Prevention of Long-term Adverse Health Outcomes With Cardiorespiratory Fitness and Physical Activity in Childhood Acute Lymphoblastic Leukemia Survivors

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Background: Most childhood acute lymphoblastic leukemia (ALL) survivors develop chronic treatment-related adverse effects several years after the end of therapy. A regular practice of physical activity and a good cardiorespiratory fitness have the potential to reduce the risk of chronic disease and improve quality of life. The aim of this study was to evaluate in a cohort of ALL survivors, the association between a good cardiorespiratory fitness or the respect of physical activity guidelines and major long-term health outcomes.

Methods: In total, 247 ALL survivors underwent a cardiopulmonary exercise test, completed a physical activity questionnaire and a battery of clinical examinations. We calculated the odds ratio to obtain the preventive fraction (PF) in order to evaluate the effects of the cardiorespiratory fitness and physical activity levels on health outcomes (ie, obesity, metabolic health, cardiac health, cognitive health and mood, bone health).

Results: Despite their young age, 88% of the participants presented at least one adverse health outcome, and 46% presented ≥ 3. Their cardiorespiratory fitness was also lower than expected with a median VO_2 peak reaching 84% of the predicted value. In the analyses using cardiorespiratory fitness, statistically significant PFs were observed for obesity (0.30), low–high-density lipoprotein-cholesterol (0.21) and depression (0.26). In the physical activity level analyses, statistically significant PFs were observed for obesity, depression, and low bone mineral density, with a PF of 0.55, 0.81, and 0.60, respectively.

Conclusions: Our results indicate that a good cardiorespiratory fitness and physical activity level induced a preventive action for most health outcomes studied and was associated with a lower late adverse effects prevalence in ALL survivors.

Key Words: Childhood leukemia, physical activity, cardiorespiratory fitness, survivorship, preventive fraction

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Childhood acute lymphoblastic leukemia (ALL) is the pediatric cancer with the highest prevalence and one of the major causes of disease-related mortality in children and young adults. During the last decades, major progress was made with regard to the treatment of ALL, and 5-year survival rates now exceed 90%.[1] As a result, there is a growing number of young adult ALL survivors. Unfortunately, this therapeutic success comes at a steep price, as most ALL survivors will develop severe chronic treatment-related late adverse effects after the end of therapy.

The Cancer Childhood Study reported that 25 years after diagnosis, 50% of ALL survivors suffer from at least one chronic medical condition and they are 3.7 times more likely than their siblings to report a severe or life-threatening medical condition.[2] Furthermore, in a clinically evaluated cohort, it was found that nearly 100% of survivors from childhood cancers (not restricted to ALL) have a chronic health condition and that two-third of them are affected by a severe or life-threatening condition.[3] These late adverse effects may include cardiotoxicity, obesity, metabolic disorders, neurocognitive impairments, or bone health issues.[4,5]

It has been observed that healthy lifestyle habits have the potential to reduce the risk of chronic disease, cancer recurrence, and quality of life in cancer survivors.[6,7] In adult survivors of childhood Hodgkin lymphoma, vigorous exercise is associated with a lower risk of cardiovascular events.[8] It has

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been extensively documented that in the general population and in cardiac patients, regular physical activity practice and a good cardiorespiratory fitness have a positive impact on the health condition.[9–11] Moreover, a recent study in adult survivors of childhood ALL has identified associations between components of physical fitness and self-reported adverse health status outcomes (ie, general health, mental health, functional impairments, activity limitations).[12] However, it is currently unknown whether a good cardiorespiratory fitness or the regular practice of physical activity is enough to induce a preventive action on late adverse effects in ALL survivors. Therefore, we evaluated in a cohort of ALL survivors, the association between a good cardiorespiratory fitness or the respect of physical activity guidelines and major long-term health outcomes.

METHODS

Participants

All childhood ALL survivors were diagnosed between 1987 and 2010 and treated according to DFCI-ALL 87-01 to 05-01 protocols[13] at Sainte-Justine University Health Center (SJUHC), Montreal (Quebec), Canada. The participants were recruited in the context of the PETALE study, a multidisciplinary research project with the goal to identify and to comprehensively characterize associated predictive biomarkers of long-term treatment-related complications in childhood ALL survivors.[14] These participants had no history of refractory or recurrent diseases and did not receive a hematopoietic stem cell transplant. These participants were almost exclusively of French Canadian descent (>95%).[14] In the current study, we restricted participants to those who were below 19 years of age at diagnosis and above 12 years of age at the moment of interview. Subjects who had suffered from congenital bone disease or who had received osteotoxic drugs for non-ALL disease were excluded. Written informed consent was obtained from every patient or parent/legal guardian. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Review Committee of SJUHC.

Assessment of Cardiorespiratory Fitness

Participants underwent a cardiopulmonary exercise test on an electromagnetic cycle ergometer (ER900; Ergoline, Bitz, Germany) following the McMaster incremental cycle protocol. Oxygen uptake was measured with a breath-by-breath system (Oxycon Pro; Viasys Healthcare, Germany) calibrated before each test. Two or the 3 following criteria had to be met for the effort to be considered maximal: respiratory exchange ratio ≥1.1; rate of perceived exertion on OMNI scale >7; maximal heart rate ≥85% predicted value.[15,16] Breath-by-breath data were averaged at 20 second intervals to determine the maximal oxygen consumption (VO_2 peak).

Predicted VO_2 peak was estimated for 18 years and above of age with the Wasserman et al[17] and Hansen et al[18] formula and with Cooper's formula[17,19] for participants below 18 years of age. As suggested by Wasserman, Hansen[17] for participants below 18 years of age, an adjustment was made for overweight participants, with an addition of 6 mL/min for each kilogram of weight above normal weight. Normal/predicted weight was calculated based on the 50th percentile of the World Health Organization body mass index (BMI) charts for children.[20] Percentage of measured versus predicted VO_2 peak was computed (measured VO_2 peak/predicted VO_2 peak x100) to evaluate the cardiorespiratory fitness. Therefore, VO_2 peak was used to represent cardiorespiratory fitness, as it is considered the gold standard in exercise physiology.[21]

Assessment of Physical Activity

The Minnesota Leisure Time Physical Activity Questionnaire[22,23] was used to assess the level of physical activity. An experienced exercise physiologist first read the 20 sports included in the questionnaire and then guided the participants to recall any other sports or leisure physical activity they might have practised in the last 3 months. Precision on frequency, duration, and intensity of the activities were asked. A metabolic equivalent value from the Compendiums of Physical Activity for Adults and for Youth[24] was used to quantify the intensity of each activity. All activities with a metabolic equivalent value ≥3 were considered of moderate-to-vigorous intensity. Total of weekly minutes of moderate-to-vigorous leisure physical activities (MVLPA) was then calculated.

