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ORIGINAL REPORT

Exercise and Risk of Major Cardiovascular Events in Adult Survivors of Childhood Hodgkin Lymphoma: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose
Survivors of Hodgkin lymphoma (HL) are at increased risk of treatment-related cardiovascular (CV) events; whether exercise modifies this risk is unknown.

Methods
Survivors of HL (n = 1,187; median age, 31.2 years) completed a questionnaire evaluating vigorous-intensity exercise behavior. CV events were collected in follow-up questionnaires and graded according to Common Terminology Criteria for Adverse Events (version 4.03). The primary end point was incidence of any major (grade 3 to 5) CV event. Poisson regression analyses were used to estimate the association between exercise exposure (metabolic equivalent [MET] hours/week^{-1}) and risk of major CV events after adjustment for clinical covariates and cancer treatment.

Results
Median follow-up was 11.9 years (range, 1.7 to 14.3 years). Cumulative incidence of any CV event was 12.2% at 10 years for survivors reporting 0 MET hours/week^{-1} compared with 5.2% for those reporting ≥ 9 MET hours/week^{-1}. In multivariable analyses, the incidence of any CV event decreased across increasing MET categories (P_{trend} = .002). Compared with survivors reporting 0 MET hours/week^{-1}, the adjusted rate ratio for any CV event was 0.87 (95% CI, 0.56 to 1.34) for 3 to 6 MET hours/week^{-1}, 0.45 (95% CI, 0.26 to 0.80) for 9 to 12 MET hours/week^{-1}, and 0.47 (95% CI, 0.23 to 0.95) for 15 to 21 MET hours/week^{-1}. Adherence to national vigorous intensity exercise guidelines (ie, ≥ 9 MET hours/week^{-1}) was associated with a 51% reduction in the risk of any CV event in comparison with not meeting the guidelines (P = .002).

Conclusion
Vigorous exercise was associated with a lower risk of CV events in a dose-dependent manner independent of CV risk profile and treatment in survivors of HL.

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INTRODUCTION

It is well-established that adult survivors of childhood Hodgkin lymphoma (HL) are at increased risk of late-occurring premature cardiovascular (CV) morbidity and mortality.[1-4] CV events are the leading competing (nonmalignant) cause of death among survivors of HL with an approximately sevenfold increased risk of death relative to age-matched counterparts.[5,6] In addition, 5-year survivors of HL have between a 2.6- and a 5.5-fold increased risk of major CV events including heart failure, myocardial infarction, pericardial disease, and valvular abnormalities compared with siblings.[1]

Adult survivors of childhood HL are subject to the normal effects of age- and/or disease-related comorbid conditions and deconditioning that may contribute to the pathogenesis of CV disease and cardiomyopathy (heart failure). These usual processes are, however, compounded by the direct effects of cancer treatment on components of the CV system, including chemotherapy-induced impairments in systolic function (ultimately leading to overt heart failure)[7] and chest-directed radiotherapy-induced coronary artery disease (CAD).[8-10] These insults occur in conjunction with so-called indirect lifestyle perturbations (eg, physical inactivity, weight gain)[11-13] that synergistically reduce CV reserve capacity, diminishing survivors' abilities to withstand normal age-related pathologies. As a result, the incidence of overt CV disease occurs at a much earlier

age than that observed in persons without a history of childhood HL treatment.[14,15]

Preventive and/or treatment strategies to offset the chronic and long-term CV consequences of childhood HL treatment are required. Regular exercise may be one effective strategy given its demonstrated efficacy in augmenting CV reserve capacity and simultaneously targeting multiple risk factors, leading to substantial reductions in the primary and secondary risk of CV events and mortality.[16-18] Whether these findings extend to adult survivors of HL with an increased CV risk phenotype has not been investigated. Accordingly, we investigated the association between exercise and risk of CV events in adult survivors of HL participating in the Childhood Cancer Survivor Study (CCSS).[19-21] We hypothesized that exercise would reduce the risk of major CV events in a dose-dependent manner beyond CV risk factors and treatment exposure.

METHODS

Patients and Study Overview

The CCSS is a retrospective cohort study with longitudinal follow-up of survivors of childhood cancer treated at 26 institutions in the United States and Canada.[19-21] Major eligibility criteria include diagnosis of cancer before age 21 years, primary initial treatment between January 1, 1970 and December 31, 1986, and survival of at least 5 years beyond the initial diagnosis. As a result of the relatively low number of major CV events in other cancer diagnoses, only adult survivors of HL were included in the present analysis. In addition, to minimize the impact of preexisting CV disease in the present analysis (those with existing disease are likely to have reduced exercise behavior because of comorbid conditions), participants reporting grade 3 to 4 CV conditions at the baseline survey were excluded from this analysis. Survivors developing a second malignant neoplasm or late recurrence (5 or more years after diagnosis) before the baseline questionnaire were also excluded because treatment information was not uniformly available. The CCSS protocol was reviewed and approved by the human subjects committee at each participating institution, and informed consent was obtained before study participation.

