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PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK FACTORS IN CHILDHOOD CANCER SURVIVORS

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Abstract

Background—Childhood cancer survivors (CCS) are at high risk of developing treatment-related late effects, including cardiovascular disease and diabetes. Late effects can be exacerbated by low physical activity (PA) levels. Relationships between PA and cardiovascular risk factors during childhood have not been well described in CCS.

Procedure—PA and cardiovascular risk factors were measured cross-sectionally in 319 CCS and 208 sibling controls aged 9–18 years. Comparisons between CCS and controls and associations of outcomes with PA (dichotomized at 60 minutes/day or treated as continuous) were performed with linear regression.

Results—Among CCS, the high PA group had lower percent fat mass (24.4 vs. 29.8%, $P < 0.0001$), abdominal subcutaneous fat (67.9 vs. 97.3 cm³, $P = 0.0004$), and abdominal visceral fat (20.0 vs. 24.9 cm³, $P = 0.007$) and greater lean body mass (41.3 vs. 39.5 kg, $P = 0.009$) than the low PA group. Comparing CCS to controls, differences in waist circumference ($P_{\text{interaction}} = 0.04$), percent fat mass ($P_{\text{interaction}} = 0.04$), and abdominal subcutaneous ($P_{\text{interaction}} = 0.02$) and visceral ($P_{\text{interaction}} = 0.004$) fat between low and high PA groups were greater in CCS than controls, possibly due to greater overall adiposity in CCS.

Conclusions—High PA in CCS resulted in an improved cardiovascular profile, consisting primarily of lower fat mass and greater lean mass, similar to that observed in controls. This suggests interventions directed to increase PA in CCS may reduce the risk of future cardiovascular disease.

Keywords

epidemiology; pediatric oncology; late effects; long term survival

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CONFLICT OF INTEREST STATEMENT: Nothing to declare.

INTRODUCTION

Over 12,000 children are diagnosed with cancer each year in the United States [1]. Due to marked improvements in treatment, over 83% of these children now survive for five years or more [2]. The number of childhood cancer survivors (CCS) currently exceeds 375,000 individuals in the United States and continues to rise [2]. Despite advances in cancer treatment, CCS face significantly increased risks of numerous treatment-related adverse late effects, including negative impacts on cardiovascular health. Notably, adult CCS experience higher than expected risks of obesity [3, 4], type 2 diabetes mellitus [5], and cardiovascular disease [6, 7], and are seven times more likely to die from cardiovascular disease than similar-aged individuals from the general population [8]. Vascular damage has been detected among both adolescent and adult CCS and is thought to be a subclinical sign of cardiovascular morbidity in CCS [9, 10].

These late effects may be exacerbated by the low levels of physical activity (PA) commonly observed among CCS [11]. Sedentary lifestyle (defined as no self-reported leisure-time PA in previous month) has been associated with obesity, hypertension, and impaired glucose tolerance among adult CCS from the Childhood Cancer Survivor Study [12]. Similarly, in a small investigation of adult survivors of pediatric sarcoma, decreased self-reported activity levels were associated with an increased number of prevalent cardiovascular risk factors (e.g., central obesity, dyslipidemia, hyperglycemia, and hypertension) [13].

The relationships between PA and cardiovascular risk factors among children who survived childhood cancer have not been well established. To address this gap in knowledge, this analysis aimed to 1) examine the cross-sectional association of self-reported PA with directly measured cardiovascular risk factors among CCS and sibling control children and to 2) assess whether the associations between PA and cardiovascular risk factors differ between CCS and controls. It was hypothesized that 1) CCS and controls who were more physically active would have more favorable levels of cardiovascular risk factors than those who were less active and 2) associations between PA and cardiovascular risk factors would differ based on CCS/control status. Cardiovascular risk factors have been reported for this study population in prior publications [14, 15]; this analysis extends that work.