Assessment of Health Outcomes

Assessment of health outcomes (ie, obesity, metabolic health, cardiac health, cognitive health and mood, bone health) are detailed below, and all the cut-off values are summarized in Table 1.

Obesity

Body composition was evaluated using 3 criteria: BMI, waist circumference, and total body fat mass percentage. According, to the World Health Organization classification, participants with BMI ≥ 30 kg.m^2 (adults) or ≥97th percentile (below 18 y of age) were considered obese.[20] For waist circumference, adult participants with ≥102 cm (men) and ≥88 cm (women)[25] and children ≥95th percentile[26] were considered abdominally obese. The total body fat mass percentage was measured by dual energy x-ray absorptiometry (Lunar Prodigy; GE Healthcare, Madison, WI). Following WHO criteria,[27] men with >25% and women with >35% total body fat percentages were considered as obese; for those below 18 years of age, reference data from the US population[28] was used and the threshold for obesity was set at ≥95th percentile.

Metabolic Health

Blood samples were drawn in the morning after an overnight fast. In adults, serum LDL-cholesterol ≥3.4 mmol/L[29] and triglycerides levels ≥1.7 mmol/L[29] were considered high. High-density lipoprotein (HDL) cholesterol <1.03 in men and <1.3 mmol/L in women were considered low.[29] In children, serum LDL-cholesterol, triglycerides, and HDL-cholesterol values were classified according to the recent guidelines of the National Heart, Lung and Blood Institute for sex and age group.[30] Fasting serum was also used to measure glucose, insulin, and glycated hemoglobin. The homeostasis model assessment (HOMA-IR) (insulin [mIU/L]×glucose [mmol/L]/22.5) was used as a surrogate estimate of insulin resistance.[31] Overall insulin resistance was defined as presenting at least one of 3 factors: blood fasting glucose ≥6.1 mmol/L, glycated hemoglobin ≥6.0%, and/or HOMA-IR ≥2.86 (adults),[32] or ≥95th percentile (children).[33] The metabolic syndrome was defined according to the criteria from the International Diabetes Federation (IDF).[34] In subjects 16 years and above of age, the metabolic syndrome was defined as having a waist circumference

TABLE 1. Binary Health Outcomes' Cut-off Values

Health Outcomes	Adults	Children
Obesity		
BMI	≥ 30 kg/m^2	≥ 97th percentile
Total body fat (%)	> 25% (men); > 35% (women)	≥ 95th percentile
Waist circumference	≥ 102 cm (men); ≥ 88 cm (women)	≥ 95th percentile
Metabolic health		
Dyslipidemia		
High triglycerides	≥ 1.7 mmol/L	According to the Guidelines of the National Heart, Lung and Blood Institute
High LDL-cholesterol	≥ 3.4 mmol/L	
Low HDL-cholesterol	< 1.03 (men); <1.3 mmol/L (women)	
Blood glucose control		
Insulin resistance	At least one of 3 factors Blood fasting glucose ≥ 6.1 mmol/L Glycated hemoglobin ≥ 6.0% HOMA-IR ≥ 2.86	At least one of 2 factors Blood fasting glucose ≥ 6.1 mmol/L Glycated hemoglobin ≥ 6.0% HOMA-IR ≥ 95th percentile
Metabolic syndrome	Waist circumference ≥ 94 cm (men) or ≥ 80 cm (women) + any 2 of Triglycerides ≥ 1.70 mmol/L or on drug treatment HDL <1.03 mmol/L (men); <1.3 mmol/L (women) or on therapy Systolic pressure ≥ 130 mm Hg or diastolic ≥ 85 mm Hg or on treatment Fasting blood glucose ≥ 5.6 mmol/L	Waist circumference ≥ 90th percentile+any 2 of Triglycerides ≥ 1.70 mmol/L HDL < 1.03 mmol/L Systolic pressure ≥ 130 mm Hg or diastolic ≥ 85 mm Hg or on treatment Fasting blood glucose ≥ 5.6 mmol/L
Cardiac health		
Reduced ejection fraction	< 55%	< 55%
Hypertension	≥ 130/85 mm Hg blood pressure or taking medication	≥ 90th percentile or taking medication
Cognitive health and mood		
Poor performance at DIVERGT tests	1 test with a score ≤ 2nd percentile or 2 tests with a score ≤ 10th percentile	
Anxiety depression	BSI subscale T-score ≥ 63	BYI module T-score ≥ 60
Bone health		
Low LS-BMD	LS-BMD ≤ −1 *z*-score	
Vertebral fracture	Presence or not	

BMI indicates body mass index; BSI, Brief Symptom Inventory; BYI, Beck Youth Inventories; HDL, high-density lipoproteins; IR, insulin resistance; LDL, low-density lipoproteins; LS-BMD, lumbar spine bone mineral density.

≥ 94 cm (men) or ≥ 80 cm (women), plus any 2 of the following factors: (i) triglycerides ≥ 1.70 mmol/L or on drug treatment; (ii) HDL < 1.03 mmol/L in men and <1.3 mmol/L in women or on therapy; (iii) systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg or on treatment and; (iv) fasting blood glucose ≥ 5.6 mmol/L. For children 10 to <16 years old, the metabolic syndrome was defined as waist circumference ≥ 90th percentile plus any 2 of: (i) triglycerides ≥ 1.70 mmol/L; (ii) HDL < 1.03 mmol/L; (iii) systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg; and (iv) fasting blood glucose ≥ 5.6 mmol/L.[35]

Cardiac Health

Cardiac transthoracic M-Mode echocardiographic assessment was performed (Vivid 9 machine; GE Medical Systems, Milwaukee, Wisconsin) to measure ejection fraction (EF) according to previously published studies and recommendations.[36–39] Subjects with an EF < 55% were considered to be having a reduced EF.[40] Arterial pressure was measured in the morning on the right arm, while seated and at rest. Participants considered to have prehypertension according to current recommendations[41] and those with hypertension were grouped together. Hypertension, in accordance with the Canadian children and adolescents guidelines,[42] is considered as ≥ 130/85 mm Hg in adults and ≥ 90th percentile according to age and height in children. Participants taking medication to treat hypertension were automatically classified as hypertensive.

