The role of physical exercise on cardiovascular disease in breast cancer patients

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The role of physical exercise on cardiovascular disease in breast cancer patients

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Voor mijn vader

CHAPTER 1

General Introduction

Over the last decades, the number of individuals living with and beyond a cancer diagnosis has gradually increased[1]–[3]. In 2020, nearly 20 million new cancer cases were detected worldwide, and projections forecast this will grow to 28.4 million new cases by 2040[2]. The increase in cancer incidence is attributed to both the growing and aging of the population, as well as changes in the prevalence of cancer risk factors[1]–[3]. In middle-to high-income countries, the increasing cancer incidence rate is, in varying degrees, paralleled by a graduate decline in mortality rates for most cancers, primarily due to (ongoing) successes in cancer care and early diagnosis[1], [2]. In the Netherlands, for example, the ten-year survival of non-metastasized breast cancer increased by 24% since 1989[4]. In this context, adequate care to reduce the impact of cancer's short- and long-term side effects and its treatment is increasingly important.

1. PHYSICAL EXERCISE

Until the 1990s, and in many countries until recently, cancer patients were advised to rest and refrain from strenuous physical activity directly after diagnosis. Over the last decades, however, physical exercise has been increasingly recognized as an effective strategy to offset various side effects in cancer patients and survivors, and inactivity is more often recognized as detrimental. In 2010, the American College of Sports Medicine (ACSM) concluded that exercise training during and after cancer treatment is generally safe and well-tolerated[5]. Also, there was sufficient evidence that exercise could improve some cancer-related adverse effects, including fatigue, physical fitness, quality of life, and physical functioning, and cancer survivors were advised to avoid inactivity and adhere to general physical activity guidelines (i.e., at least 150 minutes per week of aerobic activity and two times per week of resistance training)[5]. Since then, the number of exercise-oncology studies more than doubled to over 2500 randomized controlled trials in 2018[6]. Recent insights have been incorporated in the 2018 updated ACSM exercise guidelines for cancer survivors[6]. For 16 clinically relevant adverse effects, the available evidence in terms of exercise benefits was evaluated, and if sufficient evidence was available, a more detailed exercise prescription in terms of frequency, intensity, time, and type (FITT) of exercise was formulated.

There is yet insufficient evidence for seven health outcomes to ascertain the effect of exercise, primarily due to a lack of (randomized) studies with these parameters as the primary outcome[6] (Table 1). These outcomes include two

of the most common and burdensome long-term sequelae of cancer and its treatment; cardiotoxicity and cognitive function. Also, given that improvement in chemotherapy regimens is proposed as one of the key attributor to increased survival rates, chemotherapy treatment tolerance is a health outcome of particular clinical interest.

Table 1. Available evidence of exercise per health outcome, as described by the ACSM exercise guidelines for cancer survivors [6].

Outcome	Available evidence scored as:
Anxiety	Strong
Bone health	Moderate
Cardiotoxicity	**Insufficient**
Chemotherapy-induced peripheral neuropathy	Insufficient
Cognitive function	**Insufficient**
Depressive symptoms	Strong
Falls	Insufficient
Fatigue	Strong
Health-related quality of life	Strong
Lymphedema	Strong
Nausea	Insufficient
Pain	Insufficient
Physical function	Strong
Sexual function	Insufficient
Sleep	Moderate
Treatment tolerance	**Insufficient**

1.2 Cardiovascular disease in (breast) cancer patients

Cancer and CVD were conventionally considered two different entities and managed accordingly. However, increasing evidence suggests an overlap between the two diseases. Cancer and CVD share common risk factors, such as age, genetics, and lifestyle-related factors[7], [8]. Some even theorize that having one of the two diseases could be considered a risk factor for the onset of the respective other disease[9]. A recent study described a direct effect of the tumor on cardiac function, even before the receipt of cardiotoxic cancer treatment[10]. Vice versa, a diagnosis of heart failure is associated with enhanced tumor growth, and increased cardiac biomarkers were found to predict new-onset cancer, irrespective of risk factors for cancer[11]. Biologically, multiple pathways have

been identified that are common to both cancer and CVD, including inflammation and resistance to cell death[12]. CVD risk is further augmented during cancer treatment, especially in patients receiving anthracyclines, thoracic irradiation, or anti-HER2 agents. In a meta-analysis of nearly 50,000 cancer patients treated with contemporary anthracycline-based regimens, the incidence of cardiotoxicity was 6% (95% confidence interval (CI) 3%-9%) after a median follow-up of nine years[13]. A pooled analysis of 11,882 breast cancer patients described an LV ejection fraction (LVEF) decline of 7.5% (95%CI, 4.2%-13.1%) following trastuzumab treatment[13]. Observational data show even higher incidences, especially in older breast cancer patients (>75 years)[14] and those receiving both anthracyclines and trastuzumab[15].

Definition and diagnosis of cancer therapy-related cardiovascular toxicity

Since the development of the interdisciplinary field of cardio-oncology in the late 1990s [16], various terminologies have been proposed to describe CVD in cancer patients. Most former oncology trials reported cardiac side effects, if reported at all, via the common terminology criteria for adverse events (CTCAE), varying from grade 1 to grade 5[17]. The CTCAE scoring system often does not overlap with heart failure or conventional cardiology guidelines (such as the NYHA classification)[18]. Also, it predominantly focuses on systolic dysfunction and heart failure events, while the currently prevailing hypothesis is that CV toxicity encompasses a whole spectrum of CVD, including myocarditis and hypertension[19].

To uniform the understanding and definition of what constitutes CV toxicity, the recent definition of 'cancer therapy-related cardiovascular toxicity; CRT-CVT' was proposed and adopted in the first cardio-oncology guidelines[18], [19]. CTR-CVT includes five CV disease categories: (1) cardiac dysfunction / heart failure; (2) myocarditis; (3) arrhythmias and QT prolongation; (4) hypertension, and (5) vascular toxicity[18]. Cardiac dysfunction during or after cancer therapy, the most notorious CV complication given its association with poor prognosis[20], is currently diagnosed in the presence of CV symptoms, cardiac imaging, and cardiac biomarkers (*i.e.,* troponin and NTproBNP)[19]. Echocardiography is the first imaging modality of choice, with LVEF and global longitudinal strain (GLS) as the most important parameters. GLS is defined as the proportion of shortening of the myocardium in a longitudinal direction during systole, compared to diastole, and expressed as a (negative) percentage. This parameter has been proposed as an earlier parameter of CTR-CVT, given that a GLS decline is predictive of future

overt systolic decline and cardiomyopathy [21]. In addition to echocardiography, a cardiac MRI scan can be performed, which provides the most accurate cardiac parameters independent of patients' habitus. Also, cardiac MRI holds the potential for tissue characterization via, among others, late-gadolinium enhancement and extracellular volume fraction (ECV) measurements. These parameters are considered non-invasive measurements of focal and diffuse myocardial fibrosis, respectively[22]. Since autopsy studies describe diffuse myocardial fibrosis as a hallmark of cancer therapy-induced cardiotoxicity[23], ECV measurements seem particularly interesting in a cardio-oncology context. However, due to the limited availability and relatively high costs of cardiac MRI imaging, this modality is unsuitable for first-line imaging and, thus, complementary to echocardiography. In the UMC Utrecht, we perform cardiac MRI imaging in patients with abnormal LVEF or GLS or poor acoustic windows on echocardiography (e.g., obesity, left-sided mammary implants) or to rule out other causes of LV dysfunction, such as myocardial infarction or myocarditis[24]. It has been suggested that structural cardiac abnormalities (ECV and troponin) precede functional decline (GLS and in a later stadium LVEF)[25], although evidence from longitudinal (imaging) studies in cancer patients to support this hypothesis is limited.

The development of CVD during and after cancer survival significantly affects morbidity, quality of life, and overall survival [26]–[29]. CVD is currently the major competing cause of mortality in patients with early-stage breast cancer[30]. For older survivors or those with pre-existing CVD at the start of cancer treatment, CVD even surpasses breast cancer itself as the leading cause of death[27], [30], [31], leading some to argue that the heart has become "the victim of the modern breast cancer treatment" [32]. This context calls for preventive measures to offset the increased CVD risk. Most research has been focused on cancer treatment alterations (e.g., breath-holding radiotherapy and modifications in anthracycline schemes) and pharmacotherapeutic adjuncts, including neurohormonal therapies, renin-angiotensin-aldosterone system blockers, and dexrazoxane[19]. Although some evidence suggests that these interventions could prevent some decline in LVEF[33]–[35], no clear benefit in reducing the incidence of heart failure or other clinically relevant outcomes has been demonstrated so far.

Physical activity (PA), or the lack thereof, has been proposed as the main predisposing factor for the development and progression of CVD in the general population[36]. In populations with CVD, various aerobic exercise interventions have been found to improve cardiac outcomes [37], [38]. Mediators of these

beneficial effects include, among others, improvement of the CVD risk profile (i.e., lower blood pressure, better blood lipids profile, and higher insulin sensitivity), changes in cardiac metabolism, and decreased atherosclerotic plaque formation. To this end, exercise is considered an integral part of care in many cardiac populations, such as post-myocardial infarction patients [39], [40].

For cancer patients, however, evidence on exercise-mediated cardioprotection is limited. In rodent studies, almost all studies unanimously report positive effects of exercise on anthracycline-induced cardiotoxicity[41]. Until now, six randomized trials have studied the effect of exercise training during chemotherapy on cardiotoxicity within the first year of treatment (Table 1). Although some report positive effects on either LVEF or troponin, no study has been able to provide conclusive results that demonstrate exercise-mediated cardioprotection in a clinical setting. A study by Chung et al. did find that LVEF was preserved in the exercise arm, while a significant decline (from 71±5% to 62±2%) was observed among control participants after a follow-up of 12 months[42]. However, since overall LVEF was still remarkably high at follow-up, with no participants having an LVEF (close) to the lower limit of normal (LVEF<50%), these findings are of uncertain clinical importance. A relatively large study by Foulkes et al. demonstrated that exercise resulted in less of an increase in cardiac troponin post-chemotherapy, favoring the exercise arm[43]. These findings were not corroborated by resting cardiac imaging in this study, which is surprising, given that all prior research demonstrates that 95% of the cases with cardiotoxicity can be identified by a GLS decline within the first year after treatment[44]. The authors report better peak exercise parameters of cardiac function following exercise[43]. The study by Ma observed that the exercise program preserved LVEF, in contrast to the control arm[45]. However, given the low methodological quality of this study, results need to be interpreted with caution.

Table 2. Randomized studies on the effect of exercise on cardiotoxicity in cancer patients.

Reference	Study population		Study characteristics		Outcome				
	Patients	**AC dose (mg/m²)**	**Exercise specifications**	**Follow-up**	**Imaging modality**	**LVEF**	**GLS**	**Biomarkers (NTproBNP and troponin)**	**Tissue characterization**
Antunes, 2013	Early-stage breast cancer EX: N=47 CON: N=46	416 DOX	Aerobic and resistance, 2-3 sessions per week for 12 weeks.	12 weeks	2D-echo	EX = CON	EX = CON	EX = CON	-
Chung, 2022	Early-stage breast cancer EX: N=16 CON: N=16	240 DOX or 450 EPI	Aerobic and resistance, 2-3 sessions per week for 12 weeks.	12 weeks	2D-echo	EX > CON	-	-	-
Foulkes, 2022	Early-stage breast cancer EX: N=52 CON: N=52	240 DOX	Aerobic and resistance, 3 phases for 12 months**		Cardiac MRI, 3D-echo	EX = CON (in rest)	EX = CON (in rest)	Troponin: EX > CON NTproBNP: EX = CON	-
Hornsby, 2014	Early-stage breast cancer EX: N=16 CON: N=16	240 DOX	Aerobic, 3 sessions per week for 12 weeks.	12 weeks	2D-echo	EX = CON	-	-	-

Table 2. (Continued)

Reference	Study population		Study characteristics		Outcome				
Kirkham, 2018	Early-stage breast cancer. EX: N=13 CON: N=11	240 DOX	1 bout of aerobic exercise before each gift of DOX	12 weeks	2D-echo	EX = CON	EX = CON	EX = CON*	-
Ma, 2018	Breast cancer EX: N=31 CON: N=33	NR	Aerobic, 3 sessions per week for 16 weeks.	16 weeks	2D-echo	EX > CON*	-	-	-

* The 12-month program consisted of three phases. Phase 1, during chemotherapy: 3 sessions per week for 12 weeks, supervised. Phase 2: 4 sessions per week (2 supervised and 2 unsupervised) for 14 weeks. Phase 3: 4 sessions per week, unsupervised with remote support for 26 weeks.

** Troponin only, NTproBNP was not measured.

*** only within-group differences are tested, no between-group differences.

Abbreviations

AC = anthracyclines, CON = control, DOX = doxorubicin, EPI = epirubicin, EX = exercise, GLS = global longitudinal strain, LVEF = left ventricular ejection fraction.

To increase our knowledge of the role of exercise as a means for offsetting CTR-CVT, multiple issues need to be addressed. First, additional research on the underlying mechanisms via which exercise can potentially exert cardio-protection in cancer patients is necessary, given that pathogenesis of CVD in this patient category is likely different from non-cancer patients. Identification of these mechanisms could aid in the optimization of future exercise programs. Second, adequately powered studies with more extensive follow-up periods are necessary. Except for the investigation by Foulkes et al., all studies to date have limited sample sizes with ~10-20 participants per study arm. Also, the first subclinical changes in myocardial function following anthracyclines may up to one year after treatment to become apparent on echocardiography[44]. However, the indirect effects of cancer treatment, such as the increased risk of arterial hypertension or dyslipidemia[46], may take months or even years to alter clinical outcomes. Thus, a surveillance period that extends at least beyond the first years after treatment, is necessary to adequately establish the effect of exercise on CTR-CVT. Last, studies with more accurate outcome assessments are required. All currently available evidence is derived from studies using 2D echocardiography, mostly with LVEF as the primary outcome parameter. Prior research in cancer patients identified that variability in 2D-LVEF assessment over time could be as high as 10-13 percentage points due to acquisition differences and observer variability[47]. Cardiac MRI is currently considered the reference standard for accurate LVEF assessment[48]. An additional argument favoring cardiac MRI is that this modality has the potential for myocardial tissue characterization by, for example, visualizing and quantifying cardiac edema and fibrosis. Given the prevailing hypothesis that cardiac tissue abnormalities precede functional impairment[25], with a decline in LVEF considered a rather late sign of cardiotoxicity[44], cardiac MRI is more likely to diagnose CTR-CVT more accurately and in an earlier stage.

1.3 Cognitive function in (breast) cancer patients

Cancer-related cognitive impairment (CRCI) is common in breast cancer patients, especially in those treated with chemotherapy. The prevalence of CRCI varies across studies and depends on the definition and treatment phase (i.e., before, during, or after treatment). A recent meta-analysis indicated that approximately one in three breast cancer survivors may experience clinically significant CRCI during or after treatment[49]. Although cognitive complaints are generally mild to moderate in nature[50], they can have a profound impact on survivors' functional capacity, ability to return to work, and, thereby, their overall quality of

life[51]. Although cognitive behavioral therapy may offer a practical approach to enhancing cognitive function in daily life[52], no treatment is currently available to counteract the occurrence of CRCI.

Physical exercise during chemotherapy seems promising in terms of preventing cognitive impairment following chemotherapy[53]. Evidence from clinical studies is, however, limited and primarily based on studies that used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) questionnaire[54] which has a cognitive functioning subscale of only two items and therefore limited discriminative ability. In the systematic review by Zimmer et al, three of the included randomized trials reported statistically significant differences favoring the exercise arm, while the remaining six studies found null results[53]. None of the studies included objective cognitive testing. Also, all studies focused on the short-term effects of exercise on cognitive function, while cancer patients may experience CRCI years or even decades after treatment. Whether exercise during chemotherapy has lasting effects and thus translates into less CRCI years after treatment is currently unknown.

1.4 Chemotherapy treatment tolerance

Ongoing successes in improving (adjuvant) chemotherapy are considered the key attributors to increased survival rates in breast cancer patients. However, even in the current era of supportive care, over a quarter of breast cancer patients fail to adhere to the chemotherapy regime as prescribed[55], leading to suboptimal overall – and recurrence-free survival[56].
Prior research identified the elderly and those with a poor performance status before cancer diagnosis as being at risk for not completing chemotherapy as planned[57]. Conversely, exercise during chemotherapy may improve chemotherapy tolerance, although all currently available evidence is derived from secondary (underpowered) analyses from randomized studies. Also, there is a lack of uniformity in the definition of "chemotherapy completion", complicating the interpretation of the study results.

2. THE PACT-PACES-HEART STUDY

To improve our knowledge of the role of exercise as a means for offsetting cancer-related adverse effects in survivors, we designed a long-term follow-up study, the Pact-Paces-Heart study. This study is a combination of two previously performed randomized controlled trials; the Physical Activity during Cancer Treatment (PACT) study[58] and the comparable Physical exercise during Adjuvant Chemotherapy Effectiveness Study (PACES)[59]. Both trials included patients with non-metastasized breast cancer scheduled for adjuvant chemotherapy and reasonably capable of participating in an exercise program. The studies were conducted between 2010-2013 in the Netherlands. The PACT study reported positive effects of the 18-week moderate-to high-intensity aerobic and resistance exercise program on physical fatigue, submaximal cardiorespiratory fitness, and muscle strength. In PACES, the moderate-to high-intensity aerobic exercise program offered throughout chemotherapy treatment effectively prevented cardiorespiratory fitness, physical functioning, pain, nausea, and vomiting and improved treatment tolerance compared to non-exercise controls. For the second intervention arm, a home-based, low-intensity exercise program, similar yet smaller intervention effects than the high-intensity program were observed.

The comparability of these studies in terms of study design, study population, and timing allows for effective combining of PACT and PACES participants in the follow-up study. At the time of setting up that study, most participants were between seven and nine years after treatment (Figure 1). Eligible participants were all original PACT or PACES participants currently free of recurrent or metastasized breast cancer. The primary focus of the study was the effect of exercise on (long-term) CVD, which was assessed with a cardiac MRI, echocardiography, and a cardiopulmonary exercise test (CPET). Also, venous blood samples were drawn and stored in a biobank to enable future studies on cardiac biomarkers. To evaluate the effect of exercise on long-term cognitive function, participants were asked to complete online objective cognitive tests and questionnaires on self-reported cognitive complaints. Last, outcomes of the original PACT and PACES trials, such as fatigue and quality of life, were re-assessed in the follow-up study to enable the evaluation of the effect of the exercise program on these outcomes.

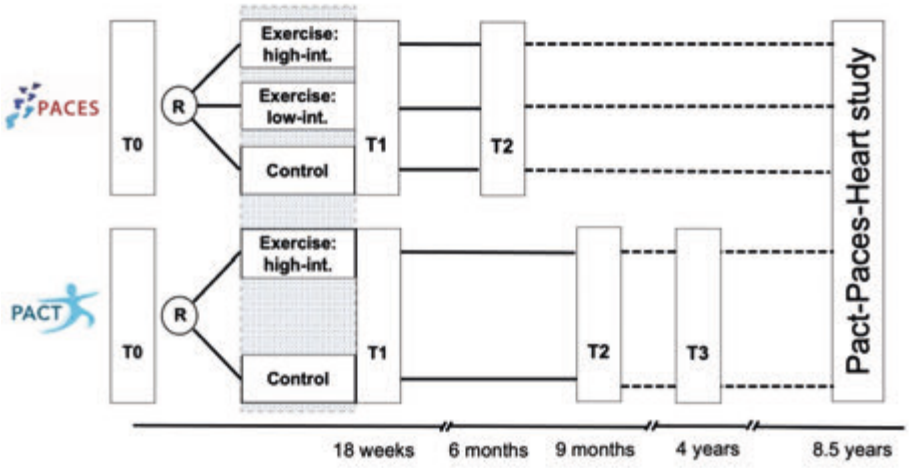

Figure 1. visualization of the design of the original PACT and PACES studies, and the follow-up Pact-Paces-Heart study.

AIM AND OUTLINE OF THIS THESIS.

The first aim of this thesis is to expand our current knowledge of exercise and physical activity in the field of cardio-oncology. **Chapter 2** aims to provide a comprehensive overview of the CV complications in adult cancer survivors years after treatment. This review focuses on the CV consequences of patients treated with radiotherapy, chemotherapy, and targeted therapy. In **Chapter 3**, we present the results of a systematic review and meta-analysis that aimed to quantify the effect of exercise on cardiotoxicity and report on mechanisms underlying exercise-mediated cardio-protection in animal studies. To describe all available evidence, we included both preclinical and clinical studies. We used a quantitative analysis to obtain a pooled estimate of the effect of exercise on cardiotoxicity and a narrative synthesis to describe all underlying pathways systematically. In **Chapter 4**, we used data from a large, previously established cohort of breast cancer survivors treated at ages 40-50 years old. Women in this cohort were included 5-7 years or 10-12 years after chemotherapy treatment. Cardiac function and physical activity were assessed with 2D echocardiography with strain analysis and questionnaires, respectively. We studied the association between self-reported physical activity in the past years and echocardiographic parameters of cardiac dysfunction. In **Chapter 5**, we present the

main results of the Pact-Paces-Heart study, *i.e.,* the effect of exercise during adjuvant chemotherapy for breast cancer on long-term cardiovascular toxicity. We compare cardiac parameters, assessed with cardiac MRI and echocardiography, between breast cancer survivors randomized to exercise during chemotherapy to non-exercise controls, on average 8.5 years post-treatment. Also, we evaluated the association between levels of physical activity during chemotherapy, independent of randomization to the exercise program, and cardiac outcomes years after treatment.

In the second part of this thesis, we focused on the role of physical exercise in improving other cancer treatment-related outcomes. In **Chapter 6**, we assessed the association between pre-treatment levels of physical fitness and chemotherapy completion rates in patients with early-stage breast cancer. We used data from the original PACT and PACES studies for these analyses, and we complemented this with medical data concerning chemotherapy completion. We also evaluated if participation in the exercise program modified the association between pre-treatment physical fitness and chemotherapy completion. In **Chapter 7**, we assessed the long-term effect of exercise during chemotherapy for breast cancer on cognitive functioning in participants of the Pact-Paces-Heart study. Cognitive outcomes included both objectively tested cognitive performance via an online neuropsychological test battery and self-reported complaints, which were assessed via questionnaires. Also, we examined the association between levels of physical activity during chemotherapy and levels of physical activity at follow-up and cognitive outcomes.

Finally, in **Chapter 8**, we discuss our main findings, as well as, with a specific focus on cardio-oncology, methodological and clinical considerations of our studies. We also report recommendations for future studies.

REFERENCES

[1] K. D. Miller et al., "Cancer treatment and survivorship statistics, 2016.," CA Cancer J Clin, vol. 66, no. 4, pp. 271–289, Jul. 2016, doi: 10.3322/caac.21349.

[2] H. Sung et al., "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.," CA Cancer J Clin, vol. 71, no. 3, pp. 209–249, May 2021, doi: 10.3322/caac.21660.

[3] J. M. Kocarnik et al., "Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019.," JAMA Oncol, vol. 8, no. 3, pp. 420–444, Mar. 2022, doi: 10.1001/jamaoncol.2021.6987.

[4] IKNL, "Overleving borstkanker." https://iknl.nl/kankersoorten/borstkanker/registratie/overleving (accessed Apr. 26, 2023).

[5] K. H. Schmitz et al., "American College of Sports Medicine roundtable on exercise guidelines for cancer survivors.," Med Sci Sports Exerc, vol. 42, no. 7, pp. 1409–1426, Jul. 2010, doi: 10.1249/MSS.0b013e3181e0c112.

[6] K. L. Campbell et al., "Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable.," Med Sci Sports Exerc, vol. 51, no. 11, pp. 2375–2390, Nov. 2019, doi: 10.1249/MSS.0000000000002116.

[7] R. J. Koene, A. E. Prizment, A. Blaes, and S. H. Konety, "Shared Risk Factors in Cardiovascular Disease and Cancer.," Circulation, vol. 133, no. 11, pp. 1104–1114, Mar. 2016, doi: 10.1161/CIRCULATIONAHA.115.020406.

[8] T. J. Pfeffer, S. Pietzsch, and D. Hilfiker-Kleiner, "Common genetic predisposition for heart failure and cancer.," Herz, vol. 45, no. 7, pp. 632–636, Nov. 2020, doi: 10.1007/s00059-020-04953-9.

[9] D. E. Giza, G. Iliescu, S. Hassan, K. Marmagkiolis, and C. Iliescu, "Cancer as a Risk Factor for Cardiovascular Disease," Curr Oncol Rep, vol. 19, no. 6, Jun. 2017, doi: 10.1007/S11912-017-0601-X.

[10] N. Pavo et al., "Cardiovascular biomarkers in patients with cancer and their association with all-cause mortality.," Heart, vol. 101, no. 23, pp. 1874–1880, Dec. 2015, doi: 10.1136/heartjnl-2015-307848.

[11] W. C. Meijers et al., "Heart Failure Stimulates Tumor Growth by Circulating Factors.," Circulation, vol. 138, no. 7, pp. 678–691, Aug. 2018, doi: 10.1161/CIRCULATIONAHA.117.030816.

[12] V. Narayan, E. W. Thompson, B. Demissei, J. E. Ho, J. L. J. Januzzi, and B. Ky, "Mechanistic Biomarkers Informative of Both Cancer and Cardiovascular Disease: JACC State-of-the-Art Review.," J Am Coll Cardiol, vol. 75, no. 21, pp. 2726–2737, Jun. 2020, doi: 10.1016/j.jacc.2020.03.067.

[13] M. Lotrionte et al., "Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity.," Am J Cardiol, vol. 112, no. 12, pp. 1980–1984, Dec. 2013, doi: 10.1016/j.amjcard.2013.08.026.

[14] E. J. A. Bowles et al., "Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study.," J Natl Cancer Inst, vol. 104, no. 17, pp. 1293–1305, Sep. 2012, doi: 10.1093/jnci/djs317.

[15] J. Chen, J. B. Long, A. Hurria, C. Owusu, R. M. Steingart, and C. P. Gross, "Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer.," J Am Coll Cardiol, vol. 60, no. 24, pp. 2504–2512, Dec. 2012, doi: 10.1016/j.jacc.2012.07.068.

[16] D. Cardinale, "[A new frontier: cardio-oncology].," Cardiologia, vol. 41, no. 9, pp. 887–891, Sep. 1996.

[17] National Cancer Institute, "Common Terminology Criteria for Adverse Events (CTCAE)." https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm (accessed Apr. 28, 2023).

[18] J. Herrmann et al., "Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement," Eur Heart J, vol. 43, no. 4, pp. 280–299, Jan. 2022, doi: 10.1093/EURHEARTJ/EHAB674.

[19] A. R. Lyon et al., "2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS).," Eur Heart J, Aug. 2022, doi: 10.1093/eurheartj/ehac244.

[20] G. M. Felker et al., "Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy.," N Engl J Med, vol. 342, no. 15, pp. 1077–1084, 2000.

[21] E. K. Oikonomou et al., "Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis.," JAMA Cardiol, vol. 4, no. 10, pp. 1007–1018, Oct. 2019, doi: 10.1001/jamacardio.2019.2952.

[22] D. R. Messroghli et al., "Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imag," J Cardiovasc Magn Reson, vol. 19, no. 1, p. 75, Oct. 2017, doi: 10.1186/s12968-017-0389-8.

[23] F. C. 3rd Brosius, B. F. Waller, and W. C. Roberts, "Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart.," Am J Med, vol. 70, no. 3, pp. 519–530, Mar. 1981, doi: 10.1016/0002-9343(81)90574-x.

[24] A. J. Teske et al., "Cardio-oncology: an overview on outpatient management and future developments.," Neth Heart J, vol. 26, no. 11, pp. 521–532, Nov. 2018, doi: 10.1007/s12471-018-1148-7.

[25] D. Cardinale, F. Iacopo, and C. M. Cipolla, "Cardiotoxicity of Anthracyclines.," Front Cardiovasc Med, vol. 7, p. 26, 2020, doi: 10.3389/fcvm.2020.00026.

[26] P. T. Bradshaw, J. Stevens, N. Khankari, S. L. Teitelbaum, A. I. Neugut, and M. D. Gammon, "Cardiovascular Disease Mortality Among Breast Cancer Survivors.," Epidemiology, vol. 27, no. 1, pp. 6–13, Jan. 2016, doi: 10.1097/EDE.0000000000000394.

[27] H. Abdel-Qadir et al., "A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer.," JAMA Cardiol, vol. 2, no. 1, pp. 88–93, Jan. 2017, doi: 10.1001/jamacardio.2016.3841.

[28] S. H. Armenian et al., "Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study.," J Clin Oncol, vol. 34, no. 10, pp. 1122–1130, Apr. 2016, doi: 10.1200/JCO.2015.64.0409.

[29] D. Schoormans, K. Czene, P. Hall, and Y. Brandberg, "The impact of co-morbidity on health-related quality of life in breast cancer survivors and controls.," Acta Oncol, vol. 54, no. 5, pp. 727–734, May 2015, doi: 10.3109/0284186X.2014.998277.

[30] H. Strongman et al., "Does Cardiovascular Mortality Overtake Cancer Mortality During Cancer Survivorship?: An English Retrospective Cohort Study," JACC CardioOncol, vol. 4, no. 1, pp. 113–123, Mar. 2022, doi: 10.1016/J.JACCAO.2022.01.102.

[31] J. L. Patnaik, T. Byers, C. DiGuiseppi, D. Dabelea, and T. D. Denberg, "Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study.," Breast Cancer Res, vol. 13, no. 3, p. R64, Jun. 2011, doi: 10.1186/bcr2901.

[32] M. G. Khouri et al., "Cancer therapy-induced cardiac toxicity in early breast cancer: addressing the unresolved issues.," Circulation, vol. 126, no. 23, pp. 2749–2763, Dec. 2012, doi: 10.1161/CIRCULATIONAHA.112.100560.

[33] E. C. van Dalen, H. N. Caron, H. O. Dickinson, and L. C. Kremer, "Cardioprotective interventions for cancer patients receiving anthracyclines.," Cochrane Database Syst Rev, vol. 2011, no. 6, p. CD003917, Jun. 2011, doi: 10.1002/14651858.CD003917.pub4.

[34] K. Ghasemi, G. Vaseghi, and M. Mansourian, "Pharmacological interventions for preventing anthracycline-induced clinical and subclinical cardiotoxicity: A network meta-analysis of metastatic breast cancer.," J Oncol Pharm Pract, vol. 27, no. 2, pp. 414–427, Mar. 2021, doi: 10.1177/1078155220965674.

[35] S. L. Heck et al., "Effect of candesartan and metoprolol on myocardial tissue composition during anthracycline treatment: the PRADA trial.," Eur Heart J Cardiovasc Imaging, vol. 19, no. 5, pp. 544–552, May 2018, doi: 10.1093/ehjci/jex159.

[36] M. A. Nystoriak and A. Bhatnagar, "Cardiovascular Effects and Benefits of Exercise.," Front Cardiovasc Med, vol. 5, p. 135, 2018, doi: 10.3389/fcvm.2018.00135.

[37] W. J. Tucker et al., "Meta-analysis of Exercise Training on Left Ventricular Ejection Fraction in Heart Failure with Reduced Ejection Fraction: A 10-year Update.," Prog Cardiovasc Dis, vol. 62, no. 2, pp. 163–171, 2019, doi: 10.1016/j.pcad.2018.08.006.

[38] L. Anderson et al., "Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis.," J Am Coll Cardiol, vol. 67, no. 1, pp. 1–12, Jan. 2016, doi: 10.1016/j.jacc.2015.10.044.

[39] J. S. Lawton et al., "2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.," J Am Coll Cardiol, vol. 79, no. 2, pp. 197–215, Jan. 2022, doi: 10.1016/j.jacc.2021.09.005.

[40] J. Knuuti et al., "2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.," Eur Heart J, vol. 41, no. 3, pp. 407–477, Jan. 2020, doi: 10.1093/eurheartj/ehz425.

[41] J. J. Chen, P.-T. Wu, H. R. Middlekauff, and K.-L. Nguyen, "Aerobic exercise in anthracycline-induced cardiotoxicity: a systematic review of current evidence and future directions," American Journal of Physiology-Heart and Circulatory Physiology, vol. 312, no. 2, pp. H213–H222, 2016, doi: 10.1152/ajpheart.00646.2016.

[42] W. P. Chung et al., "Real-time exercise reduces impaired cardiac function in breast cancer patients undergoing chemotherapy: A randomized controlled trial," Ann Phys Rehabil Med, vol. 65, no. 2, Mar. 2022, doi: 10.1016/J.REHAB.2021.101485.

[43] S. J. Foulkes et al., "Exercise for the Prevention of Anthracycline-Induced Functional Disability and Cardiac Dysfunction: The BREXIT Study," Circulation, vol. 147, no. 7, Feb. 2023, doi: 10.1161/CIRCULATIONAHA.122.062814.

[44] D. Cardinale et al., "Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy.," Circulation, vol. 131, no. 22, pp. 1981–1988, Jun. 2015, doi: 10.1161/CIRCULATIONAHA.114.013777.

[45] Z. Ma, "Effect of anthracycline combined with aerobic exercise on the treatment of breast cancer.," Pak J Pharm Sci, vol. 31, no. 3(Special), pp. 1125–1129, May 2018.

[46] J. L. Zamorano et al., "2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (E," Eur Heart J, vol. 37, no. 36, pp. 2768–2801, Sep. 2016, doi: 10.1093/eurheartj/ehw211.

[47] P. Thavendiranathan, A. D. Grant, T. Negishi, J. C. Plana, Z. B. Popović, and T. H. Marwick, "Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy," J Am Coll Cardiol, vol. 61, no. 1, pp. 77–84, Jan. 2013, doi: 10.1016/J.JACC.2012.09.035.

[48] F. Grothues et al., "Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy," American Journal of Cardiology, vol. 90, no. 1, pp. 29–34, Jul. 2002, doi: 10.1016/S0002-9149(02)02381-0.

[49] A. L. Whittaker, R. P. George, and L. O'Malley, "Prevalence of cognitive impairment following chemotherapy treatment for breast cancer: a systematic review and meta-analysis," Sci Rep, vol. 12, no. 1, Dec. 2022, doi: 10.1038/S41598-022-05682-1.

[50] J. S. Wefel, S. R. Kesler, K. R. Noll, and S. B. Schagen, "Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults," CA Cancer J Clin, vol. 65, no. 2, pp. 123–138, Mar. 2015, doi: 10.3322/CAAC.21258.

[51] T. A. Ahles and J. C. Root, "Cognitive Effects of Cancer and Cancer Treatments," Annu Rev Clin Psychol, vol. 14, pp. 425–451, May 2018, doi: 10.1146/ANNUREV-CLINPSY-050817-084903.

[52] S. Kucherer and R. J. Ferguson, "Cognitive behavioral therapy for cancer-related cognitive dysfunction," Curr Opin Support Palliat Care, vol. 11, no. 1, pp. 46–51, Mar. 2017, doi: 10.1097/SPC.0000000000000247.

[53] P. Zimmer et al., "Effects of Exercise Interventions and Physical Activity Behavior on Cancer Related Cognitive Impairments: A Systematic Review.," Biomed Res Int, vol. 2016, p. 1820954, 2016, doi: 10.1155/2016/1820954.

[54] N. K. Aaronson et al., "The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology," J Natl Cancer Inst, vol. 85, no. 5, pp. 365–376, Mar. 1993, doi: 10.1093/JNCI/85.5.365.

[55] N. Denduluri et al., "Dose Delays, Dose Reductions, and Relative Dose Intensity in Patients With Cancer Who Received Adjuvant or Neoadjuvant Chemotherapy in Community Oncology Practices," J Natl Compr Canc Netw, vol. 13, no. 11, pp. 1383–1393, Nov. 2015, doi: 10.6004/JNCCN.2015.0166.

[56] E. M. C. Feliciano et al., "Body Composition, Adherence to Anthracycline and Taxane-Based Chemotherapy, and Survival After Nonmetastatic Breast Cancer," JAMA Oncol, vol. 6, no. 2, pp. 264–270, Feb. 2020, doi: 10.1001/JAMAONCOL.2019.4668.

[57] G. H. Lyman, "Impact of chemotherapy dose intensity on cancer patient outcomes," J Natl Compr Canc Netw, vol. 7, no. 1, pp. 99–108, 2009, doi: 10.6004/JNCCN.2009.0009.

[58] N. Travier et al., "Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial.," BMC Med, vol. 13, p. 121, Jun. 2015, doi: 10.1186/s12916-015-0362-z.

[59] H. van Waart et al., "Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial.," J Clin Oncol, vol. 33, no. 17, pp. 1918–1927, Jun. 2015, doi: 10.1200/JCO.2014.59.1081.

PART 1

Physical activity and exercise in cardio-oncology

CHAPTER 2

Long-term cardiovascular health in adult cancer survivors

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ABSTRACT

The number of cancer survivors has tremendously increased over the past decades as a result of aging of the population and improvements in early cancer detection and treatment. Ongoing successes in cancer treatment are expected to result in a further increase in the number of long-term survivors. However, cancer treatment can have detrimental cardiovascular side-effects that impact morbidity and mortality, reducing quality of life in cancer survivors. The spectrum of radiotherapy- and chemotherapy-induced cardiovascular disease is broad, varying from subclinical valvular dysfunction to overt congestive heart failure, and such effects may not be apparent for more than twenty years after the initial cancer treatment. Awareness of these long-term side-effects is of crucial value in the management of these patients, in order to reduce the impact of cardiovascular morbidity and mortality. This review provides a comprehensive overview of the long-term cardiovascular complications of cancer treatments (radiotherapy and chemotherapy) in adult cancer survivors.

1. INTRODUCTION

Over the past decades, improvements in early cancer detection and treatment have significantly improved survival rates of many malignancies[1]. Furthermore, the incidence of cancer patients has increased (and will increase further) due to aging of the population[2]. As a result of these two trends, the population of cancer survivors is growing rapidly in the Western world. In 2012, nearly fourteen million cancer survivors were alive in the United States and it has been postulated that this will increase to eighteen million by 2022[2]. A similar trend is observed in Europe[3].

Within the population of cancer survivors, the awareness for health problems that can occur after cancer survival is increasing. Besides the risk of recurrent or secondary malignancies, functional disabilities and psychosocial distress, cancer survivors are prone to develop cardiovascular disease (CVD)[4], [5]. Fig. 1 provides an example on the characteristic survival pattern observed in survivors of Hodgkin's disease[6]. Compared to people without a cancer history, CVD risk is 30% higher in adult cancer survivors[7]. In addition, CVD is the most common cause of non-cancer death among cancer survivors and significantly reduces the eight-year overall survival from 81% to 60% compared to cancer survivors without CVD[8], [9].

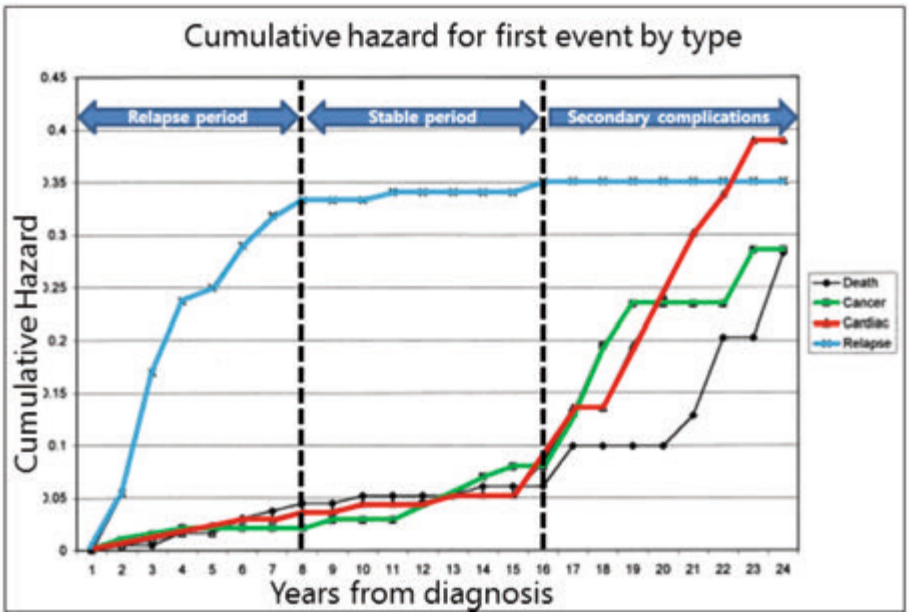

Fig. 1. Long term morbidity and mortality. The cumulative risk of death, developing a recurrence, second malignancy, or cardiac problem as first event after radiotherapy for Hodgkin's disease (adapted from[6], with permission). During the first year, relapse of the disease (blue line) is often seen followed by a clinical stable period. After approximately 16 years, a sharp increase in cardiovascular disease (red line) and secondary malignancies (green) impacts patients' overall morbidity and mortality.

Traditionally, cancer and CVD were considered two different entities. However, there is growing evidence that there might be a common biological pathway, as cancer and CVD share common risk factors such as ageing, smoking and obesity[10]. Patients with these pre-existing risk factors at baseline are also more likely to develop CVD during and after anticancer treatment[11]. Finally, preliminary evidence suggests that subclinical myocardial damage can occur prior to anticancer treatment, implicating an effect on cardiac function by the malignant process itself[12].

The spectrum of anticancer treatment-induced CVD is wide, varying from valvular heart disease (VHD) and constrictive pericarditis to ischaemic heart disease and overt congestive heart failure (CHF)[13]. The first clinical manifestations may appear more than twenty years after exposure[4]. Awareness of these long-term side effects is therefore of importance in the follow-up and management of these patients. This review provides a comprehensive overview of the long-

term cardiovascular (CV) complications of anticancer treatments (radiotherapy, chemotherapy and targeted therapy) in adult cancer survivors. Acute CV complications of anticancer treatments in adults[14], as well as long-term side effects in childhood cancer survivors will be discussed elsewhere in this issue and are out of the scope of this review.

2. LONG-TERM RADIOTHERAPY-INDUCED CARDIOVASCULAR DISEASE

Radiotherapy (RT) is an integral component of anticancer treatment in nearly 50% of cancer patients[15]. Exposure of the heart to RT has been associated with severe long-term CV complications in cancer survivors. In the 1960's, it was first recognised that thoracic RT might induce severe CV sequelae[16], which led to drastic refinements in RT techniques over the past decades. As a result, acute complications (*i.e.* acute pericarditis) have become rare and most RT-induced complications manifest ten to twenty years after exposure[17]. It is expected that the long-term complications will be reduced by the implementation of more heart-sparing techniques.

Histopathological, the hallmark of RT-induced damage is fibrosis[18]. The underlying pathophysiological mechanism inducing fibrosis formation is not fully elucidated. Current theories are based on results from animal studies and suggest a complex combination of micro- and macrovascular pathology[15], [19]. RT induces microvascular injury which eventually lead to loss of endothelial cells and endothelial dysfunction. Macrovascular damage enhances the acceleration of atherosclerosis, leading to narrowing of the lumen of coronary arteries and further deterioration of the endothelial function and ischaemia[20].

Even though RT can affect virtually every structural component of the CV system, the proximal aorta, coronary arteries, valves, pericardium, and conduction system are predominantly affected[17] (Fig. 2). Small studies have also suggested regional functional myocardial dysfunction due to direct exposure to RT[21] Risk factors for RT-induced CV complications are younger age at time of RT exposure, dose >30 Gy (Gy) or a fractional dose of >2 Gy, the use of concomitant cardiotoxic systemic chemotherapy (*i.e.* anthracyclines) and the presence of CV risk factors or pre-existing CVD at baseline[13]. As a result, RT-induced sequelae are predominantly seen in survivors of Hodgkin's disease and, to a lesser degree, survivors of breast cancer. Additionally, RT-induced complications are increasingly reported in survivors of oesophageal and lung cancer, as the survival rates of these malignancies are increasing[22], [23].

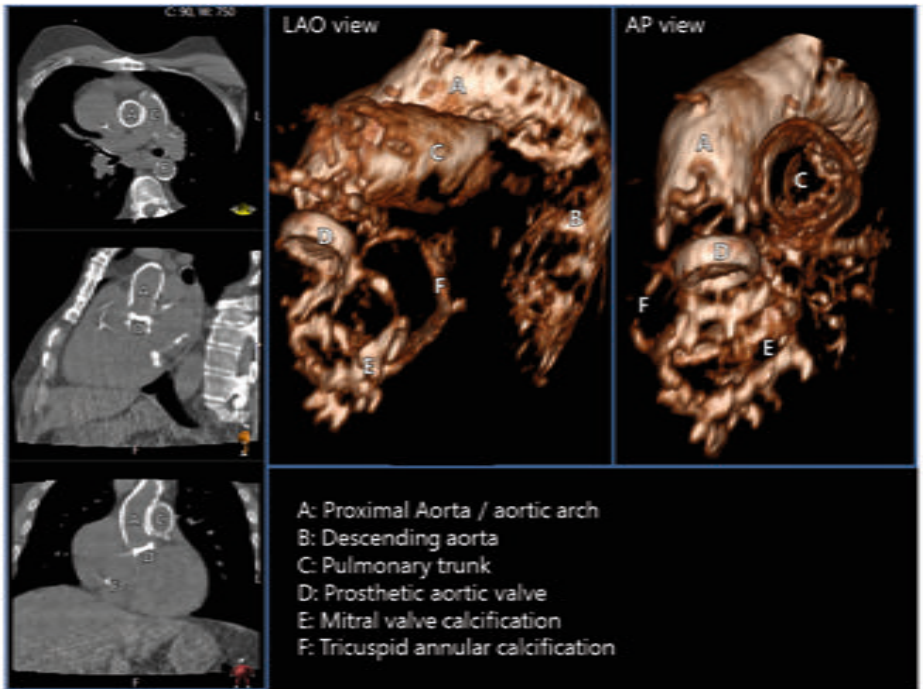

Fig. 2. Porcelain aorta. Non-contrast CT scan of a 50-year old male patient 44 years after mantle field radiation for Hodgkin disease and a mechanical aortic valve replacement 15 years ago. Note the severe calcifications in the aorta, pulmonary trunk and the mitral and tricuspid valve. LAO = Left Anterior Oblique view, AP = Antero-Posterior view.

In a large meta-analysis, pooling results of more than 45,000 survivors of Hodgkin's disease, breast cancer, lung cancer and metastatic testicular cancer, the risk of long-term heart failure was 1.8-fold increased for patients treated with mediastinal RT (95% confidence interval (CI) 1.1–3.1)[24]. In survivors of Hodgkin's disease, the 40-year cumulative incidence for any CVD was 25% (95% CI 17%–33%) for patients not treated with mediastinal RT or anthracyclines, which more than doubled to 55% (95% CI 41%–52%) for patients treated with mediastinal RT alone[25].