METHODS

Study Design

The study was approved by the Institutional Review Board Human Subjects Committees at the University of Minnesota Medical Center and Children's Hospitals and Clinics of Minnesota. All parents and pediatric participants provided written informed consent and assent, respectively. CCS were selected from Pediatric Oncology databases and were eligible to participate if they were treated for cancer at the University of Minnesota/Fairview-University Medical Center or the Children's Hospitals and Clinics of Minneapolis and St. Paul, were 9–18 years old, were in remission, and had survived ≥ 5 years after diagnosis. Hematopoietic cell transplant recipients were excluded from the study because an identical companion study was being performed simultaneously in a population of hematopoietic cell

transplant survivors. Sibling controls were eligible to participate if they were 9–18 years of age at the time of examination and had never had cancer.

A summary flow chart of CCS screening and recruitment is shown in Figure 1. Of the 723 eligible CCS identified, 66 could not be located. The remaining 657 were contacted, and consent for participation was obtained from 322 (49%). Three CCS were determined ineligible after consent, leaving a final study population of 319 CCS. There were no significant differences in age, sex, race, diagnosis, age at diagnosis, or length of follow-up (time from diagnosis to study evaluation) between the 319 CCS participants and the 338 CCS non-participants. Based on similarities in therapeutic exposures, CCS were grouped into three major diagnostic groups: leukemia (n=110), central nervous system tumors (n=82), and solid tumors (n=127).

Siblings were informed of the study by parents, and if they agreed to participate they were evaluated at the same time as the CCS. From the 322 families enrolled (including the 3 later determined to be ineligible), 164 had no eligible or consenting siblings, 124 had one sibling who participated, and 33 had more than one sibling participate (n=72). (The number of potentially eligible siblings from each family was not collected, nor was demographic information about non-participants). Twelve additional siblings from the companion study of hematopoietic cell transplant survivors who met the same sibling eligibility criteria were also included in the final control group (n=208).

Data Collection

All participants underwent a two-day examination at the University of Minnesota Clinical Research Center/Clinical and Translational Science Institute (CTSI). Height, weight, waist circumference, Tanner stage, and blood pressure were assessed according to standard protocols, as previously described [15]. Fat mass and lean body mass were measured using dual-energy X-ray absorptiometry (DXA, Lunar Prodigy scanner, software version 9.3; General Electric Medical Systems, Madison, WI). Measurements of abdominal visceral and subcutaneous adipose tissue were also obtained by computed tomography using a Siemens Sensation 16 (Siemens Medical Solutions, Malvern, PA, USA) with two separate 10 mm slices obtained at the L4–L5 interspace. The two images were subdivided into five mm slices and the 1st and 3rd five mm slices were combined and analyzed for visceral adipose tissue. The upper limit of adipose tissue density was –30 Hounsfield units (HU) and the lower limit was –190 HU. Image slices were individually analyzed by a trained technician using Fat Scan version 3.0 software (N2 System, Osaka, Japan).

After a 10- to 12-hour overnight fast, the hyperinsulinemic euglycemic clamp method was used to assess insulin sensitivity, as described previously.[15, 16] Insulin infusion was started at time 0 at a rate of 1 mU/kg/min for 3 hours. An infusion of 20% glucose was given and adjusted to maintain euglycemia (serum glucose level of 100 mg/dL [5.6 mmol/L]) with plasma glucose determined every 10 minutes. Insulin sensitivity (M) was determined by the amount of glucose required to maintain euglycemia in the final 40 minutes of the clamp study and expressed as mg/kg/min of glucose with adjustment for lean body mass (M_{lbm}). Lower M_{lbm} values are indicative of lower insulin sensitivity (i.e., greater insulin resistance).

Fasting blood samples obtained at the start of the insulin clamp were analyzed for serum lipid levels (low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides), serum insulin, and plasma glucose using a Vitros 5600 (Ortho-Clinical Diagnostics, Inc., Rochester, NY), a chemoluminescence immunoassay (Immulin Insulin DPC, Los Angeles, CA), and a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA), respectively. LDL-C was calculated by the Friedewald equation. Homeostasis model assessment insulin resistance (HOMA-IR) was calculated with fasting insulin and glucose values using the equation $HOMA-IR = [(fasting\ glucose\ units\ of\ mmol/L * insulin\ units\ in\ \mu U/mL)/22.5]$ [17].

