Associations Between Physical Activity, a Healthy Lifestyle Score, and Subsequent Morbidity in Childhood Cancer Survivors: a report from the Childhood Cancer Survivor Study

Working group and investigators

- Primary working group: Cancer control
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Background

Increasing survival rates for several types of childhood cancer during the last decades have resulted in a rapidly increasing population of childhood cancer survivors. Since many childhood cancer survivors have received intense therapy with chemotherapy, often in combination with radiation therapy and surgery, these individuals are at risk of developing side effects, such as cardiovascular disease, subsequent malignant neoplasms (SMNs), emotional health concerns, and premature death,[1 2] during decades after completed cancer treatment. While efforts have been made to choose childhood cancer therapies with less burden in terms of late effects, it takes careful decisions and well-designed studies to remove therapies with a known high chance of cancer cure to reduce the risk for future late effects. Therefore, it is important to identify modifiable preventive factors to mitigate the negative effects of childhood cancer therapy.

Physical activity is known to have several health benefits, including prevention of cardiovascular disease, a number of cancer types, emotional health concerns; and improved health-related quality of life.[3 4] Physical activity and lifestyle can also be used to treat manifest disease, e.g. diabetes mellitus, hypertension, cardiovascular disease, and clinical depression.[3] Hence, several of the late effects of childhood cancer treatment could potentially be at least partially prevented by regular physical activity, and physical activity is recommended to cancer survivors, as well as to the general population.[3] The risk for morbidity in the childhood cancer survivor population could theoretically be divided in two parts, where one part is the risk in the general population, also relevant for childhood cancer survivors (fig. 1). The other part is caused by treatment, mainly chemotherapy and radiotherapy, moderated by genetic variations and possibly by lifestyle during and after treatment. It is known that the risk for developing several late effects is moderated by genetic variations. While it is

probable, little is known on whether lifestyle habits could moderate the treatment-related late effect risk increase. As with all risks in a population, it is often impossible to attribute late effects in an individual to a specific cause, but efforts should aim to find effective means for limiting the risk in the population. Since lifestyle habits are complex behaviors and consist of several aspects in terms of both dose, type and motivational factors, lifestyle interventions could vary considerably – from general advice or paper hand-out to supervised interventions. Lifestyle also has a wide variety of effects. As an example, lifestyle can affect most of the risk factors for cardiovascular disease – body composition, hypertension, glucose metabolism, blood lipids etc. All of this must be considered when evaluating the effects of lifestyle interventions. While there will never be any lifestyle intervention program with full long-term adherence, estimates of the possible effects for such interventions could serve as motivation for deploying large-scale intensive studies designed for clinically relevant long-term effects.

There is one previous study from the CCSS where an increase in physical activity was evaluated in a sub analysis and was associated with lower mortality risk.[5] In another study, vigorous exercise in the baseline questionnaire was reported to be associated with a lower prevalence of depression and somatization and less impaired health-related quality of life.[6] There is also a previous study where health risk clustering was explored and reported without determining longitudinal associations with late effects.[7] In a recent study, Dixon et al. reported a 20% lower mortality risk for participants with a healthy lifestyle score incl. tobacco smoking, alcohol use, physical activity, and unhealthy weight (accepted for publication in The Lancet).[8] The main novel contributions in the proposed study compared to the previous studies are the analysis of morbidity outcomes rather than mortality, limiting the physical activity assessments to the more valid questions used from the Follow-Up 2 questionnaire in the original cohort and onwards, and the assessments of the importance of both mean dose and change in dose of physical activity over time.