2.1. Coronary artery disease

The association between RT and ischaemic heart disease was controversial for many years and first fully recognised after the publication of large epidemiologic studies in the 1990's on survivors of Hodgkin's disease and breast cancer[26], [27]. In a retrospective Dutch cohort study of 2524 survivors of Hodgkin's disease who were treated with RT between 1965 and 1995, a 40-year cumulative incidence for coronary artery disease (CAD) as first cardiac diagnosis after treatment of 23% (95% CI 21%–25%) was reported[25]. Within this cohort, the majority of patients developed more than one cardiac event, of which CHF was the most prevalent secondary diagnosis[25]. Compared to the general population, the risk for angina pectoris and fatal myocardial infarction was 4.1 and 3.6-fold increased for survivors of Hodgkin's disease[4]. With respect to survivors of breast cancer, a large population-based case-control study in 2168 women who underwent RT between 1958 and 2001, reported that women receiving left-sided RT had significantly higher rates of ischaemic heart disease compared to those receiving right-sided RT (mean dose to the heart for left- versus right-sided of 6.6 Gy and 2.9 Gy)[28]. The risk of major cardiac events increased linearly with 7.4% per Gy inflicted to the heart, emphasizing the need for heart-sparing techniques[28]
Although the mechanism of atherosclerotic plaque formation, –rupture and occlusion is similar as in non-radiated patients, RT-induced CAD seems to be slightly different from conventional CAD. Firstly, post-mortem examination of irradiated patients revealed that the plaques were more fibrous and contained less lipid components[18]. Secondly, plaques in irradiated patients are more often located in the ostium of arteries and tend be smoother, longer and more concentric than conventional atherosclerotic plaques[29]. Finally, the left descending coronary artery is most often affected (Figure 3) [30]. As a result, percutaneous intervention in RT-induced CAD is more challenging. Importantly, irradiated cancer survivors can remain asymptomatic for a relatively long period of time, even in presence of severe CAD and sudden cardiac death may be the first clinical manifestation[31]

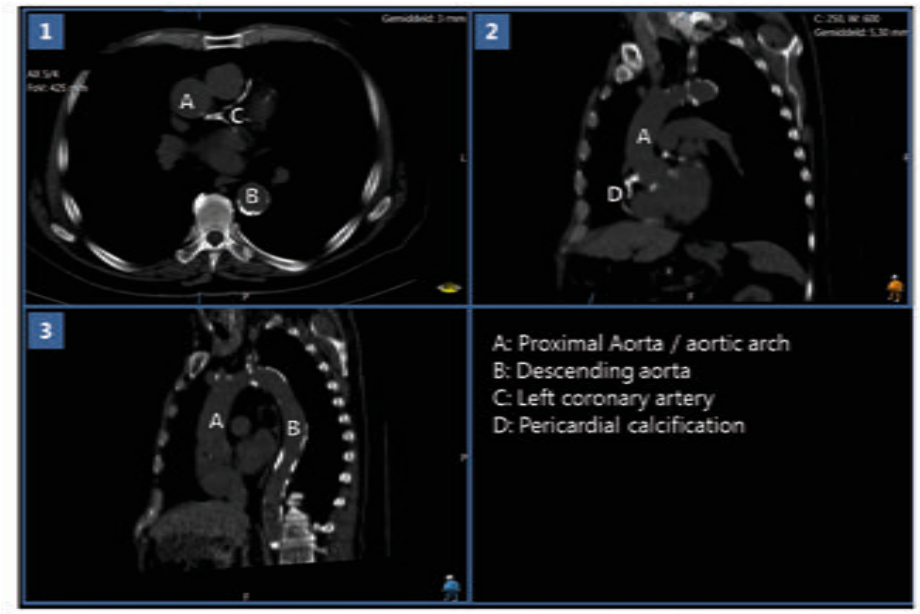

Fig. 3. Coronary sclerosis and pericardial calcification. Non-contrast CT scan of a 80-year old male patient 25 years after mantle field radiation for Hodgkin disease. Note the severe proximal coronary sclerosis (and stenosis on angiography) in the left coronary artery [panel 1]. There is pronounced pericardial calcification [panel 2] without constrictive physiology. Also note the sclerosis in the descending aorta [panel 3].

Official guidelines on screening and follow-up of cancer survivors at risk for CAD are lacking. However, according to preliminary guidelines/expert consensus, it is advised to start screening for CAD in patients who received thoracic RT five to ten years after exposure and repeat imaging every five year[20]. Imaging modality of choice is depended local preferences and availability, although cardiac CT might be preferably in a pre-operative setting to rule out a porcelain aorta. For longitudinal follow-up, stress echocardiography and cardiac magnetic resonance are both feasible modalities, as they are free of ionising radiation[20]

2.2. Valvular heart disease

RT-induced VHD is a common complication in cancers survivors irradiated with outdated RT-techniques, with incidences varying between 6 and 31%[32]–[34]. In a large case-control study among 1852 survivors of Hodgkin's disease irradiated between 1965 and 1995, the 30-year cumulative risk for any valvular involvement

was 3.0% for a dose of 30 Gy, which exponentially increased to 12.4% at doses of more than 40 Gy[35]. A splenectomy, at that time routinely performed in all patients with Hodgkin's disease for staging and treatment, more than doubled the risk for VHD (relative risk 2.3, 95% CI 1.3–4.3), suggesting a synergetic role for inflammatory factors and RT in the pathophysiology of RT-induced VHD[35]. In a more recent study among lymphoma survivors treated with an autologous haematopoietic stem-cell transplant, chemotherapy and mediastinal RT between 1988 and 2008, mild valvular involvement was identified in almost 20% of the patients. Risk factors in this cohort for VHD were RT-dose >30 Gy, female gender, age >50 years at diagnosis and >3 lines of chemotherapy prior to stem-cell transplant[36].

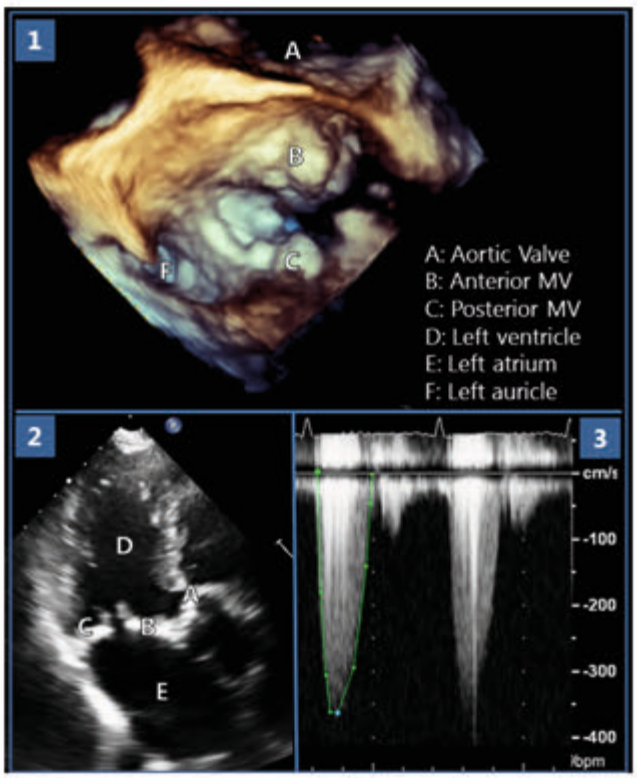

Fig. 4. Valvular heart disease. Echocardiography of a 72-year-old male patient 35 years after mantle field radiation and chemotherapy for Hodgkin's disease. He suffered from progressive aortic valve stenosis (mean pressure gradient of 40 mmHg, aortic valve area 0.50 cm2 [panel 3] and a moderate mitral insufficiency. Note the calcification of the proximal parts of the mitral valve [panel 2], this can also be appreciated on the 3D transesophageal echocardiography which is presented in the surgical view [panel 1].

Within one year after exposure, the first signs of RT-induced valvular damage can already be noted on echocardiography as valvular retractions and shortening of the mitral and aortic valve[37]. After ten to twenty years, the leaflets progressively become more fibrous leading to regurgitation and infrequently valvular stenosis. The combination of calcification of the aortic-mitral continuum and both the aortic and mitral valve, is the hallmark for RT-induced VHD on echocardiography[38]. Typically, the commissures and tips of the leaflets are relatively spared by RT (Fig. 4), in contrast to rheumatic disease induced valvular dysfunction[39]

2.3. Pericardial disease

Prior to the 1970's, acute (pleuro)pericarditis was the most common CV complication after RT, which usually presented within four weeks after exposure[17]. Nowadays, with the implementation of more heart-sparing techniques, acute pericardial complications have become rare[13]. Nevertheless, chronic pericarditis is a relatively common side effect and may occur in 2.5% of cancer survivors after RT to the heart, typically manifesting as fibrous constrictive pericarditis[40].

The majority of the patients are diagnosed with asymptomatic pericardial effusion which may resolve spontaneously, although tamponade with hemodynamic compromise can occur [40]. An onset of pericardial effusion more than two years after RT-exposure is uncommon and requires exclusion of other etiologic factors, such as infection, CHF and carcinomatous pericarditis[17]. Additionally, the presence of post-RT pericardial complications is a sign of severe mediastinal exposure and therefore almost never an entity on its own[41]. Hence, screening for other comorbidities (*i.e.* CAD) is of crucial value.

2.4. Conduction abnormalities and arrhythmias

A large spectrum of conduction abnormalities and arrhythmias has been reported in irradiated cancer survivors, including sinus node dysfunction, atrioventricular block, and (supra)ventricular arrhythmias[42]. Of the intraventricular conduction disorders, right bundle branch block is more frequently observed due to its proximity to the radiation field[17]. Furthermore, T-wave inversions were reported in 45% of breast cancer patients six months after left-sided RT[43]. However, electrocardiograms normalised in the majority after ten years. A long-term follow-up of 44,423 early-stage breast cancer patients irradiated between 1982 and 2005 showed no significant increased risk for conduction abnormalities or severe ventricular arrhythmias in this cohort[44].

3. LONG-TERM SYSTEMIC THERAPY-INDUCED CARDIOVASCULAR DISEASE

Exposure to systemic therapy (chemotherapy or targeted therapy) may pose a threat for CV health in cancer survivors in many ways. The most notorious long-term adverse effect is systemic therapy-related cardiac dysfunction. Table 1 provides an overview of current publications on long term cardiovascular complication in systemic therapy. We would like to emphasize that long-term follow-up data on CV complications are lacking in the majority of (modern) systemic therapy agents and that several of the correlations of CV complications after systemic therapy could be confounded by the concomitant use of antracyclines.

Table 1. Systemic therapy agents associated with long-term LV dysfunction.

Chemotherapy agents	
Anthracyclines	Daunorubicin[45]
	Doxorubicin[45]
	Epirubicin[45]
	Idarubicin[46]
	Mitoxantrone[46]
Alkylating agents	Cyclophosphamide[47]
Antimicrotubule agents	Docetaxel[47]
	Paclitaxel [48]
Targeted therapy agents	
Monocloncal antibodies	Trastuzumab [49]
	Pertuzumab [50]
	Bevacizumab[51]
Tyrosine kinase inhibitors	Sunitinib[51]
	Lapatinib[50]
	Pazopanib [51]
	Sorafenib[51]

3.1. Left ventricular dysfunction and congestive heart failure

Systemic therapy-related cardiac dysfunction is a relatively common complication and associated with clinical relevant CV morbidity and mortality, as well as reduced quality of life in cancer survivors[14], [52]. The incidence and extent of left ventricular (LV) dysfunction is highly depended on the type of agent used, and in most cases the cumulative dose.

Traditionally, two types of cardiotoxicity (type I and II) of systemic therapeutic agents were described, based on the potential reversibility of the induced myocardial dysfunction. Type I agents (*e.g.* anthracyclines) induce irreversible, dose-dependent myocardial dysfunction due to the induction of myocardial cell loss by apoptosis. Type II agents (*e.g.* trastuzumab) on the other hand have been found to be dose independent and typically these patients show a reversible LV dysfunction upon cessation of chemotherapy[14]. However, this classification is nowadays considered arbitrary, as new evidence among cancer survivors points out that patients treated with type II agents can develop persistent LV dysfunction[53].

3.1.1. Anthracycline-induced cardiotoxicity

Since their introduction in the 1970's, anthracyclines constitute the cornerstone for the treatment of haematologic malignancies, breast cancer and many more[45]. In the first studies, incidence of anthracycline-induced cardiotoxicity (AIC) varied between 16 and 23%[54], [55]. Several refinements in the following decades (*e.g.* reduction of cumulative dose and infusion scheme) aimed to reduce the incidence of clinically relevant cardiotoxicity. A large meta-analysis, pooling results from almost 50,000 cancer patients in the current era of adjusted chemotherapy protocols, reported an incidence in patients treated with anthracyclines for clinical overt cardiotoxicity and subclinical cardiotoxicity of %95) %6CI %9–%3) and %95) %18CI %24–%12) respectively[45].

The main underlying pathophysiological mechanism for AIC is presumably based on an interaction between anthracyclines and topoisomerase-2β, which results in DNA damage in the cardiomyocytes followed by irreversible cell loss[56]. This risk of irreversible myocardial injury increases exponentially with cumulative anthracycline dose[57], which consequently led to restrictions of administered cumulative dose. Other additional risk factors associated with an increased risk for AIC are concomitant (or previous) thoracic RT, African-American ancestry, age(<15 or >65 years), other (cardiac) comorbidities, female gender and the use of other cardiotoxic chemotherapeutic agents[45].

In the majority of patients receiving anthracyclines, AIC occurs within the first year after exposure[58]. However, clinical manifestation of AIC may appear years later, due to extensive compensatory mechanisms of the myocardium[59]. If AIC manifests as overt CHF, the response to treatment is poor and prognosis grim as the majority of patients die within two years[60], [61]. On the other hand, if prompt heart failure treatment is initiated when the first sings of LV dysfunction are detected, LV function may show some reversibility[58].

3.1.2. Non-anthracycline-induced cardiotoxicity

Targeted therapy is also associated with the occurrence of treatment-related cardiac dysfunction. Trastuzumab, a monoclonal antibody against the human epidermal growth factor receptor-2 (HER-2), was introduced in the late 1990's as adjuvant therapy for women with HER-2 positive breast cancer[50]. The first study reported an alarming high incidence for severe LV dysfunction of 27% in women treated with a combination of anthracyclines, cyclophosphamide and trastuzumab[62]. Based on the hypothesis of synergetic cardiotoxicity, trastuzumab was from that point on administered separately from anthracycline treatment and it was advised to monitor left ventricular ejection fraction (LVEF) periodically[63]. A recent meta-analysis of almost 30,000 women treated with trastuzumab reported an incidence for severe cardiotoxicity of 3% (95%CI 2.41–3.64) at three year follow-up[49]. Older age, a history of anthracycline administration, hypertension, obesity and diabetes are risk factors for trastuzumab-induced LV dysfunction[64], [65].

In a recent randomised clinical trial (RCT), patients who received anthracyclines, cyclophosphamide and paclitaxel (n = 743) were compared with patients treated with the same chemotherapy regime, but with additional weekly trastuzumab (n = 947). After seven years, cardiac events, defined as a LVEF decline of more than 10%, cardiac death or manifestations of CHF, occurred in 4% of the patients in the trastuzumab-arm versus 1.3% in the control arm[48]. The risk for cardiac events greatly increased in patients who had a LVEF of 50–55% after anthracyclines (HR 11.8, 95%CI 3.9–36.0), suggesting that sequential trastuzumab administration might aggravate underlying myocardial damage. From all patients with LVEF decline, the majority recovered to baseline within twelve months. Nevertheless, a persistent decline in LVEF was reported in 3.8% of the entire cohort, supporting the raising concern on the reversibility of trastuzumab-induced LV dysfunction on the long-term[48]. It is conceivable that trastuzumab might induce subclinical cardiotoxicity, which may go unrecognized by conventional LVEF measurements since novel cardiac imaging parameters are abnormal in an earlier stage[66]. The relevance of these observations, as well as the 'true' reversibility of these subclinical changes has to be explored in long-term follow-up studies.

Although long-term data on the cardiac outcome is lacking, it is worth mentioning the potential cardiotoxic effects of other newer targeted therapeutic agents. For pertuzumab and lapatinib, two more recent developed anti-HER2 agents, preliminary evidence suggest that cardiotoxicity might be similar or less than trastuzumab[50]. In a recent meta-analysis, antivascular endothelial growth factor (VEGF) agents, such as bevacizumab and sunitinib, are associated with increased

cardiac dysfunction and cardiac ischaemia (OR 1.35 (95%CI 1.06–1.70) and OR 2.83 (95%CI 1.72–4.65)) compared to other systemic agents[51]. For CHF or fatal CV events, no significant risk was identified.

With respect to the long-term influence of adjuvant endocrine therapies on CVD in postmenopausal breast cancer survivors, the literature is conflicting. In a recent study aromatase inhibitors are associated with a higher risk of myocardial infarction compared with tamoxifen with a HR of 2.02 (95% CI 1.16–3.53)[67] A large observational study including over 13.000 patients with over 72.00 person-years, on the other hand, showed that the risk of the most serious cardiovascular events (cardiac ischaemia or stroke) was not elevated in aromatase inhibitor users compared with tamoxifen users[68]. Prospective follow-up studies will be needed to evaluate the precise long-term risk and the identification of potential baseline risk factors in these patients.
Androgen-deprivation therapy through surgical castration is equally effective as medical castration in controlling prostate cancer. This treatment, in particular long-term treatment, has been associated with a higher risk of peripheral artery disease as well as cardiac complications[69], especially in men with a cardiovascular medical history[70] while short term treatment does not show this association at long-term follow-up[71]. It should be noted that these data come from observational studies and are therefore prone to bias. A recent systematic review pointed out the lack of published, reliable evidence (in other words, no RCTs) describing the effects of androgen-deprivation therapy on CVD risk factors[72].

3.2. Metabolic disorders

The awareness for late metabolic disorders among cancer survivors is increasing. Compared to age and gender matched controls, cancer survivors have higher incidences of hypertension (65.9% vs 59.5%), diabetes mellitus (23.4% vs 21.5%), dyslipidaemia (57.9% vs 55.9%) and obesity (43.4% vs 35.4%, $p < 0.01$ for all)[9]. These disorders can be clustered by the term 'metabolic syndrome'. Although no consensus is reached on its exact criteria, the metabolic syndrome comprises risk factors of metabolic origin that often occur simultaneously[73]. Metabolic syndrome increases the risk for atherosclerotic disease and might therefore attribute to the overall CV risk in cancer survivors[74].

3.2.1. Hypertension

The most extensively studied component of the metabolic syndrome in cancer survivors is hypertension. Although multiple systemic therapeutic agents may induce hypertension, anti VEGF agents are most often associated with the onset of hypertension[75]. Depending on the type of anti VEGF agent and patients' characteristic, the incidence of hypertension induced by anti VEGF agents varies between 11 and 43%[75]. In pooled results of 77 phase III and IV RCTs, VEGF-based chemotherapy is associated with a higher risk for hypertension and malignant hypertension, defined as >180/110 mmHg with ORs of 5.28 (95% CI 4.53–6.15) and 5.59 (95% CI 4.67–6.69) respectively[51]. Although long-term outcomes of these patients are lacking, prompt antihypertensive therapy is recommended in order to minimize long-term complications[13].

Besides anti-VEGF agents, exposure to systemic treatment with cisplatin is associated with long-term hypertension, in particular in survivors of testicular cancer. In a twenty-year follow-up study of 990 survivors of testicular cancer, exposure to cisplatin-based chemotherapy or cisplatin-based chemotherapy combined with infradiaphragmatic RT significantly increased the use of antihypertensive drugs (OR 3.1 (95%CI 1.9–5.2) and OR 3.7 (95%CI 1.6–8.9) respectively)[76]. Treatment with RT alone did not increase the risk for hypertension. Furthermore, exposure to systemic cisplatin increased the prevalence of diabetes from 4.0% in the surgery group to 15.6%. In addition, combination therapy with cisplatin and infradiaphragmatic RT also dramatically increased the risk for CAD (HR 5.3, 96%CI 1.5–18.5) compared to patients treated with surgery alone suggesting a strong influence of metabolic disorders in the pathogenesis of CAD in these patients[76].

4. FUTURE PERSPECTIVES

In the past decades, significant improvements have been made in early cancer detection and treatment leading to improved prognosis in cancer patients. However, cancer treatment has detrimental long-term effects on CV health and early recognition of unwanted side effects is needed to initiate preventive treatment at an early stage in high-risk patients. Fig. 5 provides a schematic overview of the available literature we set out in this overview article.

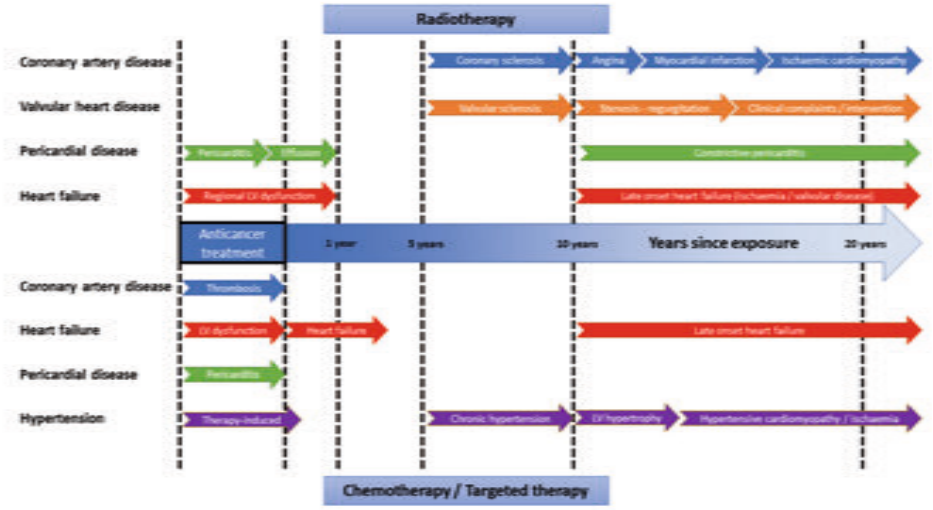

Fig. 5. Long term complications of anticancer treatment.

To answer the specific clinical problems cancer survivors nowadays face, prospective information is needed to fill the current gaps in knowledge. Of particular interest are the long-term outcomes of patients treated with non-anthracyclines as well as the role of conventional CV risk factors in cancer survivors. To do so, harmonisation of clinical healthcare pathways combined with a large registry of CV follow-up are necessary to make warranted clinical decisions. Promising initiatives so far include specialized cardio-oncology units[77] and long-term prospective screening programs for multiple CV- and other complications (*e.g.* kidney disease, depression), as is current practice in the Netherlands. It is anticipated that these and future multidisciplinary efforts will reduce the impact of anticancer treatment related side effects and thereby improve the long-term outcome of these patients considerably.

REFERENCES

[1] K. D. Miller *et al.*, "Cancer treatment and survivorship statistics, 2016.," *CA Cancer J Clin*, vol. 66, no. 4, pp. 271–289, Jul. 2016, doi: 10.3322/caac.21349.

[2] J. S. De Moor *et al.*, "Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care," *Cancer Epidemiol Biomarkers Prev*, vol. 22, no. 4, pp. 561–570, Apr. 2013, doi: 10.1158/1055-9965.EPI-12-1356.

[3] J. Ferlay *et al.*, "Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012," *Eur J Cancer*, vol. 49, no. 6, pp. 1374–1403, Apr. 2013, doi: 10.1016/J.EJCA.2012.12.027.

[4] B. M. P. Aleman *et al.*, "Late cardiotoxicity after treatment for Hodgkin lymphoma," *Blood*, vol. 109, no. 5, pp. 1878–1886, Mar. 2007, doi: 10.1182/BLOOD-2006-07-034405.

[5] F. E. Van Leeuwen and A. K. Ng, "Long-term risk of second malignancy and cardiovascular disease after Hodgkin lymphoma treatment," *Hematology Am Soc Hematol Educ Program*, vol. 2016, no. 1, pp. 323–330, 2016, doi: 10.1182/ASHEDUCATION-2016.1.323.

[6] C. K. K. Lee, D. Aeppli, and M. E. Nierengarten, "The need for long-term surveillance for patients treated with curative radiotherapy for Hodgkin's disease: University of Minnesota experience," *Int J Radiat Oncol Biol Phys*, vol. 48, no. 1, pp. 169–179, Aug. 2000, doi: 10.1016/S0360-3016(00)00647-7.

[7] M. R. Keats, Y. Cui, S. A. Grandy, and L. Parker, "Cardiovascular disease and physical activity in adult cancer survivors: a nested, retrospective study from the Atlantic PATH cohort.," *J Cancer Surviv*, vol. 11, no. 2, pp. 264–273, Apr. 2017, doi: 10.1007/s11764-016-0584-x.

[8] N. G. Zaorsky *et al.*, "Causes of death among cancer patients," *Ann Oncol*, vol. 28, no. 2, pp. 400–407, Feb. 2017, doi: 10.1093/ANNONC/MDW604.

[9] S. H. Armenian *et al.*, "Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study.," *J Clin Oncol*, vol. 34, no. 10, pp. 1122–1130, Apr. 2016, doi: 10.1200/JCO.2015.64.0409.

[10] R. J. Koene, A. E. Prizment, A. Blaes, and S. H. Konety, "Shared Risk Factors in Cardiovascular Disease and Cancer.," *Circulation*, vol. 133, no. 11, pp. 1104–1114, Mar. 2016, doi: 10.1161/CIRCULATIONAHA.115.020406.

[11] H. Abdel-Qadir *et al.*, "A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer.," *JAMA Cardiol*, vol. 2, no. 1, pp. 88–93, Jan. 2017, doi: 10.1001/jamacardio.2016.3841.

[12] N. Pavo *et al.*, "Cardiovascular biomarkers in patients with cancer and their association with all-cause mortality.," *Heart*, vol. 101, no. 23, pp. 1874–1880, Dec. 2015, doi: 10.1136/heartjnl-2015-307848.

[13] J. L. Zamorano *et al.*, "2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (E," *Eur Heart J*, vol. 37, no. 36, pp. 2768–2801, Sep. 2016, doi: 10.1093/eurheartj/ehw211.

[14] M. S. Ewer and S. M. Ewer, "Cardiotoxicity of anticancer treatments.," *Nature reviews. Cardiology*, vol. 12, no. 11. England, p. 620, Nov. 2015. doi: 10.1038/nrcardio.2015.133.

[15] M. Boerma, J. Wang, V. Sridharan, J. M. Herbert, and M. Hauer-Jensen, "Pharmacological induction of transforming growth factor-beta1 in rat models enhances radiation injury in the intestine and the heart," *PLoS One*, vol. 8, no. 7, Jul. 2013, doi: 10.1371/JOURNAL.PONE.0070479.

[16] K. E. Cohn, J. R. Stewart, L. F. Pajardo, and E. W. Hancock, "Heart disease following radiation," *Medicine*, vol. 46, no. 3, pp. 281–298, 1967, doi: 10.1097/00005792-196705000-00003.

[17] C. Jaworski, J. A. Mariani, G. Wheeler, and D. M. Kaye, "Cardiac complications of thoracic irradiation," *J Am Coll Cardiol*, vol. 61, no. 23, pp. 2319–2328, Jun. 2013, doi: 10.1016/J.JACC.2013.01.090.

[18] F. C. Brosius, B. F. Waller, and W. C. Roberts, "Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart," *Am J Med*, vol. 70, no. 3, pp. 519–530, 1981, doi: 10.1016/0002-9343(81)90574-X.

[19] F. Paris *et al.*, "Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice," *Science*, vol. 293, no. 5528, pp. 293–297, Jul. 2001, doi: 10.1126/SCIENCE.1060191.

[20] P. Lancellotti *et al.*, "Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography," *J Am Soc Echocardiogr*, vol. 26, no. 9, pp. 1013–1032, Sep. 2013, doi: 10.1016/J.ECHO.2013.07.005.

[21] R. Jurcut, J. Ector, K. Erven, H. F. Choi, and J. U. Voigt, "Radiotherapy effects on systolic myocardial function detected by strain rate imaging in a left-breast cancer patient," *Eur Heart J*, vol. 28, no. 24, p. 2966, Dec. 2007, doi: 10.1093/EURHEARTJ/EHM311.

[22] J. C. Beukema, J. A. Langendijk, and C. T. Muijs, "Cardiac toxicity in the radiation treatment of esophageal cancer: an emerging concern," *Future Cardiol*, vol. 11, no. 4, pp. 367–369, Jul. 2015, doi: 10.2217/FCA.15.44.

[23] X. Ming, Y. Feng, C. Yang, W. Wang, P. Wang, and J. Deng, "Radiation-induced heart disease in lung cancer radiotherapy: A dosimetric update," *Medicine*, vol. 95, no. 41, 2016, doi: 10.1097/MD.0000000000005051.

[24] M. T. Nolan, D. J. Russell, K. Negishi, and T. H. Marwick, "Meta-Analysis of Association Between Mediastinal Radiotherapy and Long-Term Heart Failure," *Am J Cardiol*, vol. 118, no. 11, pp. 1685–1691, Dec. 2016, doi: 10.1016/J.AMJCARD.2016.08.050.

[25] F. A. Van Nimwegen *et al.*, "Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk," *JAMA Intern Med*, vol. 175, no. 6, pp. 1007–1017, Jun. 2015, doi: 10.1001/JAMAINTERNMED.2015.1180.

[26] M. T. R. H. SL Hancock, "Factors affecting late mortality from heart disease after treatment of Hodgkin's disease," *JAMA*, vol. 16, Oct. 1993.

[27] L. S. Constine, R. G. Schwartz, D. E. Savage, V. King, and A. Muhs, "Cardiac function, perfusion, and morbidity in irradiated long-term survivors of Hodgkin's disease," *Int J Radiat Oncol Biol Phys*, vol. 39, no. 4, pp. 897–906, Nov. 1997, doi: 10.1016/S0360-3016(97)00467-7.

[28] S. C. Darby *et al.*, "Risk of ischemic heart disease in women after radiotherapy for breast cancer.," *N Engl J Med*, vol. 368, no. 11, pp. 987–998, Mar. 2013, doi: 10.1056/NEJMoa1209825.

[29] P. T. McEniery, K. Dorosti, W. A. Schiavone, T. J. Pedrick, and W. C. Sheldon, "Clinical and angiographic features of coronary artery disease after chest irradiation," *Am J Cardiol*, vol. 60, no. 13, pp. 1020–1024, Nov. 1987, doi: 10.1016/0002-9149(87)90345-6.

[30] G. Nilsson *et al.*, "Distribution of coronary artery stenosis after radiation for breast cancer," *J Clin Oncol*, vol. 30, no. 4, pp. 380–386, Feb. 2012, doi: 10.1200/JCO.2011.34.5900.

[31] E. M. van Leeuwen-Segarceanu *et al.*, "Screening Hodgkin lymphoma survivors for radiotherapy induced cardiovascular disease," *Cancer Treat Rev*, vol. 37, no. 5, pp. 391–403, Aug. 2011, doi: 10.1016/J.CTRV.2010.12.004.

[32] T. Wethal *et al.*, "Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study," *Br J Cancer*, vol. 101, no. 4, pp. 575–581, Aug. 2009, doi: 10.1038/SJ.BJC.6605191.

[33] M. B. Lund *et al.*, "Increased risk of heart valve regurgitation after mediastinal radiation for Hodgkin's disease: an echocardiographic study," *Heart*, vol. 75, no. 6, pp. 591–595, 1996, doi: 10.1136/HRT.75.6.591.

[34] M. C. Hull, C. G. Morris, C. J. Pepine, and N. P. Mendenhall, "Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy," *JAMA*, vol. 290, no. 21, pp. 2831–2837, Dec. 2003, doi: 10.1001/JAMA.290.21.2831.

[35] D. J. Cutter *et al.*, "Risk of valvular heart disease after treatment for Hodgkin lymphoma," *J Natl Cancer Inst*, vol. 107, no. 4, Apr. 2015, doi: 10.1093/JNCI/DJV008.

[36] K. Murbraech *et al.*, "Valvular Dysfunction in Lymphoma Survivors Treated With Autologous Stem Cell Transplantation: A National Cross-Sectional Study," *JACC Cardiovasc Imaging*, vol. 9, no. 3, pp. 230–239, Mar. 2016, doi: 10.1016/J.JCMG.2015.06.028.

[37] J. R. Cuomo, G. K. Sharma, P. D. Conger, and N. L. Weintraub, "Novel concepts in radiation-induced cardiovascular disease," *World J Cardiol*, vol. 8, no. 9, pp. 504–519, Sep. 2016, doi: 10.4330/WJC.V8.I9.504.

[38] D. Hering, L. Faber, and D. Horstkotte, "Echocardiographic features of radiation-associated valvular disease," *American Journal of Cardiology*, vol. 92, no. 2, pp. 226–230, Jul. 2003, doi: 10.1016/S0002-9149(03)00546-0.

[39] L. Krapf *et al.*, "Anatomical features of rheumatic and non-rheumatic mitral stenosis: potential additional value of three-dimensional echocardiography," *Arch Cardiovasc Dis*, vol. 106, no. 2, pp. 111–115, Feb. 2013, doi: 10.1016/J.ACVD.2012.11.004.

[40] M. M. Applefeld *et al.*, "The late appearance of chronic pericardial disease in patients treated by radiotherapy for Hodgkin's disease," *Ann Intern Med*, vol. 94, no. 3, pp. 338–341, 1981, doi: 10.7326/0003-4819-94-3-338.

[41] J. D. Groarke, P. L. Nguyen, A. Nohria, R. Ferrari, S. Cheng, and J. Moslehi, "Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease," *Eur Heart J*, vol. 35, no. 10, pp. 612–623, 2014, doi: 10.1093/EURHEARTJ/EHT114.

[42] R. L. Larsen, R. I. Jakacki, V. L. Vetter, A. T. Meadows, J. H. Silber, and G. Barber, "Electrocardiographic changes and arrhythmias after cancer therapy in children and young adults," *Am J Cardiol*, vol. 70, no. 1, pp. 73–77, Jul. 1992, doi: 10.1016/0002-9149(92)91393-I.

[43] J. L. L. L. LE Strender, "Incidence of heart disease and functional significance of changes in the electrocardiogram 10 years after radiotherapy for breast cancer," *Cancer*, vol. Mar 1;57(5):929-34., 1986.

[44] J. C. Rehammar *et al.*, "Risk of pacemaker or implantable cardioverter defibrillator after radiotherapy for early-stage breast cancer in Denmark, 1982-2005," *Radiother Oncol*, vol. 122, no. 1, pp. 60–65, Jan. 2017, doi: 10.1016/J.RADONC.2016.08.024.

[45] M. Lotrionte *et al.*, "Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity.," *Am J Cardiol*, vol. 112, no. 12, pp. 1980–1984, Dec. 2013, doi: 10.1016/j.amjcard.2013.08.026.

[46] P. Pellicori, A. Calicchia, F. Lococo, G. Cimino, and C. Torromeo, "Subclinical anthracycline cardiotoxicity in patients with acute promyelocytic leukemia in long-term remission after the AIDA protocol," *Congest Heart Fail*, vol. 18, no. 4, pp. 217–221, Jul. 2012, doi: 10.1111/J.1751-7133.2011.00278.X.

[47] J. R. Mackey *et al.*, "Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial," *Lancet Oncol*, vol. 14, no. 1, pp. 72–80, Jan. 2013, doi: 10.1016/S1470-2045(12)70525-9.

[48] E. H. Romond *et al.*, "Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer," *J Clin Oncol*, vol. 30, no. 31, pp. 3792–3799, Nov. 2012, doi: 10.1200/JCO.2011.40.0010.

[49] S. Mantarro *et al.*, "Risk of severe cardiotoxicity following treatment with trastuzumab: a meta-analysis of randomized and cohort studies of 29,000 women with breast cancer," *Intern Emerg Med*, vol. 11, no. 1, pp. 123–140, Feb. 2016, doi: 10.1007/S11739-015-1362-X.

[50] N. F. Pondé, M. Lambertini, and E. De Azambuja, "Twenty years of anti-HER2 therapy-associated cardiotoxicity," *ESMO Open*, vol. 1, no. 4, Jul. 2016, doi: 10.1136/ESMOOPEN-2016-000073.

[51] H. Abdel-Qadir, J. L. Ethier, D. S. Lee, P. Thavendiranathan, and E. Amir, "Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: A systematic review and meta-analysis," *Cancer Treat Rev*, vol. 53, pp. 120–127, Feb. 2017, doi: 10.1016/J.CTRV.2016.12.002.

[52] C. L. Cox, S. N. Rai, D. Rosenthal, S. Phipps, and M. M. Hudson, "Subclinical late cardiac toxicity in childhood cancer survivors: impact on self-reported health," *Cancer*, vol. 112, no. 8, pp. 1835–1844, Apr. 2008, doi: 10.1002/CNCR.23378.

[53] M. L. Telli, S. A. Hunt, R. W. Carlson, and A. E. Guardino, "Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility," *J Clin Oncol*, vol. 25, no. 23, pp. 3525–3533, Aug. 2007, doi: 10.1200/JCO.2007.11.0106.

[54] C. M. C. T. T. N. W. S. S. S. M. L. M. A C Gilladoga, "The cardiotoxicity of adriamycin and daunomycin in children," *Cancer*, no. Feb;37(2 Suppl):1070-8., 1976.

[55] P. G. S. C. T. T. G. H. M. L. M. L J Steinherz 1, "Cardiac toxicity 4 to 20 years after completing anthracycline therapy," *JAMA*, no. Sep 25;266(12):1672-7., 1991.

[56] P. Vejpongsa and E. T. H. Yeh, "Prevention of anthracycline-induced cardiotoxicity: Challenges and opportunities," *J Am Coll Cardiol*, vol. 64, no. 9, pp. 938–945, 2014, doi: 10.1016/j.jacc.2014.06.1167.

[57] S. M. Swain, F. S. Whaley, and M. S. Ewer, "Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials.," *Cancer*, vol. 97, no. 11, pp. 2869–2879, Jun. 2003, doi: 10.1002/cncr.11407.

[58] D. Cardinale *et al.*, "Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy.," *Circulation*, vol. 131, no. 22, pp. 1981–1988, Jun. 2015, doi: 10.1161/CIRCULATIONAHA.114.013777.

[59] J. C. Plana *et al.*, "Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.," *Eur Heart J Cardiovasc Imaging*, vol. 15, no. 10, pp. 1063–1093, Oct. 2014, doi: 10.1093/ehjci/jeu192.

[60] D. Cardinale *et al.*, "Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy," *J Am Coll Cardiol*, vol. 55, no. 3, pp. 213–220, Jan. 2010, doi: 10.1016/J.JACC.2009.03.095.

[61] G. M. Felker *et al.*, "Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy.," *N Engl J Med*, vol. 342, no. 15, pp. 1077–1084, 2000.

[62] D. J. Slamon *et al.*, "Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2," *N Engl J Med*, vol. 344, no. 11, pp. 783–792, Mar. 2001, doi: 10.1056/NEJM200103153441101.

[63] J. J. Moslehi, "Cardiovascular Toxic Effects of Targeted Cancer Therapies," *N Engl J Med*, vol. 375, no. 15, pp. 1457–1467, Oct. 2016, doi: 10.1056/NEJMRA1100265.

[64] Z. Jawa *et al.*, "Risk factors of trastuzumab-induced cardiotoxicity in breast cancer: A meta-analysis," *Medicine*, vol. 95, no. 44, 2016, doi: 10.1097/MD.0000000000005195.

[65] C. Guenancia *et al.*, "Obesity As a Risk Factor for Anthracyclines and Trastuzumab Cardiotoxicity in Breast Cancer: A Systematic Review and Meta-Analysis," *J Clin Oncol*, vol. 34, no. 26, pp. 3157–3165, Sep. 2016, doi: 10.1200/JCO.2016.67.4846.

[66] N. Fallah-Rad *et al.*, "The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy," *J Am Coll Cardiol*, vol. 57, no. 22, pp. 2263–2270, May 2011, doi: 10.1016/J.JACC.2010.11.063.

[67] H. Abdel-Qadir *et al.*, "The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer," *Eur J Cancer*, vol. 68, pp. 11–21, Nov. 2016, doi: 10.1016/J.EJCA.2016.08.022.

[68] R. Haque *et al.*, "Cardiovascular Disease After Aromatase Inhibitor Use," *JAMA Oncol*, vol. 2, no. 12, pp. 1590–1597, Dec. 2016, doi: 10.1001/JAMAONCOL.2016.0429.

[69] M. Sun *et al.*, "Comparison of Gonadotropin-Releasing Hormone Agonists and Orchiectomy: Effects of Androgen-Deprivation Therapy," *JAMA Oncol*, vol. 2, no. 4, pp. 500–507, Apr. 2016, doi: 10.1001/JAMAONCOL.2015.4917.

[70] S. O'Farrell, H. Garmo, L. Holmberg, J. Adolfsson, P. Stattin, and M. Van Hemelrijck, "Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer," *J Clin Oncol*, vol. 33, no. 11, pp. 1243–1251, Apr. 2015, doi: 10.1200/JCO.2014.59.1792.

[71] J. C. Voog *et al.*, "Cardiovascular Mortality Following Short-term Androgen Deprivation in Clinically Localized Prostate Cancer: An Analysis of RTOG 94-08," *Eur Urol*, vol. 69, no. 2, pp. 204–210, Feb. 2016, doi: 10.1016/J.EURURO.2015.08.027.

[72] M. L. Romo, A. M. Mccrillis, J. Brite, D. Reales, J. B. Dowd, and C. M. Schooling, "Pharmacologic androgen deprivation and cardiovascular disease risk factors: a systematic review," *Eur J Clin Invest*, vol. 45, no. 5, pp. 475–484, May 2015, doi: 10.1111/ECI.12431.

[73] K. G. M. M. Alberti, P. Zimmet, and J. Shaw, "Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation," *Diabet Med*, vol. 23, no. 5, pp. 469–480, May 2006, doi: 10.1111/J.1464-5491.2006.01858.X.

[74] E. C. de Haas, S. F. Oosting, J. D. Lefrandt, B. H. Wolffenbuttel, D. T. Sleijfer, and J. A. Gietema, "The metabolic syndrome in cancer survivors," *Lancet Oncol*, vol. 11, no. 2, pp. 193–203, Feb. 2010, doi: 10.1016/S1470-2045(09)70287-6.

[75] A. Milan, E. Puglisi, L. Ferrari, G. Bruno, I. Losano, and F. Veglio, "Arterial hypertension and cancer," *Int J Cancer*, vol. 134, no. 10, pp. 2269–2277, May 2014, doi: 10.1002/IJC.28334.

[76] H. S. Haugnes *et al.*, "Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study," *J Clin Oncol*, vol. 28, no. 30, pp. 4649–4657, Oct. 2010, doi: 10.1200/JCO.2010.29.9362.

[77] S. Barros-Gomes, J. Herrmann, S. L. Mulvagh, A. Lerman, G. Lin, and H. R. Villarraga, "Rationale for setting up a cardio-oncology unit: our experience at Mayo Clinic," *Cardiooncology*, vol. 2, no. 1, Dec. 2016, doi: 10.1186/S40959-016-0014-2.

CHAPTER 3

Efficacy of physical exercise to offset anthracycline-induced cardiotoxicity: A systematic review and meta-analysis of clinical and preclinical studies

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ABSTRACT

Background

Physical exercise is an intervention that might protect against doxorubicin-induced cardiotoxicity. In this meta-analysis and systematic review, we aimed to estimate the effect of exercise on doxorubicin-induced cardiotoxicity and to evaluate mechanisms underlying exercise-mediated cardioprotection using (pre) clinical evidence.

Methods and results

We conducted a systematic search in the databases of PubMed, EMBASE and CENTRAL. Cochrane's and SYRCLE risk of bias tool were used to assess the validity of human and animal studies, respectively. Cardiotoxicity outcomes reported by ≥3 studies were pooled and structured around the type of exercise intervention. 40 articles were included, of which three were clinical studies. Overall, in humans (sample sizes ranging from 24-61), results were indicative of exercise-mediated cardioprotection, yet not sufficient to establish whether physical exercise protects against doxorubicin-induced cardiotoxicity. In animal studies (n=37), a pooled analysis demonstrated that forced exercise interventions significantly mitigated in-vivo and ex-vivo doxorubicin-induced cardiotoxicity compared to non-exercised controls. Similar, yet slight smaller effects were found for voluntary exercise interventions. We identified oxidative stress and related pathways, and less doxorubicin accumulation as mechanisms underlying exercise-induced cardioprotection, of which the latter could act as an overarching mechanism.

Conclusion

Animal studies indicate that various exercise interventions can protect against doxorubicin-induced cardiotoxicity in rodents. Less doxorubicin accumulation in cardiac tissue could be a key underlying mechanism. Given the preclinical evidence and limited availability of clinical data, larger, methodologically rigorous clinical studies are needed in order to clarify the role of physical exercise in preventing cardiotoxicity in cancer patients.

List of abbreviations

CI	Confidence interval
DIC	Doxorubicin-induced cardiotoxicity
DOX	Doxorubicin
dP/dt-max	maximum developed pressure per time unit
dP/dt-min	Minimum developed pressure per time unit
FS	Fractional shortening
FTM	Forced treadmill intervention
HSP	Heat shock protein
LV	Left ventricle / ventricular
LVEF	Left ventricular ejection fraction
LVP	Left ventricular pressure
MDA	malondialdehyde
mPTP	mitochondrial permeability transition pore
NT-pro-bnp	amino terminal of B-type natriuretic peptide
PE	Physical exercise
PGC	peroxisome proliferator-activated receptor-gamma coactivator
SERCA	sarcoendoplasmic reticulum calcium-ATPase
SMD	Standardized mean difference
SOD	Superoxide dismutase
SYRCLE	Systematic Review Centre for Laboratory animal Experimentation
VWR	Voluntary wheel running

INTRODUCTION

Anthracyclines are a group of antineoplastic antibiotics which have an important role in the treatment of a wide variety of cancers. However, use of anthracyclines in clinical practice is associated with the development of severe side-effects, of which irreversible, dose-dependent cardiotoxicity is among the most important[1], [2]. In a pooled analysis of nearly 50 000 cancer patients treated with contemporary anthracycline-based chemotherapy regimens, incidence of clinical and subclinical cardiotoxicity after a median follow-up of 9 years was 6% (95%CI 3% - 9%) and 18% (95%CI 12% - 24%), respectively[3]. Cardiotoxicity of anthracyclines has been most extensively studied for doxorubicin (DOX), which is currently also the most commonly used anthracycline.

The pathogenesis of doxorubicin-induced cardiotoxicity (DIC), although not fully elucidated, is presumably a multifactorial complex with key roles for topoisomerase-IIβ and generation of oxidative stress. This eventually results in double-strand DNA breaks and mitochondrial dysfunction, leading to cardiomyocyte apoptosis and necrosis, with loss of functional cardiomyocytes as a result [4]–[6]. Since the myocardium has no regenerative capacities, this damage is irreversible. Compared to other cardiomyopathies, DOX-induced heart failure has a particularly poor prognosis, with more than half of the patients dying within two years after diagnosis[7]. As a result of increased incidence as well as survival of cancer patients[8], DIC still poses a real clinical challenge.

There is growing awareness of the need to develop effective strategies to reduce DIC, of which physical exercise (PE) interventions could be a promising non-pharmacological[9]. The potential of PE interventions to reduce DIC has been demonstrated in numerous preclinical studies[10]. Nevertheless, an estimate of the effect of exercise on cardiotoxicity has never been quantified. Moreover, preclinical studies often focus on single pathways or molecular/histological components, thereby targeting only a small fraction of the multifaceted pathogenesis of DIC. To fully understand the relative contribution of these mechanisms, a comprehensive overview incorporating all the hypothesized pathways is necessary.