Timing of Baseline and Follow-Up Questionnaires

All participants completed a self-administered baseline questionnaire (1994 to 1999) that included sociodemographics and history of health conditions including CV events. After baseline enrollment, new onset CV events were ascertained in periodic follow-up questionnaires, the most recent of which was administered between 2007 and 2009.

Primary and Secondary Major CV End Points

Severity of CV events was graded according to the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE; version 4.03), as was described previously.[22] Only major (grade 3 to 5) CV events were included, defined as severe (grade 3), life threatening or disabling (grade 4), or fatal (grade 5). The specific CV conditions were coronary artery disease (CAD; ie, myocardial infarction plus cardiac catheterization or angioplasty or coronary artery bypass graft, or death resulting from myocardial infarction), heart failure (ie, heart failure requiring angiotensin-converting enzyme or angiotensin receptor blockers or death resulting from heart failure), arrhythmia (ie, serious arrhythmia including atrial fibrillation, atrial flutter, ventricular tachycardia, or death resulting from arrhythmia), and valve abnormalities (ie, valve replacement). The primary end point was a composite incidence of any major (grade 3 to 5) CV event. Secondary end points were incidence of individual grade 3 to 5 CV events. If the information needed to distinguish between grades was insufficient, the lower grade was used. For assessment of cardiac mortality, the CCSS cohort was linked with the National Death Index to ascertain cardiac deaths (International Classification of Diseases, ninth revision codes 390 to 398, 402, 404, and 410 to 429 or International Classification of Diseases, tenth revision, codes I00 to I02, I05 to I09, I11, I13, I20 to I28, and I30 to I52).[22]

Exposure Assessment

In baseline and follow-up questionnaires, participants were asked detailed questions related to personal medical history, smoking status, alcohol use, height, and weight. CV risk factors included physician-diagnosed diabetes mellitus, hypertension, obesity, and dyslipidemia, and medication use related to these disorders during the previous 2-year period. Body mass index was calculated from self-reported height and weight and classified using standard criteria. For participants younger than age 20 years, obesity was defined as a body mass index in the 95th percentile or above for age- and sex-specific distributions for US children.

Exposure to vigorous intensity exercise was ascertained in the baseline questionnaire using the following single item from the Youth Risk Behavior Surveillance Survey "On how many of the past 7 days did you exercise or do sports for at least 20 minutes that made you sweat or breathe hard (eg, dancing, jogging, basketball, and so on)." This item has acceptable test-retest reliability for assessment of total minutes of vigorous exercise.[23,24] Exposure to moderate intensity or mild intensity exercise was not evaluated. To calculate the primary exposure of total vigorous intensity exercise, the frequency of reported sessions per week was multiplied by the session duration (ie, 20 minutes), weighted by the standardized classification of the energy expenditure associated with vigorous intensity exercise in metabolic equivalents METs expressed as average MET hours/week^{-1}.[25] The standard MET weighting for vigorous intensity exercise is 9 METs. Using this approach, the range of self-reported exercise behavior ranged from 0 MET hours/week^{-1} to a maximum of 21 MET hours/week^{-1}. Categories of total vigorous intensity exercise were defined as 0, 3 to 6, 9 to 12, and 15 to 21 MET hours/week^{-1}. We also calculated the proportion of participants meeting the national guidelines for vigorous intensity exercise for individuals with cancer (ie, $\geq$ 3 sessions of vigorous intensity exercise/week of $\geq$ 20 minutes in duration), the equivalent to $\geq$ 9 MET hours/week^{-1}.[26]

Statistical Analysis

Demographic, disease, and treatment characteristics were reported by exercise (MET hours/week^{-1}) categories and compared using χ^2 tests for categorical measures and analysis of variance for continuous measures. Analysis of CV incidence after the baseline questionnaire completion was conducted, treating death, second malignant neoplasms, and late recurrence as competing risks and censoring at either the completion date of the latest questionnaire or the most recent National Death Index search (December 31, 2007), whichever occurred first. Cumulative CV event incidence was estimated and compared across exercise (MET hours/week^{-1}) categories or meeting national guidelines for vigorous intensity exercise using Gray's K-sample test[27] and the cumulative incidence at 10 years from baseline was compared using permutation test.

