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# Physical Fitness and Modifiable Cardiovascular Disease Risk Factors in Survivors of Childhood Cancer – A Report from the SURfit Study

**Short title: Fitness and Cardiovascular Risk Factors**

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**Conflict of Interest statement**

None of the authors has a conflict of interest to declare.

**Author's contribution statement**

Conception and design of the study: SK, NVDW, CSR; acquisition of data: CS, SJZ, RJ, SB, JWB, NVDW; statistical analysis: CS, SK, CSR; interpretation: CS, SJZ, SK, CSR, NVDW; drafting the work: CS. All authors edited, reviewed, and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are investigated and resolved.

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**Message of the manuscript**

Better physical fitness was associated with less modifiable cardiovascular disease risk factors in childhood cancer survivors. Simple fitness measures could be used to screen survivors in follow-up care to endorse physical activity in those who have impaired fitness test performance.

**Abstract**

**Background:** Childhood cancer survivors are at risk of cardiovascular disease (CVD) because of intensive cancer therapies often accompanied by an unhealthy lifestyle. We aimed to 1) describe modifiable CVD risk factors in survivors, 2) investigate the association between different aspects of physical fitness and CVD risk factors.

**Methods:** We analyzed cross-sectional data from ≥5 year survivors, aged ≤16 years at cancer diagnosis, ≥16 years at study. We evaluated single CVD risk factors (waist circumference, blood pressure, fasting glucose, inverse high-density lipoprotein, and triglycerides), a composite CVD risk score (combined z-scores of all CVD risk factors), and the metabolic syndrome. Physical fitness measures included cardiopulmonary exercise testing (CPET), handgrip, and 1-minute sit-to-stand testing (STS). We used multivariable logistic regression for the association between fitness measures and CVD risk factors, adjusted for demographic factors and cancer therapy.

**Results:** We included 163 survivors, median age at diagnosis 7 years, median age at study 28 years. Amongst those, 27% had high waist circumference, 32% high blood pressure, 19% high triglycerides, 20% an increased composite CVD risk score, and 10% the metabolic syndrome. A better performance during CPET, handgrip, and STS was associated with a lower probability of having a high waist circumference, high triglycerides, and the metabolic syndrome.

**Conclusions:** Better aerobic fitness (CPET), and to a lesser extent handgrip and STS, were associated with less CVD risk factors. Further investigations are warranted to investigate which fitness measures should preferably be used to screen survivors to promote physical activity in those with impaired test performance.

**Key words**

Childhood cancer survivors, cardiovascular disease, metabolic syndrome, physical fitness, exercise test

## INTRODUCTION

Survival of childhood cancer has improved dramatically to over 80%[1] and the number of childhood cancer survivors is steadily increasing. But 30 years after cancer diagnosis, 70% of survivors suffer from chronic conditions as late effects of cancer treatment.[2] Among those, cardiovascular disease (CVD) is the leading nonmalignant cause of death.[3] CVD risk increases after exposure to certain cancer treatments, including anthracyclines and chest radiotherapy.[4] In addition, survivors may also be at increased risk from modifiable CVD risk factors associated with the metabolic syndrome like abdominal adiposity, hypertension, hyperglycemia, and dyslipidemia.[5] CVD risk from these modifiable factors can be reduced through a healthy and active lifestyle including sufficient physical activity.[6] Promoting healthier lifestyles and encouraging activity may also lower overall mortality in survivors.[7] As physical activity is a variable behavior and difficult to measure, physical fitness is often used as surrogate marker of physical activity.

Physical fitness is one of the strongest preventive health measures of CVD and cancer[8] and comprises muscular strength, anaerobic and aerobic capacity. Aerobic capacity is best assessed with cardiorespiratory exercise testing (CPET), but this requires an expensive evaluation by a qualified professional and may be difficult to access. In contrast, muscular strength of the upper extremity can easily be measured by a simple handgrip test.[9] The 1-minute sit-to-stand test (STS) assesses a combination of lower body muscular strength, aerobic and anaerobic capacity.[10] Simple measures of physical fitness as the handgrip and STS could be easily implemented in clinical routine to guide clinicians to estimate the CVD risk status of childhood cancer survivors. But studies are limited on the association between single aspects of physical fitness and modifiable CVD risk factors in childhood cancer survivors.