Cognitive Health and Mood

Participants underwent different tests from the DIVERGT battery.[43] The 4 tests chosen to identify cognitive impairments were: (1) Digit Span (WAIS-IV/WISC-IV); (2) Verbal Fluency-Condition 1-Letter Fluency (D-KEFS); (3) Trail Making Test-Condition 4-Number-Letter Switching (D-KEFS); (4) Grooved Pegboard-Dominant Hand. Participants who had either 1 test with a score ≤ 2nd percentile (normative data from the general population) or 2 tests with a score ≤ 10th percentile were considered as having cognitive impairments. Mood was assessed with the Brief Symptom Inventory (BSI-18) in adults[44,45] and the Beck Youth Inventories (BYI) for Anxiety and Depression modules in children.[46] Participants with T-score ≥ 63 (adults) and ≥ 60 (children) showed moderate to severe levels and were classified in the present research as probable cases of anxiety and depression.

Bone Health

Lumbar spine bone mineral density (LS-BMD) was measured using the GE Lunar Prodigy (GE Lunar

Corporation, Madison, WI) dual energy x-absorptiometry scan and age-adjusted and sex-adjusted Z-scores were calculated. Subjects with BMD ≤ -1 *z*-score compared with the normal healthy population were considered as having low BMD. The presence or absence of vertebral fractures was assessed from anterior and lateral thoracolumbar spine radiographs. Two pediatric radiologists scored the spine radiographs from T4 to L4 vertebrae using the modified Genant semiquantitative method.[47]

Preventive Fraction (PF)

The PF is a ratio used in epidemiological studies to assess the impact of an exposure factor (ie, cardiorespiratory fitness and physical activity) on a disease (ie, health outcomes).[48,49] The literature shows that it is relevant to use the PF to explore the preventive action of a good cardiorespiratory fitness and a regular practice of physical activity on health outcomes.[10] In epidemiology, the PF is derived from odds ratio (OR). Indeed, the OR is a measure of association between the cardiorespiratory fitness or the physical activity practice and the health outcomes. Therefore, the PF can be calculated when OR is under one, as PF = (1−OR).

The association between cardiorespiratory fitness and health outcomes was studied using cardiorespiratory fitness on a continuous scale. For these regression models, the PF values correspond to a reduction in the prevalence of the health outcomes with each augmentation of 10% in predicted/measured VO_2 peak ratio. The association between the physical activity level (active/not active) and health outcomes was also studied. Participants were considered active if they had practiced ≥ 150 minutes per week of MVLPA, which is the recommendation from Canadian guidelines in physical activity for adults.[50] In children and adolescents, recommendations are even higher, with 60 minutes per day of MVLPA. As very few of our 18 years and above of age survivors met this guideline, we set the threshold at 150 weekly minutes of MVPLA for everyone. Cardiorespiratory fitness and physical activity level are interconnected variables since cardiorespiratory fitness is mainly increased via MVLPA, but they can also be considered distinctively.

Statistics

Data on demography and clinical characteristics of the participants are presented with descriptive statistics. The prevalence of each adverse health outcome was calculated for the whole cohort, with stratifications for cardiorespiratory fitness and physical activity level. The associations between cardiorespiratory fitness, physical activity level, and each outcome of interest (eg, obesity, dyslipidemia, etc.) were examined with univariate crude and adjusted logistic regression models. Sex, age at diagnosis, and time since diagnosis were included in all adjusted analyses. Other variables were also included on the basis of prior knowledge about their association with studied outcomes.[51–54] Obesity, dyslipidemia, insulin resistance, and metabolic syndrome were adjusted for the Mediterranean diet score,[55] corticosteroids (CSs), and radiation therapy exposure (CRT); reduced EF for ALL risk category, and exposure to dexrazoxane; hypertension for CS and CRT; cognitive impairments for CS, CRT, and methotrexate doses; low LS-BMD for CS and z-score height; vertebral fractures for CS and low LS-BMD. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Significance level was set to $P \leq 0.05$.

RESULTS

A total of 247 participants were evaluated. One participant was excluded because of missing data. For the analyses involving cardiorespiratory fitness as the main explanatory variable, 22 other subjects were excluded for different reasons: 5 did not achieve a maximal effort based on the criteria previously described, 13 did not complete the effort test on the ergocycle (too short for the cycle ergometer, musculoskeletal pain, inappropriate clothing), and there were issues with the equipment or protocol for 4 participants. A total of 224 participants were thus retained in the analyses assessing the association between cardiorespiratory fitness and outcomes, whereas 246 were considered in the analyses involving the physical activity level. Characteristics of the participants and details of their treatments are presented in Table 2.

The prevalence of adverse health outcomes in the entire cohort is detailed in Table 3. Twelve percent of the participants had no late adverse effects at the moment of the evaluation, 19% had 1, 23% had 2, 26% had 3, 13% had 4, and 7% had ≥ 5 late adverse effects.