Following 15 minutes of quiet rest in the supine position, vascular images were obtained of the left common carotid artery using a conventional ultrasound scanner (Acuson, Sequoia 512, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA) with a 15–8 MHz linear array probe. Systolic and diastolic blood pressures were recorded with an automated blood pressure sphygmomanometer during the 10-sec carotid measurements. To measure carotid elasticity properties, electronic wall-tracking software was used for analysis of carotid cross-sectional compliance (cCSC) and distensibility (cCSD) (Vascular Research Tools 5, Medical Imaging Application, LLC, Iowa City, IA, USA).

To assess PA, participants completed the Modifiable Activity Questionnaire for Adolescents (MAQ-A), which was self-administered with parental supervision, as needed. For this study, we focused on past year leisure-time PA. Participants reported activities in which they had participated at least ten times during the past year in their leisure time, along with the number of months over the year, the average number of days per week, and the average minutes per day that each activity was performed. The MAQ-A has been shown to provide valid and reproducible estimates of past year leisure-time PA [18, 19].

Statistical Analysis

All analyses were conducted with SAS version 9.2 (SAS Institute, Inc., Cary, NC). Participants who met the U.S. federal recommendation of 60 minutes per day of moderate-to-vigorous PA in children [20, 21] were categorized as high PA while those reporting less than 60 minutes per day were categorized as low PA. Descriptive statistics are expressed as frequencies and percents or mean $\pm$ standard error (SE), as appropriate. All analyses including data from sibling controls were implemented in SAS's GENMOD procedure using generalized estimating equations (GEE) to account for intra-family correlation, with the exchangeable working correlation and robust variance estimates. All adjusted comparisons used multivariable linear regression models with adjustments for age, sex, race/ethnicity, and Tanner stage. As indicated, models were further adjusted for percent fat mass, height, and/or diagnosis when appropriate. Adjusted means were evaluated at the mean levels of covariates included in the models. A two-sided P -value <0.05 was considered to be statistically significant, although because of the large number of statistical tests carried out, those between 0.01 and 0.05 should be viewed with caution.

RESULTS

Table I presents demographic characteristics of the study population; Table II describes measures of body composition and physical activity. CCS were on average one year older than controls, but Tanner stage was similar between the two groups. CCS were shorter, had greater waist circumference and percent fat mass and lower lean body mass than controls, but there were no significant differences in weight, body mass index (BMI), abdominal subcutaneous fat, and abdominal visceral fat. After adjustment for percent fat mass, CCS had higher LDL-C (88.0 ± 1.7 vs. 84.1 ± 2.1 mg/dL, $P = 0.03$) and lower insulin sensitivity (M_{lbm}) (12.2 ± 0.3 vs. 13.3 ± 0.4 mg/kg/min, $P = 0.002$) and cCSD (30.7 ± 0.5 vs. 32.7 ± 0.6 %, $P = 0.002$) than controls. As shown in Table II, CCS were less physically active in their leisure time compared to controls.

Table III shows associations of cardiovascular risk factors with PA level ("High vs. low PA") in CCS and controls. Among CCS, the high PA group had lower percent fat mass, abdominal subcutaneous fat, and abdominal visceral fat, greater lean body mass, and marginally greater ($P = 0.07$) insulin sensitivity (M_{lbm}) compared to the low PA group. Among controls, the high PA group had greater lean body mass and marginally lower ($P = 0.05$) percent fat mass but no difference in abdominal fat and insulin sensitivity compared to the low PA group. Among both CCS and controls, there were no significant differences between the low and high PA groups for the following risk factors: waist circumference, triglycerides, HDL-C, LDL-C, systolic and diastolic blood pressure, HOMA-IR, cCSC, cCSD, and cIMT.

