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Diet, physical activity, and body composition changes during the first year of treatment for childhood acute leukemia and lymphoma

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Abstract

Background—Children who undergo treatment for childhood acute lymphoblastic leukemia (ALL) and lymphoma are at risk for several long-term health problems. Obesity, for which survivors of ALL and lymphoma are also at risk, may further exacerbate these problems. This pilot study evaluates changes in physical activity and body composition among children being treated for ALL and lymphoma and their parents.

Procedures—Recently diagnosed adolescent ALL and lymphoma patients were recruited from two pediatric hematology and oncology clinics, and matched on age, race, and gender to healthy individuals in the community. Changes in diet, physical activity and body composition were collected at baseline, 6, and 12 months.

Results—All children (n = 15) were, on average, 10.3 years of age at enrollment, and were fairly evenly distributed with regard to gender. Analyses revealed a significant difference between cases and controls with respect to the change in BMI from baseline to 12 months (p = 0.01). Additionally, controls demonstrated a significantly greater increase in moderate-vigorous physical activity (MVPA) than the cases (229.8 Metabolic equivalent of tasks [METs] vs. 23.5 METs); indicating cases remained fairly inactive over the course of treatment.

Conclusion—Our data corroborate previous findings that, following treatment for ALL and lymphoma, childhood cancer survivors tend to be less active and at greater risk for obesity than their healthy peers. The present study, which assessed cases prospectively over a 12 month period during the early phases of treatment, extends prior reports by demonstrating that these outcomes are evident at an early stage in treatment.

Keywords

childhood acute lymphoblastic leukemia and lymphoma; obesity; physical activity; diet

INTRODUCTION

Children who undergo treatment for childhood acute lymphoblastic leukemia (ALL) and lymphoma are at risk for several long-term health problems including cardiopulmonary

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toxicity, osteopenia and secondary malignancy. Obesity, for which survivors of ALL and lymphoma are also at risk, may further exacerbate these problems. A positive energy balance leading to excess weight gain may be attenuated by eating a diet rich in nutrient-dense, low calorie foods (i.e., fruits, vegetables and whole grains), and pursuing optimal levels of physical activity during the course of treatment and into later survivorship.

A number of observational studies have reported a higher prevalence of overweight and obese individuals among adult survivors of ALL than among adults in the general population.(1-5) Extending these reports from single institutions, investigators reporting on data from the Childhood Cancer Survivor Study (CCSS), a cohort of adult survivors of childhood cancer, reported that both male and female survivors treated with chemotherapy + Cranial Radiation Therapy (CRT) > 20 grays (Gy) were found to be 1.8 and 2.6 times, respectively, more likely to become obese in comparison to a sibling-control group.(6) The risk of increased adiposity has also been reported among survivors of childhood lymphoma who were, on average, 11 years post-diagnosis.(7) Many of these studies, however, represent children treated on historical protocols. Less is known about how the current treatment protocols that rely on multi-agent chemotherapy and less on cranial radiation therapy influence children's weight and body composition.

It is also unknown when these patterns of changing body composition and energy balance behaviors begin to manifest. Although cachexia during the treatment and consolidation phases is common, few studies have examined how the initial year of treatment might affect changes in body composition, diet, and physical activity levels, which may ultimately predispose a child to becoming overweight as they move through the process of treatment and into long-term survival. At least two studies of children with ALL have observed increases in weight when compared from the time of diagnosis through 3 to 4 years post diagnosis.(8, 9) These studies suggest that children newly diagnosed with ALL and adult survivors of ALL and lymphoma are likely to show greater adiposity and increased BMI than would be expected. However, because these studies have relied on normative data rather than a comparison group, it is difficult to know if these changes are attributable to the treatment or to secular or regional cohort effects. Understanding the degree of change that occurs in the first year of treatment and the factors that contribute to weight gain among this population are essential to developing effective interventions to remediate excess weight gain.

