# Impact of Exercise on Psychological Burden in Adult Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

Emily S. Tonorezos, MD MPH;[1,2] Jennifer S. Ford, PhD;[3] Linwei Wang, MS;[4] Kirsten K. Ness, PT PhD;[5] Yutaka Yasui, PhD; [5] Wendy Leisenring, ScD;[6] Charles A. Sklar, MD;[1] Leslie L. Robison, PhD;[5] Kevin C. Oeffinger, MD;[7] Paul C. Nathan, MD MSc;[8] Gregory T. Armstrong, MD; MSCE,[5] Kevin Krull, PhD;[5*] Lee W. Jones, PhD[1,2*]

[1]Memorial Sloan Kettering, New York, NY
[2]Weill Cornell Medical College, New York, NY
[3]Hunter College, City University of New York, New York, NY
[4]BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada
[5]St. Jude Children's Research Hospital, Memphis, TN
[6]Fred Hutchinson Cancer Research Center, Seattle, WA
[7]Duke University, Durham, NC
[8]The Hospital for Sick Children, Toronto, Canada

[*]Denotes equal contribution

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**Correspondence:** Emily Tonorezos, MD MPH; Memorial Sloan Kettering Cancer Center, 485 Lexington Ave, 2nd Floor; New York, NY 10017; Tonoreze@mskcc.org; Tel 646-888-8080; Fax 929-321-1518

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**Running Title:** Exercise and psychological burden

**Precis:** In this report from the Childhood Cancer Survivor Study (CCSS), vigorous exercise was associated with a lower risk of subsequent depression and somatization; even small amounts of vigorous exercise appeared to be beneficial.

## ABSTRACT

**Background:** Childhood cancer survivors are at risk for adverse psychological outcomes. Whether exercise can attenuate this risk is unknown.

**Methods:** 6,199 CCSS participants (median[range] age 34.3 years[22.0-54.0] and median[range] age at diagnosis 10.0 years[0-21.0]) completed a questionnaire assessing vigorous exercise and medical/psychological conditions. Outcomes were evaluated a median[range] of 7.8[0.1-10.0] years later and were defined as: symptom level above 90$^{th}$ percentile of population norms for depression, anxiety, or somatization on the Brief Symptom Inventory-18; cancer-related pain; cognitive impairment using a validated self-report neurocognitive questionnaire; or poor health-related quality of life (HRQOL). Log-binomial regression estimated associations between exercise [metabolic equivalent-hrs·wk$^{-1}$(MET-hrs·wk$^{-1}$)] and outcomes adjusting for cancer diagnosis, treatment, demographics, and baseline conditions.

**Results:** The prevalence of depression at follow-up was 11.4%(95%CI:10.6-12.3%), anxiety 7.4%(95%CI:6.7-8.2%) and somatization 13.9%(95%CI:13.0-14.9). The adjusted prevalence ratio (PR) for depression was 0.87(95%CI:0.72-1.05) for 3 to 6 MET-hrs·wk$^{-1}$, 0.76(95%CI:0.62-0.94) for 9 to 12 MET-hrs·wk$^{-1}$, and 0.74(95%CI:0.58-0.95) for 15 to 21 MET-hrs·wk$^{-1}$. Compared to 0 MET-hrs·wk$^{-1}$, 15 to 21 MET-hrs·wk$^{-1}$ was associated with an adjusted PR of 0.79 (95% CI: 0.62-1.00) for somatization. Vigorous exercise was associated with less impairment in physical functioning, general health, and vitality ($p_{trends}<0.001$), emotional role limitations ($p_{trend}=0.02$) and mental health ($p_{trend}=0.02$) domains, as well as higher cognitive function in domains of task completion, organization, and working memory (p's<0.05) but not cancer pain.

**Conclusion**: Vigorous exercise is associated with less psychological burden and cognitive impairment in childhood cancer survivors.