To assess whether the PA effect differed between CCS and controls, we tested the interaction between CCS/control status and PA level (high vs. low) for each cardiovascular risk factor. As depicted by the interaction plots in Figure 2, the associations between PA and waist circumference, percent fat mass, abdominal subcutaneous fat, and abdominal visceral fat appeared to be stronger in CCS than controls (all $P_{\text{interaction}} < 0.05$). In general, CCS had sharper reductions in these risk factors at the higher PA level compared to controls. There was no such evidence of effect modification by CCS/control status for the other risk factors examined in Table III (all $P_{\text{interaction}} > 0.05$).

DISCUSSION

This study found that CCS who reported higher levels of PA had lower percent fat mass and abdominal subcutaneous and visceral fat, greater lean body mass, and slightly greater insulin sensitivity compared to CCS who reported lower levels of PA. However, controls who reported higher PA had only greater lean body mass and slightly lower percent fat mass compared to controls who reported lower PA. This result may be explained by the fact that CCS have greater potential for change than controls simply because they start with poorer levels of certain cardiovascular risk factors that have finite "normal" or "healthy" ranges. In other words, while an already healthy cardiovascular profile could be improved slightly (perhaps to the top of the normal range) with PA alone, a sub-optimal or abnormal cardiovascular profile could be improved more dramatically to reach normal or even optimal levels with the same amount of PA.

Prior knowledge is very limited regarding these relationships in CCS; this study complements the literature by supporting associations previously observed between PA and adiposity in adult CCS and extends the findings to children. In a recent study of 117 adult survivors of childhood acute lymphoblastic leukemia (ALL), greater PA energy expenditure was associated with lower percent body fat but was not associated with waist circumference, HOMA-IR, or metabolic syndrome [22]. A 16-week home-based exercise intervention in a small group of 16- to 30-year-old survivors of childhood ALL resulted in significant improvements in measures of adiposity and HOMA-IR, while cIMT, lipids, and fasting plasma glucose remained unchanged; the effect on blood pressure was variable [23, 24]. The current study is the first to examine the associations between PA and directly measured subcutaneous fat, visceral fat, insulin sensitivity (M_{Ibm}), and arterial compliance and distensibility in CCS in general and specifically during childhood. Hoffman et al. reported that CCS aged <18 years performed more poorly on measures of physical function despite reporting similar levels and types of PA as their sibling controls [25]. However, measures of physical function (strength, mobility) are not equivalent to measures of cardiovascular risk or PA.

Results of the current study indicate that PA may be a useful tool for limiting excess fat mass while preserving lean mass and possibly improving insulin sensitivity in CCS children. Previously, increased fat mass [26] and decreased lean mass [27] have been independently associated with greater insulin resistance, highlighting the importance of reducing excess fat mass while simultaneously maintaining or increasing lean mass. In fact, sarcopenia, a condition of reduced lean skeletal muscle mass, and obesity have been shown to have an additive effect on insulin resistance [28]. Previous studies have also found that healthy children who are more physically active are leaner and have greater insulin sensitivity (independent of adiposity) than their less active peers, especially when engaged in vigorous PA [29–33]. After dichotomizing by high/low PA groups we documented statistically significant associations of PA with measures of adiposity but not with measures of insulin sensitivity; this may be due to low power in each of the groups, the use of a relatively crude measure of PA, and the fact that we evaluated a young population (children) in whom the elevations of cardiovascular risk factor levels are less pronounced than in the previously reported adult studies.

Unfavorable vascular endothelial thickness and function are important early markers of subclinical atherosclerosis and increased cardiovascular disease risk. Among adults, regular PA has been shown to delay, slow, or even prevent the age-associated decline in early measures of atherosclerosis such as vascular compliance and distensibility [34]. We have previously shown in this cohort that survivors of leukemia had lower carotid artery distensibility and compliance, indicating increased arterial stiffness, when compared to controls [14]. The absence of a PA effect on the vascular markers may again be due to low power, the use of a relatively crude measure of PA, and the fact that the current study was focused on children, who have not yet developed clinically significant vascular abnormalities. It is possible that as these children progress into adulthood, small deficits will become more prominent and established cardiovascular risk factors. It is well known in pediatric populations that cardiovascular risk is a continuum and that threshold levels and dichotomized classifications are less useful in establishing risk levels than in adults [35].