The aim of this meta-analysis and systematic review is two-fold; (1) to provide a pooled estimate of the effect of PE on preventing DIC and (2) to provide an overview of mechanisms underlying exercise-mediated cardioprotection in subjects receiving DOX-based chemotherapy in (pre)clinical studies.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files. This review was prospectively registered in the PROSPERO register (registration number: CRD42019118218), and the requirements for the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) Statement were followed[11]. The systematic search, selection of articles, internal validity assessment and data extraction were performed by two independent researchers (WN and DB). In cases where no consensus was reached, a third reviewer (AM) was consulted.

Search strategy and study selection

A systematic search was conducted in PubMed, EMBASE and CENTRAL databases on August 14th, 2020. The search string was a combination of search terms for anthracyclines, cardiotoxicity and exercise and was developed in collaboration with an information specialist from University Medical Center Utrecht, Utrecht, The Netherlands (Supplemental Methods). The search was limited to the English language, without a date restriction. References of included full text articles were checked to identify potentially relevant articles not found through the initial search.

Eligible studies compared any type of PE intervention, both single acute bouts and chronic exercise, in combination with anthracyclines to no intervention (i.e. anthracyclines only). Outcomes included any parameters of cardiotoxicity, such as biomarkers, imaging parameters, histopathology and clinical endpoints (i.e. heart failure). Studies with both human and animal subjects (with or without cancer) were eligible for inclusion. Studies in humans, however, had to be either RCTs with cardiotoxicity as one of the outcomes, or mechanistic studies focusing on underlying pathways in order to be deemed eligible. Since the effect of PE on anthracycline-induced cardiotoxicity has been documented previously[12] and might not be the same in children as in adults, given the relevant differences that exist between children and adults in anthracycline-induced cardiotoxicity (e.g. different pharmacokinetics of anthracyclines[13] and an increased susceptibility for cardiotoxicity in patients aged < 4 years of age[14], we excluded children from our study population. We also excluded studies combining DOX with any other drug or substance, and conference abstracts.

Data extraction & analysis

We collected data using a pre-tested extraction form including information about the study population (type of patients, sex, age), study characteristics (number of subjects per arm, duration and timing of intervention), characteristics of the anthracycline administration (timing, dose and number of doses). Cardiotoxicity outcomes, along with their corresponding group averages, measures of variability or spread (SD or SE) and group size (n), were extracted and grouped into *in-vivo* or *ex-vivo* analysis, and human or animal studies. In case results were only reported by means of graphs, we contacted authors for numeric data. If no response was obtained, the study was excluded for the quantitative analysis.

We compared outcomes between exercising and non-exercising DOX-treated subjects. Parameters indicative of cardiac function that were described in ≥3 studies and were considered sufficiently clinically and statistically homogeneous, were pooled. Random effects models were used to allow for heterogeneous underlying treatment effects, yet results were reanalyzed using fixed-effect models to explore whether this yielded differences regarding the summary inferences. Funnel plots with Egger's test were used to detect publication for outcomes that were reported by ≥10 studies[15]. Statistical heterogeneity among studies was assessed via forest plots in combination with the I^2 statistics before undertaking the meta-analysis and presenting pooled results. Outcomes were structured around the type of intervention (forced treadmill (FTM) versus voluntary wheel running (VWR)). If a study had both a FTM and VWR intervention arm, a single pairwise comparison (i.e. FTM or VWR versus control) was entered in the appropriate analysis. Continuous outcomes were presented as mean differences (MDs) with corresponding 95% confidence intervals (CIs) and the variance of the effect size (T^2) .

In a sub-analysis, we tested the effect of timing of the PE intervention with respect to DOX administration (i.e. before (preconditioning) or concomitant with DOX treatment). If a study had multiple intervention arms, the number of subjects in the control group was divided approximately evenly among the comparisons (forced or voluntary versus control), which were entered as single pairwise comparisons into the analysis. Data were analyzed with R (version 3.5.1) and RStudio (version 1.1.456, RStudio Inc., Boston, USA). A narrative synthesis was used to systematically describe the underlying mechanism for exercise-induced cardioprotection.

Risk of bias assessment

We assessed risk of bias for animal studies using the 'Systematic Review Centre for Laboratory animal Experimentation' (SYRCLE) risk of bias tool[16]. We used the Cochrane risk of bias tool (version 1) for human studies[17]. Per category, studies could either score 'high', 'low' or 'unclear' for risk of bias. Authors were contacted for further details in case of an 'unclear' score. Further internal validity was assessed via the reporting of quality indicators. The quality indicators were scored as 'yes' or 'no', corresponding to reported or unreported, respectively.

RESULTS

The search yielded 1224 original articles (Figure 1). One additional article [18] was identified through other sources. After full-text screening, 40 articles were considered eligible and included in this review. References for articles that were excluded on the basis of full-text (*n*=14) are provided in Supplemental Results A**.** Of the 40 studies included in the analysis, 3 were human RCTs[19]–[21] and the remaining 37 were conducted in rodents. Details of all study protocols are summarized in Table 1.

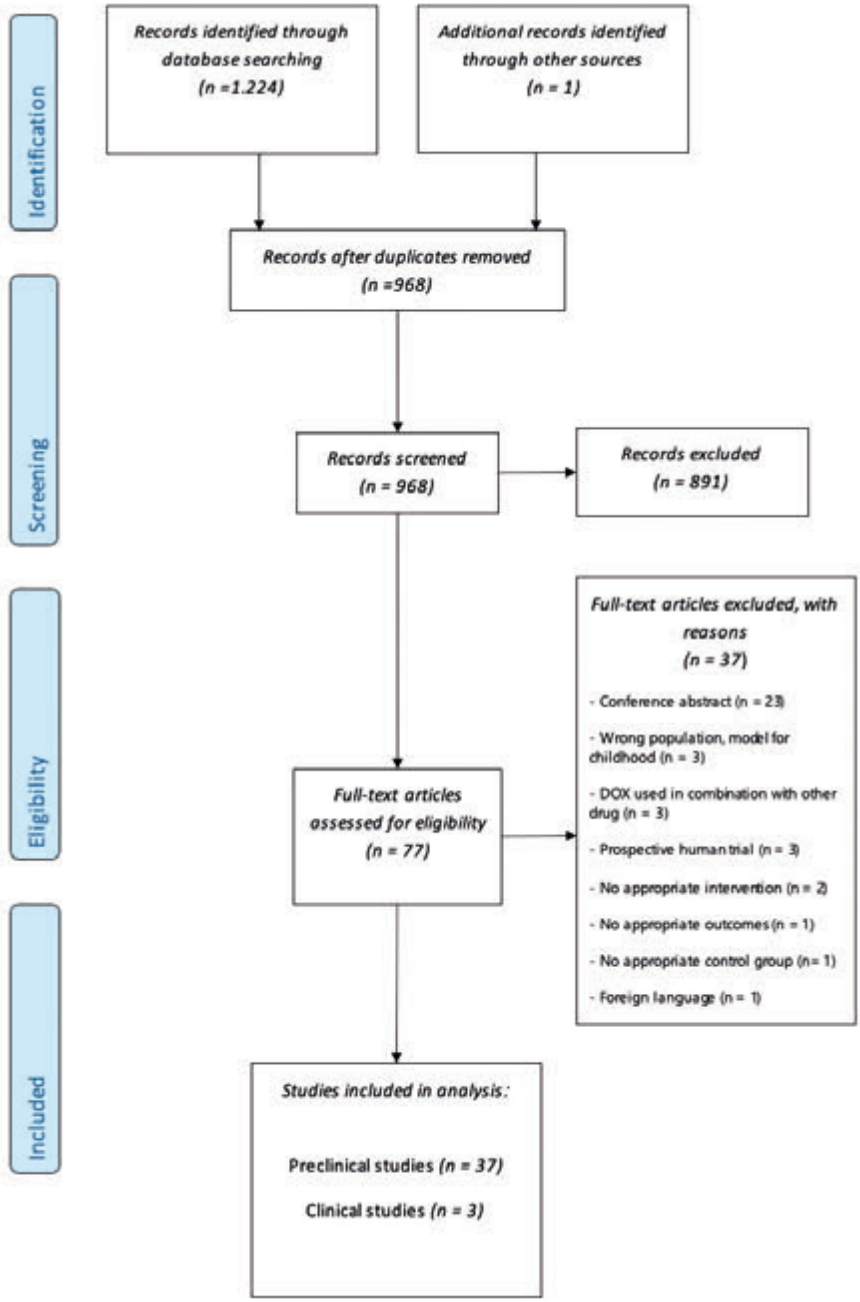


Figure 1. Flow diagram depicting the search process. The format provided by Moger et al[11] in the PRISMA statement was used.

Characteristics of the clinical studies

The three clinical studies were all conducted in breast cancer patients. Two studies by Kirkham *et.al.* made use of the same population (n=24), describing the effects of the first exercise bout before the start of AC-based chemotherapy, and of a total of four bouts on subclinical cardiotoxicity (i.e. strain and biomarkers) in the first [22]and second report[23], respectively. The PE intervention consisted of four 30-min vigorous-intensity treadmill exercise bouts before each gift of DOX. The study by Ma (n=64) evaluated the effect of a 16-week PE program during chemotherapy [21]. Women allocated to the intervention grouped attended 3 50-min supervised treadmill sessions per week, while control group participants were asked to maintain their normal activity pattern. Cardiac function was assessed with echocardiography after four cycles of anthracyclines.

Characteristics of the animal studies

In the 37 animal studies, conducted in mice or rats, the type and duration of PE interventions varied widely. The majority (*n*=21) used FTM interventions, five studies used a VWR protocol[24]–[29], and six studies included both, FTM and VWR[30]–[35]. Three studies used a swimming training protocol[36]–[38] and one study used a protocol to mimic resistance training[39]. Duration varied from a single bout[40], [41] to a PE program that lasted 21 weeks[37]. Doxorubicin was the only anthracycline administrated with variation in cumulative dose, number and frequency of doses and timing with respect to the exercise intervention (i.e. preconditioning, concomitant with DOX treatment or postconditioning). Cumulative DOX dose varied between 4-100mg/kg, with 20 mg/kg being the most used dosage (*n*=14). The majority of the studies (*n*=23) used a preconditioning protocol, where DOX was administrated up to 24 hours after completion of the intervention. Twelve studies had protocols in which, to at least some extent, DOX treatment ran parallel to the PE intervention, and two study used a postconditioning protocol[40], [42].

Lastly, cardiotoxicity was described via various outcomes, including LV function and morphology, histopathology and biochemical analysis. The former was assessed in-vivo as well as ex-vivo using echocardiography or isolated heart perfusion, respectively.

Table 1. Characteristics of the study protocols. 'Experimental groups' refers to the intervention these groups were subjected to. All the experimental groups were also subjected to DOX administration. Details regarding DOX are shown in the 'DOX characteristics' columns. DOX dosages were specified in other columns in case multiple dosage groups were used. For studies reporting different numbers regarding the study populations, the largest number reported is shown. DOX administration during exercise was started in the first week of exercise, unless stated otherwise. For Hydock, 2012, 'dly' and 'wk' in subscript refers to the drug administration schemes, which were respectively daily in 15 consecutive days and weekly in 6 weeks.

Reference	Study population			Study characteristics					DOX characteristics		
	Patients/ animals*	Sex	Age	Experimental groups (*n*)	EX specifications	EX timing w.r.t. DOX infusion	Control groups (*n*)	Timing of cardiotoxicity assessment	Timing of DOX	Dose (mg/ kg)	Number of doses(t)
Clinical studies											
Kirkham, 2017[22]	Stage I-III breast cancer patients, scheduled for DOX-containing therapy	F	50y	TM (13)	Acute: single bout of 30min at 70% HRmax	Preconditioning	No vigorous exercise for 72h prior to and 48 h after treatment (11)	24-48h after DOX treatment	24h after TM	60 mg/ m^2	1
Kirkham, 2018[23]	Stage I-III breast cancer patients, scheduled for DOX-containing therapy	F	50y	TM (13)	Chronic: 4 bouts of 30 min across 6-9 wk before each DOX gift, 70% HRmax	Concomitant	No vigorous exercise for 72h prior to and 48 h after treatment (11)	Before 1^{st} treatment (baseline) and 7-14d after last treatment	24h after each TM	Mean total 236 mg/ m^2	4 (6-9 wk)
Ma, 2018[21]	Breast cancer patients, after operation	F	43.1	TMk (31)	Chronic: 3d/wk for16 wks, 70% HRmax	Concomitant	No guidance in sports, carried out normal daily activities (33)	After last EX bout, time NS	NS	NS	4 (16wk)

Animal studies

Ahmadian, 2018[57]	Wistar rats	M	1. 3mo 2. 16mo 3. 32mo	TM (8/group)	Chronic : 5d/wk for 3wk, 15-17m/min, 25-39min/d	Preconditioning	1. SED+DOX (8/group) 2. TM+SAL (8/group)	24h after DOX	24h after TM	20	1
Alihemmati, 2019[92]	Wister rats	M	NS	TM (6)	Chronic: 5d/wk for 6wk, int. 40-90% VO2max, 60min/d	Preconditioning	1. SED+SAL (6) 2. SED+DOX (6) 3. TM+SAL (6	72h after DOX	after EX	20	1
Ascensão, 2006[58]	Wistar rats	M	6-8wk	TM (6)	Chronic: 5d/wk for 14wks. Build up to 90min/d, 30m/min (grade6 %) by wk 5.	Preconditioning	1. SED+SAL (6) 2. SED+DOX (6) 3. TM+SAL (6)	24h after DOX	24h after TM	20	1
Ascensão, 2011[64]	Wistar rats	M	6-wk	TM (5)	Acute: single bout of 60 min, ~5 min at 15m/min 0% gradient, ~10 min 23m/min 0% gradient, ~45 min 25m/min 5%gradient.	Preconditioning	1. SED+SAL (5) 2. SED+DOX (5) 3. TM+SAL (5)	5d after DOX	24h after TM	20	1
Ascensão-a, 2005[52]	Wistar rats	M	6-8wk	TM (10)	Chronic: 5d/wk for 14wk. building up to 30m/min(6%grad), 90min/d.	Preconditioning	1. SED+SAL (10) 2. SED+DOX (10) 3. TM+SAL (10)	24h after DOX	24h after TM	20	1
Ascensão-b, 2005[59]	Charles River CD1 mice	M	6-8wk	ST (11)	Chronic 5d/wk for 14wk. 1h/d.	Preconditioning	1. SED+SAL (11) 2. SED+DOX (11) 3. ST+SAL (11)	24h after DOX	24h after ST	20	1
Ashrafi, 2012[60]	Wistar rats	M	8wk	1. TM+ $DOX_{10mg/kg}$ (8) 2. TM+ $DOX_{20mg/kg}$ (8)	Chronic: 5d/wk for 3wk. 15-17m/min, 25-39 min/d.	Preconditioning	1. SED+SAL (8) 2. SED+ $DOX_{10mg/kg}$ (8) 3. SED+ $DOX_{20mg/kg}$ (8) 4. TM+SAL (8)	24h after DOX	24h after TM	1. 10 2. 20	1
Chicco, 2005[28]	Spraque-Dawley rats	F	NS	WR (7)	Chronic:voluntary for 8wk	Preconditioning	1. SED+SAL (6) 2. SED+DOX (7) 3. WR+SAL (8)	During and after perfusion	directly after WR, *ex vivo* perfusion	10 µM	For 1h
Chicco-a, 2006[49]	Spraque-Dawley rats	M	NS	TM (8)	Chronic: 5d/wk for 2wk. 15m/min, 20min/d.	Concomitant	1. SED+SAL (6) 2. SED+DOX (8) 3. TM+SAL (6)	5d after EX	During TM	2,5	6 (2wk)

Table 1. (Continued)

Reference	Study population			Study characteristics					DOX characteristics		
	Patients/ animals*	Sex	Age	Experimental groups (*n*)	EX specifications	EX timing w.r.t. DOX infusion	Control groups (*n*)	Timing of cardiotoxicity assessment	Timing of DOX	Dose (mg/ kg)	Number of doses(t)
Chicco-b, 2006[50]	Spraque-Dawley rats	M	NS	TM (15)	Chronic: 5d/wk for 12wk. Building up to 15-27 m/min (0-5% gradient), 20-60 min/d.	Preconditioning	1. SED+SAL (6) 2. SED+DOX (15) 3. TM+SAL (6)	5d after DOX	24h after TM	15	1
Dolinsky, 2013[43]	C57BL6 mice	F	10wk	TM (9-11)	Chronic: 5d/wk for 8wk, building up to 18m/min, 45min/d.	Concomitant	1. SED+SAL (9-11) 2. SED+DOX (9-11) 3. SED+DOX+RESV (9-11)	48h after EX	During TM	8	4 (4wk)
Farzanegi, 2019[38]	Wistar rats	NS	40-50wk	ST (6)	Chronic: 3d/wk for 8wk. Building up from 5 min/d to 30min/d.	Concomitant	1. SED+SAL (6) 2. SED+DOX (6) 3. SED+DOX+SAL (6) 4. SED+DOX+GA (6) 5. ST+DOX+GA (6)	Directly after completion of EX	During ST in wk 1	8,5	1
Hall, 2019[29]	Sprague-Dawley rats	F	10wk	WR (8)	Chronic: voluntary for 17 wks.	Preconditioning	1. SED+SAL (6) 2. SED+ CR (6) 3. SAL + WR (6) 4. SAL+CR+WR (8) 5. DOX (8) 6. CR+DOX (8) 7. CR+DOX+WR (8)	5d after DOX	5 d after WR	15	1
Hydock, 2008[32]	Spraque-Dawley rats	M	NS	1. TM (24) 2. WR (21)	Chronic: 1. 5d/wk for 10wk. 20-60min/d, 20-30m/min(0-18%grade). 2. voluntary for 10wk.	Preconditioning	1. SED+SAL (30) 2. SED+DOX (28) 3. TM+SAL (24) 4. WR+SAL (20)	5d or 10d after DOX	24h after TM/WR	10	1

Hydock, 2009[73]	Sprague-Dawley rats	F	NS	WR (9)	Chronic: voluntary for 7w.	Concomitant	1. SED (10) 2. SED+DOX (8)	7d after DOC	During WR, after wk 1	2,5	6 (6wk)
Hydock, 2011[35]	Sprague-Dawley rats	M	NS	1. TM (17) 2. WR (23)	Chronic: 1. 5d/wk for 10wk. .30 m/min, 60min/d. 2. Voluntary for 10wk.	Preconditioning	1. SED+SAL (11) 2. SED+DOX (14) 3. TM+SAL (12) 4. WR+SAL (17)	4 wk after DOX	24h after TM/WR	1	10 (10d)
Hydock, 2012[27]	Sprague-Dawley rats	F	NS	1. WR+ DOX_{dly} (9) 2. WR+ DOX_{wk} (10)	Chronic: voluntary for 10wk.	Concomitant	1. SED+SAL_{dly} (8) 2. SED+SAL_{wk} (7) 3. SED+DOX_{dly} (15) 4. SED+DOX_{wk} (10) 5. WR+SAL_{dly} (8) 6. WR+SAL_{wk} (8)	Directly after completion of EX	During WR	1. 1_{dly} 2. 2.5_{wk}	1. 15 (15d) 2. 6 (6wk)
Jensen, 2013[31]	Sprague-Dawley rats	F	10-11wk	1. TM (47-58) 2. WR (40-51)	Chronic: 1. 5d/wk for10wk. 13-30m/min(5-18%grade), 60min/d. 2. Voluntary for 10wk.	Preconditioning	1. SED+SAL (5-9) 2. SED+DOX (38-61)	1d, 3d, 5d, 7d or 9d after DOX	24h after TM/WR	10	1
Ji, 1993[40]	Sprague-Dawley rats	F	6mo	1. TM (7) 2. TM+REC (7)	Acute: single bout 1. Until exhaustion 2. TM+REC = 30min recovery	Postconditioning	1. SED+SAL (13) 2. SED+DOX (7) 3. TM+SAL (6) 4. TM+REC+SAL (7)	Directly after EX	24h and 30min prior to TM/TM+REC	4	2
Kanter, 1985[37]	Swiss White mice	M	5wk	ST (20)	Chronic: 5d/wk for21wk. Building up to 1h/d.	Concomitant	1. SED (20) 2. SED+DOX (22) 3. ST (21)	After 9wk of EX and after 21wk. Histology only assessed after 21wk.	During TM, starting from wk 9	4	10 (7wk)
Kavazis, 2010[61]	Sprague-Dawley rats	M	4-6mo	1. TM (7) 2. TM_{cold} (6)	Chronic: 5d/wk for 5d. 30m/min, 60min/d. Both in cold (4˚C) and normal T	Preconditioning	1. SED+SAL (8+7) 2. SED+DOX (6) 3. TM+SAL (7) 4. TM_{cold}+SAL (6)	24h after DOX	Directly after TM	20	1
Kavazis, 2014[18]	Sprague-Dawley rats	M	6mo	TM (6)	Chronic: 1x/ for 5d. 30m/min, 60min/d	Preconditioning	1. SED+SAL (6) 2. SED+DOX (6) 3. TM+SAL (6)	24h after DOX	24h after TM	20	1
Lee, 2020[89]	C57BL6 mice	M	8wk	TM (10)	Chronic: 5d/wk for 4w. 13m/min, 60min/d.	Postconditioning	1. SED+SAL (10) 2. SED+DOX (10)	24h after EX	24 before EXE	20	4 (4wk)

Table 1. (Continued)

Reference	Study population			Study characteristics					DOX characteristics		
	Patients/ animals*	Sex	Age	Experimental groups (*n*)	EX specifications	EX timing w.r.t. DOX infusion	Control groups (*n*)	Timing of cardiotoxicity assessment	Timing of DOX	Dose (mg/ kg)	Number of doses(t)
Lien, 2015[34]	Spraque-Dawley rats	M	10wk	1. TM+ $DOX_{10mg/kg}$ (10) 2. TM+ $DOX_{15mg/kg}$ (13) 3. WR+ $DOX_{10mg/kg}$ (10) 4. WR+ $DOX_{15mg/kg}$ (12)	Chronic: 1x/d for 5d. 24m/min, 60min/d.	Preconditioning	1. SED+SAL (14) 2. SED+$DOX_{10mg/kg}$ (10) 3. SED+$DOX_{15mg/kg}$ (13) 4. WR+SAL (13) 5. TM+SAL (13)	5d after DOX	24h after TM/WR	1. 10 2. 15	1
Mackay, 2019[63]	C57BL6 mice	M	5wk	TM (8)	Chronic: 1x/d for 5ds, On 70%of max speed, 60min/d	Concomitant	1. SED+SAL (9) 2. SED+DOX (8) 3. TM+SAL (11) 4. MET+SED+SAL (13) 5. MET+DOX (7)	3d after DOX	1h after TM	15	1
Marques-Aleixo, 2015[33]	Spraque-Dawley rats	M	6wk	1. TM (6) 2. WR (6)	Chronic: 1. 5d/wk for12wk, 18-27m/ min, 60 min/d. 2. Voluntary	Concomitant	1. SED+SAL (6) 2. SED+DOX (6) 3. TM+SAL (6) 4. WR+SAL (6)	48h after EX	During TM/WR, starting from wk 5	2	7 (7wk)
Marques-Aleixo, 2018[30]	Spraque-Dawley rats	M	6wk	1. TM (NS) 2. WR (NS)	Chronic: 1. 5d/wk for 14wk, 18-27m/ min, 60 min/d. 2. Voluntary	Concomitant	1. SED+SAL (NS) 2. SED+DOX (NS) 3. TM+SAL (NS) 4. WR+SAL (NS)	48h after EX	During TM/WR, starting from wk 5	2	7 (7wk)
Morton, 2019[44]	Spraque-Dawley rats	F	6mo	TM (10)	Chronic: 5d/wk for 2wk. 30m/min, 60min/d	Preconditioning	1. SED+SAL (10) 2. SED+DOX (10) 3. TM+SAL (10)	48h after DOX	24h after TM	20	1

Parry, 2015[26]	Fischer 344 rats (inoculated with tumour cells after week 11)	F	12wk	WR (36)	Chronic: voluntary for 12-13wk	Preconditioning	1. SED+SAL (30) 2. SED+DOX (36) 3. WR+SAL (30)	1d, 3d or 5d after DOX	24h after tumor reached 1cm	12	1
Pfannenstiel, 2018[39]	Spraque-Dawley rats	M	10wk	RT (15)	Chronic: RT for 12wk by encouraging rats to stand up heightening the food/water supply	Preconditioning	1. SED+SAL (9) 2. SED+DOX (15) 3. RT+SAL (9)	5d after DOX	24h after RT	12.5	1
Phungphong, 2020[74]	Sprague-Dawley rats	F	9wk	TM	Chronic: Chronic: 5 d/wk for 14d, 21 m/min, 2 x 10-30min/d	Concomitant	1. SED (11) 2. OVX (12) 3. OVX+DOX (11) 4. OVX+DOX+EST (12) 5. OCX+DOX+MCS(13)	48h after EX	during TM	2.5	6 (2d)
Shirinbayan, 2012[62]	Wistar rats	M	10wk	TM (8)	Chronic: 5d/wk for3wk, 15-17 m/min, 23-39 min/d.	Preconditioning	1. SED+SAL (8) 2. SED+$DOX_{10mg/kg}$ (8) 3. SED+$DOX_{20mg/kg}$ (8) 4. TM+SAL (8)	24h after DOX	24h after TM	1. 10 2. 20	1
Smuder, 2013[77]	Spraque-Dawley rats	M	6mo	TM (6)	Chronic: 1x/d for 10d, building up to 30m/min, 60 min/d.	Preconditioning	1. SED+SAL (6) 2. SED+DOX (6) 3. TM+SAL (6)	24h after DOX	Directly after TM	20	1
Sturgeon, 2014[45]	C57BL6 mice (injected with melanoma cells)	M	6-8wk	TM (9)	Chronic: 5 d/w for 2wk, 10m/min, 45min/d.	Concomitant	1. SED+SAL (7) 2. SED+DOX (8) 3. TM+SAL (8)	48h after EX	During TM	2	2 (2wk)
Werner, 2008[81]	1. C57BL6 mice 2. eNOS-/-micecmar 3. TERT-/-mice	M	8wk	WR (6-12)	Chronic: voluntary for 3wk.	Preconditioning	1. SED+DOX (8-12) 2. SED (8-12) 3. $WR_{6months}$ 4. $SED_{6months}$	NS	After WR (further NS)	22.5	1 (24h)

Table 1. (Continued)

Reference	Study population			Study characteristics					DOX characteristics		
	Patients/ animals*	Sex	Age	Experimental groups (*n*)	EX specifications	EX timing w.r.t. DOX infusion	Control groups (*n*)	Timing of cardiotoxicity assessment	Timing of DOX	Dose (mg/ kg)	Number of doses(t)
Wonders, 2008[41]	Sprague-Dawley rats	M	NS	TM (NS)	Acute: single bout of 60 min, ~5 min at 15m/min 0% gradient, ~10 min 23m/min 0% gradient, ~45 min 25m/min 5%gradient	Preconditioning	1. SED+SAL (NS) 2. SED+DOX (NS) 3. TM+SAL (NS)	5d after DOX	24h after TM	15	1
Yang, 2020[93]	Sprague-Dawley rats	M	NS	TM (8)	Chronic: 3d/wk for 4wk, 12 m/min, 60 min/d.	Concomitant	1. SED+SAL (8) 2. SED+DOX (8)	24h after EX	24 after DOX	??	12 (3/wk, 4wk)

Abbreviations: M = male; F = female; NS = not specified; TM = treadmill; WR = voluntary wheel running; ST = swimming training; TM+REC = treadmill + 30 minutes of recovering after exercise; TM_{cold} = treadmill at 4°C; d = days; wk =weeks; y = years; mo =months; min = minutes; SED = sedentary; SAL = saline; DOX = doxorubicin; RESV = resveratrol; GA = garlic extract. *study population in preclinical studies are animals without cancer, unless stated otherwise.

Risk of bias assessment is presented in Figure 2 and Supplemental Results B. In brief, the two clinical reports by Kirkham *et.al.* were overall scored as low risk of bias, while the study by Ma was rated as having relatively low methodological quality. The animal studies varied widely in terms of risk of bias, with most studies scoring low on the items of selection and attrition bias, and relatively high on the risk of performance bias. Risk of publication bias, i.e. detected by asymmetry in the funnel plots, was not assessed since no outcomes were reported by ≥10 studies.

Figure 2. Results of the risk of bias assessment for human studies (A), animal studies (B) and quality indicators for animal studies (C).

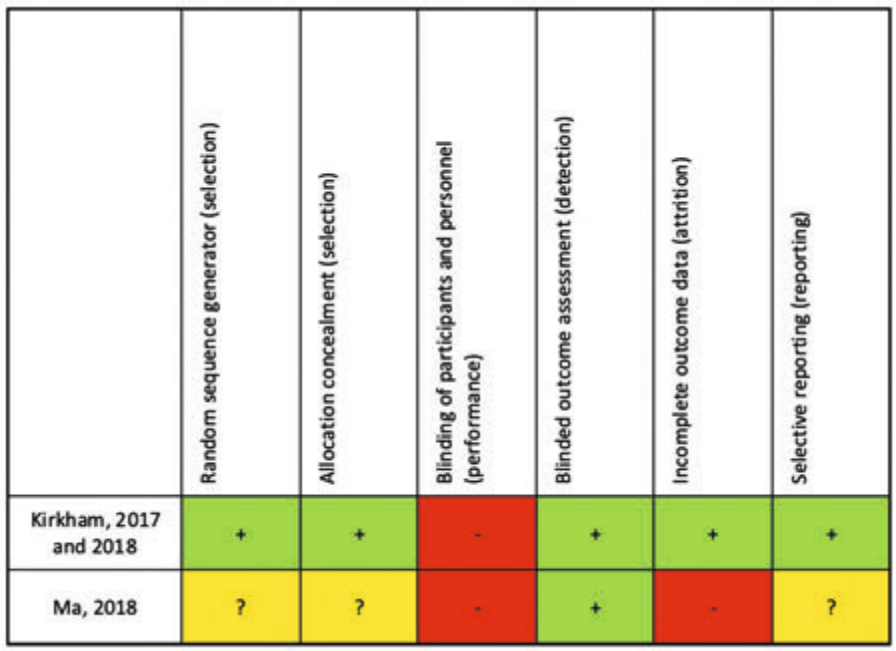


Figure 2A. Results of the risk of bias assessment for human studies. The risk of bias was assessed using the Cochrane risk of bias tool. The colour of the cells depict the estimated risk of bias for the studies shown on the y-axis in the categories shown on the x-axis. Green, yellow and red cells respectively represent a low, unclear and high risk of bias. Blinding of participants was not possible due to the nature of the intervention.

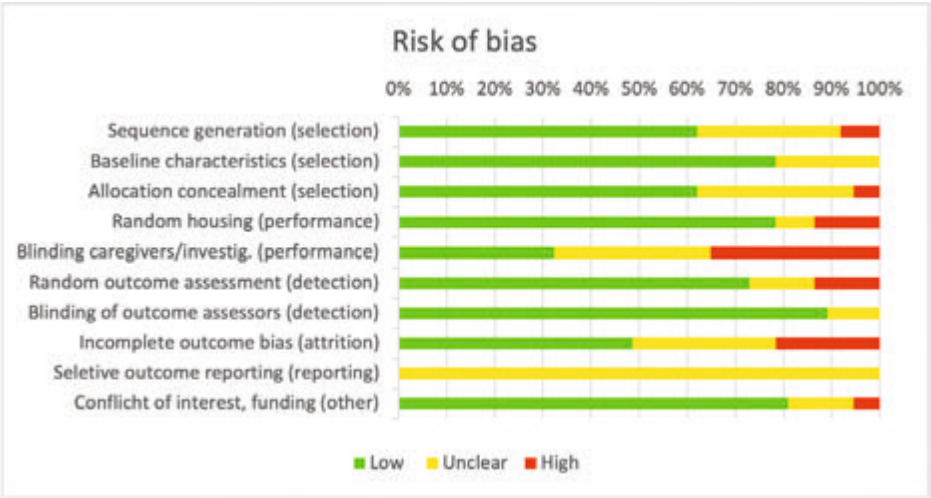


Figure 2B. Results of the risk of bias assessment for animal studies. The risk of bias was assessed using the SYRCLE risk of bias tool. Shown are the percentages of studies that were judged to have an 'unclear', 'low' or 'high' risk of bias in the categories depicted on the y-axis.

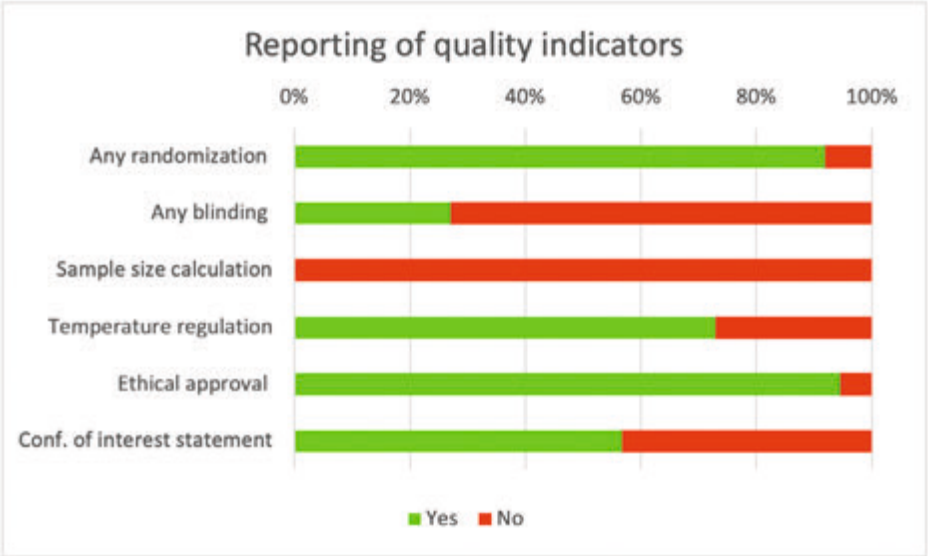


Figure 2C. The reporting of quality indicators for animal studies. Shown are the percentages of studies that did (yes) or did not (no) report the quality indicators depicted on the y-axis.

The effect of exercise on DIC

Clinical studies

A total of 3 studies reported on physical exercise on anthracycline-induced cardiotoxicity in cancer patients. However, results were not pooled since two reports made use of the same study population and had substantial clinical differences (e.g. duration of PE intervention and timing of outcome assessment) compared to the third study. The first study by Kirkham *et. al.*[22] showed that a single treadmill session mitigated increase in the amino terminal of B-type natriuretic peptide (NT-proBNP) 24-48 hours after the first anthracycline treatment. Nevertheless, echocardiographic parameters, including strain, were comparable between the exercise (*n*=13) and control group (*n*=10). In the second report[23], the four exercise bouts did not prevent a rise in cardiac biomarkers (NT-proBNP and cardiac troponin). Longitudinal strain and LVEF remained unchanged in both groups before and after chemotherapy. However, the authors reported that the PE group had fewer changes in hemodynamics than the control group. The last study reported that, in the PE group (n=31), LVEF increased significantly after chemotherapy (from 55±3.5% to 60±2.9%), while a decrease (51±5.6% to 47±2.6%, P<0.05) was observed in the control group (n=33). However, between-group differences were not presented, and risk of bias is high[21].

Animal studies: pooled analysis on in-vivo cardiotoxicity

All animal studies that assessed *in-vivo* parameters of cardiotoxicity (*n*=13)[26], [27], [31], [32], [34], [35], [39], [43]–[48], made use of echocardiographic-derived fractional shortening (FS) as a marker for systolic LV function. All studies used a treadmill intervention as PE program, except for one study that used a protocol to mimic resistance training[39]. Results of this study, as well as those from a study where no numeric data could be obtained[44], were excluded from quantitative analyses. Both of these studies found an absolute improvement in FS in exercised rodents as compared to controls of 13% and approximately 15%, respectively[39], [44].
Overall, the results of these studies demonstrated that PE interventions are able to mitigate DOX-induced impairment in FS. For studies using FTM interventions (*n*=8)[31], [32], [34], [35], [43], [45], [47], [48], FS was significantly higher in exercised versus non-exercised rodents (8.4% (95%CI: 5.4;11.5), T^2 = 18.5. (Figure 3a). A pooled analysis of the seven studies that used a VWR intervention revealed a slightly lower MD; 5.4% (95%CI: 3.6;7.2), T^2 =0[26], [27], [31], [32], [34], [35], [46]) (Figure 3b).
In a sub-analysis regarding the timing of the PE intervention, i.e. preconditioning (n=6)[26], [31], [32], [34], [35], [46] or concomitant with DOX administration (n=5)[27],

[43], [45], [47], [48], the MD was 7.0% (95%CI: 5.2; 8.7), T^2=0 and 5.9% (95%CI: 1.0; 10.7), T^2=23.8, respectively. Heterogeneity was substantial in the latter sub-analysis (I^2=78%, chi-squared test: p<0.01) (Supplemental Results C).

Ex-vivo parameter: pooled analysis on left ventricular developed pressure

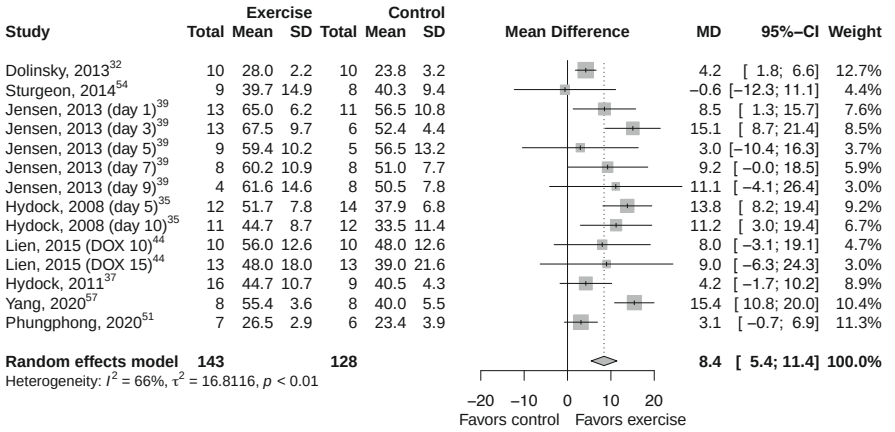
Ex-vivo cardiotoxicity was assessed in twelve animal studies via retrograde isolated heart perfusion[26]–[28], [31], [32], [34], [35], [39], [41], [46], [49], [50], in which the myocardium is perfused via the coronary system to assess cardiac function in controlled loading conditions. Left ventricular developed pressure (LVP), the maximum developed pressure per time unit (dP/dt-max) and the maximum rate decline per time unit (dP/dt-min) was measured. LVP represents cardiac function as whole, whereas the latter are indicators of systolic and diastolic function, respectively[51]. Protocols for isolated heart perfusion were mostly comparable. One exception was the study by Chicco *et. al.*[28], where DOX was administrated *ex-vivo* (i.e. the hearts were transplanted prior to DOX administration). This study, as well as a study that used a single exercise bout only[41] and the study that used a resistance intervention[39], were therefore excluded from the pooled analyses.

For LVP, all studies reported results significantly favoring PE (Figure 3c and Figure 3d). For studies using FTM interventions (*n*=6)[31], [32], [34], [35], [49], [50], our meta-analysis yielded a MD of 19.7 (95%CI:14.3;25.1) mm Hg, T^2 = 51.3, compared to the non-exercised rodents. The MD was 16.1 (95%CI:11.5;20.8) mm Hg, T^2=50.3, for studies with VWR interventions versus controls (*n*=7)[26], [27], [31], [32], [34], [35], [46]. Results of dP/dt-max and dP/dt-min were comparable to those of LVP and are presented in Supplemental Results D.

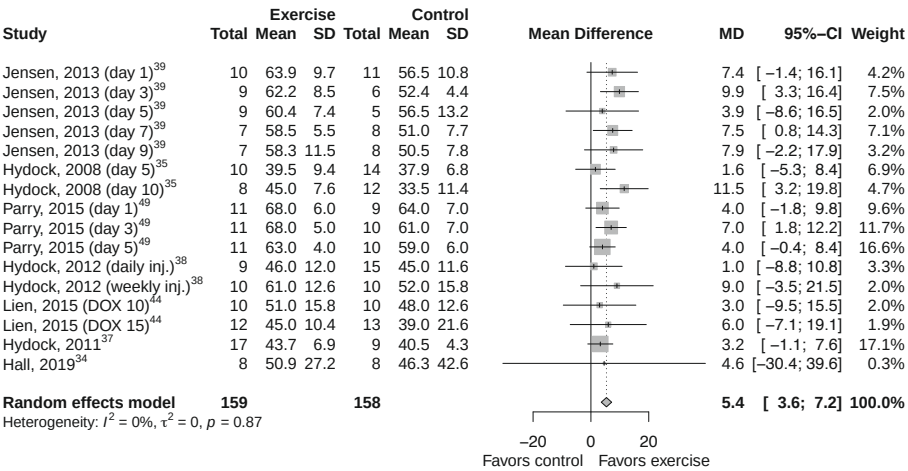
In addition to isolated heart perfusion, five studies used histology or electron microscopy to establish exercise-mediated cardioprotection *ex-vivo*[33], [37], [38], [52]. Although these studies were too clinically heterogeneous for meta-analysis, all showed that microscopically established cardiac abnormalities induced by DOX were mitigated through exercise, either via swimming training[37], [38], FTM[33], [42], [47], [48], [52], [53] or VWR[33] interventions.

The analyses of echocardiography and perfusion parameters were repeated using fixed-effect models, and yielded no relevant differences from the results based on the random effects models (data not shown).

Figure 3. Forest plot of forced (A) or voluntary (B) physical exercise interventions on fractional shortening on echocardiography (in-vivo), and of forced (C) or voluntary (D) physical exercise interventions on isolated heart perfusion(ex-vivo), compared to non-exercised controls in animal studies. Results are presented as mean difference with 95% confidence interval.



A



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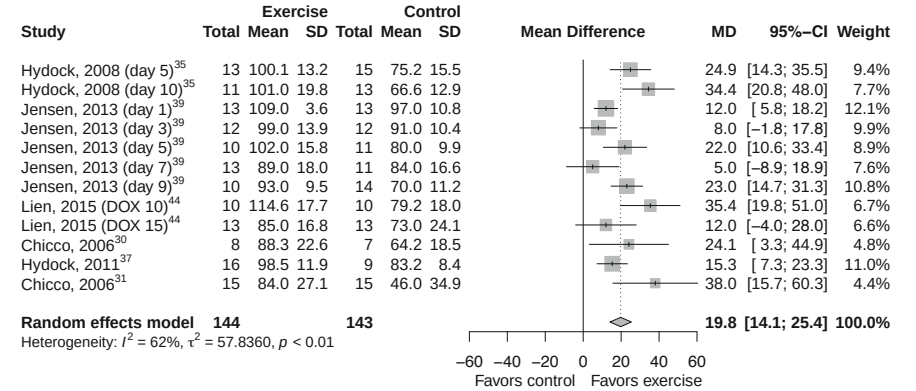

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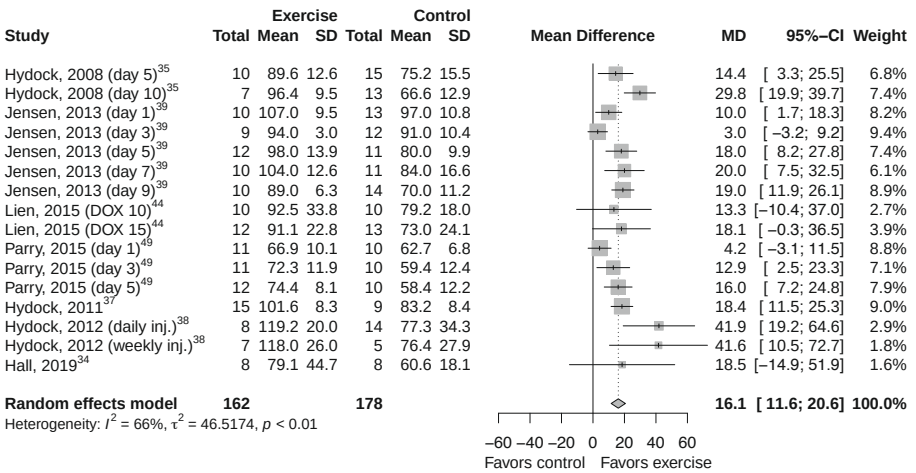


D

Mechanisms underlying exercise-mediated cardio-protection

Multiple pathways were addressed by the included studies (Table 2), and were grouped into those associated with increased oxidative stress and DOX accumulation. An overview of the available studies per pathway is presented in Table 3.

Exercise and oxidative stress

The induction of oxidative stress through inciting overproduction of reactive oxygen species is believed to play an important role in the pathogenesis of DIC, supported by increased levels of markers of oxidative stress, such as malondialdehyde (MDA), after DOX administration[54]–[56]. Increased oxidative

stress is related to a variety of other pathways or proteins, including upregulation of antioxidants or heat-shock proteins, inflammation, disruption of calcium homeostasis, autophagy and apoptosis. Oxidative stress, or one of the related pathways, is the most commonly reported mechanism; 21 studies focused on how PE influences oxidative stress[28], [33], [38]–[43], [47]–[50], [52], [53], [57]–[63]. Eighteen studies investigated the effects of PE on **antioxidants,** which can counterbalance oxidative stress [28], [33], [37], [38], [40], [42], [43], [48]–[50], [52], [53], [57]–[62], [64]. The vast majority of these studies observed a beneficial effect of PE on antioxidants, meaning upregulation of antioxidants in the PE groups compared to controls. The most frequently studied antioxidants were superoxide dismutase (SOD) and catalase (CAT). Although the effect sizes varied widely, the relative increase observed most often was in the range of 30-50%. In four of these studies, upregulation of antioxidants coincided with a reduction of DIC on either echocardiography[43] or histopathology[37], [38], [59]. Nonetheless, the role of antioxidants is ambiguous, as not all studies reported upregulation of the same antioxidants, and some studies reported conflicting results. For SOD, for example, no attenuation was found by five studies [28], [49], [50], [59], [64], while one of these studies reported upregulation of CAT [59] and three studies found a cardioprotective effect of PE against DIC via isolated heart perfusion[28], [49], [50]. In contrast, in the study by Phungphong *et.al.* using ovariectomized rats, attenuation of oxidative stress markers by PE was observed, but without preservation of LV function on echocardiography [48].

Heat shock proteins (HSPs) are proteins that increase in various situations of cellular stress, e.g. heat-shock and ischemia[65]. From the family of HSPs, HSP60; HSP70; and HSP72 were investigated by 10 studies that yielded conflicting results. While the majority described significant upregulation of HSPs by a PE intervention[28], [50], [52], [57], [58], [62], two studies reported no increase in HSP [49], [59] or even a decrease in HSP following exercise [38]. Moreover, Kavazis *et. al.*[61] found that a swimming intervention, performed under cold conditions which prevented upregulation of HSP72, still yielded cardioprotection in DOX-treated rodents.