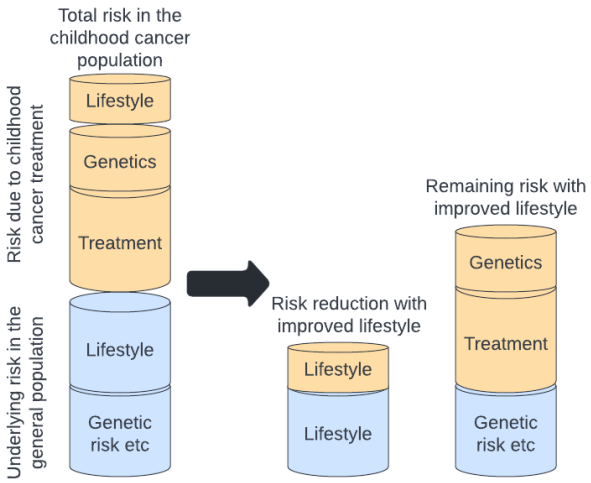

Figure 1. Conceptual model of the risk for late effects in the childhood cancer survivor population

Specific aims and hypotheses

Aim 1: To assess the associations between mean dose of and change in physical activity and the subsequent risk and improvement of individual medical conditions in childhood cancer survivors. This aim will address the following hypotheses:

- *An increase in and a high mean dose of physical activity are associated with a lower risk for developing new onset medical conditions known to be associated with physical activity in the general population, compared to a decrease in or low mean dose of physical activity. Each condition listed below is treated as a separate hypothesis. The risk for those with an increase in physical activity is expected to be similar to the risk for those with a constant high level of physical activity.*
- *An increase in and a high mean dose of physical activity is associated with a subsequent improvement of each medical condition listed below, known to be associated with physical activity in the general population, in individuals with pre-existing medical conditions at start of follow-up.*

Aim 2: To assess the associations between mean dose of and change in physical activity and subsequent risk and improvement of individual emotional health outcomes in childhood cancer survivors. This aim will address the following hypotheses:

- *An increase in and a high mean dose of physical activity are associated with a lower risk of developing new onset emotional health outcomes known to be associated with physical activity in the general population, compared to a decrease in or low mean dose of physical activity. Each condition listed below is considered a separate hypothesis.*
- *An increase in and a high mean dose of physical activity are associated with a subsequent improvement of the same emotional health outcomes in individuals with pre-existing emotional health outcomes at start of follow-up.*

Aim 3: To assess the associations between mean dose and change in physical activity and subsequent health-related quality of life (HRQoL) in childhood cancer survivors. This aim will address the following hypothesis:

- *An increase in and a high mean dose of physical activity are associated with a better trajectory for both mental and physical HRQoL, compared to a decrease in or low mean dose of physical activity.*

Aim 4 (exploratory): Define the combination of change in and mean dose of physical activity that most reduces risk for the individual medical and emotional health outcomes listed below.

Aim 5: To assess the association between a healthy lifestyle score, defined in accordance with the CCSS publication by Dixon et al.,[8] and the individual outcomes listed below. This aim will address the following hypothesis:

- *Clustering of health risk behaviors leads to an exponential risk increase that is larger than the sum of risk for each behavior, for each of the outcomes listed below.*

Aim 6: To define the population attributable fraction (PAF) of an unhealthy lifestyle on the risk for developing the individual medical and emotional conditions listed below. This aim will address the following hypotheses:

- *Poor lifestyle constitutes a significant population attributable fraction for the development of new-onset medical conditions and poor mental health in childhood cancer survivors for the outcomes listed below.*
- *This fraction is comparable to the population attributable fraction for chemotherapy but lower than the population attributable fraction for cranial radiotherapy for each of the individual outcomes listed below.*

Analysis framework

Population: The study population for aims 1-4 is all childhood cancer survivors in CCSS who have completed at least two follow-up questionnaires. Due to questions not allowing for calculation of dose of physical activity in the baseline questionnaire for the CCSS original cohort, we will use data from Follow-Up 2 in the original cohort onwards. We plan to include data from Follow-Up 7, and the study population for aims 1-4 will include >10,000 individuals, contributing >80,000 person years of follow-up. The study population for aims 5-6 is all childhood cancer survivors in CCSS with data allowing for calculation of the health behavior score, including exposures from the baseline questionnaire (>20,000 individuals per the Lancet paper by Dixon et al).[8]