We hypothesized that better performance in physical fitness tests would be associated with fewer modifiable CVD risk factors or a lower composite CVD risk score in survivors of childhood cancer. We thus aimed to 1) describe modifiable CVD risk factors, a composite CVD risk score, and the prevalence of the metabolic syndrome in young adult survivors, and 2) investigate the association between different physical fitness measures including CPET, handgrip, and STS, and modifiable CVD risk outcomes.

## MATERIALS AND METHODS

### ***Study design***

The SURfit study was a single-center randomized controlled physical activity trial including childhood cancer survivors from various pediatric oncology clinics within Switzerland and run between 2015 and 2019. The long recruitment phase was mainly due to logistics and resource restrictions at the hospital to include, test, and follow-up participants. The study protocol has been published previously.[11] Briefly, survivors were randomized to a one-year physical activity intervention and a control arm. For this study, we included all survivors undergoing the clinical baseline assessment (T0a and T0b) before randomization. At T0a, we collected demographic, cancer-related, and lifestyle characteristics, waist circumference, blood pressure, and all physical fitness measures. At T0b, blood glucose, high density lipoprotein (HDL) cholesterol, and triglyceride levels were assessed after an overnight fast. T0a and T0b were 7–14 days apart from each other. Ethics approval was granted (Ethikkommission Nordwest- und Zentralschweiz [EKNZ], reference number: EKNZ-2015-169) and all participants gave written informed consent. The SURfit study was registered at ClinicalTrials.gov (identifier: NCT02730767).

### ***Study population***

Within the SURfit study, we recruited survivors through the Swiss Childhood Cancer Registry, a nationwide registry of all patients diagnosed with leukemia, lymphoma, central nervous system tumors, malignant solid tumors, or Langerhans cell histiocytosis before age 21 years in Switzerland.[12] Inclusion criteria were age ≤16 years at cancer diagnosis, ≥5 year survival since primary cancer diagnosis or relapse, and age at study ≥16 years.[11] We used an age cut off of 16 years for the intervention trial as 16 year old individuals are already able to consent and follow the physical activity program independently, and might benefit from the intervention.

***Outcomes: Modifiable cardiovascular disease risk factors***

Modifiable CVD risk factors included single CVD risk factors, a composite CVD risk score, and the metabolic syndrome. We assessed waist circumference, systolic and diastolic blood pressure, fasting glucose, HDL cholesterol, and triglycerides as described before.[11] Fasting blood samples were processed using Roche Cobas® 8000 modular analyzer series (Roche Diagnostics, USA). We calculated z-scores using normative data of the Dutch Lifelines Cohort Study which is a representative cohort of 167,000 individuals.[13] After excluding individuals reporting cardiovascular diseases, we included 48,250 individuals between 18 to 54 years of age with a body mass index (BMI) between 20-25 kg/m$^2$, as we wanted to compare our study population with a healthy reference population. For z-score calculations, we used age (in 5-year intervals)- and sex-specific reference values.

We created a composite CVD risk score including the z-scores of all CVD risk factors, as described before[14]: The sum of the z-scores of waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood glucose, inverted HDL cholesterol, and triglycerides, divided by the number of available components; participants with less than three available components were set to missing CVD risk score (Table S1). An elevated composite score was defined as a z-score ≥1 to detect CVD risk in a relatively young population.

For the metabolic syndrome, we used cut-off levels for abnormal cardiovascular outcomes according to the International Diabetes Federation[15] as follows: High waist circumference (male ≥94 cm, females ≥80 cm), elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85mmHg and/or treatment), elevated fasting blood glucose (≥5.6 mmol/L and/or treatment), low HDL cholesterol (<1.03 mmol/L in males and <1.30 mmol/L in females and/or treatment), and elevated triglycerides (≥1.70mmol/L and/or treatment) (Table S1). Metabolic syndrome was defined as having a high waist circumference and ≥2 abnormal CVD risk factors.[15] The metabolic syndrome is therefore based on dichotomisation of CVD risk factors and those patients close to, but below the cut-offs are categorized equally “healthy” as those far away.

### *Exposure variables: Physical fitness*

We assessed aerobic fitness with cardiopulmonary exercise testing (CPET), upper body muscular strength with handgrip, and a mixed fitness measure including components of lower body strength, aerobic and anaerobic capacity, and coordination with the 1-minute sit-to-stand test (STS), as described previously.[11] For CPET, we assessed peak performance (in watt) and calculated watt per kg body weight. For handgrip, we calculated the mean weight pressed (in kg) of three trials of the dominant hand,[9] and created a variable per kg body weight. For STS, we performed two trials of maximum number of repetitions from sit to stand in one minute, at least 20 minutes apart from each other, because there was a learning curve with the second trial as described before.[16] We divided the original number of repetitions by 10 to facilitate interpretation (change in odds ratio per 10 more repetitions).

