Joint Effects of Physical Activity and Genetics on Cardiovascular Disease and Mortality Risk in Childhood Cancer Survivors

Working groups and investigators

- Primary working groups: Chronic Disease and Genetics
- Secondary working groups: Cancer Control and Epidemiology/Biostatistics

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Background

Survival following childhood cancer has improved dramatically over recent decades, with more than 85% of children in high-income countries now living at least five years beyond diagnosis.[1] As a result, the global population of childhood cancer survivors continues to grow, currently exceeding 500,000 in North America alone.[2] However, these individuals face a substantially elevated burden of chronic health conditions compared with the general population,[3] with cardiovascular disease (CVD) being a leading cause of premature morbidity and mortality.[4,5] Cardiotoxic cancer treatments—such as anthracyclines and chest-directed radiotherapy—accelerate the development of cardiomyopathy, vascular dysfunction, and metabolic abnormalities, resulting in markedly increased risks of heart failure, coronary artery disease, stroke, and sudden cardiac death.[6,7] These risks persist and intensify across the lifespan, underscoring the urgent need for effective secondary prevention strategies.

Regular physical activity is a cornerstone of cardiovascular disease prevention in the general population,[8] and is increasingly recognized as essential for long-term survivorship care.[9,10] Evidence from both observational and interventional studies indicates that higher levels of moderate-to-vigorous physical activity (MVPA) can improve cardiac function,[11] autonomic regulation,[12] metabolic control,[13] and exercise tolerance in survivors.[14] Importantly, survivors treated with cardiotoxic therapies may have impaired physiological reserve or subclinical cardiac dysfunction that could modify the cardiovascular benefits of physical activity. Furthermore, physical activity is a multidimensional behavior,[15] and current understanding in childhood cancer survivors overlooks key behavioral dimensions—such as whether MVPA is accumulated steadily or concentrated in only 1–2 days per week (the "weekend warrior" pattern), and the relative contribution of vigorous-intensity activity. In the general population, these dimensions can influence cardiometabolic adaptation and long-term disease risk,[16] but they have not been well documented in childhood cancer survivors.

In parallel, emerging data suggest that genetic predisposition to cardiovascular disease substantially modifies CVD risk in survivors, independent of treatment exposures.[17] Polygenic risk scores (PRSs)[18–20] are now able to stratify survivors by underlying susceptibility to cardiomyopathy, ischemic heart disease, and stroke. Yet, whether genetic risk amplifies or attenuates the protective impact of physical activity is unknown. Understanding this interplay is critical for advancing progress toward precision survivorship care, enabling targeted behavioral recommendations for those who stand to benefit most.

Despite the compelling rationale, major knowledge gaps remain. To date, no study in childhood cancer survivors has comprehensively characterized the dose–response association between MVPA and cardiovascular disease or mortality, evaluated whether different accumulation patterns of MVPA (e.g., concentrated vs. distributed across the week) influence risk, examined whether vigorous-intensity activity provides additional cardioprotective benefit beyond total volume, or determined whether these associations vary according to underlying genetic susceptibility to cardiovascular disease. The Childhood Cancer Survivor Study (CCSS) offers a unique opportunity to address these unmet needs due to its large sample size, long-term follow-up, rich clinical and behavioral phenotyping, and availability of polygenic risk scores.

This project will fill critical gaps in survivorship science by defining how the volume, pattern, and intensity of physical activity influence cardiovascular outcomes and whether these effects vary by genetic risk. The results will directly inform risk-stratified physical

activity guidelines and tailored interventions to reduce premature cardiovascular morbidity and mortality in the rapidly growing survivor population.

Specific aims and hypothesis

Aim 1:

To examine the association between total volume of moderate-to-vigorous physical activity (MVPA) and the risk of incident CVD and all-cause mortality(This part of the aim has been included as a necessary step in the pathway of the analysis, and it is not the focus of this concept), and to assess whether this association differs across strata of cardiovascular genetic risk.

Hypothesis:

Higher levels of MVPA will be associated with lower risk of CVD and all-cause mortality. We further hypothesize that the magnitude of these associations will vary by genetic risk for CVD.