Poisson regression was used to estimate adjusted associations between exercise exposure categories or meeting national guidelines and incidence of CV events using the logarithm of person-years as the offset. The regression model adjusted for attained age, age at diagnosis, sex, race, smoking, education, CV risk factors, baseline grade 3 to 4 (non-CV) chronic conditions, and anthracycline and chest radiation exposures as potential confounders. The potential confounders were selected on the basis of prior knowledge of covariates established to be associated with the risk of CV events in the general population (eg, hypertension, type II diabetes, age) as well as those additional factors associated with risk in individuals with cancer (eg, anthracycline dose, chest radiation). We also conducted sensitivity analyses that excluded all patients reporting grade 1 to 2 CV conditions at the baseline. There were no differences between the primary and sensitivity analyses (Data Supplement; Appendix Tables A1 and A2 [online only]); as such, only data from the primary analysis is presented. Results are reported as rate ratios with 95% CIs. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) and R version 2.14.2. All statistical inferences were two-sided.

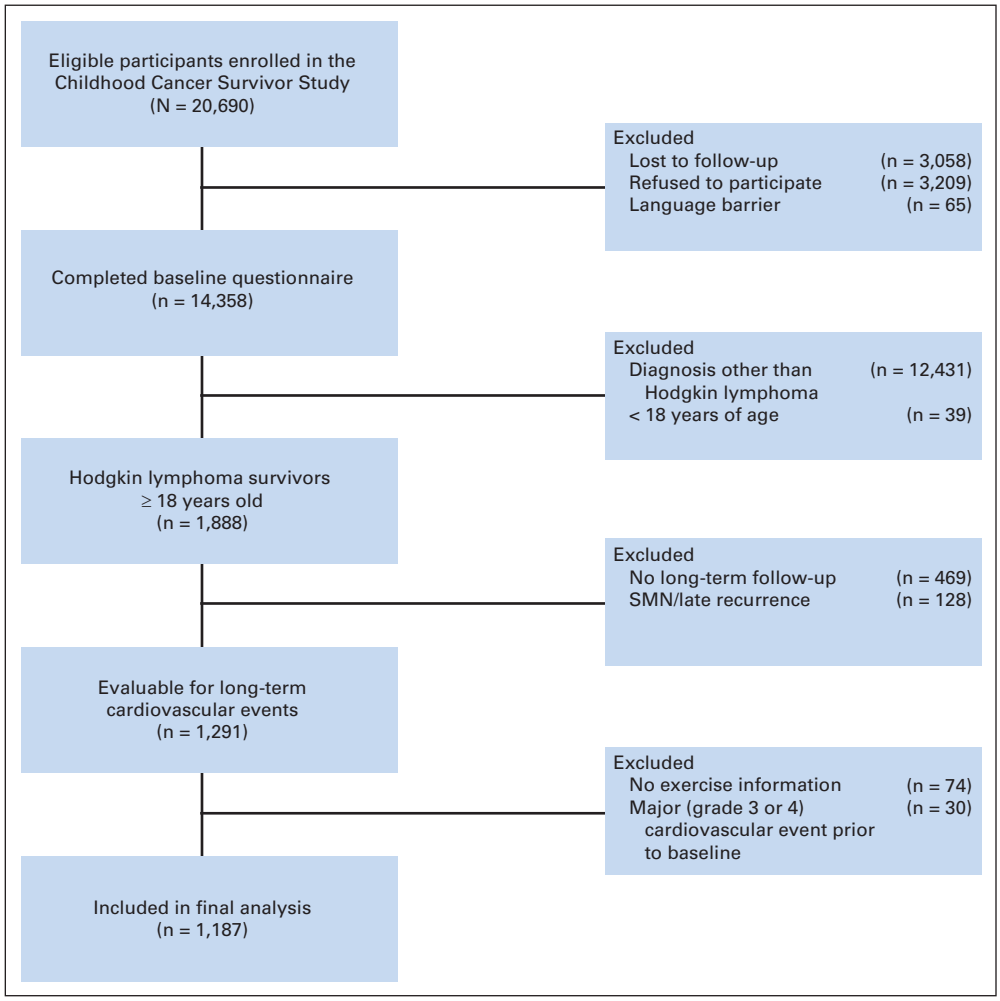

Fig 1. CONSORT diagram. SMN, second malignant neoplasm.

RESULTS

A total of 1,187 adult survivors of HL, a median of 16.7 years (range, 8.2 to 28.7 years) from diagnosis to baseline study entry, (median, age 31.2 years; range, 18.0 to 48.9 years) completed the exercise questionnaire and were deemed eligible for the present analysis (Fig 1). Patient characteristics are presented in Table 1. Mean vigorous intensity exercise behavior was 6.1 ± 6.3 MET hours/week^{-1}. Thirty-six percent of survivors of HL reported zero vigorous intensity exercise behavior.