## INTRODUCTION

The number of childhood cancer survivors living in the United States currently exceeds 420,000.[1] This number is expected to increase over the next two decades due to sustained improvements in treatment and supportive care.[2] At the same time, significant medical and psychological morbidity due to late effects of therapy has been well-documented.[3, 4] Depression,[5, 6] anxiety,[7, 8] somatization,[9] fatigue,[10] poor health-related quality of life (HRQOL),[11] suicidal ideation,[12] impaired cognitive function,[13] and reduced psychological well-being[14] are frequent among childhood cancer survivors. Of importance, these symptoms do not occur in isolation, but rather in clusters.[15, 16] Therefore, treatment strategies able to mitigate multiple symptoms simultaneously may have significant benefit for childhood cancer survivors.[17]

Exercise is a pleiotropic therapy shown to improve a broad array of psychological symptoms in patients without cancer.[18-20] In adults with or at risk for psychological disorders, regular exercise is consistently associated with fewer depressive or anxious symptoms[21-25] and less sleep disruption.[26, 27] Randomized trials demonstrate that structured exercise training lessens anxiety and depressive symptoms, and improves short-term mood, cognition, and overall HRQOL in persons with or at risk for these problems.[28-32] In the pediatric oncology setting, a limited number of studies have demonstrated that exercise can benefit fatigue and overall quality of life.[33] Yet, the potential benefit of exercise to mitigate depression, anxiety, or somatization, or to have a more durable impact on these symptoms among adult survivors of childhood cancer survivors is unknown.

Therefore, we investigated the association between vigorous exercise and subsequent psychological symptoms,  HRQOL, cancer pain, and cognitive impairmentamong adult survivors of childhood cancer in the Childhood Cancer Survivor Study (CCSS). In order to capture clinically significant psychological outcomes in a rigorous manner, we used population norms to define cases of depression, anxiety, or somatization.[34, 35]

## METHODS

### Patients and Study Overview

The CCSS is a retrospective cohort with longitudinal follow-up of survivors of childhood cancer treated at 26 institutions in the United States and Canada between 1970 and 1986. Eligibility criteria include diagnosis of cancer at < 21 years and survival at least five years from diagnosis.[34, 35] Participants or a designated proxy completed detailed a baseline questionnaire including medical history, chronic health conditions, education, smoking status, alcohol use, education, height, weight, exercise behavior and psychological symptoms (described in detail below). Other examined covariates, primarily derived from medical record review, include: age at diagnosis, gender, race, cancer diagnosis, alkylating agent exposure expressed as cyclophosphamide equivalent dose,[36] anthracycline exposure in doxorubicin equivalent dose,[37] and radiation therapy to the chest, brain or head. The CCSS protocol was reviewed and approved by the human subjects committee at each participating institution, and informed consent was obtained before study participation.

**Exercise Assessment**

Vigorous exercise was ascertained in the baseline questionnaire using the item "on how many of the past seven days did you exercise or do sports for at least 20 minutes that made you sweat or breathe hard (e.g., dancing, jogging, basketball, etc.)", as in prior studies.[38] Total vigorous exercise was calculated as follows: frequency of sessions/week multiplied by session duration, weighted by the standardized classification of the energy expenditure associated with vigorous exercise in metabolic equivalents (9 METs) and expressed as MET-hours per week ($\text{hrs}\cdot\text{wk}^{-1}$);[39] 20 minutes of vigorous exercise a week (approximately 3 minutes per day) is equivalent to 3 MET-$\text{hrs}\cdot\text{wk}^{-1}$. Levels of total vigorous exercise were defined as 0, 3 to 6, 9 to 12, and 15 to 21 MET-$\text{hrs}\cdot\text{wk}^{-1}$.[38] The proportion of participants meeting national guidelines for vigorous exercise for adult cancer survivors, equivalent to ≥ 9 MET-$\text{hrs}\cdot\text{wk}^{-1}$ was calculated.[40, 41]

**Endpoints**

Psychological outcomes were ascertained in a follow-up questionnaire completed a median of 7.8 years later (range, 0.1 -10.4). The primary endpoints were psychological symptoms (depression, anxiety, or somatization), cancer pain, domains of HRQOL, and neurocognitive dysfunction.

