Online Supplement

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

Christina Schindera, MD, Simeon Joel Zürcher, PhD, Ruedi Jung, MSc, Sarah Boehringer, Jan Willem Balder, MD, PhD, Corina Silvia Rueegg, PhD, Susi Kriemler, MD, Nicolas Xavier von der Weid, MD

Table S1. Single CVD risk factors and the definition of the metabolic syndrome according to IDF and the composite CVD risk score

Single CVD risk factors	**Composite CVD risk score**[1] (according to Kriemler et al.) =average of all z-scores listed below (1–6), abnormal CVD risk score if z-score ≥1	**Metabolic syndrome**[2] (according to IDF) =fulfilled, if abnormal waist circumference is present plus ≥2 additional abnormal criteria
Waist circumference	1. z-score waist circumference	Abnormal if - waist circumference ≥94 cm in male or - waist circumference ≥80 cm in female **(=mandatory criterion)**
Blood pressure	2. z-score systolic blood pressure 3. z-score diastolic blood pressure	Abnormal if - systolic blood pressure ≥130 mmHg and/or - diastolic blood pressure ≥85 mmHg and/or - treatment
Fasting glucose	4. z-score fasting glucose	Abnormal if - fasting glucose: ≥5.6 mmol/L and/or - treatment
HDL cholesterol	5. z-score HDL cholesterol	Abnormal if - HDL cholesterol <1.03mmol/L in male or - HDL cholesterol <1.30mmol/L in female and/or - treatment
Triglycerides	6. z-score triglycerides	Abnormal if - triglycerides ≥1.70mmol/L and/or - treatment

Abbreviations: CVD, cardiovascular disease; HDL, high-density lipoprotein; IDF, International Diabetes Federation.

Additional explanations:

[1] Composite CVD risk score: The composite CVD risk score summarizes continuous outcome parameters of the six single CVD risk factors in relation to a reference population. An elevated composte CVD risk score was defined to detect CVD risk ina relatively young study population. (Kriemler S, Zahner L, Schindler C, et al. Effect of school based physical activity program (KISS) on fitness and adiposity in primary schoolchildren: cluster randomized controlled trial. *BMJ (Clinical research ed).* 2010;340:c785)

[2] Metabolic syndrome: Existing definitions of the metabolic syndrome have shortcomings, especially for young populations, because studies use different definitions. All definitions are based on dichotomization of CVD risk factors. To be clinically diagnosed with the metabolic syndrome, the thresholds for at least three risk factors including high waist circumference must be attained. Those patients close to, but below the cutoffs are categorized equally “healthy” as those far away.

Table S2. Demographic and clinical characteristics of participating and nonparticipating childhood cancer survivors in the SURfit study

	Participants N=163 (100%)[a]	Nonparticipants N=504 (100%)[a]	P[b]
Demographic characteristics			
Male sex	91 (56%)	234 (46%)	0.089
Age at study, years			
Median [IQR]	28.4 [23.4–36.6]	28.1 [23.0–35.6]	0.319
< 30 years	88 (54%)	292 (58%)	0.219
30–39 years	47 (29%)	133 (26%)	
40–49 years	28 (17%)	70 (14%)	
Clinical characteristics			
Age at diagnosis, years	6.7 [3.1–11.8]	6.3 [2.9–11.4]	0.307
Median [IQR]			
Time since diagnosis, years	22.3 [16.0–29.1]	22.1 [16.2–29.0]	0.670
Median [IQR]			
ICCC-3 cancer diagnosis[c]			
I Leukemia	57 (35%)	171 (34%)	0.691
II Lymphoma	35 (22%)	92 (18%)	
III CNS tumor	18 (11%)	54 (11%)	
IV Neuroblastoma	7 (4%)	30 (6%)	
V Retinoblastoma	4 (3%)	10 (2%)	
VI Renal tumors	10 (6%)	42 (8%)	
VII Hepatic tumors	1 (1%)	3 (1%)	
VIII Malignant bone tumors	6 (4%)	25 (5%)	
IX Soft tissue sarcomas	13 (8%)	29 (6%)	
X Germ cell tumors	3 (2%)	13 (3%)	
XI Other malignant epithelial neoplasms	2 (1%)	9 (2%)	
Langerhans cell histiocytosis	7 (4%)	23 (5%)	

Abbreviations: CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range; N, number; HSCT, hematopoietic stem cell transplantation.