Table 2. Overview of pathways studied by the animal studies and their main results. AST = aspartate aminotransferase, CRP = C-reactive protein, CAT = catalase, DOX = doxorubicin, HSP = heat shock protein, LV = left ventricular, MDA = malondialdehyde, mPTP = mitochondrial permeability transition pore, PGC-1α= peroxisome proliferator-activated receptor-gamma coactivator 1-alpa, SERCA = sarcoendoplasmatic reticulum calcium ATP-ase, SOD = superoxide dismutase.

Reference of animal study	Pathway(s)	Effect of physical exercise intervention	Summary of main results
Ahmadian, 2018[57]	Marker of **oxidative stress** (MDA), **antioxidants** (SOD), **HSP** (HSP70), **inflammation** markers (IL-10, CRP)	Yes	Preconditioning exercise program had beneficial effect on antioxidant capacity in all three age groups, yet the strongest effect was observed in the group of young rats.
Alihemmati, 2019[92]	**Apoptosis** (Bax, BCL2, caspase-6 and gene and microRNA expression)	Yes	Preconditioning high-intensity interval training attenuated expression pro- and apoptotic factors and microRNA, counteracting myocardial apoptosis.
Ascensão, 2006[58]	Markers of **oxidative stress** (MDA, gluthatione analysis), **Antioxidants** (SOD), **HSPs** (HSP60, 70)	Yes	An endurance swimming exercise program mitigated DOX-induced oxidative damage compared to controls with positive effects on the glutathione system and HSP60.
Ascensão, 2011[64]	**Antioxidants** (SOD), **mPTP**, **apoptosis** (e.g. Bax, Bcl-2, caspase), mitochondrial functioning	Yes	The preconditioning physical exercise program resulted in lower levers of oxidative damage compared to non-exercised controls and mitigated DOX-induced alteration in myocardial mitochondria compared to non-exercised controls.
Ascensão-a, 2005[52]	Markers of **oxidative stress** (MDA, aconitase), **antioxidants** (SOD), **HSPs** (HSP60, 70), **mPTP**, **apoptosis** (Bax, Ncl-2), mitochondrial functioning	Yes	An endurance treadmill exercise intervention improved antioxidant capacity and attenuated myocardial apoptosis. Histopathology confirmed significant attenuation of cardiotoxic changes in the exercise versus control group.

Ascensão-b, 2005[59]	Markers of **oxidative stress** (MDA, aconitase, gluthatione analysis), **antioxidants** (SOD, CAT), **HSPs** (HSP60, 70), **apoptosis** (Bcl-2, Bax, ANT) mitochondrial functioning and membrane potential	Yes	A single exercise bout mitigated DOX-induced mPTP susceptibility, mitochondrial dysfunction and altered apoptotic signalling compared to non-exercised controls.
Ashrafi, 2012[60]	Markers of **oxidative stress** (MDA, NO), **antioxidants** (SOD, apelin)	Yes	A short—term physical exercise preconditioning program counteracted DOX-induced oxidative stress and upregulated oxidative capacity compared to non-exercised controls.
Chicco, 2005[28]	Marker of **oxidative stress** (MDA), **antioxidants** (SOD), **HSP** (HSP72)	Yes	A voluntary wheel-running preconditioning protocol attenuated DOX-induced alterations in lipid peroxidation compared to non-exercised controls. In addition, higher levels of HSP72 were observed in the intervention group. Cardiac function tended to less impaired in the trained group.
Chicco-a, 2006[49]	Marker of **oxidative stress** (MDA), **antioxidants** (SOD), **HSP** (HSP72), **apoptosis** (caspase-3)	Yes	A low-intensity treadmill exercise protocol mitigated DOX-induced cardiac dysfunction and apoptotic signaling compared to non-exercised controls. No significant effect on lipid peroxidation, HSP72, SOD or MHC distribution was observed.
Chicco-b, 2006[50]	Marker of **oxidative stress** (MDA), **antioxidants** (SOD), **HSP** (HSP72)	Yes	A preconditioning exercise program significantly mitigated DOX-induced impairments in cardiac function compared to non-exercised controls. In addition, an increase in lipid peroxidation and greater expression of HSP72 following exercise was observed.
Dolinsky, 2013[43]	Marker of **oxidative stress** (HNE), **antioxidants** (SOD, glutathione, catalase), **SERCA2a expression**	Yes	A preconditioning treadmill program counteracted DOX-induced LV dysfunction, lowered lipid peroxidation and increased the expression of SER2CA and SOD compared to non-exercised controls.
Farzanegi, 2019[38]	Marker of **oxidative stress** (MDA), **antioxidants** (SOD, catalase), **HSP** (HSP70)**, inflammation marker** (TNF-alpha)	Yes	A swimming program concomitant with DOX treatment decreased inflammatory markers (TNF-a), HSP70 and lipid peroxidation, while improving antioxidant enzymatic activity compared to non-exercised controls.

Table 2. (Continued)

Reference of animal study	Pathway(s)	Effect of physical exercise intervention	Summary of main results
Hall, 2019[29]	**DOX accumulation**	Yes	Voluntary wheel-running partially prevented DOX-induced LV dysfunction in-vivo and ex-vivo, and DOX accumulation in cardiac tissue. Physical exercise combined with caloric restriction yielded the most cardioprotection.
Hydock, 2008[32]	**MHC distribution isoforms**	Yes	A preconditioning forced and voluntary treadmill program prevented DOX-induced LV dysfunction in-vivo and ex-vivo. MHC-isoform distribution was preserved following exercise in DOX-treated animals.
Hydock, 2009[73]	**MHC distribution isoforms**	Yes	Access to voluntary wheel running prior to DOX treatment significantly increased expression of α-MHC isoform compared to non-exercised controls.
Hydock, 2011[35]	**SERCA2a, MHC isoform distribution**	Yes	Both forced and voluntary exercise interventions prior to DOX treatment prevented decline in DOX-induced LV dysfunction in-vivo and ex-vivo. The exercise interventions led to a preservation of MHC isoform distribution. No effect of physical exercise on SER2CA was observed.
Hydock, 2012[27]	**MHC distribution isoforms**	Yes	Compared to non-exercised controls, voluntary wheel running prevented in-vivo and ex-vivo DOX-induced impairments in LV function and preserved MHC-isoform distribution.
Jensen, 2013[31]	**DOX accumulation**	Yes	Both forced and voluntary physical exercise interventions preserved LV function (in-vivo and ex-vivo), and reduced DOX accumulation in cardiac tissue compared to non-exercised controls. No difference was observed between the two exercise programs.
Ji, 1993[40]	Marker of **oxidative stress** (MDA) antioxidants (SOD, catalase, glutathione)	No	Low-dose DOX administration did not impair oxidative functioning in cardiomyocytes, both at rest and during physical exercise.

Kanter, 1985[37]	**Antioxidants** (SOD, catalase, glutathione)	Yes	An endurance swimming protocol concomitant with DOX administration mitigated DOX-induced histopathological changes compared to non-exercised controls. No significant differences in antioxidants between exercise and non-exercised DOX-treated animals were found.
Kavazis, 2010[61]	Marker of **oxidative stress** (HNE), **antioxidants** (SOD, glutathione, catalase), **(HSP)**, **apoptosis** (caspase-3, ubiquitine, calpain, TUNEL)	Yes	A short-term preconditioning physical exercise program increased antioxidant capacity and HSP72, and against mitochondrial damage and apoptosis. Exercise-induced cardioprotection occurred independently of HSP72.
Kavazis, 2014[18]	**Gene expression** (FoxO target genes), **mitochondrial biogenesis** (PGC-1α receptor)	Yes	Compared to non-exercised controls, the short-term physical exercise intervention prior to DOX administration attenuated DOX-induced alteration in gene expression and protein abundance (PGC-1α receptor).
Lee, 2020[89]	**Antioxidants** (e.g. SOD, catalase), **auto/mitophagy** (e.g. APMK, mTOR), **apoptosis** (Bax, BCL2)	Yes	A postconditioning physical exercise program improved basal autophagy and mitophagy, and counteracted DOX-induced oxidative stress compared to non-exercised controls.
Lien, 2015[34]	**SERCA2a**	Yes	Short-term forced and voluntary exercise interventions prevented DOX-induced LV dysfunction in-vivo and ex-vivo compared to non-exercised control. Both program preserved SER2CA expression, yet the forced treadmill intervention appeared to be more effective in the higher DOX dose.
Mackay, 2019[63]	Markers of **oxidative stress** (MDA, glutathione), total iron	No	DOX treatment significantly altered myocardial iron regulation, which was not prevented by a physical exercise program nor metformin treatment prior to DOX administration.

Table 2. (Continued)

Reference of animal study	Pathway(s)	Effect of physical exercise intervention	Summary of main results
Marques-Aleixo, 2015[33]	Markers of **oxidative stress** (MDA, aconitase), **antioxidants** (SOD), **mitochondrial biogensis** (PGC-1α receptor), mitochondrial functioning	Yes	Both forced treadmill and voluntary wheel running interventions prevented DOX-induced increase in oxidative stress and preserved mitochondrial functioning. Cardiac ultra-structure alterations (e.g. percentage of abnormal mitochondria) were counteracted by the two physical exercise program. No major differences between the two physical exercise programs were found.
Marques-Aleixo, 2018[30]	**mPTP, auto/mitophagy** (e.g. Beclin2, Pink, Parkin, P62) **apoptosis** (caspases, Bax, Bcl2)	Yes	Compared to non-exercised controls, forced and voluntary physical exercise programs during DOX treatment mitigated DOX-induced mPTP susceptibility, and increased autophagic and apoptotic signaling, without substantial differences between the two exercise modalities.
Morton, 2019[44]	**mPTP**, **DOX accumulation**	Yes	Short-term preconditioning physical exercise program prevented DOX-induced LV dysfunction on echocardiography and mitigated alteration in mPTP susceptibility compared to non-exercised controls. In addition, less mitochondrial DOX accumulation and increased expression of ABC-transporters was found.
Parry, 2015[26]	**DOX accumulation**	Yes	In tumor-inoculated rats, a voluntary wheel running program prior to DOX treatment preserved cardiac function in-vivo as well as ex-vivo, and reduced DOX accumulation in cardiac tissue compared to non-exercised controls. The exercise program did not interfere with DOX' therapeutic efficacy.
Pfannenstiel, 2018[39]	Marker of **oxidative stress** (MDA), **MHC distribution isoforms**	Yes	A resistance training protocol prior to DOX treatment preserved cardiac function in DOX-treated animals and protected against MHC isoform distribution changes compared to non-exercised controls. No effect was found the exercise program on lipid peroxidation.
Phungphong, 2020[74]	Markers of **oxidative stress** (LDH, lipid peroxidation), **inflammatory markers** (IL-6), **Calcium homeostasis**, **MHC distribution isoforms**	Moderately	In ovariectomized rats, preconditioning exercise program attenuated DOX-induced oxidative stress and cardiac inflammation compared to non-exercised controls. No protective effect on cardiac function following exercise was found.

Shirinbayan, 2012[62]	Markers of **oxidative stress** (MDA, CK, CPK-MB), **antioxidants** (SOD), **HSP** (HSP70)	Yes	A preconditioning physical exercise program significantly increased HSP70 and SOD, and decreased MDA as opposed to non-exercised controls, regardless differences in DOX doses (10mg/kg or 15mg/kg).
Smuder, 2013[77]	**Autophagy** (mRNA and protein synthesis)	Yes	Compared to non-exercised controls, a preconditioning treadmill program prevented DOX-induced increase in autophagic signalling.
Sturgeon, 2014[45]	**MHC distribution isoforms**	No	In a murine model with melanoma, a physical exercise program prior to DOX treatment did not mitigate DOX-induced LV dysfunction on echocardiography nor changes in MHC isoform distribution, but improved DOX' antitumor efficacy compared to non-exercised controls.
Werner, 2008[81]	**Apoptosis** (telomere-regulating proteins, TUNEL)	Yes	A preconditioning voluntary wheel running program reduced DOX-induced p53 expression and might prevent cardiomyocyte apoptosis. In animals not treated with DOX, the exercise program upregulated telomere stabilizing proteins compared to non-exercised controls.
Wonders,2008[41]	Marker of **oxidative stress** (MDA)	Yes	An exercise bout prior to DOX treatment mitigated DOX-induced LV dysfunction on isolated heart perfusion, and attenuated increase in oxidative stress compared to non-exercised controls.
Yang, 2020[93]	**inflammation markers** (AKT, COX-2), **fibrotic markers** (TGF-β)	Yes	A physical exercise program during DOX treatment ameliorated DOX-induced expression of fibrosis factors and reduced cardiac fibrosis on histopathology compared to non-exercised controls. On echocardiography, LV function was preserved in the exercise group.

Table 3. Overview of available evidence per pathway. DOX = doxorubicin, MHC = myosin heavy chain

Pathway	N=
Antioxidants	18
Heat shock proteins	10
Cardiac inflammation	2
Calcium homeostasis	3
Mitochondrial permeability transition pore	4
peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1 alpha	2
MHC isoform distribution	6
Autophagy	3
Apoptosis	10
DOX accumulation	4

Cardiac **inflammation** and remodeling as a result of oxidative stress and impaired mitochondrial function[66] is hypothesized to be an important pathway in the development of DIC and may eventually lead to increased myocardial fibrosis[47]. Ahmadian *et.al.* demonstrated that a 3-week preconditioning program resulted in lower levels of CRP in animals younger than 3 months of age compared to controls [57]. Similarly, a treadmill program concomitant with DOX administration counteracted activation of an inflammatory response (IL-8, TNF-α) and upregulation of fibrotic markers (TGF-β1), which was supported by reduced cardiac fibrosis and preserved systolic function on histology and echocardiography, respectively [47]. Phungphong *et. al.*, using a two-week treadmill program during DOX treatment, found no attenuation of inflammatory markers (IL-6 and IL-10), but reported significantly less myocardial fibrosis in the exercise group compared controls; 7.0±0.13% versus 8.0±0.27% collagen deposition, respectively[48].

Deregulation of intracellular **calcium homeostasis** has also been proposed as a mechanism underlying DIC. This is often attributed to downregulation of sarcoendoplasmic reticulum calcium-ATPase (SERCA)2a[67]. SERCA2a is the most often expressed isoform of SERCA in cardiomyocytes and is responsible for pumping calcium from the cytosol into the sarcoplasmatic reticulum[35]. Calcium is of key importance in many cardiac functions and an interruption could result in a variety of diseases, including systolic and diastolic dysfunction and arrhythmias[68]. In two studies treadmill interventions of five days and eight weeks, respectively, prior to and during DOX treatment, partially prevented downregulation of SERCA2a [34], [43]. Lien *et. al.*, investigating DOX dosages of

10mg/kg and 15 mg/kg in forced and voluntary exercise groups, suggested that both exercise modalities can preserve SERCA2a, although the FTM group appeared more effective with the higher DOX dosage[34]. Both studies reported simultaneous preservation of systolic function. However, one study in which DOX administration significantly lowered SERCA2a by about 80%, found no effect of a 10-week preconditioning PE intervention[35].

Induction and opening of the **mitochondrial permeability transition pore** (mPTP) could result from DOX-induced oxidative stress and associated deregulation in calcium homeostasis[69]. The mPTP is a channel in the mitochondrial membrane, susceptible to calcium loading conditions. Opening of this channel enhances membrane permeability, which can lead to mitochondrial dysfunction via cessation of ATP synthesis and apoptosis[69]. Four studies investigated the effect of PE on mPTP susceptibility, all of which found that a forced preconditioning PE program, varying from a single bout to an endurance protocol of 14 weeks, had a positive effect on DOX-induced increased susceptibility to mPTP opening [44], [52], [64] [30]. These findings were corroborated by simultaneous reduction in DIC on echocardiography[44] and histopathology[52]

Another pathway related to oxidative metabolism is the **peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1 alpha**. The PGC-1 alpha plays a pivotal role in mitochondrial biogenesis as well as lipid and carbohydrate metabolism[70], and is believed to be cardioprotective, since knockout of PGC-1alpha in mice leads to cardiomyopathy[71]. One study found that a short-term PE program induced the expression of PGC-1alpha protein in cardiac (and skeletal muscle) tissue by about 50%[18]. The authors proposed that this could prevent downstream DOX-induced cardiac and skeletal muscle wasting[18]. Another study found a trend for preservation of PGC-1alpha expression by both forced and voluntary PE interventions during DOX administration, which corresponded with less cardiotoxic changes on histopathology[33].

The distribution of **MHC isoforms**, i.e. the ratio of fast α-MHC to slower, yet more metabolically efficient β-MHC, is of importance for cardiac contractility. Upregulation of β-MHC at a cost of α-MHC is reported after exposure to DOX [72], and has been attributed, in part, to DOX-induced oxidative stress[27]. Six studies found that the distribution of MHC isoforms was unfavorably affected by DOX[27], [32], [35], [39], [48], [73]. The studies by Hydock et. al.[27], [32], [35] using both forced and voluntary PE programs, found a consistent trend towards lower expression of β-MHC (approximately 5-15% reduction) following exercise. These results were corroborated by the studies of Pfannenstiel et. al.[39] and Phungphong et. al.[74] using a resistance and forced treadmill PE program, respectively. However, two

other studies found no significant effect of PE on MHC isoform distribution by DOX administration alone or in combination with a FTM intervention[45], [49].

The process of **autophagy** is important for cellular survival by regulation of energy sources, removing damaged organelles (e.g. mitochondria) or intracellular pathogens[75]. Dysregulation of autophagy could occur via DOX-induced oxidative stress and could eventually lead to non-apoptotic cell death [76]. Two studies showed that both a 12-day and a 14-week PE intervention during treatment can effectively prevent DOX-mediated increase in autophagy[30], [77]. However, using a postconditioning protocol, Lee. *et.al.* found no attenuation of autophagy in non-exercised animals, while autophagy was significantly promoted in the exercised animals[42].

Apoptosis is an important and final step in the development of DIC, which can be promoted through oxidative stress (among others via increased mPTP opening) and the formation of topoisomerase-IIDOX-DNA complexes [78], [79]. The latter is believed to be a key mechanism underlying DIC, since depletion of topoisomerase-IIβ can prevent cardiac toxicity caused by DOX[80]. Attenuation of apoptotic signaling by exercise was studied by ten studies[30], [42], [45], [48], [49], [52], [53], [61], [64], [81], of which the majority measured caspase-3 or Bcl-2 family proteins (pro- and anti-apoptotic protein Bax and Bcl-2, respectively). All of the studies of caspase-3 activity reported that various PE programs counteracted DOX-induced increase in caspase-3 activity[30], [42], [48], [49], [52], [61], [64]. Results from studies of the Bcl-2 proteins are less consistent. Alihemmati et al. found that a six-week preconditioning high-intensity interval training program significantly counteracted DOX-induced upregulation of Bax from about 50% to about 10% change and downregulation of Bcl-2 from approximately 80% to about 55% change[53]. Two other studies using a 14-week preconditioning[52] or concomitant[30] PE protocol also found relatively lower expression of Bax in the exercise groups, but no significant changes or trend in Bcl2[30], [52]. No attenuation of either Bax or Bcl2 was found by the other studies that investigated these proteins [42], [64]. Werner et al. demonstrated that a 3-week voluntary running protocol mitigated expression of pro-apoptotic proteins, including p53, compared to non-exercised controls[81]. However, another study using levels of cleaved poly(ADP-ribose) polymerase (PARP) as marker for apoptosis found no effect of either a 2-week FTM intervention or DOX administration alone on apoptotic signaling [45].

DOX accumulation

Compared to other cytosolic compartments of a cell, DOX localizes predominantly in mitochondria [44]. Four studies using FTM [31], [44] or VWR[26], [31], [46] interventions have investigated whether a PE program can counteract DOX accumulation. Three of these studies found significantly lower concentrations of DOX, varying from about 25% to 40%, in the LVs of exercised animals compared to non-exercised animals within 2 days after injection[26], [31], [44]. The study by Hall *et.al.* reported a non-significant trend of a 38% reduction of DOX accumulation in the LV, favoring the 4-months preconditioning group[46]. Parry et. al., using tumor-inoculated animals, reported no differences between the study groups in changes in DOX accumulation within the tumor [26], indicating that the PE program did not interfere with DOX's therapeutic efficacy. All four studies described preservation of myocardial function (on echocardiography or isolated heart perfusion) or histology.

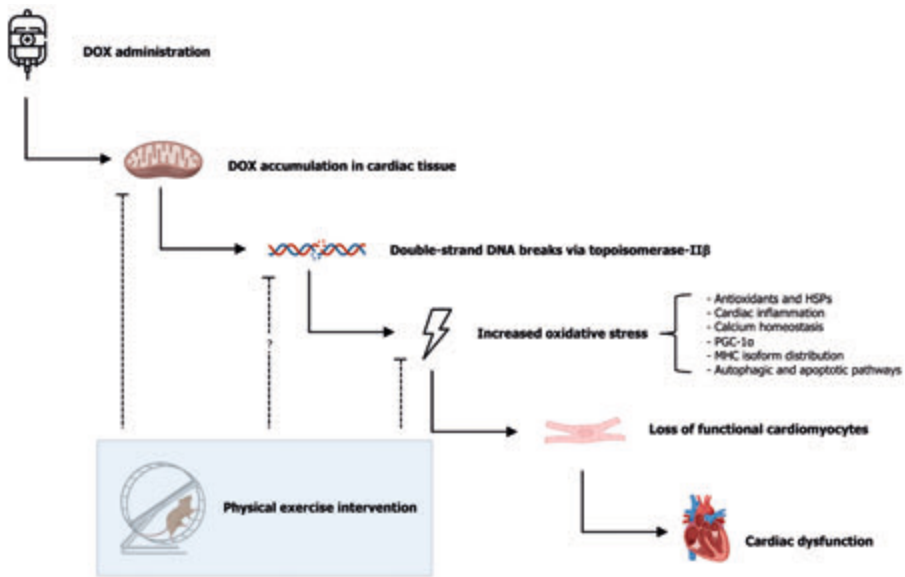


Figure 4. Suggested pathways underlying exercise-mediated protection against DIC in rodents. Exercise prevents accumulation of DOX in cardiac tissue, thereby inhibiting downstream pathways, through which DOX can induce cardiotoxicity.

Abbreviations:
DOX = doxorubicin; HSP = heat sock protein; PGC = peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1 alpha; MHC = myosin heavy chain

DISCUSSION

The aim of this meta-analysis and systematic review was to generate an estimate of the effect of PE on DIC and to systematically evaluate mechanisms underlying exercise-induced cardioprotection. The included clinical studies reported favorable results for some, but not all outcomes related to cardiac function and the available data are therefore not sufficient to demonstrate a protective effect of PE in humans. For animal studies, our meta-analysis indicated that both forced and voluntary PE interventions significantly improve in-vivo (echocardiography) and ex-vivo (isolated heart perfusion) cardiac parameters compared to non-exercised DOX-treated animals. We identified oxidative stress and related mechanisms, and less DOX accumulation in cardiac tissue, as pathways via which exercise could exert a protective effect on DIC.

Clinical studies

In the two reports by Kirkham *et. al.*, no conclusive evidence was provided that treadmill interventions are effective in preserving cardiac function following treatment with DOX[22], [23]. However, the sample size was small (n=24) and imaging was limited to 2D-echocardiography. Given the limitations of this modality in terms of temporal variability in serial LV assessment [82], [83], subtle between- and within-group changes in this small sample could remain unrecognized. Although the study by Ma was rated as having relatively low methodological quality and high risk of bias, their results were sufficiently promising to warrant replication in a larger sample of cancer patients with adequate follow-up. Currently, several clinical initiatives are ongoing. An example is the Exercise to prevent Anthracycline-induced CardioToxicity 2.0 (EXACT2) study[84], [85], which is investigating the effect of a 12-week supervised PE program during chemotherapy. Primary outcome of this RCT
(estimated study sample of n=100) is change in LVEF on 2D-echocardiography from baseline to post-treatment (13 weeks) and six months after baseline. Another example is the ongoing Pact-Paces-Heart study[86], which evaluates the effect a moderate- to-high-intensity, supervised PE program during breast cancer treatment on cardiotoxicity after a long period of follow-up (approximately 8 years after treatment). This study has a relatively large sample size (n= approximately 180) and an extensive cardiac assessment, including cardiac MRI and 3D-echocardiography. Results of these studies are expected to provide new insights into the effect of PE on cardiotoxicity in humans.

Meta-analysis in animal studies on the effect of exercise on cardiotoxicity

The animal studies in our quantitative analysis yielded evidence that PE interventions that vary in terms of type, duration, timing and intensity can provide protection against DIC. The effects of forced exercise interventions appeared slightly stronger than those of voluntary interventions. Also, contrary to other studies included in our review, the study by Sturgeon et. al., which used an exercise program with a lower intensity compared to other studies, found no protective effect of PE on cardiotoxicity[45]. This could suggest that a certain threshold of exercise-intensity is needed in order to achieve cardioprotection. Similarly, both exercise programs starting before as well as during DOX administration appeared to be cardioprotective, although effects of the former were somewhat stronger. It seems intuitive that exercise interventions during DOX administration would be (more) effective, given that our qualitative analysis on underlying pathways identified accelerated DOX clearance as an important mechanism underlying exercise-mediated cardioprotection. Nonetheless, initiating a PE program before the start of treatment is likely to have added value because of preconditioning of the cardiomyocytes via, among other pathways, upregulation of α-MHC expression or ABC transporters (as discussed in a later section). These hypotheses, however, need to be investigated in future studies.
The reported effect sizes of our meta-analysis correspond with absolute changes in percentage points in FS for FTM and VWR of 8.5% and 5.8%, respectively. In rodents, echocardiography is the modality of choice for evaluating cardiac function, since it is non-invasive, versatile, cheap and reproducible. Recently, reference values for FS for adult rats and mice were published, which ranged between 41%-48% and 31%-43%, respectively [87]. This indicates that the observed effects are likely to be of clinical importance in rodents. Also, for LVP, beneficial results were found for both FTM and VWR interventions as compared to controls. Isolated heart perfusion has been proposed as a reliable model for the assessment of myocardial function, especially since it provides insight in cardiac performance in the absence of neurohumeral influences and variation in loading conditions[88]. Thus these results, complemented by the *in-vivo*-derived evidence, support the notion that exercise indeed has cardioprotective potential in rodents.

Mechanisms underlying exercise-mediated cardioprotection

In a previous study, reduction of DOX-induced oxidative stress and less DOX accumulation have been described as pathways underlying exercise-mediated cardioprotection[10]. Our results complement the results of that study by providing an update of the novel articles on these topics, as well as describing a number of additional underlying pathways.

Oxidative stress and related pathways are the most extensively studied mechanisms, and many studies found that PE can counterbalance DOX-induced increased markers of oxidative stress [28], [33], [38], [41], [43], [50], [52], [57], [59], [61]–[64], [74], [89]. Research on how exercise could alleviate DOX-induced oxidative stress has yielded more ambiguous results. Most studies have focused on upregulation of antioxidants or HSPs. Although some of these studies yielded positive effects, others reported that attenuation of these proteins/enzymes is not necessary in order for exercise to exert its cardioprotective effect. This is supported by clinical studies in which no significant effect of antioxidants (e.g. L-carnitine, coenzyme Q10) on the incidence or extent of cardiotoxicity was found[90]. Studies of the other proposed mechanisms are limited in number and have yielded varying results. For example, caspase-3, a marker for apoptotic signaling has been investigated in seven studies, all of which reported that PE mitigated a DOX-induced increase in activity of the enzyme. Nevertheless, the only study that investigated whether this corresponded to less DIC *in-vivo* reported no attenuation in LV function by PE[74]. This finding, as well as those investigating antioxidants, suggest that other, more upstream pathways are also involved. In this regard, it is conceivable that accumulation of DOX in cardiac tissue acts as an overarching mechanism, since blocking this phenomenon effectively enables PE interventions to tackle all downstream DOX-induced effects (Figure 4). This is supported by the fact that all included studies demonstrated that lowered DOX accumulation coincided with reduced DIC[26], [31], [44], [46]. As for how PE mitigates DOX accumulation, current evidence suggests that DOX accumulation is influenced by exercise through upregulation of ABC transporters[26], [31], [44]. These transporters can export a wide range of substances, for example DOX, out of cells or cell-organelles. Knock-out mice, lacking these receptors, show prolonged presence of DOX in cardiac tissue[91]. However, since causality between upregulation of ABC transporters and reduction of DOX accumulation has not been established, lower DOX accumulation might equally result from exercise-mediated alterations in DOX uptake or metabolism. Further research

is therefore needed to elucidate the exact underlying mechanisms of exercise-mediated reduction in DOX-accumulation.

Strengths of the study are the large quantity of studies included using various PE protocols and the systematic approach to evaluate the effect of PE on cardiotoxicity and underlying mechanisms. A limitation is that many components of the methodology of the included animal studies were not adequately reported, which could limit the internal validity of these studies as well as the comparison of results across studies. For the current report, authors were contacted in case a component was scored as 'unclear'. This resulted in clarification of a substantial amount of risk of bias information, thereby improving the quality of the evidence. In addition, the wide variety of study protocols made it challenging to quantify the protective effects of specific forms of PE and to draw definitive conclusions regarding underlying mechanisms. Last, the vast majority of the preclinical studies used FS as a parameter for LV function. Since LVEF is currently recommended in clinical guidelines[83], this hampers the generalizability to cancer patients. Limitations of the clinical studies are the small sample sizes and the fact that imaging was limited to 2D-echocardiography. In addition, follow-up time was too short to detect all relevant cases of cardiotoxicity, given that anthracycline-induced cardiotoxicity can manifest within a year after treatment (i.e. not necessarily directly after completion of treatment). This limited our ability to draw any conclusions about the effects of PE on DIC in humans.

In conclusion, our meta-analysis and systematic review indicate that PE is an effective intervention for reducing DIC in rodents. Less DOX accumulation in cardiomyocytes could act as an overarching mechanism underlying the protective effects of exercise against DIC. While clinical studies in humans are limited, the observed effects are congruent with the hypothesis that PE yields cardioprotection . Larger, more sophisticated clinical studies with an adequate period of follow-up are needed in order to document the role of PE in preventing cardiotoxicity in patients with cancer.

REFERENCES

[1] Y. Octavia, C. G. Tocchetti, K. L. Gabrielson, S. Janssens, H. J. Crijns, and A. L. Moens, "Doxorubicin-induced cardiomyopathy: From molecular mechanisms to therapeutic strategies," Journal of Molecular and Cellular Cardiology, vol. 52, no. 6, pp. 1213–1225, 2012, doi: 10.1016/j.yjmcc.2012.03.006.

[2] D. Jain, "Cardiotoxicity of doxorubicin and other anthracycline derivatives," Journal of nuclear cardiology, vol. 7, no. 1, pp. 53–62, 2000, doi: 10.1067/mnc.2000.103324.

[3] M. Lotrionte et al., "Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity.," Am J Cardiol, vol. 112, no. 12, pp. 1980–1984, Dec. 2013, doi: 10.1016/j.amjcard.2013.08.026.

[4] P. A. Henriksen, "Anthracycline cardiotoxicity: An update on mechanisms, monitoring and prevention," Heart, vol. 104, no. 12, pp. 971–977, 2018, doi: 10.1136/heartjnl-2017-312103.

[5] P. Angsutararux, S. Luanpitpong, and S. Issaragrisil, "Chemotherapy-Induced Cardiotoxicity: Overview of the Roles of Oxidative Stress," Oxidative Medicine and Cellular Longevity, vol. 2015, pp. 1–13, 2015, doi: 10.1155/2015/795602.

[6] B. Kalyanaraman, "Teaching the basics of the mechanism of doxorubicin-induced cardiotoxicity: Have we been barking up the wrong tree?," Redox Biology. 2019. doi: 10.1016/j.redox.2019.101394.

[7] G. M. Felker et al., "Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy.," The New England Journal of Medicine, vol. 342, no. 15, pp. 1077–1084, 2000.

[8] M. Arnold et al., "Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study.," The Lancet. Oncology, vol. 20, no. 11, pp. 1493–1505, Nov. 2019, doi: 10.1016/S1470-2045(19)30456-5.

[9] J. M. Scott, T. S. Nilsen, D. Gupta, and L. W. Jones, "Exercise Therapy and Cardiovascular Toxicity in Cancer.," Circulation, vol. 137, no. 11, pp. 1176–1191, Mar. 2018, doi: 10.1161/CIRCULATIONAHA.117.024671.

[10] J. J. Chen, P.-T. Wu, H. R. Middlekauff, and K.-L. Nguyen, "Aerobic exercise in anthracycline-induced cardiotoxicity: a systematic review of current evidence and future directions," American Journal of Physiology-Heart and Circulatory Physiology, vol. 312, no. 2, pp. H213–H222, 2016, doi: 10.1152/ajpheart.00646.2016.

[11] D. Moher et al., "Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement (Chinese edition)," Journal of Chinese Integrative Medicine, vol. 7, no. 9, pp. 889–896, 2009, doi: 10.3736/jcim20090918.

[12] J. S. Morales et al., "Exercise Interventions and Cardiovascular Health in Childhood Cancer: A Meta-analysis.," International journal of sports medicine, vol. 41, no. 3, pp. 141–153, Mar. 2020, doi: 10.1055/a-1073-8104.

[13] M. Krischke et al., "Pharmacokinetic and pharmacodynamic study of doxorubicin in children with cancer: results of a 'European Pediatric Oncology Off-patents Medicines Consortium' trial.," Cancer chemotherapy and pharmacology, vol. 78, no. 6, pp. 1175–1184, Dec. 2016, doi: 10.1007/s00280-016-3174-8.

[14] S. E. Lipshultz et al., "Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association.," Circulation, vol. 128, no. 17, pp. 1927–1995, Oct. 2013, doi: 10.1161/CIR.0b013e3182a88099.

[15] S. J. Page MJ, Higgins JPT, "Cochrane Handbook for Systematic Reviews of Interventions," in Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019), 2019.

[16] C. R. Hooijmans, M. M. Rovers, R. B. de Vries, M. Leenaars, M. Ristkes-Hoitinga, and M. W. Langendam, "SYRCLE's risk of bias tool for animal studies," BMC Medical Research Methodology, vol. 14, no. 43, pp. 1–9, 2014, doi: 10.7507/1672-2531.20140206.

[17] J. P. T. Higgins et al., "The Cochrane Collaboration's tool for assessing risk of bias in randomised trials," BMJ (Online), vol. 343, no. 7829, pp. 1–9, 2011, doi: 10.1136/bmj.d5928.

[18] A. N. Kavazis, A. J. Smuder, and S. K. Powers, "Effects of short-term endurance exercise training on acute doxorubicin-induced FoxO transcription in cardiac and skeletal muscle.," Journal of applied physiology (Bethesda, Md. : 1985), vol. 117, no. 3, pp. 223–230, Aug. 2014, doi: 10.1152/japplphysiol.00210.2014.

[19] A. A. Kirkham et al., "Protective effects of acute exercise prior to doxorubicin on cardiac function of breast cancer patients: A proof-of-concept RCT," International Journal of Cardiology, vol. 245, pp. 263–270, 2017, doi: 10.1016/j.ijcard.2017.07.037.

[20] A. A. Kirkham et al., "The effect of an aerobic exercise bout 24 h prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: A," Breast Cancer Research and Treatment, vol. 167, no. 3, pp. 719–729, 2018, doi: 10.1007/s10549-017-4554-4.

[21] Z. Ma, "Effect of anthracycline combined with aerobic exercise on the treatment of breast cancer.," Pakistan journal of pharmaceutical sciences, vol. 31, no. 3(Special), pp. 1125–1129, May 2018.

[22] A. A. Kirkham et al., "Protective effects of acute exercise prior to doxorubicin on cardiac function of breast cancer patients: A proof-of-concept RCT," International Journal of Cardiology, vol. 245, pp. 263–270, 2017, doi: 10.1016/j.ijcard.2017.07.037.

[23] A. A. Kirkham et al., "The effect of an aerobic exercise bout 24 h prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: A," Breast Cancer Research and Treatment, vol. 167, no. 3, pp. 719–729, 2018, doi: 10.1007/s10549-017-4554-4.

[24] C. Werner et al., "Effects of Physical Exercise on Myocardial Telomere-Regulating Proteins, Survival Pathways, and Apoptosis," Journal of the American College of Cardiology, vol. 52, no. 6, pp. 470–482, 2008, doi: 10.1016/j.jacc.2008.04.034.

[25] D. S. Hydock, K. Y. Wonders, C. M. Schneider, and R. Hayward, "Voluntary wheel running in rats receiving doxorubicin: Effects on running activity and cardiac myosin heavy chain," Anticancer Research, vol. 29, no. 11, pp. 4401–4407, 2009.

[26] T. L. Parry and R. Hayward, "Exercise Training Does Not Affect Doxorubicin Anti-Tumor Efficacy While Attenuating Cardiac Dysfunction," American journal of physiology. Regulatory, integrative and comparative physiology, vol. 309, no. 6, pp. R675–R683, 2015, doi: 10.1249/01.mss.0000476828.10778.bc.

[27] D. S. Hydock, C. Y. Lien, B. T. Jensen, T. L. Parry, C. M. Schneider, and R. Hayward, "Rehabilitative exercise in a rat model of doxorubicin cardiotoxicity," Experimental Biology and Medicine, vol. 237, no. 12, pp. 1483–1492, 2012, doi: 10.1258/ebm.2012.012137.

[28] A. J. Chicco, C. M. Schneider, and R. Hayward, "Voluntary exercise protects against acute doxorubicin cardiotoxicity in the isolated perfused rat heart," American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, vol. 289, no. 2, pp. R424–R431, 2005, doi: 10.1152/ajpregu.00636.2004.

[29] S. E. Hall, A. J. Smuder, and R. Hayward, "Effects of Calorie Restriction and Voluntary Exercise on Doxorubicin-Induced Cardiotoxicity.," Integrative cancer therapies, vol. 18, p. 1534735419843999, 2019, doi: 10.1177/1534735419843999.

[30] I. Marques-Aleixo, E. Santos-Alves, J. R. Torrella, P. J. Oliveira, J. Magalhães, and A. Ascensão, "Exercise and Doxorubicin Treatment Modulate Cardiac Mitochondrial Quality Control Signaling," Cardiovascular Toxicology, vol. 18, no. 1, pp. 43–55, 2018, doi: 10.1007/s12012-017-9412-4.

[31] B. T. Jensen, C. Y. Lien, D. S. Hydock, C. M. Schneider, and R. Hayward, "Exercise mitigates cardiac doxorubicin accumulation and preserves function in the rat," Journal of Cardiovascular Pharmacology, vol. 62, no. 3, pp. 263–269, 2013, doi: 10.1097/FJC.0b013e3182982ce0.

[32] D. S. Hydock, C. Y. Lien, C. M. Schneider, and R. Hayward, "Exercise preconditioning protects against doxorubicin-induced cardiac dysfunction," Medicine and Science in Sports and Exercise, vol. 40, no. 5, pp. 808–817, 2008, doi: 10.1249/MSS.0b013e318163744a.

[33] I. Marques-Aleixo et al., "Physical exercise prior and during treatment reduces sub-chronic doxorubicin-induced mitochondrial toxicity and oxidative stress," Mitochondrion, vol. 20, pp. 22–33, 2015, doi: 10.1016/j.mito.2014.10.008.

[34] C. Y. Lien, B. T. Jensen, D. S. Hydock, and R. Hayward, "Short-term exercise training attenuates acute doxorubicin cardiotoxicity," Journal of Physiology and Biochemistry, vol. 71, no. 4, pp. 669–678, 2015, doi: 10.1007/s13105-015-0432-x.

[35] D. S. Hydock, C. Y. Lien, B. T. Jensen, C. M. Schneider, and R. Hayward, "Exercise preconditioning provides long-term protection against early chronic doxorubicin cardiotoxicity," Integrative Cancer Therapies, vol. 10, no. 1, pp. 47–57, 2011, doi: 10.1177/1534735410392577.

[36] A. Ascensão et al., "Endurance training attenuates doxorubicin-induced cardiac oxidative damage in mice," International Journal of Cardiology, vol. 100, no. 3, pp. 451–460, 2005, doi: 10.1016/j.ijcard.2004.11.004.

[37] M. M. Kanter, R. L. Hamlin, D. V. Unverferth, H. W. Davis, and A. J. Merola, "Effect of exercise training on antioxidant enzymes and cardiotoxicity of doxorubicin," Journal of Applied Physiology, vol. 59, no. 4, pp. 1298–1303, 1985, doi: 10.1152/jappl.1985.59.4.1298.

[38] P. Farzanegi et al., "Swimming exercise in combination with garlic extract administration as a therapy against doxorubicin-induced hepatic, heart and renal toxicity to rats," Toxin Reviews, vol. 0, no. 0, pp. 1–10, 2019, doi: 10.1080/15569543.2018.1559194.

[39] K. Pfannenstiel and R. Hayward, "Effects of Resistance Exercise Training on Doxorubicin-Induced Cardiotoxicity," Journal of cardiovascular pharmacology, vol. 71, no. 6, pp. 332–339, 2018, doi: 10.7570/kjo.2014.23.3.141.

[40] Li Li Ji and E. W. Mitchell, "Effects of adriamycin on heart mitochondrial function in rested and exercised rats," Biochemical Pharmacology, vol. 47, no. 5, pp. 877–885, 1994, doi: 10.1016/0006-2952(94)90488-X.

[41] K. Y. Wonders, D. S. Hydock, C. M. Schneider, and R. Hayward, "Acute Exercise Protects Against Doxorubicin Cardiotoxicity," Integrative Cancer Therapies, vol. 7, no. 3, pp. 21–24, 2008, doi: 10.1177/1534735408322848.

[42] Y. Lee, I. Kwon, Y. Jang, L. Cosio-Lima, and P. Barrington, "Endurance Exercise Attenuates Doxorubicin-induced Cardiotoxicity.," Medicine and science in sports and exercise, vol. 52, no. 1, pp. 25–36, Jan. 2020, doi: 10.1249/MSS.0000000000002094.

[43] V. W. Dolinsky et al., "Both aerobic exercise and resveratrol supplementation attenuate doxorubicin-induced cardiac injury in mice," American Journal of Physiology-Endocrinology and Metabolism, vol. 305, no. 2, pp. E243–E253, 2013, doi: 10.1152/ajpendo.00044.2013.

[44] A. B. Morton, A. Mor Huertas, J. M. Hinkley, N. Ichinoseki-Sekine, D. D. Christou, and A. J. Smuder, "Mitochondrial accumulation of doxorubicin in cardiac and diaphragm muscle following exercise preconditioning," Mitochondrion, vol. 45, pp. 52–62, 2019, doi: 10.1016/j.mito.2018.02.005.

[45] K. Sturgeon et al., "Concomitant low-dose doxorubicin treatment and exercise," American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, vol. 307, no. 6, pp. R685–R692, 2014, doi: 10.1152/ajpregu.00082.2014.

[46] S. E. Hall, A. J. Smuder, and R. Hayward, "Effects of Calorie Restriction and Voluntary Exercise on Doxorubicin-Induced Cardiotoxicity.," Integrative cancer therapies, vol. 18, p. 1534735419843999, 2019, doi: 10.1177/1534735419843999.

[47] H.-L. Yang et al., "Early Moderate Intensity Aerobic Exercise Intervention Prevents Doxorubicin-Caused Cardiac Dysfunction Through Inhibition of Cardiac Fibrosis and Inflammation.," Cancers, vol. 12, no. 5, Apr. 2020, doi: 10.3390/cancers12051102.

[48] S. Phungphong, A. Kijtawornrat, T. Kampaengsri, J. Wattanapermpool, and T. Bupha-Intr, "Comparison of exercise training and estrogen supplementation on mast cell-mediated doxorubicin-induced cardiotoxicity.," American journal of physiology. Regulatory, integrative and comparative physiology, vol. 318, no. 5, pp. R829–R842, May 2020, doi: 10.1152/ajpregu.00224.2019.

[49] A. J. Chicco, D. S. Hydock, C. M. Schneider, and R. Hayward, "Low-intensity exercise training during doxorubicin treatment protects against cardiotoxicity," Journal of Applied Physiology, vol. 100, no. 2, pp. 519–527, 2006, doi: 10.1152/japplphysiol.00148.2005.

[50] A. J. Chicco, C. M. Schneider, and R. Hayward, "Exercise training attenuates acute doxorubicin-induced cardiac dysfunction," Journal of Cardiovascular Pharmacology, vol. 47, no. 2, pp. 182–189, 2006, doi: 10.1097/01.fjc.0000199682.43448.2d.

[51] S. C. J. Kolwicz and R. Tian, "Assessment of cardiac function and energetics in isolated mouse hearts using 31P NMR spectroscopy.," Journal of visualized experiments : JoVE, no. 42, Aug. 2010, doi: 10.3791/2069.

[52] A. Ascensão et al., "Moderate endurance training prevents doxorubicin-induced in vivo mitochondriopathy and reduces the development of cardiac apoptosis," American Journal of Physiology-Heart and Circulatory Physiology, vol. 289, no. 2, pp. H722–H731, 2005, doi: 10.1152/ajpheart.01249.2004.

[53] A. Alihemmati, F. Ebadi, M. Moghadaszadeh, M. Asadi, P. Zare, and R. Badalzadeh, "Effects of high-intensity interval training on the expression of microRNA-499 and pro- and anti-apoptotic genes in doxorubicin-cardiotoxicity in rats.," Journal of electrocardiology, vol. 55, pp. 9–15, 2019, doi: 10.1016/j.jelectrocard.2019.02.009.

[54] T. Šimůnek, M. Štěrba, O. Popelová, M. Adamcová, R. Hrdina, and V. Gerši, "Anthracycline-induced cardiotoxicity: Overview of studies examining the roles of oxidative stress and free cellular iron," Pharmacological Reports, vol. 61, no. 1, pp. 154–171, 2009, doi: 10.1016/S1734-1140(09)70018-0.

[55] Y. Ichikawa et al., "Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation," Journal of Clinical Investigation, vol. 124, no. 2, pp. 617–630, 2014, doi: 10.1172/JCI72931.

[56] G. Takemura and H. Fujiwara, "Doxorubicin-Induced Cardiomyopathy. From the Cardiotoxic Mechanisms to Management," Progress in Cardiovascular Diseases, vol. 49, no. 5, pp. 330–352, 2007, doi: 10.1016/j.pcad.2006.10.002.

[57] M. Ahmadian and V. Dabidi Roshan, "Modulatory Effect of Aerobic Exercise Training on Doxorubicin-Induced Cardiotoxicity in Rats with Different Ages," Cardiovascular Toxicology, vol. 18, no. 1, pp. 33–42, 2018, doi: 10.1007/s12012-017-9411-5.

[58] A. Ascensão, R. Ferreira, P. J. Oliveira, and J. Magalhães, "Effects of Endurance Training and Acute Doxorubicin Treatment on Rat Heart Mitochondrial Alterations Induced by In Vitro Anoxia-Reoxygenation," Cardiovascular Toxicology, vol. 6, no. 3–4, pp. 159–172, 2006, doi: 10.1385/ct:6:3:159.

[59] A. Ascensão et al., "Endurance training attenuates doxorubicin-induced cardiac oxidative damage in mice," International Journal of Cardiology, vol. 100, no. 3, pp. 451–460, 2005, doi: 10.1016/j.ijcard.2004.11.004.