*Depression, Anxiety, and Somatization* were assessed using the BSI-18. The BSI-18 consists of 18 five-point Likert scale items (0="not at all," to 4="extremely") evaluating the degree to which particular symptoms distressed or bothered the patient over the past seven days. Depression, anxiety, and somatization were each assessed by 6 items for a total of 18 items. Scores were compared to population norms to generate T-scores with a mean of 50 and standard deviation of 10. The prevalence of clinically significant symptoms was defined as a T-score≥63, as per scoring standards.[42] Analyses that included cases of depression, anxiety, or somatization as outcomes excluded participants with BSI completed by proxy.

*Cancer Pain* was assessed by the single item "Do you currently have pain as a result of your cancer or similar illness, or its treatment?" Participants who reported no pain or a small amount of pain were compared to those who reported medium, a lot, or very bad excruciating pain, as previously described.[43]

*Cognition* was assessed using the CCSS-Neurocognitive Questionnaire (CCSS-NCQ), a tool developed and validated for the CCSS,[44] consisting of 25 items assessing four domains of cognition: task efficiency (encompassing attention and processing speed), emotional regulation, organization, and memory. Impaired performance was defined as a score falling ≥90$^{th}$ percentile based on sibling age and sex-adjusted norms, as in prior CCSS analyses.[44, 45]

*HRQOL* was assessed with the Medical Outcomes Study 36-Item Short-Form (SF-36).[15] The SF-36 includes questions about general health, well-being and quality of life in the previous four weeks and yields eight scaled scores: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Summary scales scores are also available for a physical composite and a mental composite. Scaled scores were generated as t-scores with mean of 50 and standard deviation of 10, and t-scores< 40 were considered impaired.

**Statistical Analysis**

Demographic, disease, and treatment characteristics were summarized for four exercise levels (in MET-hrs$\cdot$wk$^{-1}$) and compared using Chi-square tests for categorical measures and analysis of variance (ANOVA) for continuous measures.[46] Log-binomial regression was used to assess the association between the vigorous exercise levels or meeting national guidelines (i.e., < 9 versus ≥ 9 MET-hrs$\cdot$wk$^{-1}$) and prevalence of subsequent clinically significant psychological symptoms. Multivariable log-binomial models were adjusted for the following potential confounders: age at follow-up, age at diagnosis, sex, race, smoking, education, cancer diagnosis, cancer treatment variables (alkylating agents, anthracyclines, chest radiation, brain or head radiation), baseline anxiety, depression, somatization or cancer pain, and baseline or interim severe, disabling, or life-threatening chronic health conditions.[47] In models for the relationship between exercise and cognition, education was excluded as a covariate, as cognitive impairment precedes and impacts educational attainment in this population. The "COPY method" was used for the convergence issue of the models.[48] Results are reported as prevalence ratios (PRs) with the corresponding large-sample approximate 95% confidence intervals (CIs) and p-values. Statistical analyses were conducted using SAS (SAS Institute, Inc., Cary, NC). All statistical inferences were two-sided.

**RESULTS**

A total of 14,358 survivors completed the baseline CCSS questionnaire. Of these, 6,199 were included in our analysis. The most common reasons for exclusion were being under the age of 18 years at the time of the baseline questionnaire (n=3,352) or not completing both a baseline and follow-up questionnaire (n=3,192); other reasons for exclusion are displayed in **Supplemental Figure 1**. When we compared those in the final sample (N=6199) to survivors who completed a baseline questionnaire including exercise data but did not complete the follow-up questionnaire (N=2499), those with follow-up were more likely to be female, of higher educational levels, of white non-Hispanic race/ethnicity (p's < 0.01), and to be vigorously exercising at 3 to 12 MET hours/week (p<0.01). Chronic medical conditions as well as cancer diagnosis and treatment variables did not differ between these two groups. Approximately half the participants in the final sample were male (n=3176; 51.2%) and the most common cancer diagnosis was leukemia (n=1857; 30.0%) followed by Hodgkin lymphoma (n=1001; 16.1%) (**Table 1**).

