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CARDIOVASCULAR HEALTH AND FITNESS AFTER CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA

Liisa Järvelä

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ABSTRACT

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Cardiovascular health and fitness after childhood acute lymphoblastic leukaemia

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The last few decades have turned childhood acute lymphoblastic leukaemia (ALL) from a virtually incurable disease to a disease with 80–90% survival rates. However, this has not come without a cost. Various late effects of the treatment are nowadays well acknowledged, and the survivors have increased cardiovascular (CV) morbidity and mortality. While the treatment of ALL may have direct toxic effects on various organ systems, lifestyle factors affect the CV risk of the survivors as well.

Data on CV health and fitness after treatment with common Nordic protocols since 1986 has been scarce. This thesis aimed to study CV health and fitness and the effects of a 3-month exercise intervention in 16–30-year-old long-term survivors of childhood ALL.

Fitness was poor especially in female survivors. One third reported ≤1h of moderate physical activity (PA) weekly. While the levels of other CV risk factors were similar in survivors and controls, attenuations in vascular endothelium and cardiac function were found when using advanced echocardiographic methods. The exercise programme improved fitness, insulin resistance, endothelial function as well as measures of cardiac function.

While the results do not allow definite conclusions on whether the subclinical signs of cardiac and vascular endothelial dysfunction are due to the treatment of ALL or sedentary lifestyle/poor fitness after treatment, the results are interesting and emphasize the effects of PA in this population. The results indicate beneficial effects of PA on the heart health in ALL survivors and suggest that they should be encouraged to physically active lifestyle.

Keywords: acute lymphoblastic leukaemia, anthracyclines, cardiovascular health, fitness, physical activity

TIIVISTELMÄ

Liisa Järvelä

Sydänterveys ja fyysinen suorituskyky lapsuusiän akuutin lymfoblastileukemian jälkeen

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen laitos, Lastentautioppi, Turun yliopiston kliininen tohtoriohjelma (TKT); Turun yliopistollinen keskussairaala, Turku
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Lasten yleisin syöpä on akuutti lymfoblastileukemia (ALL), jonka ennuste on muutamassa vuosikymmenessä noussut läheltä nollaa 80–90 %:n tasolle. Parantuneella ennusteella on kuitenkin hintansa. ALL:n hoidolla voi olla kauaskantoisia vaikutuksia moniin elinjärjestelmiin ja esimerkiksi kuolleisuus sydän- ja verisuonisairauksiin on lisääntynyt. ALL:n hoito on Suomessa perustunut pohjoismaisiin käytäntöihin vuodesta 1986 alkaen, mutta tietoa näiden potilaiden sydän- ja verisuoniterveydestä ja kunnosta on ollut vähän. Tutkimuksen tarkoitus oli tutkia sydän- ja verisuonisairauksien riskitekijöitä ja fyysistä suorituskykyä 16–30-vuotiailla ALL:n sairastaneilla henkilöillä. Tuloksia verrattiin terveisiin verrokkeihin. Lisäksi tutkittiin 3 kk:n liikuntaintervention vaikutusta ALL:n sairastaneilla.

Tutkimuksessa havaittiin, että fyysinen suorituskyky oli huono etenkin ALL:n sairastaneilla naisilla. Vähäinen fyysinen aktiivisuus oli myös tavallista ja kolmasosa tutkituista raportoi kohtuullista rasitusta alle tunnin viikossa. Tavanomaiset sydän- ja verisuonisairauksien riskitekijät eivät eronneet ALL:n sairastaneiden ja verrokkien välillä, mutta verisuonten endoteelissa havaittiin muutoksia. Sydämen toiminnassa havaittiin muutoksia kun käytettiin kehittyneitä ultraäänimenetelmiä. Liikuntaintervention jälkeen ALL:n sairastaneiden kunto, insuliiniresistenssi, endoteelin toiminta ja sydämen toiminta paranivat.

Tutkimuksen tulokset osoittivat, että huono kunto ja vähäinen liikunta ovat tavallisia ALL:n sairastaneilla. Lisäksi verisuonten endoteelissa ja sydämen toiminnassa havaittiin muutoksia, jotka osittain paranivat liikuntaintervention aikana. Vaikka tutkimuksen perusteella ei voida tehdä varmoja johtopäätöksiä siitä, johtuvatko endoteeli- ja sydänlöydökset ALL:n hoidosta vai esimerkiksi vähäisestä liikunnasta hoitojen jälkeen, tulokset ovat kiinnostavia ja korostavat liikunnan merkitystä ALL:n jälkeen. Tulokset viittaavat siihen, että liikunnalla on positiivisia vaikutuksia ALL:n sairastaneiden sydänterveyteen ja heitä pitäisi kannustaa liikunnalliseen elämäntapaan hoitojen jälkeen.

Avainsanat: akuutti lymfoblastileukemia, antrasykliini, kunto, liikunta, sydän- ja verisuonitaudit

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ABBREVIATIONS

A–Late mitral filling

A'–Late diastolic velocity of mitral annulus

ACT–Anthracycline cardiac toxicity

ALL–Acute lymphoblastic leukaemia

BMI–Body mass index

BP–Blood pressure

CCSS–The Childhood Cancer Survivor Study

CHF–Congestive heart failure

CNS–Central nervous system

CRT–Cranial radiation therapy

CVD–Cardiovascular disease

CVRF–Cardiovascular disease risk factors

E–Early mitral filling

E'–Early diastolic velocity of mitral annulus

EF–Ejection Fraction

FMD–Flow mediated dilation

FMDauc–Flow mediated dilation area under the curve

FMDmax–Maximum value of flow mediated dilation

FS–Fractional Shortening

HDL–High density lipoprotein cholesterol

HOMA-IR–Homeostasis model assessment–insulin resistance

HSCT–haematopoietic stem cell transplantation

IGF-1–Insulin-like growth factor 1

IMT–Intima media thickness

LDL–Low density lipoprotein cholesterol

LV–Left ventricle of the heart

MET–Multiple of the resting metabolic rate

MetS–Metabolic syndrome

NOPHO–Nordic Society of Paediatric Haematology and Oncology

PA–Physical activity

PAI–Physical activity index

PCS–Peak Circumferential Strain

PCdiastSR–Peak Circumferential Diastolic Strain Rate

PCSR–Peak Circumferential Strain Rate

PLD–Peak Longitudinal Displacement

PLS–Peak Longitudinal Strain

PLV–Peak Longitudinal Velocity

PLdiastSR–Peak Longitudinal Diastolic Strain Rate

PLSR–Peak Longitudinal Strain Rate

PRD–Peak Radial Displacement

PRV–Peak Radial Velocity

TDI–Tissue Doppler Imaging

VO_{2peak}–Peak oxygen uptake

VVI–Velocity Vector Imaging

LIST OF ORIGINAL PUBLICATIONS

I Liisa S Järvelä, Harri Niinikoski, Päivi M Lähteenmäki, Olli J Heinonen, Jukka Kapanen, Mikko Arola, Jukka Kemppainen. Physical activity and fitness in adolescent and young adult long-term survivors of childhood acute lymphoblastic leukaemia. *J Cancer Surviv* 2010;4(4):339-345.

II Liisa S. Järvelä, Jukka Kemppainen, Harri Niinikoski, Jarna C. Hannukainen, Päivi M. Lähteenmäki, Jukka Kapanen, Mikko Arola, Olli J. Heinonen. Effects of a home-based exercise program on metabolic risk factors and fitness in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatric Blood & Cancer* 2012;59(1):155-160.

III Liisa S. Järvelä, Harri Niinikoski, Olli J. Heinonen, Päivi M. Lähteenmäki, Mikko Arola, Jukka Kemppainen. Endothelial Function in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia: Effects of a Home-Based Exercise Program. *Pediatric Blood & Cancer* 2013;60(9):1546-51.

IV Liisa S. Järvelä, Markku Saraste, Harri Niinikoski, Jarna Hannukainen, Olli J. Heinonen, Päivi M. Lähteenmäki, Mikko Arola, Jukka Kemppainen. Home-Based Exercise Training Improves Left Ventricle Diastolic Function in Survivors of Childhood ALL: A Tissue Doppler Imaging and Velocity Vector Imaging Study. *(Submitted)*

1 INTRODUCTION

The survival rates of childhood cancers have increased drastically during the past five decades (Madanat Harjuoja et al. 2014). During these decades, e.g. acute lymphoblastic leukaemia (ALL) has turned from a virtually incurable disease to a disease with 5-year survival rates approaching 90 % (Madanat Harjuoja et al. 2014, Hunger et al. 2012, Gatta et al. 2014). In 2014, it was estimated that approximately one in 530 young adults aged 20–39 years was a childhood cancer survivor (American Cancer Society 2014), and the proportion may still rise as the children with the highest survival rates treated during the last two decades continue to age. While the survival rate has increased, more focus has been put on survivorship and the late effects of the disease and its treatment. According to a large American questionnaire study, more than 60% of the long-term survivors of childhood cancer reported at least some morbidity, and 27.5% of the survivors reported a severe, disabling or life-threatening condition (Oeffinger et al. 2006). In a smaller European study from the Netherlands, the numbers were even higher (74.5 % and 40 % respectively) (Geenen et al. 2007). In survivors of childhood leukaemia, the relative risk for chronic health conditions was 2.2 compared with siblings, the relative risk for severe, disabling or life-threatening condition 4.1, and the relative risk for multiple conditions was 2.8 compared to siblings (Oeffinger et al. 2006).

Childhood cancer and its treatment may result in a variety of long-term effects, but second malignant neoplasms, cardiovascular diseases, pulmonary fibrosis, endocrinopathies, and neurosensory deficits are the most common concerns (Oeffinger et al. 2006, Garwicz et al. 2012, Armenian, Robison 2013). In survivors of childhood ALL, obesity, insulin resistance, and other cardiovascular disease risk factors (CVRF), as well as a sedentary lifestyle and low physical fitness (Oeffinger et al. 2001, Oeffinger et al. 2003, Jarfelt et al. 2005, van Brussel et al. 2006, Florin et al. 2007, Ness et al. 2007, Steffens et al. 2008, Oeffinger et al. 2009, Oudin et al. 2011) are common, and ALL survivors have increased risk for cardiovascular disease (CVD) (Landy et al. 2012, Kero et al. 2014, Kero et al. 2015). Some of the risk has been attributed to the adverse effects of certain chemotherapeutic agents (e.g. anthracyclines with cardiotoxicity, vincristine with neuropathy, methotrexate and cisplatin with e.g. vascular endothelium, and corticosteroids with e.g. myopathy and osteonecrosis). At the same time, it seems likely that years of treatment, hospitalisation and isolation due to the risk of infections may prevent the patients from attending regular physical activity (e.g. sports at school) and adopting a physically active lifestyle during childhood. This may, in turn, further increase the detrimental effects of the treatment on the survivors' health.

A large part of the data concerning long-term late effects of cancer treatment in childhood is from the Childhood Cancer Survivor Study (CCSS), which included survivors diagnosed with cancer between 1970 and 1986 (Robison et al. 2009). Especially the

treatment of childhood ALL has markedly changed since the CCSS era and information on survivors treated since 1986 is needed in order to plan proper follow-up care.

Information on the effects of physical activity (PA) interventions in survivors of childhood ALL is relatively scarce and previous studies have not reported on the effects of PA interventions on cardiovascular risk factors or vascular endothelial structure and function (Winter et al. 2010, Wolin et al. 2010). Such studies are needed in order to discover whether the survivors of childhood ALL can be motivated to increase their physical activity by simple interventions, and whether positive effects on CV risk factors can be achieved. In addition, anthracyclines are known to cause late cardiotoxicity (ACT), and it has been postulated that the risk of ACT increases exponentially with increasing anthracycline dose (van der Pal et al. 2012). However, it is still uncertain whether the toxic effect is truly dose-dependent, and it has been observed that even small anthracycline doses may cause late cardiotoxity (Lipshultz et al. 1991, Hudson et al. 2007, Mulrooney et al. 2009), especially in genetically susceptible individuals, as reviewed by Armenian and Bhatia (2009). Traditional cardiac ultrasound measures (ejection fraction, EF; fractional shortening, FS) are not sensitive enough to detect subtle changes in cardiac function, and late cardiac toxicity may not become evident until decades after treatment. Currently, late effect clinics for childhood cancer survivors are being established, and screening practises for late cardiac toxicity are also evolving. Thus, more sensitive methods would greatly help in determining the survivors in need of stringent cardiac monitoring.

The importance of establishing life-long follow-up programmes is further supported by the fact that epidemiologic studies in Nordic countries have shown that 5-year survivors of childhood cancers have excess mortality even 30 years or more after diagnosis (Garwicz et al. 2012), and especially their cardiovascular morbidity and mortality are elevated (Kero et al. 2014, Kero et al. 2015). Despite the improvements in mortality 5 to 10 years after diagnosis, the Standardised Mortality Ratios and Absolute Excess Risks >10 years after diagnosis have not improved during the past decades, and the late mortality seems to be mainly due to second malignant neoplasms and cardiovascular disease (Garwicz et al. 2012).

The main objective of this thesis was to study the cardiometabolic risk profile as well as the effects of a simple exercise intervention on cardiovascular health and fitness in survivors of childhood ALL. This information would be helpful in planning risk-based follow-up and further interventions in this growing population.

2 REVIEW OF THE LITERATURE

2.1 Acute lymphoblastic leukaemia in children

2.1.1 Incidence and prognosis

According to data from the USA, it has been estimated that the risk of contracting cancer between birth and 20 years of age is approximately 1 in 300 (Hewitt M et al. 2003). In Finland, 150–160 children get cancer every year, and 40–50 of them are diagnosed with leukaemia (Madanat Harjuoja et al. 2014). The most common form of leukaemia in children is ALL which comprises over 85 % of the leukaemia cases in children, and its annual incidence is about 4 per 100 000 children in the Nordic countries (Gustafsson et al. 2000, Hjalgrim et al. 2003). In Finland and other Nordic countries, over 85 % of children diagnosed with ALL become long-term survivors (> 5 years from diagnosis) (Gatta et al. 2014, Madanat Harjuoja et al. 2014).

2.1.2 Treatment

In Finland, childhood ALL is treated according to the Nordic regimen (Nordic Society of Paediatric Haematology and Oncology, NOPHO) and the treatment regimen is divided into risk groups based on certain higher risk features at diagnosis, and later on, the response to treatment. Common Nordic treatment protocols have been developed since 1981 and they were completed for each risk group in 1992 (Gustafsson et al. 2000). Since 1986, the NOPHO ALL-86 protocol was used for treatment of standar risk and intermediate risk patients in Finland while the high risk patients were still treated according to the German ALL-BFM protocol (Gustafsson et al. 2000).

Generally, the treatment of ALL includes different phases: The induction phase to induce remission; The consolidation phase to further reduce the tumour burden, including treatment targeting the leukaemic cells hidden in the central nervous system (CNS); Intensification phases (=reinductions, including treatment targeting the CNS); Possible CNS irradiation; Maintenance treatment to further eradicate possible residual disease.

The NOPHO ALL-86 treatment regimen included prednisone, vincristine, doxorubicin and asparaginase during induction, and intravenous as well as intrathecal methotrexate for CNS consolidation. Daily oral 6-Mercaptopurin and weekly methotrexate were used for maintenance until 36 months from diagnosis, and the maintenance also included pulses of intravenous methotrexate and prednisone+vincristine. The intermediate risk

patients also received early and late intensification phases and CNS irradiation (12-18Gy) before the oral maintenance treatment. (Gustafsson et al. 2000).

In the NOPHO ALL-92 protocol, started in 1992 (Gustafsson et al. 2000), the most significant change from NOPHO ALL-86 to NOPHO ALL-92 was the change in CNS prophylaxis from irradiation to methotrexate resulting in only 10 % of patients receiving irradiation compared to 60 % during NOPHO ALL-86. (Gustafsson et al. 2000, Schmiegelow et al. 2010). To achieve this, intrathecal methotrexate was added to the induction phase, and the intravenous methotrexate dose was substantially increased. In addition, the induction phase was made uniform for each risk group to allow later switching to a higher risk protocol. During NOPHO ALL-92, the treatment duration was 2.5 years in standard risk patients and 2 years in the other risk groups, and CNS irradiation (12–24 Gy) was given only to very high risk patients. In addition, for the very high risk group, the maintenance therapy was different from the other risk groups (up to 6 cycles of LSA_2L_2). However, in Finland, all high risk patients received their maintenance treatment according to the very high risk protocol irrespective of their CNS prophylaxis resulting in e.g. greater cumulative anthracycline doses (Table 1). At the time of NOPHO ALL-92, there were no uniform criteria for haematopoietic stem cell transplantation (HSCT), but generally patients with white blood cells $\geq 200 \times 10^9$/L at diagnosis were candidates for HSCT. In addition, patients with a Philadelphia chromosome, MLL-gene rearrangements or poor response to induction were candidates for HSCT. (Gustafsson et al. 2000, Schmiegelow et al. 2010).

In 2000, a new NOPHO ALL-2000 protocol was introduced with the aim to study the efficacy of vincristine+dexamethasone reinductions during maintenance therapy (Schmiegelow et al. 2010). Another goal of the new protocol was to study the feasibility of non-centralised minimal residual disease monitoring, and the criteria for HSCT were also further specified. The former high/very high risk category was then divided into high, very high and extra high risk with the very high risk group receiving cranial radiation therapy (CRT) and the extra high risk patients being candidates for HSCT at the first complete remission. During induction, the doxorubicin doses were reduced from 3 to 2, and the total anthracycline dose in the standard risk group was reduced to 80 mg/m^2. The maximal vincristine dose increased from 2.0 to 2.5 mg, and Erwinase was replaced with *E. coli* asparaginase throughout the protocol. The oral 6-mercaptopurin/methotrexate maintenance therapy was now based on thiopurine methyltransferase activity genotyping, and the treatment duration for intermediate risk patients was increased from 2 to 2.5 years. During NOPHO ALL-2000, 6.1 % of the patients were treated with HSCT at the first remission as opposed to 3.5 % during NOPHO ALL-92. (Schmiegelow et al. 2010).

The current NOPHO ALL protocol was introduced in 2008. In order to reduce toxicity of the treatment, CNS irradiation was omitted for all risk groups in the first remission, and the most profound changes were made to the high risk protocol. For the intermediate risk

treatment group, additional i.t. Methotrexate every eight weeks was added to the maintenance treatment. (Schmiegelow et al. 2010). Treatment duration is now 2.5 years in each risk group. In the current protocol, HSCT is performed in the first remission only for patients without morphological remission after the induction phase or with high levels of minimal residual disease at 3 months. The main changes in treatments with the most potential effects on cardiovascular disease risk in Nordic ALL protocols since 1986 are summarised in Table 1. Event-free survival curves for ALL from each NOPHO protocol are shown in Figure 1.

Table 1 CRT dose and cumulative doses of chemotherapeutic agents with potential effects on cardiovascular disease risk in the NOPHO ALL treatment regimen since 1986

	Doxo	Dauno	Mtx i.t.	Mtx i.v.	Pred	Dexa	Vcr	CRT
	mg/m^2	mg/m^2	number of doses	g/m^2 x doses	days on full dose (40-60 mg/m^2)	days on full dose (6-10 mg/m^2)	number of doses (1.5-2 mg/m^2)	Gy
1986								
SR	120	-	8+5	0.5–1x4+5	45+25	-	8+5	-
IR	120	120	9	0.5–1 x 4	28	28	8	12–18
HR	Varying national protocols adapted from BFM; Since 1990 NALLE-90 in Finland (similar to NOPHO 92)							
1992								
SR	120	-	13	5x8	60	-	11	-
IR	120	120	17	5x9	60	21	15	-
HR[a]	160	120	17	8x4	80	21	19	-
VHR[a]	160	240	17	8x2	55	21	20	18–24
2000								
SR	80		13	5x8	35	25[b]	11[b]	-
IR	80	120	16	5x8	35	39[b]	15[b]	-
HR	240	60	13	8x4	35	24+35[c]	14+7[c]	-
VHR	240	90	15	8x2	35	14+50[c]	13 +10[c]	18–24
extra HR[d]	120	30[d]	8[d]	8x2	35		6[d]	
2008	Not published in full							

[a]In Finland, HR maintenance treatment according to VHR (LSA_2L_2); [b]0 or 8 additional doses depending on randomization; [c]Every 4 weeks until 2 years from diagnosis; [d]LSA_2L_2 continued until HSCT in first remission; CRT=Cranial radiation therapy; Dauno=Daunorubicin; Dexa=Dexamethasone; Doxo=Doxorubicin; HSCT=Haematopoietic stem cell transplantation; HR=High risk; Ida=Idarubicin; IR=Intermediate risk; i.t. = Intrathecal; i.v. = Intravenous; Mtx=Methotrexate; Pred=Prednisolone; SR=Standard risk;Vcr=Vincristine; VHR=Very high risk;

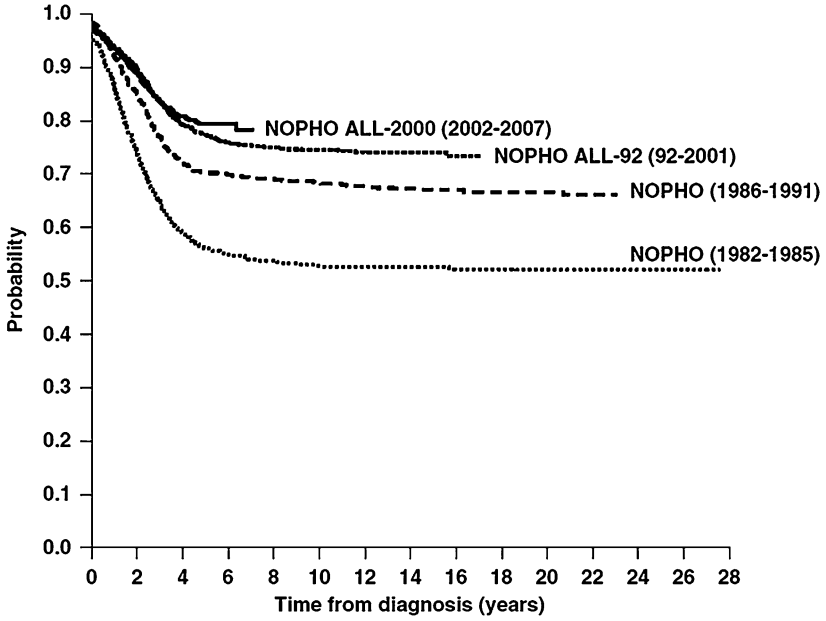

Figure 1 Event-free survival (EFS) in four consecutive Nordic Society of Paediatric Haematology and Oncology (NOPHO) cohort periods. (In Schmiegelow et al. 2010. Reprinted by permission from Macmillan Publishers Ltd: Leukemia (2010) 24, 345–354; doi:10.1038/leu.2009.251)

2.1.3 Long-term effects

As the increasing survival rates have shown, modern ALL treatment is usually very effective, but it has the potential to damage various organ systems and cause different late effects. Among the most commonly reported concerns after ALL treatment are second malignant neoplasms, cardiovascular diseases (CVD), musculoskeletal problems, endocrinopathies, and neurologic conditions, as reviewed by Ness et al. (2011). Adult survivors of childhood leukaemia face a considerable burden of illness that may affect various aspects of their lives (Oeffinger et al. 2006, Mody et al. 2008). The CCSS has shown that survivors of childhood leukaemia report e.g. increased prevalence of chronic health conditions, poorer health status and decreased abilities to work compared to their siblings (Oeffinger et al. 2006, Mody et al. 2008). It is also noteworthy, that the increased risk for chronic health conditions does not seem to plateau even decades after treatment (Armstrong et al. 2014). Armstrong et al. (2014) showed that, compared to siblings, the hazard ratios for severe, disabling, life-threatening or fatal conditions still continues to rise in childhood leukaemia survivors aged ≥ 35 years, especially with regard to cardiovascular diseases (Armstrong et al. 2014). Of the childhood cancer survivors with no such conditions by the age of 35 years, 25.9 % will have at least one such condition during the next ten years while the number in siblings is only 6 % (Armstrong et al. 2014). By the age of 50

years, 53.6 % of the survivors have at least one severe, disabling, life-threatening or fatal health condition (vs. 19.8 % in siblings) (Armstrong et al. 2014). However, it seems possible that females and males as well as younger and older children may be prone to somewhat different late effects (Armstrong et al. 2007, Nottage et al. 2014, Lipshultz et al. 2015), and various biological factors may affect the individual risk for late effects after different treatment modalities.

Previous data on late effects of leukaemia and other cancer treatment in childhood is largely based on the Childhood Cancer Survivor Study (CCSS) that describes late effects in survivors of childhood cancer (leukaemia, CNS malignancy, Hodgkin and non-Hodgkin lymphoma, Wilms tumour, neuroblastoma, soft-tissue sarcoma, bone tumour). In the CCSS, the diagnoses were made between 1970–1986, and the results have been mainly based on questionnaires and smaller clinical subsets (Robison et al. 2009). Even though the CCSS has provided an enormous amount of data on the late effects of childhood cancers, both the treatment and prognosis of childhood ALL have markedly changed since the era included in the CCSS, and information on survivors treated since 1986 is needed in order to plan proper follow-up care. While the use of prophylactic cranial irradiation has diminished decreasing the proportion of survivors affected by radiation-related late effects, the changes in chemotherapy regimens and supportive care have resulted in increased survival of high risk patients potentially increasing the proportion of survivors affected by chemotherapy-related late effects. In addition, the use of HSCT with total body irradiation conditioning may have further changed the late effect profile of ALL survivors.