Cumulative Incidence

Median follow-up was 11.9 years (range, 1.7 to 14.3 years). During this period, a total of 135 CV events were reported, including 21 CV-related deaths. The median overall time from baseline assessment of exercise behavior to first incidence of a CV event was 6.3 years. The cumulative incidence of any CV event was 12.2% at 10 years for survivors reporting 0 METs, 11.9% for those reporting 3 to 6 METs, compared with 5.2% for those reporting ≥ 9 METs ($P < .001$). Compared with those reporting fewer than 9 MET hours/week^{-1}, the incidence of the primary end point (any CV event), as well as all secondary end points except incidence of serious arrhythmias, were significantly lower in survivors meeting national vigorous intensity exercise guidelines (≥ 9 MET hours/week^{-1}; Figs 2A through 2D).

Multivariable Analyses

There was a strong, graded inverse relationship between total vigorous intensity exercise (total MET hours/week^{-1}) and incidence of any CV event ($P_{trend} = .002$; Table 2; Fig 3). Specifically, compared with survivors reporting 0 MET·hours/week^{-1}, the adjusted rate ratio was 0.87 (95% CI, 0.56 to 1.34) for 3 to 6 MET·hours/week^{-1}, 0.45 (95% CI, 0.26 to 0.80) for 9 to 12 MET·hours/week^{-1}, and 0.47 (95% CI, 0.23 to 0.95) for 15 to 21 MET hours/week^{-1}. Adherence to guidelines for vigorous intensity exercise (ie, ≥ 9 MET·hours/week^{-1}) was associated with an adjusted 51% decrease in the risk of any CV event in comparison with not meeting the guidelines (< 9 MET·hours/week^{-1}; Table 3).

For secondary clinical end points, there was a strong graded inverse relationship between total MET hours/week^{-1} and incidence of CAD events ($P_{trend} = .005$; Table 2; Fig 3). With the exception of heart failure events and compared with those reporting fewer than 9 MET hours/week^{-1}, there were inverse relationships between meeting the national exercise guidelines (≥ 9 MET hours/week^{-1}) and incidence valve replacement, serious arrhythmia, and CV-related death (Table 3).

DISCUSSION

Vigorous exercise was associated with substantial reductions in the risk of major CV events in a large population of adult survivors of

Table 1. Demographic and Treatment Characteristics of the Participants

Characteristic	All Patients		MET · hours/week^{-1} 0		3 to 6		9 to 12		15 to 21		*P*
	No.	%	No.	%	No.	%	No.	%	No.	%	
Participants	1,187	100	426	35.9	317	26.7	269	22.7	175	14.7	
Age at interview, years											
Mean	41.9		42.7		41.6		41.5		41.0		.008
Range	21.9-57.9		23.5 - 57.7		24.7 - 57.9		21.9 - 55.5		24.9 - 56.5		
Age at diagnosis, years											
Mean	14.4		14.7		14.3		14.1		13.8		.06
Range	2.4-21.0		2.5 - 21.0		2.7 - 21.0		2.4 - 20.9		3.7 - 20.9		
Interval between diagnosis and study entry, years											
Mean	16.7		17.6		16.8		16.5		16.5		.014
Range	8.2-28.7		8.2 - 27.8		8.2 - 28.5		8.3 - 28.7		8.2 - 28.6		
Male	632	53.2	209	49.1	162	51.1	142	52.8	119	68.0	< .001
Race											.47
Non-Hispanic white	1,080	91.0	387	90.8	288	90.9	250	92.9	155	88.6	
Other group	107	9.0	39	9.2	29	9.1	19	7.1	20	11.4	
BMI, kg/m^2											
Mean	26.1		26.3		26.3		26.0		25.7		.61
Range	12.8 - 65.8		14.6 - 47.9		12.8 - 63.2		15.6 - 65.8		15.4 - 46.1		
Smoking											.046
Current	179	15.1	79	18.5	50	15.8	27	10.0	23	13.1	
Former	325	27.4	113	26.5	76	24.0	82	30.5	54	30.9	
Never	683	57.5	234	54.9	191	60.3	160	59.5	98	52.0	
Cancer treatment											
Chemotherapy											
Any chemotherapy	674	63.0	241	63.6	174	60.0	163	64.4	96	64.9	.73
Alkylating agent	637	59.8	229	60.7	162	55.9	156	61.9	90	61.2	.46
Anthracycline	213	20.0	75	19.9	52	17.9	55	21.8	31	21.1	.70
Anthracycline dose, mg/m^2											.95
None	302	81.2	238	82.6	197	79.1	116	81.1	853	81.1	
< 250 mg/m^2	41	11.0	27	9.4	28	11.2	16	11.2	112	10.6	
≥ 250 mg/m^2	29	7.8	23	8.0	24	9.6	11	7.7	87	8.3	
Radiation therapy											
Any radiation therapy	1,026	91.4	361	89.8	280	92.1	237	91.2	148	94.3	.37
Chest	908	85.7	324	85.3	254	88.5	198	80.8	132	89.2	.044
Chest RT dose											
None	152	14.4	56	14.7	33	11.5	47	19.3	16	10.9	.054
< 20 Gy	22	2.1	11	2.9	4	1.4	5	2.0	2	1.4	
20-< 30 Gy	188	17.8	57	15.0	51	17.8	44	18.0	36	24.5	
30-< 40 Gy	350	33.1	137	36.1	98	34.1	62	25.4	53	36.1	
40-< 50 Gy	320	30.2	110	28.9	93	32.4	78	32.0	39	26.5	
≥ 50 Gy	26	2.5	9	2.4	8	2.8	8	3.3	1	0.7	
Abdominal or pelvic	620	58.5	214	56.5	169	58.9	148	60.4	89	60.1	.75
CV risk factors											
Diabetes mellitus	52	4.4	20	4.7	20	6.3	8	3.0	4	2.3	.11
Hypertension	294	24.8	120	28.2	87	27.4	57	21.2	30	17.1	.011
Dyslipidemia	224	18.9	96	22.5	62	19.6	48	17.8	18	10.3	.006
Obesity	231	19.6	85	20.1	69	21.8	46	17.4	31	17.7	.52
Any of the above 4 factors	517	43.6	195	45.8	151	47.6	111	41.3	60	34.3	.021

