding acquisition, investigation, methodology, writing–original draft, project administration, writing–review and editing. **G.T. Armstrong:** Resources, funding acquisition, investigation, project administration, writing–review and editing. **N.Z. Mubdi:** Funding acquisition, investigation, project administration, writing–review and editing. **A. McDonald:** Resources, data curation, funding acquisition, methodology, writing–original draft, project administration, writing–review and editing. **P.C. Nathan:** Resources, investigation, methodology, writing–review and editing. **C.A. Sklar:** Resources, funding acquisition, investigation, writing–review and editing. **L.V. Ramanathan:** Formal analysis, funding acquisition, investigation, writing–review and editing. **L.L. Robison:** Data curation, supervision, funding acquisition, investigation, methodology, writing–review and editing. **K.C. Oeffinger:** Conceptualization, funding acquisition, investigation, visualization, methodology, writing–original draft, writing–review and editing. **E.S. Tonorezos:** Conceptualization, supervision, funding acquisition, investigation, visualization, methodology, writing–original draft, writing–review and editing.

Acknowledgments

This work was supported by NCI grant CA187397 (E.S. Tonorezos, J.F. Chou, J.M. Clark, C.S. Moskowitz, J.S.Ford, G.T.Armstrong, N.Z.Mubdi, A. McDonald, L.V. Ramanathan, L.L. Robison, and K.C. Oeffinger), NCI grant CA55727 (G.T. Armstrong), and American Institute of Cancer Research (E.S. Tonorezos). Support to St. Jude Children's Research Hospital was also provided by the Cancer Center Support (CORE) grant CA21765 (G.T. Armstrong, A. McDonald, and L.L. Robison), Meg Berté Owen Fund (D.N. Friedman, N.Z. Mubdi, and E.S. Tonorezos), and American Lebanese Syrian Associated Charities (G.T. Armstrong, A. McDonald, and L.L. Robison).

Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Received December 18, 2023; revised February 2, 2024; accepted April 19, 2024; published first April 23, 2024.

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