Over a third of survivors reported no vigorous exercise (n=2170; 35%) and more than half (n=3689; 59%) did not meet national exercise guidelines for vigorous activity. Exercising survivors were younger, had a lower prevalence of cardiovascular risk factors and were more likely to be male. There was no association between psychological symptoms or major chronic health conditions and exercise at baseline (p's>0.05; **Table 1**). During a median of 7.8 years (range, 0.1-10.4 years) follow-up, the prevalence of depression was 11.4% (95% CI:10.6%-12.3%), anxiety 7.4% (95% CI: 6.7%-8.2%) and somatization 13.9% (95% CI: 13.0%-14.9%).

**Exercise and Psychological Symptoms**

Vigorous exercise was associated with lower prevalence of depression ($p_{trend}$=0.003), and somatization ($p_{trend}$=0.005; **Figure 1**), but not anxiety ($p_{trend}$=0.75). Compared to 0 MET-hrs$\cdot$wk$^{-1}$, 15 to 21 MET-hrs$\cdot$wk$^{-1}$ was associated with an adjusted PR of 0.74 (95% CI: 0.58-0.95); $p_{trend}$ =0.004) for depression, and 0.79 (95% CI: 0.62-1.00; $p_{trend}$ =0.003) for somatization. Among those survivors adherent to national guidelines for vigorous activity (≥ 9 MET-hrs$\cdot$wk$^{-1}$ ), compared to those who did not meet guidelines (**Supplement Table 1**), the adjusted PR for cases of depression was 0.80 (95%CI: 0.68-0.94; p=0.009) and adjusted PR for cases of somatization was 0.83 (95% CI: 0.72-0.94; p=0.001).

Regarding cognition, fewer impairments in task completion ($p_{trend}$<0.001), organization ($p_{trend}$=0.038), and working memory ($p_{trend}$=0.003) were observed (**Figure 1**) among exercising survivors, compared to those who were not exercising vigorously. Among those meeting national exercise guidelines for vigorous activity, task completion was less likely to be impaired (PR 0.79; 95%CI: 0.71-0.88; $p_{trend}$<0.001), compared to those not meeting guidelines, although differences were not observed for the other domains of cognitive function (**Supplement Table 1**). Vigorous exercise was not associated with less cancer pain (**Figure 1**).

In reference to HRQOL, vigorous exercise was associated with less impairment in physical functioning, general health, and vitality ($p_{trends}$<0.001), as well as emotional role limitations ($p_{trend}$=0.02) and mental health ($p_{trend}$=0.02) domains (**Figure 2**). Compared to no vigorous exercise, those meeting national exercise guidelines (≥ 9 MET-hrs·$wk^{-1}$) had a lower adjusted prevalence of poor HRQOL in domains of physical functioning (PR 0.77; 95% CI:0.66-0.89; p<0.001), general health (PR 0.85; 95%CI: 077-0.92; p<0;001), and vitality (PR 0.82; 95% CI:0.75-0.87; p<0.001) (**Figure 2**).

## DISCUSSION

The principal finding from this large cohort of childhood cancer survivors is that vigorous exercise is associated with a lower risk of depression, somatization, or cognitive impairment. Survivors meeting national exercise guidelines for vigorous activity had an approximately 20% lower risk of depression or somatization, compared to those who did not meet guidelines. To our knowledge, our study is the first to observe this relationship among adult survivors of childhood cancer with a range of diagnoses and treatment exposures, thereby adding to the growing body of evidence for the widespread benefit of exercise and importance for the rapidly growing population of childhood cancer survivors.

In this cohort, over 70% of survivors had at least one of the following: psychological symptoms, cognitive impairment, cancer pain, or poor health-related quality of life. Yet, our results suggest that even small amounts of vigorous exercise may ameliorate these outcomes. Our study significantly extends prior work in exercise-oncology research by investigating the impact of exercise on psychological outcomes classified according to standard definitions and population-based cutoffs to define clinically significant psychological and cognitive symptoms, as well as cancer pain and quality of life. In addition, our analysis captured clinically significant outcomes up to 10 years after exercise assessment. Prior studies in non-cancer adult populations consistently demonstrate that regular exercise is associated with short-term improvements in mood and risk of new onset major depression or cognitive impairment, but demonstrating an impact on longer-term predefined outcomes is a major strength of this investigation.[24, 49-52]