Aim 2:

To evaluate whether individuals who accumulate a given weekly volume of MVPA in fewer, longer sessions (e.g., 1–2 days/week) differ in risk of incident CVD and all-cause mortality compared with those who accumulate the same weekly volume of MVPA in more frequent, shorter sessions (≥3 days/week), and to determine whether these associations differ across cardiovascular genetic risk strata.

Hypothesis:

Among individuals with equivalent weekly MVPA volume, those who concentrate their activity into 1–2 days per week will have similar or somewhat greater protection against CVD and all-cause mortality compared with those distributing activity across ≥3 days/week, and the magnitude of this difference will vary by genetic risk for CVD.

Aim 3:

To determine whether a higher proportion of vigorous physical activity (VPA) within total MVPA is associated with additional protection against incident CVD and all-cause mortality, and whether these associations differ across cardiovascular genetic risk strata.

Hypothesis:

A greater proportion of VPA within total MVPA will be independently associated with lower risk of CVD and all-cause mortality, with potential variation in the strength of the associations across genetic risk strata.

Analysis framework

Population

Participants enrolled in the CCSS free of CVD at baseline, with available data on polygenetic risk scores and self-reported physical activity. 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.

Exposure variables

Physical activity will be assessed using self-reported frequency and duration of MVPA

performed for at least 10 continuous minutes in the past week. Weekly minutes of MVPA will be calculated by summing minutes of moderate activity and double-weighting vigorous activity, consistent with public health guideline methodology. For Aim 1, total MVPA will be examined continuously (restricted cubic splines) and in guideline-based categories (<150, 150–299, ≥300 min/week), and additionally by percentile-based groupings ($P_{0–10}$, $P_{10–50}$, $P_{50–90}$, $P_{90–100}$) to harmonize stratified PRSs analyses. For Aim 2, patterns of accumulation will be defined as weekend warrior (≥150 min/week with ≥50% accumulated in 1–2 days), regularly active (≥150 min/week on ≥3 days), or inactive (<150 min/week). For Aim 3, intensity composition will be quantified as the percentage of MVPA performed at vigorous intensity (0%, >0–<25%, 25–<50%, 50–<75%, ≥75%) while adjusting for total MVPA to separate intensity from volume effects. Across all aims, each physical activity exposure will also be evaluated jointly with cardiovascular PRSs strata (low, intermediate, high) to test whether the cardiovascular benefits of MVPA differ according to inherited susceptibility.

Generic polygenic risk score (PRS)

For strata of cardiovascular genetic risk (consistent with prior PRS-based CVD studies), we propose a quintile-based categorization using MetaPRS (PGS005253) as generic PRS:

- Low genetic risk: Q1 (lowest 20%)
- Intermediate genetic risk: Q2-Q4 (middle 60%)
- High genetic risk: Q5 (highest 20%)

This is a commonly used approach that provides clear risk stratification while avoiding unnecessary fragmentation of the sample. We propose to apply the PRS to all individuals in CCSS, with adjustment for genetic principal components to account for population structure.

Outcomes

Cardiovascular outcomes in this project will be based on events already centrally ascertained and graded within CCSS using the CCSS–modified CTCAE v5 system. The primary endpoint will be MACE, defined as the first occurrence of any of the following: cardiomyopathy/heart failure (grade 3–5), coronary artery disease/myocardial infarction (grade 3–5), stroke (grade 3–5), and other cardiovascular-related mortality (other grade 5 cardiac events).[21] Grouped categories and individual CTCAE-graded major adverse cardiovascular events can be found in **eTable 1**. All-cause mortality will constitute the secondary outcome and will be based on previously established linkages to the US National Death Index. Time at risk will start at the PA assessment and end at first MACE, death, loss to follow-up, or end of follow-up.

Statistical analysis

CCSS analyst will use Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of physical activity and PRSs with MACE (**Tables 2-3**) and all-cause mortality (**eTables 3-4**). Time-at-risk will start at the date of physical activity assessment and continue until the first event, death, loss to follow-up, or end of study follow-up.

PRSs will be operationalized in three strata (low, moderate, high), with low genetic risk serving as the reference category in all joint and stratified models. Interaction terms will be included to evaluate effect modification by PRSs across the three physical activity dimensions (MVPA volume, accumulation pattern, and proportion of vigorous activity). To further interpret effect heterogeneity, we will present joint exposure estimates across

combined PA–PRSs categories.