The purpose of this study was to evaluate changes in body mass, diet, physical activity, and body composition among children being treated for two common childhood cancers—ALL and lymphoma—in comparison to a matched-health control group. To do this, serial measurements assessing diet intake, physical activity and body composition were conducted over the course of one year post-diagnosis.

METHODS

Eligibility, recruitment and enrollment

Children who were newly diagnosed with ALL or lymphoma were identified through patient registries at the pediatric hematology and oncology clinics at Duke University Medical Center (DUMC) and the University of North Carolina at Chapel Hill (UNC-CH), and were referred by their treating physicians. Patients were considered eligible if they were within 5 months of diagnosis, between the ages of 4 and 18 years, had a confirmed diagnosis of ALL or lymphoma, and their parents were able to speak and read English. Exclusion criteria included children who had Down syndrome or another chronic illness affecting appetite or weight regulation and those who were unable to engage in age appropriate physical activity (i.e., severe rheumatoid arthritis, or wheel-chair bound). Referred patients were contacted by

research staff during their regularly scheduled clinic visit at which time eligibility was confirmed and the study goals and procedures were fully explained to the patient and their legal guardian. Informed consent was obtained from parents and assent was obtained from children over the age of 12 years. Patients were offered incentives for completing baseline and follow-up assessments and measures ($20 for each of the 3 visits).

A control group consisting of healthy children was recruited simultaneously from the community. Children in the control group were matched 1:1 on age, race and gender to enrollees being treated for ALL/lymphoma. The study was approved by institutional review boards at DUMC, UNC-CH and The University of North Carolina at Greensboro.

Participants

During the 19-month recruitment period (April 2007-November 2008), there were 43 children diagnosed with ALL or lymphoma between the two institutions. A total of nine families refused to enroll citing competing time commitments and feeling overwhelmed by their child's new diagnosis and treatment. Others (n = 12) were deemed ineligible due to the study's age restriction, language requirement, or having another chronic condition affecting mobility. Of the 21 children initially consented, two dropped-out after consent due to parents feeling overwhelmed by their child's treatment, two dropped-out after completing the 6-month assessment for reasons related to other time commitments, one passed away due to their illness, and one moved out of state. This left 15 children with baseline, 6 month and 12 month data.

Measures

Anthropometrics and body composition—Child heights and weights were measured using a Seca portable stadiometer and Tanita BWB-800 digital scale. For descriptive purposes, BMI z scores and percentiles were calculated using the Centers for Disease Control and Prevention SAS macro which computes age and gender-adjusted standardized scores.(10)

A multiple detector fan-beam dual energy x-ray absorptiometry (DXA) densitometer (Hologic QDR4500 with version 12.7 software) calibrated daily using an anthropomorphic phantom was used to measure percent body fat (%BF), lean mass, and bone mineral density (BMD). The procedure involved having children maintain a recumbent position for approximately 10 minutes during a three scan session. Measurements of bone mineral content (BMC-g) and bone area (BA-cm^2) were obtained for the whole body, lumbar spine (L1-L4), and right hip. Whole body scans also provided readings for fat and lean mass to the nearest $1/10^{th}$ of a gram.

Physical activity—The GT1M ActiGraph accelerometer (Manufacturing Technologies Inc., Fort Walton Beach, FL) was used to objectively measure physical activity. This dual-axis accelerometer (dimensions: 3.8 × 3.7 × 1.8 cm; wt: 27 g) is designed to measure human motion in three different planes representing physical activity. All units recorded activity counts in 60-second epochs. The ActiGraph has been shown to provide valid and reliable estimates of physical activity in both adults (11, 12) and children (13-15). Accelerometers were worn on the waist above the right hip and secured using an elastic belt. Participants were instructed to wear the accelerometer continuously during the 24 hour day, except while bathing or swimming. They were asked to wear the accelerometer for 7 days and then return it to the research office using a pre-addressed, postage-paid envelope. A SAS program was modified slightly from its original use to read downloaded ActiGraph data and produce the necessary outcomes.(16) The data were reduced to include waking hours between 6am and 12am. The algorithm used 20 minute blocks of consecutive zero counts to identify the non-

wear time on days of measurement. A day was considered valid if the participant wore the accelerometer for at least 6 hours between 6am and 12am. Child-specific cut-points were used to categorize physical activity into the outcome categories of interest, namely sedentary (< 1.5 Metabolic equivalent of task [METs]) and moderate-vigorous physical activity - MVPA (> 3 METs).(17) Light physical activity (1.5 – 3 METs) was not included in the analyses. The decision to merge moderate and vigorous activity was made due to low levels of vigorous activity in the sample.