Exposure: The exposures for aims 1-4 are the mean dose of physical activity and the change in dose over time. The dose will be calculated as metabolic equivalent task (MET) minutes per week, based on questions on duration and frequency of moderate and vigorous physical activity. Both mean dose and change in physical activity will be analyzed as continuous variables. We will consider performing supplementary analyses with categorized exposures for illustration of effects sizes. For aims 5-6, we

will use the healthy lifestyle score developed by Dixon et al.[8] Lifestyle factors, including smoking, alcohol use, physical activity, and unhealthy weight, will be assigned a score of 0 (unhealthy) or 1 (healthy) and combined to create a lifestyle score ranging from 0-4 for each survey time-point. We will define unhealthy as: ever smoked more than 100 cigarettes, heavy or risky drinking (>7 drinks/week or >3 drinks/day for women, >14 drinks/week or >4 drinks/day for men), body mass index <18·5 (underweight) or ≥30 (obese) kg/m2, and sedentary (0-3 MET-h/week of activity). For low physical activity (3-6 MET-h/week) a score of 0.5 will be assigned. The lifestyle score will be categorized as unhealthy (0-2), moderately healthy (2.5-3), and healthy (3.5-4).

Outcomes: Each aim will include several outcomes, treated as individual hypotheses. The events will be collected from CTCAE for late effects included there. Depression and anxiety will be assessed from the the 18-item Brief Symptom Inventory-18 (BSI-18), which includes symptoms over the previous 7 days.[9] The BSI-18 has a summary scale (the global distress index) and three subscales (depression, anxiety, and somatization). Raw scores are converted to T-scores based on U.S. population norms and dichotomized using a cutpoint of 63. Participants with a T-score ≥63 (90th percentile) on either depression or anxiety will be classified as having clinically significant concerns.[9] The Medical Outcomes Short Form-36 (SF-36) will be used to evaluate HRQOL.[9] Participants answer 36 questions about general health, well-being, and quality of life over the previous 4 weeks. The SF-36 has two component summary scales. Data will be presented as T-scores, with a general population mean of 50 and SD of 10. The component summary scales will be analyzed as continuous variables. Outcomes will be collected until Follow-Up 7.

Table 1. Outcomes studied in the concept proposal, categorized according to outcome group and the relevant aims where it is included.

Group	**Outcome**	**Outcome categories**	**Origin**	**Relevant aims**
Metabolic syndrome	Hypertension	CTCAE grades 2+	CTCAE	1, 4-6
Metabolic syndrome	Cholesterol	CTCAE grades 2+	CTCAE	1, 4-6
Metabolic syndrome	Diabetes mellitus	CTCAE grades 2+	CTCAE	1, 4-6
Metabolic syndrome	Obesity	BMI 30-34.9, 35-39.9, 40+	CTCAE	1, 4
Cardiovascular	Heart attack	CTCAE grades 3+	CTCAE	1, 4-6
Cardiovascular	Congestive heart failure	CTCAE grades 2+, 3+	CTCAE	1, 4-6
Cardiovascular	Stiff or leaky valves	CTCAE grades 4+	CTCAE	1, 4-6
Cardiovascular	Arrhythmia	CTCAE grades 2+	CTCAE	1, 4-6
Cardiovascular	Stroke	CTCAE grades 4+	CTCAE	1, 4-6
Liver	Fatty liver	Any CTCAE grade	CTCAE	1, 4-6
Musculoskeletal	Joint replacement	CTCAE grades 3+	CTCAE	1, 4-6
Musculoskeletal	Osteoporosis	CTCAE grade 2	CTCAE	1, 4-6
Respiratory	Any respiratory	CTCAE grades 2+	CTCAE	1, 4-6
SMN	Subsequent malignant neoplasms	CTCAE grades 3+	SMN data	1, 4-6
Emotional	Anxiety	Clinically significant, yes/no[9]	BSI-18	2, 4-6
Emotional	Depression	Clinically significant, yes/no[9]	BSI-18	2, 4-6

Quality of life	Health-related quality of life	Physical and mental component summary scales	SF-36	3-6

Statistical analyses:

Aim 1: To assess the associations between mean dose and change in physical activity and the risk of individual medical conditions in childhood cancer survivors.
Aim 2: To assess the associations between mean dose and change in physical activity and individual emotional health outcomes in childhood cancer survivors.