Dose–response associations will be modeled using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles of the exposure distributions. Proportional hazards assumptions will be tested using Schoenfeld residuals and standard diagnostic checks. For visualization of dose–response patterns, we will derive model-based predicted event curves from the Cox models (**Figures 1-2**, and **eFigures 3-6**). These curves are solely intended to support interpretability and communication of results. All statistical inference will be based exclusively on hazard ratios and their confidence intervals.

Sensitivity analyses will include:

1. additionally adjusting for BMI (mediator sensitivity, **eTables 5-6**),
2. excluding first 2 years of follow-up (reverse causation, **eTables 7-8**),
3. excluding those with fair/poor baseline health (**eTables 9-10**),
4. adjusting for cancer treatment exposures (excluding cancer types, **eTables 11-12**)

All analyses will be performed in R, with reporting consistent with STROBE guidelines (**eTable 2**).

Covariates: We used a directed acyclic graph (DAG, **eFigure 2**) to define the minimally sufficient adjustment set needed to estimate the total causal effect of post-diagnosis physical activity on cardiovascular morbidity and all-cause mortality among childhood cancer survivors. Based on this framework, age at baseline, sex, area deprivation index (ADI, neighborhood socioeconomic status variable based on 17 neighborhood-based socioeconomic status measures including income, employment, education, and housing characteristics that are collected as part of the American Community Survey),[22,23] self-reported general health (evaluated using the question 'Would you say that your health is excellent, very good, good, fair, or poor?' and categorized as poor general health if responded "poor" or "fair" following prior reports),[24] cancer type, and lifestyle risk factors (smoking, alcohol use) were identified as common causes of both physical activity behavior and CVD risk. These variables will therefore be included in all primary multivariable models.

To ensure comprehensive control of treatment-related confounding while preserving analytic parsimony, we will adjust only for therapies with established associations with cardiovascular toxicity and premature mortality: cumulative anthracycline dose and chest-directed radiotherapy. Additionally, a composite cardiotoxicity risk indicator will be derived according to previous guidelines. The high risk group was defined as those who received cumulative anthracycline (doxorubicin-equivalent) dose $\geq$250 mg/m^2, or radiation dose to the chest $\geq$30 Gy, or anthracycline dose $\geq$100 mg/m^2 combined with radiation dose to the chest $\geq$15 Gy. The low risk group was defined as anthracycline dose $<$100 mg/m^2 and radiation dose to the chest $<$15 Gy. The moderate risk group contains everyone else.

Body mass index (BMI) was identified as a mediator of the effect of physical activity on cardiovascular outcomes through improvements in cardiometabolic health and will not be included in primary models to avoid over-adjustment bias. Follow-up time and year of diagnosis were identified as colliders or descendants of colliders and will not be conditioned on to avoid collider stratification bias. Although race/ethnicity is included in the causal model to represent structural inequities affecting cardiovascular outcomes, its effects are transmitted through ADI, healthcare, and behavioral pathways already accounted for, and it is therefore not included in the minimal adjustment set.

The DAG-informed approach ensures appropriate control of confounding, preserves important mediating pathways through which physical activity exerts its benefits, and maximizes causal interpretability of estimated associations.

Main tables and figures

Table 1. Baseline characteristics of survivors (Overall and by PRSs strata)

	Participants				**p-values**		
	Total participants (N=X)	High genetic risk (N=X)	Intermediate genetic risk (N=X)	Low genetic risk (N=X)	High vs. intermediate genetic risk	High vs. low genetic risk	Intermediate vs. low genetic risk
Sex							
Female							
Male							
Race ethnicity							
Non-Hispanic white							
Non-Hispanic black							
Hispanic							
Other							
Age at diagnosis (years)							
Age at baseline (years)							
Primary cancer diagnosis							
Acute lymphoblastic leukemia							
Acute myeloid leukemia							
Other leukemia							
Hodgkin lymphoma							
Non-Hodgkin lymphoma							
CNS tumor							
Wilms tumor							
Retinoblastoma							
Soft tissue sarcoma							
Neuroblastoma							
Osteosarcoma							
Ewing sarcoma							
Other							
Radiation to the chest or TBI (Gy)							
None							
<30							
≥30							
Alkylating agents (cyclophosphamide equivalent dose [mg/m^2])							
None							
<4000							
≥4000 and <8000							
≥8000							
Glucocorticoids (mg/m^2)							
None							
<8000							
≥8000							
Platinum agents							
None							
Yes							
Anthracycline agents (mg/m^2)							
None							
<200							