This study's cross-sectional design and retrospective measure of PA restricted the ability to make causal inferences. Prospective longitudinal cohorts or randomized controlled trials will be needed to verify such inferences. Another limitation was the inability to completely control for differences in treatment. Diagnostic group served as a proxy for treatment regimen in this analysis. In post-hoc analyses, controlling for cranial radiation, corticosteroid therapy, or vincristine chemotherapy instead of diagnosis did not substantially alter the results. We also considered possible implications of lower extremity surgical procedures such as amputation, femur resection, and/or limb salvage, but too few CCS were affected (one amputation, two femur resections, and one limb salvage) to permit an analysis.

The pattern of adverse body composition in CCS suggests that as these children progress into adulthood, these levels will likely become overtly abnormal. The finding that higher PA was associated with levels of risk factors similar to those observed in controls suggests that greater levels of PA could serve as a tangible target in mitigating the already high cardiovascular risk of CCS.

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References

1. American Cancer Society. Cancer facts & figures. 2011. <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspe-029771.pdf>. Accessed April 9, 2014
2. Howlader, N.; Noone, AM.; Krapcho, M.; Garshell, J., et al. SEER cancer statistics review 1975–2010. National Cancer Institute; http://seer.cancer.gov/csr/1975_2010/. Accessed April 9, 2014
3. Siviero-Miachon AA, Spinola-Castro AM, Guerra-Junior G. Adiposity in childhood cancer survivors: Insights into obesity physiopathology. *Arq Bras Endocrinol Metabol*. 2009; 53:190–200. [PubMed: 19466212]
4. Veringa SJ, van Dulmen-den Broeder E, Kaspers GJVeening MA. Blood pressure and body composition in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2012; 58:278–282. [PubMed: 21793179]
5. Meacham LR, Sklar CA, Li S, Liu Q, et al. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: A report for the childhood cancer survivor study. *Arch Intern Med*. 2009; 169:1381–1388. [PubMed: 19667301]
6. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: Retrospective analysis of the childhood cancer survivor study cohort. *Bmj*. 2009; 339:b4606. [PubMed: 19996459]
7. Tukenova M, Guibout C, Oberlin O, Doyon F, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol*. 2010; 28:1308–1315. [PubMed: 20142603]
8. Mertens AC, Liu Q, Neglia JP, Wasilewski K, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: The childhood cancer survivor study. *J Natl Cancer Inst*. 2008; 100:1368–1379. [PubMed: 18812549]
9. Brouwer CA, Postma A, Hooimeijer HL, Smit AJ, et al. Endothelial damage in long-term survivors of childhood cancer. *J Clin Oncol*. 2013
10. Dengel DR, Ness KK, Glasser SP, Williamson EB, et al. Endothelial function in young adult survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2008; 30:20–25. [PubMed: 18176175]