[a] Column percentages are given.
[b] p-values comparing participants and nonparticipants of the SURfit study calculated from chi-squared tests for categorical variables and from t-tests for continuous variables.
[c] Three missing cancer diagnoses in the group of nonparticipating survivors.

TABLE S3. Association between physical fitness and modifiable cardiovascular disease risk factors. Results from univariable (model 1) and multivariable (models 2 and 3) logistic regression analyses. 163 survivors, median age at study 28.4 years

	High waist circumference[a]	**High blood pressure**[b]	**High fasting glucose**[c]	**Low HDL cholesterol**[d]	**High Triglycerides**[e]	**High composite CVD risk score**[f]	**Metabolic syndrome**[g]
	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value
	Model 1[h]						
Peak performance (watt)							
per kg BW	0.08 (0.03-0.22) p<0.01	0.98 (0.57-1.67) p=0.94	0.41 (0.11-1.61) p=0.20	0.38 (0.19-0.79) p=0.01	0.28 (0.13-0.58) p<0.01	0.21 (0.10-0.47) p<0.01	0.14 (0.05-0.41) p<0.01
Hand grip strength (kg)							
per kg BW[i]	0.91 (0.88-0.95) p<0.01	1.01 (0.99-1.03) p=0.51	0.99 (0.94-1.04) p=0.69	0.98 (0.96-1.01) p=0.24	0.99 (0.96-1.01) p=0.35	0.95 (0.92-0.98) p<0.01	0.91 (0.87-0.96) p<0.01
1-min sit-to-stand test							
per 10 more repetitions	0.67 (0.50-0.89) p<0.01	1.16 (0.90-1.50) p=0.27	1.06 (0.55-2.05) p=0.86	0.80 (0.57-1.12) p=0.19	0.69 (0.49-0.96) p=0.03	0.84 (0.63-1.13) 0.25	0.66 (0.45-0.97) p=0.04
	Model 2[j]						
Peak performance (watt)							
per kg BW	0.10 (0.04-0.27) p<0.01	0.84 (0.46-1.53) p=0.58	0.42 (0.09-1.85) p=0.25	0.35 (0.16-0.79) p=0.01	0.15 (0.06-0.40) p<0.01	0.14 (0.06-0.37) p<0.01	0.09 (0.03-0.33) p<0.01
Hand grip strength (kg)							
per kg BW[i]	0.88 (0.83-0.92) p<0.01	0.99 (0.97-1.01) p=0.36	0.98 (0.93-1.04) p=0.52	0.98 (0.95-1.00) p=0.09	0.96 (0.94-0.99) p=0.02	0.93 (0.90-0.97) p<0.01	0.86 (0.80-0.92) p<0.01
1-min sit-to-stand test							
per 10 more repetitions	0.68 (0.50-0.94) p=0.02	1.08 (0.81-1.43) p=0.62	1.08 (0.53-2.21) p=0.83	0.77 (0.54-1.10) p=0.16	0.57 (0.39-0.84) p<0.01	0.78 (0.56-1.09) 0.14	0.54 (0.34-0.86) p<0.01
	Model 3 (final)[k]						
Peak performance (watt)							

per kg BW	0.08 (0.03-0.24) p<0.01	0.82 (0.44-1.52) p=0.53	0.52 (0.12-2.23) p=0.38	0.37 (0.16-0.84) p=0.02	0.16 (0.06-0.45) p<0.01	0.15 (0.06-0.41) p<0.01	0.10 (0.03-0.37) p<0.01
Hand grip strength (kg)							
per kg BW[i]	0.88 (0.83-0.92) p<0.01	0.99 (0.97-1.01) p=0.35	1.00 (0.95-1.05) p=0.88	0.97 (0.94-1.00) p=0.08	0.96 (0.92-0.99) p<0.01	0.93 (0.90-0.97) p<0.01	0.85 (0.79-0.92) p<0.01
1-minute sit-to-stand test							
per 10 more repetitions	0.63 (0.44-0.90) p=0.01	1.04 (0.76-1.41) p=0.81	1.25 (0.54-2.89) p=0.60	0.83 (0.57-1.21) p=0.32	0.64 (0.42-0.96) p=0.03	0.80 (0.56-1.14) p=0.21	0.54 (0.32-0.91) 0.02

Abbreviations: BW, body weight; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein.