≥200 and <350							
≥350							
Smoking history							
Never							
Previous							
Current							
Area deprivation index							
Poor general health							
No							
Yes							
Body mass index at baseline (kg/m^2)							
Underweight (<18.5)							
Healthy weight (>18.5 to <25.0)							
Overweight (>25.0 to <30)							
Obesity (>30)							
Cardiomyopathy							
Grade 3–5							
Heart failure							
Grade 3–5							
Coronary artery disease							
Grade 3–5							
Myocardial infarction							
Grade 3–5							
Stroke							
Grade 3–5							
Other cardiovascular-related mortality (Grade 5)							
No							
Yes							
All-cause mortality							
No							
Yes							

Values are mean ± SD or N (%). Abbreviations: cm, centimeters; Gy, gray; kg/m^2, kilograms/meters^2; MACE: major adverse cardiovascular event, METs, Metabolic Equivalents of Task; mg/m^2, milligrams/meters^2; min/week, minutes/week, MVPA, moderate-to-vigorous physical activity; ng/mL, nanograms/milliliter, TBI, Total body irradiation; VO_2peak, peak of oxygen consumption; WHO, world health organization.
Body mass index: underweight (<18.5 kg/m^2), healthy weight (>18.5 to <25.0 kg/m^2), overweight (>25.0 to <30 kg/m^2) and obesity (>30 kg/m^2).
Smoking history: never (no previous tobacco use), previous (tobacco use in the past) and current (tobacco use within the last 30 days).

Table 2. Joint exposure analysis (PRSs × MVPA categories) and risk of MACE

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
Not meeting MVPA guidelines		1.00 (ref.)						1.00 (ref.)
Meeting guidelines through a regular active pattern (≥3 days/week)		1.00 (ref.)						1.00 (ref.)
Meeting guidelines via the WW pattern (defined as accumulating ≥50% of MVPA over 1–2 days/week)								
VPA proportion of MVPA (min/week)								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.

Table 3. Dose–response associations of physical activity categories × PRSs and risk of MACE

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)
P_{10}–P_{50}								
P_{50}–$P9_0$								
P_{90}–P_{100}								
VPA proportion of MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		
P_{10}–P_{50}								
P_{50}–$P9_0$								
P_{90}–P_{100}								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.
Effect modification on multiplicative scale total volume of physical activity×PRS: p-value=X.
Effect modification on multiplicative scale MVPA×PRS: p-value=X.
Effect modification on multiplicative scale VPA×PRS: p-value=X.

Figure 1. Dose–response curves for total MVPA and MACE

- **Restricted cubic splines**
- **Stratified by PRSs (joint analysis)**

Supplementary material

eTable 1. Childhood Cancer Survivor Study interpretation of the chronic disease Common Terminology Criteria for Adverse Events (version 5)

Condition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cardiomyopathy / heart failure	N/A	Not on medications	Requiring medications	Heart transplant	Death
Coronary artery disease	N/A	N/A	Anti-anginal medications only	Requiring procedure (catheterization, angioplasty, bypass graft)	Death
Stroke	N/A	N/A	N/A	Stroke	Death

Abbreviations: N/A = not applicable, as not defined by CCSS per methodology first published by Oeffinger et al., New England J Med 2006.

eTable 2. STROBE Statement: Checklist of items that should be included in reports of cross-sectional studies.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	X
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	X
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	X
Objectives	3	State specific objectives, including any prespecified hypotheses	X
Methods			
Study design	4	Present key elements of study design early in the paper	X
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	X
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X
Bias	9	Describe any efforts to address potential sources of bias	X
Study size	10	Explain how the study size was arrived at	X

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	X
		(*b*) Describe any methods used to examine subgroups and interactions	X
		(*c*) Explain how missing data were addressed	X
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	X
		(*e*) Describe any sensitivity analyses	X
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X
		(b) Give reasons for non-participation at each stage	X
		(c) Consider use of a flow diagram	X
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X
		(b) Indicate number of participants with missing data for each variable of interest	X
Outcome data	15	Report numbers of outcome events or summary measures	X
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X