### *Covariates: Demographic, cancer-related, and lifestyle characteristics*

We collected sex, age at study, and all cancer-related characteristics from medical records. We calculated cumulative doses of anthracyclines [mg/m$^2$][17] and cumulative doses of steroids [g/m$^2$].[18] Due to low numbers of participant within different locations of radiotherapy, we generated a combined group with any cranial, thoracic, abdominal, and total body irradiation to CVD-relevant radiotherapy (yes/no). We collected lifestyle characteristics during clinical assessments (body mass index, smoking status). Physical activity levels at baseline were assessed by accelerometers worn between T0a and T0b. Moderate to vigorous physical activity (MVPA) was categorized into inactive (<150 min MVPA/week) and active (≥150 min MVPA/week) according to the World Health Organization.[19]

### *Statistical analysis*

We used descriptive statistics to present demographic, cancer-related, and modifiable CVD risk factors. In the univariable logistic regression model, we investigated the association between different physical fitness measures and single CVD risk factors (abnormal versus normal) (model 1). In multivariable models, we adjusted for age at study and sex (model 2), and additionally for cumulative anthracycline dose (continuous), cumulative steroid dose (continuous), and CVD-relevant radiotherapy (yes/no) (model 3, main model). All p-values were two sided and we considered a $p<0.05$ as significant. We used STATA software (Version 15.1, Stata Corporation, Austin, TX).

RESULTS

**Study population**

Among 658 contacted survivors, 163 participated in the SURfit baseline assessment at T0a and 158 at T0b (participation rate 25%) (Figure S1). Median age at cancer diagnosis was 6.7 years, and median time since diagnosis 22.3 years (Table 1). The most common cancer diagnoses were leukemia (35%), lymphoma (22%), and central nervous system tumors (11%). A detailed list of all cancer diagnoses is displayed in Table S2, online supplement. Anthracyclines were given to 64%, steroids to 53% of survivors. Thirty-six percent of survivors underwent CVD-relevant radiotherapy. Among participants, 31% were overweight or obese, 23% were current smokers, and 84% adhered to physical activity recommendations. Two survivors underwent limb salvage therapy and eight survivors developed growth hormone deficiency and underwent growth hormone treatment (Table 1).

SURfit participants and nonparticipants did not differ in basic demographic and clinical characteristics (Table S2, online supplement).

**Modifiable cardiovascular disease risk factors**

Survivors had increased z-scores for most single CVD risk factors compared to age- and sex-matched reference values of normal weight, and males tended to have higher z-scores compared to females (Table 2). High blood pressure (32%), high waist circumference (27%), and high triglycerides (19%) were the most frequent abnormal CVD risk factor (Table 2, Figure 2). Overall, the composite CVD risk score was increased with a mean z-score of 0.35 (standard deviation [SD] 0.90), and males had higher z-scores (0.50, SD 0.99) than females (0.16, SD 0.74) (Table 2).

**Associations between aerobic fitness (CPET) and cardiovascular disease risk factors**

Better peak performance during the CPET (watt per kg body weight) was associated with a lower risk of having a high waist circumference, low HDL cholesterol, high triglyceride levels, a high composite CVD risk score, and having the metabolic syndrome (Table S4, model 3; Figure 1). These associations were comparable among the unadjusted and adjusted analyses (models 2 and 3).

**Associations between muscular strength (handgrip test) and cardiovascular disease risk factors**

More strength in the handgrip test (per kg body weight) was associated with a lower risk of having a high waist circumference, high triglycerides, a high composite risk score, and having the metabolic syndrome (Table S4, model 3; Figure 1). The associations between handgrip and CVD risk factors were comparable between models 1, 2, and 3, except for high triglycerides, where the association changed from univariable to the multivariable models.

**Associations between mixed fitness (STS) and disease risk factors**

More repetitions during the STS (per 10 more repetitions) were associated with a decreased risk for having a high waist circumference, high triglycerides, and having the metabolic syndrome (Table S4, model 3; Figure 1). Again, age at study, sex, and cancer treatment did not change these associations between models 1, 2, and 3.