11. Stolley MR, Restrepo J, Sharp LK. Diet and physical activity in childhood cancer survivors: A review of the literature. *Ann Behav Med*. 2010; 39:232–249. [PubMed: 20559768]
12. Meacham LR, Chow EJ, Ness KK, Kamdar KY, et al. Cardiovascular risk factors in adult survivors of pediatric cancer—a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev*. 2010; 19:170–181. [PubMed: 20056636]
13. Hoffman KE, Derdak J, Bernstein D, Reynolds JC, et al. Metabolic syndrome traits in long-term survivors of pediatric sarcoma. *Pediatr Blood Cancer*. 2008; 50:341–346. [PubMed: 17918262]
14. Dengel DR, Kelly AS, Zhang L, Hodges JS, et al. Signs of early sub-clinical atherosclerosis in childhood cancer survivors. *Pediatr Blood Cancer*. 2013
15. Steinberger J, Sinaiko AR, Kelly AS, Leisenring WM, et al. Cardiovascular risk and insulin resistance in childhood cancer survivors. *J Pediatr*. 2012; 160:494–499. [PubMed: 21920542]
16. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, et al. Insulin resistance during puberty: Results from clamp studies in 357 children. *Diabetes*. 1999; 48:2039–2044. [PubMed: 10512371]
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, et al. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985; 28:412–419. [PubMed: 3899825]
18. Aaron DJ, Kriska AM, Dearwater SR, Cauley JA, et al. Reproducibility and validity of an epidemiologic questionnaire to assess past year physical activity in adolescents. *Am J Epidemiol*. 1995; 142:191–201. [PubMed: 7598119]
19. Aaron DJ, Storti KL, Robertson RJ, Kriska AM, et al. Longitudinal study of the number and choice of leisure time physical activities from mid to late adolescence: Implications for school curricula and community recreation programs. *Arch Pediatr Adolesc Med*. 2002; 156:1075–1080. [PubMed: 12413332]
20. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American heart association's strategic impact goal through 2020 and beyond. *Circulation*. 2010; 121:586–613. [PubMed: 20089546]
21. U.S. Department of health and human services. Physical activity guidelines for Americans. Vol. 2008. Washington dc;
22. Tonorezos ES, Robien K, Eshelman-Kent D, Moskowitz CS, et al. Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia. *Cancer Causes Control*. 2013; 24:313–321. [PubMed: 23187859]
23. Jarvela LS, Kempainen J, Niinikoski H, Hannukainen JC, et al. Effects of a home-based exercise program on metabolic risk factors and fitness in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2012; 59:155–160. [PubMed: 22184098]
24. Jarvela LS, Niinikoski H, Heinonen OJ, Lahtenmaki PM, et al. Endothelial function in long-term survivors of childhood acute lymphoblastic leukemia: Effects of a home-based exercise program. *Pediatr Blood Cancer*. 2013; 60:1546–1551. [PubMed: 23606359]
25. Hoffman MC, Mulrooney DA, Steinberger J, Lee J, et al. Deficits in physical function among young childhood cancer survivors. *J Clin Oncol*. 2013; 31:2799–2805. [PubMed: 23796992]
26. Muller MJ, Lagerpusch M, Enderle J, Schautz B, et al. Beyond the body mass index: Tracking body composition in the pathogenesis of obesity and the metabolic syndrome. *Obes Rev*. 2012; 13(Suppl 2):6–13. [PubMed: 23107255]
27. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third national health and nutrition examination survey. *J Clin Endocrinol Metab*. 2011; 96:2898–2903. [PubMed: 21778224]
28. Moon SS. Low skeletal muscle mass is associated with insulin resistance, diabetes, and metabolic syndrome in the Korean population: The Korea national health and nutrition examination survey (KNHANES) 2009–2010. *Endocr J*. 2014; 61:61–70. [PubMed: 24088600]
29. Jimenez-Pavon D, Kelly J, Reilly JJ. Associations between objectively measured habitual physical activity and adiposity in children and adolescents: Systematic review. *Int J Pediatr Obes*. 2010; 5:3–18. [PubMed: 19562608]
30. Kim Y, Lee S. Physical activity and abdominal obesity in youth. *Appl Physiol Nutr Metab*. 2009; 34:571–581. [PubMed: 19767790]

31. Baxter-Jones AD, Eisenmann JC, Mirwald RL, Faulkner RA, et al. The influence of physical activity on lean mass accrual during adolescence: A longitudinal analysis. *J Appl Physiol.* 2008; 105:734–741. [PubMed: 18467546]
32. Berman LJ, Weigensberg MJ, Spruijt-Metz D. Physical activity is related to insulin sensitivity in children and adolescents, independent of adiposity: A review of the literature. *Diabetes Metab Res Rev.* 2012; 28:395–408. [PubMed: 22389103]
33. Schmitz KH, Jacobs DR Jr, Hong CP, Steinberger J, et al. Association of physical activity with insulin sensitivity in children. *Int J Obes Relat Metab Disord.* 2002; 26:1310–1316. [PubMed: 12355326]
34. Seals DR, Desouza CA, Donato AJTanaka H. Habitual exercise and arterial aging. *J Appl Physiol.* 2008; 105:1323–1332. [PubMed: 18583377]
35. Steinberger J, Daniels SR, Eckel RH, Hayman L, et al. Progress and challenges in metabolic syndrome in children and adolescents: A scientific statement from the american heart association atherosclerosis, hypertension, and obesity in the young committee of the council on cardiovascular disease in the young; council on cardiovascular nursing; and council on nutrition, physical activity, and metabolism. *Circulation.* 2009; 119:628–647. [PubMed: 19139390]

Figure 1.