Abbreviations: BMI, body mass index; CV, cardiovascular; MET, metabolic equivalent.

childhood HL even after controlling for important clinical covariates (including CV risk factors, treatment exposures, and other chronic health conditions). Our article is the first, to our knowledge, to show this graded inverse association in survivors of childhood cancer at risk for treatment-related cardiac events and thus adds to the wealth of evidence suggesting that regular exercise reduces the risk of CV disease in noncancer populations.[16-18]

Emerging evidence suggests that regular exercise in the period after the completion of primary adjuvant therapy is associated with, in general, substantial reductions in all-cause mortality after an adult diagnosis of early breast cancer[28-30]; a population that is also at higher risk of late-occurring CV toxicity resulting from adjuvant cancer therapy.[15] However, all studies to date have used broad clinical event classifications (such as death from other causes or total deaths), thus,

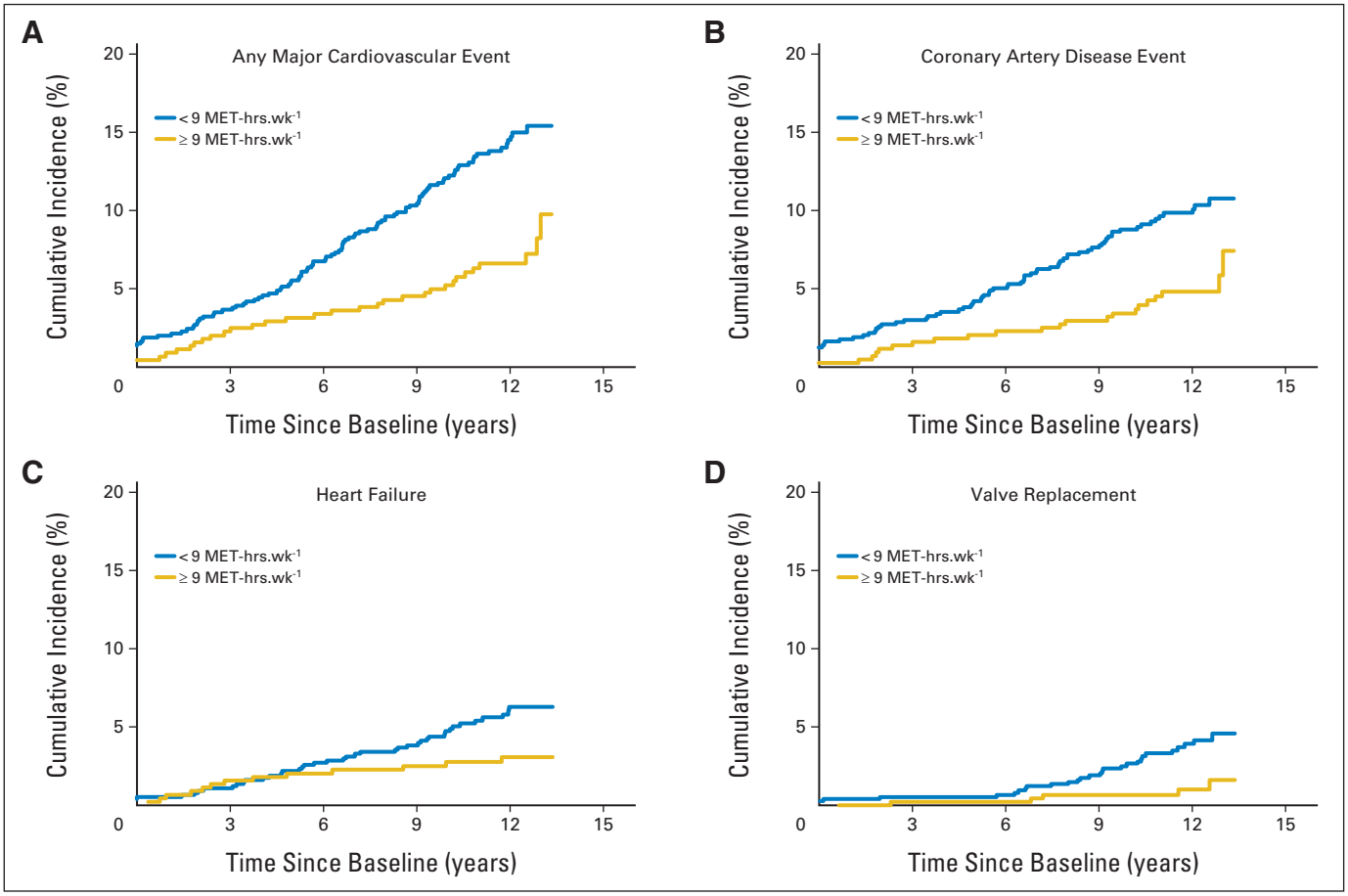

Fig 2. Cumulative incidence of (A) any major cardiovascular event ($P < .001$), (B) coronary artery disease ($P = .002$), (C) heart failure ($P = .028$), and (D) valve replacement ($P = .006$) according to meeting national guidelines for vigorous intensity exercise (ie, < 9 *v* ≥ 9 metabolic equivalent [MET] hours/week^{-1}).

the impact of exercise on the incidence of CV-related deaths or the type and nature of CV events has not been examined. Use of the CCSS cohort wherein CV events have been carefully ascertained and adjudicated[3,22] provides new insights into the cause-specific CV benefits of exercise in adult survivors of HL. As such, to our knowledge, our findings are the first to show that regular exercise deecreases CV-specific events in a cancer population with an increased CV toxicity risk phenotype.