2.2 Cardiovascular late effects after childhood acute lymphoblastic leukaemia

2.2.1 Cardiovascular disease risk factors

According to epidemiological and large cohort studies, survivors of childhood ALL have increased risk for cardiovascular morbidity and mortality (Mertens et al. 2008, Mulrooney et al. 2009, Garwicz et al. 2012, Kero et al. 2014, Kero et al. 2015), and some studies have indicated that compared to control populations of siblings, the risk for cardiovascular diseases is even more pronounced in female survivors than males (Mulrooney et al. 2009, Kero et al. 2014). In addition to the direct toxic effects of the treatment on e.g. myocardium and vascular endothelium (Lipshultz et al. 1991, Muszynska et al. 2001, Murata et al. 2001, Wu et al. 2002, Lipshultz et al. 2005, Nuver et al. 2005, Oeffinger 2008), damage to other organ systems may contribute to the survivors' risk of CVD (Ness et al. 2011). For example, obesity, insulin resistance, a sedentary lifestyle, and physical activity limitations due to e.g. neuropathy, osteonecrosis or other musculoskeletal problems may further increase the detrimental effects of the treatment on the cardiovascular health of the survivors.

Several studies have shown that cardiovascular disease risk factors (CVRF) such as obesity, insulin resistance, high blood pressure and dyslipidemia are common in survivors of childhood ALL (Talvensaari et al. 1996, Oeffinger et al. 2001, Link et al. 2004, Jarfelt et al. 2005, Steffens et al. 2008, Oeffinger et al. 2009, Meacham et al. 2010, Oudin et al. 2011, Landy et al. 2012, Veringa et al. 2012, Nottage et al. 2014). The main factors affecting cardiovascular health in ALL survivors are summarised in Figure 2.

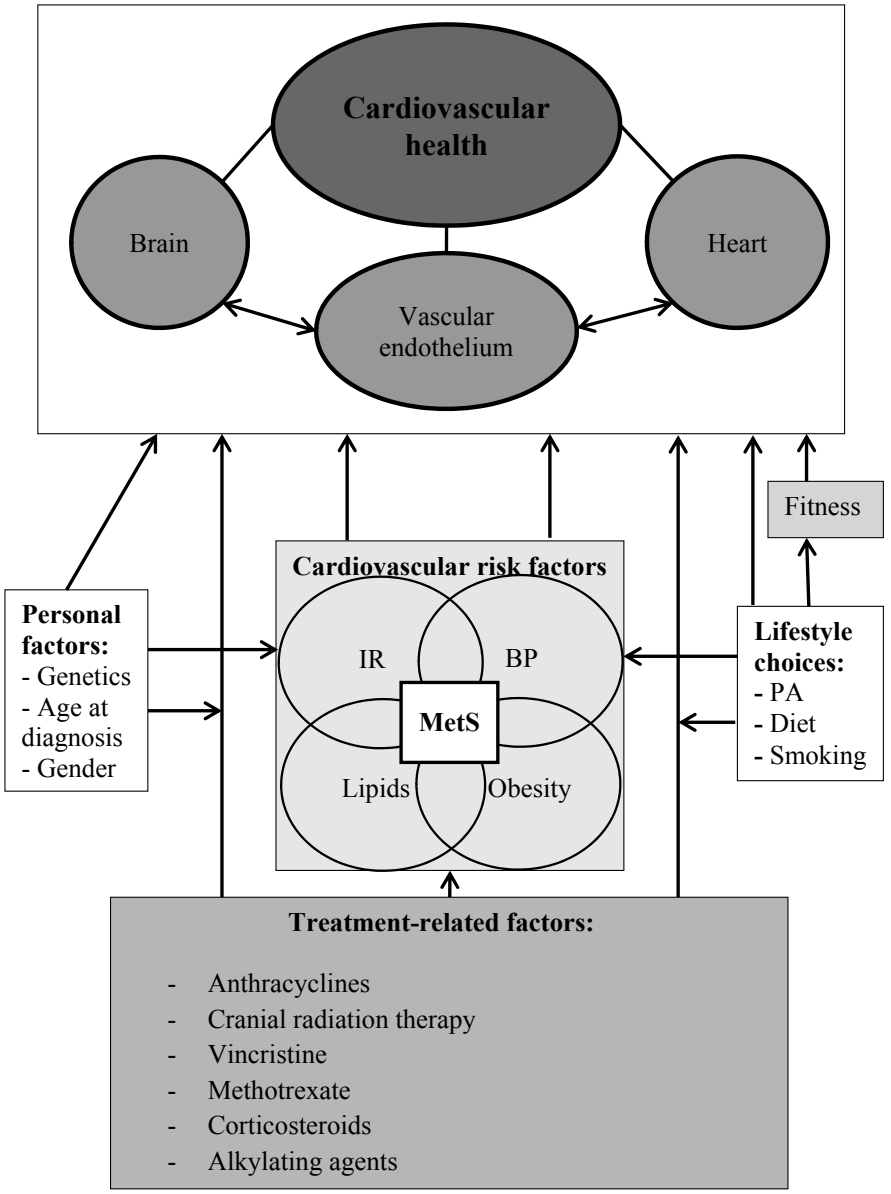

Figure 2 Factors affecting cardiovascular health in ALL survivors. BP = Blood pressure; IR = Insulin resistance; MetS = Metabolic syndrome; PA = Physical activity;

2.2.1.1 Overweight and obesity

A number of studies have evaluated the change in body mass index (BMI) during treatment of childhood ALL and a recent meta-analysis concluded that the mean increase in BMI z-score during treatment is 0.81 (Zhang et al. 2015). Age- and gender adjusted BMI seems to increase steeply during the first year after diagnosis (Breene et al. 2011, Esbenshade et al. 2011, Love et al. 2011, Fuemmeler et al. 2013, Arpe et al. 2015). Some of the studies have stated that the weight gain still continues for at least the first year post-treatment while others have suggested a plateau or slight decrease in relative age- and gender-adjusted BMI after completion of treatment (Nysom et al. 1999, Reilly et al. 2000, Sklar et al. 2000, Baillargeon et al. 2007, Heath et al. 2010).

Various studies have tried to explore whether some demographic or treatment-related factors would help to determine the patients most at risk for excess weight gain during treatment. The effects of e.g. age at diagnosis, gender, BMI at diagnosis, CRT and corticosteroid treatment have been discussed, but some of the results are in part contradictory. Many studies have concluded that a younger age at diagnosis is a risk factor for excess weight gain during or after ALL treatment (Reilly et al. 2000, Baillargeon et al. 2007, Razzouk et al. 2007, Garmey et al. 2008, Arpe et al. 2015), but this has not been found in all studies (Nysom et al. 1999, Sklar et al. 2000, Chow et al. 2007, Asner et al. 2008, Esbenshade et al. 2011) and some have even concluded the opposite in long-term survivors treated without CRT (Oeffinger et al. 2001). However, this may be due to differences in the length of follow-up or the fact that especially the retrospective studies have not necessarily controlled for the relative BMI at diagnosis. On the one hand, lower relative BMI at diagnosis has been associated with relatively more excess weight gain during treatment (Baillargeon et al. 2007, Razzouk et al. 2007, Arpe et al. 2015), but at the same time, being overweight at the time of diagnosis is a risk factor for being overweight or obese at the end of treatment (Razzouk et al. 2007, Asner et al. 2008, Esbenshade et al. 2011). It also seems that as there are great discrepancies in the prevalence of overweight and obesity in the population between different countries or different states of the USA, the proportion of overweight and obesity at the time of diagnosis varies greatly between the studies, possibly interfering with the conclusions (Reilly et al. 2000, Chow et al. 2007, Asner et al. 2008, Surapolchai et al. 2010, Breene et al. 2011, Esbenshade et al. 2011, Love et al. 2011).

In addition to the differences in prevalence of overweight and obesity in different countries, somewhat different criteria have been used in defining overweight and obesity in children and adolescents ($\geq 85^{th}$ percentile and $\geq 95^{th}$ percentile in the USA vs $\geq 95^{th}$ percentile and $\geq 97{,}5^{th}$ percentile in Switzerland vs BMI Standard Deviation Score 1.3-2.3 and >2.3 in the UK). Thus, there is some variation in the percentages of overweight and obesity at the end of treatment or follow-up reported in Europe and the USA (Jarfelt et al. 2005, Asner et al. 2008, Garmey et al. 2008, Breene et al. 2011, Esbenshade et al.

2011). Approximately 47–67 % of the long-term survivors have been reported to be overweight or obese and 17–32 % obese (Asner et al. 2008, Garmey et al. 2008, Breene et al. 2011), but somewhat smaller numbers have also been reported. For example, in a Swedish study 34 % of the survivors were overweight and none were obese after a median follow-up time of 20 years from diagnosis, but the proportion of survivors with BMI above +2SD was 22 %, thus greatly exceeding the expected frequency of 2.5 % (Jarfelt et al. 2005). It is also noteworthy that in the Swiss study most of the overweight and obese survivors had gained their excess weight only after cessation of therapy (Asner et al. 2008) contradicting the findings from e.g. UK (Breene et al. 2011, Harper et al. 2013).

In addition to the effects of age at diagnosis, female gender has been suggested as a risk factor for overweight and obesity after treatment, especially in the older studies where CRT was more commonly used (Warner et al. 2002, Oeffinger et al. 2003, Chow et al. 2007, Garmey et al. 2008, Breene et al. 2011, Veringa et al. 2012), but not all studies have supported this (Nysom et al. 1999, Sklar et al. 2000, Jarfelt et al. 2005, Nathan et al. 2006, Razzouk et al. 2007, Nottage et al. 2014). In addition, some of the more recent studies with a shorter follow-up have also suggested the opposite with a greater proportion of males being overweight during or after treatment (Esbenshade et al. 2011, Love et al. 2011, Arpe et al. 2015), but long-term data for these studies is still lacking. Interestingly, Harper et al. (2013) suggested that in contrast to the increase in weight standard deviation scores in chemotherapy-only treated females, in males the initial increase in relative BMI is mostly explained by a reduction in the height standard deviation score, and according to their preliminary data, this effect in males seems to resolve by final height (Harper et al. 2013). While many studies have concluded that CRT increases the risk for overweight and obesity after ALL treatment (Nysom et al. 1999, Mayer et al. 2000, Sklar et al. 2000, Warner et al. 2002, Oeffinger et al. 2003, Garmey et al. 2008, Geenen et al. 2010, Nottage et al. 2014), studies on chemotherapy-only treated patients have also shown excess weight gain during treatment (Breene et al. 2011). In addition, one of the more recent studies has even suggested that high risk patients treated with CRT may be even less overweight than the chemotherapy-only treated patients at the end of treatment (Esbenshade et al. 2011). However, this may be due to other disease- and treatment-related factors, and may of course be reversed in the long run.

2.2.1.2 Other cardiovascular disease risk factors

In addition to overweight and obesity, other cardiovascular disease risk factors (CVRF) have been subjects of interest in many studies. Many of the studies have used either the number of the components of metabolic syndrome (MetS; Table 2) and the thresholds defined in the definitions of the MetS (Alberti et al. 2009), or the diagnosis of hypertension, dyslipidemia, and diabetes. In addition, many studies have used the homeostasis model assessment for insulin resistance (HOMA-IR), calculated according

to the Matthew's formula (insulin (mU/L) x glucose (mmol/L)/22.5) (Matthews et al. 1985), as a measure for insulin resistance.

Table 2 Criteria for the metabolic syndrome

Waist circumference	≥ 94 cm for males and ≥ 80 cm for females
Triglycerides	≥ 1.7 mmol/l or medication
High density lipoprotein	< 1.0 mmol/l in males and < 1.3 mmol/l in females or medication
Blood pressure	Systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg or medication
Elevated fasting glucose	≥ 5.6 mmol/l or medication

According to Alberti et al. 2009, presence of ≥ 3 of these criteria constitutes the metabolic syndrome

Based on self-reports from the CCSS, ALL survivors are more likely than siblings to take medication for hypertension or diabetes (Meacham et al. 2010) which is a crude measure for increased CVRFs in ALL survivors. In the St. Jude Lifetime cohort of 784 ALL survivors, the prevalence of MetS was 33.6 % at the median age of 31.7 years (26.1 years since diagnosis), and all CVRFs except increased fasting glucose and LDL cholesterol were more common in ALL survivors than controls (Nottage et al. 2014). The prevalence of CVRFs has also been evaluated in smaller subsets of the CCSS. These studies have suggested a rather similar prevalence of 2 or more components of the MetS in ALL survivors and the control population (Gurney et al. 2006), as supported by a Dutch study as well (Geenen et al. 2010). However, in the CCSS subset, the prevalence of hypertension was more common in male survivors than controls, and abdominal obesity defined by increased waist circumference was more common in female survivors than controls (Gurney et al. 2006), as also supported by the St. Jude Lifetime cohort (Nottage et al. 2014). In the ALLIFE study of adult survivors of childhood ALL diagnosed between 1970 and 2000, survivors had significantly higher HOMA-IR than controls, but other CVRFs did not differ from those of the control population that was, on average, 10 years older than the survivors (Oeffinger et al. 2009). In general, the prevalence of multiple (≥2) CVRFs has been in the region of 30 % in long-term survivors of childhood ALL in the USA (Oeffinger et al. 2001, Gurney et al. 2006) while small studies have estimated that over 60 % of the survivors may have at least one CVRF (Oeffinger et al. 2001). The numbers in Europe may be somewhat lower, as in a French study, 26 % of ALL survivors had at least 1 component of the MetS and 20 % had multiple (Oudin et al. 2011). In addition, the prevalence of MetS in the control population may be lower in European studies (Oudin et al. 2011, Geenen et al. 2010) than American studies possibly explaining

the differences in prevalence in survivors as well. Nevertheless, it is possible that especially the comparisons that are based on cut-off values defined for adult populations may underestimate the importance of CVRFs in ALL survivors, as even the long-term survivors in many studies are only adolescents and young adults, and some of the studies have associated higher risk of MetS with an older attained age at the study time (Chow et al. 2010, Surapolchai et al. 2010, Nottage et al. 2014). In addition to categorizing the CVRFs as components of the MetS, Steinberger et al. (2012) compared the CVRFs as continuous variables between childhood cancer survivors and siblings. They found that despite similar prevalence of the MetS, already at a mean time of 10 years from the diagnosis, leukaemia survivors had higher adiposity, waist circumference, total and LDL cholesterol as well as lower insulin sensitivity than the controls, and they were also significantly shorter at that time (Steinberger et al. 2012).

In a subset from the CCSS, a history of CRT substantially increased the risk for low peak growth hormone levels in stimulation tests, increased waist circumference, fasting insulin, HOMA-IR, dyslipidemia and multiple components of the MetS in ALL survivors, and increased the prevalence of multiple MetS components from 20 % in non-irradiated subjects to 60 % in the CRT group (Gurney et al. 2006). The role of CRT has been supported in numerous studies (Nysom et al. 1999, Oeffinger et al. 2001, Link et al. 2004, Oeffinger et al. 2009, Geenen et al. 2010, Veringa et al. 2012, Nottage et al. 2014), but not all studies have found this association (Oudin et al. 2011). While some studies have found negative associations between growth hormone levels and various CVRFs in CRT treated survivors (Link et al. 2004), it seems possible that changes in treatment regimens towards more intensive chemotherapy and limited use of CRT have changed CRTs role as a risk factor in patients treated with more recent protocols, and other factors than growth hormone deficiency may explain the excess in CVRFs in survivors treated with chemotherapy only. Similarly, female gender has been suggested as a risk factor for other CVRFs than obesity as well (Nysom et al. 1999, Gurney et al. 2006, Chow et al. 2007, Oeffinger et al. 2009), but not all studies have supported this (Jarfelt et al. 2005, Nottage et al. 2014).

While the role of CRT has decreased during the past decades, HSCT, especially with total body irradiation conditioning, has emerged as an additional risk for CVRFs compared to standard treatment without irradiation (Taskinen 2000, Steffens et al. 2008, Chow et al. 2010, Armenian et al. 2011, Oudin et al. 2011), and MetS seems to be associated with insufficient growth hormone secretion after HSCT (Taskinen et al. 2007). Taskinen et al. (2000) studied 23 HSCT survivors (15 ALL, median age 20.4 years), and found increased prevalence of hyperinsulinaemia, abnormal glucose metabolism, hypertriglyceridaemia, low HDL and abdominal obesity compared to healthy controls or ALL survivors treated without HSCT. The prevalence of hyperinsulinaemia was 52 % among HSCT survivors, 31 % among ALL non-HSCT group and 0 % in healthy controls while the numbers for hyperinsulinaemia and hypertriglyceridemia combined were 39 %, 8 % and 0 %, respectively (Taskinen et al. 2000). A more recent study in younger ALL survivors

(median age 15 years) supported their findings suggesting that after total body irradiation based HSCT, waist-to-hip ratio, fasting insulin, HOMA-IR, triglycerides and HDL cholesterol were significantly worse compared to ALL survivors treated with conventional therapy (Chow et al. 2010). The proportion of survivors with multiple components of the MetS in their study was 53.9 % in HSCT treated patients and 20.9 % in conventionally treated ALL survivors at median age of 15 years while the risk for MetS was even 16-fold after HSCT compared to conventional therapy (Chow et al. 2010).

2.2.2 Cardiac effects of the treatment

Cardiotoxicity from chemotherapy is especially important in children as the heart has to respond to the child's growth and the expected survival time may be decades longer than in adult cancer patients. Thus, even mild injury to myocardiocytes from chemotherapy during childhood may become significant in later life. Anthracyclines (e.g. doxorubicin and daunorubicin) are the most common and best acknowledged causes of cancer therapy-related cardiotoxicity leading to congestive heart failure (CHF). However, radiation to the chest may also contribute to cardiac toxicity of cancer treatment, and some studies have associated cardiotoxicity with alkylating agents (e.g. cyclophosphamide, cisplatin) as well, as reviewed by Simbre et al. (2005). Of the chemotherapeutic agents used in treatment of childhood ALL, also vincristine, cytarabine and asparaginase have been associated with cardiac effects, but the mechanisms are more poorly understood (Simbre et al. 2005).

Anthracyclines are known to cause cardiac toxicity which may manifest as acute presenting within hours or days after administration, early-onset presenting within one year of treatment, or late-onset cardiotoxicity presenting over 1 year after treatment (Barry et al. 2007). Even though acute cardiotoxicity is very rare, even fatal ventricular arrhythmias and CHF are possible during anthracycline treatment (Adams, Lipshultz 2005). However, the most common form of anthracycline cardiac toxicity (ACT) is the late-onset ACT which originates in subtle damage to myocardiocytes during anthracycline therapy. Late anthracycline cardiac toxicity may not manifest until decades after treatment (Mulrooney et al. 2009, Adams, Lipshultz 2005), and generally, survivors treated with higher cumulative doses are considered to be at increased risk for ACT (Lipshultz et al. 1991, Lipshultz et al. 1995, Krischer et al. 1997, Sorensen et al. 2003, Lipshultz et al. 2005, van Dalen et al. 2006, Hudson et al. 2007, Mulrooney et al. 2009, van der Pal et al. 2010).

2.2.2.1 Incidence and risk factors for anthracycline cardiac toxicity

There is considerable variation between studies in the reported incidences of clinical congestive heart failure (CHF) after childhood cancer, as the studies have included

survivors with a variety of cancer diagnoses treated with variable anthracycline and radiation doses. In children treated for any cancer, cumulative incidences of approximately 2–4 % for CHF have been reported at 20 years after diagnosis (Kero et al. 2014, van der Pal et al. 2012), and 7.5 % at 30 years after diagnosis (van der Pal et al. 2012). However, in children treated with cumulative anthracycline doses ≥ 300 mg/m², the cumulative incidence has been estimated to be around 10 % at 20 years after diagnosis (van Dalen et al. 2006), and there seems to be no plateau with increasing follow-up time (van Dalen et al. 2006, Kero et al. 2014). In leukaemia survivors, the hazard ratio for CHF compared to siblings ranges from 4.2 to 6.6 depending on the study (Mulrooney et al. 2009, Kero et al. 2014).

It has been stated that the incidence of CHF increases exponentially with increasing anthracycline doses (van der Pal et al. 2012), but there may be other factors than dose alone that modify the risk. Some patients seem to be susceptible to smaller anthracycline doses. Even cumulative doses as low as 45–100 mg/m2 may cause late cardiotoxicity in some individuals (Lipshultz et al. 1991, Lipshultz et al. 2005, Hudson et al. 2007), and clinical studies have shown impaired cardiac measures compared to controls also in asymptomatic childhood cancer survivors treated with low anthracycline doses (Lipshultz et al. 1991, Hudson et al. 2007, van der Pal et al. 2010). It is clear that studies evaluating the incidence of clinical CHF may underestimate the importance of ACT, as subtle changes may be seen in asymptomatic survivors years before the clinical manifestations. Thus, it may well be that no safe dose exists at all (Lipshultz et al. 1991, Lipshultz et al. 2005, van der Pal et al. 2010).

In addition to the effects of anthracycline dose, female sex (Lipshultz et al. 1995, Krischer et al. 1997) and younger age at diagnosis (Lipshultz et al. 1991, Lipshultz et al. 1995, Sorensen et al. 2003, Dorup et al. 2004, Mulrooney et al. 2009, van der Pal et al. 2010) have been associated with higher risk of anthracycline cardiotoxicity. Furthermore, it has been suggested that certain genetic factors are associated with increased risk of cardiotoxicity already with small or moderate anthracycline doses (101-150 mg/m2) (Blanco et al. 2012), and the risk for ACT seems to vary greatly between different genotypes (Visscher et al. 2012).

2.2.2.2 Mechanism of anthracycline cardiac toxicity

The mechanisms of anthracycline induced cardiotoxicity are not yet fully understood, and several mechanisms have been proposed (Barry et al. 2007). The use of anthracyclines causes formation of oxygen-free radicals that damage cardiac myocytes through various mechanisms, and this may lead to loss of myofibrillar content and vacuolar degeneration, apoptosis, and ultimately myocardial necrosis and fibrosis (Adams, Lipshultz 2005, Berry, Jorden 2005, Barry et al. 2007). Eventually, these changes lead to thinning of the

left ventricular (LV) wall causing increased wall stress and afterload, and decreased myocardial contractility (Adams, Lipshultz 2005, Berry, Jorden 2005, Barry et al. 2007).

Loss of myocardiocytes during anthracycline therapy and decreased collagen production in the myocardiocytes are thought to lead to enlargement of the remaining myocardiocytes (Lipshultz et al. 1991, Muszynska et al. 2001, Lipshultz et al. 2005). It has been suggested that during the first years after treatment, this results in a close to normal myocardial mass in relation to body surface area, and echocardiographic measures remain normal (Barry et al. 2007). During longer follow-up time, however, the LV mass may not be able to grow adequately as the child grows, causing reduction in the LV thickness-dimension ratio and an increase in afterload (Lipshultz et al. 1991, Lipshultz et al. 2005). This inadequate growth may be of more significance in younger patients and it may well be the explanation for greater susceptibility for late CHF in younger patients as younger age at diagnosis associates with decreased LV wall thickness and LV mass in long-term follow-up (Lipshultz et al. 1995). The decrease in contractility is suggested to be partly due to the thinning LV and elevated afterload, and partly due to the irreversible damage to mitochondrial function, calcium homeostasis mechanisms and contractile system of the myocardiocytes caused by the anthracycline therapy (Lipshultz et al. 1991, Lipshultz et al. 1995, De Beer et al. 2001, Jung, Reszka 2001, Zhou et al. 2001, Lipshultz et al. 2005). Together, these mechanisms explain the development of late and very late CHF after anthracycline treatment in childhood (Lipshultz et al. 2005, Barry et al. 2007).

Lipshultz et al. (2005) showed that despite the improving values during the first years after doxorubicin therapy for childhood ALL, long-term follow-up shows decreased LV mass, increased afterload, and progressive deficits in LV contractility (Lipshultz et al. 2005). It should also be noted that late anthracycline cardiotoxicity often presents as diastolic dysfunction, and CHF can be present even with mild systolic dysfunction or preserved EF (Barry et al. 2007). The clinical course of anthracycline cardiotoxity in survivors of childhood ALL seems to be from dilated cardiomyopathy at the early stage to restrictive cardiomyopathy with abnormal diastolic function and elevated LV filling pressure at the later stage (Lipshultz et al. 1991, Adams, Lipshultz 2005, Lipshultz et al. 2005).

2.3 Endothelial function as an early marker of cardiovascular disease

The arterial wall consists of three layers: intima, media and adventitia. The intima layer includes the endothelium, a monolayer of endothelial cells that plays an essential role in the regulation of vascular tone (Kuvin, Karas 2003) while the media layer contains elastic fibres essential for the cushioning effect needed to generate continuous blood flow (Safar et al. 2003). The endothelial layer has the potential to release various vasoactive substances like nitric oxide, endothelin, prostacyclin, and angiotensinogen, and it also takes part in the processes of cell proliferation, thrombosis, inflammation, and oxidation

(Kuvin, Karas 2003). In healthy arteries, administration of endothelium dependent vasodilators, such as acetylcholine and bradykinin, or increasing shear stress by increasing blood flow causes an increase in the production of endothelium derived vasodilator factors like nitric oxide (Widlansky et al. 2003).

Atherosclerotic arteries lose their ability to dilate normally in response to increased blood flow or administration of acetylcholine (Nabel et al. 1990). This reduced response is also seen in angiographically clean arteries of atherosclerotic patients (Nabel et al. 1990). At the same time, the dilatation response via smooth muscle relaxation caused by nitroglycerin in these arteries remains (Nabel et al. 1990). Thus, the current understanding is that the loss of endothelium-dependent vasodilatation is an early step in the atherosclerotic process (Kuvin, Karas 2003, Widlansky et al. 2003).