# DISCUSSION

Single CVD risk factors were abnormal in up to one-third of childhood cancer survivors many years after cancer diagnosis with male survivors doing worse compared to female survivors. Better physical fitness was associated with having less modifiable single (high waist circumference, high triglycerides) or combined CVD risk factors (composite CVD risk score and metabolic syndrome), respectively. Associations were strongest for aerobic fitness, and weaker for muscular strength and mixed fitness measures. Cancer treatment with anthracyclines, steroids, and CVD-relevant radiotherapy did not change the strength of associations suggesting that survivors predisposed to CVD may be able to modify their cardiovascular risk through physical fitness.

Our results are in line with other studies showing that CVD risk factors and the metabolic syndrome are prevalent in survivors. Smith and colleagues assessed 1598 adult survivors at St. Jude Children's Research Hospital in the U.S. and found that 47% of survivors had high waist circumference and 32% a high fasting glucose, compared to 27% and 4% in our study population.[20] Additional factors like lifestyle might explain the different CVD risk profiles: the prevalence of overweight and obesity was 66% in the U.S. and 34% in our cohort, and less than half of the U.S. survivors were physically active[20] while only a minority was insufficiently active in our cohort. Also, a higher percentage of cranial radiotherapy (34%) in the U.S. compared to our study (22%) might have contributed to the difference among populations, as radiotherapy to the hypothalamic-pituitary axis induces growth hormone deficiency which is a known risk factor for modifiable CVD risk factors.[21] In the multicenter French L.E.A. cohort of 650 leukemia survivors with a mean age of 24 years, 17% (versus 27% in our study) had high waist circumference, 37% (versus 32%) high blood pressure, 12% (versus 19%) high triglycerides, and 7% (versus 10%) the metabolic syndrome.[22] Also, a study from the Netherlands reported a metabolic syndrome prevalence of 15% in adult survivors,[23] which is comparable to our results.

Other studies also reported an association between lifestyle and modifiable CVD risk factors in childhood cancer survivors. Smith showed that adherence to a healthy lifestyle including sufficient physical activity, a normal BMI and a healthy diet was associated with a lower risk of having the metabolic syndrome.[20] As we found in our study, this association persisted after adjusting for treatment-related risk factors.[20] Thus, survivors predisposed to CVD may importantly be able to modify this risk through lifestyle changes. In line with this hypothesis, the North American Childhood Cancer Survivor Study reported that the incidence of CVD decreased across increasing levels of self-reported physical activity in 1187 survivors of Hodgkin's lymphoma.[24] Another study from the U.S. reported that 119 survivors with high physical activity and aerobic fitness levels (6-minute walking test) had lower waist circumferences compared to those survivors with low physical activity and endurance levels,[25] but blood pressure and glucose homeostasis did not differ (as in our study). We also reported a consistent association between all three fitness measures and high waist circumference. As high waist circumference was prevalent in 27% of our survivors, encouraging survivors to increase physical activity might have great benefit; by how much this association is mediated by body fat or BMI is not clear. Also high triglycerides, but not hypertension and high glucose were associated with physical fitness, which is consistent with other studies.[6,25] It is possible, that fasting glucose is not a good proxy for impaired glucose regulation as young people with severe insulin resistance are still able to sufficiently regulate their fasting blood glucose levels. [26] Hypertension at baseline might have been overestimated due to external factors such as general excitement at the first study visit, stress, and white-coat hypertension.

While the associations between physical fitness measures and CVD risk factors, the composite CVD risk score, and the metabolic syndrome are compelling, there was a large difference in magnitude of risk reduction noted with the different tests. Aerobic fitness (CPET) showed the strongest association with individual and composite CVD risk factors, muscular strength was less strongly associated, and the mixed fitness test (STS) showed the weakest, but still clearly positive associations. Aerobic fitness has been shown in many studies to be a strong predictor of cardiovascular morbidity and mortality supporting our findings.[27] Also low muscle strength was associated with premature mortality,[28,29] but many studies have not adjusted for aerobic fitness, that is often related to muscular strength. Confounding by aerobic fitness may therefore be more important than muscular strength as driver for CVD risk factor reduction. As STS is a complex construct of aerobic, anaerobic, coordinative, and strength components, it is premature to value its meaning in association with CVD risk factors based on a cross-sectional study. In our study, we assessed overall physical fitness levels with the STS, which proved to be a reliable and valid test in other populations.[30] It is a simple test, needs little equipment and expertise compared to CPET, but has not yet been investigated in childhood cancer survivors as predictor for CVD risk. Our study showed that the STS was associated with high waist circumference, high triglycerides, and the metabolic syndrome, but not with a high composite CVD risk score (associated with CPET and handgrip test) and high HDL cholesterol (associated with CPET only). We therefore suggest that the STS could be used as a screening tool if access to CPET is not available or time is restricted. Further studies should investigate the value of STS in predicting CVD risk factors in childhood in childhood cancer survivors. As many survivors have poor physical fitness,[31] and physical fitness is a strong predictor of cardiovascular risk factors,[32] implementing an active lifestyle in survivors, especially with a focus on aerobic fitness and to a lesser extent to muscular strength and mixed fitness might have great benefit.