		(*b*) Report category boundaries when continuous variables were categorized	X
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	X
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X
Discussion			
Key results	18	Summarise key results with reference to study objectives	X
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X
Generalisability	21	Discuss the generalisability (external validity) of the study results	X
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X

Note: An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

eTable 3. Joint exposure analysis (PRSs × MVPA categories) and risk of all-cause mortality

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without all-cause mortality	HR (95% CI)	n with/without all-cause mortality	HR (95% CI)	n with/without all-cause mortality	HR (95% CI)	n with/without all-cause mortality	HR (95% CI)
MVPA (min/week)								
Not meeting MVPA guidelines		1.00 (reference)						1.00 (reference)
Meeting guidelines through a regular active pattern (≥3 days/week)		1.00 (reference)						1.00 (reference)
Meeting guidelines via the WW pattern (defined as accumulating ≥50% of MVPA over 1–2 days/week)								
VPA proportion of MVPA (min/week)								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.

eTable 4. Dose–response associations of physical activity categories × PRSs and risk of all-cause mortality

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without all-cause mortality	HR (95% CI)	n with/without all-cause mortality	HR (95% CI)	n with/without all-cause mortality	HR (95% CI)	n with/without all-cause mortality	HR (95% CI)
MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								
VPA proportion of MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.
Effect modification on multiplicative scale total volume of physical activity×PRS: p-value=X.
Effect modification on multiplicative scale MVPA×PRS: p-value=X.
Effect modification on multiplicative scale VPA×PRS: p-value=X.

eTable 5. Joint exposure analysis (PRSs × MVPA categories) and risk of MACE, additionally adjusting for BMI (mediator sensitivity)

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
Not meeting MVPA guidelines		1.00 (reference)						1.00 (reference)
Meeting guidelines through a regular active pattern (≥3 days/week)		1.00 (reference)						1.00 (reference)
Meeting guidelines via the WW pattern (defined as accumulating ≥50% of MVPA over 1–2 days/week)								
VPA proportion of MVPA (min/week)								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.

eTable 6. Dose–response associations of physical activity categories × PRSs and risk of MACE, additionally adjusting for BMI (mediator sensitivity)

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								
VPA proportion of MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.
Effect modification on multiplicative scale total volume of physical activity×PRS: p-value=X.
Effect modification on multiplicative scale MVPA×PRS: p-value=X.
Effect modification on multiplicative scale VPA×PRS: p-value=X.

eTable 7. Joint exposure analysis (PRSs × MVPA categories) and risk of MACE, excluding first 2 years of follow-up (reverse causation)

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
Not meeting MVPA guidelines		1.00 (reference)						1.00 (reference)
Meeting guidelines through a regular active pattern (≥3 days/week)		1.00 (reference)						1.00 (reference)
Meeting guidelines via the WW pattern (defined as accumulating ≥50% of MVPA over 1–2 days/week)								
VPA proportion of MVPA (min/week)								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.

eTable 8. Dose–response associations of physical activity categories × PRSs and risk of MACE, excluding first 2 years of follow-up (reverse causation)

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								
VPA proportion of MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.
Effect modification on multiplicative scale total volume of physical activity×PRS: p-value=X.
Effect modification on multiplicative scale MVPA×PRS: p-value=X.
Effect modification on multiplicative scale VPA×PRS: p-value=X.

eTable 9. Joint exposure analysis (PRSs × MVPA categories) and risk of MACE, excluding those with fair/poor baseline health

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
Not meeting MVPA guidelines		1.00 (reference)						1.00 (reference)
Meeting guidelines through a regular active pattern (≥3 days/week)		1.00 (reference)						1.00 (reference)
Meeting guidelines via the WW pattern (defined as accumulating ≥50% of MVPA over 1–2 days/week)								
VPA proportion of MVPA (min/week)								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.

eTable 10. Dose–response associations of physical activity categories × PRSs and risk of MACE, excluding those with fair/poor baseline health

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								
VPA proportion of MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.
Effect modification on multiplicative scale total volume of physical activity×PRS: p-value=X.
Effect modification on multiplicative scale MVPA×PRS: p-value=X.
Effect modification on multiplicative scale VPA×PRS: p-value=X.