Aims 1-2: We will consider a separate time-to-event analysis for each outcome using piecewise exponential models. Our baseline measure of physical activity will be at the second follow-up questionnaire (around 2003) for the CCSS original cohort where we have reliable questionnaire information on dose of physical activity. Physical activity will also be calculated at the fourth follow-up questionnaire (around 2007), the fifth follow-up questionnaire (around 2014), and the sixth follow-up questionnaire (around 2017) as available. The number of MET minutes per week (physical activity) will be calculated from all available questionnaires prior to the outcome of interest (or censoring). Mean MET minutes per week and change in MET minutes*week^{-1} per year will be estimated for each individual by a random effects model with subject-specific random intercept and slope: these will be used in subsequent analyses as the main exposure variables of interest that quantify individual survivors' overall level and change in physical activity. Both these exposures will be included as mutually adjusted exposure variables in the models. The primary analysis will use physical activity from the first two physical activity assessments for each individual, at-risk period starting at the second ascertainment with the rest of the questionnaires used for outcome ascertainment. We will also consider using the first three assessments for exposure for those with at least four follow-ups. For each outcome, participants with pre-existing outcomes at start of the at-risk period will be excluded in that analysis for the first hypotheses of Aims 1 and 2. The analysis of the second hypotheses will only include participants with pre-existing outcomes and will use change in outcome grade as outcome, adjusting for the initial outcome grade. Each model will include the main exposures of interest (i.e., the derived physical activity dose and change) and predefined potential confounders known to affect the risk for the outcomes. The outcomes are treated independently and the only competing risk is death. If the null hypothesis cannot be rejected for any outcome in an outcome group, we will consider creating a composite outcome for that outcome group. No correction will be performed for multiple testing since the outcomes are treated as separate hypotheses of individual interest. The covariates to be included in the statistical models will be:

- Sex
- Age at diagnosis
- Year of diagnosis

- Chemotherapy previously reported to be associated with each outcome.
- Radiation treatment (different levels of detail depending on outcome – e.g. chest, head, abdomen).
- Age at start of follow-up
- Socioeconomic variables (attained education, marital status, insurance status, and household income)
- Race/ethnicity
- Smoking
- Alcohol consumption
- BMI at baseline.

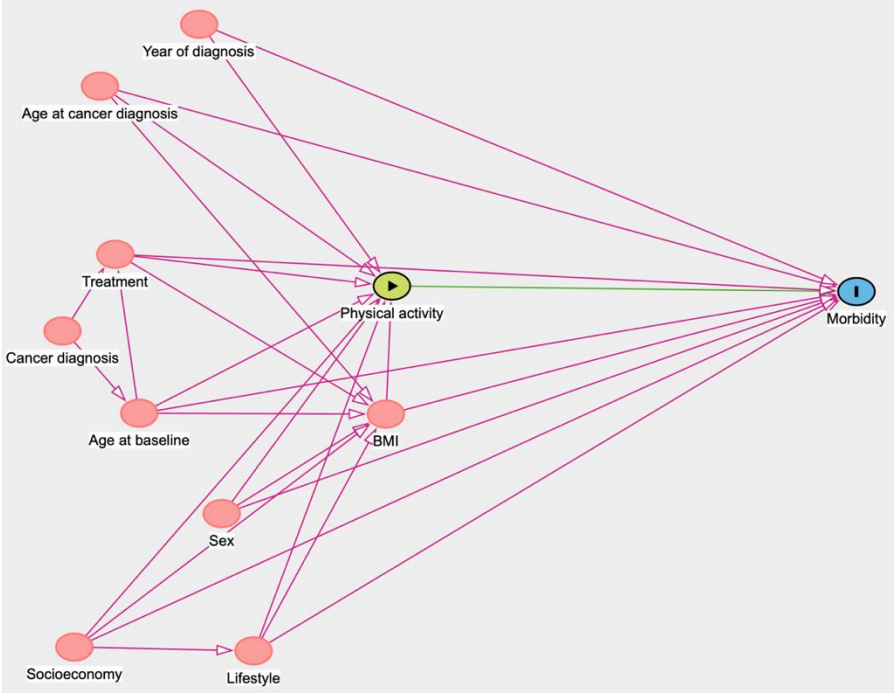

Figure 2. Directed acyclic graph showing possible confounders to include in the statistical analyses.