Adult survivors of childhood HL are generally at risk of two distinct but related forms of CV morbidity and mortality: cardiomyopathy associated with heart failure and CAD (atherosclerosis).[31] Regular exercise may be equally effective at decreasing the risk of both entities in adult survivors of HL. The increased incidence of CAD in survivors of HL is primarily driven by chest irradiation.[1] Irradiation, with or without concurrent anthracycline chemotherapy, triggers a chronic proinflammatory/proreactive oxygen species (ROS) response that occurs in

Table 2. RRs of Major (grade 3 to 5) CV Events According to Quartile of Total Exercise (total MET hours/week^{-1})*

	MET · hours/week^{-1}											
	0		3 to 6			9 to 12			15 to 21			
CV Event	No.	RR	No.	RR	95% CI	No.	RR	95% CI	No.	RR	95% CI	P_{trend}
No. at risk	426		317			269			175			
Any major CV event	60	ref	44	0.87	0.56 to 1.34	19	0.45	0.26 to 0.80	12		0.23 to 0.95	.002
Coronary artery disease	45	ref	28	0.71	0.42 to 1.21	14	0.52	0.28 to 0.96	8		0.14 to 0.91	.005
Heart failure	20	ref	22	1.40	0.72 to 2.79	6	0.48	0.18 to 1.30	7		0.50 to 2.96	.69
Valve replacement	15	ref	13	1.24	0.55 to 2.79	1	0.12	0.02 to 0.95	4	0.90	0.29 to 2.81	.21
Serious arrhythmia†	8	ref	5	—	—	3	—	—	1	—	—	—

Abbreviations: CV, cardiovascular; MET, metabolic equivalent; ref, referent; RR, rate ratio.
*Adjusted for attained age, age at diagnosis, sex, race, smoking status, education, and CV disease risk factor profile as time dependent variables, anthracycline exposure, chest radiation exposure, and baseline (grade 3 or 4) chronic (non-CV) conditions.
†Result from multivariable analysis was not available due to the small number of events.