Structural changes in the arterial wall can be measured non-invasively e.g. by measuring carotid intima media thickness (IMT) with ultrasound. Celermajer et al. (1992) described brachial artery flow mediated dilatation (FMD) as a non-invasive tool for early detection of endothelial dysfunction in children and adults at risk for atherosclerosis (Celermajer et al. 1992), and guidelines for the ultrasound assessment of brachial FMD were published in 2002 (Corretti et al. 2002). For example, the Cardiovascular Risk in Young Finns Study and the Special Turku Coronary Risk Factor Intervention Project have further developed the paradigm and produced a vast amount of data regarding non-invasively evaluated endothelial structure and function in healthy children, adolescents and young adults as well as the relationship between CVRFs and measures of vascular endothelial structure and function, as reviewed by Magnussen et al. (2012) and Juonala et al. (2013). A simplified illustration of FMD measurement is presented in Figure 3.

According to the Cardiovascular Risk in Young Finns Study, CVRFs present in childhood are predictive of measures of endothelial structure and function in adulthood (Magnussen et al. 2012, Juonala et al. 2013). Moreover, the role of childhood risk factors is also supported by findings on the correlations of metabolic risk factors and arterial pulse contour analysis-derived stiffness index, found already in children aged 6–8 years (Veijalainen et al. 2013). Furthermore, studies in older adults have suggested that carotid IMT (Lorenz et al. 2007) and endothelial dysfunction measured with brachial FMD may predict later cardiovascular events (Yeboah et al. 2007, Yeboah et al. 2009).

The presence of cardiovascular risk factors initiates a chronic inflammatory process, which with time causes the vascular endothelium to lose its normal regulatory functions such as vasodilator and anti-thrombotic factors (Widlansky et al. 2003). It has also been stated that insulin resistance and endothelial dysfunction may be the linking factors between metabolic and cardiovascular disease, as they seem to have a reciprocal relationship (Kim et al. 2006). In addition to the effects of CVRFs on vascular endothelium, cancer chemotherapy (e.g. anthracyclines, cisplatin, methotrexate) has been suggested to have direct toxic effects on vascular endothelium (Murata et al. 2001, Wu et

al. 2002, Nuver et al. 2005, Oeffinger 2008) potentially increasing the role of endothelial dysfunction in the development of MetS and CVD in childhood cancer survivors.

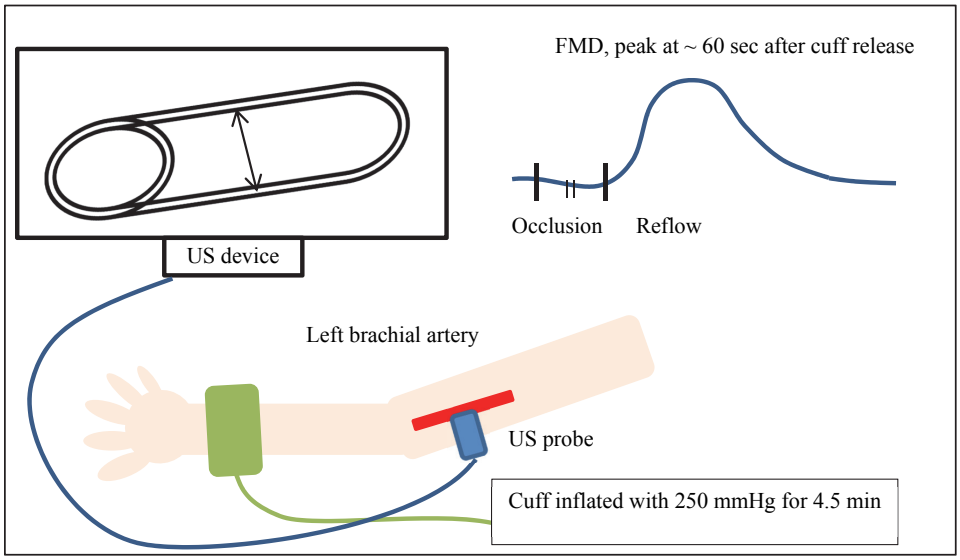

Figure 3 Simplified illustration of measuring flow mediated dilation. FMD=Flow mediated dilation; US=Ultrasonography; (Modified from Shimokawa 2000, IS096 Keynote Lecture: Clinical Assessment of Endothelial Function, 64th Scientific session of the Japanese Circulation society, http://www.j-circ.or.jp/english/sessions/reports/64th-ss/shimokawa.htm)

Doxorubicin has been shown to cause apoptosis of vascular endothelial cells (Murata et al. 2001, Wu et al. 2002), and it has been suggested that the chemotherapy-induced changes in the vessel wall could lead to permanent deficits in vascular endothelial function (Dengel et al. 2008). In adults, cisplatin-based chemotherapy for testicular cancer caused a significant increase in carotid IMT but did not affect brachial FMD (Nuver et al. 2005). At the same time, the plasma von Willebrandt factor level increased, which is suggestive of damage to endothelial cells by cisplatin therapy (Nuver et al. 2005). While it seems clear that radiation to the neck may have direct effects on carotid IMT (King et al. 1999, Meeske et al. 2009), Brouwer et al. (2013) found that childhood cancer survivors treated with radiation to the neck or chest areas also had increased femoral IMT (Brouwer et al. 2013). With these studies in mind, endothelial structure and function, as intermediate markers of atherosclerosis, could be useful tools in evaluating cardiovascular risk in childhood ALL survivors.

A small number of studies have evaluated endothelial structure and function, mainly carotid IMT and brachial FMD, after childhood ALL (Oeffinger et al. 2001, Link et al.

2004, Dengel et al. 2008, Jang et al. 2013) and there are no previous studies on the effects of interventions on these measures in ALL survivors. Oeffinger et al. (2001) studied IMT in 26 ALL survivors at a mean age of 20.6 years and found no difference in IMT between the survivors treated with CRT or chemotherapy only, but no comparison to healthy controls was made (Oeffinger et al. 2001). Link et al. (2004) studied IMT in 29 ALL survivors treated with CRT and found increased IMT compared to controls at right carotid bifurcation (Link et al. 2004). Dengel et al. (2008) studied endothelial function in 75 young adult survivors of childhood ALL and found a significantly smaller peak FMD in survivors than controls, and the results were similar in survivors treated with CRT and chemotherapy only (Dengel et al. 2008). The only study focusing on children shortly after anthracycline treatment for ALL also reported attenuated FMD compared to controls at 2–85 month after the last anthracycline dose (mean cumulative dose 142.5 ± 18.2 mg/m^2) (Jang et al. 2013). Based on measurements of both FMD and sublingual nitroglycerin-induced endothelium-independent dilatation, Dengel et al. (2008) concluded that the poorer response in survivors is solely due to endothelial dysfunction as opposed to a decline in smooth muscle function (Dengel et al. 2008).

2.4 Physical activity and fitness after childhood acute lymphoblastic leukaemia

In addition to the possible direct effects of ALL treatment on the heart, muscles, nervous system and endocrine functions, sedentary lifestyle during and after ALL treatment may contribute to the development of overweight and other cardiovascular risk factors, mobility limitations, fatigue, poor physical fitness as well as impaired quality of life in ALL survivors (Ness et al. 2011). The Childhood Cancer Survivors Study has shown that adult survivors of childhood ALL are less likely than their siblings or the general population to meet the physical activity recommendations and more likely to lead an inactive lifestyle (Florin et al. 2007, Ness et al. 2009). Risk factors for inactive lifestyle in the CCSS included CRT treatment, female sex, older attained age, black race, underweight, obesity, lower educational level, smoking and current depression (Ness et al. 2009). Generally, studies on physical activity and fitness in ALL survivors are relatively small and variable in methodology and timing, but larger, controlled studies have been recently published (Ness et al. 2015). Studies on PA and fitness after childhood ALL are summarised in Table 3 and Table 4.

In the CCSS cohort, levels of PA were compared to the recommendations of Centers for Disease Control and Prevention (Adults: ≥ 30 min of moderate PA ≥ 5 times a week or vigorous activity ≥ 20 min ≥ 3 times a week) (Pate et al. 1995, Florin et al. 2007, Ness et al. 2009). Based on these criteria, 53 % of ALL survivors and 48 % of controls did not meet the CDC recommendations and 23 % of the survivors reported no PA during the preceding month (vs 20 % of the controls). Female gender was considered a risk factor for sedentary

lifestyle, as 58 % of the female survivors did not meet the recommendations and 25 % reported no PA (Florin et al. 2007, Ness et al. 2009). Based on different criteria, smaller studies from the USA have reported 35–67 % of survivors being sedentary (Prestor et al. 2000, Oeffinger et al. 2001). A Swedish study, however, reported similar levels of PA in ALL survivors and controls (Follin et al. 2010), but comparisons to the American studies are not made as data on number of sedentary subjects is lacking. Only seven of the studies in adult survivors have examined fitness compared to control subjects or reference values reporting attenuated exercise capacity and knee extensor strength as well as impaired performance in various tests of mobility (Prestor et al. 2000, Bär et al. 2007, Ness et al. 2007, Ness et al. 2012, Tonorezos et al. 2013, Christiansen et al. 2015, Ness et al. 2015).

Studies on younger survivors including also children and adolescents have relatively mixed results: While some have reported similar levels of PA compared to controls (Heath et al. 2010), others have reported attenuated levels of PA especially in CRT treated survivors (Warner et al. 1998, Mayer et al. 2000), but also in those treated with chemotherapy only (Tillmann et al. 2002). In the study by Bertorello et al. (2011), as many as 39 % of the survivors reported having no PA (Bertorello et al. 2011). In a Finnish study by Taskinen et al. (2013), the majority (58 %) of ALL survivors treated without CRT or HSCT exercised < 1 time a week and only 22 % exercised regularly (> 3 times a week). None of the ALL survivors treated with HSCT exercised regularly in this study (Taskinen et al. 2013).

A variety of fitness measures have been used in the studies, including maximal exercise tests to measure exercise capacity (peak oxygen uptake VO_{2peak}; ml/kg/min) as well as measures of muscle strength and motor performance, motor function and mobility measures, and some of the variation in selected tests is likely to be due to the broad age range of the participants (Table 4). Studies with a broader age range or older survivors have found reduced exercise capacity compared to control subjects (Warner et al. 1997, Bell et al. 2006, Bär et al. 2007, Tonorezos et al. 2013, Ness et al. 2015) or normal values (Lipshultz et al. 1991, Turner Gomes et al. 1996, Prestor et al. 2000, van Brussel et al. 2006, Christiansen et al. 2015), but two studies on only children have not supported this (Hauser et al. 2001, Bär et al. 2007). However, most of these studies are rather small, and in addition to differences in methodology, there is great variability in the time since diagnosis and the attained age at the study time, which most likely affects the conclusions between the studies. In addition, despite a general effect, some have suggested reduced exercise capacity in only certain subgroups of survivors (Hauser et al. 2001). According to a meta-analysis of 102 ALL survivors aged 7–19 years, physical fitness as measured with maximal exercise testing is attenuated in ALL survivors and compared to siblings, the reduction in peak oxygen uptake (VO_{2peak}) is estimated to be about 13 % (~ 6 ml/kg/min) (van Brussel et al. 2005). However, most of the existing studies were excluded from the meta-analysis mainly due to incomplete description of methodology (van Brussel et al. 2005) (Table 4).

Of the studies focusing on muscle strength, motor performance, motor function and mobility tests, three reports including only adult survivors of childhood ALL found e.g. attenuated knee extensor strength, timed up-and-go time, ankle dorsiflexion range and 2- and 6-minute walk test results (Ness et al. 2007, Ness et al. 2012, Ness et al. 2015). Hand grip strength in the study by Ness et al. (2007) was normal, but in that study, CRT associated with impaired strength in females (Ness et al. 2007), and various other treatment-related factors have been associated with impaired fitness as well (Ness et al. 2015).

Studies with children among the studied survivors have shown attenuations in e.g. strength, balance, running speed and agility domains, hand grip strength, passive ankle dorsiflexion range, knee extensor strength, timed up-and-go test and ball skills/hand-eye coordination domains of the Movement ABC (Wright et al. 1998, Wright e al. 2005, van Brussel et al. 2006, Akyay et al. 2014), while others have reported normal results in the gross motor function tests and muscle strength (Wright et al. 1998, Taskinen et al. 2013, Akyay et al. 2014). Results on hand grip strength have been mixed (Wright et al. 1998, Akyay et al. 2014), and in one study, attenuated muscle strength was seen only in HSCT survivors (Taskinen et al. 2013). Of these studies, only one concluded that CRT associated with poorer balance (Wright et al. 2005), but in the rest of the studies, CRT either had no effect on muscle strength and motor performance/function or conclusions could not be made due to uniform treatment or lack of comparisons between treatment groups (Table 4).

In contrast to the findings of Wright et al. (2005) indicating a negative association between time since treatment and balance, Hartman et al. (2013) found that motor performance and passive ankle dorsiflexion range improved with increasing time after completion of treatment indicating a recovery after returning to normal daily life. However, Florin et al. (2007) and Ness et al. (2009) suggested that older attained age associates with decreased PA in adult survivors, but this seems to be the case in the general population as well (Florin et al. 2007, Ness et al. 2009). Heath et al. (2010) also had similar findings in children after ALL.

Results of the studies on physical activity and fitness in ALL survivors are summarised in Table 3 and Table 4. Some studies including leukaemia survivors did not differentiate between ALL and other leukaemias or reported results only for mixed cancer populations, and these are not included in the tables (Hovi et al. 1993, Matthys et al. 1993, Sharkey et al. 1993, Jenney et al. 1995, Pihkala et al. 1995, Black et al. 1998, Zalewska Szewczyk et al. 1999, Hogarty et al. 2000, Demark Wahnefried et al. 2005, De Caro et al. 2006, Keats et al. 2006, Tercyak et al. 2006, Finnegan et al. 2007, Reeves et al. 2007, Hartman et al. 2008, San Juan et al. 2008, Winter et al. 2009, Hovi et al. 2010, De Caro et al. 2011, Rueegg et al. 2012, Hoffman 2013, Miller et al. 2013, Slater et al. 2015). Studies performed during active treatment are not included in the tables either.

Table 3 Summary of the main findings from studies on physical activity in survivors of childhood ALL

Study	N	Diagnosis	Number of CRT treated	Age at Study	Timing of the study[3]	Controls	Physical Activity Measures	Results	Gender Effect	CRT Effect
Bertorello 2011	95	ALL	Not reported	10–30y	Long-term survivors	No	Questionnaire	61 % reported doing PA (14 % >3 times a week), 39 % reported no PA	No	No
Florin 2007[1]	2648	ALL	1473 (65 %)[4]	18.0–44.0y	Long-term survivors	No (general population)	Self-report (CDC[5] recommendations)	More likely not to meet CDC[5] recommendations for PA (53 % vs 48 %); More likely to be inactive (23 % vs 20 %)	Females more at risk	Increases risk
Follin 2010	29	ALL (GH deficient),16 received GH for 5y	All CRT	22–32y (non-GH 19–32y)	Long-term survivors	29 healthy controls	Four-grade questionnaire	PA remained similar in both groups during follow-up. No difference to controls	Not studied	Not studied
Hansen 2014[2]	98	Mixed, 50 ALL	7 (14 %)	12.2–17.9y	After treatment	No	Self-report (CDC[5] recommendations)	12 % met the CDC[5] recommendations on PA for for children	Males more active	Not studied
Heath 2010	19	ALL	No CRT	6.3–15.8y	After treatment	No (normal values)	Actigraph (2 weekdays and 2 weekend days)	Individual mean daily MVPA 28-286 min (average 141 min close to healthy), average < 60min/day in 3/19	MVPA higher in males	NA
Jarfelt 2006	35	ALL	19 (54 %)	20–32y	Long-term survivors	No	Questionnaire	No difference between CRT and nonCRT-treated; 53 % of males and 44 % of females reported < 1 physical activity session weekly	Not studied	No
Mayer 2000	39	ALL	25 (64 %)	10.7–20.5y	After treatment	35 healthy controls	Questionnaire	PA attenuated only in CRT treated	Not studied	Increases risk

Study	N	Diagnosis	Number of CRT treated	Age at Study	Timing of the study[3]	Controls	Physical Activity Measures	Results	Gender Effect	CRT Effect
Ness 2009[1, 2]	9301	Mixed, 2734 ALL	Not clearly stated	≥ 18 years	Long-term survivors	2886 siblings and the general population	Questionnaire (CDC[5] recommendations; inactive = no leisure-time PA during the past month.	More likely not to meet CDC[5] recommendations (ALL males 48 % vs 46 %; ALL females 58 % vs 50 %); More likely to be inactive (ALL males 21 % vs 14 %; ALL females 25 % vs 14 %)	Females more at risk	Increased risk
Ness 2015	365	ALL	149 (41 %)	28.6 ± 5.9y	Long-term survivors	365 healthy controls	Daily levels of MVPA evaluated with actigraphs	Daily MVPA lower in CRT and nonCRT compared to controls (15±13, 17±14 and 21±18 min/day)	Not studied	No
Oeffinger 2001	26	ALL	10 (38 %)	18–32y	Long-term survivors	No	Paffenbarger Physical Activity Index	35 % sedentary lifestyle	Not studied	No
Prestor 2000	46	ALL	All CRT	18–33y	Long-term survivors	No (normal values)	Asked about physical inactivity	67 % sedentary	Not studied	NA
Taskinen 2013	79	ALL (34 HSCT)	No CRT (TBI in HSCT)	9.2–20.1y (HSCT 9.0–30.0y)	Long-term survivors	522 healthy controls	Interview; 45 min of moderate activity equaled one session	58 % of non-HSCT exercised <1 time per week, 22% of non-HSCT exercised > 3 times a week (none of HSCT)	Not studied	NA
Tillmann 2002	28	ALL	No CRT	5.7–14.7y	After treatment	28 healthy controls	Questionnaire; 3-day accelerometer periods	Weekly PA lower in survivors; Accelerometer count correlated with questionnaire results	No	NA

Study	N	Diagnosis	Number of CRT treated	Age at Study	Timing of the study[3]	Controls	Physical Activity Measures	Results	Gender Effect	CRT Effect
Warner 1998[2]	56	Mixed, 35 ALL	All CRT	7.2–18.2y	After treatment	32 siblings	PA calculated as TDEE/BMR	PA level lower in ALL survivors than controls and other cancer survivors	Not studied	NA
Wright 2005	99	ALL	Not reported	5.1–25.2y	After treatment	89 healthy controls	CSAPPA	lower CSAPPA scores	Not Studied	Increases risk

BMR = Basal metabolic rate; CDC = Centers for Disease Control and prevention; CRT = Cranial radiation therapy; CSAPPA = Children's Self-perceptions of Adequacy in and Predilection for Physical Activity Scale; GH = Growth hormone; HSCT = Haematopoietic stem cell transplantation; MVPA = Moderate and vigorous physical activity; NA = Not applicable; PA = Physical Activity; TBI = Total body irradiation; TDEE = Total daily energy expenditure;
[1]Mostly overlapping studies from the same cohort; [2]Studies on mixed cancer populations were only included if they reported results separately for ALL survivors; [3]Long-term survivors ≥ 5 years since diagnosis; [4]Data on CRT not available for the whole cohort; [5]CDC recommendations: Children (6–17y) ≥60 min of MVPA daily. Adults (18–64y) ≥30 min of moderate PA ≥5 days a week or ≥20 min of vigorous activity ≥3 days a week (later revised to ≥150 minutes of moderate PA or ≥75 minutes of vigorous PA weekly, http://www.health.gov/paguidelines/)

Table 4 Summary of the main findings from studies on fitness in survivors of childhood ALL

Study	N	Diagnosis	Number of CRT treated	Age at Study	Timing of the study[4]	Controls	Type of fitness Test and Outcome	Results	Gender Effect	CRT Effect
Akyay 2014	18	ALL	17 (39 %)	5-21y	After treatment (2-60mo)	18 healthy controls	HGS; TUG	TUG attenuated; No difference in HGS	No	No
Bell 2006	35	ALL	All CRT	Boys 12.4 ± 3.4y; Girls 11.8 ± 3.7y	After treatment (≥ 1.5)	32 healthy controls	VO_{2peak}, treadmill-test; Perception of effort, the Childrens' effort rating table	VO_{2peak} attenuated (39.9 vs 47.6. in boys; 30.5 vs 41.3 ml/kg/min in girls). No difference in perception of effort at low and moderate intensity exercise.	No	NA
van Brussel 2006	13	ALL	No CRT	8.6-23.7y	Long-term survivors	No (normal values)	VO_{2peak}, maximal cycle ergometer test; Anaerobic capacity, Wingate aerobic exercise test; Muscle strength; Movement ABC	VO_{2peak}, anaerobic capacity and knee extensor strength attenuated. 7/13 had impaired results in Movement ABC ball skills/hand-eye-coordination domain	Not studied	Not studied
Bär 2007	19	ALL (all males, 9 children, 10 adults)	Not reported	9–15y; 20-28y	After treatment (children); Long-term survivors (adults)	29 healthy controls (adults divided in trained/ untrained	VO_{2peak}, maximal cycle ergometer test	Adults: VO_{2peak} attenuated (trained 46.75, untrained 32.8, survivors 24.4 ml/kg/min); Children: No difference (controls 28, survivors 31.15 ml/kg/min)	NA	Not studied
Christiansen 2015	138	ALL	20 (14 %)	18.6-46.5y	Long-term survivors	No (normal values)	VO_{2peak}, maximal cycle ergometer test	Anthracycline dose ≤120 mg/m2: VO_{2peak} attenuated in 48 %; Anthracycline dose 121-485mg/m^2: VO_{2peak} attenuated in 67 %	Not studied	Not studied

Study	N	Diagnosis	Number of CRT treated	Age at Study	Timing of the study[4]	Controls	Type of fitness Test and Outcome	Results	Gender Effect	CRT Effect
Hartman 2013	34	ALL	No CRT	9.0-18.7y	Long-term survivors	No (normal values)	Functional exercise capacity, 6MW (at the latest follow-up only); Movement ABC; Passive ADROM	6MW impaired; Motor performance improved from end of treatment to latest follow-up. Passive ADROM limited in 68 % at end of treatment and in 21% at the latest follow-up.	Not studied	Not studied
Hauser 2001[1]	38	ALL	Not reported	5.8 ± 2.3y	After treatment (≥ 6 mo)	38 healthy controls	VO_{2peak}, maximal treadmill test (estimated VO_2 at anaerobic treshold)	Normal stress echocardiography: No difference (49.5 vs 50.2 ml/kg/min). Abnormal stress echocardiography (10/38): attenuated VO_{2peak} (35.4 ml/kg/min) and anaerobic treshold	Not studied	Not studied
Jarfelt 2006	30	ALL	18 (60 %)	20–32y	Long-term survivors	No	METs, maximal exercise test on a treadmill (23) or cycle ergometer (7)	Lower exercise capacity in CRT vs nonCRT treated males and in GH deficient vs non-GH deficient males.	Not studied	In males
Lipshultz 1991[2]	115	ALL	Not reported	3.9-31.7y	After treatment (1-15y after last anthracycline)	No	Exercise duration, maximal treadmill test	Median exercise duration/expected duration was 80 %	Not studied	Not studied
Ness 2007	75	ALL	50 (67 %)	30.2 ± 7.1y	Long-term survivors	No (normal values)	VO_{2peak},DASI; Muscle strength; hand grip strength; Functional mobility, TUG and 2MW	Knee extensor strength, TUG time, 2MW and estimated VO_{2peak} attenuated	Females more at risk after CRT	In females

Study	N	Diagnosis	Number of CRT treated	Age at Study	Timing of the study[4]	Controls	Type of fitness Test and Outcome	Results	Gender Effect	CRT Effect
Ness 2012	415	ALL	110 (26.5%)	21.9-52.3y	Long-term survivors	No (normal values)	Walking efficiency, 6MW; Mobility, TUG; Active ADROM; Lower extremity muscle strength;	6MW attenuated in 46.5 %; 54.5 % had at least one physical performance limitation	Limited mobility more common in females	No
Ness 2015	365	ALL	149 (41 %)	28.6 ± 5.9y	Long-term survivors	365 healthy controls	Submaximal cardiopulmonary exercise test; Muscle strength; Flexibility; ADROM	Attenuated exercise capacity (-5.4 in CRT;-2.0 ml/kg/min in non-CRT), quadriceps strength/endurance, flexibility/ADROM	Not studied	Yes
Prestor 2000[2]	46	ALL	All CRT	18-33y	Long-term survivors	No (normal values)	Exercise work capacity, submaximal exercise tolerance test	Exercise capacity below expected in 48%	Not studied	NA
Taskinen 2013	79	ALL (34 HSCT)	No CRT (TBI in HSCT)	9.2-20.1y (HSCT 9.0-30.0y)	Long-term survivors	522 healthy controls	6 tests to assess muscle endurance, strength, flexibility and speed	Non-HSCT comparable to controls; HSCT inferior results in 4/6 of the muscle tests	Not studied	NA
Tonorezos 2013	115	ALL	39 (33.9 %)	18-37y	Long-term survivors	compared to population study	VO_{2peak}, maximal treadmill test	Attenuated VO_{2peak} (30.7 vs 39.9 ml/kg/min); 67 % with low fitness (26 % of control population).	No	In females

Study	N	Diagnosis	Number of CRT treated	Age at Study	Timing of the study[4]	Controls	Type of fitness Test and Outcome	Results	Gender Effect	CRT Effect
Turner-Gomes 1996[2]	19	ALL	Not reported	7.7-23.8y	After treatment (1.1-7.1y)	No (normal values)	Maximal exercise capacity, cycle ergometer test; Leg muscle function, 30-sec maximal effort on an isokinetic cycle ergometer	12/19 completed the test. Maximal attained capacity 67.5 ± 24.8 % of predicted.	Not studied	Not studied
Warner 1997[1, 3]	56	Mixed, 35 ALL	All CRT	7-19y	After treatment (≥1.5y)	32 siblings	VO_{2peak}, maximal treadmill test	VO_{2peak} attenuated (males 39.9 vs 47.6 ml/kg/min; females 30.5 vs 41.3 ml/kg/min).	No	NA
Wright 1998	36	ALL	29 (81 %)	5-14 y	After treatment (≥12 mo)	36 healthy controls	Motor Function, GMFM and BOTMP; HGS, blood pressure cuff; Passive ADROM	Attenuations in strength, balance, running speed and agility tests (BOTMP), impaired handgrip strength and passive ADROM	Not Studied	Not Studied

ADROM = Ankle dorsiflexion range of motion; BOTMP= Bruininks-Oseretsky Test for Motor Proficiency; CRT = Cranial radiation therapy; DASI= Duke Activity Status Index; GH = Growth hormone; GMFM = Gross Motor Function Measure Test; HGS = Handgrip strength; HSCT = Haematopoietic stem cell transplantation; MET = Multiple of the resting metabolic rate/Metabolic equivalent; NA = Not applicable; TBI = Total body irradiation; TUG = Timed up-and-go test; VO_{2peak} = Peak oxygen uptake; 2MW=2-minute walk test; 6MW=6-minute walk test;
[1]Included in the meta-analysis by van Brussel et al. (2005); [2]Excluded from the van Brussel et al. (2005) meta-analysis due to incomplete description of methodology; [3]Studies on mixed cancer populations were only included if they reported results separately for ALL survivors; [4]Long-term survivors ≥ 5 years since diagnosis;

2.4.1 Exercise interventions after childhood acute lymphoblastic leukaemia

There are no published studies on the effects of exercise interventions on PA or fitness in adult survivors of childhood ALL, and only one study focuses solely on younger survivors of childhood ALL describing the effects of an exercise intervention on fitness in children (Takken et al. 2009). Four other studies performed after completion of therapy have included other leukaemias or mixed cancer populations in addition to ALL survivors (Sharkey et al. 1993, San Juan et al. 2008, Keats, Culos-Reed 2008, Blaauwbroek et al. 2009), and 6 studies including only ALL patients were performed during maintenance treatment (Marchese et al. 2004, San Juan et al. 2007a, San Juan et al. 2007b, Moyer-Mileur et al. 2009, Perondi et al. 2012, Esbenshade et al. 2014). The details and results of these studies reporting on effects of intervention on PA or fitness are summarised in Table 5.