Aim 3: To assess the associations between mean dose and change in physical activity and health-related quality of life (HRQoL) in childhood cancer survivors.
We will use linear regression with change in score on the SF-36 physical and mental component summary scales (from follow-up 2 to follow-up 7) as the outcome. Models will be adjusted for the component summary scales at start of follow-up and the other variables described in Aims 1 and 2 above. Physical activity will be handled as in Aims 1 and 2.

Aim 4 (exploratory): Define the combination of change in and mean dose of physical activity that most reduces risk for the individual medical and emotional health outcomes listed below.
We will use 70% of the study sample, created by stratified random sampling stratified by childhood cancer diagnosis and decade for diagnosis, to model the risk for developing the outcomes associated with different trajectories of physical activity, and different mean levels of physical activity. Using the fitted model, we use a receiver operating characteristic (ROC) curve to find the threshold with the maximum true positive rate (TPR on Y-axis) and minimum false positive rate (FPR on X-axis). Finally, we will validate our finding using the remainder of the study sample (30%). This aim will not include HRQoL outcomes.

Aim 5: To assess the association between a healthy lifestyle score, defined in accordance with Dixon et al., and the individual outcomes listed.
We will consider piecewise exponential models, with start of follow-up at time of the first questionnaire with information on the healthy lifestyle score until death or loss to follow-up. The analyses will be adjusted for the potential confounders. Since lifestyle behaviors are dynamic and assessed at multiple survey time-points, they will be included as time-varying covariates so that changes over time will be accounted for in the analyses. Further, since lifestyle impacts health over long time periods and to minimize the possibility of bias due to reverse causality from lifestyle change or weight loss prompted by chronic illness (such as cachexia associated with a second malignancy or low physical activity due to progressive heart failure), the lifestyle score will be shifted back five years following Dixon et al.'s approach. The following covariates will be included in the model:

- Sex
- Age at diagnosis
- Year of diagnosis
- Age at start of follow-up
- Socioeconomic variables (attained education, marital status, insurance status, and household income)
- Race/ethnicity
- Cyclophosphamide equivalent dose
- Doxorubicin equivalent dose
- Cisplatin equivalent dose
- Radiation treatment (different levels of detail depending on outcome – e.g. chest, head, abdomen).

Aim 6: To define the population attributable fraction (PAF) of an unhealthy lifestyle on the risk for developing the individual medical and emotional conditions listed.

We will estimate population attributable fraction of an outcome associated with an exposure of interest as the proportion of outcome cases that is reduced by eliminating the exposure while holding all the other covariates in the model unchanged. We consider three exposures – lifestyle, chemotherapy, and radiotherapy. Lifestyle will be defined according to the score by Dixon et al. Chemotherapy will be defined as receiving alkylating agents, anthracyclines, or platinum exceeding previously reported thresholds for respective outcome. Radiotherapy will be defined as receiving any radiotherapy. The population attributable fractions for these three risk factors will be compared.

References:

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DRAFT OF PLANNED TABLES AND FIGURES

Table 1a. Demographic, lifestyle, diagnosis, and treatment variables according to mean dose and change in physical activity.