[a] High waist circumference: ≥94 cm in male, ≥80 cm in female.
[b] 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 ≥85mmHg and/or treatment.
[c] 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.
[d] 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.
[e] 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.
[f] High composite CVD risk score was defined as a z-score ≥1.
[g] Metabolic syndrome was defined according to the International Diabetes Federation.
[h] unadjusted.
[i] kg/kg body weight x 100.
[j] adjusted for age at study and sex.
[k] adjusted for age at study, sex, cumulative anthracycline dose, cumulative steroid dose, and CVD relevant radiotherapy (cranial, thoracic, abdominal, total body irradiation).

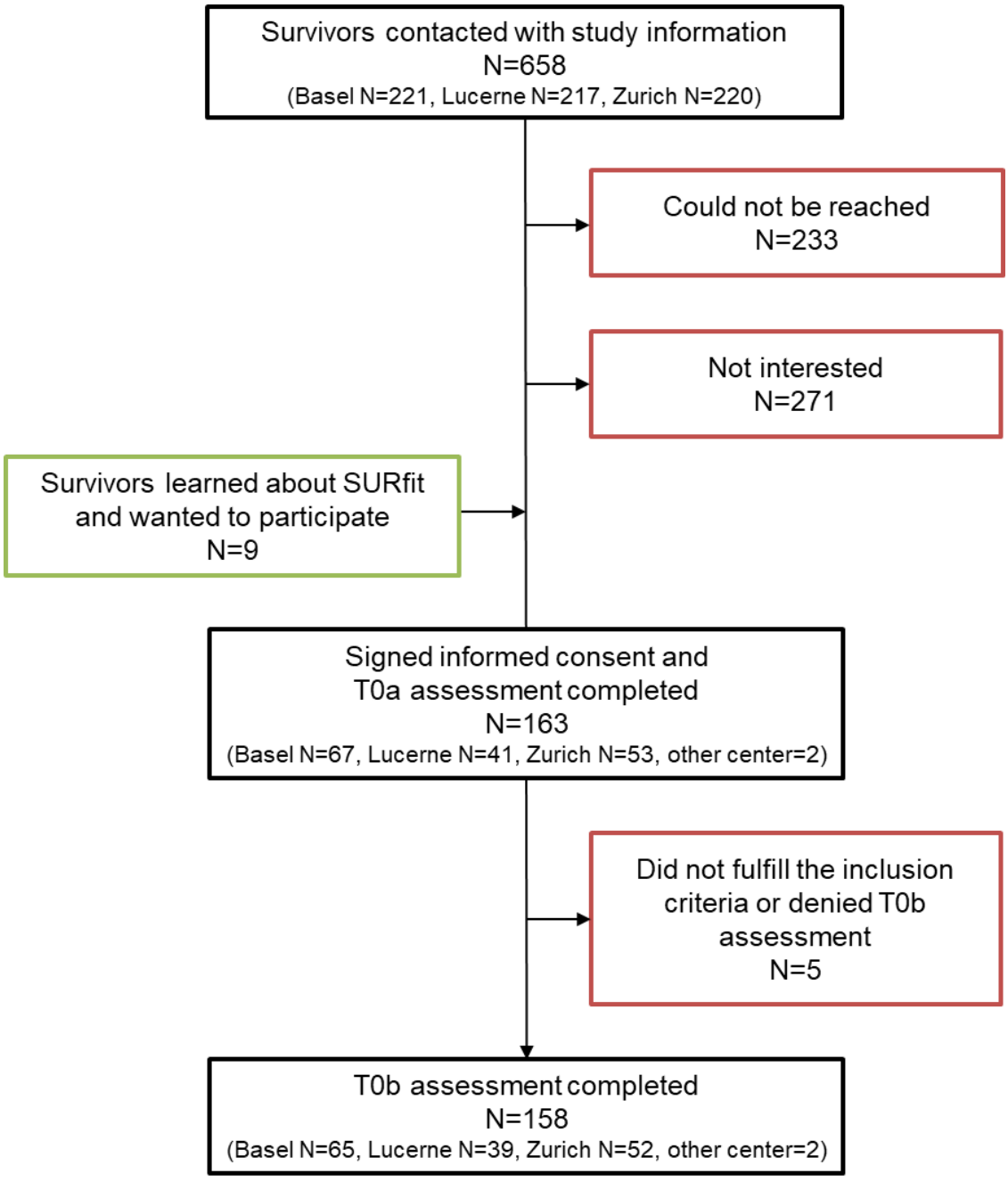

FIGURE S1 Population tree of childhood cancer survivors recruited into the SURfit study who participated in the baseline assessments (T0a and T0b)