Dietary Intake—Information about each child's diet was collected via a food diary, which was turned in at each of the three study visits. Participants' parents were asked to choose two days during the week (one weekday and one weekend day) that their child was wearing the accelerometer and write down everything the child ate and drank on those days. Participants were provided with training to complete the food diaries, and were given a packet with 2-dimensional visuals to assist in determining portion sizes. For all foods and drinks consumed (except for water), participants were asked to record the time, the type and brand of food, the portion size, and whether the food was consumed as part of a meal or a snack. This data was analyzed using Nutrition Data System for Research software version 2007, developed by the Nutrition Coordinating Center (NCC) at The University of Minnesota in Minneapolis. Macro and micronutrient content, fruit and vegetable intake and the consumption of chips and salty snacks, sugar-sweetened beverages and milk were analyzed to identify trends across participants. This method has been validated with the doubly-labeled water method of energy expenditure and has been shown to be a fairly accurate method of assessing energy intake.(18-20)

Analyses

All data were reviewed and double-key entered into a custom-designed data entry program (CS Pro – US Census Bureau). To evaluate if the matching procedure was successful, baseline differences with respect to demographics between cases and controls were first tested. Paired t-tests were used to evaluate differences between matched cases and controls for main measures of diet, physical activity, and body composition at each time point. Paired t-tests also were used to evaluate differences between mean change scores (12 month values – baseline values). Incomplete data for physical activity and dietary data resulted in listwise deletion (n = 14 matched pairs available for physical activity and n = 9 matched pairs available for diet data).

RESULTS

Initial analyses revealed that case and control groups did not differ on age, gender or race. All children (n = 15) were, on average, 10.3 years of age at enrollment and were fairly evenly distributed with regard to gender (7 female and 8 male dyads). Given the small sample size, race was dichotomized as white and non-white; the sample was predominately white, with 3 cases and 2 controls being identified as "non-white". Most cases had a diagnosis of ALL (n = 12), while the remainder were diagnosed with lymphoma (n = 3). Only two of the cases received radiation; eight cases received Dexamethasone and the remaining seven received Prednisone. Cases were treated on the following protocols: AALL0232 (n = 7), AALL0331 (n = 3), AALL0434 (n = 1), ABVD (n = 2), CCG59704 (n = 1). The average time between diagnosis and consent was 58.3 days (SD = 44.4), with the range of 7 to 153 days.

Anthropometrics and body composition

Anthropometric measurements as observed at baseline, 6 months, and 12 months for cases and controls can be viewed in Table I. No statistically significant differences between cases

and controls were observed for each of the time points, though it is worth noting that, children with cancer tended to have lower BMI scores at baseline (cases BMI = 19.1 vs. control BMI = 21.4). There was a significant difference between cases and controls with respect to the change in BMI from baseline to 12 months (p = 0.01). The mean BMI score for cases increased by 2.31, and for controls, it only increased by 0.11. A graphic depiction of the change in BMI z scores for cases and controls can be seen in Figure 1.

Some significant differences in body composition were found between cases and controls (Table II). Cases had significantly higher percent fat body mass than controls at both baseline (30.3% vs. 24.9%, respectively) and 12 months (31.1% vs. 24.2%, respectively) and significantly less percent lean body mass than controls (6.3 kg less at baseline and 5.2 kg less) at 12 months. Figure 2 illustrates the changes seen in kg lean mass, fat mass and trunk fat mass for both cases and controls. Between baseline and 12 months, cases had sharper increases in both fat mass (1.4 kg more) and trunk fat mass (1.2 kg more) than controls. Cases also gained 0.6 kg more lean mass than controls during this time period. These increases were not statistically significant, however they are representative of a possible trend.