Three of these studies examined the effects of home-based exercise programmes (Blaauwbroek et al. 2009, Moyer-Mileur et al. 2009, Esbenshade et al. 2014). In the study by Blaauwbroek et al. (2009), 10 weeks of home-based exercise with pedometers and telephone counseling increased the number of daily steps by 54 % in survivors of mixed cancers (Blaauwbroek et al. 2009). Fatigue measures also improved in this study, but fitness was not measured (Blaauwbroek et al. 2009). The other two home-based interventions were conducted during maintenance treatment (Moyer-Mileur et al. 2009, Esbenshade 2014). In the study by Moyer-Mileur et al. (2009), aerobic fitness and PA improved in both the intervention and control group, while the intervention group performed better at 12 months (Moyer-Mileur et al. 2009). The remaining eight studies included a supervised or partly supervised exercise programme, but the only study performed on ALL survivors suffered greatly from poor adherence as only 4 of the 9 participants completed the programme and no differences were found after the intervention (Takken et al. 2009). The three supervised interventions on mixed cancer populations after treatment and four in ALL patients during maintenance treatment were able to show improvements in PA or at least some of the studied fitness tests (Sharkey et al. 1993, Keats, Culos-Reed 2008, Marchese e al. 2004, San Juan et al. 2007a, San Juan et al. 2007b, San Juan et al. 2008, Perondi et al. 2012, Tanir, Kuguoglu 2013), the results being at least partly maintained during a longer follow-up (San Juan et al. 2007b, Keats, Culos-Reed 2008) (Table 5).

Table 5 Summary of main finding from studies on exercise interventions after childhood ALL or during maintenance treatment

Study	N	Diagnosis	Age at Study	Timing of the study[2]	Controls	Setting	Type of intervention (Aerobic/Resistance)	Length of intervention	Results
Takken 2009	9	ALL	6-14y	After treatment (1-3 y)	No	Supervised and home-based	Mixed; 2 weekly 45 min session at local PT and ≥ 2 weekly home exercises	12 weeks	4/9 completed and included in the analyses. No change in muscle strength, VO_{2peak}, TUDS, TUG
Blaauwbroek 2009	46	Mixed, 22 leukaemias	18-61y	Long-term survivors	33 healthy controls	Home-based	Aerobic; Counseling to enhance daily PA. One home-visit, 3 telephone calls (weeks 3, 6 and 9). Pedometers 2 weeks at the beginning and weeks 4 and 10.	10 weeks with counseling; Additional follow-up at 36 weeks	78 % did not meet PA recommendations (≥ 150 min of MVPA per week). During intervention, daily steps increased 54 %, fatigue decreased; Improvements in fatigue remained at 36 weeks (did not change in controls)
Keats 2008	10	Mixed, 4 leukaemias	14-18y	After treatment (mean 5.2y since diagnosis)	No	Supervised	Mixed; Weekly group sessions (weeks 1-8: 30 min education, 45 min aerobic, 15 min strength/flexibility; weeks 9-16: 90 minutes of variable activities)	16 weeks; Follow-ups at 3 months postintervention and 12 mo from beginning.	First 8 weeks PA and 1-mile walk/run improved and remained above baseline at last follow-up. Upper body strength and flexibility increased for 16 weeks and remained above baseline
San Juan 2008	8	4 ALL, 4 AML (HSCT)	8-16y	After treatment (8.9 ± 4.5 mo from HSCT)	8 healthy controls (no intervention)	Supervised	Mixed; 3 group sessions per week, 90-120 min each at a hospital gym, duration and intensity increased gradually	8 weeks	TUDS and VO_{2peak} attenuated at baseline. TUDS, TUG, muscle strength and VO_{2peak} improved (25.9 to 31.1. ml/kg/min).

Study	N	Diagnosis	Age at Study	Timing of the study[2]	Controls	Setting	Type of intervention (Aerobic/Resistance)	Length of intervention	Results
Sharkey 1993	10	Mixed, 5 ALL	19± 3y	After treatment (≥ 1 y)	No	Supervised and home-based	Aerobic; Two sessions per week at the hospital; weeks 7-12 one additional 60 min session per week at home	12 weeks	Total exercise time increased significantly (13%). Mean VO_{2peak} increased 8 % (not significant)
Esbenshade 2014	17	ALL	5–10y	During maintenance	No	Home-based	Mixed;Flexibility, strength and balance exercises thrice weekly and general fitness activities thrice weekly (á 30–45 min), weekly phone calls	12 weeks	12/17 children completed intervention; Especially the mean values of flexibility (ADROM and sit and reach), HGS and 6MW improved (statistical testing not reported)
Marchese 2004	13	ALL	4.3-10.6y	During maintenance	15 ALL patients	Supervised and home-based	Mixed; 5 individual PT sessions (weeks 0, 2, 4, 8 and 12) and an individualized home-exercise programme	4 months	Knee extension strength and active ADROM improved; No difference between the groups in ankle dorsiflexion strength, TUDS, 9 min run-walk test
Moyer-Milleur 2009	6	ALL	4-10y	During maintenance	7 ALL patients	Home-based	Mixed; Individualized exercise programme (≥ 15-20 min MVPA ≥ 3 times a week), reviewed monthly	12 months (assesment every 3 months)	Number of PACER laps and PA increased baseline vs 12 mo; Percentual change different only for pedometer counts

Study	N	Diagnosis	Age at Study	Timing of the study[2]	Controls	Setting	Type of intervention (Aerobic/Resistance)	Length of intervention	Results
Perondi 2012	6	ALL	6–16	During maintenance	No	Supervised	Mixed; High-intensity strength exercises and aerobic exercises (á 1h, twice weekly)	12 weeks	Sub-maximal strength improved for bench-press, lat pull down, leg press and leg extension
San Juan 2007 a[1] and b[1]	7	ALL	4-7y	During maintenance	No	Supervised	Mixed; 3 group sessios per week, 90-120 min each at a hospital gym, duration and intensity increased gradually	16 weeks (+ follow-up after 20 weeks of detraining)	VO_{2peak}, muscle strength endurance, TUDS and TUG increased; Strength endurance remained improved after detraining, other results partially maintained.
Tanir 2013	19	ALL	8–12y	During maintenance	21 ALL patients	Supervised and home-based	Mixed; Active range of motion (3/day, 5 days/week), leg muscle strength (3/day, 3 days/week) and aerobic exercises (á 30 min, 3/week); Two home-visits, 4 phone calls	3 months	9MW, TUDS, TUG and leg strength improved in the intervention group

[1]Parts of the same study; [2] Long-term survivors ≥ 5 years since diagnosis; ADROM = Ankle dorsiflexion range of motion; BMT = Bone marrow transplantation; HGS=Hand grip strength; HSCT = Haematopoietic stem cell transplantation; MET = Multiple of the resting metabolic rate/Metabolic equivalent; MVPA = Moderate to vigorous physical activity; PA = Physical activity; PACER = Progressive Aerobic Cardiovasculr Endurance Run test; PT= Physical therapist; QOL = Quality of life; TUDS = timed up-an-down stairs test; TUG = timed up-and-go test; VO_{2peak} =Peak oxygen uptake; 6MW=6-minute walk test; 9MW=9 minute walk test;

3 OBJECTIVES OF THE STUDY

The objective of this thesis was to evaluate physical fitness, metabolic risk factors, endothelial function and cardiac function in long-term survivors of childhood ALL treated with Nordic treatment protocols since 1986, and to study the effects of an exercise intervention in this population. Such information is needed in order to plan appropriate follow-up care for the growing population of survivors of childhood ALL.

The specific study aims were:

1. To evaluate physical activity, fitness and traditional cardiovascular risk factors in long-term survivors of childhood ALL in comparison to healthy peers (I, III)

2. To evaluate endothelial function in long-term survivors of childhood ALL in comparison to healthy peers (III)

3. To evaluate cardiac function in long-term survivors of childhood ALL with conventional methods (Echocardiography, Tissue Doppler Imaging) and Velocity Vector Imaging to detect early signs of late anthracycline cardiotoxicity (IV)

4. To evaluate the effects of a home-based exercise intervention on physical activity, fitness, traditional cardiovascular risk factors and endothelial function in long-term survivors of childhood ALL (II, III)

5. To evaluate the effects of a home-based exercise intervention on tissue Doppler imaging measures and velocity vector imaging measures in long-term survivors of childhood ALL (IV)

4 MATERIALS AND METHODS

4.1 Subjects and study day

Local files of the NOPHO database were used to identify 16 to 30 year-old survivors of childhood ALL (age at diagnosis ≤16 y) from Turku and Tampere University Hospital districts. The inclusion criteria were diagnosis made in 1986 or later, treatment according to the Nordic regimen (Gustafsson et al. 2000), and first continuous remission without bone-marrow transplantation. Patients with Down's syndrome were excluded. Seventy-seven patients met these criteria and were invited to take part in this study. Twenty-one ALL survivors (27 % of the eligible cohort) participated in the clinical cross-sectional baseline study. A questionnaire was posted to the rest of the cohort for more information, for example, on how the participants represented the whole survivor cohort. Twenty-four ALL-survivors (43 % of the non-participants) returned the postal questionnaire (Figure 4). In addition, the representativeness of the sample was analysed with regard to information available from the local files of the NOPHO database (i.e. age, sex, age at diagnosis, treatment protocol, and treatment intensity).

The characteristics of the participating survivors are shown in Table 6. Twenty-one (10 males) childhood ALL long-term survivors were studied. The current age of the participants was 16–30 years. The diagnosis was set between 1986 and 1996 and possible treatment modifications were tracked from the patient files. The median time since diagnosis was 15.9 years (range 11.3–21.4 y). Age and sex matched controls (N=21) consisted of the patients' siblings (5/21), friends, and other non-athletic healthy adolescents and adults.

The study day was planned so as to be executable during one day. All the laboratory measures and ultrasound studies (vascular endothelium and echocardiography) were performed in the morning while the fitness tests were performed during afternoon, after an appropriate time from lunch (~2 hours).

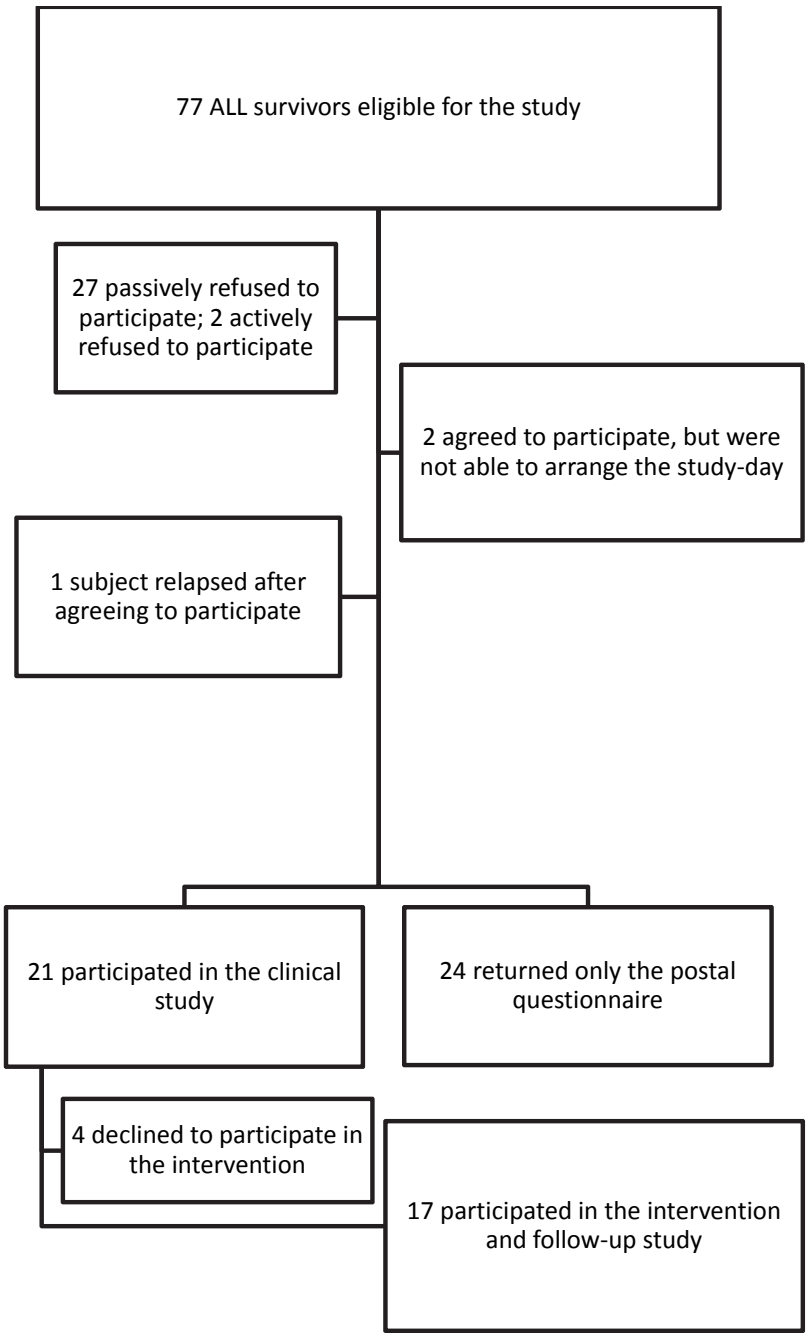

Figure 4 Flow chart of the study participants

Table 6 Characteristics of the ALL survivors participating in the study

Patient Number	Protocol	Risk group	Sex	Age (y)	Age at Diagnosis (y)	Time since Diagnosis (y)	Total Anthracycline Dose (mg/m2)	CRT	Participation in the Intervention
1	NOPHO 86	SR	female	21.2	3.8	17.4	120	no	yes
2	NOPHO 86	SR	female	21.7	5.4	16.4	120	no	yes
3	NOPHO 86	SR	female	26.7	5.3	21.4	120	no	yes
4	NOPHO 86	SR	male	20.2	3.8	16.4	120	no	yes
5	NOPHO 86	SR	male	20.5	3.3	17.2	120	no	no
6	NOPHO 86	SR	male	26.0	5.4	20.7	120	no	yes
7	NOPHO 86	IR	female	18.9	2.2	16.7	240	no	no
8	NOPHO 86	IR	female	24.9	3.5	21.4	240	yes	yes
9	NOPHO 86	IR	male	25.1	6.4	18.7	240	yes	yes
10	NOPHO 86	IR	male	30.3	12.6	17.6	240	yes	yes
11	NOPHO 92	SR	male	16.9	4.9	12.0	120	no	no
12	NOPHO 92	SR	male	19.6	4.7	14.9	120	no	yes
13	NOPHO 92	IR	female	16.7	2.8	13.9	240	no	no
14	NOPHO 92	IR	female	17.0	2.3	14.7	240	no	yes
15	NOPHO 92	IR	female	21.5	5.6	15.9	240	no	yes
16	NOPHO 92	IR	female	24.1	12.9	11.3	240	no	yes
17	NOPHO 92	IR	female	28.2	12.7	15.5	240	no	yes
18	NOPHO 92	IR	male	17.9	2.3	15.6	240	no	yes
19	NOPHO 92	HR	female	22.8	7.0	15.8	370	yes	yes
20	NOPHO 92	HR	male	16.9	1.6	15.3	340	no	yes
21	NOPHO 92	HR	male	26.5	12.1	14.4	370	yes	yes

CRT= Cranial Radiation Therapy; HR= High risk treatment; IR=Intermediate risk treatment; SR=Standard risk treatment. For high risk patients in Finland, the NOPHO ALL-92 protocol was already started in 1990 as NALLE90 and HR patients were treated according to the very high risk regimen; (Modified from Järvelä et al. J Cancer Surviv (2010) 4:339–345)

4.2 Measures of physical activity and fitness

All the participants completed questionnaires on their physical activity (PA) and health. The questionnaires consisted of suitable sections from the Finnish FINRISKI study (Lahti-Koski et al. 2008). In addition, frequency, duration and intensity of PA were reported according to Raitakari et al. (1996). Based on these, a physical activity index (PAI, MET h/week; MET=Multiple of the resting metabolic rate) was calculated as a multiple of the resting metabolic rate by multiplying the mean frequency, duration, and intensity of weekly PA (Raitakari et al. 1996). One MET h/week is equivalent to approximately 12 minutes of moderate intensity activity weekly while 5 MET h/week corresponds to ≈ 1 hour of moderate activity weekly.

Physical fitness was measured with maximal exercise testing ($VO_{2\ peak}$) and standard muscle strength tests used at the Paavo Nurmi testing centre. All the exercise tests were performed by the same experienced exercise physiologist who was blinded to patient history. An electronically braked cycle ergometer (model 800 S, Ergoline, Mijnhardt, The Netherlands) with a direct automatic respiratory gas measurement system (model 202; Medikro, Kuopio, Finland) was used to perform the $VO_{2\ peak}$ measurements. The initial load that the test started with was 20 W in females and 50 W in males, and the load was increased every minute with 20 W in females and 25 W in males. During the test, the participants were verbally encouraged and supported to continue pedaling until exhaustion. The test stopped at subjective exhaustion. All the participants reached a respiratory exchange ratio >1.10 indicating that all the participants reached their $VO_{2\ peak}$. Average of the last four 15 second collection intervals of the test was used to determine $VO_{2\ peak}$.

Muscle strength tests were performed after the peak oxygen uptake test with an appropriate rest between the tests. The muscle strength tests started with explosive power of the lower extremities. It was measured by vertical squat jump on a contact mat connected to an electronic timer (Digitest 1000, Newtest, Oulu, Finland), and maximal vertical jump height was determined from the mean flight time of three separate jumps. Maximal isometric handgrip strength was measured as a mean of three maximal trials as well. A dynamometer (In Good Shape, Metitur, Jyväskylä, Finland) was used to perform the measures and each of the three trials lasted 2–4 s, with rest intervals of 30 s. Dynamic endurance fitness of trunk extension and flexion were measured by traditional sit-up and back tests on an apparatus that was individually adjustable (Viljanen et al. 1991). The number of repetitions were counted for 30 s in the back test and for 60 s in the sit-up test. A 30-second full squatting test without extra weights was used to determine dynamic endurance muscle strength of lower extremities. Lastly, upper body strength was measured with a dynamic lifting test of upper arms. This test was performed by lifting hand weights (5 kg for females and 10 kg for males) upwards from shoulder level to

extended elbows. The test was stopped when the subject could not keep up continuous performance, and the result was expressed per arm.

4.3 Anthropometric measures and cardiovascular risk factors

Anthropometric measures consisted of body weight, height, waist, and hip circumference, and fat percent. Body weight was measured to the nearest 0.1 kg with an electronic scale (Seca Model 910, Vogel&Halke, Hamburg, Germany) with the subject wearing light underwear. Height was measured with a wall-mounted Harpenden stadiometer (Holtain, Crymych, UK) to the nearest millimeter. BMI was then calculated as kilograms per meter squared. Hip circumference was measured at trochanter level and waist circumference at the midlevel between the lateral costal arch and the iliac crest. Waist-to-hip ratio was then calculated. A Harpenden skinfold caliper (model HSK-BI, British Indicators, West Sussex, UK) was used to perform skinfold measurements at four points (subscapular, triceps, biceps, and suprailiac), and the percentage of fat was estimated according to Durnin and Womersley (Durnin, Womersley 1974). Resting blood pressure (BP) was measured with an oscillometric BP monitor (Omron M4; Omron Matsusaka, Matsusaka, Japan) from right arm at sitting and supine positions three times after appropriate rest, and the mean of the three measurements was used.

The prevalence of metabolic syndrome was assessed by the criteria of 2009 Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (Alberti et al. 2009), described in Table 2. The presence of any three abnormal findings out of five constitutes the diagnosis of MetS (Alberti et al. 2009).

4.4 Laboratory assays

Laboratory analyses were performed at the Turku University Hospital laboratory (TYKSLAB, Hospital District of Southwest Finland) from venous blood samples collected after overnight fasting. Enzymatic colorimetric assays were used to determine plasma glucose (Glucose oxidase; Modular P800, Roche Diagnostics GmbH, Mannheim, Germany), total cholesterol (Cholesterol esterase, cholesterol oxidase; Modular P800, Roche Diagnostics GmbH, Mannheim, Germany), and triglyceride concentrations (Lipoprotein lipase, glycerokinase, glycerol phosphate oxidase; Modular P800, Roche Diagnostics GmbH, Mannheim, Germany). Plasma insulin (ECLIA; Modular E 170, Roche Diagnostic GmbH, Mannheim, Germany) and serum Insulin-like growth factor 1 (IGF-1; Immulite 1000, Diagnostic Products Corporation, Los Angeles, CA, USA) were

determined by immunochemiluminometric assay method and plasma high density lipoprotein cholesterol (HDL) by homogeneous enzymatic colorimetric assay (Cholesterol esterase, cholesterol oxidase; Modular P800, Roche Diagnostics GmbH, Mannheim, Germany). The Friedewald formula (LDL = total cholesterol – HDL – 0.45 x triglycerides) was used to calculate plasma low density lipoprotein cholesterol (LDL). One subject was excluded from the LDL cholesterol calculation due to high triglyceride concentration > 4 mmol/l. In addition, HOMA-IR (homeostasis model assessment, insulin resistance) index was calculated using Matthew's formula (insulin (mU/l) x glucose (mmol/l) /22.5) (Matthews et al. 1985).

An oral glucose tolerance test was also performed. The participants were administered an oral glucose load of 75 g and plasma glucose and insulin concentrations were measured immediately before and 120 minutes after the glucose load.

4.5 Endothelial function and carotid intima media thickness

One experienced specialist performed all the vascular endothelial ultrasound studies (IMT, FMD) with the Acuson 128 XP-10 ultrasound system (Siemens, Mountain View, CA, USA). IMT and FMD analyses were then performed offline from stored digital images by one analyst. All the ultrasound studies and offline analyses were performed blinded to patient history.

The left common carotid artery was scanned and the image was focused on the posterior (far) wall for IMT measures. A 5-second scan of the magnified image was stored in digital format, and the best quality end-diastolic frame was selected for subsequent offline analyses. IMT was measured from the posterior common carotid wall approximately 10-20 mm below the bifurcation, and at least three measurements were performed to derive the mean carotid IMT.

FMD was assessed from the left brachial artery by measuring the left brachial artery diameter at rest and during reactive hyperaemia. To induce reactive hyperaemia, a pneumatic tourniquet was placed around the forearm, and a pressure of 250 mmHg was held for 4.5 minutes to induce increased flow after release. To calculate FMD, the brachial artery diameter was assessed at rest, and 20, 40, 60, 80 and 100 seconds after the cuff release. Five-second clip images at each time point were saved for later offline analyses. From these clips, brachial artery diameter was measured three times at end diastole at each time point, and the average of the three measurements at each time point was used. FMD at each time point was then calculated and expressed as a percentage relative to the resting scan. In addition to the FMD values at each time point, the maximal FMD values (FMDmax; %) as well as the absolute change in brachial artery diameter (mm) were selected for statistical analysis. Furthermore, the total dilatation response was assessed, and

this was defined as the area under the dilatation response-versus time -curve between 20 and 100 seconds after hyperemia (FMDauc; % x s).

4.6 Cardiac measures

Transthoracic echocardiography was performed by one experienced specialist using the Acuson 128 XP-10 ultrasound system (Siemens, Mountain view, CA, USA) according to the recommendations of the American Society of Echocardiography. The echocardiographist was blinded to patient history. Standard echocardiographic measures were performed and M-mode from the parasternal long axis view was used to calculate LV EF and FS. In addition, tissue Doppler imaging (TDI) was used to analyse LV diastolic function, and The Syngo dynamics velocity vector imaging software (Syngo VVI 2.00; Siemens, Mountain view, CA, USA) was used for offline analyses of the LV deformation. The offline analyses were performed by one analyst who was blinded to patient history as well as the study date.