TABLE 2. Characteristics of the Participants and Details of the Treatments

Characteristics	Total (N = 246)
Sex (n [%])	
Male	122 (49.6)
Female	124 (50.4)
Age at interview (y)	
Mean (SD)	22.2 (6.3)
Median (range)	21.8 (8.5-41.0)
Age at cancer diagnosis (y)	
Mean (SD)	6.7 (4.6)
Median (range)	4.8 (0.9-18.0)
Time from diagnosis (y)	
Mean (SD)	15.5 (5.2)
Median (range)	15.2 (5.4-28.2)
Risk groups (n [%])	
Standard risk	112 (45.5)
High+very high risk	134 (54.5)
CRT exposure (n [%])	
Yes	147 (40.2)
No	99 (59.8)
Treatment protocol (n [%])	
DFCI 87-01	24 (9.8)
DFCI 91-01	46 (18.7)
DFCI 95-01	73 (29.7)
DFCI 2000-01	76 (30.9)
DFCI 2005-01	27 (11.0)
Corticosteroids (N = 241)	
Mean (SD)	11,206.8 (5162.2)
Median (range)	9088.4 (4028.8-30,204.9)
CS > 134,13.93 mg/m^2 (N [%])	60 (24.9)
Methotrexate (N = 241)	
Mean (SD)	6311.2 (1539.9)
Median (range)	6578.0 (853.6-12,784.1)
MTX > 7222.67 mg/m^2 (N [%])	60 (24.9)
Doxorubicin (N = 241)	
Mean (SD)	183.0 (119.3)
Median (range)	225.0 (41.5-472.9)
Dexrazoxane (N = 241)	
Yes	72 (29.9)
No	169 (70.1)

CRT doses ranged between 12 and 20 Gy (median 18.0 Gy).
CRT indicates conformal radiation therapy; CS, corticosteroids; DFCI, Dana Farber Cancer Institute; MTX, methotrexate.

TABLE 3. Prevalence of Adverse Health Outcomes Among ALL Survivors

		Cardiorespiratory Fitness (VO_2 Peak Ratio)		Physical Activity Level (MVLPA/wk)	
	Total (N = 246) (%)	< 100% (N = 184)	≥ 100% (N = 40)	< 150 min (N = 126)	≥ 150 min (N = 120)
Obesity	128 (52.03)	98 (53.26)	18 (45.00)	77 (61.11)	51 (42.50)
BMI ≥ 30	35 (14.23)	28 (15.22)	3 (7.50)	25 (19.84)	10 (8.33)
High percentage total body fat	105 (42.68)	79 (42.93)	16 (40.00)	71 (56.35)	34 (28.33)
High waist circumference	78 (31.71)	61 (33.15)	9 (22.50)	44 (34.92)	34 (28.33)
Metabolic health					
Dyslipidemia	102 (41.46)	79 (42.93)	14 (35.00)	58 (46.03)	44 (36.67)
Low HDL-cholesterol	57 (23.17)	46 (25.00)	9 (22.50)	36 (28.57)	21 (17.50)
LDL-cholesterol	43 (17.48)	33 (17.93)	7 (17.50)	22 (17.46)	21 (17.50)
High triglycerides	30 (12.20)	23 (12.50)	2 (5.00)	20 (15.87)	10 (8.33)
Insulin resistance	42 (17.07)	33 (17.93)	3 (7.50)	28 (22.22)	14 (11.67)
Metabolic syndrome*	22 (8.98)	18 (9.78)	2 (5.00)	13 (10.32)	9 (7.56)
Cardiac health					
Reduced ejection fraction	53 (21.54)	33 (17.93)	10 (25.00)	26 (20.63)	27 (22.50)
Hypertension	30 (12.20)	22 (11.96)	3 (7.50)	11 (8.73)	19 (15.83)
Cognitive health and mood					
Poor performance at DIVERGT tests	68 (27.64)	53 (28.80)	6 (15.00)	37 (29.37)	31 (25.83)
Anxiety†	21 (9.63)	16 (9.70)	2 (5.41)	11 (9.91)	10 (9.35)
Depression†	24 (11.01)	20 (12.12)	1 (2.70)	19 (17.12)	5 (4.67)
Bone health					
Low LS-BMD	54 (21.95)	44 (23.91)	6 (15.00)	34 (26.98)	20 (16.67)
Vertebral fracture*	57 (23.27)	40 (21.74)	9 (23.08)	28 (22.22)	29 (24.37)

*1 missing value.
†28 missing values.
BMI indicates body mass index; LS-BMD, lumbar spine bone mineral density; MVLPA, moderate and vigorous physical activities.

The mean VO_2 peak value obtained during the exercise effort test was 32.2 ± 8.4 mL/kg/min, and the mean of measured/predicted VO_2 peak ratio was $86 \pm 17\%$ (median: 84%, range: 38 to 129): 17% of the participants had a VO_2 peak greater or equal ($\geq 100\%$) to their predicted value. Mean MVLPA was 28 ± 30 minutes per day (median: 21 min, range: 0 to 238). In total, 49% of the participants practised ≥ 150 minutes per week of MVLPA 3 months before the evaluation. Daily minutes of MVLPA were correlated with the ratio of measured/predicted VO_2 peak (Spearman correlation = 0.284, $P < 0.0001$).

The relationship between a good cardiorespiratory fitness and the prevalence of each health outcome was evaluated using the PF as an association measure, and similarly to the physical activity level. Crude and adjusted PF according to these 2 explanatory variables (ie, cardiorespiratory fitness, physical activity level) are presented in Table 4. Complete results of adjusted analysis can be found in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/JPHO/A285). For cardiorespiratory fitness, significant adjusted PFs ($P < 0.01$) were observed for obesity (0.30), as assessed with BMI (0.29), body fat percentage (0.22) or waist circumference (0.25). The significant PF ($P < 0.01$) was also observed for low HDL-cholesterol (0.21) and for depression (0.26). Although the PF for other variables was not significant, they all indicated a positive impact of a higher VO_2 peak, except for hypertension. For the physical activity level, obesity based on total body fat, depression and low LS-BMD were all reduced in the active group, with PF of 0.55 ($P < 0.05$), 0.81 ($P < 0.01$), and 0.60 ($P < 0.01$), respectively.