eTable 11. Joint exposure analysis (PRSs × MVPA categories) and risk of MACE, adjusting for cancer treatment exposures (excluding cancer types)

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
Not meeting MVPA guidelines		1.00 (ref.)						1.00 (ref.)
Meeting guidelines through a regular active pattern (≥3 days/week)		1.00 (ref.)						1.00 (ref.)
Meeting guidelines via the WW pattern (defined as accumulating ≥50% of MVPA over 1–2 days/week)								
VPA proportion of MVPA (min/week)								

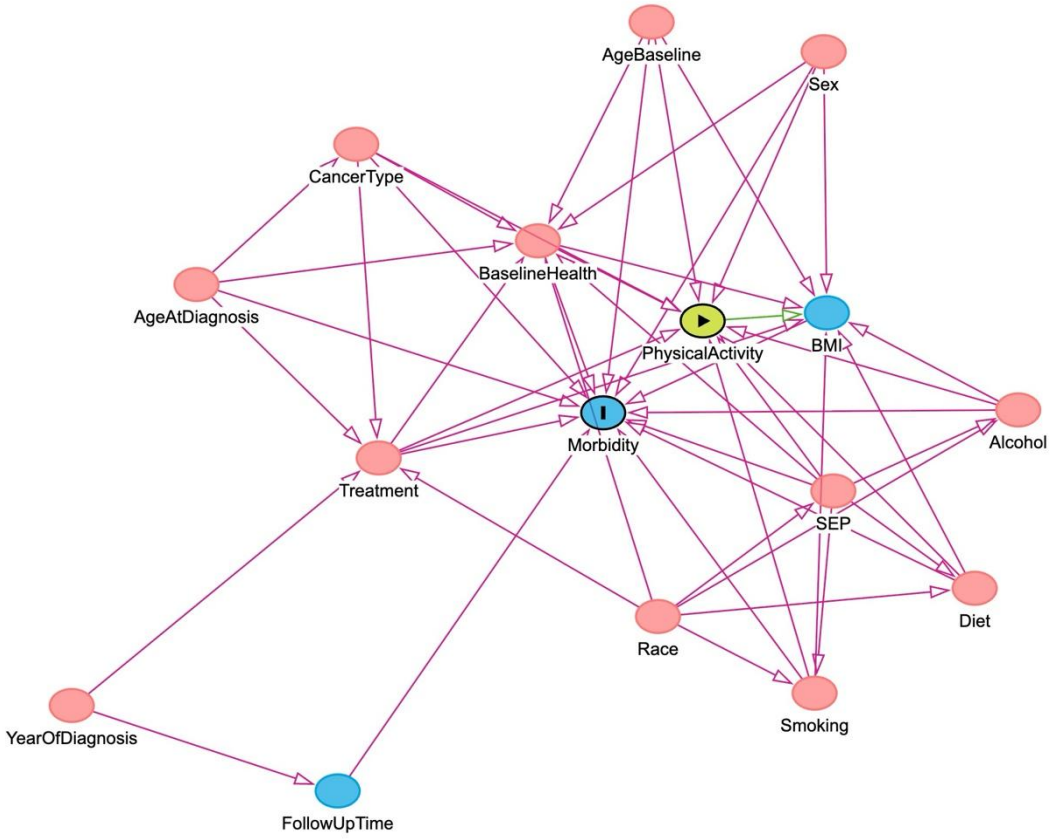
The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.

eTable 12. Dose–response associations of physical activity categories × PRSs and risk of MACE, adjusting for cancer treatment exposures (excluding cancer types)

	Total participants		High genetic risk		Intermediate genetic risk		Low genetic risk	
	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)	n with/without MACE	HR (95% CI)
MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								
VPA proportion of MVPA (min/week)								
P_0–P_{10}		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		
P_{10}–P_{50}								
P_{50}–P_{90}								
P_{90}–P_{100}								

The analyses were all based on multivariable Cox proportional hazards models. Bold face values indicate $p<0.05$.
Effect modification on multiplicative scale total volume of physical activity×PRS: p-value=X.
Effect modification on multiplicative scale MVPA×PRS: p-value=X.
Effect modification on multiplicative scale VPA×PRS: p-value=X.

eFigure 1. Participant flow diagram



eFigure 2. Full DAG including mediators/colliders

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