Digitally stored standard 2D parasternal short-axis and apical four-chamber views of the left ventricle were used to perform VVI analyses. The LV endocardial contour was manually traced approximately 1 mm into the endocardium to avoid tracking of the blood. Papillary muscle insertions were avoided as well as possible (Carasso et al. 2012). The tracing was done from the base of the septal mitral valve leaflet to the base of the lateral mitral valve leaflet in the apical four-chamber view, and around the left ventricle starting at the 12 o'clock position of the parasternal short axis view at three levels (basal, mid/papillary muscle and apex) (Figure 5). Peak longitudinal strain (PLS), peak longitudinal strain rate (PLSR), peak longitudinal diastolic strain rate (PLdiastSR), peak longitudinal velocity (PLV), and peak longitudinal displacement (PLD) were analysed in six segments per view from the apical 4 chamber views. Peak circumferential strain (PCS), peak circumferential strain rate (PCSR), peak circumferential diastolic strain rate (PCdiastSR) as well as peak radial velocity (PRV) and displacement (PRD) were analysed in six segments per view from the three short-axis planes. All the analysed views were traced three times and the average of the three measurements was used for statistical analysis. This was done to avoid possible bias due to differences in placing the trace. To gain longitudinal measures, results from the apical 4 chamber view were averaged across the six segments. Each of the outcome variables was also compared between the basal (segments 1 and 4), mid-level (segments 2 and 5) and apical (segments 3 and 6) segments of the LV in 4-chamber view. To gain global circumferential measures, measures from the parasternal short-axis planes were averaged across the six segments in each view and also across all the 18 segments.

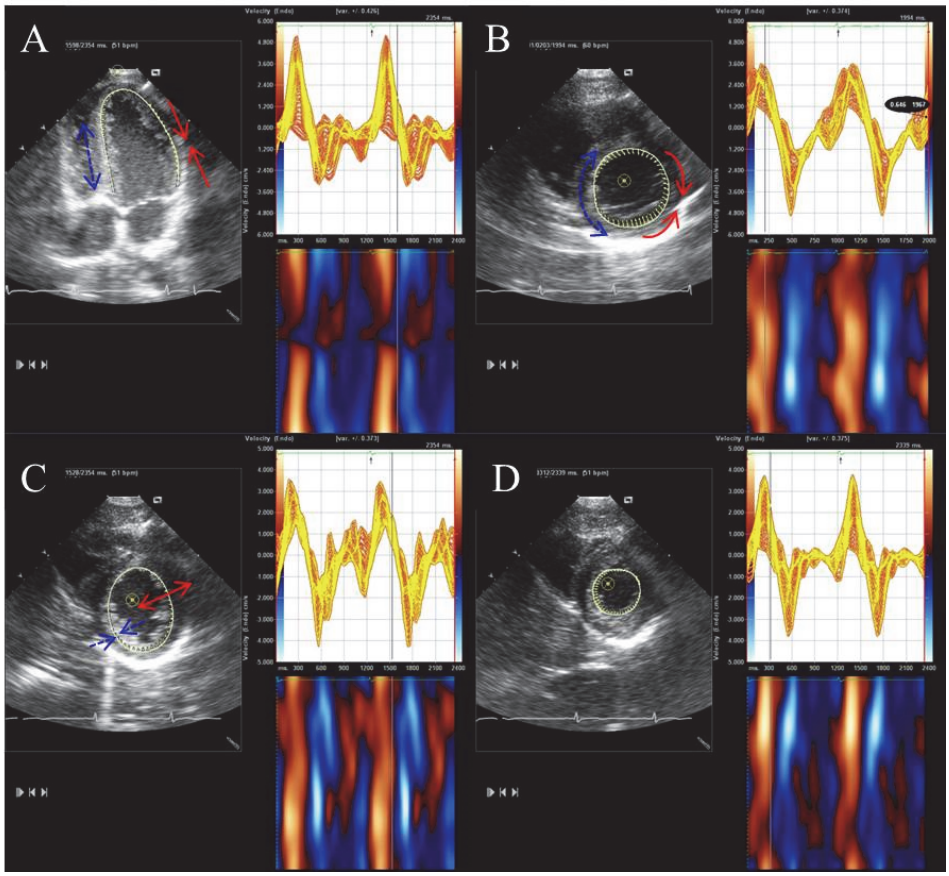

Figure 5 Examples of longitudinal VVI measures from apical 4 chamber view (A), and circumferential VVI measures from the basal level of short-axis view (B), mid/papillary level of the short-axis view (C) and apical level of the short-axis view (D). The direction of the yellow arrows represents the direction of motion while the arrow length represents velocity. Red indicates systole and blue indicates diastole, and the red and blue arrows indicate the direction of longitudinal (A), circumferential (B) and radial (C) myocardial deformation during each phase

4.7 Questionnaires for non-participants

In addition to the ALL survivors who took part in the clinical study, additional 24 survivors returned a postal questionnaire sent to the non-participants. The questionnaire was a shorter version of the one described including also information on the reasons for not participating in the clinical study. The most common reasons for nonparticipation were mainly logistic, i.e. long distance from the study center (41.7%) and difficulties in arranging the day free from work or school (33.3%).

4.8 Physical activity intervention

Seventeen (81 %) of the 21 survivors participating in the baseline cross-sectional study agreed to participate in the physical activity intervention and completed the follow-up study (Figure 4, Table 6). Four of the participants at the baseline study declined to participate in the intervention and follow-up study mainly because they felt that the study day was too strenuous (long distance and/or sore muscles after the exercise test), and they all performed below the expected values at the baseline maximal exercise test. All the fitness tests, echocardiographic and endothelial measures, questionnaires on physical activity, anthropometric measures, blood pressure and part of the laboratory measures (fasting glucose, insulin, cholesterol and triglycerides) were repeated after the exercise intervention according to exactly the same methods and by the same analysts. The offline analyses of the cardiac and endothelial ultrasound studies were performed blinded, so that the analyst was unaware of the study date (i.e. baseline study or follow-up) and whether the subject was an ALL survivor or a control.

The physical activity intervention was planned and executed as a home-based exercise programme, so that the participants would beable to integrate it more easily into their varying everyday life conditions. The planned duration of the exercise programme was 12 weeks. However, due to e.g. school examination weeks and upper respiratory tract infections, the true mean duration of the programme was 16.0 ± 2.9 weeks.

The home exercise programme was developed for this purpose by the research group's experts in sports and exercise medicine and exercise science. At the baseline visit, each subject was given an illustrated home muscle-training programme, and instructions to perform the programme 3–4 times a week at home. All the subjects were informed and motivated similarly by one person who went through the programme with each participant to ensure that they knew how to perform the exercises safely and adequately. The home muscle-training programme included 8 exercises to strengthen gluteal and lower limb muscles, shoulders and upper limb muscles, abdominal muscles, and back muscles. The participants were instructed to do as many repeats as possible for each of the exercises, and repeat the cycle three times per session. In addition to the muscle-training programme, the subjects were encouraged to undertake aerobic exercise of their own choice (e.g., walking, jogging, aerobics) at least three times per week for 30 min per session either as a warm-up for the muscle-training programme or on separate days. In addition, all the participants received Omron walking style II® pedometers (Omron healthcare, Kyoto, Japan) and information on the general daily step goals to motivate them to increase physical activity by monitoring the steps taken.

During the exercise programme, the subjects were contacted by telephone at approximately 2 week intervals to provide counseling and motivation. The telephone calls included the following questions: 1) What kind of physical activity and exercises the

participants had done and how often? 2) Had they had any problems with the exercises, time or motivation? 3) Had they had any concerns about their health since the last contact? 4) How do they think they could improve their performance, or what could help them to increase their physical activity, if they had not met the goals? The issues that were raised were then discussed with the participant, and they were encouraged to do the exercises, and given tips on how to fit more PA into their everyday life.

4.9 Ethics

The Commission on Ethics of Southwest Finland Hospital District accepted the research protocol, and informed consent was obtained from each participant.

4.10 Statistical analysis

The baseline comparisons between the ALL survivors and controls were done by analysis of matched pairs with linear mixed models where the pair was used as the random effect. Weight, HOMA-IR, plasma insulin, cholesterol, LDL, triglycerides, FMD at 60 seconds, and maximal absolute change in brachial artery diameter were not normally distributed and therefore they were log transformed. Categorical variables were analysed with Fischer's exact test.

The results of the endothelial measures were also analysed separately for males and females using the methods described above. At baseline, FMDmax and maximal absolute change in brachial artery diameter in males, and FMD at 60 seconds in females were not normally distributed and therefore they were log transformed.

Comparisons between the clinical study participants at baseline and the postal questionnaire group were done by the two-sample t-test and Fischer's exact test. Age at diagnosis, body weight, and BMI were non-normally distributed and therefore log transformed.

Comparisons between the results at baseline and after the intervention were performed with linear mixed models for repeated effects. Back extensor test results were x^2 transformed and PAI, HOMA-IR, fasting plasma insulin, cholesterol, LDL, triglycerides, and maximal absolute change in brachial artery diameter were log transformed due to non-normal distribution.

The effects of the exercise programme on endothelial measures were also analysed separately for males and females using the same methods described above. In males, FMDmax was not normally distributed and therefore it was log transformed. In females, IMT was not normally distributed, and normal distribution could not be achieved with

transformations. Hence IMT in females was analysed with a paired non-parametric test (Wilcoxon signed rank).

Spearman correlation coefficient was calculated for non-normally distributed variables (age at diagnosis, anthracycline dose, BMI, weight). Otherwise the Pearson correlation coefficient was used.

Data are given as means and standard deviations. P-values less than 0.05 were considered statistically significant. Statistical computations were carried out using SAS® release 9.1/2005 and 9.4/2013 (SAS Institute Inc., Cary, N.C., USA).

5 RESULTS

5.1 The baseline study

5.1.1 Physical activity and fitness (I)

Both the ALL survivors and controls had similar physical demands in their work (p=0.33), and the majority of the participants had sedentary jobs or were students. Self-reported mean intensity, frequency and duration of PA were similar in survivors and controls (p=1.0, p=0.73 and p=0.12 respectively). Thus, the Physical activity index (MET h/week) did not differ between the groups either (p=0.52) (Figure 6). 30 % of the male survivors and 36.4 % of the female survivors reported very low levels of weekly physical activity (PAI ≤5 MET h/week; 5 MET ≈ 1 hour of moderate walking per week). The ALL survivors and controls did not differ in their conceptions of their own physical fitness (p=0.45) and current health status (p=0.48), and all the ALL survivors considered their current health average or better.

At baseline, VO_{2peak} (p=0.01) and maximal work load (p<0.01) were 14 % lower in the ALL survivors than controls. Maximal heart rate (p=0.50) and respiratory exchange ratio (p=1.00) were similar in survivors and controls, and indicated that the tests were maximal (respiratory exchange ratio >1.10). ALL survivors performed poorer than controls in the sit-up test (p=0.02) and maximal vertical jump test (p<0.01) while the results of the back extensor test (p=0.14), full squatting test (p=0.12), upper arm test (p=0.18) and maximal hand grip strength (p=0.19) did not differ significantly between the groups (Figure 6, Figure 7, Figure 8, Table 8).

VO_{2peak} was also analysed according to the age- and sex-specific reference values used in our centre (Shvartz, Reibold 1990): 5/10 of the male survivors and all the 11 female survivors performed below the age- and sex-specific weight-adjusted reference values. Of the four survivors not willing to participate in the intervention, two were males and two were females, and they all performed below expected at the baseline study. Of the controls, 3/10 of the males and 7/11 of the females performed below the expected age- and sex-specific values.

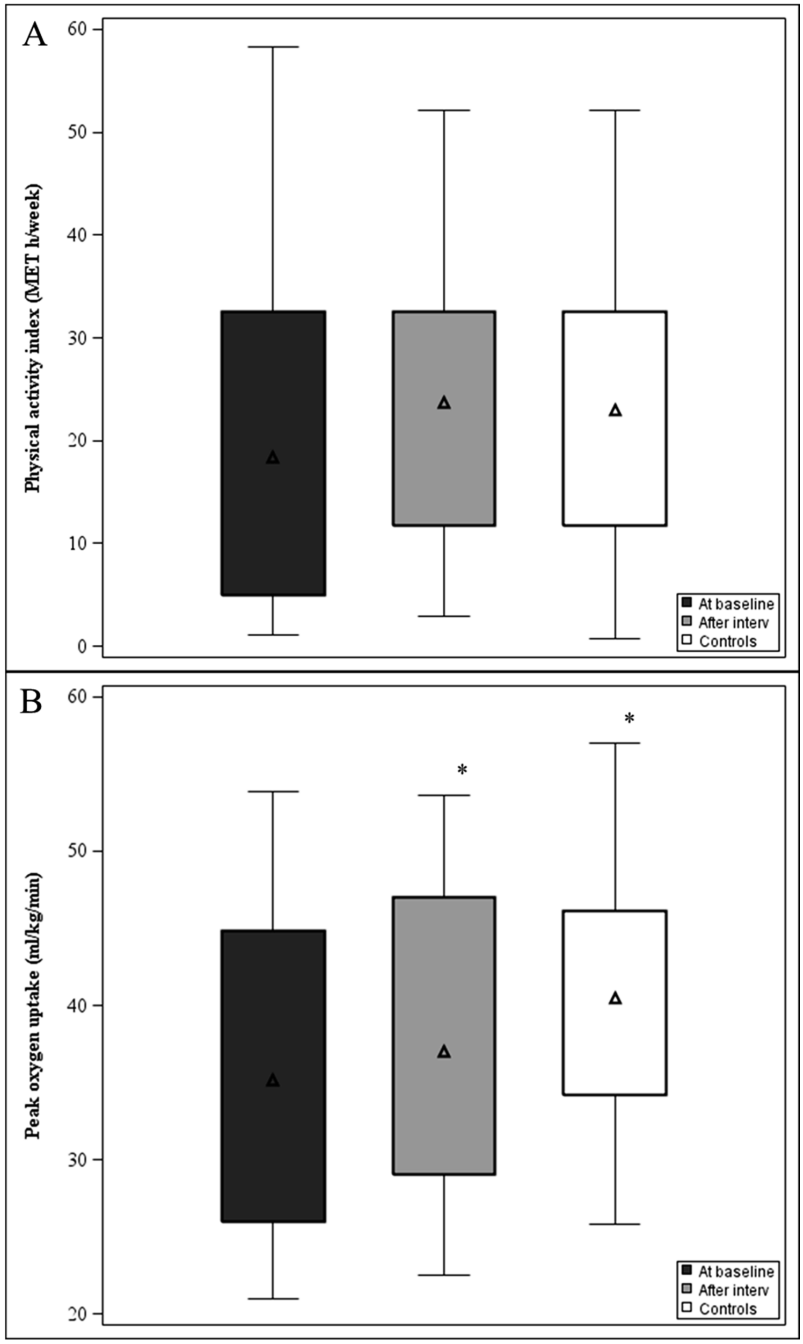

Figure 6 Physical activity index (A) and peak oxygen uptake (B) in ALL survivors at baseline and after the intervention, and in controls. Lower limit of the box = lower quartile; Upper limit of the box = Upper quartile; Whiskers = Minimum and maximum; o = Outlier (≥ 1.5 interquartile range above or below the box); Δ = Mean; * p<0.05 compared to ALL survivors at baseline

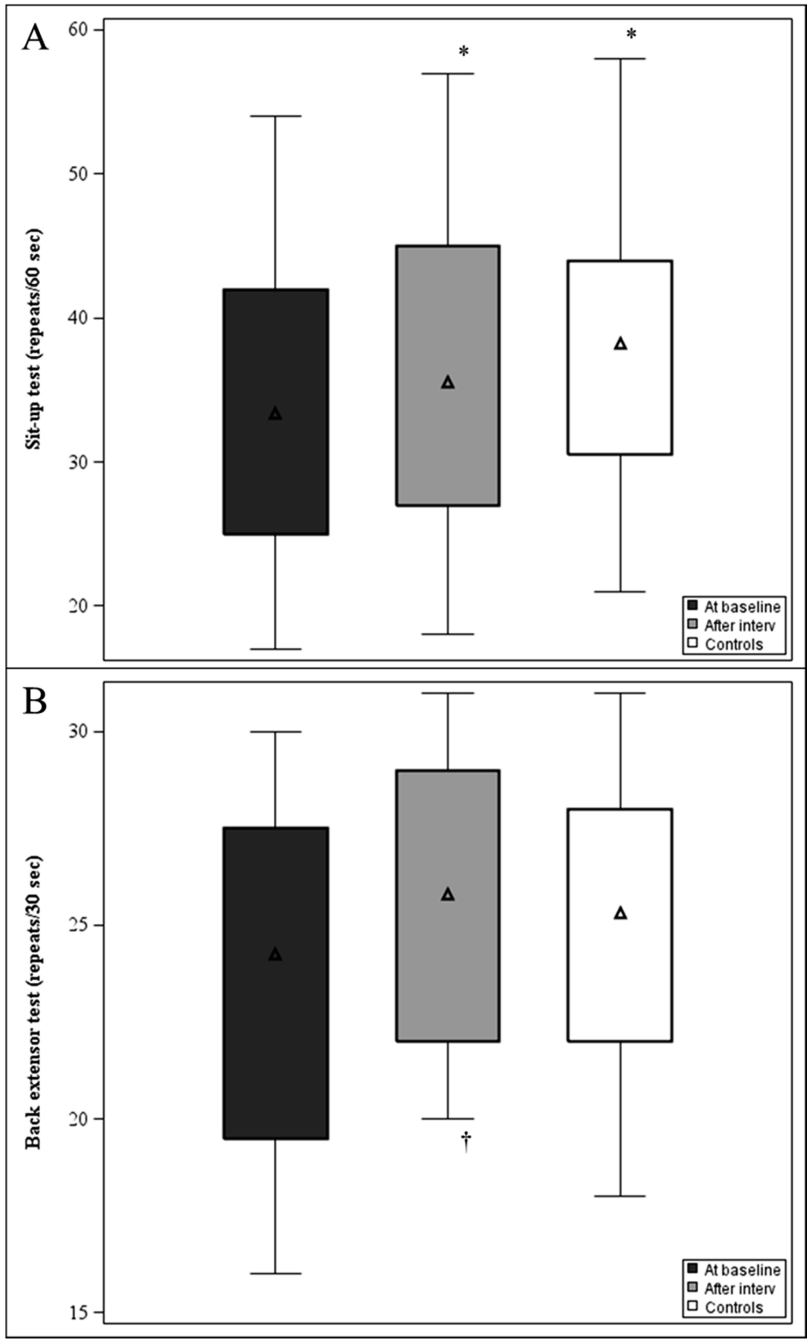

Figure 7 Sit-up (A) and back extensor (B) test results in ALL survivors at baseline and after the intervention, and in controls. Lower limit of the box = lower quartile; Upper limit of the box = Upper quartile; Whiskers = Minimum and maximum; o = Outlier (≥ 1.5 interquartile range above or below the box); Δ = Mean; † p<0.01 and * p<0.05 compared to ALL survivors at baseline

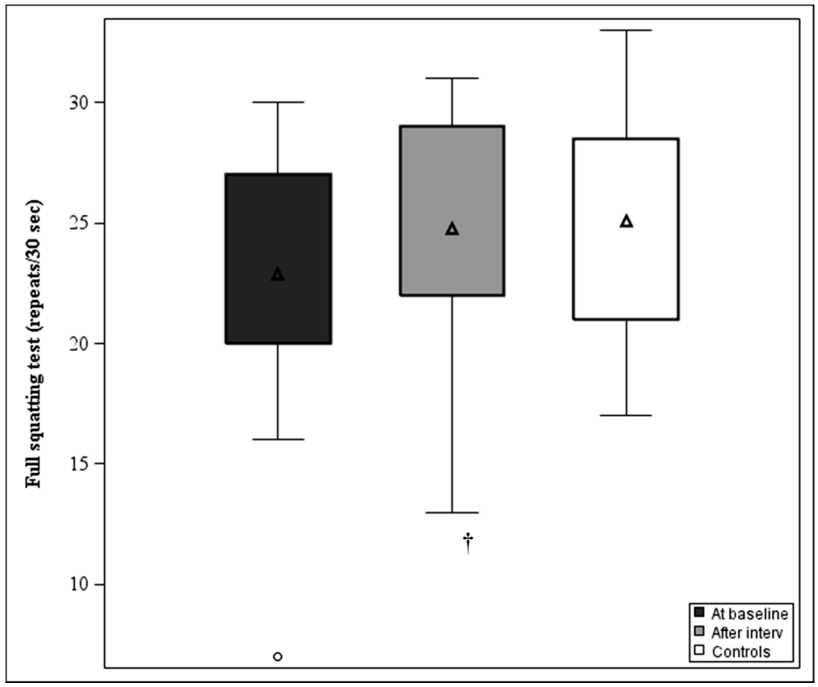

Figure 8 Results of the full squatting test in ALL survivors at baseline and after the intervention, and in controls. Lower limit of the box = lower quartile; Upper limit of the box = Upper quartile; Whiskers = Minimum and maximum; o = Outlier (≥ 1.5 interquartile range above or below the box); Δ = Mean; † p<0.01 compared to ALL survivors at baseline

5.1.2 Anthropometric measures and cardiovascular risk factors (I)

At baseline, there were no significant differences in height (p=0.11), weight (p=0.70), BMI (p=0.34), waist circumference (p=0.29), waist-to-hip ratio (p=0.34) or percentage of fat (p=0.11) between the ALL survivors and controls. Supine diastolic BP was higher in ALL survivors than controls (p=0.02) while the difference in systolic BP or sitting diastolic BP was not statistically significant. Eight of the ALL survivors (38 %) and seven of the controls (33 %) were overweight (BMI > 25), and 4/8 of the overweight survivors had received CRT. At the baseline study, four of the ALL survivors (19 %) and two of the controls (9.5 %) met the criteria for MetS while the number of participants with 0, 1, 2 or at least three criteria for the MetS did not differ significantly between the ALL survivors, controls, and ALL survivors after intervention (p=0.80) (Table 7, Table 9).

Table 7 Number of participants with each criteria of the metabolic syndrome, and with 0, one, two or at least three of these criteria

	ALL survivors at baseline (N=21)	ALL survivors after the exercise programme (N=17)	Controls (N=21)
	N (%)	N (%)	N (%)
Waist circumference ≥ 94 cm for males and ≥ 80 cm for females	7 (33 %)	5 (29 %)	5 (24 %)
Triglycerides ≥ 1.7 mmol/l or medication	3 (14 %)	3 (18 %)	4 (19 %)
HDL < 1.0 mmol/l in males and < 1.3 mmol/l in females or medication	1 (5 %)	1 (6 %)	1 (5 %)
Blood pressure syst ≥ 130 mmHg or diast ≥ 85 mmHg or medication	12 (57 %)	6 (35 %)	8 (38 %)
Elevated fasting glucose ≥ 5.6 mmol/l or medication	0	1 (6 %)	1 (5 %)
0 criteria	8 (38 %)	8 (47 %)	10 (48 %)
1 criteria	7 (33 %)	5 (29 %)	4 (19 %)
≥ 1 criteria	13 (62 %)	9 (53 %)	11 (52 %)
2 criteria	2 (10 %)	2 (12 %)	5 (24 %)
≥ 3 criteria (MetS)	4 (19 %)	2 (12 %)	2 (10 %)

The criteria are presented according to Alberti et al. (2009); Presence of ≥ 3 criteria constitutes metabolic syndrome (MetS)

5.1.3 Laboratory assays

At the baseline study, fasting plasma glucose (4.98±0.30 vs 4.97±0.39 mmol/l, p=0.90), insulin (10.0±6.18 vs 9.81±4.29 mU/l, p=0.86), total cholesterol 4.10±1.01 vs 4.19±0.60 mmol/l, p=0.53), HDL cholesterol (1.58±0.31 vs 1.72±0.39 mmol/l, p=0.17), LDL cholesterol (2.02±0.97 vs 1.95±0.45 mmol/l, p=0.20) and triglycerides (1.15±0.99 vs 1.12±0.54 mmol/l, p=0.62) as well as HOMA-IR (2.22 ± 1.39 vs 2.17 ± 0.98, p=0.89) were similar in ALL survivors and controls. S-IGF-1 did not differ between the survivors and controls either (29.8±11.3 vs 33.9±10.0 nmol/l, p=0.09).

Results of the oral glucose tolerance test were similar in ALL survivors and controls (5.04 ± 0.30 vs 5.12 ± 0.46 mmol/l, p=0.48 for glucose at 0 min;9.62 ± 5.82 vs 9.43 ± 4.33 mU/l, p=0.97 for insulin at 0 min; 5.23 ± 1.12 vs 5.63 ± 1.36 mmol/l, p=0.31 for glucose at 120 min; 49.00 ± 38.27 vs 57.24 ± 47.09 mU/l, p=0.93 for insulin at 120 min).

5.1.4 Endothelial function and carotid intima media thickness (III)

At the baseline study, FMDauc was significantly smaller in childhood ALL survivors than controls (p=0.02). FMD at 40 seconds was also significantly lower in survivors than controls (p=0.01) while FMDmax did not differ significantly between the survivors and controls (p=0.06). The baseline diameter of the brachial artery (p=0.56) or the maximal absolute change in brachial artery diameter (p=0.16) did not differ between the groups. IMT was similar in survivors and controls (p=0.44) at the baseline study (Table 10).

Due to the somewhat different findings on endothelium in males and females, the results were also analysed separately for each gender. In males, both the FMDauc (p=0.03) and FMDmax (p=0.01) were lower in survivors than controls. FMD at 80 seconds and FMD at 100 seconds were also significantly lower in male survivors than controls (p<0.01 and p=0.04) while the baseline brachial artery diameter (p=0.43) or maximal absolute change in brachial artery diameter (p=0.54) did not differ between the groups. IMT did not differ between the groups (p=0.81). (Figure 9, Table 10).