DISCUSSION

The aim of our study was to explore the association between a good cardiorespiratory fitness or the respect of physical activity guidelines and major long-term health outcomes. The PF analysis identifies a prophylactic effect of cardiorespiratory fitness on the health outcomes studied. Indeed, according to the adjusted analyses with cardiorespiratory fitness, our results showed a 1% to 30% reduction in the prevalence of adverse health outcomes, depending on the outcome studied. Thus, the PF for all health outcomes—except one (hypertension)—indicated a reduction of prevalence with an increase of 10% in each measured/predicted VO_2 peakratio. This is consistent with previous studies, in other populations, which show that small increases in VO_2 peak or regular physical activity are beneficial.[56–59] Our findings are important because despite the young age (median of 22 y old) of our cohort, 88% of the ALL survivors presented at least one late adverse effect and 46% presented ≥ 3. Behavioral changes such as nondrug therapies have a very important role in late adverse effects. Thereby, as discussed below, the findings with regard to preventive actions of cardiorespiratory fitness and physical activity level in the health outcomes studied are outstanding.

Obesity

From all the health outcomes, the ones related to body composition appeared to be the most closely associated with a good cardiorespiratory fitness. Using at least one of the criteria chosen to define obesity (ie, BMI, waist circumference, or body fat percentage), 52% of our cohort of ALL survivors was obese. In all populations, exercise interventions to increase

TABLE 4. Crude and Adjusted Preventive Fractions (PF = 1–OR) for Adverse Health Outcomes Associated With Cardiorespiratory Fitness and Physical Activity Level

	Cardiorespiratory Fitness (VO_2 Peak Ratio—for 10% Increments) PF (95% CI)		Physical Activity Level (≥150 min MVLPA/wk) PF (95% CI)	
	Crude	Adjusted	Crude	Adjusted
Obesity	0.24 (0.11-0.36)**	0.30 (0.15-0.43)**	0.53 (0.22-0.72)**	0.25 (−0.35-0.59)
BMI ≥ 30	0.18 (−0.03 to 0.35)	0.29 (0.07-0.46)**	0.63 (0.20-0.83)*	0.35 (−0.64 to 0.74)
High percentage total body fat	0.10 (−0.05 to 0.23)	0.22 (0.03-0.38)**	0.69 (0.48-0.82)**	0.55 (0.10-0.78)*
High waist circumference	0.10 (0.04-0.33)*	0.25 (0.08-0.38)**	0.26 (−0.27 to 0.57)	−0.08 (−1.03 to 0.42)
Dyslipidemia	0.20 (0.05-0.32)**	0.20 (0.04-0.33)*	0.32 (−0.13 to 0.59)	0.05 (−0.72 to 0.47)
Low HDL-chol	0.18 (0.01-0.32)*	0.21 (0.03-0.35)**	0.47 (0.02-0.71)*	0.36 (−0.27-0.68)
High LDL-chol	0.07 (−0.14 to 0.24)	0.01 (−0.25 to 0.22)	0.00 (−0.94 to 0.48)	−0.78 (−3.06 to 0.23)
High triglycerides	0.16 (−0.07 to 0.35)	0.17 (−0.10 to 0.37)	0.52 (−0.08 to 0.78)	0.34 (−0.68 to 0.74)
Insulin resistance	0.15 (−0.05 to 0.32)	0.16 (−0.06 to 0.33)	0.54 (0.07 to 0.77)*	0.45 (−0.20 to 0.75)
Metabolic syndrome	0.14 (−0.14 to 0.34)	0.18 (−0.13 to 0.40)	0.29 (−0.73 to 0.71)	−0.19 (−2.63 to 0.61)
Reduced ejection fraction	0.07 (−0.13 to 0.24)	0.04 (−0.18 to 0.22)	−0.12 (−1.05 to 0.39)	−0.09 (−1.2 to 0.46)
Hypertension	−0.07 (−0.36 to 0.16)	−0.2 (−0.59 to 0.1)	−0.97 (−3.33 to 0.11)	−1.66 (−5.82 to −0.03)*
Cognitive impairments	0.15 (−0.02 to 0.29)	0.09 (−0.11 to 0.25)	0.16 (−0.47 to 0.52)	0.21 (−0.46 to 0.57)
Anxiety	0.13 (−0.16 to 0.35)	0.13 (−0.17 to 0.35)	0.06 (−1.31 to 0.62)	0.14 (−1.32 to 0.68)
Depression	0.26 (0.03-0.44)	0.26 (0.02-0.43)**	0.76 (0.34-0.91)	0.81 (0.39-0.94)**
Low LS-BMD	0.19 (0.02-0.33)*	0.18 (−0.02-0.33)	0.46 (−0.01-0.71)	0.60 (0.20-0.80)**
Vertebral fracture	0.09 (−0.09 to 0.25)	0.05 (−0.18 to 0.23)	−0.13 (−1.04 to 0.38)	−0.05 (−1.01 to 0.45)

Models for all outcome variables were adjusted for age, sex, and age at diagnosis. Obesity, dyslipidemia, insulin resistance, and metabolic syndrome were also adjusted for diet, corticosteroids cumulative dose (CS), and exposure to radiotherapy (CRT); reduced ejection fraction for ALL risk category and exposure to dexrazoxane; hypertension for CS and CRT; cognitive impairments for CS, CRT, and methotrexate doses; low BMD for CS and *z*-score height; vertebral fractures for CS and low BMD.

BMI indicates body mass index; CI, confidence interval; CRT, conformal radiation therapy; CS, corticosteroid; HDL-chol., high-density lipoprotein cholesterol; LDL-chol., low-density lipoprotein cholesterol; LS-BMD, lumbar spine bone mineral density; MVLPA, moderate and vigorous leisure physical activities; OR, odds ratio; PF, preventive fraction.

*$P < 0.05$.

**$P < 0.01$.

energy expenditure and diet modifications to reduce energy intake should both be part of the treatment for obesity.[60] In ALL survivors, each increment of 10% in the measured/predicted VO_2 peak ratio was associated with a preventive action of 30% in obesity ($P < 0.01$) in adjusted analysis. In obese people, it is interesting to note that even a modest weight loss (5% to 10%) can induce positive health benefits and reduce cardiovascular risk.[61] Moreover, physical activity plays an important role in weight management and obesity.[62] In ALL survivors, a higher physical activity level was found associated with 55% lower prevalence of obesity, only defined with the total body fat percentage.