Physical activity

For directly measured physical activity, both cases and controls exhibited non-significant decreases in sedentary behavior over the course of the 12 month study (Table III). At 6 months and again at 12 months, cases performed significantly less moderate/vigorous physical activity (MVPA) than the controls. Over the 12-month course of the study, controls demonstrated a significantly greater increase in MVPA than the cases (229.8 METS vs. 23.5 METS); indicating cases remained fairly inactive over the course of the year relative to the controls.

Diet

There were few differences observed between cases and controls in terms of diet (Table IV). While cases had a slightly lower energy intake as measured in kcal than the healthy controls, there were no significant differences between cases and controls with regard to percent calories from carbohydrates, protein or fat. Cases and controls reported consuming, on average, 0 to 2 servings of fruits and vegetables per day, which is well below the USDA recommendation of 5 servings per day. At 12 months, there was a significant difference between cases and controls in the number of servings of sugared soda consumed per day, however the overall quantity was quite small (0.2 servings case vs. 1.3 servings control). No significant differences were observed in consumption of dairy products, which was measured discretely in servings of milk, cheese and yogurt.

DISCUSSION

The current study was intended to assess changes in diet, physical activity, and body composition among children treated for ALL and lymphoma compared to a healthy control group. Recently diagnosed ALL and lymphoma patients between the ages of 4 and 18 years were recruited from DUMC and UNC-CH pediatric hematology and oncology clinics and matched on age, race, and gender to healthy individuals in the community. Measurements were collected at baseline, 6, and 12 months.

While cases and controls did not differ significantly in terms of energy intake or diet quality, we observed some differences between groups with regard to body composition. Cases had significantly less lean body mass and had a significantly greater percentage of fat body mass than controls at baseline and at 12 months. BMI z scores (zBMI) were not significantly

different at any time point; however, there was a significant difference between groups with respect to zBMI change over time. Cases tended to have lower scores at baseline, which increased considerably over the course of a year and were slightly higher at 12 months. During this time period, cases also had sharper increases in fat mass and trunk fat mass than controls. Both cases and controls became less sedentary during the course of the study; though, they differed significantly in levels of physical activity. Controls not only engaged in significantly more MVPA at both 6 and 12 months, but the overall increase in MVPA for this group at 12 months was also considerably greater than was observed in the cases.

Our data corroborate previous findings that, following treatment for ALL and lymphoma, childhood cancer survivors tend to be less active and at greater risk for obesity than their healthy peers.(1-4) Many of these studies were retrospective (5, 8) and conducted a number of years post-diagnosis.(2, 4, 7) The present study, which assessed cases prospectively over a 12-month period during the early phases of treatment, extends findings of prior reports by demonstrating that these outcomes are evident at an early stage in treatment. Moreover, we obtained these results from a population treated using current protocols, of which only two cases received radiation. This is a further extension of the literature as previous research is largely based on data collected from patients treated using historical protocols,(3, 4, 8) which typically included irradiation. Although previous research concludes that irradiated patients are at greatest risk for obesity,(2, 8) our findings indicate that radiation is perhaps not the only factor contributing to obesity in childhood cancer survivors. While Nysom et. al.(7) compared their sample of cancer patients to local data on healthy controls, we are not aware of any studies using a matched-healthy control group. This is important because such methods help to elucidate deviations from normative growth and physical activity among cancer survivors.