In females, FMD at 40 seconds was lower in survivors than controls (p=0.02), but there were no significant differences in FMDauc (p=0.16), FMDmax (p=0.32), baseline brachial artery diameter (p=0.91), maximal absolute change in brachial artery diameter (p=0.44) or IMT (p=0.34) between the female survivors and controls. (Figure 9, Table 10).

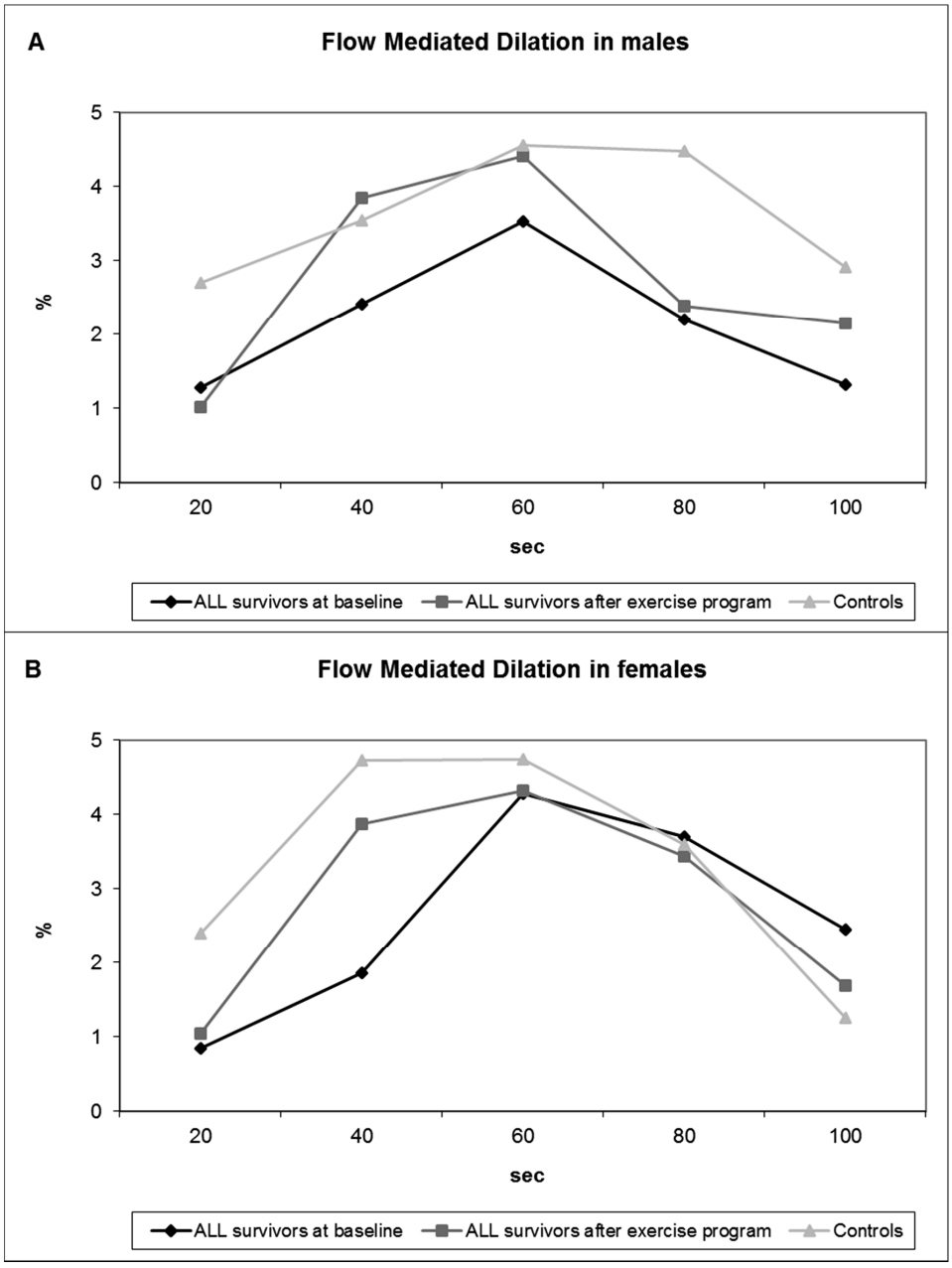

Figure 9 Mean values of flow mediated dilation in males (A) and females (B) at each time point in ALL survivors at baseline and after the exercise programme, and in controls

5.1.5 Cardiac measures (IV)

5.1.5.1 Basic echocardiographic measures

At the baseline study, systolic function was normal in both groups. The mean LV EF was 60.7 ± 4.7 % in ALL survivors and 62.3 ± 3.7 % in controls (p=0.22). The mean LV FS was 32.6 ± 3.1 % in ALL survivors and 34.0 ± 2.8 % in controls (p=0.13). There were no significant differences between the ALL survivors and controls in LV end-systolic and end-diastolic dimensions or volumes, intraventricular septum thickness, LV posterior wall thickness or LV mass. Mitral early (E) and late (A) filling waves, or E/A did not differ significantly between the ALL survivors and controls.

5.1.5.2 Tissue Doppler Imaging

Diastolic function was also evaluated with TDI. At the baseline study, early diastolic lateral mitral annulus velocity E'lat (32.8 ± 5.7 vs 38.0 ± 6.2 cm/s, p=0.01) and the ratio of early and late diastolic lateral mitral annulus velocities (E'/A'lat; 1.6 ± 0.5 vs 2.1 ± 0.6 cm/s, p=0.01) were significantly lower in ALL survivors than controls indicating attenuated diastolic function. In addition, E/E'lat was significantly higher in ALL survivors than controls (2.8 ± 0.4 vs 2.4 ± 0.6, p=0.04). Septal and lateral mitral ring displacement which are surrogates for overall longitudinal function of the septum and lateral wall respectively, were similar in ALL survivors and controls.

5.1.5.3 Velocity Vector Imaging

The circumferential and longitudinal deformation of the LV was further analysed with the VVI method. The results were compared between the ALL survivors and controls at each of the 4 measurement planes (basal, mid/papillary and apical level of the parasternal short axis view and apical 4-chamber view) as well as between the measurement planes in both groups.

All segments from the parasternal short-axis views were analysable in ALL survivors. In controls, 9/126 segments at the basal level, 15/126 segments at the mid-level and 7/126 segments at the apex level were excluded due to inadequate tracing (poor image quality) or absence of the view (1 view absent in controls at basal level, 2 at mid-level and 1 at apex level). All segments from the apical 4-chamber views were analysable in ALL survivors and 1/126 segments was excluded in controls due to inadequate tracing.

Results of the VVI analyses are presented in Figure 10, Figure 11, Figure 12 and Table 11. Of the circumferential measures, PCS and PCSRwere significantly lower in ALL survivors than controls at apex (p=0.02 and p=0.01 respectively), and a similar but non-significant trend in mean values was seen also at basal and mid-level indicating attenuations in the circumferential deformation of the LV. In addition, PCS, PCSR and PCdiastSR were significantly higher towards the apex in both ALL survivors and controls (p<0.01 for each), as expected.

The LV longitudinal measures were similar in ALL survivors and controls Table 11. PLV and PLD were significantly higher at the basal than the mid or apical level of the apical 4-chamber view in both survivors and controls (p<0.01 for each), as expected.

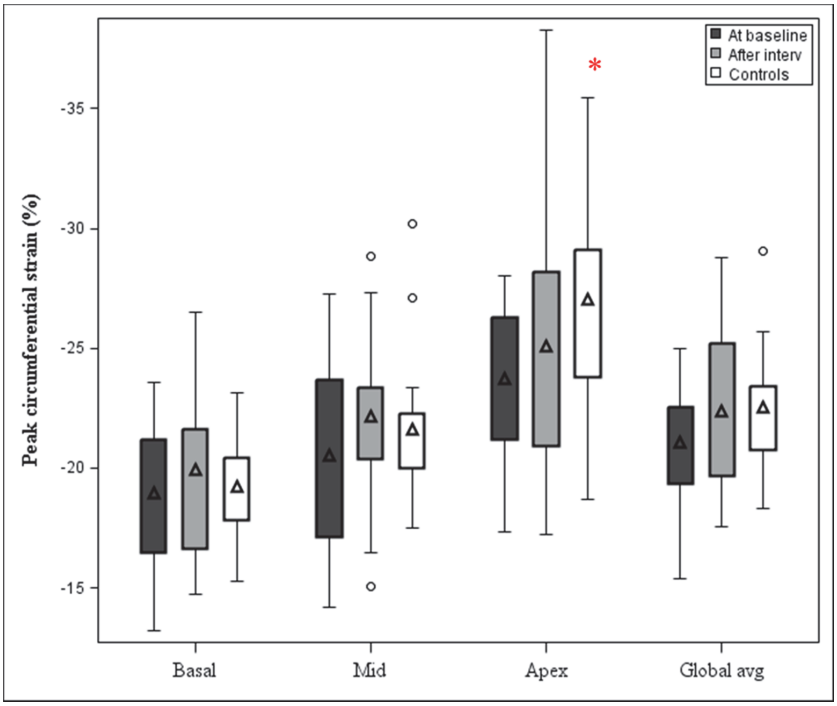

Figure 10 Peak circumferential strain (PCS) at three planes of the parasternal short axis view in ALL survivors at baseline and after the intervention, and in controls. Lower limit of the box = lower quartile; Upper limit of the box = Upper quartile; Whiskers = Minimum and maximum; o = Outlier (≥ 1.5 interquartile range above or below the box); Δ = Mean; * p<0.05 compared to ALL survivors at baseline

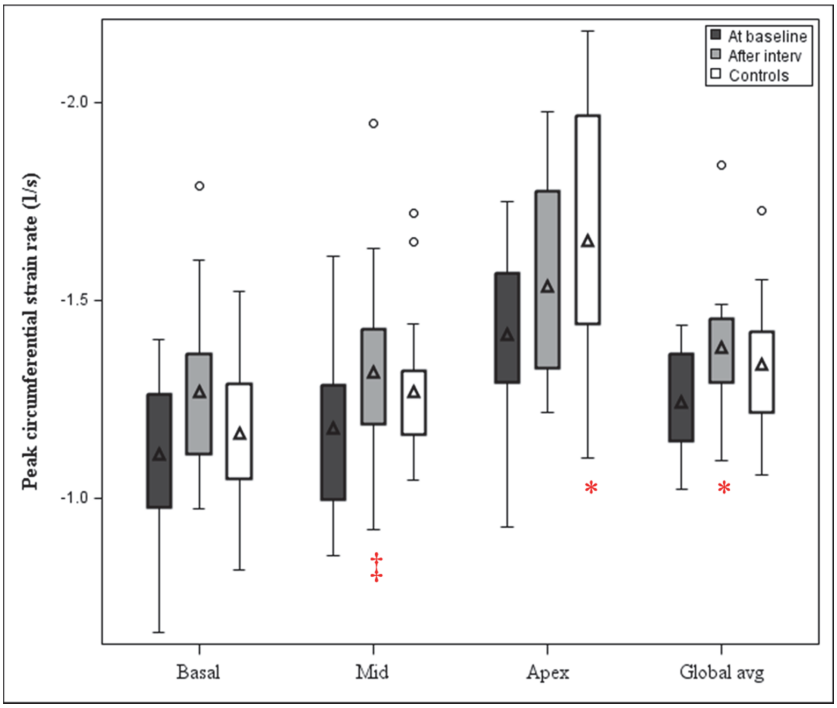

Figure 11 Peak circumferential strain rate (PCSR) at three planes of the parasternal short axis view in ALL survivors at baseline and after the intervention, and in controls. Lower limit of the box = lower quartile; Upper limit of the box = Upper quartile; Whiskers = Minimum and maximum; o = Outlier (≥ 1.5 interquartile range above or below the box); Δ = Mean; * p<0.05 and ‡ p=0.05 compared to ALL survivors at baseline

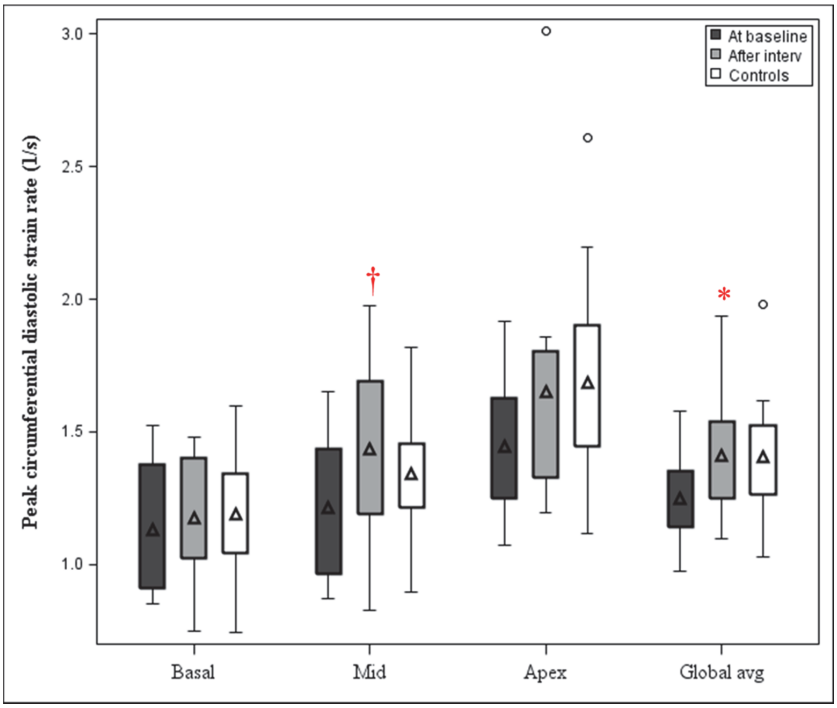

Figure 12 Peak circumferential diastolic strain rate (PCSR) at three planes of the parasternal short axis view in ALL survivors at baseline and after the intervention, and in controls. Lower limit of the box = lower quartile; Upper limit of the box = Upper quartile; Whiskers = Minimum and maximum; o = Outlier (≥ 1.5 interquartile range above or below the box); Δ = Mean; † p<0.01 and * p<0.05 compared to ALL survivors at baseline

5.1.6 Associations (I)

In ALL survivors at the baseline study, the age at diagnosis correlated positively with current BMI (r=0.57, p<0.01), weight (r=0.53, p=0.01), waist circumference (r=0.62, p<0.01), and waist-to-hip ratio (r=0.49, p=0.02), but not significantly with VO_{2peak} (r=-0.42, p=0.06). Only one of the overweight survivors had been diagnosed before the age of 5 years, and the positive correlation between BMI and age at diagnosis remained after including the postal questionnaire group (r=0.47, p<0.01). Of the laboratory measures, the age at diagnosis correlated with cholesterol (r=0.50, p=0.02) and IGF-1 (r=-0.44, p=0.05), but this association may be explained by current age as well. Time since the diagnosis did not correlate with anthropometric measures, BP, exercise test results or laboratory measures while the current age correlated only with waist-to-hip ratio (r=0.56, p<0.01), total cholesterol (r=0.56, p<0.01) and IGF-1 (r=-0.56, p<0.01). As expected, PAI correlated positively with VO_2 peak (r=0.64, p<0.01) and other exercise test results, except for the shoulder test and hand grip strength.

At each of the three short-axis planes, PCdiastSR correlated negatively with the cumulative anthracycline dose (r=-0.49, p=0.03 at basal; r=-0.48, p=0.03 at mid-level; r=-0.43, p=0.05 at apex) indicating attenuated values with increasing anthracycline dose. At apex, the anthracycline dose also associated with PCS (r=0.59, p<0.01) and PRD (r=-0.45, p=0.04) in a way that higher anthracycline dose associated with attenuated PCS and PRD. Of the global circumferential measures, global PCS (r=0.55, p<0.01), PRD (r=-0.44, p=0.04) and PCdiastSR (r=-0.56, p=0.01) associated with the cumulative anthracycline dose indicating associations between higher anthracycline dose and attenuated PCS, PRD and PCdiastSR, but for PCSR the association was not significant (r=0.40, p=0.08). The associations between the anthracycline dose and longitudinal VVI measures as well as TDI measures were not significant.

5.1.7 Representativeness of the sample (I)

Possible differences between the participating survivors and the rest of the eligible cohort were analysed using the local part of the NOPHO register database. No differences were found in age (22.1±4.1y vs 22.1±3.8y, p=0.98), age at diagnosis (5.7±3.7y vs 6.4±4.7y, p=0.95), time since diagnosis (16.3±2.7y vs 15.7±3.8y, p=0.51), sex (males 47.6 % vs 55.4 %, p=0.61), treatment intensity (standard risk 38.1 % vs 27.3 %; intermediate risk 47.6 % vs 43.6 %; high risk 14.3 % vs 29.1 %; p=0.39) and treatment protocol (NOPHO ALL-86 47.6 % vs 40.0 %; NOPHO ALL-92 52.4 % vs 56.4 %; NOPHO ALL-2000 0% vs 3.6 %; p=0.89) between the participating survivors and the rest of the ALL-survivor cohort.

Twenty-four ALL-survivors (43 % of the non-participants) returned the postal questionnaire posted to the non-participants, and their results were compared to the participating survivors. The postal questionnaire group reported similar conceptions of their own physical fitness (p=0.33), current health status (p=0.51), and physical demands in their work (p=0.76) than the participating survivors. Physical activity index as well as self-reported mean intensity, frequency and duration of PA were similar in both groups of survivors (p=0.53, p=0.82, p=0.85, and p=0.40 respectively). The self-reported height (p=0.74), weight (p=0.58), and calculated BMI (p=0.63) did not differ between the participating survivors and the postal questionnaire group. In the postal questionnaire group, 10/24 (42 %) of the survivors had a BMI > 25 based on their self-report while 38 % (8/21) of the survivors participating in the clinical study were overweight. All the respondents considered their current health average or better as did the participating survivors.

5.2 After the physical activity intervention

5.2.1 Physical activity and fitness (II)

The questionnaires regarding physical activity were repeated after the exercise programme. The mean PAI increased 29 %, but the difference between studies was not statistically significant (p=0.09). (Figure 6, Table 8).

At the beginning of the exercise programme, the survivors received pedometers and were asked to keep diaries on their PA and steps taken. However, these diaries were poorly filled in and due to the large amount of missing values, analysing the diaries was omitted. During the telephone contacts included in the intervention, the participants reported performing the muscle strength exercises and for example walking, jogging and other aerobic exercises as instructed.

$VO_{2\ peak}$ (p=0.01) and maximal work load (p=0.02) improved by 5 % after the exercise programme while the maximal heart rate (p=0.05) and respiratory exchange ratio (p=0.09) did not change statistically significantly. In addition, the results of the sit-up test, back extensor test and full squatting test improved after the intervention (p=0.01, p<0.01, and p<0.01 respectively) (Figure 6, Figure 7, Figure 8, Table 8).

Table 8 Fitness measures in ALL survivors at baseline, ALL survivors after the intervention, and in controls

	ALL survivors at baseline			ALL survivors after the intervention				Controls			
	N	Mean	SD	N	Mean	SD		N	Mean	SD	
Max work load (W/kg)	17	3.05	0.79	17	3.19	0.81	*	21	3.50	0.8	†
$VO_{2\ peak}$ (ml/kg/min)	17	35.2	10.1	17	37.1	9.4	*	21	40.5	8.8	†
Max heart rate (bpm)	17	188.4	7.3	17	192.0	8.6	‡	21	189.7	7.6	
RER	17	1.24	0.06	17	1.22	0.06		21	1.24	0.07	
PAI (MET h/week)	17	18.36	15.46	17	23.70	16.30		21	23.00	15.44	
Sit-Ups (repeats/60sec)	17	33.4	10.7	17	35.5	12.0	*	20	38.2	9.2	*
Back extensors (repeats/30sec)	16	24.3	4.8	16	25.8	3.8	†	21	25.3	3.4	
Max vertical jump (cm)	17	24.7	7.8	17	25.2	7.6		21	29.5	7.1	†
Full squatting (repeats/30sec)	17	22.9	6.2	17	24.8	4.8	†	20	25.1	4.7	
Upper arm (max repeats per side)	17	21.8	7.7	17	23.5	7.0		21	22.8	6.9	
Maximal handgrip (N)	17	435.4	140.4	17	446.8	153.8		21	461.1	148.8	

‡ p=0.05, * p<0.05, † p<0.01 compared to ALL survivors at baseline; bpm=Beats per minute; PAI=Physical activity index; RER=Respiratory exchange ratio; VO2peak=Peak oxygen uptake. (Modified from Järvelä et al. J Cancer Surviv (2010) 4:339–345 and Järvelä et al. Pediatr Blood Cancer 2012;59:155–160)

Table 9 Anthropometric measures and cardiovascular risk factors in ALL survivors at baseline, ALL survivors after the intervention, and in controls

	ALL survivors at baseline			ALL survivors after the intervention				Controls			
	N	Mean	SD	N	Mean	SD		N	Mean	SD	
Height (cm)	17	170.1	8.1	17	170.0	8.1		21	173.2	8.9	
Weight (kg)	17	72.9	13.9	17	72.9	13.8		21	70.2	17.3	
BMI (kg/m²)	17	25.1	3.9	17	25.1	3.9		21	23.2	4.3	
Waist (cm)	17	83.9	11.0	17	82.2	11.0	†	21	78.6	10.8	
Waist-to-hip ratio	17	0.87	0.06	17	0.84	0.06	†	21	0.84	0.06	
Percentage of fat (%)	17	27.7	8.3	17	26.8	8.5	*	21	24.4	9.3	
Sitting syst BP (mmHg)	17	130.1	12.1	17	125.6	13.9		20	127.6	12.0	
Sitting diast BP (mmHg)	17	81.7	7.6	17	78.1	11.0		20	76.8	8.2	
Supine syst BP (mmHg)	17	123.3	9.9	17	120.8	12.3		21	121.1	9.7	
Supine diast BP (mmHg)	17	73.4	7.6	17	69.7	7.2	*	21	68.6	5.6	*

† $p<0.01$, * $p<0.05$ compared to ALL survivors at baseline; BMI=Body mass index; BP=Blood pressure; diast=Diastolic; syst=Systolic; (Modified from Järvelä et al. J Cancer Surviv (2010) 4:339–345 and Järvelä et al. Pediatr Blood Cancer 2012;59:155–160)

5.2.2 Anthropometric measures and cardiovascular risk factors (II)

The effects of the intervention on anthropometric measures as well as cardiovascular risk factors are presented in Table 9. Waist circumference, waist-to-hip-ratio and percentage of fat decreased significantly ($p<0.01$, $p<0.01$, and $p=0.04$ respectively) while weight ($p=0.98$) and BMI ($p=0.87$) remained similar after the exercise programme. In addition, supine diastolic BP decreased ($p=0.03$). The number of ALL survivors meeting the criteria for MetS decreased by 50 % from four to two (23.5 % vs 11.8 %) during the intervention (Table 7).

5.2.3 Laboratory assays (II)

After the exercise programme, fasting plasma insulin (10.06 ± 6.71 vs 7.00 ± 4.11 mU/l, $p<0.01$) and HOMA-IR (2.24 ± 1.52 vs 1.50 ± 0.83, $p<0.01$) improved significantly. Fasting plasma glucose, total cholesterol, HDL, LDL and triglyceride values did not change after the exercise programme ($p=0.39$, $p=0.18$, $p=0.09$, $p=0.54$ and $p=1.00$ respectively).

5.2.4 Endothelial function and carotid intima media thickness (III)

After the exercise programme, FMD at 40 seconds ($p<0.01$) and IMT ($p=0.02$) improved significantly while FMDauc ($p=0.27$) and FMDmax ($p=0.23$) remained similar (Table 10). In males, FMD at 40 seconds improved after the exercise programme ($p=0.02$). The mean value of FMDmax in males improved by 29.5 %, but the difference was not quite statistically significant ($p=0.05$). FMDauc and IMT did not change statistically significantly in males ($p=0.11$, and $p=0.11$ respectively). In females, IMT improved after the exercise programme ($p=0.04$), but there were no significant changes in FMDauc or FMDmax ($p=0.75$, and $p=0.98$ respectively). Brachial artery diameter ($p=0.96$ for all, $p=0.19$ for males and $p=0.27$ for females) or maximal absolute change in brachial artery diameter ($p=0.83$ for all, $p=0.57$ for males and $p=0.44$ for females) did not change after the intervention. (Figure 9, Table 10).

Table 10 Intima media thickness and flow mediated dilation in ALL survivors at baseline and after the intervention, and in controls

	ALL survivors at baseline			ALL survivors after the intervention			Controls		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
IMT (mm)	17	0.48	0.04	17	0.46	0.05 *	21	0.46	0.07
Brachial artery baseline diameter (mm)	17	3.42	0.49	17	3.41	0.56	21	3.46	0.60
FMDmax (%)	17	4.39	2.76	16	4.93	2.41	21	5.78	2.16
FMDauc (% x s)	15	202.1	163.08	16	253.4	183.66	19	291.09	132.30 *
Males									
IMT (mm)	8	0.49	0.05	8	0.47	0.05	10	0.47	0.08
Brachial artery baseline diameter (mm)	8	3.64	0.34	8	3.83	0.37	10	3.76	0.70
FMDmax (%)	8	3.77	2.12	8	4.88	1.31 ‡	10	5.28	1.35 *
FMDauc (% x s)	7	200.15	80.60	7	244.66	97.81	9	288.55	88.01 *
Females									
IMT (mm)	9	0.47	0.04	9	0.46	0.04 *	11	0.45	0.07
Brachial artery baseline diameter (mm)	9	3.26	0.53	9	3.05	0.43	11	3.18	0.33
FMDmax (%)	9	4.94	3.25	9	4.96	3.10	11	6.24	2.68
FMDauc (% x s)	8	203.84	218.21	9	260.19	236.54	10	293.38	167.66

* $p<0.05$ and ‡ $p=0.05$ compared to ALL survivors at baseline; FMDauc = Flow mediated dilation area under the curve; FMDmax = maximal flow mediated dilation; IMT = Intima media thickness; (Modified from Järvelä et al. Pediatr Blood Cancer 2013;60:1546–1551)

5.2.5 Cardiac measures (IV)

5.2.5.1 Basic echocardiographic measures

There were no significant differences in systolic function between the studies. LV EF was 61.0 ± 3.5 % at baseline and 60.8 ± 3.5 % after the intervention (p=0.82), and LV FS 32.8 ± 2.3 % at baseline and 32.9 ± 2.5 % after the exercise programme (p=0.84). There were no changes in LV end-systolic and end-diastolic dimensions or volumes, intraventricular septum thickness, LV posterior wall thickness or LV mass. Early diastolic mitral filling wave E increased between the studies (87.8 ± 12.5 cm/s vs 95.3 ± 10.5 cm/s, p=0.04) indicating improved diastolic function, while mitral late filling wave A and E/A remained similar.