Dyslipidemia

In our cohort, >40% of ALL survivors presented a dyslipidemia and more than a quarter were insulin resistant. The beneficial influence of exercise on blood lipid profile has been assessed by several randomized control trials and other studies. Indeed, the mean increase in HDL-cholesterol with exercise training across the studies was of 4.6%,[63] whereas the mean decreases in LDL-cholesterol and triglycerides were of 3.7% and 5.0%.[63] In our study, each increment of 10% in measured/predicted VO_2 peak ratio was accompanied by a preventive action of 21% in low HDL-cholesterol prevalence ($P < 0.01$). However, there is variability in the responsiveness of blood lipids to physical activity that could be explained by several confounding variables like use of medication, age, hormonal status, cigarette smoking, or genetics.[63] The intertwined relation of nutrition and physical activity represents a limit in the interpretation of our results. In fact, the quantity and quality of food intake can be influenced by higher levels of physical activity.[64] A part of the results obtained with the reduced prevalence of obesity and metabolic disorders could be explained by nutrition. Thus, we reduced this impact by adjusting the analysis using a Mediterranean diet score.[55]

Depression

The positive impact of exercise on depression is well known in clinical populations[65] and in cancer survivors (primarily breast).[66] According to meta-analyses, effect size for exercise interventions on depression in clinical population is large, ranging from −0.72 to −1.4.[66,67] Effects have been comparable with psychotherapy and medications, especially for subjects with mild/moderate depression levels.[66,67] In cancer survivors (primarily breast), a meta-analysis concluded that exercise led to a small improvement in depression (effect size of −0.22).[66] However, the impact of exercise on anxiety and depression symptoms in childhood cancer survivors has not been evaluated previously.[68] Our findings show that 11% of our ALL survivors had high levels of depression symptoms, which shows the importance of this health outcome. Both a higher cardiorespiratory fitness and physical activity level were associated with a

preventive action in depression frequency (PF of 0.26 and 0.81, $P < 0.01$, respectively). Nevertheless, it seems essential to clarify that, in adults and in children, better sleeping patterns,[69] an increase in self-esteem,[61] stress reduction, and socialization[70] can help prevent depression when the participant practices regular physical activity.

Low LS-BMD

Survivors of ALL are at increased risk for skeletal morbidities, including BMD deficits.[71] Low physical activity levels both during and after treatment for childhood cancer can contribute to cardiac deconditioning and skeletal muscle atrophy.[72] Low LS-BMD is present in 22% of our cohort. This proportion is comparable with the results observed by other teams.[52,71,73] Our results show that cardiorespiratory fitness induces a preventive action of 18% for LS-BMD, while a preventive action of 60% ($P < 0.01$) is observed for the physical activity level. These results were adjusted for height and cumulative dose of CSs. A high level of physical activity is thus associated with better LS-BMD outcomes even if cardiorespiratory fitness is not high. This can be explained by the fact that cardiorespiratory fitness is primarily increased via cardiovascular training such as running and cycling, whereas LS-BMD is increased especially with weight-bearing exercises and with resistance training.[9] In other cohorts of ALL survivors, lower activity level was correlated to low LS and total-BMD[74] and muscle strength was associated with BMD in the extremities.[75] In people with a similar state to the ALL survivors', as in premenopausal women, resistance training, and high-intensity weight-bearing exercise can induce an increase of 1% to 2% at the lumbar spine and femoral neck.[76,77] A limited number of studies exists on bone health and exercise interventions that have been conducted in cancer survivors. Indeed, one study assessed the effect of exercise on BMD (total body) in childhood cancer survivors, showing a statistically significant positive intervention effect.[78] These results, combined with ours, suggests that physical activity interventions, including muscle strengthening, may improve bone health in ALL survivors.

Other Health Outcomes

A good cardiorespiratory fitness and regular physical activity induce a preventive action for most health outcomes studied, however, it seems that there was no preventive action on hypertension. The literature seems to agree that physical activity has a positive impact on hypertension. Indeed, physical activity helps to reduce the resting systolic and diastolic blood pressure from 11.0 to 3.2 and 7.7 to 2.5 mm Hg, respectively.[79] Yet, some research reports that there might be certain subgroups of hypertensive patients that are more responsive to blood pressure lowering effects of physical activity than others.[80] One of the reasons that could also explain the lack of preventive action for hypertension is the inclusion of prehypertension in our classification for hypertension. The authors assumed that the preventive action of cardiorespiratory fitness or physical activity in blood pressure in these subjects might be lower than in class 1 or 2 hypertensive subjects. Moreover, the optimal physical activity prescription for the prevention of hypertension remains unclear.[81] In this sense, some other health outcomes studied in cognitive functions were not significant, although other studies have found results.[82–85] However, there are few studies in cancer patients on the effect of physical activity, especially on cognitive functions. Results from cross-sectional studies suggest that higher levels of physical activity are associated with fewer declines in cognitive function.[86] The observational and cross-sectional nature of our study limits the interpretation. Thus, further replication analysis and confirmation of these findings are needed.

CONCLUSIONS

This study demonstrated that a good cardiorespiratory fitness induced a preventive action for most health outcomes studied and was associated with lower late adverse effects prevalence in ALL survivors, especially for obesity, HDL-cholesterol, and depression. Physical activity was associated with lower prevalence of low LS-BMD. A slight increase in cardiorespiratory fitness gave ALL survivors better preventative action on health outcomes. Our study provides a quantitative framework to precisely target future interventional studies and measure their impact on diverse health outcomes in ALL survivors. Clinicians and researchers have an important role to play in the reduction of late adverse effects in ALL survivors. This study provides additional evidence with regard to the benefits of physical activity for cancer survivors.