	NEGATIVE CHANGE IN PHYSICAL ACTIVITY	POSITIVE CHANGE IN PHYSICAL ACTIVITY	NO CHANGE IN PHYSICAL ACTIVITY
Number of participants			
Sex, female			
Bmi at start of follow-up			
Mean dose of physical activity, MET minutes/wk			
Change in physical activity, MET minutes/wk			
Age at baseline			
Years of follow-up			
Race/ethnicity			
Non-hispanic white			
Non-hispanic black			
Hispanic			
Other			
Educational attainment			
Household income			
Marital status			
Health insurance status			
Smoking history			
Never			
Past			
Current			
Heavy/risky drinking of alcohol			
Drug use			
Year of primary cancer diagnosis			
Age at primary cancer diagnosis			
Type of primary cancer diagnosis			
Received radiation treatment			
Received alkylating agents			
Received anthracyclines			
Received platinum			
Received epipodophyllotoxins			
Received high dose mtx (show if included in models for emotional health/HR-QoL)			
Received it mtx (show if included in models for emotional health/HR-QoL)			
Cumulative corticosteroid dose			
Hematopoietic stem cell transplant			

Table 1b. Demographic, lifestyle, diagnosis, and treatment variables according to the healthy lifestyle score.

	UNHEALTHY LIFESTYLE	MODERATELY HEALTHY LIFESTYLE	HEALTHY LIFESTYLE
Number of participants			
Sex, female			
Bmi at start of follow-up			
Mean dose of physical activity, MET minutes/wk			
Change in physical activity, MET minutes/wk			
Age at baseline			
Years of follow-up			
Race/ethnicity			
Non-hispanic white			
Non-hispanic black			
Hispanic			
Other			
Educational attainment			
Household income			
Marital status			
Health insurance status			
Smoking history			
Never			
Past			
Current			
Heavy/risky drinking of alcohol			
Drug use			
Year of primary cancer diagnosis			
Age at primary cancer diagnosis			
Type of primary cancer diagnosis			
Received radiation treatment			
Received alkylating agents			
Received anthracyclines			
Received platinum			
Received epipodophyllotoxins			
Received high dose mtx (show if included in models for emotional health/HR-QoL)			
Received it mtx (show if included in models for emotional health/HR-QoL)			
Cumulative corticosteroid dose			
Hematopoietic stem cell transplant			

Table 2a. Outcomes in absolute numbers, n (%), according to change in physical activity.

	NEGATIVE CHANGE IN PHYSICAL ACTIVITY	POSITIVE CHANGE IN PHYSICAL ACTIVITY	NO CHANGE IN PHYSICAL ACTIVITY
METABOLIC SYNDROME			
Hypertension, grade 2-5			
Cholesterol, grade 2-5			
Diabetes mellitus, grade 2-5			
Obesity			
BMI ≥30			
BMI ≥35			
BMI ≥40			
CARDIOVASCULAR DISEASE			
Heart Attack, grade 3-5			
Congestive heart failure			
Grade 2-5			
Grade 3-5			
Stif or leaky valves, grade 4-5			
Arrhythmia, grade 2-5			
Stroke, grade 4-5			
LIVER			
Fatty liver			
MUSCULOSKELETAL			
Joint replacement, grade 3-5			
Osteoporosis, grade 2			
RESPIRATORY			
Any respiratory disease, grade 2-5			
SMN			
SMN, grade 3-5			
EMOTIONAL			
Anxiety			
Depression			
HEALTH-RELATED QUALITY OF LIFE			
Physical component summary scale			
Mental component summary scale			

Table 2b. Outcomes in absolute numbers, n (%), according to healthy lifestyle score.

	UNHEALTHY LIFESTYLE	MODERATELY HEALTHY LIFESTYLE	HEALTHY LIFESTYLE
METABOLIC SYNDROME			
Hypertension, grade 2-5			
Cholesterol, grade 2-5			
Diabetes mellitus, grade 2-5			
Obesity			
BMI ≥30			
BMI ≥35			
BMI ≥40			
CARDIOVASCULAR DISEASE			
Heart Attack, grade 3-5			
Congestive heart failure			
Grade 2-5			
Grade 3-5			
Stiff or leaky valves, grade 4-5			
Arrhythmia, grade 2-5			
Stroke, grade 4-5			
LIVER			
Fatty liver			
MUSCULOSKELETAL			
Joint replacement, grade 3-5			
Osteoporosis, grade 2			
RESPIRATORY			
Any respiratory disease, grade 2-5			
SMN			
SMN, grade 3-5			
EMOTIONAL			
Anxiety			
Depression			
HEALTH-RELATED QUALITY OF LIFE			
Physical component summary scale			
Mental component summary scale			

Table 3a. Relative rates (RR) for associations between mean dose and change in physical activity and the development of new outcomes.