While there is disagreement in the literature about whether gender moderates risk for obesity in childhood cancer survivors,(2, 8) our limited sample size hindered our ability to provide conclusive results regarding gender. Future studies would be strengthened if participants were recruited from multiple institutions in order to obtain a larger sample size needed to adequately explore gender differences. It is also important to highlight that the present study demonstrated a number trends, which despite failing to reach standard levels of significance, are none the less notable. Should these trends be confirmed; our data suggests that at diagnosis, cancer patients are in a diminished state that improves over the course of treatment and recovery. This trend could represent a regression to the mean, however, the DXA results show this weight gain is marked by greater increases in fat mass than lean relative to their health counterparts suggesting this may not just be a return to baseline. These trends were only observed over the course of the first 12 months of treatment and therefore more data are needed to determine whether these trends are enduring. In evaluating this research, we must bear in mind that cancer treatments vary in intensity, and there are phases in which the drugs and doses administered change. As a result, patients' diet and physical activity are likely to fluctuate throughout treatment.

There are a number of clinical issues relevant to cancer treatment that may make it difficult for patients to maintain a healthy diet and physical activity. Treatment regimens, such as chemotherapy, may impact lean muscle development, making participation in physical activity much less enjoyable due to the resulting increase in fatigue and diminished coordination. Various treatments may also alter the way foods taste resulting in children to narrowing their food variety. Both dexamethasone and prednisone, steroids commonly used in conjunction with chemotherapy, are known to significantly increase appetite (21) making it difficult for patients and parents to choose healthy food options. Furthermore, after an extended period of receiving corticosteroids, patients may develop habits of eating in the absence of hunger, hindering the ability to recognize satiety after treatment ends. In short,

adopting a healthy lifestyle during treatment can be an enormous challenge for patients and families.

The Children's Oncology Group recommends targeting the beginning of the maintenance phase for nutritional and behavioral interventions.(5) To date, however, there has been little progress toward the development and evaluation of evidence-based health promotion programs for this patient population. Given the changes to diet, physical activity, and body composition during the first year of treatment, it may be important to promote awareness of the necessity of engaging in healthy eating habits and participating in physical activity early during initial treatment phases. As children begin to regain strength and stamina, it will become essential to have health promotion programs available that can be disseminated through long-term survivorship clinics. Further research is needed to identify patient-centered strategies that will enhance the likelihood of children and families adopting healthy lifestyles as they move into the maintenance phase of treatment. Given the geographic dispersion of children at any one pediatric treatment center and the infrequent visitation of patients during this phase, intervention programs may need to capitalize on distance-based methods and remote delivery (mailings, eHealth/mHealth). While continued research may be needed to further elucidate the mechanisms by which children with ALL and lymphoma are at increased risk for obesity later in life, the time is ripe to begin advancing health promotion interventions tailored to this unique population.

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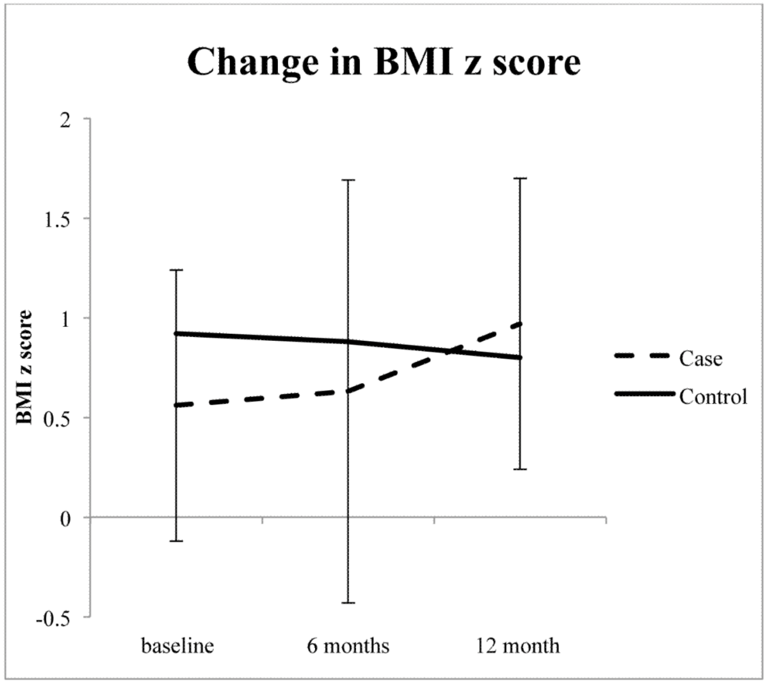