Our study has some strengths and limitations. This study is one of the first studies in survivors that assessed different physical fitness measures. We used comprehensive and standardized assessments for physical fitness and CVD risk factors, and assessors were blinded to CVD risk status of survivors. We collected comprehensive data on cancer related characteristics. A limitation of our study is the cross-sectional design; we cannot investigate causality between physical fitness and modifiable CVD risk factors. We included a heterogeneous group of survivors in terms of exposures, so stratification of CVD risk by cancer group was not possible. Third, we had a low participation rate in our main study, as the SURfit study demanded several visits and additional weekly hours of physical activity over one year. Although some basic demographic and clinical characteristics were comparable between participants and nonparticipants, selection bias cannot be excluded. Survivors who participate in a physical activity trial are known to be healthier compared to nonparticipants. This rather underestimates the prevalence of CVD risk factors and the association between physical fitness and CVD risk factors due to less variability in the outcome. We used a Dutch rather than a

Swiss reference population for the estimation of the composite CVD risk score, which may hamper generalizability.

Our study reports important findings relevant for survivorship care. Adult childhood cancer survivors participating in the SURfit study had a high prevalence of modifiable CVD risk factors; therefore, preventive measures are crucial to decrease overall CVD risk. We could show that better aerobic fitness, and to a lesser extend strength and mixed fitness, were predictive for less modifiable CVD risk factors, and that even simple fitness tests like the handgrip and STS were associated with some, but not allmodifiable CVD risk factors. Survivors may therefore specially profit from increasing aerobic fitness by endurance training, but also integrate strength and overall physical fitness components such as anaerobic and coordination training. Further studies are warranted to investigate whether assessment of physical fitness can be extended or replaced bysimple tests like the STS and to more precisely endorse type, frequency, and intensity of physical activity in those survivors who have impaired test performance.

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**TABLE 1.** Demographic, cancer-related, and lifestyle characteristics of adult childhood cancer survivors participating in the SURfit baseline assessment; N=163

| | Total N=163 (100%)[a] | Male N=91 (56%)[a] | Female N=72 (44%)[a] |
|---|---|---|---|
| **Demographic characteristics** | | | |
| Age at study, years | | | |
| Median [IQR] | 28.4 [23.4–36.6] | 28.5 [22.8–36.5] | 28.2 [24.2–36.7] |
| < 30 years | 88 (54%) | 49 (54%) | 39 (54%) |
| 30-39 years | 47 (29%) | 25 (28%) | 22 (31%) |
| 40-49 years | 28 (17%) | 17 (18%) | 11 (15%) |
| **Cancer-related characteristics** | | | |
| Age at diagnosis, years | | | |
| Median [IQR] | 6.7 [3.1–11.8] | 7.5 [3.1–12.2] | 5.9 [3.1–11.7] |
| Time since diagnosis, years | | | |
| Median [IQR] | 22.3 [16.0–29.1] | 22.4 [16.2–27.6] | 22.1 [15.0–30.2] |
| ICCC-3 cancer diagnoses | | | |
| I Leukemia | 57 (35%) | 31 (34%) | 26 (36%) |
| II Lymphoma | 35 (22%) | 26 (29%) | 9 (13%) |
| III CNS tumor | 18 (11%) | 12 (13%) | 6 (8%) |
| IV-XIII Other tumors | 53 (32%) | 22 (24%) | 31 (43%) |
| History of relapse | 15 (9%) | 7 (8%) | 8 (11%) |
| Any chemotherapy | 187 (91%) | 81 (89%) | 67 (93%) |
| Anthracyclines | 105 (64%) | 62 (68%) | 43 (60%) |
| Median [IQR], mg/m² | 180 [120–250] | 160 [118–210] | 180 [150–360] |
| Steroids | 87 (53%) | 49 (54%) | 38 (53%) |
| Median [IQR], g/m² | 3.4 [2.1–4.9] | 3.1 [2.1–4.2] | 3.6 [3.1–4.9] |
| CVD-relevant radiotherapy | 59 (36%) | 31 (34%) | 28 (39%) |
| Cranial[b] | 35 (22%) | 20 (22%) | 15 (21%) |
| Thoracic[b,c] | 27 (17%) | 15 (17%) | 12 (17%) |
| Abdominal[b,c] | 31 (19%) | 16 (18%) | 15 (21%) |
| Growth hormone deficiency and treatment | 8 (5%) | 4 (4%) | 4 (6%) |
| Limb salvage therapy | 2 (1%) | 1 (<1%) | 1 (<1%) |
| **Lifestyle characteristics** | | | |
| Body mass index, kg/m$^2$ | | | |
| Median [IQR] | 23.4 [21.0–26.1] | 23.9 [22.0–26.4] | 22.9 [20.5–25.4] |
| Underweight, <18.5 | 7 (4%) | 4 (4%) | 3 (4%) |
| Normal weight, 18.5–24.9 | 102 (63%) | 52 (57%) | 50 (69%) |
| Overweight, 25.0–29.9 | 40 (25%) | 28 (31%) | 12 (17%) |
| Obese, ≥30.0 | 14 (9%) | 7 (8%) | 7 (10%) |
| Current smokers[d] | 36 (23%) | 23 (26%) | 13 (18%) |
| Physical activity levels at baseline[e] | | | |
| Median [IQR] MVPA, min/day | 38 [25–53] | 39 [26–57] | 38 [24–48] |
| Inactive (<150 min MVPA/week) | 25 (16%) | 12 (14%) | 13 (19%) |
| Active (≥150 min MVPA/week) | 131 (84%) | 75 (86%) | 56 (81%) |