[60] J. Ashrafi and V. D. Roshan, "Is Short-term Exercise a Therapeutic Tool for Improvement of Cardioprotection Against DOX-induced Cardiotoxicity? An Experimental Controlled Protocol in Rats," Asian Pacific Journal of Cancer Prevention, vol. 13, no. 8, pp. 4025–4030, 2012, doi: 10.7314/apjcp.2012.13.8.4025.

[61] A. N. Kavazis, A. J. Smuder, K. Min, N. Tümer, and S. K. Powers, "Short-term exercise training protects against doxorubicin-induced cardiac mitochondrial damage independent of HSP72," American Journal of Physiology-Heart and Circulatory Physiology, vol. 299, no. 5, pp. H1515–H1524, 2010, doi: 10.1152/ajpheart.00585.2010.

[62] V. Shirinbayan and V. D. Roshan, "Pretreatment Effect of Running Exercise on HSP 70 and DOX-Induced Cardiotoxicity," Asian Pacific Journal of Cancer Prevention, vol. 13, no. 11, pp. 5849–5855, 2012, doi: 10.7314/apjcp.2012.13.11.5849.

[63] A. D. Mackay et al., "Multitissue analysis of exercise and metformin on doxorubicin-induced iron dysregulation," American Journal of Physiology-Endocrinology and Metabolism, vol. 316, no. 5, pp. E922–E930, 2019, doi: 10.1152/ajpendo.00140.2018.

[64] A. Ascensão et al., "Acute exercise protects against calcium-induced cardiac mitochondrial permeability transition pore opening in doxorubicin-treated rats," Clinical Science, vol. 120, no. 1, pp. 37–49, 2011, doi: 10.1042/CS20100254.

[65] I. J. Benjamin and D. R. McMillan, "Stress (heat shock) proteins: molecular chaperones in cardiovascular biology and disease.," Circulation research, vol. 83, no. 2, pp. 117–132, Jul. 1998, doi: 10.1161/01.res.83.2.117.

[66] R. Tanaka et al., "Reactive fibrosis precedes doxorubicin-induced heart failure through sterile inflammation.," ESC heart failure, vol. 7, no. 2, pp. 588–603, Apr. 2020, doi: 10.1002/ehf2.12616.

[67] M. Arai et al., "Sarcoplasmic reticulum genes are selectively down-regulated in cardiomyopathy produced by doxorubicin in rabbits.," Journal of molecular and cellular cardiology, vol. 30, no. 2, pp. 243–254, Feb. 1998, doi: 10.1006/jmcc.1997.0588.

[68] I. E. Hof et al., "Prevalence and cardiac phenotype of patients with a phospholamban mutation.," Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation, vol. 27, no. 2, pp. 64–69, Feb. 2019, doi: 10.1007/s12471-018-1211-4.

[69] R. J. Parks, E. Murphy, and J. C. Liu, "Mitochondrial Permeability Transition Pore and Calcium Handling.," Methods in molecular biology (Clifton, N.J.), vol. 1782, pp. 187–196, 2018, doi: 10.1007/978-1-4939-7831-1_11.

[70] H. Liang and W. F. Ward, "PGC-1alpha: a key regulator of energy metabolism.," Advances in physiology education, vol. 30, no. 4, pp. 145–151, Dec. 2006, doi: 10.1152/advan.00052.2006.

[71] O. Kärkkäinen et al., "Heart specific PGC-1α deletion identifies metabolome of cardiac restricted metabolic heart failure.," Cardiovascular research, vol. 115, no. 1, pp. 107–118, Jan. 2019, doi: 10.1093/cvr/cvy155.

[72] E. L. de Beer, A. E. Bottone, J. van Der Velden, and E. E. Voest, "Doxorubicin impairs crossbridge turnover kinetics in skinned cardiac trabeculae after acute and chronic treatment.," Molecular pharmacology, vol. 57, no. 6, pp. 1152–1157, Jun. 2000.

[73] D. S. Hydock, K. Y. Wonders, C. M. Schneider, and R. Hayward, "Voluntary wheel running in rats receiving doxorubicin: Effects on running activity and cardiac myosin heavy chain," Anticancer Research, vol. 29, no. 11, pp. 4401–4407, 2009.

[74] S. Phungphong, A. Kijtawornrat, T. Kampaengsri, J. Wattanapermpool, and T. Bupha-Intr, "Comparison of exercise training and estrogen supplementation on mast cell-mediated doxorubicin-induced cardiotoxicity.," American journal of physiology. Regulatory, integrative and comparative physiology, vol. 318, no. 5, pp. R829–R842, May 2020, doi: 10.1152/ajpregu.00224.2019.

[75] D. Glick, S. Barth, and K. F. Macleod, "Autophagy: cellular and molecular mechanisms.," The Journal of pathology, vol. 221, no. 1, pp. 3–12, May 2010, doi: 10.1002/path.2697.

[76] N. Koleini and E. Kardami, "Autophagy and mitophagy in the context of doxorubicin-induced cardiotoxicity," Oncotarget, vol. 8, no. 28, pp. 46663–46680, 2017, doi: 10.18632/oncotarget.16944.

[77] A. J. Smuder, A. N. Kavazis, K. Min, and S. K. Powers, "Doxorubicin-induced markers of myocardial autophagic signaling in sedentary and exercise trained animals," Journal of Applied Physiology, vol. 115, no. 2, pp. 176–185, 2013, doi: 10.1152/japplphysiol.00924.2012.

[78] S. Zhang et al., "Identification of the molecular basis of doxorubicin-induced cardiotoxicity," Nature Medicine, vol. 18, no. 11, pp. 1639–1642, 2012, doi: 10.1038/nm.2919.

[79] P. Angsutararux, S. Luanpitpong, and S. Issaragrisil, "Chemotherapy-Induced Cardiotoxicity: Overview of the Roles of Oxidative Stress," Oxidative Medicine and Cellular Longevity, vol. 2015, pp. 1–13, 2015, doi: 10.1155/2015/795602.

[80] S. Zhang et al., "Identification of the molecular basis of doxorubicin-induced cardiotoxicity," Nature Medicine, vol. 18, no. 11, pp. 1639–1642, 2012, doi: 10.1038/nm.2919.

[81] C. Werner et al., "Effects of Physical Exercise on Myocardial Telomere-Regulating Proteins, Survival Pathways, and Apoptosis," Journal of the American College of Cardiology, vol. 52, no. 6, pp. 470–482, 2008, doi: 10.1016/j.jacc.2008.04.034.

[82] P. Thavendiranathan, A. D. Grant, T. Negishi, J. C. Plana, Z. B. Popović, and T. H. Marwick, "Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy.," Journal of the American College of Cardiology, vol. 61, no. 1, pp. 77–84, Jan. 2013, doi: 10.1016/j.jacc.2012.09.035.

[83] J. C. Plana, P. Thavendiranathan, C. Bucciarelli-Ducci, and P. Lancellotti, "Multi-Modality Imaging in the Assessment of Cardiovascular Toxicity in the Cancer Patient.," JACC. Cardiovascular imaging, vol. 11, no. 8, pp. 1173–1186, Aug. 2018, doi: 10.1016/j.jcmg.2018.06.003.

[84] M. R. Keats, S. A. Grandy, N. Giacomantonio, D. MacDonald, M. Rajda, and T. Younis, "EXercise to prevent AnthrCycline-based Cardio-Toxicity (EXACT) in individuals with breast or hematological cancers: a feasibility study protocol.," Pilot and feasibility studies, vol. 2, p. 44, 2016, doi: 10.1186/s40814-016-0084-9.

[85] "ClinicalTrials.gov," ClinicalTrials.gov Identifier: NCT03748550. https://www.clinicaltrials.gov/ct2/show/NCT03748550?cond=NCT03748550&draw=2&rank=1 (accessed Dec. 20, 2020).

[86] "Netherlands Trial Register," NTR 7042. https://www.trialregister.nl/trial/7042 (accessed Oct. 16, 2020).

[87] S. Zacchigna et al., "Toward standardization of echocardiography for the evaluation of left ventricular function in adult rodents: a position paper of the ESC Working Group on Myocardial Function.," Cardiovascular research, May 2020, doi: 10.1093/cvr/cvaa110.

[88] M. E. Reichelt, L. Willems, B. A. Hack, J. N. Peart, and J. P. Headrick, "Cardiac and coronary function in the Langendorff-perfused mouse heart model.," Experimental physiology, vol. 94, no. 1, pp. 54–70, Jan. 2009, doi: 10.1113/expphysiol.2008.043554.

[89] Y. Lee, I. Kwon, Y. Jang, L. Cosio-Lima, and P. Barrington, "Endurance Exercise Attenuates Doxorubicin-induced Cardiotoxicity.," Medicine and science in sports and exercise, vol. 52, no. 1, pp. 25–36, Jan. 2020, doi: 10.1249/MSS.0000000000002094.

[90] D. T. Vincent, Y. F. Ibrahim, M. G. Espey, and Y. J. Suzuki, "The role of antioxidants in the era of cardiooncology.," Cancer chemotherapy and pharmacology, vol. 72, no. 6, pp. 1157–1168, Dec. 2013, doi: 10.1007/s00280-013-2260-4.

[91] J. van Asperen, O. van Tellingen, F. Tijssen, A. H. Schinkel, and J. H. Beijnen, "Increased accumulation of doxorubicin and doxorubicinol in cardiac tissue of mice lacking mdr1a P-glycoprotein.," British journal of cancer, vol. 79, no. 1, pp. 108–113, Jan. 1999, doi: 10.1038/sj.bjc.6690019.

[92] A. Alihemmati, F. Ebadi, M. Moghadaszadeh, M. Asadi, P. Zare, and R. Badalzadeh, "Effects of high-intensity interval training on the expression of microRNA-499 and pro- and anti-apoptotic genes in doxorubicin-cardiotoxicity in rats.," Journal of electrocardiology, vol. 55, pp. 9–15, 2019, doi: 10.1016/j.jelectrocard.2019.02.009.

[93] H.-L. Yang et al., "Early Moderate Intensity Aerobic Exercise Intervention Prevents Doxorubicin-Caused Cardiac Dysfunction Through Inhibition of Cardiac Fibrosis and Inflammation.," Cancers, vol. 12, no. 5, Apr. 2020, doi: 10.3390/cancers12051102.

[94] F. Wang et al., "Aerobic Exercise During Early Murine Doxorubicin Exposure Mitigates Cardiac Toxicity.," Journal of pediatric hematology/oncology, vol. 40, no. 3, pp. 208–215, Apr. 2018, doi: 10.1097/MPH.0000000000001112.

[95] K. Sturgeon, G. Muthukumaran, D. Ding, A. Bajulaiye, V. Ferrari, and J. R. Libonati, "Moderate-intensity treadmill exercise training decreases murine cardiomyocyte cross-sectional area.," Physiological reports, vol. 3, no. 5, May 2015, doi: 10.14814/phy2.12406.

[96] A. Calvé, R. Haddad, S.-N. Barama, M. Meilleur, I. A. Sebag, and L. E. Chalifour, "Cardiac response to doxorubicin and dexrazoxane in intact and ovariectomized young female rats at rest and after swim training.," American journal of physiology. Heart and circulatory physiology, vol. 302, no. 10, pp. H2048-57, May 2012, doi: 10.1152/ajpheart.01069.2011.

[97] R. Hayward, C.-Y. Lien, B. T. Jensen, D. S. Hydock, and C. M. Schneider, "Exercise training mitigates anthracycline-induced chronic cardiotoxicity in a juvenile rat model.," Pediatric blood & cancer, vol. 59, no. 1, pp. 149–154, Jul. 2012, doi: 10.1002/pbc.23392.

[98] E. J. Howden et al., "Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients.," European journal of preventive cardiology, vol. 26, no. 3, pp. 305–315, Feb. 2019, doi: 10.1177/2047487318811181.

[99] D. S. Hydock, T. L. Parry, B. T. Jensen, C.-Y. Lien, C. M. Schneider, and R. Hayward, "Effects of endurance training on combined goserelin acetate and doxorubicin treatment-induced cardiac dysfunction.," Cancer chemotherapy and pharmacology, vol. 68, no. 3, pp. 685–692, Sep. 2011, doi: 10.1007/s00280-010-1523-6.

[100] L. W. Jones et al., "Exercise and Risk of Cardiovascular Events in Women With Nonmetastatic Breast Cancer.," Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 34, no. 23, pp. 2743–2749, Aug. 2016, doi: 10.1200/JCO.2015.65.6603.

[101] M. S. Krause et al., "MRP1/GS-X pump ATPase expression: is this the explanation for the cytoprotection of the heart against oxidative stress-induced redox imbalance in comparison to skeletal muscle cells?," Cell biochemistry and function, vol. 25, no. 1, pp. 23–32, 2007, doi: 10.1002/cbf.1343.

[102] C. Matsuura et al., "Exercise training in doxorubicin-induced heart failure: effects on the L-arginine-NO pathway and vascular reactivity.," Journal of the American Society of Hypertension : JASH, vol. 4, no. 1, pp. 7–13, 2010, doi: 10.1016/j.jash.2009.10.005.

[103] A. C. Nagy, P. GulAcsi-BArdos, Z. CserEp, L. Hangody, and T. Forster, "Late cardiac effect of anthracycline therapy in physically active breast cancer survivors - a prospective study.," Neoplasma, vol. 64, no. 1, pp. 92–100, 2017, doi: 10.4149/neo_2017_111.

[104] T. L. Parry, D. S. Hydock, B. T. Jensen, C.-Y. Lien, C. M. Schneider, and R. Hayward, "Endurance exercise attenuates cardiotoxicity induced by androgen deprivation and doxorubicin.," Canadian journal of physiology and pharmacology, vol. 92, no. 5, pp. 356–362, May 2014, doi: 10.1139/cjpp-2013-0294.

[105] F. Sharifi, V. D. Roshan, and Z. Mazaheri, "Effect of pretreatment of aerobic training on doxorubicininduced left ventricular apoptosis gene expression in aging rat model," Modares Journal of Medical Sciences: Pathobiology, vol. 19, no. 2, pp. 29–43, 2016.

[106] T. Shimauchi et al., "TRPC3-Nox2 complex mediates doxorubicin-induced myocardial atrophy," JCI insight, vol. 2, no. 15, 2017, doi: 10.1172/jci.insight.93358.

[107] K. Y. Wonders, D. S. Hydock, S. Greufe, C. M. Schneider, and R. Hayward, "Endurance exercise training preserves cardiac function in rats receiving doxorubicin and the HER-2 inhibitor GW2974.," Cancer chemotherapy and pharmacology, vol. 64, no. 6, pp. 1105–1113, Nov. 2009, doi: 10.1007/s00280-009-0967-z.

SUPPLEMENTAL MATERIAL

Supplemental Methods

Search strings

Pubmed

PubMed	
Chemotherapy	Anthracyclines[Mesh] OR Chemotherapy, Adjuvant[Majr:NoExp] OR Mitoxantrone[Mesh] OR doxorubicin[Title/Abstract] OR DOX[Title/Abstract] OR Adriamycin[Title/Abstract] OR Daunorubicin[Title/Abstract] OR Cerubidine[Title/Abstract] OR Idarubicin[Title/Abstract] OR Idamycin[Title/Abstract] OR Epirubicin[Title/Abstract] OR Ellence[Title/Abstract] OR Mitoxantrone[Title/Abstract] OR Novantrone[Title/Abstract]
Cardiotoxicity	Cardiotoxicity[MeSH Terms] OR Cardiovascular Diseases[Majr:NoExp] OR Heart Failure[Majr] OR cardiotoxicity[Title/Abstract] OR cardiomyopathy[Title/Abstract] OR cardiomyopathies[Title/Abstract] OR cardiotoxic[Title/Abstract] OR CTRCD[Title/Abstract] OR Cardiac Failure[Title/Abstract] OR Cardiac damage[Title/Abstract] OR Cardiac dysfunction[Title/Abstract] OR Cardiac myopathy[Title/Abstract] OR cardiac apoptosis[Title/Abstract] OR heart failure[Title/Abstract] OR heart toxicity[Title/Abstract] OR heart damage[Title/Abstract] OR heart dysfunction[Title/Abstract] OR myocardial failure[Title/Abstract] OR Myocardial toxicity[Title/Abstract] OR myocardial damage[Title/Abstract] OR myocardial dysfunction[Title/Abstract] OR "ventricular failure"[Title/Abstract] OR "ventricular toxicity"[Title/Abstract] OR "ventricular damage"[Title/Abstract] OR "ventricular dysfunction"[Title/Abstract] OR cardiomyocyte damage[Title/Abstract] OR cardiomyocyte toxicity[Title/Abstract] OR cardiomyocyte dysfunction[Title/Abstract] OR cardiomyocyte apoptosis[Title/Abstract] OR "cardiomyocytes damage"[Title/Abstract] OR "cardiomyocytes toxicity"[Title/Abstract] OR "cardiomyocytes apoptosis"[Title/Abstract] OR "cardiomyocytes dysfunction"[Title/Abstract] OR cardiac injury[Title/Abstract] OR heart failures[Title/Abstract] OR heart toxicities[Title/Abstract] OR "ventricular toxicities[Title/Abstract] OR myocardial oxidative damage[Title/Abstract] OR cardiac oxidative damage[Title/Abstract]
Exercise	Exercise[MeSH Terms] OR sports[MeSH Terms] OR Exercise Therapy[MeSH Terms] OR kinesiotherapy[Title/Abstract] OR walking[Title/Abstract] OR weight lifting[Title/Abstract] OR sport[Title/Abstract] OR sports[Title/Abstract] OR ((Physical[Title/Abstract] OR Aerobic[Title/Abstract] OR exercise[Title/Abstract] OR endurance[Title/Abstract] OR fitness[Title/Abstract] OR training[Title/Abstract]) AND (activity[Title/Abstract] OR exercise[Title/Abstract] OR therapy[Title/Abstract] OR program[Title/Abstract] OR training[Title/Abstract] OR conditioning[Title/Abstract] OR activities[Title/Abstract] OR exercises[Title/Abstract] OR therapies[Title/Abstract] OR programs[Title/Abstract] OR trainings[Title/Abstract])) OR ((Activity[Title/Abstract]) AND (program[Title/Abstract] OR conditioning[Title/Abstract]))))

Embase

EmBase	
Chemotherapy	'anthracycline antibiotic agent'/exp OR 'cancer chemotherapy'/mj OR 'mitoxantrone'/de OR 'doxorubicin':ti,ab,kw OR 'DOX':ti,ab,kw OR 'Adriamycin':ti,ab,kw OR 'Daunorubicin':ti,ab,kw OR 'Cerubidine':ti,ab,kw OR 'Idarubicin':ti,ab,kw OR 'Idamycin':ti,ab,kw OR 'Epirubicin':ti,ab,kw OR 'Ellence':ti,ab,kw OR 'Mitoxantrone':ti,ab,kw OR 'Novantrone':ti,ab,kw
Cardiotoxicity	'Cardiotoxicity'/exp OR 'cardiovascular disease'/mj OR 'Heart Failure'/exp OR 'cardiotoxicity':ti,ab,kw OR 'cardiomyopathy':ti,ab,kw OR 'cardiomyopathies':ti,ab,kw OR 'cardiotoxic':ti,ab,kw OR 'CTRCD':ti,ab,kw OR 'Cardiac Failure':ti,ab,kw OR 'Cardiac damage':ti,ab,kw OR 'Cardiac dysfunction':ti,ab,kw OR 'Cardiac myopathy':ti,ab,kw OR 'cardiac apoptosis':ti,ab,kw OR 'heart failure':ti,ab,kw OR 'heart toxicity':ti,ab,kw OR 'heart damage':ti,ab,kw OR 'heart dysfunction':ti,ab,kw OR 'myocardial failure':ti,ab,kw OR 'Myocardial toxicity':ti,ab,kw OR 'myocardial damage':ti,ab,kw OR 'myocardial dysfunction':ti,ab,kw OR 'ventricular failure':ti,ab,kw OR 'ventricular toxicity':ti,ab,kw OR 'ventricular damage':ti,ab,kw OR 'ventricular dysfunction':ti,ab,kw OR 'cardiomyocyte damage':ti,ab,kw OR 'cardiomyocyte toxicity':ti,ab,kw OR 'cardiomyocyte dysfunction':ti,ab,kw OR 'cardiomyocyte apoptosis':ti,ab,kw OR 'cardiac injury':ti,ab,kw OR 'heart failures':ti,ab,kw OR 'heart toxicities':ti,ab,kw OR 'ventricular toxicities':ti,ab,kw OR 'myocardial oxidative damage':ti,ab,kw OR 'cardiac oxidative damage':ti,ab,kw
Exercise	'Exercise'/exp OR 'sport'/exp OR 'kinesiotherapy'/exp OR 'sport':ti,ab,kw OR 'sports':ti,ab,kw OR 'walking':ti,ab,kw OR 'weight lifting':ti,ab,kw OR (('Physical':ti,ab,kw OR 'Aerobic':ti,ab,kw OR 'exercise':ti,ab,kw OR 'endurance':ti,ab,kw OR 'fitness':ti,ab,kw OR 'training':ti,ab,kw) AND ('activity':ti,ab,kw OR 'exercise':ti,ab,kw OR 'therapy':ti,ab,kw OR 'program':ti,ab,kw OR 'training':ti,ab,kw OR 'conditioning':ti,ab,kw OR 'activities':ti,ab,kw OR 'exercises':ti,ab,kw OR 'therapies':ti,ab,kw OR 'programs':ti,ab,kw OR 'trainings':ti,ab,kw)) OR (('Activity':ti,ab,kw) AND ('program':ti,ab,kw OR 'conditioning':ti,ab,kw))

Cochrane

#1	MeSH descriptor: [Anthracyclines] this term only
#2	MeSh descriptor: [Chemotherapy, Adjuvant] this term only
#3	MeSh descriptor: [Mitoxantrone] this term only
#4	'doxorubicin' OR 'DOX' OR 'Adriamycin' OR 'Daunorubicin' OR 'Cerubidine' OR 'Idarubicin' OR 'Idamycin' OR 'Epirubicin' OR 'Ellence' OR 'Mitoxantrone' OR 'Novantrone'
#5	MeSh descriptor: [Cardiotoxicity] explode all trees
#6	MeSH descriptor: [Cardiovascular Diseases] this term only
#7	MeSH descriptor: [Heart Failure] explode all trees
#8	"cardiotoxicity" OR "cardiomyopathy" OR "cardiomyopathies" OR "cardiotoxic" OR "CTRCD" OR "Cardiac Failure" OR "Cardiac damage" OR "Cardiac dysfunction" OR "Cardiac myopathy" OR "cardiac apoptosis" OR "heart failure" OR "heart toxicity" OR "heart damage" OR "heart dysfunction" OR "myocardial failure" OR "Myocardial toxicity" OR "myocardial damage" OR "myocardial dysfunction" OR "ventricular failure" OR "ventricular toxicity" OR "ventricular damage" OR "ventricular dysfunction" OR "cardiomyocyte damage" OR "cardiomyocyte toxicity" OR "cardiomyocyte dysfunction" OR "cardiomyocyte apoptosis" OR "cardiomyocytes damage" OR "cardiomyocytes toxicity" OR "cardiomyocytes dysfunction" OR "cardiomyocytes apoptosis" OR "cardiac injury" OR "heart failures" OR "heart toxicities" OR "ventricular toxicities" OR "myocardial oxidative damage" OR "cardiac oxidative damage"
#9	MeSH descriptor: [Exercise] explode all trees
#10	MeSH descriptor: [Sports] explode all trees
#11	MeSH descriptor: [Exercise Therapy] explode all trees
#12	"sport" OR "sports" OR "walking" OR "weight lifting" OR "kinesiotherapy" OR (("Physical" OR "Aerobic" OR "exercise" OR "endurance" OR "fitness" OR "training") AND ("activity" OR "exercise" OR "therapy" OR "program" OR "training" OR "conditioning" OR "activities" OR "exercises" OR "therapies" OR "programs" OR "trainings")) OR (("Activity") AND ("program" OR "conditioning"))
Search	(#1 OR #2 OR #3 OR #4) AND (#5 OR #6 OR #7 OR #8) AND (#9 OR #10 OR #11 OR #12) in Trials

SUPPLEMENTAL RESULTS A

References of articles excluded on the basis of full-text screening

All conference abstracts are not shown. [94]–[107]

[94] F. Wang et al., "Aerobic Exercise During Early Murine Doxorubicin Exposure Mitigates Cardiac Toxicity.," Journal of pediatric hematology/oncology, vol. 40, no. 3, pp. 208–215, Apr. 2018, doi: 10.1097/MPH.0000000000001112.

[95] K. Sturgeon, G. Muthukumaran, D. Ding, A. Bajulaiye, V. Ferrari, and J. R. Libonati, "Moderate-intensity treadmill exercise training decreases murine cardiomyocyte cross-sectional area.," Physiological reports, vol. 3, no. 5, May 2015, doi: 10.14814/phy2.12406.

[96] A. Calvé, R. Haddad, S.-N. Barama, M. Meilleur, I. A. Sebag, and L. E. Chalifour, "Cardiac response to doxorubicin and dexrazoxane in intact and ovariectomized young female rats at rest and after swim training.," American journal of physiology. Heart and circulatory physiology, vol. 302, no. 10, pp. H2048-57, May 2012, doi: 10.1152/ajpheart.01069.2011.

[97] R. Hayward, C.-Y. Lien, B. T. Jensen, D. S. Hydock, and C. M. Schneider, "Exercise training mitigates anthracycline-induced chronic cardiotoxicity in a juvenile rat model.," Pediatric blood & cancer, vol. 59, no. 1, pp. 149–154, Jul. 2012, doi: 10.1002/pbc.23392.

[98] E. J. Howden et al., "Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients.," European journal of preventive cardiology, vol. 26, no. 3, pp. 305–315, Feb. 2019, doi: 10.1177/2047487318811181.

[99] D. S. Hydock, T. L. Parry, B. T. Jensen, C.-Y. Lien, C. M. Schneider, and R. Hayward, "Effects of endurance training on combined goserelin acetate and doxorubicin treatment-induced cardiac dysfunction.," Cancer chemotherapy and pharmacology, vol. 68, no. 3, pp. 685–692, Sep. 2011, doi: 10.1007/s00280-010-1523-6.

[100] L. W. Jones et al., "Exercise and Risk of Cardiovascular Events in Women With Nonmetastatic Breast Cancer.," Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 34, no. 23, pp. 2743–2749, Aug. 2016, doi: 10.1200/JCO.2015.65.6603.

[101] M. S. Krause et al., "MRP1/GS-X pump ATPase expression: is this the explanation for the cytoprotection of the heart against oxidative stress-induced redox imbalance in comparison to skeletal muscle cells?," Cell biochemistry and function, vol. 25, no. 1, pp. 23–32, 2007, doi: 10.1002/cbf.1343.

[102] C. Matsuura et al., "Exercise training in doxorubicin-induced heart failure: effects on the L-arginine-NO pathway and vascular reactivity.," Journal of the American Society of Hypertension : JASH, vol. 4, no. 1, pp. 7–13, 2010, doi: 10.1016/j.jash.2009.10.005.

[103] A. C. Nagy, P. GulAcsi-BArdos, Z. CserEp, L. Hangody, and T. Forster, "Late cardiac effect of anthracycline therapy in physically active breast cancer survivors - a prospective study.," Neoplasma, vol. 64, no. 1, pp. 92–100, 2017, doi: 10.4149/neo_2017_111.

[104] T. L. Parry, D. S. Hydock, B. T. Jensen, C.-Y. Lien, C. M. Schneider, and R. Hayward, "Endurance exercise attenuates cardiotoxicity induced by androgen deprivation and doxorubicin.," Canadian journal of physiology and pharmacology, vol. 92, no. 5, pp. 356–362, May 2014, doi: 10.1139/cjpp-2013-0294.

[105] F. Sharifi, V. D. Roshan, and Z. Mazaheri, "Effect of pretreatment of aerobic training on doxorubicininduced left ventricular apoptosis gene expression in aging rat model," Modares Journal of Medical Sciences: Pathobiology, vol. 19, no. 2, pp. 29–43, 2016.

[106] T. Shimauchi et al., "TRPC3-Nox2 complex mediates doxorubicin-induced myocardial atrophy," JCI insight, vol. 2, no. 15, 2017, doi: 10.1172/jci.insight.93358.

[107] K. Y. Wonders, D. S. Hydock, S. Greufe, C. M. Schneider, and R. Hayward, "Endurance exercise training preserves cardiac function in rats receiving doxorubicin and the HER-2 inhibitor GW2974.," Cancer chemotherapy and pharmacology, vol. 64, no. 6, pp. 1105–1113, Nov. 2009, doi: 10.1007/s00280-009-0967-z.

SUPPLEMENTAL RESULTS B

Risk of bias assessment

The risk of bias assessment for the human studies is presented in Figure 2a. The two studies by Kirkham et al.[22], [23] were scored as one, since they made use of the same study population and largely the same methodology. These studies were scored as low risk of bias on all items. An exception was the item on performance bias which was scored as 'high', since blinding was not possible due to the nature of the intervention. For Ma, the items on selection bias were scored 'unclear', since no information on the randomization procedure was provided. Performance bias was scored as high risk of bias, similar to the reports by Kirkham et al. Since information on loss of participations was not adequately provided, the risk of attrition bias was rated as high. The item on selective reporting could not be assessed, as no pre-specified protocol was available.

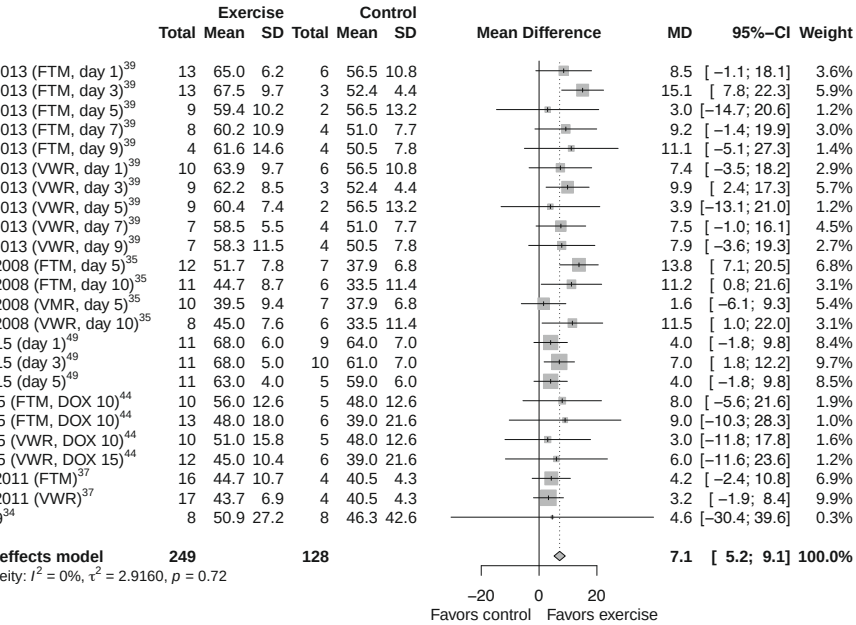
The risk of bias assessment and reporting of quality indicators for the animal studies are presented in Figure 2b and Figure 2c, respectively. Many studies did not adequately report on important aspects of the methodology; hence most items were initially scored as 'unclear'. After contacting authors (response rate: 73%, n=29/40), 127 of the 'unclear' ratings were modified to either 'low' (*n*=109) or 'high' (*n*=18) risk of bias. Risk of selection bias, assessed via entries on random sequences generation, comparability of baseline characteristics and concealment of allocation, were scored low in approximately two-thirds of the studies, 'unclear' in about 25% and high in the remaining studies. Compared to other sources of bias, risk of performance bias comprising entries on random housing and blinding of the trial caregivers and researchers (when possible), was scored high in 14% and 35%, respectively. Risk of detection bias (random outcome assessment and blinding of outcome assessors) were scored relatively low. Drop-outs were inadequately reported in approximately one-fifth of the studies, leading to a high risk of attrition bias in these studies. The item on reporting bias, i.e. whether outcomes were selectively reported, was scored 'unclear' for all studies, since no-preregistered protocols were available.

As for the reporting of methodology, none of the studies provided a sample size calculation, and many studies did not mention any form of blinding. Ethical approval was, however, reported in the vast majority of the studies.

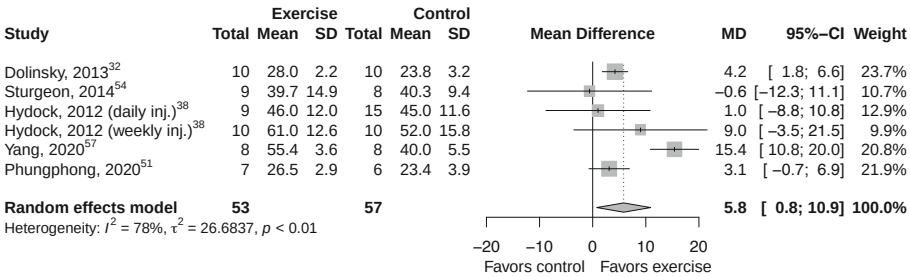
SUPPLEMENTAL RESULTS C

Sub-analysis on the timing of the physical exercise intervention

Forest plot (Supplemental Figure 1) present the results of the preconditioning physical exercise interventions (i.e. started before DOX treatment) and plot (Supplemental Figure 2)) presents the results of those interventions given concomitant with DOX administration.



1



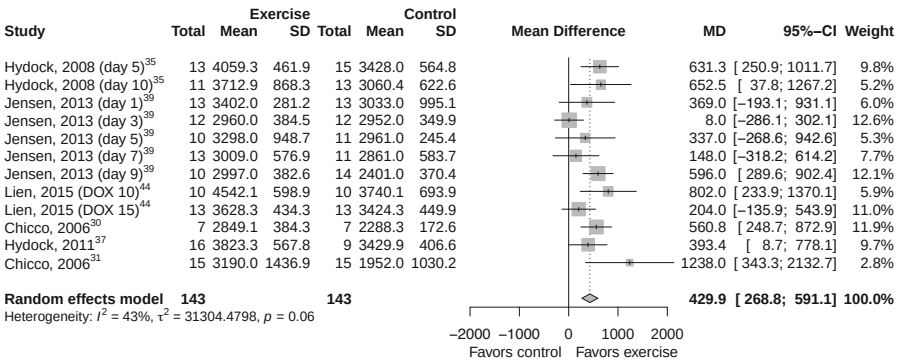
2

SUPPLEMENTAL RESULTS D

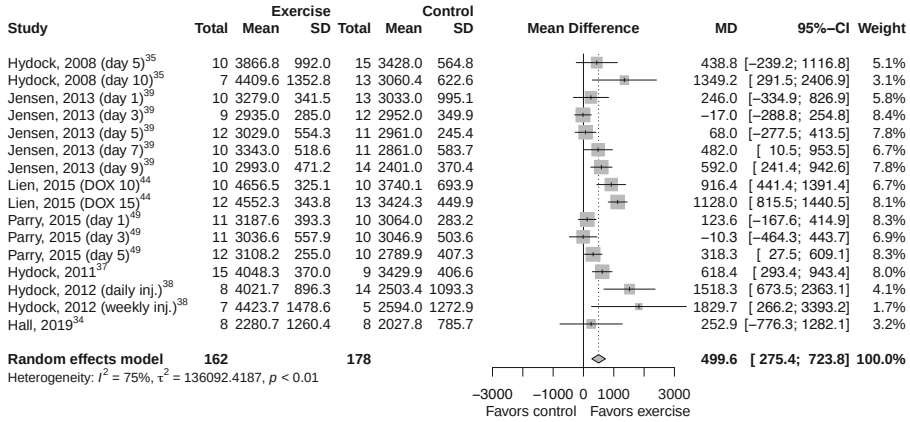
Results on +dP/dt and –dP/dt

For both +dP/dt and –dP/dt, results are favoring physical exercise groups (Supplemental Figures 3-6). In +dp/dt, a pooled analysis of studies using forced exercise interventions demonstrated a MD of 430.8 mm Hg (95CI%: 267.5; 594.1), T^2=21392.1. Results were comparable, yet slighter stronger in the analysis on voluntary exercise interventions; MD of 500.3 mm Hg (95CI%: 274.7; 725.9), T^2=138438.2.

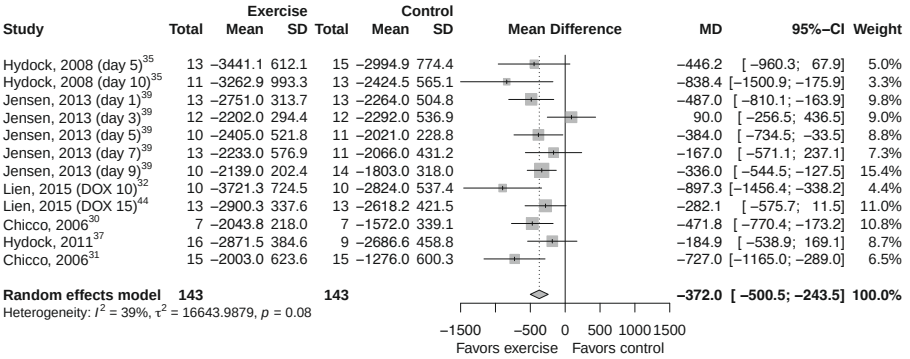
In –dP/dt, a MD of -374.5 (95%CI:-508.9; -240.1), T^2=20895.3, and -407.5 (9%CI: -596.9; -218.1) mm Hg was found for respectively forced and voluntary exercise interventions compared to non-exercised rodents.



3


Exercise
Control
Study Total Mean SD Total Mean SD
Mean Difference
MD 95%–CI Weight
Hydock, 2008 (day 5)[35] 10 3866.8 992.0 15 3428.0 564.8 438.8 [–239.2; 1116.8] 5.1%
Hydock, 2008 (day 10)[35] 7 4409.6 1352.8 13 3060.4 622.6 1349.2 [291.5; 2406.9] 3.1%
Jensen, 2013 (day 1)[39] 10 3279.0 341.5 13 3033.0 995.1 246.0 [–334.9; 826.9] 5.8%
Jensen, 2013 (day 3)[39] 9 2935.0 285.0 12 2952.0 349.9 –17.0 [–288.8; 254.8] 8.4%
Jensen, 2013 (day 5)[39] 12 3029.0 554.3 11 2961.0 245.4 68.0 [–277.5; 413.5] 7.8%
Jensen, 2013 (day 7)[39] 10 3343.0 518.6 11 2861.0 583.7 482.0 [10.5; 953.5] 6.7%
Jensen, 2013 (day 9)[39] 10 2993.0 471.2 14 2401.0 370.4 592.0 [241.4; 942.6] 7.8%
Lien, 2015 (DOX 10)[44] 10 4656.5 325.1 10 3740.1 693.9 916.4 [441.4; 1391.4] 6.7%
Lien, 2015 (DOX 15)[44] 12 4552.3 343.8 13 3424.3 449.9 1128.0 [815.5; 1440.5] 8.1%
Parry, 2015 (day 1)[49] 11 3187.6 393.3 10 3064.0 283.2 123.6 [–167.6; 414.9] 8.3%
Parry, 2015 (day 3)[49] 11 3036.6 557.9 10 3046.9 503.6 –10.3 [–464.3; 443.7] 6.9%
Parry, 2015 (day 5)[49] 12 3108.2 255.0 10 2789.9 407.3 318.3 [27.5; 609.1] 8.3%
Hydock, 2011[37] 15 4048.3 370.0 9 3429.9 406.6 618.4 [293.4; 943.4] 8.0%
Hydock, 2012 (daily inj.)[38] 8 4021.7 896.3 14 2503.4 1093.3 1518.3 [673.5; 2363.1] 4.1%
Hydock, 2012 (weekly inj.)[38] 7 4423.7 1478.6 5 2594.0 1272.9 1829.7 [266.2; 3393.2] 1.7%
Hall, 2019[34] 8 2280.7 1260.4 8 2027.8 785.7 252.9 [–776.3; 1282.1] 3.2%
Random effects model 162 178 499.6 [275.4; 723.8] 100.0%
Heterogeneity: I^2 = 75%, τ^2 = 136092.4187, p < 0.01
–3000 –1000 0 1000 3000
Favors control Favors exercise

4


Exercise
Control
Study Total Mean SD Total Mean SD
Mean Difference
MD 95%–CI Weight
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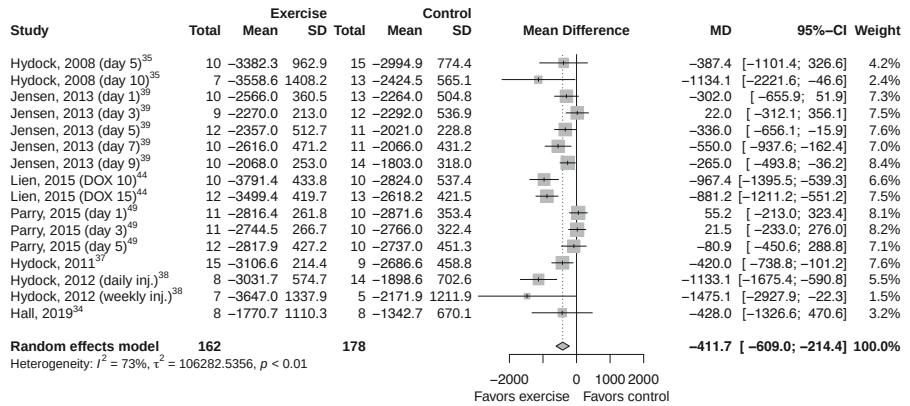
Hydock, 2008 (day 10)[35] 11 –3262.9 993.3 13 –2424.5 565.1 –838.4 [–1500.9; –175.9] 3.3%
Jensen, 2013 (day 1)[39] 13 –2751.0 313.7 13 –2264.0 504.8 –487.0 [–810.1; –163.9] 9.8%
Jensen, 2013 (day 3)[39] 12 –2202.0 294.4 12 –2292.0 536.9 90.0 [–256.5; 436.5] 9.0%
Jensen, 2013 (day 5)[39] 10 –2405.0 521.8 11 –2021.0 228.8 –384.0 [–734.5; –33.5] 8.8%
Jensen, 2013 (day 7)[39] 13 –2233.0 576.9 11 –2066.0 431.2 –167.0 [–571.1; 237.1] 7.3%
Jensen, 2013 (day 9)[39] 10 –2139.0 202.4 14 –1803.0 318.0 –336.0 [–544.5; –127.5] 15.4%
Lien, 2015 (DOX 10)[32] 10 –3721.3 724.5 10 –2824.0 537.4 –897.3 [–1456.4; –338.2] 4.4%
Lien, 2015 (DOX 15)[44] 13 –2900.3 337.6 13 –2618.2 421.5 –282.1 [–575.7; 11.5] 11.0%
Chicco, 2006[30] 7 –2043.8 218.0 7 –1572.0 339.1 –471.8 [–770.4; –173.2] 10.8%
Hydock, 2011[37] 16 –2871.5 384.6 9 –2686.6 458.8 –184.9 [–538.9; 169.1] 8.7%
Chicco, 2006[31] 15 –2003.0 623.6 15 –1276.0 600.3 –727.0 [–1165.0; –289.0] 6.5%
Random effects model 143 143 –372.0 [–500.5; –243.5] 100.0%
Heterogeneity: I^2 = 39%, τ^2 = 16643.9879, p = 0.08
–1500 –500 0 500 1000 1500
Favors exercise Favors control

5


Exercise
Control
Study Total Mean SD Total Mean SD
Mean Difference
MD 95%–CI Weight
Hydock, 2008 (day 5)[35] 10 –3382.3 962.9 15 –2994.9 774.4 –387.4 [–1101.4; 326.6] 4.2%
Hydock, 2008 (day 10)[35] 7 –3558.6 1408.2 13 –2424.5 565.1 –1134.1 [–2221.6; –46.6] 2.4%
Jensen, 2013 (day 1)[39] 10 –2566.0 360.5 13 –2264.0 504.8 –302.0 [–655.9; 51.9] 7.3%
Jensen, 2013 (day 3)[39] 9 –2270.0 213.0 12 –2292.0 536.9 22.0 [–312.1; 356.1] 7.5%
Jensen, 2013 (day 5)[39] 12 –2357.0 512.7 11 –2021.0 228.8 –336.0 [–656.1; –15.9] 7.6%
Jensen, 2013 (day 7)[39] 10 –2616.0 471.2 11 –2066.0 431.2 –550.0 [–937.6; –162.4] 7.0%
Jensen, 2013 (day 9)[39] 10 –2068.0 253.0 14 –1803.0 318.0 –265.0 [–493.8; –36.2] 8.4%
Lien, 2015 (DOX 10)[44] 10 –3791.4 433.8 10 –2824.0 537.4 –967.4 [–1395.5; –539.3] 6.6%
Lien, 2015 (DOX 15)[44] 12 –3499.4 419.7 13 –2618.2 421.5 –881.2 [–1211.2; –551.2] 7.5%
Parry, 2015 (day 1)[49] 11 –2816.4 261.8 10 –2871.6 353.4 55.2 [–213.0; 323.4] 8.1%
Parry, 2015 (day 3)[49] 11 –2744.5 266.7 10 –2766.0 322.4 21.5 [–233.0; 276.0] 8.2%
Parry, 2015 (day 5)[49] 12 –2817.9 427.2 10 –2737.0 451.3 –80.9 [–450.6; 288.8] 7.1%
Hydock, 2011[37] 15 –3106.6 214.4 9 –2686.6 458.8 –420.0 [–738.8; –101.2] 7.6%
Hydock, 2012 (daily inj.)[38] 8 –3031.7 574.7 14 –1898.6 702.6 –1133.1 [–1675.4; –590.8] 5.5%
Hydock, 2012 (weekly inj.)[38] 7 –3647.0 1337.9 5 –2171.9 1211.9 –1475.1 [–2927.9; –22.3] 1.5%
Hall, 2019[34] 8 –1770.7 1110.3 8 –1342.7 670.1 –428.0 [–1326.6; 470.6] 3.2%
Random effects model 162 178 –411.7 [–609.0; –214.4] 100.0%
Heterogeneity: I^2 = 73%, τ^2 = 106282.5356, p < 0.01
–2000 0 1000 2000
Favors exercise Favors control

6

CHAPTER 4

Physical activity and cardiac dysfunction in long-term breast cancer survivors: A cross-sectional study

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M.M. Stuiver
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B.M.P. Aleman
P.C. van der Meer
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JACC CardioOncology, 2022, Apr 19;4(2):183-191.

ABSTRACT

Background

Higher levels of physical activity (PA) are associated with a lower risk of cardiovascular disease in the general population. Whether the same holds for women who underwent treatment for breast cancer (BC) is unclear.

Objective

The aim of this study was to evaluate the association between PA in a typical week in the past 12 months and cardiac dysfunction in BC survivors.

Methods

We used data from a cohort of BC survivors, who were treated at ages 40-50 years (N=559). The association between PA and global longitudinal strain (GLS) and left ventricular ejection fraction (LVEF) was evaluated using both linear and modified Poisson regression analyses adjusted for relevant confounders.

Results

In total, 559 BC survivors were included, with median age of 55.5 years and median time since treatment of 10.2 years. GLS was less favorable in inactive survivors (-17.1%) than in moderately inactive (-18.4%), moderately active (-18.2%), and active survivors (-18.5%), with an adjusted significant difference for active versus inactive survivors (β=-1.31 (95%CI:-2.55,-0.06)). Moderately active (n=57/130) and active survivors (n=87/124) had significantly lower risks of abnormal GLS, defined as >-18%, compared to inactive survivors (n=17/26) (relative risk [RR]=0.65 (95%CI:0.45-0.94) and RR=0.61 (95%CI:0.43-0.87), respectively). LVEF (in normal ranges in all activity categories) was not associated with PA.