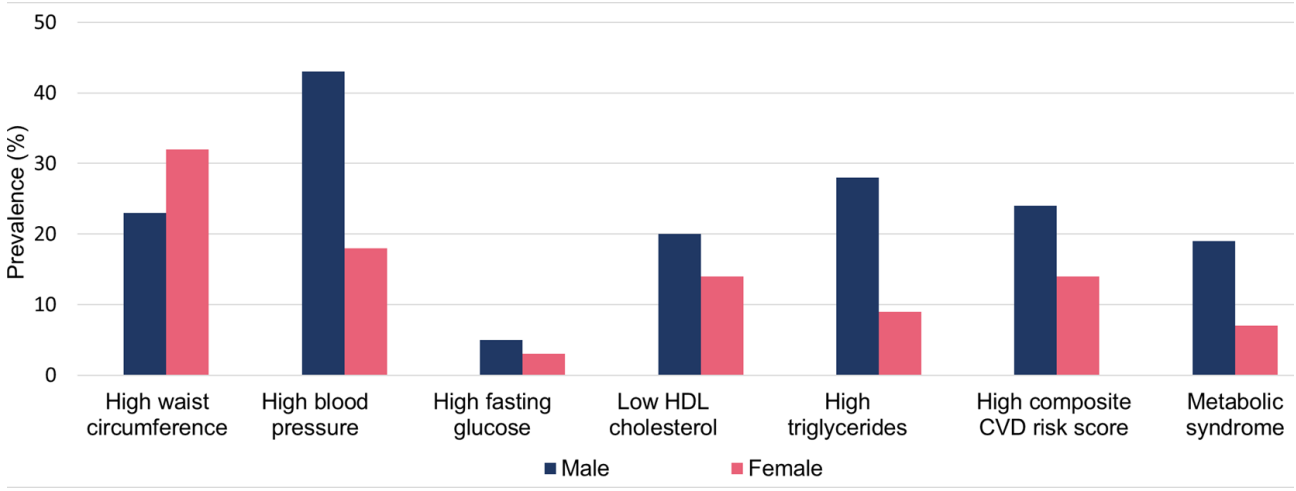

FIGURE S2. Prevalence of abnormal cardiovascular risk factors, high composite cardiovascular risk score, and metabolic syndrome in male and female childhood cancer survivors. N=163, median age at study 28.4 years.

Abbreviations: CVD, cardiovascular disease; HDL, high-density lipoprotein.

Supplemental Text.

Detailed exclusion criteria for the SURfit participants

Exclusion criteria were participation in another clinical trial, inability to exercise or exercise being potentially harmful, pregnant or breastfeeding, cardiac arrhythmias under exercise, diagnosis of diabetes <3 months previously, detection or presence of a clinical condition that needs immediate treatment, planned surgeries within the subsequent 12 months that interfere with physical exercise, major musculoskeletal injuries <2 months previously, change in medication that interferes with CVD risk factors <1 month previously, >4 hours of reported vigorous physical activities per week, and inability to understand and follow procedures of intervention.

Description of assessment modifiable cardiovascular disease risk factors.

Body mass index

Standing height and weight were taken by standard procedures, barefoot and in underwear. Height was determined to the nearest 0.5 cm, weight to the nearest 0.1 kg.

Waist circumference

Waist circumference was measured with a medical measuring tape to the nearest 0.5 cm at the narrowest part of the torso (the middle between lower rib arch and spina iliaca) in relaxed, standing position at the end of expiration.

Blood pressure

Systolic and diastolic blood pressure was measured in sitting position on the left upper arm after at least 5 min rest using an automated oscillography (DINAMAP® ProCare [GE Medical Systems, Tampa, Florida, USA]). Based on the recommendations of the American Heart Association, the mean of two readings with a one-minute interval between them were recorded. If the difference between the two readings was >5 mmHg, another two readings was taken.

Fasting blood samples

Fasted blood samples were taken in the morning after an overnight fast of at least 8 h. Glucose was analyzed within a few hours after sampling at the laboratory of the University Hospital of Basel. The other parameters assessed in the blood serum and plasma were centrifuged, divided into 1.0 ml aliquots and stored at −70 °C to be analyzed at a later time point when a test kit could be completed at a the certified laboratory of the Endonet and Bone Research Unit, Basel. Blood lipids Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides were measured by standard method on an autoanalyser (COBAS Integra 800; Roche Diagnostics, Basel, Switzerland). Intra-assay and inter-assay CVs were between 1.6–2.2% for total cholesterol, 2.4–3.6% for HDL, 0.7–2.1% for LDL, and 1.1–3.7% for triglycerides, respectively.