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REFERENCES

1. Brenner H, Kaatsch P, Burkhardt-Hammer T, et al. Long-term survival of children with leukemia achieved by the end of the second millennium. *Cancer*. 2001;92:1977–1983.
2. Mody R, Li S, Dover DC, et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood*. 2008;111:5515–5523.
3. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA*. 2013;309:2371–2381.
4. Fulbright JM, Raman S, McClellan WS, et al. Late effects of childhood leukemia therapy. *Curr Hematol Malign Rep*. 2011;6:195–205.
5. Nathan PC, Wasilewski-Masker K, Janzen LA. Long-term outcomes in survivors of childhood acute lymphoblastic leukemia. *Hematol Oncol Clin North Am*. 2009;23:1065–1082; vi-vii.
6. Speed-Andrews AE, Courneya KS. Effects of exercise on quality of life and prognosis in cancer survivors. *Curr Sports Med Rep*. 2009;8:176–181.
7. Speck RM, Courneya KS, Masse LC, et al. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv*. 2010;4:87–100.
8. Jones LW, Liu Q, Armstrong GT, et al. Exercise and risk of major cardiovascular events in adult survivors of childhood hodgkin lymphoma: a report from the childhood cancer survivor study. *J Clin Oncol*. 2014;32:3643–3650.
9. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174:801–809.
10. Caru M, Kern L, Bousquet M, et al. Preventive fraction of physical fitness on risk factors in cardiac patients: retrospective epidemiological study. *World J Cardiol*. 2018;10:26–34.
11. Glazer NL, Lyass A, Esliger DW, et al. Sustained and shorter bouts of physical activity are related to cardiovascular health. *Med SciSports Exerc*. 2013;45:109–115.
12. Wilson CL, Howell CR, Partin RE, et al. Influence of fitness on health status among survivors of acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2018;65:e27286.

13. Silverman LB, Stevenson KE, O'Brien JE, et al. Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985-2000). *Leukemia*. 2010;24:320–334.
14. Marcoux S, Drouin S, Laverdiere C, et al. The PETALE study: late adverse effects and biomarkers in childhood acute lymphoblastic leukemia survivors. *Pediatr Blood Cancer*. 2017;64:6–14.
15. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012;126:2261–2274.
16. Robergs RA, Landwehr R. The surprising history of the "HRmax = 220-age" equation. *J Exerc Physiol Online*. 2002;5:1–10.
17. Wasserman K, Hansen JE, Sue DY, et al. Principles of exercise testing and interpretation. In: Weinberg R, ed. *Normal Values*, 4th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2005:160–182.
18. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129(2 pt 2): S49–S55.
19. Cooper DM, Weiler-Ravell D, Whipp BJ, et al. Growth-related changes in oxygen uptake and heart rate during progressive exercise in children. *Pediatr Res*. 1984;18:845–851.
20. de Onis M, Onyango AW, Borghi E, et al. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007;85:660–667.
21. Shephard RJ, Allen C, Benade A, et al. The maximum oxygen intake: an international reference standard of cardio-respiratory fitness. *Bull World Health Organ*. 1968;38:757–764.
22. Taylor HL, Jacobs DR Jr, Schucker B, et al. A questionnaire for the assessment of leisure time physical activities. *J Chron Dis*. 1978;31:741–755.
23. Kriska AM, Caspersen CJ. Introduction to a collection of physical activity questionnaires. *Med Sci Sports Exerc*. 1997;29:5–9.
24. Ridley K, Ainsworth BE, Olds TS. Development of a compendium of energy expenditures for youth. *Int J Behav Nutr Phys Activity*. 2008;5:45–53.
25. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet (London, England)*. 2005;366: 1059–1062.
26. Katzmarzyk PT. Waist circumference percentiles for Canadian youth 11-18y of age. *Eur J Clin Nutri*. 2004;58:1011–1015.
27. World health organization. Physical status: the use and interpretation of anthropometry: Report of a WHO Expert Committee. Geneva, Switzerland; 1995.
28. Ogden CL, Li Y, Freedman DS, et al. Smoothed percentage body fat percentiles for U.S. children and adolescents, 1999-2004. *Natl Health Stat Rep*. 2011;43:1–7.
29. Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult–2009 recommendations. *Can J Cardiol*. 2009; 25:567–579.
30. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213–S256.
31. Matthews DR, Hosker JP, Rudenski AS, 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.
32. Chen J, Wildman RP, Hamm LL, et al. Association between inflammation and insulin resistance in U.S. nondiabetic adults: results from the Third National Health and Nutrition Examination Survey. *Diabetes Care*. 2004;27:2960–2965.
33. Allard P, Delvin EE, Paradis G, et al. Distribution of fasting plasma insulin, free fatty acids, and glucose concentrations and of homeostasis model assessment of insulin resistance in a representative sample of Quebec children and adolescents. *Clin Chem*. 2003;49:644–649.
34. Punthakee Z, Goldenberg R, Katz P. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. *Can J Diab*. 2018;42(suppl 1):S10–S15.
35. Zimmet P, Alberti KG, Kaufman F, et al. The metabolic syndrome in children and adolescents—an IDF consensus report. *Pediatr Diab*. 2007;8:299–306.
36. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10:165–193.
37. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur J Echocardiogr*. 2016;17:1321–1360.
38. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
39. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Investig*. 1975; 56:56–64.
40. Ueda T, Kawakami R, Nishida T, et al. Left ventricular ejection fraction (EF) of 55% as cutoff for late transition from heart failure (HF) with preserved EF to HF with mildly reduced EF. *Circ J*. 2015;79:2209–2215.
41. Stern RH. The new hypertension guidelines. *J Clin Hypertens (Greenwich, Conn)*. 2013;15:748–751.
42. Paradis G, Tremblay MS, Janssen I, et al. Blood pressure in Canadian children and adolescents. *Health Rep*. 2010;21:15–22.
43. Krull KR, Okcu MF, Potter B, et al. Screening for neurocognitive impairment in pediatric cancer long-term survivors. *J Clin Oncol*. 2008;26:4138–4143.
44. Recklitis CJ, Parsons SK, Shih M-C, et al. Factor structure of the brief symptom inventory—18 in adult survivors of childhood cancer: results from the childhood cancer survivor study. *Psycholog Assess*. 2006;18:22–32.
45. Derogatis LR. *Brief Symptom Inventory (BSI) Administration, Scoring, and Procedures Manual*. Minneapolis, MN: National Computer Systems (NCS); 2000.
46. Beck J. *Beck Youth Inventories—Second edition for Children and Adolescents Manual*. San Antonio, TX: PsychCorp; 2005.
47. Genant HK, Wu CY, van Kuijk C, et al. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Research*. 1993;8:1137–1148.
48. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. *Am J Epidemiol*. 1974;99: 325–332.
49. Gargiullo PM, Rothenberg RB, Wilson HG. Confidence intervals, hypothesis tests, and sample sizes for the prevented fraction in cross-sectional studies. *Stat Med*. 1995;14:51–72.
50. Tremblay MS, Warburton DE, Janssen I, et al. New Canadian physical activity guidelines. *Appl Physiol Nutr Metab*. 2011;36: 36–46.
51. Krull KR, Brinkman TM, Li C, et al. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report from the St Jude lifetime cohort study. *J Clin Oncol*. 2013;31:4407–4415.
52. Gurney JG, Kaste SC, Liu W, et al. Bone mineral density among long-term survivors of childhood acute lymphoblastic leukemia: results from the St. Jude Lifetime Cohort Study. *Pediatr Blood Cancer*. 2014;61:1270–1276.
53. Nottage KA, Ness KK, Li C, et al. Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia—From the St. Jude Lifetime Cohort. *Br J Haematol*. 2014;165:364–374.
54. Walter S, Tiemeier H. Variable selection: current practice in epidemiological studies. *Eur J Epidemiol*. 2009;24:733–736.
55. Martinez-Gonzalez MA, Fernandez-Jarne E, Serrano-Martinez M, et al. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. *Eur J Clin Nutr*. 2004;58: 1550–1552.