Flow chart showing the screening and recruitment of childhood cancer survivors.

Abbreviations: CCS, childhood cancer survivors.

Figure 2.

CCS/control status $\times$ PA level (low versus high PA) interaction plots for waist circumference, percent fat mass, abdominal subcutaneous fat, and abdominal visceral fat. These plots assess whether the difference between high and low PA was the same for CCS and controls for each of these four cardiovascular risk factors.

Abbreviations: CCS, childhood cancer survivors; PA, physical activity.

Table 1

Characteristics of CCS and Sibling Controls

		CCS (N=319)		Controls (N=208)		
		N (%)	Mean ± SE	N (%)	Mean ± SE	P
Age (years)			14.6 ± 0.1		13.6 ± 0.2	<0.0001
Sex						
Male		171 (53.6)		112 (53.9)		0.93
Female		148 (46.4)		96 (46.2)		
Race/ethnicity^a						0.0008
White Non-Hispanic		274 (85.9)		194 (93.3)		
Others		45 (14.1)		14 (6.7)		
White Hispanic		4 (1.3)		4 (1.9)		
Black		14 (4.4)		2 (1.0)		
Other		27 (8.5)		8 (3.8)		
Tanner Stage			3.6 ± 0.1		3.3 ± 0.1	0.07
1		33 (10.3)		34 (16.5)		
2		54 (16.9)		31 (15.1)		
3		39 (12.2)		36 (17.5)		
4		88 (27.6)		45 (21.8)		
5		105 (32.9)		60 (29.1)		
Diagnosis						
Leukemia (ALL, AML)		110 (34.5)		NA		
Central nervous system		82 (25.7)				
Solid tumors		127 (39.8)				
Time from diagnosis to study (years)			10.1 ± 0.2		NA	
Cranial Radiation Therapy						
Yes		37 (11.6)		NA		

	CCS (N=319)		Controls (N=208)		P
	N (%)	Mean ± SE	N (%)	Mean ± SE	
No	282 (88.4)				
Corticosteroid Therapy					
90 days	94 (29.5)		NA		
<90 days	225 (70.5)				
Vincristine Chemotherapy					
Yes	212 (66.5)		NA		
No	107 (33.5)				

^aWhite Hispanic, black, and other categories were collapsed for the comparison between CCS and controls. ALL-, acute lymphoblastic leukemia; AML-, acute myeloid leukemia; CCS, childhood cancer survivors; NA, not applicable; SE, standard error.

Table II

Body Composition and Physical Activity in CCS and Sibling Controls

	CCS (N=319)	Controls (N=208)	
	Mean $\pm$ SE	Mean $\pm$ SE	<i>P</i>
Height (cm)	158.2 $\pm$ 0.6	159.9 $\pm$ 0.7	0.01
Weight (kg)	57.2 $\pm$ 1.1	57.0 $\pm$ 1.2	0.85
Body Mass Index (kg/m ²)	22.4 $\pm$ 0.3	21.8 $\pm$ 0.4	0.08
Waist Circumference (cm)	73.1 $\pm$ 0.9	71.1 $\pm$ 1.0	0.02
Percent Fat Mass (%)	28.1 $\pm$ 0.8	25.9 $\pm$ 0.9	0.007
Abdominal Subcutaneous Fat (cm ³)	85.2 $\pm$ 4.5	77.0 $\pm$ 4.9	0.07
Abdominal Visceral Fat (cm ³)	22.3 $\pm$ 1.1	21.0 $\pm$ 1.2	0.17
Lean Body Mass (kg)	38.4 $\pm$ 0.5	39.9 $\pm$ 0.6	0.01
Leisure-time Physical Activity (min/day)	46.6 $\pm$ 3.2	55.8 $\pm$ 4.0	0.01

All means and *P*-values are adjusted for age, sex, race/ethnicity, and Tanner stage. CCS, childhood cancer survivors; SE, standard error.