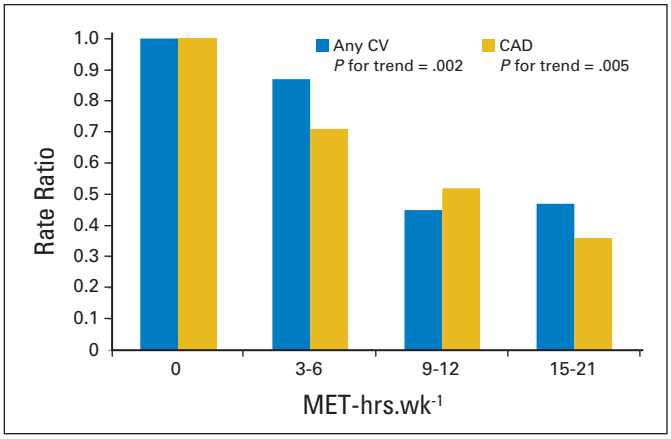

Fig 3. Adjusted risk ratios of any major cardiovascular (CV) event and coronary artery disease (CAD) events according to quartile of total vigorous intensity exercise (total metabolic equivalent [MET] hours/week^{-1}).

conjunction with secondary adverse lifestyle perturbations (physical inactivity, decreased VO_{2peak}, and obesity) that predispose to the accelerated development of traditional CV risk factors such as hyperlipidemia, hypertension, and type II diabetes.[7] In concert, these events produce a proinflammatory systemic milieu that accelerates alterations in the endothelial lining and arterial wall function to drive atherosclerosis.[7,32] In contrast, aerobic training may suppress systemic low-grade inflammation[33,34] as well as ROS levels through increased expression of endogenous antioxidant enzyme machinery.[35-37] There is also unequivocal evidence that aerobic training is an effective treatment for traditional CV risk factors such as abnormal lipids, hypertension, and metabolic dysregulation.[38] These effects are postulated to contribute, in part, to the strong inverse relationship between regular exercise and incidence of CAD.[39] Whether aerobic exercise favorably modifies traditional or nontraditional CV risk factors in the oncology setting has received limited attention, with mixed results.[38]

Anthracyclines are the primary contributor to cardiotoxicity resulting from direct cardiac myocyte apoptosis (leading to decreased contractility) and elevated afterload (increased wall stress).[31] In contrast, aerobic training improves myocardial contractility, diastolic relaxation and filling, and stroke volume (increased cardiac output),[40,41] as well as decreasing sympathetic tone with a concomitant increase in vagal activity[42,43] and attenuates pathologic left ventricular remodelling.[38] Increases in the peak arteriovenous oxygen difference demonstrates that aerobic training also possesses effects beyond the heart through improvements in peripheral vascular and/or increased O_2 usage in the skeletal muscles (via enhanced capillary surface area and oxidative capacity).[44] In concert, these physiologic adaptations augment O_2 delivery and/or usage, measured as improved peak $\dot{V}o_2$. Aerobic training may improve peak $\dot{V}o_2$ in adult survivors of childhood cancer with asymptomatic, subclinical left ventricular dysfunction,[45] although aerobic training did not improve VO_{2peak} or clinical outcomes in adult survivors of cancer with overt heart failure.[46]

Our data create a strong rationale for the development of a systematic research agenda to investigate the efficacy of aerobic exercise to prevent and/or delay treatment-associated CV toxicity in survivors of HL. Important currently unanswered questions include identification of the optimal timing (during and/or after treatment exposure) as well as intensity and dose of exercise to prevent/delay CV toxicity. It will also be critical to elucidate the molecular and systemic mechanisms of action; these efforts may lead to predictive biomarkers correlating with exercise response, which in turn may enable selection of survivors most likely to benefit from exercise treatment. From a clinical perspective, our findings provide clear evidence that, in addition to screening cardiac function and traditional CV risk factors,[22] physicians should also screen adult survivors on exercise behavior. Consistent with national exercise recommendations,[26] our findings support that sedentary survivors, when appropriate, be advised to achieve at least 20 minutes of vigorous intensity exercise on three or more days per week (ie, ≥ 9 METs). Oncologist-based recommendations are an effective strategy to increase exercise behavior in survivors of cancer.[47] Such approaches may be well received by survivors as well as family members/caregivers given that such approaches allow survivors to take a proactive role in prevention/attenuation of CV late effects.[48]

Our study has important limitations. With our design, it was not possible to delineate whether higher levels of exercise simply reflects lower CV or other chronic disease burden and/or long-term symptoms as opposed to a direct exercise-induced effect. Only data from randomized controlled trials can address this question. Higher levels of exercise behavior also may be associated with better adherence to other health behaviors (eg, diet, alcohol consumption). Exercise was assessed by a self-reported single-item questionnaire that only evaluated vigorous intensity exercise. Single-item self-report measures of exercise behavior have well-known limitations and therefore some misclassification of exercise exposure is expected. Indeed, it is possible that patients reclassified or upgraded participation in lower intensity exercise to vigorous intensity exercise. In addition, it is not known whether exercise participation at moderate or mild intensity levels also decreases the risk of CV events.