Abbreviations: CNS, central nervous system; CVD, cardiovascular disease; ICCC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range; MVPA, moderate to vigorous physical activity; N, number.

[a] Column percentages are given.
[b] Including total body irradiation.
[c] Including cranio-spinal radiotherapy.
[d] assessed in 158 participants.

[e] assessed between T0a and T0 by accelerometer in 156 participants and categorized according to the World Health Organization.

**TABLE 2.** Modifiable cardiovascular disease risk factors in survivors, N=163 (56% male), median age 28.4 years

| | Total, N=163 | Male, n=91 | Female, n=72 | p-value[a] |
|---|---|---|---|---|
| **Waist circumference**[b], cm (n=162) | | | | |
| Mean (range) | 83 (59-138) | 87 (62-138) | 78 (59-109) | NA |
| Mean z-score (SD) | 0.33 (1.80) | 0.57 (2.00) | 0.04 (1.47) | 0.062 |
| High waist circumference[b], n (%) | 44 (27%) | 21 (23%) | 23 (32%) | 0.221 |
| **Systolic blood pressure**[c], mmHg (N=163) | | | | |
| Mean (range) | 122 (87-173) | 128 (97-160) | 115 (87-173) | NA |
| Mean z-score (SD) | 0.16 (1.25) | 0.33 (1.2) | -0.06 (1.2) | 0.047 |
| **Diastolic blood pressure**[c], mmHg (N=163) | | | | |
| Mean (range) | 75 (50-103) | 77 (55-103) | 73 (50-101) | NA |
| Mean z-score (SD) | 0.79 (1.27) | 0.98 (1.26) | 0.58 (1.3) | 0.057 |
| High blood pressure[c], n (%) | 52 (32%) | 39 (43%) | 13 (18%) | 0.001 |
| **Fasting glucose**[d], mmol/L (n=154) | | | | |
| Mean (range) | 4.7 (3.6-9.9) | 4.9 (3.6-9.9) | 4.6 (3.8-7.0) | NA |
| Mean z-score (SD) | -0.02 (1.31) | 0.05 (1.44) | -0.11 (1.13) | 0.474 |
| High fasting glucose[d], n (%) | 6 (4%) | 4 (5%) | 2 (3%) | 0.608 |
| **HDL cholesterol**[e], mmol/L (n=157) | | | | |
| Mean (range) | 1.46 (0.68-2.35) | 1.32 (0.68-2.12) | 1.64 (0.85-2.35) | NA |
| Inverted mean z-score (SD) | 0.10 (0.99) | 0.23 (0.97) | -0.07 (0.99) | 0.055 |
| Low HDL cholesterol[e], n (%) | 28 (18%) | 18 (20%) | 10 (14%) | 0.497 |
| **Triglycerides**[f], mmol/L (n=158) | | | | |
| Mean (range) | 1.33 (0.52-15.33) | 1.54 (0.52-15.33) | 1.05 (0.52-2.76) | NA |
| Mean z-score (SD) | 0.75 (2.40) | 0.89 (3.00) | 0.53 (1.27) | 0.352 |
| High triglycerides[f], n (%) | 31 (19%) | 25 (28%) | 6 (9%) | 0.008 |
| **Composite CVD risk score**[g] (N=163) | | | | |
| Mean z-score (SD) | 0.35 (0.90) | 0.50 (0.99) | 0.16 (0.74) | 0.017 |
| High composite CVD risk score[g], n (%) | 32 (20%) | 22 (24%) | 10 (14%) | 0.101 |
| **Metabolic syndrome**[h], n (%) (N=162) | 17 (10%) | 13 (14%) | 4 (6%) | 0.070 |