Conclusion

In long-term BC survivors, higher PA levels were associated with better GLS, but not LVEF, with the relatively largest benefit for doing any activity versus none. This finding suggests that increasing PA may contribute to cardiovascular health benefits, especially in inactive survivors.

Abbreviations

BMI	body mass index
CVD	Cardiovascular disease
EPIC	European Prospective Investigation into Cancer and Nutrition
GLS	Global longitudinal strain
HARBOR study	identifying subgroups with High cArdiovascular Risk in Breast cancer survivORS
IMN	internal mammary nodes
IQR	interquartile range
LV	left ventricle / ventricular
LVEF	left ventricular ejection fraction
NKI – AVL	Netherlands Cancer Institute – Antoni van Leeuwenhoek
RR	relative risk
SD	standard deviation
UMCG	University Medical Center Groningen

BACKGROUND

The population of breast cancer survivors has grown substantially over the last decades, due to, among other factors, improvements in early detection and anticancer regimens[1]. Advances in primary treatment and cures are expected to further increase the number of breast cancer survivors. Consequently, adequate evaluation of long-term side effects of breast cancer treatment is of increasing importance.

A severe, long-term side-effect of breast cancer treatment is cardiovascular disease (CVD), which includes a variety of clinical manifestations and may eventually lead to a decline in LVEF[2]. Breast cancer survivors more than seven years after treatment have an almost two-fold increased risk of CVD-related mortality compared to age-matched women without cancer[3]. Among patients with pre-existent CVD who survived more than 5 years after treatment, cardiovascular death has even replaced breast cancer-related death as the leading cause of mortality[4]. The risk of developing CVD depends on the type of breast cancer treatment (and for anthracycline and radiotherapy, its cumulative dose) as well as patient-related factors[2], [5]. A linear relationship between cumulative anthracycline dose and cardiac dysfunction has been demonstrated[6]. Radiation exposure of the heart may lead to an increased risk of coronary artery disease, valvular heart disease and heart failure[2]. As for patient-related risk factors, women with an unfavorable cardiovascular risk profile (e.g., elderly, presence of hypertension, diabetes mellitus, and obesity) have a higher risk of developing CVD[5]. Accordingly, strategies that aim to reduce CVD risk should preferably target both treatment- and patient-related factors.

Physical activity has been found to be associated with lower CVD risk in non-cancer populations[7]. However, less evidence is available on whether physical activity can also decrease CVD risk in cancer patients and survivors, given that CVD pathogenesis may be different in this population due to exposure to potential cardiotoxic treatment. Two observational studies reported that, in breast cancer survivors with no prior history of CVD, higher levels of leisure-time physical activity were associated with a lower cumulative incidence of cardiovascular clinical endpoints, including myocardial infarction and heart failure, independent of the presence of other cardiovascular risk factors[8], [9]. Cardiac dysfunction during and after cancer treatment is currently considered as a gradual phenomenon, where progressive subclinical declines in parameters of cardiac function (i.e.,

global longitudinal strain (GLS) and left ventricular ejection fraction (LVEF)) can eventually lead to overt heart failure[10]. The association between physical activity and GLS and LVEF in breast cancer survivors is currently unknown. If such an association exists, this could prompt further research and ultimately have implications regarding physical activity recommendations for future breast cancer patients undergoing treatment with cardiotoxic regimens.
This study aimed to evaluate the association between current levels of physical activity and cardiac dysfunction in breast cancer survivors. We hypothesize that higher physical activity levels are associated with more favorable values for GLS and LVEF.

METHODS

Setting and participants

Data from the HARBOR study (identifying subgroups with High cArdiovascular Risk in Breast cancer survivORS) were used for the current analysis. The study design and results of this study have been published previously[6]. In brief, the HARBOR study was a cross-sectional investigation of long-term cardiac dysfunction in breast cancer survivors 5-7 or 10-12 years after treatment. Patients were treated between 2002-2007 and 2008-2012 for invasive breast cancer (TNM stage I-III) or ductal carcinoma *in situ* (DCIS), with or without anthracyclines (N=306, 54.7%, and N=253, 45.3%, respectively), at ages 40-50 years in either the Netherlands Cancer Institute – Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, or the University Medical Center Groningen (UMCG), Groningen. Exclusion criteria were history of radiotherapy or chemotherapy for other malignancies and history of CVD before breast cancer diagnosis. A total of 569 women were enrolled in this study. The HARBOR study is registered with ClinicalTrials.gov, identifier NCT02485626 and approved by the institutional review board of the NKI-AVL.

Cardiovascular measurements

All women underwent cardiovascular assessment, including physical examination, blood and urine sampling, and a 2D echocardiogram. Physical examination included blood pressure measurement and evaluation of signs of heart failure (i.e., pedal edema, pulmonary congestion). Echocardiograms were performed using a GE Vivid E9 machine (GE, Horten, Norway) and a Philips iE33 (Philips Healthcare, DA Best, the Netherlands) in the UMCG and NKI, respectively. All echocardiographic measurements were analyzed centrally (UMCG). In line

with current guidelines[11], left ventricular (LV) volumes and ejection fraction were assessed via Simpson's biplane algorithm on the apical 2- and 4-chamber view and, in case of insufficient imaging quality (N=89, 15.6%), a range was reported based in visual inspection. GLS was measured using apical 2-, 3- and 4-chamber view with TomTec software (TomTec Imaging Software Systems, Unterschleissheim, Germany). Imaging quality was insufficient for GLS analyses in 13.1% (N=74) of the participants. The inter-observer reliability (intraclass correlation coefficient) for the GLS analyses was 0.70 (95%CI 0.59-0.70) in a random subset of 102 subjects[6].

Physical activity

All participants completed a questionnaire that contained questions on physical activity in the past 12 months, assessing both occupational and leisure activities, based on questions from the European Prospective Investigation into Cancer and Nutrition (EPIC) physical activity questionnaire[12] (Supplemental Material A). For occupational activities, participants reported their current employment status and the intensity of the activities carried out at work (i.e., best described as 'sedentary,' 'standing', 'manual' or 'heavy manual'). For recreational activities, the total hours per week spent on walking, cycling, sports, and gardening were recorded for summer and winter separately to limit seasonal influences.
To obtain a total physical activity score, we used the validated Cambridge Physical Activity Index ('Cambridge Index')[13]. In a cohort of 1941 healthy individuals from ten European countries, the Cambridge Index correlated strongest with physical activity energy expenditure and time spent in moderate and vigorous physical activity, compared to other questionnaire-derived physical activity indices[14]. This categorical index, ranging from 'inactive', 'moderately inactive', 'moderately active' to 'active', is derived by cross-tabulating the level of occupational activities with the combined hours per week spent on cycling and sports activity (Table 1). In calculating this index, all physical activity variables were scored as missing if none of the questions were answered, with the assumption being that these participants did not complete the questionnaire. All other variables were set to zero if at least one question was completed, the assumption being that these participants completed the questionnaire but were not engaged in all activities[15]. The maximum hours/week spent on any given physical activity variable was set to 40 hours/week, and summer and winter scores were averaged to obtain an average score for the past year.

Table 1. Calculation of the Cambridge Physical Activity Index: a cross-tabulation of occupational activities with recreational activities.

	Time spent in sports and cycling (h/week)			
	None	**≤3.5**	**>3.5 to ≤7.0**	**>7.0**
Sedentary	Inactive	Moderately inactive	Moderately active	Active
Standing	Moderately inactive	Moderately active	Active	Active
Manual	Moderately inactive	Active	Active	Active
Heavy manual	Active	Active	Active	Active
Unknown/missing	Inactive	Moderately inactive	Moderately active	Active

Statistical analysis

Characteristics of the study participants were computed per Cambridge category and expressed as mean ± standard deviation (SD), median [25th and 75th percentiles [Q1-Q3], or frequencies (percentages). Linear regression models were used with Cambridge Index as the independent and either GLS or LVEF as dependent variables and results presented as the regression coefficient with 95% confidence interval (CI). GLS and LVEF were also dichotomized into impaired versus normal using clinically accepted cut-offs, i.e., GLS >-18% / ≤-18%[16] and LVEF <53% / ≥53%[17]. The association between physical activity and dichotomized GLS or LVEF was investigated using modified Poisson regression with robust standard errors (sandwich estimator[18]. Results are presented as relative risk (RR) with 95%CI. We did not perform Poisson regression with dichotomized LVEF because only 34 patients had a LVEF <53%, of whom only one participant was in the inactive reference group.

For sensitivity analyses, we repeated the analyses after excluding patients whose (level of) occupational activity data were missing (N=88, 15.7%). Also, analyses were repeated with multiple imputation (n=50) by fully conditional specification for GLS, since missing data on this variable exceeded 10% (MICE package, 2021[19]). Last, given that both GLS and LVEF are expressed as percentages bound between 0-100, we reanalyzed our data via a beta-regression model[20]. All models were adjusted for age, BMI, radiotherapy (none versus right-sided, left-sided, or internal mammary chain), time since diagnosis (5-7 years or 10-12 years after treatment), and clinically documented cumulative dose of anthracyclines. The cumulative dose of epirubicin was transformed into a

doxorubicin equivalence dose in a similar manner to the original HARBOR analyses[6]. In addition, we added adjustment for the presence of CVD risk factors at time of study visit (hypertension, hypercholesterolemia, diabetes mellitus, smoking; none versus 1-2, or ≥3 risk factors) to the model. These risk factors were defined as follows; hypertension as having a blood pressure higher than 140 mm Hg (systolic) and 90 mm Hg (diastolic), or being treated with antihypertensive medication, hypercholesterolemia as having a total cholesterol ≥6.5 mmol/L or being treated with statins, and diabetes as having a fasting glucose ≥6.5mmol/L or being treated with glucose-lowering medication. Last, we explored whether the treatment with anthracyclines modified the association between physical activity and cardiac dysfunction by adding an interaction term to the fully adjusted model.
A p-value <0.05 was considered significant, and all analyses were performed using R software (R version 4.0.3).

RESULTS

In total, 569 breast cancer survivors participated in the HARBOR study, of whom 10 (1.8%) were excluded from the current analysis due to the absence of physical activity data. Characteristics of the study population (N=559) are presented in Table 2. Median [Q1-Q3] ages at diagnosis and at time of study participation were 46.9 [43.8-49.5] years and 55.5 [52.7-58.5] years, respectively.
Using the Cambridge Physical Activity Index, 28 participants (5.0%) were classified as inactive, 127 (22.7%) as moderately inactive, 154 (27.5%) as moderately active, and 250 (44.7%) as active at the time of the study visit. Most breast cancer survivors reported a sedentary occupation, with very few describing their occupational activities as 'manual' or 'heavy manual'.

In the inactive category, the median [Q1-Q3] time since diagnosis was 7.4 [6.9-11.1] years, with two-thirds of the survivors being between 5-7 years post-diagnosis. In the three other categories, the median time since diagnosis was more than ten years. Cardiovascular risk factors were relatively common, especially in inactive survivors. Hypertension, for example, was prevalent in 53.6% (N=15/28), 35.4% (N=45/127), 37.5% (N=57/154), and 37.2% (N=93/250) in participants in the inactive, moderately inactive, moderately active, and active categories, respectively.

Approximately half of the survivors were treated with anthracycline-based chemotherapy regimens in all activity categories. Median [Q1-Q3] cumulative

doxorubicin (equivalent) dose was 202 [191-243] mg/m2 (inactive category), 240 [203-242] mg/m2 (moderately inactive category)
and 240 [203-300] mg/m2 (both moderately active and active category). The vast majority (>90%) of the participants received breast/chest wall irradiation. Relatively few participants received additional treatment with potentially cardiotoxic anti-HER2 drug trastuzumab; N=2 (7.1%), N=12 (9.4%), N=16 (10.4%), and N=19 (7.6%) for survivors in the inactive, moderately inactive, moderately active, and active category, respectively.

Association between physical activity and cardiac dysfunction

GLS was least favorable (-17.1%) in inactive survivors, and better in moderately inactive (-18.4%), moderately active (-18.2%) and active survivors (-18.5%) (Table 3). Corresponding adjusted β-coefficients, compared to inactive survivors, were 95%) 1.12- CI:-2.41, 0.17), -0.92 (95% CI:-2.21, 0.38) and -1.31 (95% CI:-2.55, -0.06), respectively. Similarly, higher physical activity was associated with a lower risk of impaired GLS: RR 0.71 (95% CI: 0.50,1.02) for moderately inactive, RR 0.65 (95% CI: 0.45,0.94) for moderately active and RR 0.61 (95% CI: 0.43,0.87) for the most active, compared to inactive survivors, (Central illustration).
For LVEF, mean values did not differ and were within normal ranges in all four physical activity categories. Compared to inactive survivors, adjusted β-coefficients for moderately inactive, moderately active and active were 0.27 (95% CI: -1.64,2.18), 0.20 (95% CI: -1.70,2.09) and 0.35 (95% CI: -1.48,2.18), respectively. All interaction terms were non-significant (p>0.10).

Table 2. Characteristics of the study sample per Cambridge Physical Activity Index category at the time of study visit. Presented as mean ± SD or median [Q1-Q3].

	Inactive	**Mod. inactive**	**Mod. active**	**Active**	**Total**
	N=28	**N=127**	**N=154**	**N=250**	**N=559**
Age at diagnosis, years	46.8 [44.5–48.7]	46.4 [43.7–49.5]	46.3 [43.3–49.6]	47.1 [44.0–49.4]	46.9 [43.8-49.5]
Age at inclusion, years	55.2 [51.9–57.0]	56.0 [53.4–59.2]	55.1 [52.2–57.6]	55.4 [53.0–58.6]	55.5 [52.7-58.5]
Follow-up time, years	7.4 [6.9-11.1]	10.4 [6.8-11.6]	10.4 [6.9-11.6]	10.1 [6.7-11.6]	10.2 [6.8- 11.6]
5 – 7 years, %	19 (67.9)	58 (45.7)	76 (49.4)	121 (48.4)	274 (49.0)
10 – 12 years, %	9 (32.1)	69 (54.3)	78 (50.6)	129 (51.6)	285 (51.0)
Cardiovascular risk factors*, %					
Hypertension	15 (53.6)	45 (35.4)	57 (37.5)	93 (37.2)	210 (37.7)
Hypercholesterolemia	9 (32.1)	43 (33.9)	45 (29.2)	79 (31.6)	176 (31.5)
Diabetes mellitus	4 (14.3)	8 (6.3)	9 (5.8)	17 (6.8)	38 (6.8)
Smoking, %					
Never	12 (42.9)	47 (37.0)	65 (42.2)	99 (39.6)	223 (39.9)
Former	10 (35.7)	55 (43.3)	65 (42.2)	123 (49.2)	253 (45.3)
Current	6 (21.4)	24 (18.9)	23 (14.9)	28 (11.2)	81 (14.5)
Unknown	0	1 (0.8)	1 (0.6)	0	2 (0.4)
Body mass index, mg/m^2	29.3 ± 6.0	26.2 ± 4.8	25.3 ± 4.1	25.7± 4	25.9± 4.4
Anthracyclines, %	15 (53.6)	66(52.0)	88 (57.1)	137 (54.8)	306 (54.7)
Cumulative dox. dose†, mg/m^2	202.5 [191-243]	240.0 [203-242]	240.0 [203-300]	240.0 [203-300]	240.0 [203-293

Radiotherapy field, %					
Left-sided	15 (53.6)	52 (40.9)	57 (37.0)	114 (45.6)	238 (42.6)
Right-sided	9 (32.1)	61 (48.0)	79 (51.3)	107 (42.8)	256 (45.8)
IMN	3 (10.7)	9 (7.1)	7 (4.5)	18 (7.2)	37 (6.6)
None	1 (3.6)	5 (3.9)	11 (7.1)	11 (4.4)	28 (5.0)
Trastuzumab, %	2 (7.1)	12 (9.4)	16 (10.4)	19 (7.6)	49 (8.8)

*Cardiovascular risk factors are defined as follows: hypertension = having a blood pressure higher than 140 mm Hg (systolic) and 90 mm Hg (diastolic), or being treated with antihypertensive medication, hypercholesterolemia = having total cholesterol ≥6.5 mmol/L or being treated with statins, diabetes mellitus = glucose ≥6.5 mmol/L or being treated with glucose-lowering medication.

ǂ These numbers are only applicable for those treated with anthracyclines. (N=306)

Abbreviations:

Anthracyc = anthracyclines, dox = doxorubicin (equivalent), IMN = internal mammary nodes, mod = moderately.

Table 3. Association between Cambridge Index and cardiotoxicity.

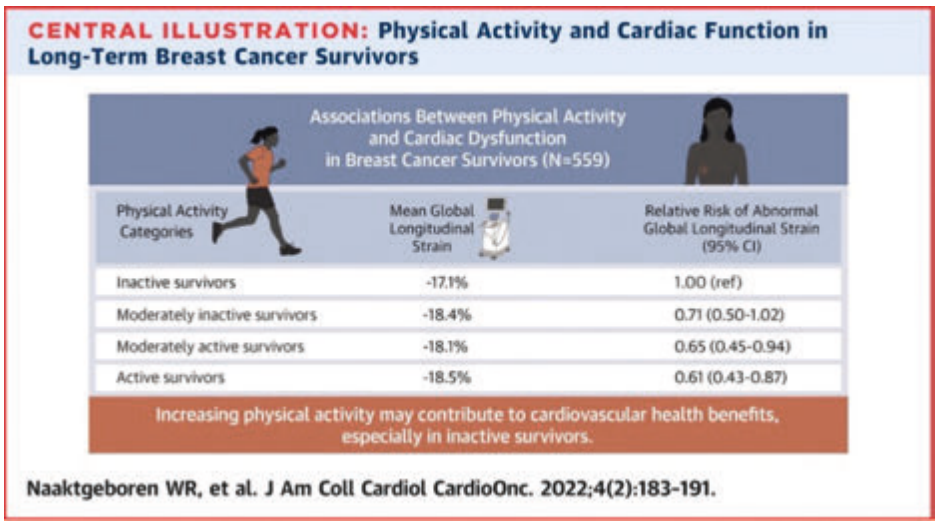
	Inactive N=28	**Mod. inactive N=127**	**Mod. active N=154**	**Active N=250**
GLS (%)*				
- Mean GLS (%)	-17.1 ± 2.31	-18.4 ± 3.40	-18.2 ± 2.55	-18.5 ± 3.14
- Unadjusted β (95%CI)	Ref.	-1.31 (-2.59, -0.02) §	-1.12 (-2.39, 0.15)	-1.47 (-2.70, -0.24) §
- Part. adjusted β (95%CI) ǂ	Ref.	-1.14 (-2.43, 0.15)	-0.87 (-2.16, 0.42)	-1.29 (-2.54, -0.05) §
- Fully adjusted β (95%CI)ǂ	Ref.	-1.12 (-2.41, 0.17)	-0.92 (-2.21, 0.38)	-1.31 (-2.55, -0.06) §
GLS (>-18%)*				
- n/N at risk (%)	17/26 (65.4)	54/115 (47.0)	57/130 (43.8)	87/214 (40.7)
- Unadjusted RR (95%CI)	Ref.	0.72 (0.51, 1.01)	0.67 (0.48, 0.94) §	0.62 (0.45, 0.86) §
- Part. adjusted RR (95%CI)*	Ref.	0.72 (0.50, 1.03)	0.68 (0.47, 0.98) §	0.61 (0.43, 0.88) §
- Fully adjusted RR (95%CI)**	Ref.	0.71 (0.50, 1.02)	0.65 (0.45, 0.94) §	0.61 (0.43, 0.87) §
LVEF (%)				
- Mean LVEF (%)	58.7 ± 4.61	59.2 ± 3.97	58.9 ± 4.48	59.1 ± 5.00
- Unadjusted β (95%CI)	Ref.	0.49 (-1.40, 2.38)	0.25 (-1.61, 2.11)	0.40 (-1.40, 2.21)
- Part. adjusted β (95%CI)*	Ref.	0.37 (-1.55, 2.28)	0.28 (-1.62, 2.18)	0.39 (-1.44, 2.23)
- Fully adjusted β (95%CI)**	Ref.	0.27 (-1.64, 2.18)	0.20 (-1.70, 2.09)	0.35 (-1.48, 2.18)
LVEF (<53%)				
- n/N at risk (%)	1/27 (3.6)	5/127 (3.9)	10/163 (6.5)	18/249 (7.2)

* GLS data was not available for N=74 (13.2%). ǂAdjusted for age, BMI, radiotherapy field, cumulative anthracycline dose. ǂǂadditionally adjusted for the presence of cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, smoking). § These findings correspond with a p-value <0.05.

Abbreviations:

CI = confidence interval, GLS = global longitudinal strain, mod = moderately, part = partial, RR = relative risk.

All sensitivity analyses (i.e. exclusion of participants for whom (levels of) occupational activities were not recorded (n=88, 15.7%), using imputed data for GLS (missing in n=74 (13.2%) and the use of a beta-regression model for continuous outcomes, yielded comparable results and did not change the conclusions (data not shown).



DISCUSSION

In this cross-sectional study of breast cancer survivors, we found that higher levels of self-reported physical activity were associated with more favorable GLS values, but not with LVEF. This was after accounting for treatment-related risk factors (i.e., cumulative dosage anthracyclines and thoracic irradiation) as well as patient-related risk factors (i.e., age, BMI, and cardiovascular risk factors). Considering that subclinical cardiac dysfunction (i.e., impaired GLS) may precede adverse (cardiovascular) events, these results suggest that efforts to increase physical activity levels by, for example, offering a physical activity program, may contribute to reducing cardiovascular morbidity in breast cancer survivors.

Previous studies have extensively documented the association between physical activities and CVD risk in non-cancer populations[7]. Increased physical activity has been linked to lower incidence of various CVD, including coronary artery disease and heart failure. Conversely, having a largely sedentary lifestyle, reflected by low levels of physical activity, is hypothesized to be a main predisposing factor for the development and progression of CVD[21]. A meta-analysis of 38 prospective cohort studies (including approximately 271,000

participants) and an individual patient data meta-analysis (8 studies, N=36,383), both described a non-linear dose-response relationship between higher self-reported leisure physical activities and lower risk of all-cause mortality over a follow-up period with a median of 12 years (range 4-40 years) and 5.8 years (range 3-15 years), respectively [22] [23]. Both studies reported that the most substantial reduction of risk was observed among moderately inactive patients compared to those who are not active, with relatively little additional risk reduction for the more active categories[22] [23]. For cancer patients and survivors, less evidence on the relationship between physical activity and CVD is available. The pathogenesis of CVD in this population is likely different, given that patientsmight be treated with cardiotoxic regimens. Anthracyclines may inhibit topoisomerase-Iiβ, thereby causingdouble-strand DNA breaks, which eventually may lead to irreversible loss of functional cardiomyocytes and fibrosis[24]. Pathogenesis of radiation-induced coronary artery disease is presumably a multifactorial process with key roles for endothelial injury and inflammation[25]. As a result, cancer patients may present with premature CVD, sometimes even in the absence of traditional cardiovascular risk factors. Evidence of physical activitybased on non-cancer populations may therefore not necessarily generalize to cancer patients and survivors. Two previous studies among breast cancer survivors demonstrated that leisure-time physical activity after treatment was associated with a graded decrease of CVD[8], [9]. Our observation of a reduction in subclinical cardiac dysfunction (GLS) with increased physical activity is in line with these studies. The reduction was most apparent for inactive versus non-inactive survivors and differences in the magnitude of the association were relatively small among breast cancer survivors categorized as either moderately inactive, moderately active, or active. Similarly, we also observed a higher burden of cardiovascular risk factors among inactive patients. These findings must be interpreted with caution given the small numbers in the inactive category. However, it adds support to the proposition that even a relatively modest increase in daily physical activity may be valuable.

We observed a significant association between physical activity and subclinical cardiac dysfunction (i.e., impaired GLS) but not LVEF. GLS abnormalities were common (44%). In contrast, LVEF was within the normal range in nearly all patients (94%), which may have impeded accurate estimation of the association between abnormal LVEF and physical activity. The higher prevalence of impaired GLS compared to decreased LVEF may be explained by the prevailing hypothesis that considers cancer therapy-related cardiac dysfunction as a continuous phenomenon, in which GLS is thought to be an earlier marker of cardiotoxicity

than decreased LVEF [10]. Previous studies found that abnormalities in GLS can be detected during or shortly after the course of chemotherapy[26]–[28]. A drop in LVEF, on the other hand, is proposed as a 'late' parameter of cardiotoxicity, occurring only after cardiac compensatory mechanisms fail. Exception to this is a decline in LVEF during trastuzumab treatment, which occurs in approximately 10% of all patients and is mostly reversible upon cessation of treatment[29], [30]. LVEF is, in contrast to GLS, a volume-derived index which is, on echocardiography, indirectly measured from estimations of LV volumes in systole and at the end of diastole[31]. LVEF is therefore highly dependent on the pre- and afterload[32]. As such, LVEF is not only a parameter of myocardial contractility, but also of LV remodeling. GLS, on the other hand, tracks the myocardium directly and quantifies changes in longitudinal lengthening per cardiac segment throughout the cardiac cycle[31]. This makes GLS less load-dependent and more suitable to detect regional myocardial changes, including tissue composition (e.g., interstitial fibrosis)[33]), compared to LVEF. Thus, GLS may be a better parameter for assessment of cardiac function. This is further supported by evidence from studies demonstrating that GLS is a better predictor of all-cause mortality than LVEF[34], [35]. Nevertheless, since the first trial among cancer patients undergoing anthracycline-based chemotherapy (N=307) failed to demonstrate the benefit of the GLS-guided versus LVEF-guided approach for cardioprotection[36], future studies are needed to document the prognostic value of GLS in cancer patients in terms of clinical outcomes.

Given the cross-sectional design of our study, we cannot establish the direction of the association observed with certainty. It is theoretically possible that impaired cardiac function has led to lower physical activity levels (reverse causation). Nonetheless, we speculate that the opposite, i.e., higher levels of physical activity have led to less cardiac dysfunction, is more likely to underlie the association observed [37], [38]. First, from a biological standpoint, a protective effect of physical activity on subclinical cardiac dysfunction is plausible, given that preclinical studies describe various pathways via which physical exercise can yield cardioprotection during and after treatment, including less chemotherapy accumulation in the myocardium following physical exercise[39]. Second, it seems less likely that subclinical cardiac dysfunction results in lower physical activity levels, as patients are unlikely to experience symptoms solely from impaired GLS, with LVEF in normal ranges. Third, the observed effect of physical activity on cardiac dysfunction is consistent with previous evidence from randomized studies in non-cancer populations, documenting beneficial effects of physical exercise on cardiac function, including LVEF [40], [41]. The limited evidence from studies

in cancer patients also points towards the hypothesis of exercise-mediated cardioprotection, although no clear benefit has been demonstrated thus far on LVEF or GLS [42]–[45]. Last, analyses were adjusted for relevant confounders, including cardiovascular risk factors.

Limitations Important strengths of our study include the use of two valid markers of cardiac dysfunction, the large study population, and the availability of accurate data on potential confounders. However, several limitations should also be considered when interpreting our results. First, not all physical activities were recorded in the questionnaire, including light-to-moderate activities. Hence, we were unable to calculate the total energy expenditure per day. However, the Cambridge Index is a validated index that has , compared to other EPIC-derived indices, the highest correlation with objectively measured physical activity[14]. Second, physical activities were self-reported and therefore vulnerable to misclassification. This would, on average, most likely have led to over-reporting of the amount of physical activity. Although GLS was unknown to the participants and very few participants had cardiovascular symptoms[6], misclassification of physical activity-category could have underestimated our association, since those with an inactive lifestyle would be more likely to over-report their activities. Third, additional subgroup analyses (i.e., in patients treated with anthracyclines and with and without trastuzumab) were deemed inappropriate, since only a small numbers of patients received sequential treatment with trastuzumab (N=46/316). Last, GLS was missing in 74 (13.2%) women. This was unrelated to physical activity (data not shown), but participants with missing GLS were more likely to have been treated with higher cumulative anthracycline dosages (150.8 vs. 121.5 mg/m2, p=0.82) and had higher mean BMI (26.9 vs. 25.7 kg/m2, p=0.037). This may have led to underestimating the association between physical activity level and GLS, although multiple imputation did not result in any relevant difference in our inferences.

In conclusion, we found that higher physical activity levels are associated with less cardiac dysfunction as expressed by GLS, but not LVEF, independent of CV risk factors and potential cardiotoxic breast cancer treatment. A relatively large risk reduction was observed for moderately inactive survivors compared to inactive breast cancer survivors. This suggests that physical activity programs may contribute to reducing cardiovascular morbidity in breast cancer survivors, and particularly among those who are physically inactive. Future, prospective randomized studies are needed to determine whether cardiac dysfunction following breast cancer treatment can be reduced by physical activity programs.

REFERENCES

[1] K. D. Miller *et al.*, "Cancer treatment and survivorship statistics, 2016.," *CA: a cancer journal for clinicians*, vol. 66, no. 4, pp. 271–289, Jul. 2016, doi: 10.3322/caac.21349.

[2] J. L. Zamorano *et al.*, "2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (E," *Eur Heart J*, vol. 37, no. 36, pp. 2768–2801, Sep. 2016, doi: 10.1093/eurheartj/ehw211.

[3] P. T. Bradshaw, J. Stevens, N. Khankari, S. L. Teitelbaum, A. I. Neugut, and M. D. Gammon, "Cardiovascular Disease Mortality Among Breast Cancer Survivors.," *Epidemiology (Cambridge, Mass.)*, vol. 27, no. 1, pp. 6–13, Jan. 2016, doi: 10.1097/EDE.0000000000000394.

[4] H. Abdel-Qadir *et al.*, "A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer.," *JAMA Cardiol*, vol. 2, no. 1, pp. 88–93, Jan. 2017, doi: 10.1001/jamacardio.2016.3841.

[5] M. Lotrionte *et al.*, "Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity.," *Am J Cardiol*, vol. 112, no. 12, pp. 1980–1984, Dec. 2013, doi: 10.1016/j.amjcard.2013.08.026.

[6] J. N. Jacobse *et al.*, "Myocardial dysfunction in long-term breast cancer survivors treated at ages 40-50 years.," *European journal of heart failure*, vol. 22, no. 2, pp. 338–346, Feb. 2020, doi: 10.1002/ejhf.1610.

[7] G. Wang, M. Pratt, C. A. Macera, Z.-J. Zheng, and G. Heath, "Physical activity, cardiovascular disease, and medical expenditures in U.S. adults.," *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine*, vol. 28, no. 2, pp. 88–94, Oct. 2004, doi: 10.1207/s15324796abm2802_3.

[8] L. W. Jones *et al.*, "Exercise and Risk of Cardiovascular Events in Women With Nonmetastatic Breast Cancer.," *J Clin Oncol*, vol. 34, no. 23, pp. 2743–2749, Aug. 2016, doi: 10.1200/JCO.2015.65.6603.

[9] K. H. Kim *et al.*, "Association between physical activity and subsequent cardiovascular disease among 5-year breast cancer survivors.," *Breast cancer research and treatment*, vol. 188, no. 1, pp. 203–214, Jul. 2021, doi: 10.1007/s10549-021-06140-8.

[10] D. Cardinale, F. Iacopo, and C. M. Cipolla, "Cardiotoxicity of Anthracyclines.," *Frontiers in cardiovascular medicine*, vol. 7, p. 26, 2020, doi: 10.3389/fcvm.2020.00026.

[11] R. M. Lang *et al.*, "Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.," *European heart journal cardiovascular Imaging*, vol. 16, no. 3, pp. 233–270, Mar. 2015, doi: 10.1093/ehjci/jev014.

[12] A. E. Cust *et al.*, "Validity and repeatability of the EPIC physical activity questionnaire: a validation study using accelerometers as an objective measure.," *The international journal of behavioral nutrition and physical activity*, vol. 5, p. 33, Jun. 2008, doi: 10.1186/1479-5868-5-33.

[13] N. J. Wareham *et al.*, "Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.," *Public health nutrition*, vol. 6, no. 4, pp. 407–413, Jun. 2003, doi: 10.1079/PHN2002439.

[14] T. Peters *et al.*, "Validity of a short questionnaire to assess physical activity in 10 European countries.," *European journal of epidemiology*, vol. 27, no. 1, pp. 15–25, Jan. 2012, doi: 10.1007/s10654-011-9625-y.

[15] M. Haftenberger *et al.*, "Physical activity of subjects aged 50-64 years involved in the European Prospective Investigation into Cancer and Nutrition (EPIC).," *Public health nutrition*, vol. 5, no. 6B, pp. 1163–1176, Dec. 2002, doi: 10.1079/PHN2002397.

[16] E. K. Oikonomou *et al.*, "Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis.," *JAMA cardiology*, vol. 4, no. 10, pp. 1007–1018, Oct. 2019, doi: 10.1001/jamacardio.2019.2952.

[17] J. C. Plana *et al.*, "Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.," *Eur Heart J Cardiovasc Imaging*, vol. 15, no. 10, pp. 1063–1093, Oct. 2014, doi: 10.1093/ehjci/jeu192.

[18] G. Zou, "A modified poisson regression approach to prospective studies with binary data.," *American journal of epidemiology*, vol. 159, no. 7, pp. 702–706, Apr. 2004, doi: 10.1093/aje/kwh090.

[19] S. van Buuren and K. Groothuis-Oudshoorn, "mice: Multivariate Imputation by Chained Equations in R," *Journal of Statistical Software; Vol 1, Issue 3 (2011)* , Dec. 2011.

[20] S. Ferrari and F. Cribari-Neto, "Beta Regression for Modelling Rates and Proportions," *Journal of Applied Statistics*, vol. 31, no. 7, pp. 799–815, 2004, doi: 10.1080/0266476042000214501.

[21] M. A. Nystoriak and A. Bhatnagar, "Cardiovascular Effects and Benefits of Exercise.," *Frontiers in cardiovascular medicine*, vol. 5, p. 135, 2018, doi: 10.3389/fcvm.2018.00135.

[22] H. Löllgen, A. Böckenhoff, and G. Knapp, "Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories.," *International journal of sports medicine*, vol. 30, no. 3, pp. 213–224, Mar. 2009, doi: 10.1055/s-0028-1128150.

[23] U. Ekelund *et al.*, "Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis.," *BMJ (Clinical research ed.)*, vol. 366, p. l4570, Aug. 2019, doi: 10.1136/bmj.l4570.

[24] P. A. Henriksen, "Anthracycline cardiotoxicity: An update on mechanisms, monitoring and prevention," *Heart*, vol. 104, no. 12, pp. 971–977, 2018, doi: 10.1136/heartjnl-2017-312103.

[25] E. Belzile-Dugas and M. J. Eisenberg, "Radiation-Induced Cardiovascular Disease: Review of an Underrecognized Pathology.," *Journal of the American Heart Association*, vol. 10, no. 18, p. e021686, Sep. 2021, doi: 10.1161/JAHA.121.021686.

[26] Y. Kang *et al.*, "Early detection of anthracycline-induced cardiotoxicity using two-dimensional speckle tracking echocardiography.," *Cardiology journal*, vol. 20, no. 6, pp. 592–599, 2013, doi: 10.5603/CJ.2013.0158.

[27] M. Florescu, L. S. Magda, O. A. Enescu, D. Jinga, and D. Vinereanu, "Early detection of epirubicin-induced cardiotoxicity in patients with breast cancer.," *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*, vol. 27, no. 1, pp. 83–92, Jan. 2014, doi: 10.1016/j.echo.2013.10.008.

[28] C. Charbonnel *et al.*, "Assessment of global longitudinal strain at low-dose anthracycline-based chemotherapy, for the prediction of subsequent cardiotoxicity.," *European heart journal. Cardiovascular Imaging*, vol. 18, no. 4, pp. 392–401, Apr. 2017, doi: 10.1093/ehjci/jew223.

[29] N. F. Pondé, M. Lambertini, and E. de Azambuja, "Twenty years of anti-HER2 therapy-associated cardiotoxicity.," *ESMO open*, vol. 1, no. 4, p. e000073, 2016, doi: 10.1136/esmoopen-2016-000073.

[30] E. de Azambuja *et al.*, "A pooled analysis of the cardiac events in the trastuzumab adjuvant trials.," *Breast cancer research and treatment*, vol. 179, no. 1, pp. 161–171, Jan. 2020, doi: 10.1007/s10549-019-05453-z.

[31] M. Cikes and S. D. Solomon, "Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure.," *European heart journal*, vol. 37, no. 21, pp. 1642–1650, Jun. 2016, doi: 10.1093/eurheartj/ehv510.

[32] P. L. M. Kerkhof, P. M. van de Ven, B. Yoo, R. A. Peace, G. R. Heyndrickx, and N. Handly, "Ejection fraction as related to basic components in the left and right ventricular volume domains.," *International journal of cardiology*, vol. 255, pp. 105–110, Mar. 2018, doi: 10.1016/j.ijcard.2017.09.019.

[33] T.-H. Park *et al.*, "Impact of myocardial structure and function postinfarction on diastolic strain measurements: implications for assessment of myocardial viability.," *American journal of physiology. Heart and circulatory physiology*, vol. 290, no. 2, pp. H724-31, Feb. 2006, doi: 10.1152/ajpheart.00714.2005.

[34] J. J. Park, J.-B. Park, J.-H. Park, and G.-Y. Cho, "Global Longitudinal Strain to Predict Mortality in Patients With Acute Heart Failure.," *Journal of the American College of Cardiology*, vol. 71, no. 18, pp. 1947–1957, May 2018, doi: 10.1016/j.jacc.2018.02.064.

[35] T. Stanton, R. Leano, and T. H. Marwick, "Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring.," *Circulation. Cardiovascular imaging*, vol. 2, no. 5, pp. 356–364, Sep. 2009, doi: 10.1161/CIRCIMAGING.109.862334.

[36] P. Thavendiranathan *et al.*, "Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy.," *Journal of the American College of Cardiology*, vol. 77, no. 4, pp. 392–401, Feb. 2021, doi: 10.1016/j.jacc.2020.11.020.

[37] A. B. HILL, "THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION?," *Proceedings of the Royal Society of Medicine*, vol. 58, no. 5, pp. 295–300, May 1965.

[38] K. M. Fedak, A. Bernal, Z. A. Capshaw, and S. Gross, "Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology.," *Emerging themes in epidemiology*, vol. 12, p. 14, 2015, doi: 10.1186/s12982-015-0037-4.

[39] W. R. Naaktgeboren *et al.*, "Efficacy of Physical Exercise to Offset Anthracycline-Induced Cardiotoxicity: A Systematic Review and Meta-Analysis of Clinical and Preclinical Studies.," *Journal of the American Heart Association*, vol. 10, no. 17, p. e021580, Sep. 2021, doi: 10.1161/JAHA.121.021580.

[40] W. J. Tucker *et al.*, "Meta-analysis of Exercise Training on Left Ventricular Ejection Fraction in Heart Failure with Reduced Ejection Fraction: A 10-year Update.," *Progress in cardiovascular diseases*, vol. 62, no. 2, pp. 163–171, 2019, doi: 10.1016/j.pcad.2018.08.006.

[41] R. Martland, V. Mondelli, F. Gaughran, and B. Stubbs, "Can high-intensity interval training improve physical and mental health outcomes? A meta-review of 33 systematic reviews across the lifespan.," *Journal of sports sciences*, vol. 38, no. 4, pp. 430–469, Feb. 2020, doi: 10.1080/02640414.2019.1706829.

[42] A. A. Kirkham *et al.*, "The effect of an aerobic exercise bout 24 h prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: A," *Breast Cancer Res Treat*, vol. 167, no. 3, pp. 719–729, 2018, doi: 10.1007/s10549-017-4554-4.

[43] A. A. Kirkham *et al.*, "Protective effects of acute exercise prior to doxorubicin on cardiac function of breast cancer patients: A proof-of-concept RCT," *Int J Cardiol*, vol. 245, pp. 263–270, 2017, doi: 10.1016/j.ijcard.2017.07.037.

[44] Z. Ma, "Effect of anthracycline combined with aerobic exercise on the treatment of breast cancer.," *Pak J Pharm Sci*, vol. 31, no. 3(Special), pp. 1125–1129, May 2018.

[45] J. Ansund *et al.*, "High intensity exercise during breast cancer chemotherapy - effects on long-term myocardial damage and physical capacity - data from the OptiTrain RCT.," *Cardio-oncology (London, England)*, vol. 7, no. 1, p. 7, Feb. 2021, doi: 10.1186/s40959-021-00091-1.

CHAPTER 5

Effect of physical exercise during adjuvant chemotherapy for breast cancer on long-term cardiovascular toxicity

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ABSTRACT

Background

Animal data suggest that exercise during chemotherapy is cardioprotective, but clinical evidence to support this is limited. This study evaluated the effect of exercise during chemotherapy for breast cancer on long-term cardiovascular toxicity.

Methods

This is a follow-up study of two previously performed randomized trials in breast cancer patients allocated to exercise during chemotherapy or non-exercise controls. Cardiac imaging parameters, including T1 mapping (native T1, extracellular volume fraction (ECV)), left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS), cardiorespiratory fitness, and physical activity levels, were acquired 8.5 years post-treatment.

Results

In total, 185 breast cancer survivors were included (mean age 58.9 ± 7.8 years), of whom 99% and 18% were treated with anthracyclines and trastuzumab, respectively. ECV and Native T1 were 25.3 ± 2.5% and 1026 ± 51ms in the control group, and 24.6 ± 2.8% and 1007 ± 44ms in the exercise group, respectively. LVEF was borderline normal in both groups, with an LVEF<50% prevalence of 22.4% (n=40/178) in all participants. Compared to control, native T1 was statistically significantly lower in the exercise group (β=-20.16, 95% confidence interval (CI): -35.35; -4.97). We found no effect of exercise on ECV (β=-0.69, 95%CI: -1.62; 0.25), LVEF (β=-1.36, 95%CI: -3.45; 0.73) or GLS (β=0.31, 95%CI: -0.76; 1.37). Higher self-reported physical activity levels during chemotherapy were significantly associated with better native T1 and ECV.

Conclusion

In long-term breast cancer survivors, exercise and being more physically active during chemotherapy were associated with better structural but not functional cardiac parameters. The high prevalence of cardiac dysfunction calls for additional research on cardioprotective measures, including alternative exercise regimens.

Keywords: breast cancer – cardiotoxicity – physical activity – cardiac MRI

Trial registration: International Clinical Trial Registry Platform, NTR 7247.

Abbreviations:

BC	breast cancer
CVD	cardiovascular disease
ECV	extracellular volume fraction
FU	follow-up
GLS	global longitudinal strain
IQR	interquartile range
LGE	late gadolinium enhancement
LV	left ventricle/ventricular
LVEF	left ventricular ejection fraction
PA	physical activity
PACES	Physical exercise during Adjuvant Chemotherapy Effectiveness Study
PACT	Physical Activity during Cancer Treatment
PASE	physical Activity Scale for the Elderly
RV	right ventricle/ventricular
SD	standard deviation
SQUASH	Short QUestionnaire to Assess Health-enhancing physical activity
UMCU	University Medical Center Utrecht

INTRODUCTION

In light of the growing number of breast cancer (BC) survivors[1], evaluating the long-term consequences of BC treatment is increasingly important. Cardiovascular disease (CVD) is among the most severe sequelae of BC treatment, given its association with increased morbidity and mortality[2].

Exercise during chemotherapy is an established strategy to enhance or maintain cardiorespiratory fitness (CRF) in BC patients undergoing treatment[3]. Also, there is emerging evidence that weekly exercise during anthracycline-based chemotherapy may prevent detrimental cardiac function and structure changes up to the first year after treatment[4-8]. This is supported by a biological rationale, with rodent studies almost unanimously reporting cardioprotective effects of exercise interventions started before, during, or after treatment with anthracyclines[9]. However, if and to what extent this translates into better long-term cardiac measurements in BC survivors is unknown.

The current study evaluated the effects of an aerobic and resistance exercise intervention during adjuvant chemotherapy for BC on mitigating long-term cardiotoxicity and impaired CRF compared to non-exercise controls. Given that anthracycline-based chemotherapy is considered to impact CVD risk significantly, we hypothesized that if exercise is capable of yielding cardioprotection during this relatively short but intense period, allocation to an exercise intervention during chemotherapy will translate into reduced long-term cardiovascular toxicity. In addition, we hypothesized that BC survivors who are more active years after treatment have better CRF.

METHODS

Study participants and design

This study (registered with ICTRP, NTR7247) is a long-term follow-up (FU) investigation of two previously performed prospective randomized controlled trials; the Physical Activity during Cancer Treatment (PACT, N=204) study and the Physical Exercise during Adjuvant Chemotherapy Effectiveness Study (PACES, N=230), both conducted between 2009-2013[10,11]. The PACT and PACES study included participants with non-metastatic breast cancer, free or serious comorbidities (e.g. cardiovascular disease) that would impede physical activity. These studies reported the positive effects of an exercise program

during adjuvant chemotherapy for non-metastasized breast cancer on various outcomes, including fatigue, exercise capacity, and symptom burden. In PACT, participants were randomized to either an 18-week, supervised moderate-to high-intensity aerobic and resistance exercise program or usual care. PACES was a three-armed trial, where participants were randomly allocated to a supervised moderate-to high-intensity aerobic and resistance exercise program (comparable to PACT's intervention), a home-based low-intensity program, or usual care. The design and timing of data collection are shown in Figure 1.

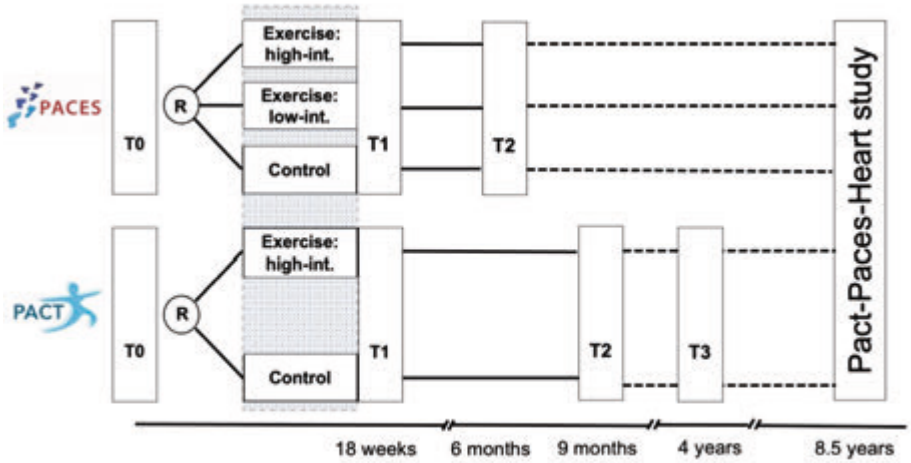

Figure 1. Original PACT and PACES study, and the follow-up Pact-Paces-Heart study.

PACES was a three-armed randomized trial comparing the effects of supervised, moderate-to high-intensity and home-based, low-intensity exercise to usual care. PACT was a two-arm randomized study, where the exercise arm was similar to PACES' moderate-to high-intensity program. For PACT, a previous questionnaire study was performed.