Fig. 1.
Changes in BMI z Score

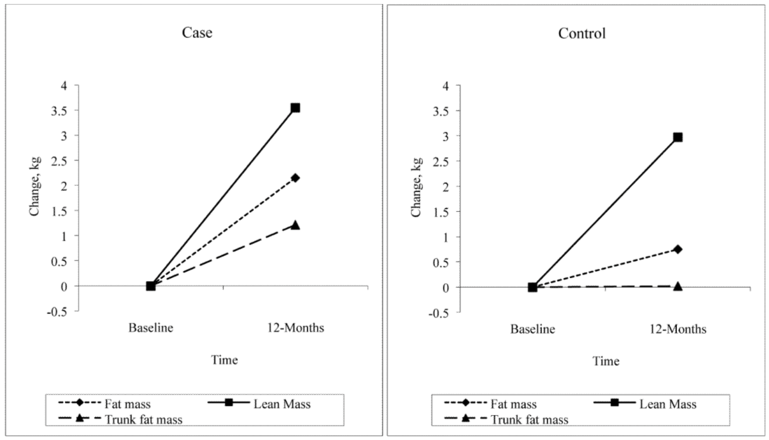

Fig. 2.
Change in fat mass and lean body mass from baseline to 12 months by group

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TABLE I

Anthropometrics at baseline, 6 months, and 12 months

Variable	Baseline (n= 15)		6 months (n = 15)		12 Months (n= 15)		Mean Δ		
	Mean	SD	Mean	SD	Mean	SD	Base-12M	SD	p-value
BMI z score									
Case	0.56	(0.68)	0.63	(1.06)	0.97	(0.73)	0.41	(0.61)	
Control	0.92	(0.88)	0.88	(0.90)	0.80	(0.85)	−0.12	(0.29)	0.01
BMI									
Case	19.13	(2.60) †	20.25	(4.58)	21.44	(4.33)	2.31	(2.68)	
Control	21.06	(3.84) †	21.36	(4.29)	21.17	(3.87)	0.11	(1.12)	0.01
Weight z score									
Case	0.57	(0.82)	0.58	(1.24)	0.84	(1.01)	0.26	(0.59)	
Control	0.80	(1.10)	0.73	(1.13)	0.67	(1.07)	−0.12	(0.20)	0.04
Height z score									
Case	0.41	(1.24)	0.18	(1.25)	0.13	(1.13)	−0.28	(0.37)	
Control	0.24	(1.08)	0.16	(1.04)	0.16	(1.06)	−0.08	(0.24)	0.12

† Baseline BMI approached significance (p = 0.055)

TABLE II

Body composition from baseline to 12 months

	Baseline (n= 15)		12 Months (n = 15)		Mean Δ		
Variable M	**Mean**	**SD**	**Mean**	**SD**	**Base-12M**	**SD**	**p-value**
BMC, */kg							
Case	1.36	(0.71)	1.43	(0.68) ‡	0.07	(0.16)	
Control	1.47	(0.65)	1.65	(0.69) ‡	0.17	(0.11)	0.00
BMD, */g/cm**2							
Case	0.88	(0.19)	0.91	(0.16)	0.03	(0.08)	
Control	0.88	(0.19)	0.93	(0.19)	0.05	(0.04)	0.13
Fat body mass, kg							
Case	12.59	(6.75)	15.83	(10.46)	3.23	(5.22)	
Control	11.97	(7.79)	12.33	(8.23)	0.36	(2.36)	0.09
Lean body mass, kg							
Case	27.63	(12.74) ‡	31.34	(13.20) ‡	3.71	(2.01)	
Control	33.97	(15.38) ‡	36.55	(16.03) ‡	2.58	(2.27)	0.23
Trunk fat mass, kg							
Case	5.14	(3.33)	6.55	(5.32)	1.41	(2.77)	
Control	4.31	(3.61)	4.32	(3.6)	0.01	(1.2)	0.09
% fat body mass							
Case	30.25	(5.87) ‡	31.07	(8.75) ‡	0.82	(5.63)	
Control	24.88	(9.17)‡	24.21	(9.62) ‡	−0.67	(2.45)	0.36
% lean body mass							
Case	66.53	(5.60) ‡	65.98	(8.31) ‡	−0.56	(5.21)	
Control	71.96	(8.70) ‡	72.46	(9.11)‡	0.50	(2.37)	0.49

*/*BMC=bone mineral content; BMD=bone mineral density (g/cm**2).