Exercise may ameliorate treatment or stress-related chronic inflammation,[53, 54] oxidative stress,[55, 56] impaired neurotransmission,[57, 58] or cytokine and hormonal derangements.[59] Cognitive impairment is a common late effect in childhood and adult cancer survivors widely attributed to certain systemic therapies as well as cranial radiation therapy,[60] through a variety of mechanisms including impaired neurogenesis.[61, 62] Intriguingly, in a murine model of whole-body radiation, exercise blunted an anticipated decline in memory via increases in hippocampal plasticity;[62] other investigations suggest that cardiorespiratory fitness may directly impact brain function, or that the psychological benefit of exercise may be via improved sleep duration or quality.[9, 63-65]

It is important to note the clinical and research implications of these findings. In the CCSS, all participants are five years or more from the completion of therapy at baseline assessment. Therefore, quantification of vigorous exercise and psychological symptoms or cognitive impairment occurred well after treatment was over. For clinicians caring for adult survivors of childhood cancer, our results imply that exercise assessment and recommendation after treatment represents an opportunity to improve future emotional and cognitive health. Whether an exercise intervention will prove beneficial for these survivors will require further study. Nonetheless, asking childhood cancer survivors about exercise behavior and discussing suggested benefits of engaging in vigorous physical activity is a reasonable extension of this work.

Our study has important limitations. Although the multivariable analyses adjusted for potentially confounding variables including baseline emotional symptoms, it was not possible to delineate whether the association between exercise and lower risk of depression or somatization represents a direct benefit of exercise. In addition, exercise was assessed by a self-administered questionnaire; some misclassification of exposure as well as residual confounding could have occurred. Our exercise measure only assessed vigorous-intensity exercise. Thus, it is possible that respondents re-classified or ‘up-graded’ participation in lower intensity exercise to vigorous-intensity exercise. Notably, these forms of misclassification are likely to bias towards the null and so do not explain our findings suggesting a cognitive and emotional benefit. Statistical modeling did not adjust for multiple testing. Classical theory of multiple testing applies when testing a single hypothesis multiple times, whereas all outcomes were designated a priori based on prior evidence suggesting a potential benefit from vigorous exercise. The possibility that exercising survivors were more likely to use psychoactive medications, such as antidepressants, and therefore less likely to report symptoms such as depression, should be considered. Prior work in CCSS, however, suggests that use of psychoactive medications is associated with worsened neurocognitive outcomes.[66, 67] Therefore, use of psychoactive medications among exercising survivors is unlikely to explain our findings. Finally, all psychological symptoms were self-reported; thus, some misclassification is possible, although outcomes were designated by predefined thresholds and population norms.[42]

In conclusion, our results demonstrate that exercise is associated with better emotional, cognitive, and quality of life outcomes, independent of chronic medical conditions, in childhood cancer survivors. These findings suggest that vigorous exercise could have a significant benefit on the long-term health and wellbeing of this population.

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**Figure 1.** Prevalence Ratios (PR) of psychological symptoms according to levels of vigorous exercise (total MET-hrs $wk^{-1}$) among 6,199 survivors of childhood cancer.

**Figure 2.** Prevalence Ratios (PR) of domains of health-related quality of life according to levels of vigorous exercise (total MET-hrs $wk^{-1}$) among 6,199 survivors of childhood cancer.

**Table 1. Demographic and treatment characteristics of 6199 adult survivors of childhood cancer by levels of vigorous exercise (total MET-hours week$^{-1}$).**