For the current study, all BC participants of the original PACT and PACES studies were, in principle, eligible. Exceptions were those who: (i) died during FU; (ii) were not considered eligible by their treating physician (e.g., too mentally burdensome or severe neuropathy); (iii) received chemotherapy, targeted therapy, or thoracic irradiation for recurrent or metastasized breast cancer or other malignancies after the completion of the original PACT and PACES; and (iv) those who dropped-out during the original PACT study (n=19) or actively declined invitations for future FU studies (n=11) at the time of the first FU study[12]. All participants provided written

informed consent, and the study was approved by the institutional review board of the University Medical Center Utrecht (UMCU), Utrecht, The Netherlands.

Study procedures

All PACT and PACES participants were screened for eligibility by their treating physician. If participants had died during FU, the cause of death (defined as cancer, CVD, or other) was obtained. Eligible women were invited by their treating physician (or the study team for PACT participants who, during the first FU study, consented to be approached for future studies) for a one-time study visit at the UMCU. During the study visit, participants underwent a cardiac MRI including T1 mapping, echocardiography, a cardiopulmonary exercise test, a venous blood test, and an interview (Table 1; detailed information on study outcomes is provided in Supplementary file B). In addition, participants were asked to complete online questionnaires on patient-reported outcomes (data not included in the current manuscript).

Statistical analyses

Intention-to-treat linear or logistic regression models were used with treatment allocation (control versus exercise (i.e. the PACT and PACES moderate-to high-intensity exercise groups) as independent variables and cardiovascular toxicity parameters as dependent variables. For the logistic models, we used the following cut-offs; LVEF <50%/≥50%[13], GLS >-18%/≤-18%[14], native T1 ≥1020ms/<1020 and ECV ≥28%/<28%. The latter two are based on institutional reference values (UMCU). These analyses were repeated with self-reported PA during chemotherapy as the main independent variable, regardless of treatment allocation. This was defined as the change in the sum score of self-reported PA between the end of chemotherapy (T1) and (T0), expressed as a Z-score, given that the two studies used different questionnaires [10,11]. The potential non-linearity of this relationship was evaluated using restricted cubic splines models.

All models were adjusted for study (PACT vs. PACES), age, thoracic radiotherapy, cumulative doxorubicin (equivalent) dosage, and treatment with or without trastuzumab. Also, the influence of cardiovascular risk factors was explored by adding a composite score to the adjusted model. Cardiovascular risk factors were defined as follows: hypertension as having a blood pressure ≥140 mm Hg (systolic) and ≥90 mm Hg 90 (diastolic), being treated with antihypertensive medication; hypercholesterolemia as having a to total cholesterol ≥6.5 mmol/L and LDL≥

3.5 mmol/L or being treated with lipid-lowering drugs; diabetes mellitus as having a HbA1c>42 mmol/L, or being treated with glucose-lowering medication; obesity as having a BMI >30 kg/m^2; and smoking as being a current smoker. The interaction between treatment allocation and doxorubicin (equivalent) dosage was tested by adding an interaction term to the fully adjusted model. In case of evidence of interaction (p-value<0.10), subsequent stratified analyses were provided for the following doxorubicin (equivalent) dosage strata; ≤210 mg/m^2, 210-300 mg/m^2, and ≥300 mg/m^2).

Table 1. Outcomes measures of the Pact-Paces-Heart study.

Measure instrument	Assessment	Parameter(s)
Cardiac MRI	Cardiac structure	T1 mapping: Native T1 and ECV, and LGE
	Cardiac function	left-ventricular EF, right-ventricular EF
Echocardiography	Cardiac deformation	global longitudinal strain
	Diastolic function	Diastolic function
Cardiopulmonary exercise test	Cardiorespiratory fitness	VO_2peak
Venous blood sample	Hematocrit, CV risk profile	Hematocrit, HbA1C, blood lipids, renal function.
SQUASH questionnaire	Self-reported physical activity	Moderate-to high-intensity leisure and sport physical
Face-to-face interview	Physical activity in the distant past	MET-hours/week

Abbreviations:
CV = cardiovascular, ECV = extracellular volume, LGE = late gadolinium enhancement, MET = metabolic equivalent task, SQUASH = Short Questionnaire to assess Health-enhancing physical activity.

As sensitivity analyses, we explored whether adding data from participants in the low-intensity PACES program to the exercise group changed the outcomes of the intention-to-treat analyses. Due to low numbers in the low-intensity group, we did not perform separate analyses. Also, for those outcomes expressed as proportions (i.e., LVEF, GLS, and ECV), we reanalyzed the data using beta-regression models instead of linear models, assuming that a beta-distribution might better fit the outcomes[15]. For the analysis of CRF, analyses were repeated without excluding data of participants with submaximal tests (n=22). Last, we repeated the analyses using multiple imputations (n=50) by fully conditional specification for ECV and GLS since missing data on these parameters exceeded

10% (11.6% and 17.15%, respectively)[19]. All analyses were performed with R (version 4.0.3.) and Rstudio software (version 1.3.1093).

RESULTS

The mean interval between initial cancer diagnosis and completion of FU assessment was 8.5±1.1 years. Of the original PACT (N=204) and PACES (N=230) participants, 304 participants were invited for the FU study, of whom 185 women (n=185/304; 61%) were included. Ineligible participants were generally evenly distributed across study arms, and no cardiac-related deaths were recorded. Four participants only completed the online questionnaires. Thus 181 patients were included in the current analyses (Figure 2).

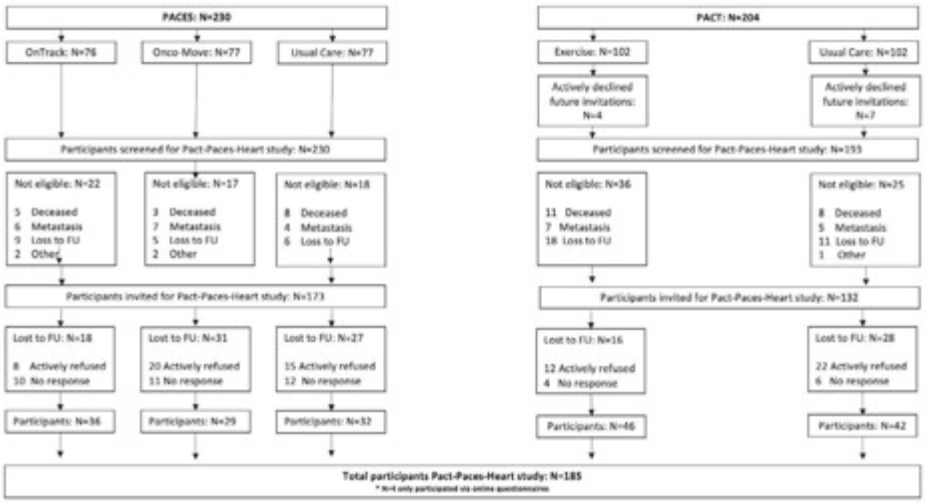

Figure 2. Flowchart of participants in the Pact-Paces-Heart study. Participants of PACT and PACES are combined in the follow-up Pact-Paces-Heart study.

Participants were comparable to non-participants for most of the original PACT and PACES baseline characteristics (Supplemental Tables 1a and 1b), except that participants had a lower BMI, higher CRF before chemotherapy, and a higher exercise intervention attendance rate.

Of the 181 participants, 80 had been allocated to a moderate-to high-intensity exercise program, 29 to the low-intensity exercise program, and 72 received care as usual. These groups had comparable characteristics during the FU study visit (Table 2). All participants, except one, were treated with anthracyclines. The low-intensity exercise group had higher cumulative dosages (292 [240-332] mg/m^2) and more often received trastuzumab (20.7%) compared to the moderate-to high-intensity and control group (235 [210-300] mg/m^2 and 240 [210-300] mg/m^2, and 16.7% and 11.3%, respectively). Cardiac comorbidities were documented for 23 participants, with a history of ischemic heart disease being the most common diagnosis.

Table 2. Characteristics of the Pact-Paces-Heart study per study group at the time of study visit.
Presented as mean ± SD, median [interquartile range], or number (percentages).

	Control N=72	**Mod.-to high-int. ET N=80**	**Low-int. ET N=29**
Age, years	58.5 ± 7.5	59.1 ± 7.2	59.5 ± 10.2
Original study			
PACT, %	40 (55.6)	46 (57.5)	0 (0)
PACES, %	32 (44.4)	34 (42.5)	29 (100)
Follow-up time, years	8.6 ± 1.1	8.4 ± 1.2	8.9 ± 0.9
Menopausal status, %			
Premenopausal	4 (5.6)	6 (7.5)	2 (6.9)
Postmenopausal	67 (93.0)	73 (91.3)	27 (93.1)
Unknown	1 (1.4)	1 (1.2)	0 (0.0)
Receptor status			
Triple-negative	9 (12.5)	16 (20.0)	4 (13.8)
ER/PR+, HER2+	10 (13.9)	13 (16.2)	6 (20.7)
ER/PR-, HER2+	3 (4.2)	8 (10.0)	1 (3.4)
ER/PR+, HER2-	50 (69.4)	43 (53.8)	18 (62.1)
Radiotherapy, %			
No RT	18 (25.0)	20 (25.0)	9 (31.0)
Left-sided	27 (37.5)	33 (41.2)	12 (41.4)
Right-sided	27 (37.5)	27 (33.8)	8 (27.6)

Table 2. (Continued)

	Control N=72	Mod.-to high-int. ET N=80	Low-int. ET N=29
Anthracyclines, %*			
No anthracyclines	0 (0)	1 (1.3)	0 (0)
Doxorubicin	41 (56.9)	39 (48.8)	22 (75.9)
Epirubicin	30 (41.7)	39 (48.8)	6 (20.7)
Unknown	2 (2.8)	0 (0)	1 (3.4)
Cumul. dox. (equi.) dose, mg/m‡	240 [210-300]	237 [210-300]	293 [241-352]
Trastuzumab, %	8 (11.1)	13 (16.2)	6 (20.7)
Medication use, %			
Cardiovascular	12 (16.7)	18 (22.5)	6 (20.7)
Anti-diabetic	3 (4.2)	1 (1.2)	1 (3.4)
Statins	6 (8.3)	5 (6.2)	3 (10.3)
Hormonal replacement	16 (22.2)	8 (10.0)	4 (13.8)
Others	31 (43.1)	23 (28.7)	4 (13.8)
Any comorbidity, %	31 (43.1)	28 (35.0)	8 (27.6)
Cardiovascular risk factors, %‡			
Hypertension	17 (23.6)	25 (31.2)	7 (24.1)
Hypercholesterolemia	19 (26.4)	34 (42.5)	8 (27.6)
Diabetes Mellitus	8 (11.1)	2 (2.5)	2 (6.9)
Obesity	10 (13.9)	14 (17.7)	2 (6.9)
Smoking, current	3 (4.2)	2 (2.5)	1 (3.4)
Cardiac comorbidities, %§			
Arrhythmias	5 (6.9)	3 (3.8)	0 (0.0)
Ischemic heart disease	2 (2.8)	2 (2.5)	3 (10.3)
Impaired EF / heart failure	1 (1.4)	4 (5.0)	0 (0.0)
Other	1 (1.4)	1 (1.2)	0 (0.0)
None	63 (87.5)	70 (87.4)	26 (89.7)

Table 2. (Continued)

	Control N=72	Mod.-to high-int. ET N=80	Low-int. ET N=29
Physical activity before diagnosis‖			
PACT, min/week	180.0 [60-365]	180.0 [110-270]	NA
PACES, sum score	64 [41-107]	80 [54-121]	79 [46-148]
Unknown	2 (2.8)	1 (1.2)	1 (3.4)

* Some patients have received both doxorubicin and epirubicin.

ǂ Calculated using Doxorubicin: Epirubicin ratio = 1:0.7

ǂ Cardiovascular risk factors are defined as follows:

- Hypertension = having a blood pressure higher than 140 mm Hg (systolic) and 90 mm Hg (diastolic) or being treated with antihypertensive medication.
- Hypercholesterolemia = having total cholesterol ≥6.5 mmol/L and LDL≥ 3.5 mmol/L or being treated with lipid-lowering drugs.
- Diabetes mellitus = HbA1c>42 mmol/L, or being treated with glucose-lowering medication.
- Obesity = having a BMI >30 kg/m^2
- Smoking = current smoker.

§ Only those requiring treatment. Four participants (in the control arm) already had documented cardiac comorbidities (arrhythmias) at baseline.

‖ The original PACT and PACES study used different questionnaires to assess physical activity before diagnosis; the SQUASH[48] and PASE[49], respectively. The SQUASH score indicates minutes per week of moderate-to high-intensity leisure and sports physical activity, defined as any activity corresponding with an equivalent metabolic task (MET) -value of 4 and higher. The PASE score combines information on occupation, leisure, and household activities and ranges from 0 to 793, where higher scores correspond with greater physical activity.

Abbreviations:

AC = anthracyclines, cumul. = cumulative, dox = doxorubicin, EF = ejection fraction, equi = equivalent, ET = exercise training, int.= intensity, min. = minutes, mod. = moderate, NA = not applicable, PACES = Physical exercise during Adjuvant Chemotherapy Effectiveness Study, PACT = Physical Activity during Cancer Treatment, RT = radiotherapy.

Cardiovascular outcomes

Cardiac imaging parameters and CRF are shown in Table 3.
For ECV, mean values were within normal ranges for most participants; 25.3±%2.5 in the control group, 24.6±%2.8 in the moderate-to high-intensity exercise group, and 25.5±%2.7 in the low-intensity exercise group. The proportion of survivors with abnormal values was 14.3% (N=9/63), 11.4% (N=8/70), and 22.2% (N=6/27), respectively. Mean native T1 was normal in the moderate-to high-intensity exercise group (1007±44 ms) but elevated in the control group (1026±51 ms) and the low-intensity exercise group (51±1029 ms).
Abnormal native T1 values were prevalent in 37.7% (N=29/77), 50% (N=35/70), and 53.6% (N=15/28), respectively. Late gadolinium enhancement (LGE) was present in approximately 25% of participants, almost all with mid-wall enhancement. We found borderline normal mean LVEF values in all three groups, with the lowest mean LVEF in the moderate-to high-intensity exercise group (53.0±7.8%). This group also had the highest proportion with an LVEF<50%: 27.8% (N=22/79), followed by 20.7% (N=6/29) in the low-intensity exercise group and 17.1% (N=12/70) in the control group. The prevalence of abnormal ECV and native T1 was similar between those with impaired and normal LVEF, although LGE was more common in those with impaired LVEF (Figure 3). For GLS, mean values were borderline normal in all groups. However, abnormal values were common. Diastolic function was normal in nearly half of the participants, with most diastolic dysfunction reported in the moderate-to high-intensity exercise group (N=15/80, 18.8%). CRF at FU was comparable across study arms.

Table 3. Cardiac outcomes per study group.
Presented as mean ± SD, median [interquartile range], or number (percentages).

Imaging modality	Parameter	Control N=72	Mod.-to high-int. ET N=80	Low-int. ET N=29
Cardiac MRI*				
	Extracellular volume fraction, %†	25.3 ± 2.5	24.6 ± 2.8	25.5 ± 2.7
	ECV>28%‡	9 (14.3)	8 (11.4)	6 (22.2)
	Native T1, ms§	1026± 51	1007 ± 44	1029 ± 51
	Native T1>1020ms‡	35 (50.0)	29 (37.7)	15 (53.6)
	Late gadolinium enhancement, %‖			
	Mid-wall	14 (21.5)	21 (27.3)	5 (17.9)
	Sub-endocardial	0 (0.0)	1 (1.3)	0 (0.0)
	Other	0 (0.0)	1 (1.3)	2 (7.2)
	None	51 (78.5)	54 (70.1)	21 (75.0)

Table 3. (Continued)

Imaging modality	Parameter	Control N=72	Mod.-to high-int. ET N=80	Low-int. ET N=29
	Left ventricular EF, %	54.6 ± 4.9	53.0 ± 7.8	54.2 ± 7.3
	LV EF<50%	12 (17.1)	22 (27.8)	6 (20.7)
	Left ventricular EDV, ml/m2	80.9 ± 11.6	82.7 ± 16.9	85.6 ± 15.7
	Left ventricular ESV, ml/m^2	37.6 ± 8.9	39.8 ± 13.9	39.6 ± 12.6
	Right ventricular EF, %	57.2 ± 4.8	55.1 ± 6.6	57.4 ± 5.3
	RV EF<50%	5 (7.1)	13 (16.5)	2 (6.9)
Echocardiography				
	Global long. strain, %#	-18.7 ± 3.0	-18.3 ± 2.9	-17.6 ± 2.4
	GLS>-18%	23 (36.5)	26 (41.9)	15 (60.0)
	Diastolic function			
	Normal	34 (47.2)	38 (47.5)	13 (44.8)
	Intermediate	33 (45.8)	27 (33.8)	11 (37.9)
	Impaired	5 (6.9)	15 (18.8)	5 (17.2)
Cardiopulmonary exercise test^				
	VO_2peak, ml/kg/min	25.5 ± 5.8	24.9 ± 6.5	24.0 ± 7.1

* All MRI information in n=3 (1.7%) for the following reasons: non-MR compatible cardiac device (n=1) and severe claustrophobia (n=2).
ǂ Missing in n=21 (11.6%) for the following reasons: no cardiac MRI performed (n=3), not possible to administrate IV contrast (n=8), technical issue (n=6), poor quality (n=3), no ECG gating possible due to atrial fibrillation (n=1).
ǂ Institutional reference values (UMCU)
§ Missing in n=6 (3.3%) for the following reasons: no cardiac MRI performed (n=3), poor quality (n=2), no ECG gating possible due to atrial fibrillation (n=1).
|| Missing in n=11 (6.7%) for the following reasons: no cardiac MRI performed (n=3), not possible to administrate IV contrast (n=8).
Missing in n=31 (17.1%) for the following reason: imaging quality too poor for strain analysis (n=30) and atrial fibrillation (n=1).
^ Missing in n=30 (16.6%) for the following reasons: submaximal exercise test (n=22), logistic constraints (n=3), newly-diagnosed atrial fibrillation (n=1), severe hypertension (n=1), newly-diagnosed severe left-ventricular dysfunction on cardiac imaging (n=1), unwillingness to perform the test (n=1), hamstring injury (n=1).
Abbreviations:
ECV = extracellular volume, EF = ejection fraction, EDV = end-diastolic, ET=exercise training, ESV = end-systolic, GLS = global longitudinal strain, int. = intensity, LV = left ventricle/ventricular, mod. = moderate, RV = right ventricle/ventricular.

Figure 3. Relationship between structural and functional cardiac parameters using cardiac MRI. In (A) and (B), the relationship between ECV and native T1 and LVEF is depicted, respectively. The grey lines indicate the thresholds used for cut-off. Figure 2C describes the presence and absence of LGE in patients with normal and impaired LVEF. Each woman symbol represents 5 participants.

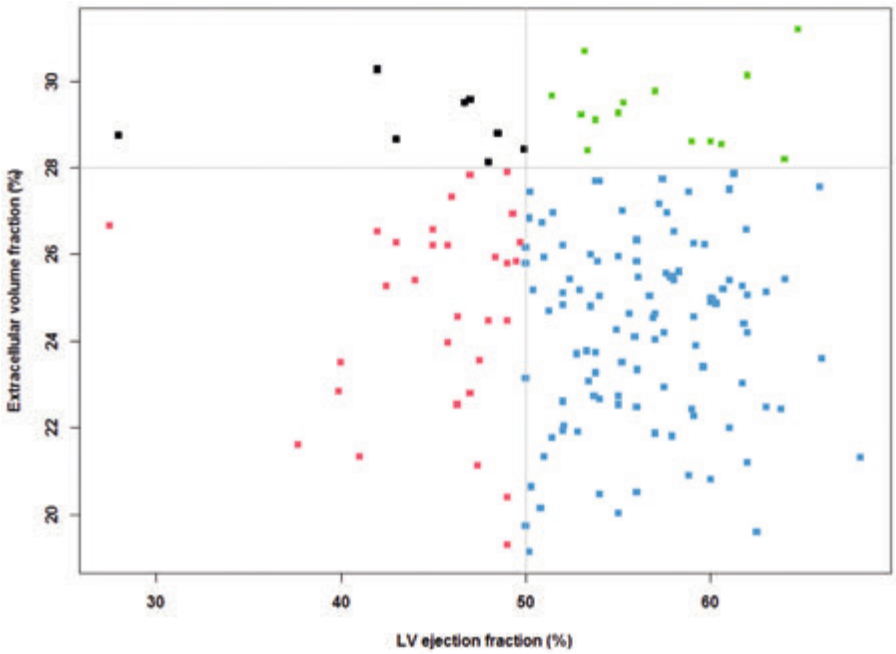

Figure 3a.

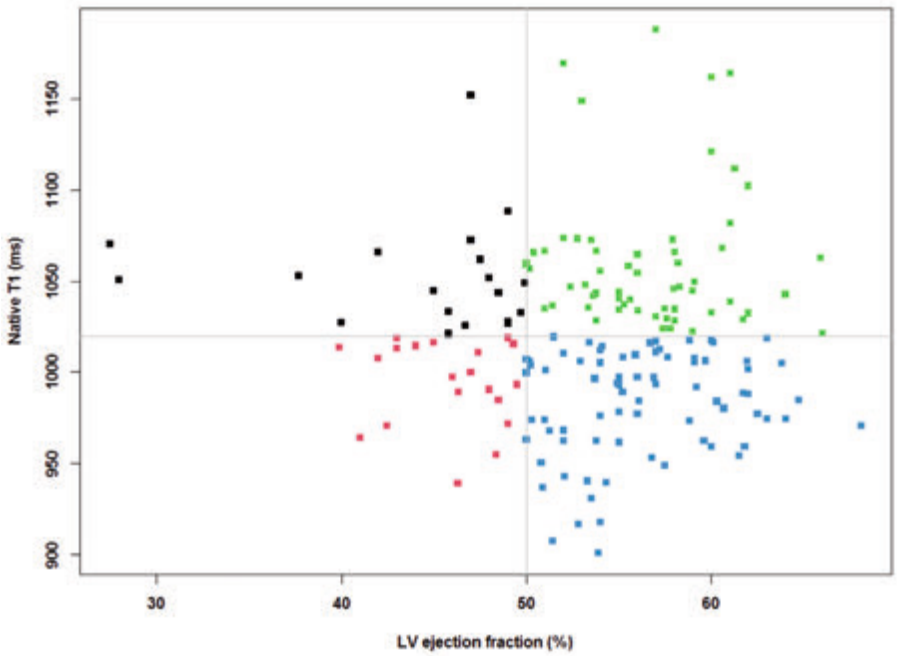

Figure 3b.

Figure 3c.

Abbreviations:
CT: chemotherapy, ECV: extracellular volume fraction, GLS: global longitudinal strain, LVEF: left ventricular ejection fraction, PACES: Physical exercise during Adjuvant Chemotherapy Effectiveness Study, PACT: Physical Activity during Cancer Treatment, SD: standard deviation.

Table 4. Effect of participation in a moderate-to high-intensity exercise program during chemotherapy on cardiac outcomes based on an intention-to-treat analysis.

Imaging modality	Parameter	Regression model	Unadjusted estimate (95%CI)	Partially adjusted* estimate (95%CI)	Fully adjusted† estimate (95%CI)
Cardiac MRI					
	ECV	Linear	-0.79 (-1.69, 0.11)	-0.80 (-1.71, 0.11)	-0.69 (-1.62, 0.25)
	ECV (>28%)	logistic	0.77 (0.27, 2.16)	0.71 (0.23, 2.13)	0.76 (0.24, 2.34)
	Native T1	Linear	**-19.89 (-35.12, -4.66)**	**-20.58 (-35.41, -5.75)**	**-20.16(-35.35, -4.97)**
	Native T1 (>1020 ms)	Logistic	0.60 (0.31, 1.16)	0.56 (0.28, 1.10)	0.53 (0.26, 1.07)
	LVEF	Linear	-1.67 (-3.79, 0.45)	-1.51 (-3.61, 0.60)	-1.36 (-3.45, 0.73)
	LVEF (<50%)	logistic	1.87 (0.86, 4.23)	1.85 (0.82, 4.34)	1.67 (0.72, 3.99)
Echocardiography					
	GLS	Linear	0.40 (-0.63, 1.42)	0.37 (-0.68, 1.42)	0.31 (-0.76, 1.37)
	GLS (>-18%)	Logistic	1.26 (0.61, 2.59)	1.30 (0.61, 2.77)	1.34 (0.63, 2.88)
Cardiopulmonary exercise testing					
	VO_2peak	Linear	-0.68 (-2.83, 1.47)	-0.13 (-2.08, 1.82)	0.21 (-1.69, 2.10)

* Partially adjusted includes adjustments for age, radiotherapy (none versus left-sided or right-sided), cumulative doxorubicin equivalent dosage, trastuzumab treatment, and study (PACT vs. PACES).

† Fully adjusted is the partially adjusted model with extra adjustment for cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity, and being a current smoker; none versus one or >1).

Abbreviations:

CI = confidence interval, ECV = extracellular volume, CV = cardiovascular, GLS = global longitudinal strain, LVEF = left ventricular ejection fraction.

Effect of exercise during chemotherapy on long-term cardiovascular toxicity

We did not find a significant effect of moderate-to high-intensity exercise program on ECV (β=-0.69, 95%CI: -1.62;0.25) nor on abnormal ECV (OR=0.76, 95%CI: 0.24;2.34, Table 4). Native T1 was statistically significantly lower in the exercise group compared to controls (β=95% ,20.16-CI: -35.35;-4.97). The odds of having an abnormal native T1 appeared lower in the exercise group (OR 0.53, 95%CI: 0.26;1.07). We found no benefit of exercise for LVEF or GLS (β=-1.36, 95%CI: -3.45;0.73 and β=0.31, 95%CI: -0.76;1.37), nor on the likelihood of having an abnormal LVEF or GLS (OR=1.67, 95%CI: 0.72;3.99); OR=1.34, 95%CI: 0.63;2.88), respectively. Also, we found no significant effect of exercise on VO_{2peak} (β=0.21, 95%CI: -1.69;2.10). Additional correction for the presence of CV risk factors yielded comparable results. We found an interaction between doxorubicin equivalent dosage and exercise only for ECV (p=0.05). Subsequent stratified analyses did not generate a clear dose-response relationship, although the largest effect was observed among those treated with higher dosages (first stratum: β=-0.56, 95%CI: -2.09;0.98), second stratum: β=-0.42, 95%CI: -2.41;1.57 and third stratum: β=-0.76, 95%CI: -2.15;0.64). The sensitivity analyses, where data of the participants in the low-intensity were combined with those in the moderate-to high-intensity exercise group and with multiple imputation for ECV and GLS, did not change the overall conclusions (Supplementary Table 2 and Supplementary Table 3 respectively). The sensitivity analysis with beta-regression models (for ECV, GLS, and LVEF) and those without exclusion of submaximal CPETs yielded similar results to those generated with the former analyses (data not shown)

Self-reported physical activity during chemotherapy and long-term cardiovascular toxicity

The associations between the change of PA during chemotherapy (i.e., independent of original treatment allocation) and long-term cardiovascular parameters are presented in Table 5. An increase in PA was associated with better ECV (β=-0.48, 95%CI: -0.95;-0.01) and native T1 values (β=-8.54, 95%CI: -16.47;-0.16). Higher PA levels were also non-statistically significantly associated with better other cardiac imaging parameters and CRF.
No evidence for non-linearity was found (p>0.10) (Table 5).

Table 5. Association between change in self-reported physical activity during chemotherapy and cardiac outcomes.

Imaging modality	Parameter	Regression model	Unadjusted estimate (95%CI)	Partially adjusted* estimate (95%CI)	Fully adjusted‡ estimate (95%CI)
Cardiac MRI					
	ECV	Linear	-0.39 (-0.83, 0.05)	**-0.47 (-0.93, -0.01)**	-0.48 (-0.95, -0.01)
	ECV (>28%)	logistic	0.73 (0.44, 1.20)	0.66 (0.37, 1.15)	0.66 (0.36, 1.18)
	Native T1	Linear	-6.92 (-14.72, 0.89)	**-8.78 (-16.44, -1.13)**	**-8.54 (-16.47, -0.61)**
	Native T1 (>1020 ms)	Logistic	0.84 (0.60, 1.15)	0.78 (0.55, 1.10)	0.77 (0.54, 1.10)
	LVEF	Linear	-0.25 (-1.27, 0.77)	-0.13 (-1.18, 0.92)	0.10 (-0.97, 1.16)
	LVEF (<50%)	logistic	0.97 (0.67, 1.43)	0.97 (0.66, 1.44)	0.87 (0.57, 1.32)
Echocardiography					
	GLS	Linear	-0.04 (-0.52, 0.44)	-0.05 (-0.55, 0.45)	-0.07 (-0.59, 0.44)
	GLS (>-18%)	Logistic	0.85 (0.60, 1.19)	0.86 (0.60, 1.21)	0.88 (0.61, 1.26)
Cardiopulmonary exercise testing					
	VO_2peak	Linear	0.44 (-0.66, 1.53)	0.10 (-0.90, 1.09)	0.08 (-0.94, 1.09)

* Partially adjusted includes adjustments for age, radiotherapy (none versus left-sided or right-sided), cumulative doxorubicin equivalent dosage, trastuzumab treatment, and study (PACT vs. PACES).

‡ Fully adjusted is the partially adjusted model with extra adjustment for cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity, and being a current smoker; none versus 1 or >1).

Abbreviations:

CI = confidence interval, ECV = extracellular volume, GLS = global longitudinal strain, LVEF = left ventricular ejection fraction.

Physical activity years after treatment and cardiovascular toxicity

Levels of moderate-to high-intensity leisure and sports PA at FU were comparable for the control and the moderate-to high-intensity exercise group (155 [60-360] min/week and 150 [60-368] min/week, respectively) and higher in the low-intensity exercise group (240 [30-360] min/week). The MET-hours/week participants engaged in over the last years were comparable across the study arms (Supplementary Table 4). We did not observe a statistically significant association between PA patterns at FU and cardiac imaging parameters, but higher PA levels at FU were associated with higher VO_{2peak} values (β=0.70, 95%CI: 0.42;0.98, Supplementary Table 5).

DISCUSSION

This analysis of a large cohort of BC survivors indicates that exercise during chemotherapy improved native T1 values but not ECV or functional cardiac imaging parameters after a mean FU time of 8.5 years. Higher self-reported PA levels during chemotherapy, independent of the exercise program, were associated with better ECV and native T1 values. At FU, higher PA levels were associated with better CRF but not with cardiac imaging parameters. We found structural and functional cardiac abnormalities in a relatively high proportion of the BC survivors in our study.

Many rodent studies support the hypothesis that exercise during anthracycline-based chemotherapy yields short-term cardioprotection via, among other pathways, reducing the intracardial accumulation of anthracyclines[9]. Exercise also has salutary effects on cardiac function in non-cancer populations[20]. However, clinical trials in cancer patients have yielded mixed results[4-8]. Our study provides the first-long term results on the effect of exercise on long-term cardiovascular toxicity. We observed an effect of exercise and higher levels of PA on native T1 (and on ECV in the analyses with self-reported PA) but not on functional cardiac parameters. Native T1 and ECV are relatively new parameters and are proposed as non-invasive surrogate markers of cardiac tissue composition[17]. Native T1 is a composite signal of all cardiac T1 values, including intra- and extracellular components. Since the myocardial volume primarily consists of cardiomyocytes, these cells form the bulk of the native T1 signal. ECV, by definition, represents the proportion of extracellular volume, and it is assumed that ECV changes are primarily driven by interstitial fibrosis[17]. These parameters have received increasing attention based on the assumption

that tissue damage precedes functional decline. Indeed, most[18-21]but not all[22] studies have described elevated native T1 and ECV values in the context of preserved LVEF in adult cancer survivors treated with anthracyclines. In our study, we observed that native T1 abnormalities were prevalent, while ECV values were within normal ranges for most participants, suggesting that other mechanisms than fibrosis play a role. High native T1 values are reported in the context of (chronic) cardiac inflammation[17], while systemic anti-inflammatory effects are reported following exercise[23. Whether this could explain the finding of lower native T1 in the exercise group is worthy of future research. Of clinical importance, both native T1 and ECV have been described as independent prognostic factors for all-cause mortality or heart failure hospitalization[24,25]. Native T1 was even superior to LVEF in predicting all-cause mortality and major adverse cardiocerebrovascular events[33]. This suggests that exercise during chemotherapy could be useful to offset the increased CVD risk in BC survivors. However, we observed a non-significant yet opposite trend on the functional cardiac parameters (i.e., less favorable LVEF and GLS in the exercise group). Although we do not believe that this indicates a harmful effect of exercise on cardiac functioning, more high-quality, randomized studies that are prospectively designed to analyze cardiac outcomes during and after chemotherapy are needed to investigate the cardioprotective effects of exercise more robustly.

There is a large body of evidence supporting the positive effects of exercise on enhancing CRF and PA in the timeframe surrounding BC treatment[3]. A recent randomized study described that a 24-week exercise intervention performed during chemotherapy was more effective in terms of less CRF decline post-chemotherapy compared to participants that participated in the exercise intervention after the completion of chemotherapy [26]. A recent study found that a 24-week exercise intervention, performed both during or after chemotherapy, was associated with less decrease in CRF compared to controls, with larger effects in the group that exercised during chemotherapy [27].However, less is known about the effectiveness of exercise interventions in promoting CRF and PA years after treatment. A two-year FU study found, comparable to our results, no (significant) effect of exercise on CRF or PA[28]. This contrasts with two other studies, including the former PACT FU study, which reported higher PA levels in BC survivors who exercised during chemotherapy after a FU of 4 and 5 years[12,29]. Given that PA levels years after treatment were associated with better CRF, and considering the importance of CRF in terms of symptom burden and survival after cancer[30], our results provide additional evidence

that BC survivors could benefit from efforts to maintain their PA levels during (long-term) survivorship.

Strengths and limitations

Strengths of our study include the in-depth cardiac assessment, including a multiparametric cardiac MRI scan, in combination with CRF and PA measurements, in a large sample after an appropriate FU period of, on average, 8.5 years post-treatment. The first potential study limitation is the possibility of selective response. Inherent to our study design, we cannot rule out that participation was related to (not) having CVD. Also, we observed a lower BMI, higher CRF before chemotherapy and a higher attendance rate among participants, compared to non-participants. This could have resulted in a lower prevalence of cardiac abnormalities among our relatively fit and healthy subset of participant, which could have limited our ability to study an effect of exercise on CVD. However, given that participation rates were similar across the trial arms with no cardiac deaths reported during FU and that some of our primary outcome parameters (i.e., ECV and GLS) are related to subclinical (asymptomatic) CVD, a selective response seems less likely. A second limitation is that no pre-treatment cardiac measurements were available. Hence, we could not establish baseline comparability between groups for these measures nor correct for any relevant baseline differences in our analyses. Third, GLS was missing for 31 participants (17.1%). This occurred more often in patients with left-sided than right-sided breast cancer (58.1% versus 49.3%) and with higher BMI (28.2 ±4.4 versus 25.3 ±4.0 kg/m2). This might have underestimated the prevalence of GLS abnormalities but is unlikely to influence the analysis of exercise effects. Multiple imputation analyses support the latter. Last, participants, relative to non-participants, had higher adherence rates, which might limit the generalizability of our results to the whole BC population.

Future directions

We found an LVEF<50% prevalence in almost a quarter of our study population after a mean FU of 8.5 years, which is higher than described in a former study among anthracycline-treated patients[31]. This is surprising, given our, apart from having BC, healthy sample at diagnosis. The clinical significance of this finding warrants further (longitudinal) exploration. Also, preclinical studies have used exercise interventions with volumes and intensities that would not be feasible in cancer patients undergoing treatment[9], and a recent meta-analysis

observed only a positive effect of exercise on LVEF when limiting the analyses to studies with ≥36 exercise sessions[46]. Thus, future studies considering different exercise interventions or exercise interventions combined with other approaches (pharmacological adjuncts, dietary restrictions [32]) may be needed to offset long-term cardiotoxicity.

CONCLUSION

A supervised moderate-to-high intensity aerobic and resistance exercise intervention during chemotherapy improved native T1, but not ECV or functional cardiac imaging parameters, in long-term BC survivors. Self-reported increase in PA during chemotherapy was associated with better T1 mapping indices. Higher PA levels were associated with better CRF years after treatment but not with cardiac imaging parameters. The high prevalence of cardiac abnormalities calls for more research on cardioprotective measures, including alternative exercise regimens or pharmacological adjuncts, to offset the increased risk of cardiac dysfunction in BC survivors undergoing chemotherapy.

REFERENCES

[1] K. D. Miller *et al.*, "Cancer treatment and survivorship statistics, 2016.," *CA Cancer J Clin*, vol. 66, no. 4, pp. 271–289, Jul. 2016, doi: 10.3322/caac.21349.

[2] H. Abdel-Qadir *et al.*, "A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer.," *JAMA Cardiol*, vol. 2, no. 1, pp. 88–93, Jan. 2017, doi: 10.1001/jamacardio.2016.3841.

[3] J. A. Ligibel *et al.*, "Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline.," *J Clin Oncol*, vol. 40, no. 22, pp. 2491–2507, Aug. 2022, doi: 10.1200/JCO.22.00687.

[4] E. J. Howden *et al.*, "Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients.," *Eur J Prev Cardiol*, vol. 26, no. 3, pp. 305–315, Feb. 2019, doi: 10.1177/2047487318811181.

[5] Z. Ma, "Effect of anthracycline combined with aerobic exercise on the treatment of breast cancer.," *Pak J Pharm Sci*, vol. 31, no. 3(Special), pp. 1125–1129, May 2018.

[6] W.-P. Chung *et al.*, "Real-time exercise reduces impaired cardiac function in breast cancer patients undergoing chemotherapy: A randomized controlled trial.," *Ann Phys Rehabil Med*, vol. 65, no. 2, p. 101485, Mar. 2022, doi: 10.1016/j.rehab.2021.101485.

[7] J. Ansund *et al.*, "High intensity exercise during breast cancer chemotherapy - effects on long-term myocardial damage and physical capacity - data from the OptiTrain RCT.," *Cardiooncology*, vol. 7, no. 1, p. 7, Feb. 2021, doi: 10.1186/s40959-021-00091-1.

[8] A. A. Kirkham *et al.*, "Exercise training affects hemodynamics not cardiac function during anthracycline-based chemotherapy.," *Breast Cancer Res Treat*, vol. 184, no. 1, pp. 75–85, Nov. 2020, doi: 10.1007/s10549-020-05824-x.

[9] W. R. Naaktgeboren *et al.*, "Efficacy of Physical Exercise to Offset Anthracycline-Induced Cardiotoxicity: A Systematic Review and Meta-Analysis of Clinical and Preclinical Studies.," *J Am Heart Assoc*, vol. 10, no. 17, p. e021580, Sep. 2021, doi: 10.1161/JAHA.121.021580.

[10] N. Travier *et al.*, "Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial.," *BMC Med*, vol. 13, p. 121, Jun. 2015, doi: 10.1186/s12916-015-0362-z.

[11] H. van Waart *et al.*, "Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial.," *J Clin Oncol*, vol. 33, no. 17, pp. 1918–1927, Jun. 2015, doi: 10.1200/JCO.2014.59.1081.

[12] L. Witlox *et al.*, "Four-year effects of exercise on fatigue and physical activity in patients with cancer.," *BMC Med*, vol. 16, no. 1, p. 86, Jun. 2018, doi: 10.1186/s12916-018-1075-x.

[13] J. L. Zamorano *et al.*, "2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (E," *Eur Heart J*, vol. 37, no. 36, pp. 2768–2801, Sep. 2016, doi: 10.1093/eurheartj/ehw211.

[14] E. K. Oikonomou *et al.*, "Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis.," *JAMA Cardiol*, vol. 4, no. 10, pp. 1007–1018, Oct. 2019, doi: 10.1001/jamacardio.2019.2952.

[15] F. Cribari-Neto and A. Zeileis, "Beta Regression in R," *J Stat Softw*, vol. 34, no. 2, pp. 1–24, 2010, doi: 10.18637/jss.v034.i02.

[16] W. J. Tucker *et al.*, "Meta-analysis of Exercise Training on Left Ventricular Ejection Fraction in Heart Failure with Reduced Ejection Fraction: A 10-year Update.," *Prog Cardiovasc Dis*, vol. 62, no. 2, pp. 163–171, 2019, doi: 10.1016/j.pcad.2018.08.006.

[17] D. R. Messroghli *et al.*, "Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imag," *J Cardiovasc Magn Reson*, vol. 19, no. 1, p. 75, Oct. 2017, doi: 10.1186/s12968-017-0389-8.

[18] J. H. Jordan *et al.*, "Anthracycline-Associated T1 Mapping Characteristics Are Elevated Independent of the Presence of Cardiovascular Comorbidities in Cancer Survivors.," *Circ Cardiovasc Imaging*, vol. 9, no. 8, Aug. 2016, doi: 10.1161/CIRCIMAGING.115.004325.

[19] T. Ferreira de Souza *et al.*, "Anthracycline Therapy Is Associated With Cardiomyocyte Atrophy and Preclinical Manifestations of Heart Disease.," *JACC Cardiovasc Imaging*, vol. 11, no. 8, pp. 1045–1055, Aug. 2018, doi: 10.1016/j.jcmg.2018.05.012.

[20] I. Harries *et al.*, "Cardiovascular magnetic resonance characterisation of anthracycline cardiotoxicity in adults with normal left ventricular ejection fraction.," *Int J Cardiol*, vol. 343, pp. 180–186, Nov. 2021, doi: 10.1016/j.ijcard.2021.08.037.

[21] G. C. Meléndez *et al.*, "Myocardial Extracellular and Cardiomyocyte Volume Expand After Doxorubicin Treatment Similar to Adjuvant Breast Cancer Therapy.," *JACC. Cardiovascular imaging*, vol. 13, no. 4. pp. 1084–1085, Apr. 2020. doi: 10.1016/j.jcmg.2019.10.020.

[22] A. Kimball *et al.*, "Late characterisation of cardiac effects following anthracycline and trastuzumab treatment in breast cancer patients.," *Int J Cardiol*, vol. 261, pp. 159–161, Jun. 2018, doi: 10.1016/j.ijcard.2018.03.025.

[23] J. F. Meneses-Echávez *et al.*, "The Effect of Exercise Training on Mediators of Inflammation in Breast Cancer Survivors: A Systematic Review with Meta-analysis.," *Cancer Epidemiol Biomarkers Prev*, vol. 25, no. 7, pp. 1009–1017, Jul. 2016, doi: 10.1158/1055-9965.EPI-15-1061.

[24] A. Kiaos, D. Antonakaki, M.-A. Bazmpani, C. Karvounis, O. Rimoldi, and T. D. Karamitsos, "Prognostic value of cardiovascular magnetic resonance T1 mapping techniques in non-ischemic dilated cardiomyopathy: A systematic review and meta-analysis.," *Int J Cardiol*, vol. 312, pp. 110–116, Aug. 2020, doi: 10.1016/j.ijcard.2020.04.052.

[25] V. O. Puntmann *et al.*, "Native T1 and ECV of Noninfarcted Myocardium and Outcome in Patients With Coronary Artery Disease.," *J Am Coll Cardiol*, vol. 71, no. 7, pp. 766–778, Feb. 2018, doi: 10.1016/j.jacc.2017.12.020.

[26] G. G. F. van der Schoot *et al.*, "Optimal Timing of a Physical Exercise Intervention to Improve Cardiorespiratory Fitness: During or After Chemotherapy," *JACC CardioOncol*, vol. 4, no. 4, pp. 491–503, Nov. 2022, doi: 10.1016/J.JACCAO.2022.07.006.

[27] G. G. F. van der Schoot *et al.*, "Optimal Timing of a Physical Exercise Intervention to Improve Cardiorespiratory Fitness: During or After Chemotherapy," *JACC CardioOncol*, vol. 4, no. 4, pp. 491–503, Nov. 2022, doi: 10.1016/J.JACCAO.2022.07.006.

[28] K. A. Bolam, S. Mijwel, H. Rundqvist, and Y. Wengström, "Two-year follow-up of the OptiTrain randomised controlled exercise trial.," *Breast Cancer Res Treat*, vol. 175, no. 3, pp. 637–648, Jun. 2019, doi: 10.1007/s10549-019-05204-0.

[29] N. Mutrie *et al.*, "Five-year follow-up of participants in a randomised controlled trial showing benefits from exercise for breast cancer survivors during adjuvant treatment. Are there lasting effects?," *J Cancer Surviv*, vol. 6, no. 4, pp. 420–430, Dec. 2012, doi: 10.1007/s11764-012-0233-y.

[30] Y. Ezzatvar *et al.*, "Cardiorespiratory fitness and all-cause mortality in adults diagnosed with cancer systematic review and meta-analysis.," *Scand J Med Sci Sports*, vol. 31, no. 9, pp. 1745–1752, Sep. 2021, doi: 10.1111/sms.13980.

[31] D. Cardinale *et al.*, "Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy.," *J Am Coll Cardiol*, vol. 55, no. 3, pp. 213–220, Jan. 2010, doi: 10.1016/j.jacc.2009.03.095.

[32] P. Antunes *et al.*, "Effects of Exercise on Cardiac Function Outcomes in Women Receiving Anthracycline or Trastuzumab Treatment for Breast Cancer: A Systematic Review and Meta-Analysis," *Applied Sciences*, vol. 11, no. 18. 2021. doi: 10.3390/app11188336.

SUPPLEMENTAL FILE A: ADDITIONAL INFORMATION ON STUDY OUTCOMES.

Cardiac MRI

Scans were performed on a 1.5T clinical MRI-scanner (Ingenia, Software release 4.1-5.3, Philips Healthcare). All exams (except two) were reviewed by the same cardiovascular imaging expert (TL) blinded to original treatment allocation. T1 maps were acquired in three short-axis views (basal, mid-ventricular, and apical) using a modified Look-Locker inversion (MOLLI) recovery sequence. Extracellular volume (ECV) fraction was calculated as (1 - hematocrit (%) * $\Delta R1_{myocardium}$*$\Delta R1_{blood}$), where ΔR1 is defined as 1/T1. T1 maps were anonymously analyzed using dedicated postprocessing software (Medis Suite version 3.2.48.2, MapMaker ECV Application version 2.2.44) by a single researcher (WN). Intra-rater reliability coefficient in a subset of 15 scans was 0.94 (95%CI 0.86;0.98) for ECV and 0.88 (95%CI 0.73;0.95) for native T1. For native T1 and ECV, the mean score of the three short-axis slices was used in the final analyses.

All patients underwent steady-state free precession sequences in multiple orientations for assessment of wall motion and measurement of functional parameters for both LV and right ventricle (RV). Except for ejection fraction (EF), all values were indexed to body surface area. All patients underwent viability and phase-sensitive inversion recovery enhancement imaging after administration of double-dose (0.2 mmol/kg) gadolinium-based contrast agent gadobutrol (Gadovist, Bayer Healthcare). Segmental late gadolinium enhancement patterns were classified as follows: subendocardial, mid-wall, transmural or epicardial.