	MEAN PHYSICAL ACTIVITY DOSE	**CHANGE IN PHYSICAL ACTIVITY**
	RR (95% CI)	RR (95% CI)
METABOLIC SYNDROME		
Hypertension, grade 2-5		
Cholesterol, grade 2-5		
Diabetes mellitus, grade 2-5		
Obesity		
BMI ≥30		
BMI ≥35		
BMI ≥40		
CARDIOVASCULAR DISEASE		
Heart Attack, grade 3-5		
Congestive heart failure		
Grade 2-5		
Grade 3-5		
Stiff or leaky valves, grade 4-5		
Arrhythmia, grade 2-5		
Stroke, grade 4-5		
LIVER		
Fatty liver		
MUSCULOSKELETAL		
Joint replacement, grade 3-5		
Osteoporosis, grade 2		
RESPIRATORY		
Any respiratory disease, grade 1-5		
SMN		
SMN, grade 3-5		
EMOTIONAL		
Anxiety		
Depression		
HEALTH-RELATED QUALITY OF LIFE		
Physical component summary scale		
Mental component summary scale		

Adjusted for x, y, z. Should also include forest plot illustrating the results.

Table 3b. Relative rates (RR) for associations between the healthy lifestyle score and the outcomes, and PAF for lifestyle, chemotherapy, and radiotherapy for each outcome.

	MODERATELY HEALTHY LIFESTYLE	UNHEALTHY LIFESTYLE	LIFESTYLE	CHEMO-THERAPY	RADIO-THERAPY
	RR (95% CI)	RR (95% CI)	PAF, %	PAF, %	PAF, %
METABOLIC SYNDROME					
Hypertension, grade 2-5					
Cholesterol, grade 2-5					
Diabetes mellitus, grade 2-5					
Obesity					
BMI ≥30					
BMI ≥35					
BMI ≥40					
CARDIOVASCULAR DISEASE					
Heart Attack, grade 3-5					
Congestive heart failure					
Grade 2-5					
Grade 3-5					
Stiff or leaky valves, grade 4-5					
Arrhythmia, grade 2-5					
Stroke, grade 4-5					
LIVER					
Fatty liver					
MUSCULOSKELETAL					
Joint replacement, grade 3-5					
Osteoporosis, grade 2					
RESPIRATORY					
Any respiratory disease, grade 2-5					
SMN					
SMN, grade 3-5					
EMOTIONAL					
Anxiety					
Depression					
HEALTH-RELATED QUALITY OF LIFE					
Physical component summary scale					
Mental component summary scale					

Reference is a healthy lifestyle. Adjusted for xx, yy, zz. Should also include forest plot illustrating the results.

Table 4. Relative rates (RR) for associations between mean dose and change in physical activity and change in CTCAE grade of preexisting outcomes.

	MEAN PHYSICAL ACTIVITY DOSE	CHANGE IN PHYSICAL ACTIVITY
	RR (95% CI)	RR (95% CI)
METABOLIC SYNDROME		
Hypertension, grade 2-5		
Cholesterol, grade 2-5		
Diabetes mellitus, grade 2-5		
Obesity, BMI ≥30		
CARDIOVASCULAR DISEASE		
Heart Attack, grade 3-5		
Congestive heart failure, grade 2-5		
Arrhythmia, grade 2-5		
RESPIRATORY		
Any respiratory disease, grade 2-5		
EMOTIONAL		
Anxiety		
Depression		
HEALTH-RELATED QUALITY OF LIFE		
Physical component summary scale		
Mental component summary scale		

Adjusted for x, y, z.

Figures:
1a: Flow chart for participants in aims 1-4.
1b: Flow chart for participants in aims 5-6.

2: Bar chart illustrating the PAF for lifestyle, chemotherapy, and radiotherapy for each outcome.