‡Means of cases and controls are significantly different ($p < 0.05$)

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TABLE III

Children's sedentary and MVPA from baseline to 12 months

Variable	Baseline (n = 14)		6 Months (n = 14)		12 Months (n = 14)		Mean Δ		
	Mean	SD	Mean	SD	Mean	SD	Base-12M	SD	p-value
Sedentary									
Case	640.03	(291.29)	636.89	(281.96)	596.04	(238.49)	−43.98	(302.3)	
Control	519.00	(252.22)	484.60	(161.29)	489.80	(239.11)	−29.20	(209.26)	0.89
MVPA*									
Case	113.60	(218.68)	214.83	(233.91)‡	137.09	(218.02)‡	23.49	(111.28)	
Control	152.21	(208.36)	482.84	(335.93)‡	382.01	(318.51)‡	229.80	(281.69)	0.01
Counts									
Case	298.44	(281.5)	604.25	(615.57)‡	469.97	(523.75)‡	171.53	(356.32)	
Control	499.89	(712.32)	1615.44	(1091.55)‡	1526.20	(1437.31)‡	1026.31	(1381.82)	0.02

*MVPA = moderate/vigorous physical activity

‡Indicates significant difference between cases and controls

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Table IV

Average intake of selected nutrients and food groups at baseline and 12 months

		Baseline (n = 8)		12 Months (n = 8)	
		Mean	***SD***	**Mean**	***SD***
Energy (kcal)	Case	1521	650	1610	354
	Control	1685	630	1831	435
% Calories from Carbohydrates	Case	51.7	7.3	47.9	6.2
	Control	53.1	3.9	54.5	7.9
% Calories from Protein	Case	16.8	2.9	16.6	2.5
	Control	16.5	3.9	15.3	3.2
% Calories from Fat	Case	32.7	6.4	36.5	6.1
	Control	31.2	5.0	31.1	8.5
Calcium (mg)	Case	961	757	759	281
	Control	1112	349	763	290
Added Sugar (g)	Case	50	21	46	21
	Control	55	31	95	46
Food Groups (serving size)					
Fruit (1/2 cup)[1]	Case	0.39	.61	1.06	1.25
	Control	0.41	0.40	0.58	0.74
Vegetables (1/2 cup)[2]	Case	2.75	4.10	1.33	.78
	Control	1.08	.63	1.29	.91
Fried Potatoes and Snack Chips (1/2 cup or 1 ounce)	Case	.95	1.09	.50	.56
	Control	.72	1.01	.71	.72
Soda/Soft drinks (1 cup)	Case	.48	.80	.00	.00
	Control	.09	.27	1.14	1.32 ‡
Sweet Beverages (non-soda) (1 cup)	Case	.61	.98	.61	.68
	Control	.25	.55	.34	.59
Milk (Whole, Reduced Fat, Skim (1 cup)	Case	.71	.51	.55	.84
	Control	1.62	1.22	.88	.82
Cheese (1 and V ounce)	Case	.81	.59	.92	1.21
	Control	.80	.56	.60	.28

		Baseline (n = 8)		12 Months (n = 8)	
		Mean	***SD***	**Mean**	***SD***
	Case	.01	.04	.04	.12
Yogurt (1 cup)	Control	.09	.17	.07	.14

[‡] Means of cases and controls are significantly different ($p < 0.05$)

[1] Does not include 100% fruit juice

[2] Does not include fried potatoes