56. Warburton DE, Bredin SS. Reflections on physical activity and health: what should we recommend? *Can J Cardiol*. 2016;32:495–504.
57. Myers J, McAuley P, Lavie CJ, et al. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis*. 2015;57:306–314.
58. Swank AM, Horton J, Fleg JL, et al. Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail*. 2012;5:579–585.
59. Skinner JS, Wilmore KM, Krasnoff JB, et al. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. *Med Sci Sports Exerc*. 2000;32:157–161.
60. McQueen MA. Exercise aspects of obesity treatment. *Ochsner J*. 2009;9:140–143.
61. Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord*. 1992;16:397–415.
62. Wiklund P. The role of physical activity and exercise in obesity and weight management: time for critical appraisal. *J Sport Health Sci*. 2016;5:151–154.
63. Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. *Med Sci Sports Exerc*. 2001;33(suppl 6):S502–S515; discussion S28–S29.
64. Joseph RJ, Alonso-Alonso M, Bond DS, et al. The neurocognitive connection between physical activity and eating behaviour. *Obes Rev*. 2011;12:800–812.
65. Ranjbar E, Memari AH, Hafizi S, et al. Depression and exercise: a clinical review and management guideline. *Asian J Sports Med*. 2015;6:2–8.
66. Craft LL, Vaniterson EH, Helenowski IB, et al. Exercise effects on depressive symptoms in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2012;21:3–19.
67. Rethorst CD, Wipfli BM, Landers DM. The antidepressive effects of exercise: a meta-analysis of randomized trials. *Sports Med (Auckland, NZ)*. 2009;39:491–511.
68. Braam KI, van der Torre P, Takken T, et al. Physical exercise training interventions for children and young adults during and after treatment for childhood cancer. *Cochrane Database Syst Rev*. 2016;3:Cd008796.
69. Youngstedt SD. Effects of exercise on sleep. *Clin Sports Med*. 2005;24:355–365; xi.
70. Vankim NA, Nelson TF. Vigorous physical activity, mental health, perceived stress, and socializing among college students. *Am J Health Promot*. 2013;28:7–15.
71. Kaste SC, Jones-Wallace D, Rose SR, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. *Leukemia*. 2001;15:728–734.
72. Huang TT, Ness KK. Exercise interventions in children with cancer: a review. *Int J Pediatr*. 2011;2011:461512.
73. Mandel K, Atkinson S, Barr RD, et al. Skeletal morbidity in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2004;22:1215–1221.
74. Tillmann V, Darlington AS, Eiser C, et al. Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. *J Bone Miner Res*. 2002;17:1073–1080.
75. Joyce ED, Nolan VG, Ness KK, et al. Association of muscle strength and bone mineral density in adult survivors of childhood acute lymphoblastic leukemia. *Arch Phys Med Rehab*. 2011;92:873–879.
76. Wallace BA, Cumming RG. Systematic review of randomized trials of the effect of exercise on bone mass in pre- and postmenopausal women. *Calcif Tissue Int*. 2000;67:10–18.
77. Kelley GA, Kelley KS. Efficacy of resistance exercise on lumbar spine and femoral neck bone mineral density in premenopausal women: a meta-analysis of individual patient data. *J Women Health (2002)*. 2004;13:293–300.
78. Hartman A, te Winkel ML, van Beek RD, et al. A randomized trial investigating an exercise program to prevent reduction of bone mineral density and impairment of motor performance during treatment for childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2009;53:64–71.
79. Ghadieh AS, Saab B. Evidence for exercise training in the management of hypertension in adults. *Can Fam Physician*. 2015;61:233–239.
80. Blumenthal JA, Siegel WC, Appelbaum M. Failure of exercise to reduce blood pressure in patients with mild hypertension. Results of a randomized controlled trial. *JAMA*. 1991;266:2098–2104.
81. Diaz KM, Shimbo D. Physical activity and the prevention of hypertension. *Curr Hypertens Rep*. 2013;15:659–668.
82. Lees C, Hopkins J. Effect of aerobic exercise on cognition, academic achievement, and psychosocial function in children: a systematic review of randomized control trials. *Prev Chronic Dis*. 2013;10:E174.
83. Wahren J, Felig P, Ahlborg G, et al. Glucose metabolism during leg exercise in man. *J Clin Investig*. 1971;50:2715–2725.
84. Manson JE, Spelsberg A. Primary prevention of non-insulin-dependent diabetes mellitus. *Am J Prevent Med*. 1994;10:172–184.
85. Oshida Y, Yamanouchi K, Hayamizu S, et al. Long-term mild jogging increases insulin action despite no influence on body mass index or VO^2 max. *J Appl Physiol (Bethesda, MD: 1985)*. 1989;66:2206–2210.
86. Zimmer P, Baumann FT, Oberste M, et al. Effects of exercise interventions and physical activity behavior on cancer related cognitive impairments: a systematic review. *BioMed Res Int*. 2016;2016:1820954.