5.2.5.2 Tissue Doppler Imaging

During the intervention, early diastolic lateral mitral annulus velocity E' increased significantly (31.8 ± 5.5 vs 35.0 ± 5.4cm/s, p<0.01) indicating improved diastolic function while A', E'/A', and septal velocities did not change.

5.2.5.3 Velocity Vector Imaging

The circumferential and longitudinal deformation of the LV was analysed with the VVI method. One of the 102 segments at the basal level and 10/102 segments at the apex level of the short-axis planes were excluded at the post-intervention study (1 subject with an unanalysable or missing view at the apical level). All segments at the mid/papillary muscle level of the parasternal short-axis views and apical 4-chamber views were analysable at post-intervention.

PCdiastSR increased significantly after the exercise programme (p<0.01) at the mid/papillary muscle level of the cardiac short axis views indicating improvement in circumferential diastolic deformation of the cardiac muscle. In addition, the global PCSR and PCdiastSR increased between the studies (p=0.04 and p=0.03 respectively). The LV longitudinal measures did not change between the studies (Figure 10, Figure 11, Figure 12, Table 11).

Table 11 Velocity Vector Imaging measures in ALL survivors at baseline, ALL survivors after the intervention, and in controls

	ALL survivors at baseline			ALL survivors after the intervention				Controls			
Parasternal Short Axis View	N	Mean	SD	N	Mean	SD		N	Mean	SD	
Basal											
PRV (cm/s)	17	2.51	0.54	16	2.65	0.46		18	2.57	0.36	
PCS (%)	17	-18.95	3.06	16	-19.94	3.54		18	-19.23	2.23	
PCSR (1/s)	17	-1.11	0.20	16	-1.27	0.22		18	-1.16	0.18	
PRD (mm)	17	5.06	1.13	16	5.21	0.95		18	5.25	0.77	
PCdiastSR (1/s)	15	1.13	0.24	16	1.18	0.23		18	1.19	0.23	
Mid											
PRV (cm/s)	17	2.51	0.53	17	2.70	0.45		18	2.57	0.34	
PCS (%)	17	-20.53	3.79	17	-22.17	3.79		17	-21.64	2.99	
PCSR (1/s)	16	-1.18	0.21	17	-1.32	0.24	‡	18	-1.27	0.18	
PRD (mm)	17	5.22	1.31	17	5.52	1.13		17	5.40	0.74	
PCdiastSR (1/s)	17	1.21	0.26	17	1.43	0.33	†	18	1.34	0.23	
Apex											
PRV (cm/s)	17	2.28	0.33	14	2.43	0.51		19	2.44	0.42	
PCS (%)	17	-23.72	3.49	14	-25.09	5.51		19	-27.06	4.89	*
PCSR (1/s)	17	-1.41	0.20	13	-1.54	0.28		19	-1.65	0.33	*
PRD (mm)	17	4.69	0.86	14	4.76	1.01		19	5.12	0.90	
PCdiastSR (1/s)	17	1.44	0.25	14	1.65	0.46		18	1.69	0.39	
Global											
PRV (cm/s)	17	2.43	0.36	14	2.58	0.26		15	2.53	0.31	
PCS (%)	17	-21.07	2.80	14	-22.41	3.35		14	-22.54	2.88	
PCSR (1/s)	16	-1.24	0.13	13	-1.38	0.18	*	14	-1.34	0.17	
PRD (mm)	17	4.98	0.90	14	5.12	0.70		14	5.23	0.76	
PCdiastSR (1/s)	16	1.25	0.18	14	1.41	0.24	*	14	1.40	0.24	
Apical 4-chamber view											
PLV (cm/s)	17	2.80	0.43	17	2.88	0.71		20	2.77	0.49	
PLS (%)	17	-18.43	2.85	17	-18.03	3.53		20	-17.56	2.06	
PLSR (1/s)	17	-1.00	0.17	17	-1.00	0.28		20	-0.93	0.14	
PLD (mm)	17	6.16	1.09	17	6.28	1.39		20	6.06	0.97	
PLdiastSR (1/s)	17	1.05	0.21	17	1.05	0.30		19	1.02	0.19	

‡ $p=0.05$; * $p<0.05$; † $p<0.01$ compared to ALL survivors at baseline; Global measures are calculated from means of 18 segments across the SAX levels; PCdiastSR=Peak Circumferential Diastolic Strain Rate; PCS=Peak Circumferential Strain; PCSR=Peak Circumferential Strain Rate; PLD=Peak Longitudinal Displacement; PLdiastSR=Peak Longitudinal Diastolic Strain Rate; PLS=Peak Longitudinal Strain; PLSR=Peak Longitudinal Strain Rate; PLV=Peak Longitudinal Velocity; PRD=Peak Radial Displacement; PRV=Peak Radial Velocity; SAX=Short axis of the heart;

6 DISCUSSION

6.1 Study population and design of the intervention

The interest of this study were 16–30 year-old survivors of childhood ALL, because there had been no previous physical activity interventions in this population (Winter et al. 2010, Wolin et al. 2010). Adolescent and young adult survivors of this age face considerable challenges as they gain independence from their parents, form relationships, finish their education and find their occupation. At the same time, the regular control visits at the treating centre cease, and after that, most of the survivors are currently not followed up regarding their past disease or its potential late effects in Finland. Late effect programmes are, however, currently also under establishment in Finland (Taskinen et al. 2014). To include as homogenously treated group of survivors as possible in this age range, survivors treated with NOPHO ALL-86 or newer treatment regimens were included, and to gain sufficient number of participants, survivors from both Turku and Tampere University Hospital districts were invited. Due to long distance of some of the participants to the study location, and to minimise the school or workdays that the participants miss, the study was planned to be executable during a single day before and after the intervention.

Based on the analyses on the representativeness of the sample, our group of participants was similar to the rest of the eligible cohort in terms of current age, age at diagnosis, time since diagnosis, treatment protocol and intensity of the treatment, as well as their current perceptions on their own health and fitness. The self-reported levels of PA and BMI were also similar among the participating survivors and the postal questionnaire respondents. Thus, we assume that the sample represented the eligible cohort well. As expected, the reasons for non-participation were mostly due to long distance or difficulties in arranging the day free from work or school. In addition, the reasons for declining participation in the intervention and follow-up after the baseline study included strenuousness of the study day and especially the fitness tests. It is of note that people with low physical fitness are not used to sore muscles and exercising to their maximum in the fitness tests may be very off-putting, thus resulting in discouragement rather than encouragement.

The intervention was planned as home-based for two reasons. As the focus was on long-term survivors, the intention was to plan the intervention to be as simple as possible as to easily integrate it into the varying life circumstances of the participants, and to provide an example of relatively easy and cheap ways to improve fitness. In addition, the long distance of many of the participants from the study centre would not have enabled supervised/group sessions.

The participants also received pedometers and information on daily step goals to provide additional motivation to increase their daily PA. Generally, unsealed pedometers with diaries and information on step goals seem the most effective way to promote PA with pedometers (Bravata et al. 2007, Clemes, Parker 2009). However, the compliance towards the pedometers or at least filling in the diaries on daily steps was poor in the present study. In future studies, recording pedometer count only during certain weeks of the intervention might be a more successful strategy, as most of the existing studies have used 7-day recordings (Bravata et al. 2007, Clemes, Parker 2009), and reporting the counts from the device's memory on a weekly bases e.g. via telephone or web-based diaries should be considered. Furthermore, better compliance could be achieved with smart-phone applications, especially among children and young adults.

Overall, the intervention was successful in increasing fitness and improving CVRFs as well as endothelial function and cardiac measures. However, diary data on adherence to the programme was too incomplete to be analysed, and thus, conclusions on the compliance could not be made.

6.2 Physical activity and fitness

Directly measured VO_{2peak} is considered to be the best measure of physical fitness (Shephard et al. 1968). Peak oxygen uptake associates strongly with mortality in healthy individuals as well as those with existing cardiovascular disease, and there is growing evidence that physical inactivity and poor physical fitness are far more harmful than overweight alone (Blair et al. 1996, Wei et al. 1999, Laukkanen et al. 2001, Myers et al. 2002, Blair 2009, Kodama et al. 2009, DeFina et al. 2015). In the present study, survivors of childhood ALL had poorer physical fitness than the controls, and most notably, 5/10 of the males and 11/11 of the studied female survivors performed below their expected age-, gender- and weight-adjusted values. Accompanied with our results on anthropometric, endothelial, and cardiac measures, physical fitness seems to be an important aspect of the long-term survivors' health. Based on the PAI, recent levels of physical activity were similar in both ALL survivors and controls. However, it is alarming that over one third of the female survivors and almost one third of the male survivors had PAI $\leq$ 5MET h/week indicating $\leq$ one hour of moderate activity per week. It should also be kept in mind that the survivors tended to overestimate their fitness at baseline, and overestimation of current levels of PA and fitness is also likely in clinical practise.

Van Brussel et al. (2005) systematically reviewed the studies on physical fitness after ALL in children. In line with our findings, they concluded that VO_{2peak} tends to be reduced, and the difference to healthy controls is approximately 6 ml/kg/min or 13 % (van Brussel et al. 2005). More recently, Christiansen et al. (2015) studied maximal exercise capacity in 138 adult long-term survivors of childhood ALL diagnosed between

1970 and 2002, aged 18.6–46.5 years and treated according to the Nordic regimen in Norway. They found that 48 % of the survivors treated with low cumulative anthracycline doses (40-120 mg/m^2) had VO_{2peak} below expected while 67 % of the survivors treated with higher anthracycline doses (ad 485 mg/m^2) performed below the expected values (Christiansen et al. 2015). Their findings represent a survivor population most closely comparable to ours, and their results are in line with those of the present study. The mean VO_{2peak} in the study by Christiansen et al. (2015) was also comparable to ours in both the lower and higher dose anthracycline groups (34.4 ± 8.3 and 34.6 ± 8.8 ml/kg/min) (Christiansen et al. 2015).

Tonorezos et al. (2013) also studied maximal exercise capacity in a sample quite comparable to ours. One hundred and fifteen ALL survivors aged 18–37 years and diagnosed between 1970 and 2000 were studied (Tonorezos et al. 2013). Compared to the population controls, the ALL survivors in their study had attenuated VO_{2peak}, and the results remained similar after adjusting for body weight (mean difference 8.9 ml/kg/min), i.e. obesity did not seem to explain the lower fitness in their study (Tonorezos et al. 2013). Close to our findings, 66.7 % of the ALL survivors (79.7 % of females and 50.0 % of males) in their study were classified as having low cardiorespiratory fitness compared to 26.3. % of the population controls (females 28.0 %. males 24.1 %). Most strikingly, the estimated maximal METs in ALL survivors corresponded to that of 70-year-old individuals without cancer (Tonorezos et al. 2013). Tonorezos et al. (2013) also evaluated the effects of different treatment modalities on fitness. VO_{2peak} was lower in the CRT treated, but the effect of CRT was significant only in females while in males, the anthracycline dose seemed significant in multivariate models. Treatment with cyclophosphamide or dexamehasone did not affect the results significantly, and VO_{2peak} was also attenuated in those treated without anthracyclines (Tonorezos et al. 2013). However, the effect of e.g. vincristine was not addressed. Overall, the studied treatment-related factors accounted only for a small proportion of the variation in their sample (Tonorezos et al. 2013), and it seems likely that the reasons for attenuated fitness after ALL are multifactorial.

In addition to the impaired VO_{2peak} in the present study, the ALL survivors had a poorer performance than the controls in the 60-second sit-up test and maximal vertical jump test. A possible explanation for the poorer performance in these but not all muscle tests is that the abdominal and leg muscles may be more affected by a sedentary lifestyle. Another explanation is that, for example, the 60-second sit-up test requires more endurance than the 30-second back muscle and squatting tests. In addition, the attenuated performance in the vertical jump test might be due to e.g. prolonged effect of neuropathy caused by vincristine treatment. There are no previous reports on vertical jump test after ALL, but attenuated knee extensor strength (van Brussel et al. 2006, Ness et al. 2007) and passive ankle dorsiflexion range of motion (Wright et al. 1998, Hartman et al. 2013) have been reported, and these changes have been attributed to vincristine treatment.

Studies on motor evoked potentials at the end of ALL therapy and 5 years later have found prolonged latencies suggestive of demyelination and also attenuated amplitudes at the peripheral motor nerves suggestive of axonal injury and/or loss of muscle fibres, and vincristine has been suggested as a likely cause for these findings (Harila-Saari et al. 2001, Lehtinen et al. 2002). In addition to vincristine, corticosteroids and anthracyclines may potentially cause impairments in muscle function as reviewed by Scheede-Bergdahl (2013). The potential mechanisms include toxic effects on muscle satellite cells, denervation and mitochondrial dysfunction, and it has been hypothesised that chemotherapy during childhood may lead to progressive amplification of mitochondrial mutations leading to mitochondrial dysfunction in skeletal muscles in the long-term (Scheede Bergdahl, Jagoe 2013).

During the exercise intervention in the present study, VO_{2peak} and maximal work load improved by 5 % while the results of the sit-up, back extensor, and squatting tests improved by 6–8 %. A number of studies have described the effects of exercise programmes in adult cancer patients and survivors, but only a few have measured peak oxygen uptake, possibly due to the strenuousness of the method. A recent meta-analysis concluded that exercise is effective in improving aerobic and musculoskeletal fitness during and after cancer treatment in adults (McMillan, Newhouse 2011), and Repka et al. (2014) concluded that the effects of exercise on fitness and fatigue are similar in adult survivors of different cancer types (Repka et al. 2014). Compared to the present study, relatively similar improvements have been demonstrated in different patient populations. In the study by Laaksonen et al. (2000), 20–40 year old men with diabetes mellitus type 1 were engaged in a 12–16 week exercise intervention consisting of moderate aerobic exercises of 30–60 minutes, 3–5 times a week. During the intervention, mean VO_{2peak} improved 2.7 ml/kg/min (6 %) (Laaksonen et al. 2000).

Effects of exercise interventions in patients with heart failure were recently meta-analysed by Ismail et al. (2013). While the improvement in cardiorespiratory fitness seems greater with increasing exercise intensity, the mean difference in VO_{2peak} after moderate exercise training was 2.17 ml/kg/min in patients with heart failure, but due to the low baseline values (mean 16.3 ml/kg/min), the weighted mean percent change was relatively high 13 % (Ismail et al. 2013). However, the results vary considerably between studies with different duration and settings (Ismail et al. 2013). As expected, studies on more intensive, supervised interventions tend to result in greater improvements in fitness (Ismail et al. 2013). In the study of adults with MetS at mean age of 50 years, 12 weeks of supervised aerobic exercise thrice a week improved VO_{2peak} by a mean of 4.4 ml/kg/min (11 %), and combined aerobic and strength training by 3.1 ml/kg/min (10 %) while strength training alone only improved maximal strength (Stensvold et al. 2010).

The mean values of PAI (MET h/week) improved by 29 % in the present study, but the improvement was not statistically significant. In addition to overestimation of their

current fitness at baseline, it is possible that the participants over-reported their PA at baseline and the reports at post-intervention might have been more realistic. In addition, despite the wide use of the PAI questionnaire in larger studies, its discriminative ability may be too poor in a small sample like ours as those with reported PA 2–6 times a week remain in the same category if the length and intensity of their exercise do not change.

Overall, the improvement in fitness in the present study is comparable to that expected from a home-based intervention. It is likely that a more intensive intervention with supervised training sessions would have yielded greater results. However, accompanied with the improvements in the other studied parameters, the intervention seems successful.

Currently, data on long-term effects of exercise interventions after childhood cancer is still scarce. Keats et al. (2008) studied the effects of a 16-week intervention with weekly group-session among childhood cancer survivors and concluded that despite a decline in results after the intervention, levels of PA, cardiorespiratory endurance, and muscle strength remained above baseline at the 12 month follow-up (Keats, Culos-Reed 2008). Studies in adult cancer patients have provided some data from repeated exercise tests to suggest that the positive effects of high-intensity resistance training on both muscle strength and cardiorespiratory fitness would persist at least one year beyond the intervention (De Backer et al. 2008) while others have concluded that at least the effects of a less intense home-based exercise intervention on fitness gradually fade during 6–12 months, and the effect on PA is not sustained (Thorsen et al. 2007). De Backer et al. (2008) did not report on PA and despite the difference between baseline and the long-term follow-up, the difference between patients and controls was not maintained at the long-term follow-up (De Backer et al. 2008) possibly indicating only somewhat slower fading of the effects after a more intense training programme. However, these results may not be generalisable to long-term survivors of childhood ALL, as they were executed shortly after treatment. In addition, there are great differences in hospitalisation practices between different cancers and especially between children and adults, and the spontaneous recovery is likely to be different in children and adults as well.

The present study did not explore the reasons for low PA and sedentary lifestyle in ALL survivors. However, it can be hypothesised that 2–2.5 years of treatment and prolonged inactivity during childhood is likely to disrupt learning of athletic skills, and limitations in attending PA and e.g. team sports during early school years may interfere with the development of muscle function and adopting a physically active lifestyle. Parental attitudes play a great role in adopting a physically active lifestyle as well, as they may encourage a sedentary lifestyle while trying to protect their child from infections. In addition, phychosocial late effects like persistent fatigue have been reported in survivors of childhood ALL (Zeller et al. 2014), possibly associating with a lack of initiative and even depression which may further hinder the survivors abilities to attend PA. It is also

noteworthy that survivors with chronic fatigue seem to be less physically active than survivors without fatigue (Zeller et al. 2014).

Arroyave et al. (2008) studied the perceived barriers to improving exercise behaviours in adolescents and young adults after cancer treatment in childhood. Similar to studies in adult cancer patients reporting mostly time-constrains/being too busy, lack of will-power and fatigue as barriers to exercise (Courneya et al. 2005, Ottenbacher et al. 2011), the most commonly reported barriers among survivors of childhood cancer were being too tired, too busy, not belonging to a gym, and preferring other activities like TV, computers and books (Arroyave et al. 2008).

6.3 Cardiovascular disease risk factors and endothelial function

At the baseline study, BMI, fat %, and waist-to-hip ratio as well as fasting plasma insulin, glucose, cholesterol, and triglyceride values were similar in ALL survivors and controls. Supine diastolic blood pressure was higher in survivors, but overall the cardiovascular risk factor status was relatively similar in survivors and controls. Despite the fact that there were no significant differences in the occurrence of the Mets criteria between the groups, it is still noteworthy that 19 % of the ALL survivors had MetS compared to 10 % of the controls, and 62 % of the ALL survivors already met at least one of the criteria for MetS as adolescents or young adults. These numbers are quite comparable to those from the USA, where Nottage et al. (2014) found that in a slightly older population of ALL survivors, about one third of the ALL survivors had MetS (Nottage et al. 2014), and in a subset from the CCSS, the number was 17 % (Gurney et al. 2006). However, the prevalence of MetS seems to be equally high in the controls (Geenen et al. 2010, Gurney et al. 2006), and it is possible that the small sample in the present study may also accentuate the percentual difference between the groups. The number of survivors with at least two components of the MetS in the present study is also comparable to the studies from the USA (Oeffinger et al. 2001, Gurney et al. 2006), but somewhat higher than in other European studies (Geenen et al. 2010, Oudin et al. 2011) potentially reflecting the differences in the general population as well. CRT and growth hormone deficiency have been suggested as a potential cause for increased prevalence of CVRFs after ALL, especially in older studies (Nysom et al. 1999, Oeffinger et al. 2001, Link et al. 2004, Oeffinger et al. 2009, Geenen et al. 2010, Veringa et al. 2012, Nottage et al. 2014). However, in the present study, only five of the participants had received CRT. As a surrogate for GH status, IGF-1 values were comparable in ALL survivors and controls, and the cardiovascular risk factor status was equally poor in both groups. In contrast to some of the previous studies (Chow et al. 2010, Surapolchai et al. 2010, Nottage et al. 2014), the current age or time since diagnosis did not associate with most of the CVRFs either, but an older age at diagnosis associated with e.g. higher BMI as in another relatively small study as well (Oeffinger et al. 2001).

During the exercise programme, waist circumference, waist-to-hip ratio, fat %, diastolic blood pressure, fasting plasma insulin and HOMA-IR improved significantly, and especially the changes in fasting insulin and HOMA-IR were very notable. In addition, improvements in endothelial measures were seen after the exercise programme. There are no previous exercise interventions in childhood cancer survivors reporting on CVRFs and endothelial function. However, similar to the findings of the present study, Stensvold et al. (2010) found that in adults with MetS, 12 weeks of aerobic interval training, strength training or combination of these resulted in improvements in fitness, waist circumference and endothelial function (Stensvold et al. 2010). Despite no change in BMI in the presents study, the fat % and waist circumference improved indicating positive changes in body composition as also reported in adults with MetS (Stensvold et al. 2010). A meta-analysis on studies on breast cancer patients and survivors also concluded that despite an improvement in fitness, exercise alone does not seem to improve BMI significantly (McNeely et al. 2006).

Previous studies in healthy individuals have shown that in young adults e.g. higher waist circumference and fasting insulin levels associate with increasing IMT during a six-year follow-up (Koskinen et al. 2009). During these six years, recovery of MetS was associated with positive effects on vascular properties when compared with those in whom it persisted or appeared during the follow-up (Koskinen et al. 2010). In addition, it has been suggested that exercise also has other beneficial effects on vascular endothelium independent of the traditional CVRFs (Green et al. 2003, Pahkala et al. 2011).

In e.g. adults with type 2 diabetes, it has been stated that exercise improves endothelial function irrespective of glycemic control (Okada et al. 2010), and a recent meta-analysis concluded that the mean effect of exercise interventions on FMD in type 2 diabetic adults is approximately 2.23 percent units (Montero et al. 2013). A recent meta-analysis by Ashor et al. (2015) concluded that both aerobic and resistance training improve endothelial function measured with FMD in different adult populations, and they suggested a dose-response relationship between the aerobic exercise intensity and endothelial function, indicating a 1 percent unit improvement in FMD per 10 % increase in relative exercise intensity (VO_{2peak}) (Ashor et al. 2015). In line with this, FMD in the present study improved 0.54 percent units at the group level while VO_{2peak} improved by 5%.

The intervention in the present study was of a mixed type (aerobic and resistance training combined), and it is likely that in addition to VO_{2peak}, more intensive aerobic training would have yielded greater improvements in endothelial function as well. However, as the aim was to study a simple intervention executable without the study as well, our results on endothelial function and CVRFs combined were encouraging.

Despite a similar trend in FMDmax, FMDauc and IMT in both males and females at baseline, the effects of exercise were more clearly seen in males with regard to FMD and

in females with regard to IMT. However, there is no obvious explanation for this difference. In healthy adolescents, FMD is lower in males than females as was the case in present study as well (Pahkala et al. 2011). A study in healthy adolescents also suggested that gender does not significantly affect the effect of physical activity on FMD and IMT (Pahkala et al. 2011). However, the effect may be weaker in females due to the overall lower levels of PA (Pahkala et al. 2008). It is possible that the weaker improvement in FMD in females after the intervention in the present study is due to better baseline FMD and possibly lower adherence to the intervention, as higher amount of exercise may be needed to improve values within the normal range (Green et al. 2004).

The effects of exercise on FMD are mediated through functional adaptation and increased bioactivity of NO in the short-term, while structural changes are likely to occur in the long-term if the increase in exercise is maintained (Green et al. 2004). With regard to IMT, it is possible that rather than structural changes, the short-term changes are mediated through changes in vascular tone (Thijssen et al. 2012) as supported by the decrease in diastolic blood pressure in the present study. In addition, we did not adjust the study dates with the menstrual cycle of the females in this study, and it is possible that the varying estrogen levels may have affected the results in females (Hashimoto et al. 1995). However, it is also possible that the findings on IMT in females were coincidental as the sample size in the present study was small, especially when analysing the results separately for each gender. Thus, larger studies on this matter are needed before drawing definite conclusions on this gender difference in IMT response to the intervention found in present study. As some of the endothelial measures were statistically borderline significant, it is possible that a greater sample size would have shown the differences more clearly allowing also for comparisons between the different treatment characteristics and other factors possibly explaining the somewhat different results in males and females. Furthermore, the baseline FMD may also affect the magnitude of the response to training (Green et al. 2003).

In population-based studies, impaired brachial FMD seems to associate with increased CVD risk even after adjusting for traditional CVRFs, and based on a meta-analysis, a decrease of 1 percent unit in FMD is associated with an 8 % increase in future cardiovascular risk, while a decrease of 1 SD is associated with a 22 % increase in CVD risk (Inaba et al. 2010). Similar associations have also been shown for carotid IMT, and a recent meta-analysis concluded that in adults aged <45 years, carotid IMT associated with increased risk of first myocardial infarction or stroke, and a 1 SD increase in carotid IMT increased the risk 40 % after adjusting for other CVRFs (Eikendal et al. 2015). It can be hypothesised that in addition to the effects of e.g. sedentary lifestyle, endothelial damage caused by cancer treatment may be an important independent factor behind the increased cardiovascular risk in cancer survivors as previous studies have shown impaired FMD or carotid distensibility and compliance already in children shortly after cancer treatment or HSCT (Jang et al. 2013, Jenei et al. 2013, Turanlahti et al. 2013, Dengel et

al. 2014); these changes may be present before the emergence of traditional cardiovascular risk factors (Jenei et al. 2013, Turanlahti et al. 2013, Dengel et al. 2014).