Table III

Cardiovascular Risk Factors by PA Level in CCS and Sibling Controls

	CCS ^a				Controls			Interaction Models
	Low PA <60 min/day (N=202)	High PA 60 min/day (N=84)	High vs Low PA		Low PA <60 min/day (N=112)	High PA 60 min/day (N=80)	High vs Low PA	
	Mean ± SE	Mean ± SE	P	P	Mean ± SE	Mean ± SE	P	
Waist Circumference (cm)	74.3 ± 1.1	72.2 ± 1.5	0.16		69.2 ± 1.2	70.2 ± 1.4	0.56	<i>P</i> _{interaction}
Percent Fat Mass (%)	29.8 ± 0.9	24.4 ± 1.3	<.0001		26.6 ± 1.1	23.9 ± 1.3	0.05	0.04
Abdominal Subcutaneous Fat (cm ³) ^b	97.3 ± 5.7	67.9 ± 8.0	0.0004		78.3 ± 6.6	69.1 ± 7.5	0.30	0.02
Abdominal Visceral Fat (cm ³) ^b	24.9 ± 1.3	20.0 ± 1.8	0.007		20.9 ± 1.5	21.1 ± 1.8	0.93	0.004
Lean Body Mass (kg) ^b	39.5 ± 0.5	41.3 ± 0.7	0.009		39.7 ± 0.6	41.1 ± 0.6	0.02	0.99
Triglycerides (mg/dL) ^c	94.5 ± 5.0	92.8 ± 7.1	0.82		81.0 ± 5.2	74.0 ± 5.3	0.24	0.81
HDL-C (mg/dL) ^c	48.0 ± 1.0	48.6 ± 1.4	0.68		47.7 ± 1.3	48.7 ± 1.4	0.53	0.53
LDL-C (mg/dL) ^c	90.5 ± 2.3	88.5 ± 3.3	0.55		79.9 ± 3.5	78.7 ± 3.7	0.71	0.63
Systolic Blood Pressure (mmHg) ^{b,c}	110.7 ± 1.0	112.4 ± 1.4	0.26		109.1 ± 1.3	109.6 ± 1.4	0.70	0.81
Diastolic Blood Pressure (mmHg) ^{b,c}	58.1 ± 0.7	58.6 ± 1.0	0.57		57.1 ± 1.0	56.3 ± 1.0	0.42	0.40
Insulin Sensitivity (mg glucose/kg lean body mass/min) ^c	11.9 ± 0.4	13.0 ± 0.6	0.07		12.4 ± 0.5	12.7 ± 0.6	0.63	0.38
HOMA-IR ^c	2.16 ± 0.18	2.21 ± 0.25	0.84		2.01 ± 0.21	2.20 ± 0.25	0.42	0.39
cCSC (mm ² /mmHg) ^c	0.16 ± 0.004	0.16 ± 0.006	0.54		0.18 ± 0.01	0.18 ± 0.01	0.85	0.70
cCSD (%) ^c	29.9 ± 0.7	30.9 ± 0.9	0.28		34.3 ± 1.0	34.0 ± 1.1	0.82	0.61
cIMT (mm) ^c	0.44 ± 0.004	0.45 ± 0.006	0.77		0.44 ± 0.007	0.44 ± 0.006	0.89	0.38

All means and P-values are adjusted for age, sex, race/ethnicity, and Tanner stage.

^a Additional adjustment for diagnosis in all models of CCS.^b Additional adjustment for height.^c Additional adjustment for percent fat mass. CCS, childhood cancer survivors; cCSC, carotid cross-sectional compliance; cCSD, carotid cross-sectional distensibility; cIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment insulin resistance; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; SE, standard error.