Abbreviations: CVD, cardiovascular disease; HDL, high-density lipoprotein; N, number; NA, not applicable; SD, standard deviation.

[a] p-values calculated from chi-squared tests for categorical and from unpaired t-tests for continuous variables comparing males and females.
[b] High waist circumference: ≥94 cm in male, ≥80 cm in female.

[c] Mean blood pressure values included 6 survivors treated with antihypertensive drugs, 2 survivors being normotensive and 4 survivors hypertensive (132/94 mmHg, 135/92 mmHg, 150/74 mmHg, 173/101 mmHg). High blood pressure: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or treatment.
[d] Mean fasting glucose included 1 survivor treated with insulin and having a high fasting glucose (9.9 mmol/L). High fasting glucose: ≥5.6 mmol/L and/or treatment.
[e] Mean HDL cholesterol included 5 survivors treated with lipid-lowering drugs; 1 survivor had a missing HDL cholesterol value, 3 survivors had normal HDL cholesterol levels and 1 survivor had a reduced/abnormal HDL cholesterol level (0.68 mmol/L). Low HDL cholesterol: <1.03mmol/L in male and <1.30mmol/L in female and/or treatment.
[f] Mean triglycerides included 5 survivors treated with lipid-lowering drugs; 1 survivor had a missing triglyceride value, 3 survivors had normal HDL cholesterol levels and 1 survivor had an elevated triglyceride level (1.9 mmol/L). High triglycerides: ≥1.70mmol/L and/or treatment.
[g] High composite CVD risk score was defined as a z-score ≥1.
[h] Metabolic syndrome was defined according to the International Diabetes Federation.

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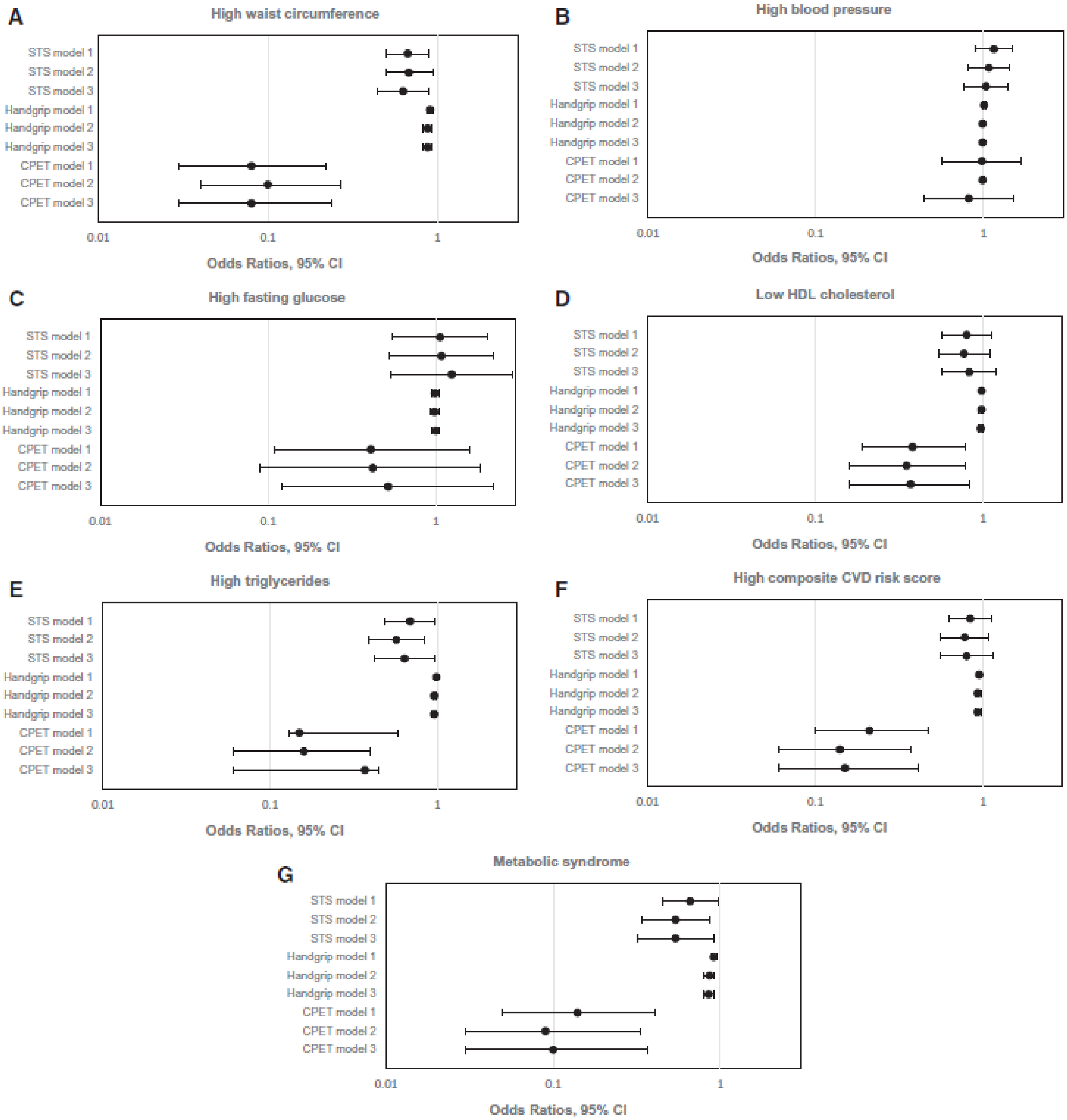
**Figure legend**