While the excess weight gain during the first year of ALL treatment is likely to be at least partly due to increased appetite caused by the corticosteroid treatment (Chow et al. 2007, Jansen et al. 2009, Arpe et al. 2015), eating habits may also become distorted during the treatment as the uncomfortable treatments or diminished appetite during periods of nausea may cause the parents to comfort or reward their child with unhealthy food. Interview studies have suggested that parents feel responsible and stressed for the feeding difficulties experienced during treatment and both positive and negative coping strategies may emerge (Skolin et al. 2001, Fleming et al. 2015). Consequently, these altered eating habits may be difficult to abandon after treatment, possibly resulting in a prolonged unhealthy diet. Studies in adult survivors of childhood cancer have suggested equal adherence to dietary guidelines among cancer survivors and siblings or the general population, but the adherence to guidelines seems, nevertheless, insufficient (Landy et al. 2013, Berdan et al. 2014).

The concept of ideal cardiovascular health has been recently described by the American Heart Association, and it consists of seven factors including four ideal health behaviors and three ideal health factors (Lloyd Jones et al. 2010). The four ideal health behaviors are nonsmoking, BMI <25, and PA as well as diet consistent with current guidelines while the three ideal health factors include normal levels of total cholesterol, BP, and fasting glucose without medication (Lloyd Jones et al. 2010). In the Finnish Special Turku Coronary Risk Factor Intervention Project for Children, repeated dietary counselling was administered from infancy until 20 years of age, and they concluded that the risk for a low number (≤3/7) of ideal cardiovascular health metrics was lower among the adolescents in the intervention group compared to controls (Pahkala et al. 2013). In addition, the number of ideal cardiovascular health metrics in adolescents associated with vascular endothelial measures indicating that diet counselling is likely to be effective in promoting ideal cardiovascular health (Pahkala et al. 2013).

The present study did not focus on the effects of diet, but in addition to physical activity, healthy eating habits should be acknowledged as part of a healthy lifestyle among childhood ALL survivors as well. Very generally perceived barriers to healthy eating such as “not available at home”, “hard to get when dining out”, and “do not like the taste” have been reported among childhood cancer survivors, while barriers to limiting the consumption of high-fat foods included “commercials that make high-fat foods tempting” and “hard to get low-fat foods when dining out” (Arroyave et al. 2008). Even though these results on barriers to healthy eating may differ between the USA and Finland, they may not be that different from the general population. Parents play a key role, especially when it comes to availability of healthy products at home. With regard to eating healthy, both the parents and children should be the focus of future interventions.

In addition to the effects of healthy behaviours, it is likely that other mechanisms may also affect the development of overweight and obesity after ALL. However, little is known about the exact mechanisms between ALL and obesity, especially in the long-term. A further analysis of the ALLIFE cohort of 18–37 year-old ALL survivors revealed an increased leptin:adiponectin ratio in subjects with increased HOMA-IR (HOMA-IR>2.86) (Tonorezos et al. 2012). However, this was not seen in normal-weighted subjects (BMI<25) with increased HOMA-IR (Tonorezos et al. 2012). The authors have hypothesised that due to ALL or its therapy, the survivors might have a form of central leptin resistance that leads to inappropriate storing of energy, and this could be caused by either damage to the hypothalamus itself, disruption of communication between the hypothalamus and blood, or down-regulation of the hypothalamic leptin receptors (Tonorezos et al. 2012).

6.4 Subclinical anthracycline cardiac toxicity

A number of studies have attempted to evaluate the prevalence of subclinical ACT in childhood cancer survivors with varying methods. While van der Pal (2010) reported subclinical attenuations in LV FS (<30%) in 27 % of long-term survivors of childhood cancer treated with anthracyclines (van der Pal et al. 2010), Lipshultz et al. (1991) found that even 57 % of ALL survivors had signs of increased afterload or decreased contractility in echocardiography at a median of 6.4 years after anthracycline-containing treatment (Lipshultz et al. 1991). In a more recent study of 138 adult survivors of childhood ALL, Christiansen et al. (2015) reported that 12 % of the survivors had systolic dysfunction (LV EF <50 % or FS <25 % in males and <27 % in females), and 15 % had diastolic dysfunction (Christiansen et al. 2015).

Despite some evidence of the predictive value of left ventricular dimensions and LV FS at the end of therapy vs long-term follow-up (Lipshultz et al. 2005), it seems likely that traditional echocardiographic measures (LV dimensions, EF and FS) are not sensitive enough to identify individual survivors at risk of late ACT in the long-term. In the study by Lipshultz et al. (2005), all the children with late anthracycline-induced CHF had a previous history of early CHF after anthracycline therapy, and due to the relatively short follow-up (median 11.8 years after treatment), their sample did not include any cases of late ACT without early CHF (Lipshultz et al. 2005). As long-term survivors of childhood ALL also have increased risk for CV risk factors and later on other cardiovascular disease than anthracycline-induced CHF alone, further studies have concluded that LV FS is not sensitive enough to identify survivors at risk for premature CVD after childood cancer (Lipshultz et al. 2012).

The problem with the traditional echocardiographic measures is that when a clinically significant reduction in EF or FS can be found, the disease is likely to have progressed

relatively far and the effect of treatment may be limited. A recent prospective study in adult cancer patients with regular echocardiographic controls and early treatment in those with echocardiographic signs of ACT (>10 % unit decline and EF <50%) suggested that 9 % of the adults developed signs of ACT, and these signs were seen within 3–6 months after treatment (Cardinale et al. 2015). While 71 % of their cohort experienced partial recovery of EF, only 11 % completely recovered during the follow-up (Cardinale et al. 2015). The findings by Cardinale et al. (2015) also suggest that acute, early and late ACT may be parts of the same continuum rather than distinct phenomena (Cardinale et al. 2015). While it can be hypothesised that prospective studies with advanced methods and a long follow-up are likely to find early signs of ACT in those developing late ACT, the findings from adults may not be generalisable to children as growth demands and a longer life-expectancy may affect the course of ACT in children. Whatever the case may be, sensitive methods and prospective studies are needed in order to detect individuals with asymptomatic left ventricular dysfunction at an early stage, to provide appropriate medication for survivors at risk for CHF. It has been anticipated that the new non-invasive cardiac imaging techniques like advanced echocardiographic methods and cardiac MRI will provide screening-tools for the early detection of late ACT allowing interventions aimed at preventing CHF (Ness et al. 2011). However, the clinical significance of these methods remains to be seen.

Diastolic function can be evaluated with Doppler measurements of mitral inflow velocities and Tissue Doppler Imaging measures of mitral annular velocity. Abnormalities of myocardial relaxation are one of the earliest abnormalities of diastolic function, and invasive measures of myocardial relaxation correlate well with the TDI-derived velocity of mitral annular movement during early diastole, E' (Oh et al. 2011). Generally, attenuated E' as a sign of impaired myocardial relaxation is considered the first sign of diastolic dysfunction, and it remains attenuated at different stages of diastolic dysfunction (Oh et al. 2011). Studies in the general population suggest that E' is an independent predictor of cardiovascular and cardiac events (Kuznetsova et al. 2014). In addition to disease processes, E' also attenuates with aging as myocardial relaxation reduces (Oh et al. 2011). At early stages of diastolic dysfunction, the early mitral inflow velocity E also becomes attenuated and E/A reversed while the E deceleration time increases. At moderate stage, however, a pseudonormalisation of E occurs (Oh et al. 2011). Additionally, characteristic to diastolic dysfunction, an increased E/E' is a sign of increased LV filling pressure (Oh et al. 2011).

In the present study, early diastolic lateral mitral annulus velocity E' and E'/A' were attenuated and the ratio of early mitral inflow velocity E to E' increased at the LV lateral free wall in ALL survivors compared to controls indicating impaired LV relaxation and attenuated diastolic function in survivors. These finding are in line with previous studies showing attenuations in TDI-measures of diastolic function after anthracycline-containing treatment for childhood ALL (Rathe et al. 2007, Bayram et al. 2015,

Christiansen et al. 2015) and other cancers (Kapusta et al. 2000, Stapleton et al. 2007, Karakurt et al. 2008, Brouwer et al. 2011, Alehan et al. 2012, Yagci Küpeli et al. 2012). For example, Christiansen et al. (2015) found attenuated E' in anthracycline-treated ALL survivors at a median of 23.4 years since diagnosis, and increased E/E' in survivors treated with moderate-to-high anthracycline doses (>120 mg/m^2).

There are no previous studies on PA or exercise interventions in ALL survivors reporting on TDI measures. However, in their cross-sectional study, Christiansen et al. (2015) found that attenuations in E' correlated with poorer fitness (VO_{2peak}) (Christiansen et al. 2015). During the intervention in the present study, E and lateral E' improved indicating positive effects of increased PA on heart health of the survivors.

While TDI-based methods can also be used to measure regional myocardial dysfunction, more advanced ultrasound deformation techniques like 2-D speckle tracking echocardiography (STE) and VVI can be used to measure myocardial displacement, velocity, strain, and strain rate. Strain (%) is calculated from the change in length compared to the original length and it represents myocardial deformation, while strain rate (1/s) reflects this deformation per a time unit, i.e. speed (Abraham et al. 2007). As the heart shortens and lengthens in both longitudinal and circumferential direction, both longitudinal and circumferential strain and strain rate can be measured (Abraham et al. 2007) (Figure 5). Unlike TDI, STE methods and VVI are not limited by angle dependency and the required frame rate is lower (Oh et al. 2011). These methods are likely to be more sensitive than TDI in detecting subtle abnormalities in cardiac function, and they may also provide additional information on myocardial deformation after cancer treatment as reviewed by Mele et al. (2015).

Previous prospective speckle tracking echocardiographic studies in both children and adults (Fallah-Rad et al. 2011, Sawaya et al. 2011, Stoodley et al. 2011, Al Biltagi et al. 2012, Poterucha et al. 2012, Sawaya et al. 2012, Kang et al. 2013, Mavinkurve-Groothuis et al. 2013, Negishi et al. 2013, Stoodley et al. 2013a, Stoodley et al. 2013b, Florescu et al. 2014) have found attenuations in global longitudinal strain during or shortly after completion of anthracycline therapy and these changes seem to present earlier than changes in LV FS or EF. However, some of the studies have suggested that during a follow-up of 12 months, the attenuations seen with STE seem to resolve in most of the patients (Stoodley et al. 2013a). In addition to systolic longitudinal measures, Stoodley et al. (2013) studied diastolic measures with STE in breast cancer patients, and suggested that attenuated diastolic function associates with reductions in systolic strain (Stoodley et al. 2013b). Yoon et al. (2015) studied both longitudinal and circumferential (mid-level) STE measures in 40 children with acute leukaemia at a median of 9.2 months after HSCT (Yoon et al. 2015). Compared to controls, the patients had attenuated LV global circumferential strain, strain rate, diastolic strain rate, as well as longitudinal diastolic

strain rate. Circumferential strain and diastolic strain rate were especially affected in those treated with the highest (>400mg/m^2) cumulative anthracycline dose (Yoon et al. 2015).

Despite the fact that the acute or short-term changes in STE measures after anthracycline therapy seem rather similar in children and adults, these previous prospective studies do not yet have data extending to long-term survivors, and the results are likely to reflect acute or early anthracycline toxicity. As the risk for late ACT may be greater in growing children than adults, the significance of these short-term findings as predictors of late ACT remains to be seen in further studies.

As most of the previous studies describe only short-term effects of anthracycline treatment, data on myocardial deformation studies in long-term survivors of childhood cancer is scarce, and only a few studies have been published. Cheung et al. (2010) used STE to study myocardial deformation measures at a median of 6.3 years (range 2.7–19.8 y) after anthracycline (120–470 mg/m^2) treatment in childhood, and found attenuations in LV global longitudinal, circumferential, and radial strain, as well as circumferential strain rate compared to controls (Cheung et al. 2010). Christiansen et al. (2015) studied adult long-term survivors of childhood ALL, and found attenuated longitudinal strain in anthracycline treated survivors compared to those treated without anthracyclines. However, systolic or diastolic strain rate or circumferential measures were not reported in their study (Christiansen et al. 2015).

In addition to these published studies with other STE methods, only two previous publications have described VVI in survivors of childhood cancer (Park et al. 2009, Moon et al. 2014). Park et al. (2009) studied only longitudinal VVI measures in anthracycline treated (90–342 mg/m^2) children at least 3 years after treatment. Consistent with our findings, they found no difference in peak longitudinal global strain or strain rate between childhood cancer survivors and controls, but suggested attenuated longitudinal systolic and diastolic strain rate at septal segments (Park et al. 2009). Moon et al. (2014) analysed both longitudinal and circumferential (mid-level) VVI measures in childhood cancer patients with normal LV FS at a mean of 3.9 ± 4.0 years after diagnosis (mean anthracycline dose 356 ± 106 mg/m^2), and found an attenuated longitudinal strain and diastolic strain rate as well as circumferential strain, strain rate, and diastolic strain rate (Moon et al. 2014). Of these parameters, the diastolic strain rate seemed the most affected (Moon et al. 2014). In the present study, subclinical attenuations in circumferential strain and systolic and diastolic strain rate were seen in ALL survivors compared to healthy controls. However, it is not clear whether these findings are directly due to the long-term effects of anthracycline treatment in childhood or rather due to a sedentary lifestyle or poor fitness.

Generally, physical fitness is an indirect measure of heart health, but based on the present study, it is not possible to conclude whether those with signs of ACT have adopted a sedentary lifestyle after ALL treatment resulting in poor physical fitness, or whether the

TDI and VVI findings are merely related to poor physical fitness. However, improvements in these measures were seen after the exercise programme.

Previous studies on VVI and other STE methods after childhood cancer have either focused only on longitudinal or systolic measures, or the circumferential measures have been analysed only at one (basal or mid-cavity) level of the short-axis planes (Cheung et al. 2010, Poterucha et al. 2012, Yagci Küpeli et al. 2012, Mavinkurve-Groothuis et al. 2013, Moon et al. 2014, Christiansen et al. 2015, Yoon et al. 2015) while in the present study, circumferential VVI measures were analysed at three short-axis planes (basal, mid, apical), and diastolic strain rate was also included in the analyses. In addition to the differences in methodology, the Christiansen et al. (2015) study is the only one focusing on long-term survivors of childhood ALL (Christiansen et al. 2015). However, despite the differences in methodology and patient characteristics (anthracycline dose and length of follow-up), the findings of the present study on circumferential strain, strain rate and diastolic strain rate are in line with the previous studies (Cheung et al. 2010, Mavinkurve-Groothuis et al. 2013, Moon et al. 2014, Christiansen et al. 2015). Together with the results from the only study with circumferential VVI measures after childhood cancer (Moon et al. 2014), the present findings suggest that circumferential measures may be more sensitive than longitudinal measures in detecting subclinical signs of cardiac dysfunction in very long-term survivors of cancer in childhood. However, it is possible that including three views in the analysis of longitudinal function would bring additional value as well.

In the study population of the present study, VVI circumferential diastolic strain rate associated with anthracycline dose indicating greater attenuations in those treated with higher anthracycline dose as also reported by Yoon et al. (2015) in HSCT-treated patients (Yoon et al. 2015). In the present study, PCS also associated with anthracycline dose, but the association between systolic PCSR and anthracycline dose was not significant. Such an association was found in the STE study of Cheung et al. (2010), but they did not measure diastolic strain rate. Moon et al. (2014) also reported differences in circumferential systolic strain and strain rate between different anthracycline doses with a cut-off value of 300 mg/m^2, but as the study group in present study only included three survivors with anthracycline dose > 300mg/m^2, these kinds of comparisons were omitted.

After the exercise programme presented in the present study, improvements were seen in peak circumferential systolic and diastolic strain rate indicating positive effects of exercise on the myocardium in long-term survivors of childhood ALL. To date, there are no prior reports on the effects of exercise interventions on VVI or other myocardial deformation methods after childhood ALL or other cancer. These findings are novel and emphasise the positive effects of exercise in this population. However, the improvements were seen in partly different measures than the attenuations compared to the controls at the baseline study indicating that despite the positive effects of exercise, not all findings

are reversible. This also supports the idea that the attenuations at the baseline may be due to the anthracycline treatment rather than a sedentary lifestyle alone. However, it is possible that a longer or more intensive exercise programme might have been able to induce improvements in the baseline attenuations at the apex level as well.

Most of the previous studies on the effects of exercise on cardiac strain measures have been performed either in athletes or in previously sedentary adults with extreme training (triathlon) (Rojek et al. 2014), and are thus not comparable to present intervention. A study with longer lifestyle intervention in extremely obese adolescents showed improvement in longitudinal strain and diastolic strain rate measured with VVI (Obert et al. 2013). However, we do not know the magnitude of exercise effects on these measures in healthy but sedentary young adults.

6.5 Strengths and limitations of the study

The present study has various strengths. Physical activity interventions among long-term survivors of childhood cancer and especially adolescent and adult survivors of childhood ALL are still scarce, and the present study is among the first interventions focusing on adolescent and young adult survivors of childhood ALL. Instead of a mixed cancer population, the present study focused on a single diagnostic group treated as uniformly as possible. Moreover, the age range was relatively narrow, including survivors in the beginning of their adult life. Together, these criteria made the participating group as homogenous as possible. Another strength of the present study is that one analyst was able to perform all the endothelial and echocardiographic measures, fitness tests and anthropometric measures, respectively. This is especially important as new echocardiographic methods were used and the effects of an intervention were studied. Of note is that the present study is also among the first few studies on VVI in this population and the first to describe the effects of an exercise intervention on endothelial function and cardiac measures after ALL or other cancer treatment in childhood, thus presenting novel findings.

The main limitation in the present study is the relatively small sample size. Twenty-seven percent of the eligible cohort participated in the baseline study which is somewhat lower than the participation rate in recent cross-sectional studies in adult survivors of childhood ALL (Tonorezos et al. 2013, Zeller et al. 2013, Christiansen et al. 2015); it may well be that the differences in the setting and the inclusion of an intervention might have affected the participation rate compared to these studies. Efforts were made to evaluate the representativeness of the sample, and the analysis of the treatment-related background data and inclusion of the postal questionnaire group suggested that the sample represented the whole cohort well. However, as the proportion of survivors treated with high risk protocols was somewhat higher among the nonparticipants, it is possible that the

survivors most likely affected by the treatment were slightly underrepresented in this study. Additionally, some of the results were borderline significant, and it is possible that a larger sample size would have affected these borderline results. Guidelines on brachial FMD suggest including at least 20–30 subjects per group to allow sufficient statistical power (Corretti et al. 2002), and this was the target number of recruited survivors in present study as well. In future studies, analysing intraobserver variability would also be of help in assessing the statistical power.

We were not able to recruit a matched control group consisting solely of siblings, but in future studies, an all-sibling control group might further increase the comparability of the groups, and with a limited number of patients, recruiting a larger control group with e.g. three matched controls might be of value in increasing the power of the study as well. Moreover, extending the intervention to the control group might also have allowed more conclusions on the reversibility of the findings on vascular endothelium and the heart, as we would have been able to compare whether the effects of exercise are equal in ALL survivors and controls.

Lack of compliance with pedometers and/or physical activity diaries prevented reliable assessment of compliance with the intervention, as the PAI questionnaires also seemed too insensitive for this purpose in this rather small study group, and efforts should be made to overcome these obstacles in future studies. On the one hand, the lack of compliance with pedometers/diaries may still support the idea that in order to be effective, an intervention in this age group has to be simple and easily integrated into daily life. While a long-term follow-up would have been interesting in evaluating whether more permanent changes can be induced with this kind of intervention, we were not able to include e.g. a one-year follow-up of the intervention in this study. The study day was very strenuous for the participants and it seemed likely that many of the participants would have dropped out from a long-term follow-up. Together with our findings on possible over-reporting of PA at baseline and lack of compliance with the diaries, it seems likely that a long-term follow-up with only a partial sample would not have been powerful enough to allow clear conclusions. However, this should also be taken into account when planning future studies.

6.6 Future directions

Survivors aged between 16–30 years are at a critical point in their lives, where the follow-up in their original treating centre has ended and the survivors should be finding an occupation and beginning their adult life with all its challenges. To integrate sufficient levels of PA into the survivors' lives, patient education and promoting a physically active, heart-healthy lifestyle should be one of the most important focuses of long-term follow-up clinics that are currently under establishments in many countries. Cardiorespiratory

fitness is a strong predictor of CVD and all-cause mortality as well as cancer mortality in adult populations, and its role seems to be greater than that of the other established cardiovascular risk factors (Myers et al. 2002, Kodama et al. 2009, Schmid, Leitzmann 2015). Thus, increasing PA and fitness should be the primary goal of lifestyle interventions aimed at decreasing cardiovascular risk and mortality. In the present study, a simple home-based exercise programme was able to improve fitness, insulin resistance, endothelial measures, and cardiac measures but not BMI. This supports the idea that PA has beneficial health effects despite there being no change in BMI, and efforts aimed at increasing PA should be the primary means to health-promotion in ALL survivors as well.

In the future, simple means to promote PA in the daily lives of patients and survivors are needed to promote cardiovascular health and diminish late effects of ALL treatment in childhood. Even though the number of patients receiving CRT has further decreased since our cohort, the issues of sedentary lifestyle, poor fitness and cardiovascular health still seem current with patients diagnosed in the 2010's, as the survivors' fitness seems to be attenuated irrespective of their CRT status (Tonorezos et al. 2013, Ness et al. 2015).

As the current evidence on the long-term effects of interventions in cancer patients or survivors is still scarce (Jankowski et al. 2014), we do not know what is the most efficient way to promote PA and fitness in childhood cancer survivors. However, the findings of the present study indicate that it is nevertheless time to pay attention to these matters in clinical practice as well. If physical therapy resources are not prophylactively available at the university clinics, the attitudes of the personnel should be discussed to avoid unnecessary restrictions to PA during treatment, and especially during the maintenance phase. After treatment, these matters should be discussed with the survivors and parents at least yearly. In addition, a physical therapy session with individual recommendations on PA should be given for each patient at least at the end of the induction phase, at the end of treatment, and at adolescence, or at the time of transition to primary health care or long-term survivor care in order to promote a healthy, physically active lifestyle in the long-term.

Low PA was more common among female survivors than males in the present study, as is also the case in healthy Finnish adolescents (Pahkala et al. 2007), and this should be taken into consideration as well when planning ways to motivate the survivors to increase PA. It is of note that all the survivors in the present study considered their health to be average or better at the baseline study. While information on healthy lifestyle is given, we should be careful to avoid discouraging the survivors, especially during their adolescence, and the benefits of performing fitness tests have to be thought through individually.

Even though the clinical significance of the subclinical signs of ACT found with TDI and VVI remains to be seen in further studies, the positive effects of the exercise programme on these parameters as well as metabolic factors and vascular endothelium further

emphasise the importance of a physically active lifestyle on the health of the survivors. While it is encouraging that even a relatively simple home-based intervention was able to induce positive changes, efforts should be made to promote a heart-healthy, physically active lifestyle after ALL treatment in childhood. As long-term dietary interventions also seem effective in promoting cardiovascular health in healthy adolescents (Pahkala et al. 2013), the inclusion of a dietary component should also be considered in future intervention studies, especially if executed during or shortly after treatment.

While the prognostic significance of the cardiac findings should be evaluated in longitudinal studies, preferably beginning from diagnosis, the present findings in long-term survivors support the importance of long-term cardiac follow-up in this population. As only partial recovery of ACT-related CHF can be expected, even after prompt initiation of treatment based on reductions in EF (Cardinale et al. 2015), the new echocardiographic methods as well as cardiac MRI methods may become significant screening tools in the future (Ylänen et al. 2013, Ylänen et al. 2014). While the risk-based cardiac follow-up should be continued throughout life (once in every 1-5 years depending on age and treatment modalities), adding the new methods to the cardiac follow-up might be of value in the early recognition of those with emerging problems.

7 SUMMARY AND CONCLUSIONS

In this study of 16–30 year-old childhood ALL survivors, the following results were obtained:

- The cardiovascular risk factor status was equally poor in ALL survivors and age- and sex-matched controls
- Insufficient physical activity was alarmingly common in ALL survivors as one third of the ALL survivors reported less than one hour of moderate activity weekly
- Physical fitness was lower in ALL survivors compared with the controls, and especially female survivors performed poorly
- Endothelial function was attenuated in ALL survivors compared to the controls, and this was seen especially in males
- Subclinical attenuations in cardiac function were found in ALL survivors compared to controls with both TDI and VVI echocardiographic methods
- The exercise programme improved insulin sensitivity, fitness and endothelial function as well as echocardiographic TDI and VVI measures

Despite the rather similar CVRF status in ALL survivors and controls, the number of survivors who already had at least one established CV risk factor (62 %) at this young age underlines the importance of cardiovascular risk factor status in this population, as their risk for cardiovascular morbidity and mortality may also be increased due to the independent effects of sedentary lifestyle and anthracycline treatment on e.g. vascular endothelium. Insufficient physical activity and poor physical fitness were alarmingly common especially among female survivors. While the present findings on the effects of exercise on endothelium are encouraging, larger studies with controlled interventions would be needed to further clarify the somewhat different findings on endothelium in males and females. In addition, controlled interventions would be needed to confirm whether the effect of exercise on endothelium is equal in ALL survivors and controls. In addition, despite the improvements in some of the VVI measures after the exercise programme, not all baseline findings were reversible with exercise, thus possibly suggesting permanent effects of anthracycline treatment.

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