| | MET hours week$^{-1}$ | | | | | |
|---|---|---|---|---|---|---|
| **Characteristics** | **All Patients** No. (%) | **0** | **3 to 6** | **9 to 12** | **15 to 21** | **P-value** |
| **Participants** | 6199 (100) | 2170 (35.0) | 1699 (27.4) | 1457 (23.5) | 873 (14.1) | |
| **Age at diagnosis, years** | | | | | | 0.072 |
| Median | 10.0 | 10.3 | 9.8 | 9.8 | 9.7 | |
| Range | 0.0 - 21.0 | 0.0 - 21.0 | 0.0 - 21.0 | 0.0 - 21.0 | 0.0 - 20.9 | |
| **Age at questionnaire, years** | | | | | | <0.001 |
| Mean | 34.0 | 34.0 | 33.0 | 33.0 | 33.0 | |
| Range | 22.0 - 54.0 | 23.0 - 53.0 | 23.0 - 53.0 | 23.0 - 54.0 | 22.0 - 53.0 | |
| **Sex of patient** | | | | | | <0.001 |
| Male | 3176 (51.2) | 1003 (46.2) | 843 (49.6) | 776 (53.3) | 554 (63.5) | |
| **Race/ethnicity** | | | | | | 0.243 |
| Non-Hispanic White | 5541 (89.4) | 1933 (89.1) | 1529 (90.0) | 1313 (90.1) | 766 (87.7) | |
| **BMI, kg/m$^2$** | | | | | | 0.029 |
| Mean | 26.4 | 26.6 | 26.4 | 26.3 | 25.9 | |
| Range | 10.4-73.2 | 10.4 - 73.2 | 13.6 - 58.6 | 13.8 - 59.8 | 12.4 - 59.4 | |
| **Smoking** | | | | | | <0.001 |
| Current | 972 (15.7) | 384 (17.7) | 270 (15.9) | 180 (12.4) | 138 (15.8) | |
| Former | 1039 (16.8) | 365 (16.8) | 266 (15.7) | 249 (17.1) | 159 (18.2) | |
| Never | 4185 (67.5) | 1420 (65.5) | 1161 (68.4) | 1028 (70.6) | 576 (66.0) | |
| **Highest education** | | | | | | <0.001 |
| Lower than or high school | 1139 (18.4) | 523 (24.1) | 253 (14.9) | 203 (13.9) | 160 (18.3) | |
| **Diagnosis** | | | | | | 0.236 |
| Leukemia | 1857 (30.0) | 600 (27.6) | 531 (31.3) | 459 (31.5) | 267 (30.6) | |
| CNS | 766 (12.4) | 289 (13.3) | 194 (11.4) | 165 (11.3) | 118 (13.5) | |
| Hodgkin lymphoma | 1001 (16.1) | 353 (16.3) | 264 (15.5) | 233 (16.0) | 151 (17.3) | |
| Non Hodgkin lymphoma | 576 (9.3) | 197 (9.1) | 164 (9.7) | 131 (9.0) | 84 (9.6) | |
| Kidney (Wilms) | 438 (7.1) | 151 (7.0) | 133 (7.8) | 96 (6.6) | 58 (6.6) | |
| Neuroblastoma | 249 (4.0) | 85 (3.9) | 70 (4.1) | 61 (4.2) | 33 (3.8) | |
| Soft tissue sarcoma | 628 (10.1) | 221 (10.2) | 168 (9.9) | 157 (10.8) | 82 (9.4) | |
| Bone cancer | 684 (11.0) | 274 (12.6) | 175 (10.3) | 155 (10.6) | 80 (9.2) | |
| **Chemotherapy** | | | | | | |
| Any chemotherapy | 4376 (78.0) | 1484 (77.0) | 1233 (79.3) | 1048 (78.3) | 611 (77.6) | 0.417 |
| Alkylating dose (CED), mg/m$^2$ | | | | | | 0.804 |
| None | 2747 (53.3) | 948 (54.0) | 770 (53.4) | 652 (52.9) | 377 (52.3) | |
| >0-<4000 | 482 (9.4) | 158 (9.0) | 146 (10.1) | 110 (8.9) | 68 (9.4) | |
| 4000-8000 | 587 (11.4) | 200 (11.4) | 170 (11.8) | 130 (10.6) | 87 (12.1) | |
| ≥8000 | 1334 (25.9) | 450 (25.6) | 355 (24.6) | 340 (27.6) | 189 (26.2) | |