Our study questionnaire only assessed exercise behavior for the week before the CCSS baseline assessment, the relationship between lifetime exercise exposure and/or change in exercise levels and CV toxicity could not be addressed. Finally, all CV events, as well as cardiovascular risk factors, were self-reported without medical record confirmation, and thus, some misclassification is possible. To minimize possible misclassification, we only included

Table 3. RRs of Major (grade 3 to 5) CV Events According to Meeting National Guidelines for Vigorous-Intensity Exercise (ie, < 9 *v* ≥ 9 MET hours/week^{-1})*

	MET hours/week^{-1}						
	< 9 (n = 743)			≥ 9 (n = 444)			
CV Event	No.	RR	95% CI	No.	RR	95% CI	*P*
Any major CV event	104	ref	ref	31	0.49	0.31 to 0.76	.002
Coronary artery disease	73	ref	ref	23	0.53	0.32 to 0.89	.01
Heart failure	41	ref	ref	12	0.63	0.33 to 1.23	.18
Valve replacement	28	ref	ref	5	0.36	0.14 to 0.95	.04
Serious arrhythmias†	13	ref	ref	4	—	—	—

Abbreviations: CV, cardiovascular; MET, metabolic equivalent; ref, referent; RR, rate ratio.
*Adjusted for attained age, age at diagnosis, sex, race, smoking status, education, and CV disease risk factor profile as time-dependent variables, anthracycline exposure, chest radiation exposure, and baseline (grade 3 or 4) chronic (non-CV) conditions.
†Result from multivariable analysis was not available as a result of the small No. of events.

grade 3 to 4 events (serious/disabling or life-threatening), which are less likely to be misreported.[3,22]

In summary, our findings indicate that adoption of regular exercise consistent with national vigorous exercise recommendations in currently sedentary survivors could confer substantial public health benefits in the rapidly growing population of survivors of childhood cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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Provision of study materials or patients: Gregory T. Armstrong
Collection and assembly of data: Gregory T. Armstrong, Leslie L. Robison, Kevin C. Oeffinger
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Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Exercise and Risk of Major Cardiovascular Events in Adult Survivors of Childhood Hodgkin Lymphoma: A Report From the Childhood Cancer Survivor Study

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Appendix

Table A1. RRs of Major (grade 3 to 5) CV Events According to Quartile of Total Exercise (total MET hours/week^{-1}; sensitivity analysis)*

	MET · hours/week^{-1}											
	0		3 to 6			9 to 12			15 to 21			
CV Event	No.	RR	No.	RR	95% CI	No.	RR	95% CI	No.	RR	95% CI	P_{trend}
No. at Risk	371		278			242			159			
Any major CV event	46	ref	37	0.93	0.57 to 1.53	13	0.42	0.22 to 0.82	6	0.29	0.10 to 0.81	.001
Coronary artery disease	34	ref	23	0.70	0.38 to 1.29	10	0.44	0.21 to 0.92	4	0.19	0.05 to 0.80	.002
Heart failure	16	ref	18		0.74 to 3.35	3	0.25	0.06 to 1.12	3	0.79	0.22 to 2.80	.22
Valve replacement	10	ref	10	—	—	1			2			
Serious arrhythmia†	6	ref	5	—	—	1	—	—	1	—	—	—

Abbreviations: CV, cardiovascular; MET, metabolic equivalent; ref, referent; RR, rate ratio.
*All patients presented with any grade 1 to 4 CV condition at baseline are excluded from this analysis.
†Statistical testing was not possible due to small numbers.

Table A2. RRs of Major (grade 3 to 5) CV Events According to Meeting National Guidelines for Vigorous Intensity Exercise (ie, < 9 *v* ≥ 9 MET hours/week^{-1}; sensitivity analysis)*

	MET hours/week^{-1}					
	< 9 MET hours/week^{-1} (n = 649)			≥ 9 MET hours/week^{-1} (n = 401)		
CV Event	No.	RR	95% CI	No.	RR	95% CI	*P*
Any major CV event	83	ref	ref	19	0.39	0.22 to 0.68	$< .001$
Coronary artery disease	57	ref	ref	14	0.42	0.22 to 0.80	.008
Heart failure	34	ref	ref	6	0.34	0.13 to 0.90	.030
Valve replacement	20	ref	ref	3	—	—	
Serious arrhythmias	11	ref	ref	2	—	—	—

Abbreviations: CV, cardiovascular; MET, metabolic equivalents; ref, referent; RR, rate ratio.
*All patients presented with any grade 1 to 4 CV condition at baseline are excluded from this analysis.