**FIGURE 1.** Associations between physical fitness measures and abnormal cardiovascular disease risk factors. Results from univariable (model 1) and multivariable (models 2 and 3) logistic regression analyses. Model 1: unadjusted; model 2: adjusted for sex and age at study; model 3 [final model]: adjusted for sex, age at study, cumulative anthracycline dose (continuous), cumulative steroid dose (continuous), and cardiovascular relevant radiotherapy (yes [cranial, thoracic, abdominal, total body irradiation] / no). N=163 survivors, median age at study 28.4 years.

Abbreviations: CI, confidence interval; CPET, cardiorespiratory exercise testing; CVD, cardiovascular disease; HDL, high-density lipoprotein; STS, 1-minute sit-to-stand test.


A
High waist circumference
STS model 1
STS model 2
STS model 3
Handgrip model 1
Handgrip model 2
Handgrip model 3
CPET model 1
CPET model 2
CPET model 3
0.01
0.1
1
Odds Ratios, 95% CI
B
High blood pressure
STS model 1
STS model 2
STS model 3
Handgrip model 1
Handgrip model 2
Handgrip model 3
CPET model 1
CPET model 2
CPET model 3
0.01
0.1
1
Odds Ratios, 95% CI
C
High fasting glucose
STS model 1
STS model 2
STS model 3
Handgrip model 1
Handgrip model 2
Handgrip model 3
CPET model 1
CPET model 2
CPET model 3
0.01
0.1
1
Odds Ratios, 95% CI
D
Low HDL cholesterol
STS model 1
STS model 2
STS model 3
Handgrip model 1
Handgrip model 2
Handgrip model 3
CPET model 1
CPET model 2
CPET model 3
0.01
0.1
1
Odds Ratios, 95% CI
E
High triglycerides
STS model 1
STS model 2
STS model 3
Handgrip model 1
Handgrip model 2
Handgrip model 3
CPET model 1
CPET model 2
CPET model 3
0.01
0.1
1
Odds Ratios, 95% CI
F
High composite CVD risk score
STS model 1
STS model 2
STS model 3
Handgrip model 1
Handgrip model 2
Handgrip model 3
CPET model 1
CPET model 2
CPET model 3
0.01
0.1
1
Odds Ratios, 95% CI
G
Metabolic syndrome
STS model 1
STS model 2
STS model 3
Handgrip model 1
Handgrip model 2
Handgrip model 3
CPET model 1
CPET model 2
CPET model 3
0.01
0.1
1
Odds Ratios, 95% CI