| Anthracycline dose, mg/m$^2$ | | | | | | 0.256 |
| None | 3470 (64.5) | 1218 (65.8) | 951 (63.7) | 815 (63.4) | 486 (64.5) | |
| >0-<250 | 685 (12.7) | 217 (11.7) | 194 (13.0) | 162 (12.6) | 112 (14.9) | |
| ≥250 | 1226 (22.8) | 416 (22.5) | 347 (23.3) | 308 (24.0) | 155 (20.6) | |
| **Radiation therapy** | | | | | | |
| Any radiation therapy | 4032 (68.1) | 1413 (68.8) | 1119 (68.4) | 945 (67.7) | 555 (66.7) | 0.563 |
| Chest | 1571 (28.5) | 570 (29.8) | 427 (27.9) | 344 (26.5) | 230 (29.8) | 0.184 |
| Chest direct dose | | | | | | 0.027 |
| None | 1650 (51.4) | 545 (49.0) | 461 (52.0) | 398 (53.9) | 246 (51.9) | |
| <20 Gy | 226 (7.0) | 76 (6.8) | 65 (7.3) | 54 (7.3) | 31 (6.5) | |
| 20-<30 Gy | 398 (12.4) | 134 (12.0) | 97 (10.9) | 89 (12.0) | 78 (16.5) | |
| 30-<40 Gy | 510 (15.9) | 202 (18.1) | 144 (16.3) | 97 (13.1) | 67 (14.1) | |
| 40-<50 Gy | 363 (11.3) | 131 (11.8) | 96 (10.8) | 86 (11.6) | 50 (10.5) | |
| ≥50 Gy | 65 (2.0) | 25 (2.2) | 23 (2.6) | 15 (2.0) | 2 (0.4) | |
| Brain or head | 2048 (37.1) | 724 (37.9) | 549 (35.9) | 498 (38.4) | 277 (35.8) | 0.412 |
| All head direct dose | | | | | | 0.099 |
| None | 1650 (44.7) | 545 (43.0) | 461 (45.8) | 398 (44.5) | 246 (47.2) | |
| <20 Gy | 39 (1.1) | 10 (0.8) | 9 (0.9) | 12 (1.3) | 8 (1.5) | |
| 20-<30 Gy | 1191 (32.3) | 398 (31.4) | 341 (33.9) | 296 (33.1) | 156 (29.9) | |
| 30-<40 Gy | 114 (3.1) | 33 (2.6) | 35 (3.5) | 28 (3.1) | 18 (3.5) | |
| 40-<50 Gy | 143 (3.9) | 62 (4.9) | 31 (3.1) | 30 (3.4) | 20 (3.8) | |
| ≥50 Gy | 551 (14.9) | 219 (17.3) | 129 (12.8) | 130 (14.5) | 73 (14.0) | |
| **CV risk factors** | | | | | | |
| Diabetes mellitus | 191 (3.1) | 71 (3.3) | 60 (3.5) | 39 (2.7) | 21 (2.4) | 0.314 |
| Hypertension | 669 (10.8) | 301 (13.9) | 176 (10.4) | 127 (8.7) | 65 (7.4) | <0.001 |

| | MET hours week$^{-1}$ | | | | | |
|---|---|---|---|---|---|---|
| **Characteristics** | **All Patients** | **0** | **3 to 6** | **9 to 12** | **15 to 21** | **P-value** |
| Dyslipidemia | 427 (6.9) | 183 (8.4) | 100 (5.9) | 101 (6.9) | 43 (4.9) | 0.001 |
| Obesity | 1318 (21.3) | 496 (22.9) | 384 (22.6) | 288 (19.8) | 150 (17.2) | 0.001 |
| **Any major chronic conditions at baseline** | 592 (9.5) | 236 (10.9) | 147 (8.7) | 125 (8.6) | 84 (9.6) | 0.055 |
| **Psychological conditions at baseline** | 1328 (21.4) | 490 (22.7) | 352 (20.8) | 294 ( 20.3) | 192 (22.2) | 0.290 |

Abbreviations: BMI, body mass index; CED: cyclophosphamide equivalent dose;[36] CV, cardiovascular; MET, metabolic equivalent.
Psychological conditions at baseline includes: depression, anxiety, somatization, or cancer pain