The following imaging parameters were used:
- Field of view: 320x320 mm
- Matrix: 256x256
- Flip angle: 60˚
- Parallel imaging acceleration factor: 3
- Slice thickness: 8.0mm
- Echo time: 1.7ms
- Repetition time; 4.0ms

T1 mapping parameters:
- Field of view: 300x300mm
- Matrix: 256x256
- Flip angle: 35°
- Parallel imaging acceleration factor: 2
- Slice thickness: 8.0mm
- Echo time: 1.1ms
- Repetition time; 4.0ms

Echocardiography

Transthoracic 2D-echocardiograms were acquired using a GE Vivid E9 or E95 machine. In line with current guidelines for adult cancer survivors[50], measurements of LV function, dimensions, and diastology were performed using one cardiac cycle. Diastolic function was scored as normal, indeterminate, or diastolic dysfunction, according to the most recent guidelines[51]. Global longitudinal strain (GLS) was assessed via 2D-speckle tracking echocardiography in the apical four-, three – and two-chamber views using offline EchoPAC software (version 2.03, GE Vingmed, Horten, Norway). All echocardiography data were collected by the same researcher (WN), after receiving sufficient training in GLS analysis[52], and were reviewed by the same cardiologist (AT), blinded for original treatment allocation.

Cardiopulmonary exercise tests

Cardiorespiratory fitness was assessed with a cardiopulmonary exercise test with continuous breathing gas analysis. Cycling workload increased every minute by 10,15 or 20 W till exhaustion, on the basis of participants' symptoms or at the discretion of the supervising physician. Peak oxygen uptake (VO_2Peak) was defined as the average value for the last 30 seconds before exhaustion and expressed in ml/kg/min. Only maximum exercise tests, defined as those where the respiratory exchange rate ≥1.1, were included in the analysis.

Venous blood sample

A fasting venous blood sample was taken to determine hematocrit (for ECV calculation), renal function, and presence of diabetes mellitus and hypercholesterolemia.

Physical activity

Physical activity was assessed with the Short Questionnaire to Assess Health enhancing physical activity (SQUASH)[48]. This questionnaire comprises questions on commuting activing, leisure-time and sports activities, household activities and work-related activities. We calculated the minutes per week of moderate-to high-intensity leisure and sport physical activity, which include all activities that correspond with a MET-value of ≥ 3.0. To obtain an estimate for physical activity participants engaged in over the past years (i.e. since completion of the original PACT and PACES studies), we used a structured, face-to-face interview[53]. All interviews were performed by the same researcher (WN). Total physical activity scores were derived in MET-hours per week[53].

Supplementary table 1a. Characteristics at baseline of original PACT participants, and those of participants and non-participants of the Pact-Paces-Heart study. Presented as mean ± SD, median (interquartile range) or number (percentages).

	Total PACT N=204	**Non-participants N=116**	**Participants N=88***
Age, years	49.6 ± 8.0	49.2 ± 8.8	50.1 ± 6.9
Study group, %			
Control	102 (50.0)	60 (51.7)	42 (47.7)
Intervention	102 (50.0)	56 (48.3)	46 (52.3)
Treatment characteristics			
AC dose, mg/m^2	256.5 ± 79.9	260.6 ± 87.8	251.1 ± 68.4
Herceptin, %	30 (14.8)	16 (13.9)	14 (15.9)
Radiotherapy, %	141 (69.1)	81 (69.8)	60 (68.2)
Cardiovascular risk factors			
Hypertension, %ǂ	25 (12.3)	15 (12.9)	10 (11.4)
Body mass index, kg/m^2	26.2 ± 4.8	26.8 ± 5.1	25.3 ± 4.4
Obesity, %ǂǂ	35 (17.2)	23 (20.0)	12 (13.6)
Any comorbidity, %	26 (12.7)	15 (12.9)	11 (12.5)
Physical fitness			
VO_2 $peak_{baseline}$	23.8 ± 5.4	22.9 ± 5.1	25.1 ± 5.5
VO_2 $peak_{end\ chemo}$	21.1 ± 5.3	20.7 ± 5.4	21.6 ± 5.1
Attendance rate§			
N of classes, %	83.3 (69.4-90.9]	78.8 (59.7-87.2]	86.1 (77.8-91.2]
>80%, %	54 (52.9)	21 (37.5)	33 (71.7)

* Of whom n=2 only participated via online questionnaires.

ǂ Hypertension is defined as systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg, or documented hypertension.

ǂǂ Obesity is defined as having a BMI>30 kg/m^2.

§ Only applicable for participants in the exercise arm.

Supplementary Table 1b. Characteristics at baseline of original PACES participants, and those of participants and non-participants of the Pact-Paces-Heart study. Presented as mean ± SD, median (interquartile range) or number (percentages).

	Total PACES **N=230**	**Non-participants** **N=133**	**Participants*** **N=97**
Age, years	50.7 ± 9.1	50.6 ± 9.7	50.7 ± 8.4
Study group, %			
Control	77 (33.5)	45 (34.1)	32 (32.7)
Onco-Move	77 (33.5)	47 (35.6)	30 (30.6)
On-Track	76 (33.0)	40 (30.3)	36 (36.7)
Treatment characteristics			
AC dose, mg/m^2	280.2 ± 65.5	283.5 ± 67.0	276.1 ± 63.61
trastuzumab %	55 (23.9)	29 (22.0)	26 (26.5)
Radiotherapy, %	180 (79.3)	103 (79.8)	77 (78.6)
Cardiovascular risk factors			
Hypertension, %†	36 (15.7)	20 (15.2)	16 (16.3)
Body mass index, kg/m^2	26.0 ± 4.5	26.4 ±4.9	25.5 ± 3.8
Obesity, %‡	37 (16.2)	26 (20.0)	11 (11.2)
Smoking (baseline), %	29 (12.6)	18 (13.6)	11 (11.2)
Any comorbidity, %	75 (32.6)	15 (12.9)	11 (12.5)
Cardiac comorbidity, %	7 (3.0)	6 (4.5)	1 (1.0)
Physical fitness			
$MSEC_{baseline}$	256.1 ± 48.5	251.1 ± 50.5	262.9 ± 44.9
$MSEC_{end\ chemo}$	218.8 ± 61.5	208.3 ± 66.0	232.4 ± 52.4
Attendance rate§			
N of classes, %	76.7 (60.7-85.2]	74.5 (56.9-83.6]	79.1 (65.2-86.3]
>80%, %	30 (39.5)	13 (32.5)	17 (47.2)

* Of whom n=2 only participated via online questionnaires.

† Hypertension is defined as having a documented diagnosis of hypertension.

‡ Obesity is defined as having a BMI>30 kg/m^2.

§ Only applicable for participants in the supervised exercise arm.

Supplementary Table 2. Effect of randomization to an exercise program (low-intensity or a moderate-to high-intensity) during chemotherapy on cardiac outcomes based on an intention-to-treat analysis.

Imaging modality	Parameter	Regression model	Unadjusted estimate (95%CI)	Partially adjusted* estimate (95%CI)	Fully adjusted† estimate (95%CI)
Cardiac MRI					
	ECV	Linear	-0.52 (-1.36, 0.32)	-0.57 (-1.44, 0.30)	-0.47 (-1.33, 0.40)
	ECV (>28%)	logistic	1.01 (0.41, 2.58)	0.95 (0.37, 2.51)	0.98 (0.38, 2.64)
	Native T1	Linear	**-13.94 (-28.51, 0.63)**	**-19.03 (-33.32, -4.74)**	**-19.05 (-33.61, -4.48)**
	Native T1 (>1020 ms)	Logistic	0.72 (0.39, 1.32)	0.60 (0.31, 1.15)	0.57 (0.29, 1.10)
	LVEF	Linear	-1.31 (-3.33, 0.70)	-1.25 (-3.32, 0.82)	-1.01 (-3.06, 1.04)
	LVEF (<50%)	logistic	1.69 (0.81, 3.71)	1.70 (0.78, 3.88)	1.53 (0.69, 3.54)
Echocardiography					
	GLS	Linear	0.59 (-0.33, 1.52)	0.49 (-0.48, 1.46)	0.44 (-0.53, 1.41)
	GLS (>-18%)	Logistic	1.55 (0.80, 3.03)	1.48 (0.75, 2.98)	1.50 (0.76, 3.02)
Cardiopulmonary exercise testing					
	VO_2peak	Linear	-0.92 (-2.97, 1.12)	-0.34 (-2.27, 1.59)	-0.07 (-1.92, 1.79)

* Partially adjusted includes adjustments for age, radiotherapy (none versus left-sided or right-sided), cumulative doxorubicin equivalent dosage, trastuzumab treatment and study (PACT vs PACES).

† Fully adjusted is the partially adjusted model with extra adjustment for the presence of cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity and being a current smoker; none versus 1 or >1).

Supplementary Table 3. Effect of participation in a moderate-to high-intensity exercise program during chemotherapy on cardiac outcomes based on an intention-to-treat analysis using unimputed versus imputed dataset.

Imaging modality	Parameter	Regression model	Unimputed analyses*,ǂ estimate (95%CI)	Imputed analyses* estimate (95%CI)
Cardiac MRI				
	ECV	Linear	-0.69 (-1.62, 0.25)	-0.65 (-1.58, 0.28)
	ECV (>28%)	logistic	0.76 (0.24, 2.34)	0.98 (0.87, 1.101)
Echocardiography				
	GLS	Linear	0.31 (-0.76, 1.37)	0.53 (-0.49, 1.56)
	GLS (>-18%)	Logistic	1.34 (0.63, 2.88)	1.09 (0.92, 1.30)

* Analyses are adjusted includes adjustments for age, radiotherapy (none versus left-sided or right-sided), cumulative doxorubicin equivalent dosage, trastuzumab treatment, study (PACT vs PACES) and the presence of cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity and being a current smoker; none versus 1 or >1).

ǂ GLS and ECV measurements could not be completed in 17.1% (31/181) and 11.6% (21/181) of all participants, respectively.

Supplementary Table 4. Physical activity patterns per study group in the Pact-Paces-Heart study.
Presented as median [interquartile range].

		Control N=72	Mod.-to high-int. EX N=80	low-int. EX N=29
Current physical activity (self-reported) [a]				
	Moderate-to high-intensity leisure and sport physical activity, min/week[b]	155 [60-360]	150 [60-368]	240 [30-360]
Physical activity in the distant past (face-to-face interview)[c]				
	Total MET-hours/ week	259 [227-295]	266 [236-298]	246 [227-282]
	Moderate-to high-intensity MET-hours/week	86 [56 -126]	94 [63-131]	72 [44-120]

[a] Data on leisure and sport physical activity data were missing in 7/181 (3.9%) participants.

[b] Moderate-to high-intensity activities were defined as activities that corresponded with a metabolic equivalent task (MET) -value of 3 and higher.

[c] Interviews were not conducted in 4/181 (2.2%) due to logistic constraints.

Supplementary table 5. Association between self-reported moderate-to high-intensity leisure and sport physical activity at follow-up and cardiovascular outcomes.

Imaging modality	Parameter	Regression model[a]	Unadjusted estimate (95%CI)	Fully adjusted[b] estimate (95%CI)
Cardiac MRI				
	ECV	Linear	0.11 (-0.04, 0.25)	0.12 (-0.03, 0.27)
	ECV (>28%)	logistic	1.06 (0.91, 1.23)	1.08 (0.92, 1.25)
	Native T1	Linear	-0.20 (-2.66, 2.26)	-0.14 (-2.61, 2.34)
	Native T1 (>1020 ms)	logistic	0.97 (0.87, 1.08)	0.96 (0.86, 1.06)
	LVEF	Linear	-0.15 (-0.48, 0.18)	-0.11 (-0.45, 0.23)
	LVEF (<50%)	logistic	1.06 (0.94, 1.19)	1.06 (0.93, 1.20)
Echocardiography				
	GLS	Linear	0.14 (-0.01, 0.30)	0.15 (-0.02, 0.31)
	GLS (>-18%)	Logistic	1.08 (0.97, 1.23)	1.08 (0.97, 1.22)
Cardiopulmonary exercise testing				
	VO_2peak	Linear	**0.53 (0.21, 0.85)**	**0.70 (0.42, 0.98)**

[a] All estimates are presented per 100 min/week of reported activity.

[b] Adjusted for age, radiotherapy (none versus left-sided or right-sided), cumulative doxorubicin equivalent dosage, trastuzumab treatment, study (PACT vs PACES) and the presence of cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity and being a current smoker; none versus 1 or >1).

PART 2

Physical exercise and its effect on other cancer-related outcomes

CHAPTER 6

Physical fitness and chemotherapy tolerance in patients with early-stage breast cancer

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ABSTRACT

Introduction

An optimal relative dose intensity (RDI) of adjuvant chemotherapy is associated with better survival in patients with breast cancer. Little is known about the role of physical fitness in attaining an adequate RDI in patients with early-stage breast cancer. We investigated the association between pre-treatment physical fitness and RDI in this population.

Methods

We pooled individual patient data from two randomized exercise trials that studied exercise programs in early breast cancer: the PACES (n=230) and the PACT (N=204) study. Logistic regression models were used to evaluate the association between pre-treatment fitness and achieving an optimal RDI (≥85%). In addition, we added an interaction term to the model to explore the potential moderating effect of participating in an exercise program.

Results

Data were available for 419 patients (mean age at diagnosis 50.0±8.6 years). In the total sample, lower pre-treatment physical fitness was associated with significantly lower odds of achieving ≥85% RDI: age-adjusted OR 0.66 [95%CI 0.46-0.94]. In patients allocated to the supervised exercise intervention during chemotherapy (n=173), the association between pretreatment physical fitness and RDI was almost completely mitigated, while it was more pronounced in patients who received care as usual (n=172, $p_{interaction}$: 0.022).

Conclusion

Early-stage breast cancer patients with relatively lower levels of pretreatment physical fitness have lower odds of achieving an optimal dose of chemotherapy. Given that physical fitness is modifiable, and our results suggest that following a moderate-to-high intensity exercise training during chemotherapy could improve treatment completion, clinicians should not refrain from referring patients to supportive exercise programs because of low fitness.

INTRODUCTION

Over the past decades, 5-year breast cancer survival rates have continued to improve and are currently higher than 90% in the Netherlands for early-stage breast cancer[1]. Improvement in chemotherapy is considered as one of the key elements that have contributed to this increased survival rate[2]. The amount of chemotherapy received is often expressed as relative dose intensity (RDI), which is the ratio of the actual versus the planned dose intensity. In the adjuvant setting, a RDI of 85% is a widely accepted threshold, as patients who achieve this threshold have a greater likelihood of improved outcomes, including recurrence-free and overall survival[3]. Failure to achieve the 85% RDI is reported in over a quarter of breast patients, mostly due to toxicity, even in the current era of adequate supportive care (e.g. effective antiemetics) and tailored treatment regimens[3], [4]. In a study of more than 10,000 breast cancer patients treated with contemporary chemotherapy regimens, dose delay ≥7 days or dose reduction of ≥15% was observed in 37% and 35% of the cases, respectively[3] Hence, strategies to increase the likelihood of achieving 85% RDI in this patient population are warranted.

Currently, breast cancer patients at risk of not completing their planned chemotherapy treatment are the elderly and those with poor performance status[3]. There is also some evidence that pretreatment low lean body mass[5], [6] and low self-reported exercise levels are related to decreased chemotherapy completion rates[7], whereas exercise during chemotherapy might have a beneficial effect on treatment tolerance. The latter was observed in the randomized Physical Exercise During Adjuvant Chemotherapy Effectiveness Study (PACES), in which doses adjustments occurred less frequently in the exercise groups compared to the controls[8]. Recently, first evidence was provided that pretreatment physical fitness was associated with better chemotherapy tolerance [9]. Whether subsequent participation in an exercise program modifies this association has not been investigated.

Therefore, we conducted a secondary analysis of data from two randomized controlled trials (RCTs), including PACES, that evaluated the effects of a supervised exercise program during adjuvant chemotherapy for early-stage breast cancer. We assessed the association between pre-treatment physical fitness and completing chemotherapy treatment (attaining >85% RDI). Additionally, we explored whether participating in an exercise program modifies this association.

METHODS

Setting and participants

Data from the Physical Activity during Chemotherapy Treatment (PACT) study and Physical Exercise During Adjuvant Chemotherapy Effectiveness Study (PACES) were used for the current analysis. The study design and results of the PACT study[10]–[12] and PACES[8], [13] have been published elsewhere. In brief, the original multicenter studies were both conducted in the Netherlands between 2009 and 2013 and investigated the effect of an exercise program during adjuvant chemotherapy on fatigue, cardiorespiratory fitness, quality of life, and further secondary outcomes. In the PACT study, breast cancer patients were randomly allocated to either an 18-week moderate-to-high-intensity, supervised exercise program (n=102) or a usual care (UC) control group (n=102). PACES had two intervention groups and a UC control group (n=77). The interventions in PACES were a low-intensity, home-based exercise program (n=77) and a moderate-to-high intensity supervised exercise program (n=76). The latter was rather similar to PACT's intervention, both comprising two combined aerobic and resistance exercise sessions per week. In addition, participants allocated to these study arms were asked to be physically active for at least 30 minutes per day for 5 days per week. In both studies, adherence to the exercise program was recorded by case report files. The attendance rate for the supervised exercise sessions was 83% and 71% in PACT and PACES, respectively [8], [11]In PACT, the intervention started within 6 weeks after diagnosis with a fixed duration of 18 weeks. The PACES interventions started before chemotherapy and continued until three weeks post-chemotherapy. Inclusion criteria for PACT and PACES were comparable and comprised a histological diagnosis of early breast cancer, being scheduled for adjuvant chemotherapy, having no contra-indications for physical activity in terms of malnutrition, serious orthopedic, cardiovascular or pulmonary diseases and having basic fluency in the Dutch language. For PACT, patients had to be aged between 25-75 years, whereas PACES did not have any age restrictions. Patients were excluded from PACT if they had a Karnofsky performance status score <60. All subjects provided written informed consent and the PACT and PACES studies were approved by the institutional review boards of the University Medical Center Utrecht and The Netherlands Cancer Institute respectively.

Study measures

Treatment data were extracted from the medical records. This included planned and actually administered chemotherapy (type, dose and duration). For each agent, both the planned and actual dose intensity (DI) were calculated by dividing the total cumulative dose, expressed in mg per m^2 body surface area (BSA), by treatment duration in weeks[14]. These analyses were limited to chemotherapeutic agents and thus not incorporate the usage of monoclonal antibodies (i.e. trastuzumab). Treatment duration was calculated as the duration between the first day of chemotherapy administration and the day of completion of the last cycle. RDI was calculated by dividing actual DI by planned DI and was expressed as a percentage. An overall RDI per regimen was calculated by averaging the RDI of all agents included in that regime, regardless whether agents were given simultaneously or as a sequential drug combination[14]. In case a switch from one type of chemotherapy to another occurred, RDI for the first and remaining part of the new regimen were calculated separately and averaged to obtain one RDI per patient.

Physical fitness was assessed in PACT and PACES before randomization and after the exercise intervention had been completed. In the PACT study, a cardiopulmonary exercise test (CPET) with continuous breathing gas analysis was used, where cycling workload was increased every minute by 10, 15 or 20 W till exhaustion, symptom limitation or at the discretion of the supervising physician. Peak oxygen uptake (VO_2Peak) was defined as the average value for the last 30 seconds before exhaustion and was expressed in ml/kg/min. In PACES, physical fitness was assessed with a Steep Ramp Test (SRT). After a 3-minute warm-up at 10 W, resistance increased by 25 W per 10 seconds until exhaustion and until the revolutions per minute dropped below 60 despite strong verbal encouragement. The outcome of this test, the maximum short exercise capacity (MSEC), is defined as the highest workload achieved before patients can no longer maintain a cadence >60 RPM. A more detailed description of both tests is provided in the protocol papers of the original studies[8], [11]. The outcomes of the CPET (VO_2Peak) and SRT (MSEC) have been shown to be strongly correlated (ranging from 0.73 to 0.86) in healthy and diseased populations including cancer survivors[15]–[20].

Statistical analyses

A binary threshold of 85% RDI per chemotherapy regimen was used as the outcome variable. This was chosen on the basis of the predictive value of this threshold in terms of overall survival in the adjuvant treatment setting[21]. Baseline characteristics were computed for the overall cohort and expressed as means (SD) or frequencies (percentages).

Measurements for fitness, expressed either as VO_2peak (PACT) or MSEC (PACES), were converted into Z-scores by subtracting the mean and then dividing by the standard deviation. Binary logistic regression models were used with Z-scores for fitness as explanatory variable and RDI (<85%/≥85%) as dependent variable. Potential confounders for these analyses were defined *a priori* using directed acyclic graphs[22] and included age, BMI, presence or absence of comorbidities, breast cancer subtype (triple negative; HR+/Her2Neu-; HR-/Her2Neu+, HR+/Her2Neu+). Potential confounders were only included as covariates in the analyses if they were associated with both the explanatory and the outcome variables in the data, as based on the point-estimates of association regardless of statistical significance, and changed the estimate of the odds ratio (OR) for the central determinant by >10% when added to the model[23]. All models were adjusted for study (PACT or PACES). A non-linear term (restricted cubic spline) was used to investigate a possible threshold effect of physical fitness on 85% RDI%.

To explore whether participation in a moderate-to-high intensity exercise program modifies the association between pretreatment fitness and 85% RDI we added an interaction term to the adjusted model. All exercise analyses were on an intention-to-treat basis and limited to the moderate-to-high-intensity supervised exercise and UC groups only, because the home-based exercise group of PACES was too small. ORs and their 95% confidence intervals (95% CI) were calculated for each group, including the low-intensity, home-based group of PACES, separately (the latter only for exploratory purpose).

All data were analyzed with R (version 3.4.3) and Rstudio software (Version 1.2.5001, Rstudio Inc., Boston, USA). A two-sided p-value of 0.05 was considered statistically significant.

RESULTS

Participants

A total of 434 breast cancer patients participated in PACT or PACES, of whom 22 were excluded from the current analysis due to the absence of sufficient information on chemotherapy regimen (n=10) or because no baseline fitness test had been performed (n=5). Characteristics of the total sample (n=419) are presented in Table 1.

Table 1. Baseline characteristics of the combined study of the PACT and PACES studies of patients with breast cancer receiving adjuvant chemotherapy.

	All patients (n=419)	
	Mean	**SD**
Age (y)	50.0	8.6
Height (m)	168.4	6.5
Weight (kg)	73.8	13.7
BMI (kg/m^2)	26.0	4.6
MSEC (W) (n=222)*	255.4	48.9
VO_2Peak (mL/min/kg) (n=197)**	23.8	5.25
	%	**N=**
Original study - PACT - PACES	47.0 53.0	197 222
Study arm - PACT: intervention - PACT: control - PACES: supervised, high-intensity - PACES: home-based, low-intensity - PACES: care as usual	23.9 23.2 17.4 17.6 17.9	100 97 73 74 75
Presence of comorbidities (%)	22.0	92
T stage		
- 1	55.4	232
- 2	38.9	163
- 3	4.1	17
- 4	1.0	4
- missing	0.7	3
N class		
- 0	43.9	184

Table 1. (Continued)

	All patients (n=419)	
	Mean	**SD**
- 1	46.8	196
- 2	6.7	28
- 3	2.6	11
Receptor status		
- Triple negative	17.4	73
- HER+, ER or PR+	17.2	72
- HER+, ER or PR-	5.5	23
- HER-, ER or PR+	60.0	250
Type of chemotherapy		
- TAC	32.9	13
- FEC or AC	14.3	60
- AC/EC, followed by taxanes	26.3	110
- 3 FEC + docetaxel	23.4	98
- Other	3.1	11

* only for PACT participants. ** only for PACES participants. MSEC: maximum short exercise capacity. TAC: docetaxel, doxorubicin, cyclophosphamide. FEC: 5-FU, epirubicin, cyclophosphamide. AC: doxorubicin, cyclophosphamide.

The most frequently administrated chemotherapy regimen was the combination of docetaxel, doxorubicin and cyclophosphamide (TAC), followed by a sequential treatment regimen that comprises an anthracycline (doxorubicin or epirubicin) and cyclophosphamide, followed by either docetaxel or paclitaxel. More detailed information on chemotherapy regimens is provided in the Table in Supplemental Digital Content 1.

In total, 43 patients (10.3%) did not achieve ≥85% RDI (Table 2). Most common reasons for poor chemotherapy tolerance were neuropathy (N=11, 26.8%), nausea and/or vomiting (N=5, 12.2%), myelosuppression (N=4, 9.8%), cardiac signs and/or symptoms (N=4, 9.8%) and malaise (N=4, 9.8%). For N=8 (19.5%), the specific reason for dose modification was not reported.

Table 2. Reasons for not achieving ≥85% relative dose intensity of the chemotherapy regime as planned.

	N=	%
Neuropathy	11	26,8
Nausea and/or vomiting	5	12,2
Myelosupression	4	9,8
Cardiac signs and/or symptoms	4	9,8
Malaise	4	9,8
Own initiative	3	7,3
Febrile neutropenia	3	7,3
Gastro-intestinal symptoms	1	2,4
Unknown	8	19,5
Total	*43*	*100,0*

Association between fitness and RDI

When adjusted for study, lower pre-treatment physical fitness was associated with lower odds of achieving ≥85% RDI: OR 0.60 (95% CI 0.42-0.84). There was no indication of non-linearity (p=0.80), suggesting no threshold effect. Of the possible confounders assumed within the causal model, only age was associated with both determinant and outcome. When correcting for age and study, low pre-treatment physical fitness remained associated with not achieving RDI ≥85%; OR 0.66 (95%CI 0.46-0.94).

Participation in an exercise program significantly modified the association between baseline fitness and RDI ≥85% ($p_{interaction}$=0.022). In subsequent stratified analyses, for participants of the moderate-to-high intensity supervised exercise program (n=173) and the low-intensity home-based exercise program of PACES (n=74), pre-treatment physical fitness was not associated with an RDI ≥85%: OR 0.95 (95%CI 0.54-1.56) and OR 0.88 (95%CI 0.38-2.09), respectively. In contrast, in patients allocated to the UC groups (n=172), the association between lower pre-treatment physical fitness and not reaching RDI ≥85% was more pronounced; OR 0.31 (95%CI 0.13-0.63).

Table 3. The association between baseline physical fitness and not achieving ≥85% relative dose intensity of the chemotherapy regime as planned.

Overall analysis			
	N included in analysis	Odds ratio	95% confidence interval
Baseline physical fitness	419	0.66	0.46 – 0.94
Stratified analyses per randomization*			
Supervised, moderate-to-high intensity exercise program	173	0.95	0.54 – 1.56
Homebased, low-intensity exercise program**	77	0.88	0.38 – 2.09
Care as usual	169	0.31	0.13 – 0.63

All presented results are adjusted for age and study (PACT vs PACES).

* Participation in a supervised, moderate-to-high exercise program moderates the association between baseline physical fitness and RDI ≥85% ($p_{interaction}$=0.022).

** this group consists of PACES participants only.

DISCUSSION

In the present study, we found that breast cancer patients with lower pre-treatment physical fitness had a lower likelihood of completing chemotherapy as planned. Accordingly, assessing pretreatment physical fitness could aid in identifying those at risk for not completing chemotherapy. This subgroup of patients is in need of supportive care and might benefit from an exercise program. Our explorative analysis supports the idea that a moderate-to-high intensity exercise program might mitigate the association between low pretreatment physical fitness and not achieving sufficient RDI. Although the current evidence for the effectiveness of exercise programs to improve treatment completion is inconclusive, with few other options available to improve physical fitness, and considering that exercise is safe for cancer patients[24]and has many positive effects on chemotherapy-related symptoms (e.g. fatigue)[24], referral to an exercise program could be considered, even, or maybe especially, for patients with lower pretreatment fitness.

When considering the known association between attaining at least 85% RDI and efficacy of chemotherapy in terms of survival and disease progression, the findings of this study point out the importance of pretreatment fitness. Recently, it was shown that patients with RDI <85% have a 38% increased risk of dying from breast cancer compared to those with RDI ≥85%[25]. Accordingly, sufficient baseline fitness, or following an exercise program during chemotherapy to

mitigate the risk of not achieving 85% RDI due to compromised baseline fitness, can be related to improved survival for early-stage breast cancer patients. Indeed, Courneya et al.[26] found, in an exploratory follow-up analysis (median of 7.5 years) of their randomized exercise trial during chemotherapy, that disease-free survival tended to be higher in patients who had been allocated to an exercise group during treatment, as compared to those who were allocated to the control group (disease-free survival (DFS) 82.7% vs. 75.6%, respectively; hazard ratio (HR), 0.68; 95%CI, 0.37–1.24). Hayes et al. found similar hazard ratios for DFS in their follow up of two exercise trials (HR: 0.66, 95% CI 0.38–1.17; p = 0.16)[27]. Although these studies are clearly underpowered for such analyses, they show consistent results.

Our findings that higher pre-treatment physical fitness is associated with a lower risk of dose modifications is in line with a recently published study[9]. This secondary analysis of the previously conducted START and CARE study showed that breast cancer patients in the highest 20% vs lowest 80% of absolute VO_2Peak were approximately two times more likely to achieve 85% RDI[9]. Given that this analysis included breast cancer patients recruited between 2002-2005 (START) and 2008-2011 (CARE), our results complement this study by demonstrating that, in women treated with contemporary chemotherapy regimens where chemotherapy tolerance is higher (~80% versus ~90% achieved RDI ≥85% respectively), pretreatment physical fitness remains a significant factor associated with chemotherapy completion. Moreover, we found that physical exercise, and specifically exercise with a moderate-to-high intensity, modified the association between pretreatment physical fitness and chemotherapy tolerance, suggesting that the subgroup of patients with lower pretreatment physical fitness might benefit from referral to an exercise program.

Our finding that patients with relatively low physical fitness have lower odds of completing chemotherapy may be, at least to some extent, related to the amount and quality of skeletal muscle mass. In patients with breast cancer it has been shown that a higher relative lean mass is associated with a lower risk of chemotherapy modifications[5] and that skeletal muscle gauge (product of muscle quantity and quality) is associated with severe toxicities and hospitalization[6]. Similar results have also been reported for colorectal cancer patients[28], [29]. Nevertheless, in a recent pooled analysis of two exercise trials (n=543 breast cancer patients), body composition, including lean body mass, was not found to be associated with chemotherapy tolerance[9]. The authors speculate that their relative fit and healthy study sample could explain this discrepancy in results. Further studies are warranted to document whether standard chemotherapy

dosing to body surface area, compared to lean mass, is more likely to result in toxicities in patients with relatively low lean body mass. It has been proposed that standard chemotherapy dosing in relation to body surface area, compared to lean mass, may more easily lead to toxicities in patients with relatively low lean body mass. In addition, endurance exercise may protect the muscle from anthracycline-induced atrophy[30]–[32], but it is currently unknown if this relates to better chemotherapy completion rates.

In the explorative analysis, we found that exercise might counteract the increased risk of compromised pretreatment physical fitness. To date, few exercise trials have analyzed chemotherapy completion, and these show mixed results. A systematic review concluded that evidence is not sufficient to affirm that exercise has an effect on chemotherapy completion rate[33]. This was corroborated by a more recent analysis by Mijwel et al. of the OptiTrain study, in which no beneficial effect of aerobic nor resistance training on chemotherapy completion was found[30]. Also, Kirkham et al. found no difference in frequency of dose adjustments for the total sample of breast cancer patients in their nonrandomized study comparing combined strength and endurance exercise with historical controls who received care as usual[34]. They did, however, find significantly less dose adjustments for regimens containing doxorubicin in the exercise group[34]. Nonetheless, in the reported studies chemotherapy completion was a secondary outcome. In addition, pretreatment physical fitness was not incorporated in any of these analyses and it is conceivable that participants of these trials were relatively healthy[35]. Therefore, in light of our results indicating that those with lower pretreatment physical fitness levels are more likely to benefit from an exercise program, future studies with chemotherapy completion as a primary outcome and a representative study population for the breast cancer population as whole, are required to pertain an effect of exercise on chemotherapy completion.

The major strength of our study lies in the availability of a large patient sample, derived from RCTs, thereby providing detailed information on physical fitness as well as chemotherapy data. Although our results are based on secondary analyses of two different studies, we adjusted for study in our analyses and we used z-scores for the outcomes of interest.

As limitations we would note that home-based exercise group of the PACES trial was relatively small prohibiting a proper dose-response analysis for that subgroup. Also, the two different yet highly correlated measures were used to assess physical fitness in the two studies: VO_2Peak (PACT) or MSEC (PACES). The impact on our analyses was, however, limited by using a Z-score for physical fitness measurements and adjusting our analyses for original study participation

(PACT vs PACES). Furthermore, our data need to be interpreted with some caution, given the fact that the confidence intervals around the ORs for both the high- and low intensity exercise groups overlap slightly with those of the UC groups. Last, we cannot rule out the possibility that clinicians selected chemotherapy regimens according to pretreatment physical fitness (i.e. those with lower fitness receive less intense regimens), which could have diluted our results.

Despite these cautionary remarks, the results of our study clearly suggest that in patients with early-stage breast cancer, a lower level of physical fitness at the start of adjuvant chemotherapy is associated with a higher risk of not attaining 85% RDI thereby compromising long-term patient outcome. Physical exercise while receiving chemotherapy, and specifically exercise with moderate-to-high intensity, might mitigate this association. Hence, assessing pretreatment physical fitness is of importance to identify those patients at risk for not completing chemotherapy, and who might therefore gain additional benefit from an exercise program as supportive care.

REFERENCES

[1] IKNL, "Overleving borstkanker." https://iknl.nl/kankersoorten/borstkanker/registratie/overleving (accessed Apr. 26, 2023).

[2] L. Rossi et al., "Impact of Adjuvant Chemotherapy on Breast Cancer Survival: A Real-World Population," PLoS One, vol. 10, no. 7, Jul. 2015, doi: 10.1371/JOURNAL.PONE.0132853.

[3] G. H. Lyman, "Impact of chemotherapy dose intensity on cancer patient outcomes," J Natl Compr Canc Netw, vol. 7, no. 1, pp. 99–108, 2009, doi: 10.6004/JNCCN.2009.0009.

[4] N. Denduluri et al., "Dose Delays, Dose Reductions, and Relative Dose Intensity in Patients With Cancer Who Received Adjuvant or Neoadjuvant Chemotherapy in Community Oncology Practices," J Natl Compr Canc Netw, vol. 13, no. 11, pp. 1383–1393, Nov. 2015, doi: 10.6004/JNCCN.2015.0166.

[5] M. M. G. A. van den Berg et al., "Body composition is associated with risk of toxicity-induced modifications of treatment in women with stage I-IIIB breast cancer receiving chemotherapy," Breast Cancer Res Treat, vol. 173, no. 2, pp. 475–481, Jan. 2019, doi: 10.1007/S10549-018-5014-5.

[6] S. S. Shachar et al., "Body Composition as a Predictor of Toxicity in Patients Receiving Anthracycline and Taxane-Based Chemotherapy for Early-Stage Breast Cancer," Clin Cancer Res, vol. 23, no. 14, pp. 3537–3543, Jul. 2017, doi: 10.1158/1078-0432.CCR-16-2266.

[7] I. Usiskin, F. Li, M. L. Irwin, B. Cartmel, and T. Sanft, "Association between pre-diagnosis BMI, physical activity, pathologic complete response, and chemotherapy completion in women treated with neoadjuvant chemotherapy for breast cancer," Breast Cancer, vol. 26, no. 6, pp. 719–728, Nov. 2019, doi: 10.1007/S12282-019-00974-3.

[8] H. van Waart et al., "Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial.," J Clin Oncol, vol. 33, no. 17, pp. 1918–1927, Jun. 2015, doi: 10.1200/JCO.2014.59.1081.

[9] K. Y. An et al., "Exercise and health-related fitness predictors of chemotherapy completion in breast cancer patients: pooled analysis of two multicenter trials," Breast Cancer Res Treat, vol. 188, no. 2, pp. 399–407, Jul. 2021, doi: 10.1007/S10549-021-06205-8.

[10] L. Witlox et al., "Four-year effects of exercise on fatigue and physical activity in patients with cancer.," BMC Med, vol. 16, no. 1, p. 86, Jun. 2018, doi: 10.1186/s12916-018-1075-x.

[11] N. Travier et al., "Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial.," BMC Med, vol. 13, p. 121, Jun. 2015, doi: 10.1186/s12916-015-0362-z.

[12] M. J. Velthuis et al., "Physical Activity during Cancer Treatment (PACT) Study: design of a randomised clinical trial," BMC Cancer, vol. 10, Jun. 2010, doi: 10.1186/1471-2407-10-272.

[13] H. van Waart, M. M. Stuiver, W. H. van Harten, G. S. Sonke, and N. K. Aaronson, "Design of the Physical exercise during Adjuvant Chemotherapy Effectiveness Study (PACES): a randomized controlled trial to evaluate effectiveness and cost-effectiveness of physical exercise in improving physical fitness and reducing fatigue.," BMC Cancer, vol. 10, p. 673, Dec. 2010, doi: 10.1186/1471-2407-10-673.

[14] D. L. Longo, P. L. Duffey, V. T. DeVita, M. N. Wesley, S. M. Hubbard, and R. C. Young, "The calculation of actual or received dose intensity: a comparison of published methods," J Clin Oncol, vol. 9, no. 11, pp. 2042–2051, 1991, doi: 10.1200/JCO.1991.9.11.2042.

[15] B. C. Bongers, S. I. De Vries, P. J. M. Helders, and T. Takken, "The steep ramp test in healthy children and adolescents: reliability and validity," Med Sci Sports Exerc, vol. 45, no. 2, pp. 366–371, Feb. 2013, doi: 10.1249/MSS.0B013E31826E32C5.

[16] B. C. Bongers, M. S. Werkman, H. G. M. Arets, T. Takken, and H. J. Hulzebos, "A possible alternative exercise test for youths with cystic fibrosis: the steep ramp test," Med Sci Sports Exerc, vol. 47, no. 3, pp. 485–492, Mar. 2015, doi: 10.1249/MSS.0000000000000440.

[17] I. C. De Backer, G. Schep, A. Hoogeveen, G. Vreugdenhil, A. D. Kester, and E. van Breda, "Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test," Arch Phys Med Rehabil, vol. 88, no. 5, pp. 610–616, May 2007, doi: 10.1016/J.APMR.2007.02.013.

[18] R. Rozenberg, J. B. J. Bussmann, E. Lesaffre, H. J. Stam, and S. F. E. Praet, "A steep ramp test is valid for estimating maximal power and oxygen uptake during a standard ramp test in type 2 diabetes," Scand J Med Sci Sports, vol. 25, no. 5, pp. 595–602, Oct. 2015, doi: 10.1111/SMS.12357.

[19] M. M. Stuiver et al., "Validation and Refinement of Prediction Models to Estimate Exercise Capacity in Cancer Survivors Using the Steep Ramp Test," Arch Phys Med Rehabil, vol. 98, no. 11, pp. 2167–2173, Nov. 2017, doi: 10.1016/J.APMR.2017.02.013.

[20] A. T. R. Weemaes, M. Beelen, B. C. Bongers, M. P. Weijenberg, and A. F. Lenssen, "Criterion Validity and Responsiveness of the Steep Ramp Test to Evaluate Aerobic Capacity in Survivors of Cancer Participating in a Supervised Exercise Rehabilitation Program," Arch Phys Med Rehabil, vol. 102, no. 11, pp. 2150–2156, Nov. 2021, doi: 10.1016/J.APMR.2021.04.016.

[21] S. Liutkauskiene, S. Grizas, K. Jureniene, J. Suipyte, A. Statnickaite, and E. Juozaityte, "Retrospective analysis of the impact of anthracycline dose reduction and chemotherapy delays on the outcomes of early breast cancer molecular subtypes," BMC Cancer, vol. 18, no. 1, Apr. 2018, doi: 10.1186/S12885-018-4365-Y.

[22] I. Shrier and R. W. Platt, "Reducing bias through directed acyclic graphs," BMC Med Res Methodol, vol. 8, 2008, doi: 10.1186/1471-2288-8-70.

[23] Twisk JWR, "Introduction in Applied Biostatistics," Amsterdam (the Netherlands): Reed Business Education, 2014.

[24] K. L. Campbell et al., "Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable," Med Sci Sports Exerc, vol. 51, no. 11, pp. 2375–2390, Nov. 2019, doi: 10.1249/MSS.0000000000002116.

[25] E. M. Cespedes Feliciano et al., "Body Composition, Adherence to Anthracycline and Taxane-Based Chemotherapy, and Survival After Nonmetastatic Breast Cancer.," JAMA Oncol, vol. 6, no. 2, pp. 264–270, Feb. 2020, doi: 10.1001/jamaoncol.2019.4668.

[26] K. S. Courneya et al., "Effects of exercise during adjuvant chemotherapy on breast cancer outcomes," Med Sci Sports Exerc, vol. 46, no. 9, pp. 1744–1751, 2014, doi: 10.1249/MSS.0000000000000297.

[27] S. C. Hayes et al., "Exercise following breast cancer: exploratory survival analyses of two randomised, controlled trials," Breast Cancer Res Treat, vol. 167, no. 2, pp. 505–514, Jan. 2018, doi: 10.1007/S10549-017-4541-9.

[28] S. Kurk et al., "Skeletal muscle mass loss and dose-limiting toxicities in metastatic colorectal cancer patients," J Cachexia Sarcopenia Muscle, vol. 10, no. 4, pp. 803–813, Aug. 2019, doi: 10.1002/JCSM.12436.

[29] E. M. Cespedes Feliciano et al., "Muscle mass at the time of diagnosis of nonmetastatic colon cancer and early discontinuation of chemotherapy, delays, and dose reductions on adjuvant FOLFOX: The C-SCANS study," Cancer, vol. 123, no. 24, pp. 4868–4877, Dec. 2017, doi: 10.1002/CNCR.30950.

[30] S. Mijwel, K. A. Bolam, J. Gerrevall, T. Foukakis, Y. Wengström, and H. Rundqvist, "Effects of Exercise on Chemotherapy Completion and Hospitalization Rates: The OptiTrain Breast Cancer Trial," Oncologist, vol. 25, no. 1, pp. 23–32, Jan. 2020, doi: 10.1634/THEONCOLOGIST.2019-0262.

[31] S. Mijwel et al., "Exercise training during chemotherapy preserves skeletal muscle fiber area, capillarization, and mitochondrial content in patients with breast cancer," FASEB J, vol. 32, no. 10, pp. 5495–5505, Oct. 2018, doi: 10.1096/FJ.201700968R.

[32] A. E. Hiensch et al., "Doxorubicin-induced skeletal muscle atrophy: Elucidating the underlying molecular pathways," Acta Physiol (Oxf), vol. 229, no. 2, pp. 1–18, Jun. 2020, doi: 10.1111/APHA.13400.

[33] K. A. Bland, K. Zadravec, T. Landry, S. Weller, L. Meyers, and K. L. Campbell, "Impact of exercise on chemotherapy completion rate: A systematic review of the evidence and recommendations for future exercise oncology research," Crit Rev Oncol Hematol, vol. 136, pp. 79–85, Apr. 2019, doi: 10.1016/J.CRITREVONC.2019.02.005.

[34] A. A. Kirkham et al., "Impact of Exercise on Chemotherapy Tolerance and Survival in Early-Stage Breast Cancer: A Nonrandomized Controlled Trial," J Natl Compr Canc Netw, vol. 18, no. 12, pp. 1670–1677, Dec. 2020, doi: 10.6004/JNCCN.2020.7603.

[35] S. M. Gollhofer et al., "Factors influencing participation in a randomized controlled resistance exercise intervention study in breast cancer patients during radiotherapy," BMC Cancer, vol. 15, no. 1, Mar. 2015, doi: 10.1186/S12885-015-1213-1.

APPENDIX 1: CHEMOTHERAPY REGIMENS

Abbrevation	Agents included	Total N= 419	%
TAC	Docetaxel, doxorubin, cyclophoshamide	139	32.9
FEC or AC	5-fluorocacil, epirubicin, cyclophosphamide (FEC), doxorubicin and cyclophosphamide (AC)	60	14.3
FEC + doce.	5-fluorocacil, epirubicin, cyclophosphamide, docetaxel	98	23.3
AC/EC followed by taxanes (sequential regime)	Doxorubicin, cyclophosphamide, paclitaxel	110	26.3
Miscellaneous	Docetaxel, capecitabine, paclitaxel, epirubicin, cyclophosphamide	12	2.9

Description of regimens classified as 'miscellaneous':
- Combination therapy docetaxel and capecitabine (n=5)
- Combination therapy of capecitabine and paclitaxel (n=3)
- Monotherapy paclitaxel (n=3)
- Epirubicin, cyclophosphamide and docetaxel, all given sequential (n=1)

CHAPTER 7

Effect of physical exercise during adjuvant chemotherapy for breast cancer on long-term tested and perceived cognition: Results of a pragmatic follow-up study

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UNDER REVIEW

ABSTRACT

Purpose

Cancer-related cognitive impairment (CRCI) following chemotherapy is commonly reported in breast cancer survivors, even years after treatment. Data from preclinical studies suggest that exercise during chemotherapy may prevent or diminish cognitive problems; however, clinical data are scarce.

Methods

This is a pragmatic follow-up study of two original randomized trials, which compares breast cancer patients randomized to exercise during chemotherapy to non-exercise controls 8.5 years post-treatment. Cognitive outcomes include an online neuropsychological test battery and self-reported cognitive complaints. Cognitive performance was compared to normative data and expressed as age-adjusted z-scores.

Results

A total of 143 patients participated in the online cognitive testing. Overall, cognitive performance was mildly impaired on some, but not all, cognitive domains, with no significant differences between groups. Clinically relevant cognitive impairment was present in 25% to 40% of all participants, regardless of study group. We observed no statistically significant effect of exercise, or being physically active during chemotherapy, on long-term cognitive performance or self-reported cognition, except for the task reaction time, which favored the control group (β=-2.04, 95% confidence interval: -38.48; -2.38). We observed no significant association between self-reported higher physical activity levels during chemotherapy or at follow-up and better cognitive outcomes.

Conclusion

In this pragmatic follow-up study, exercising and being overall more physically active during or after adjuvant chemotherapy for breast cancer did not yield better tested or self-reported cognitive functioning, on average, 8.5 years after treatment. Future prospective studies are needed to document the complex relationship between exercise and CRCI in cancer survivors.

INTRODUCTION

Over the last decades, the number of individuals living with and beyond a breast cancer diagnosis has increased[1]–[3]. Projections forecast that the population of cancer survivors will continue to grow in future years[4]. In this context, adequate care of cancer (therapy)-related side effects is increasingly important.

Cancer-related cognitive impairment (CRCI) is among the most common and burdensome side-effects in both breast cancer patients and survivors. The prevalence of CRCI varies widely across studies, with a mean prevalence of 44% for self-reported CRCI [5]. Prior research has reported that effects on cognitive performance can be detected even 20 years after treatment[6]. The pathophysiology of CRCI is multifactorial, with key roles for (anthracycline-based) chemotherapy, having cancer itself, and co-existing fatigue[5]. In most patients, complaints of CRCI are mild to moderate[7], yet they can profoundly impact the quality of life[8]. Although some interventions are promising, no strategy is currently widely implemented or accepted to prevent CRCI in breast cancer patients[9]

Physical exercise during chemotherapy has been proposed as a strategy to prevent CRCI. Rodent studies describe various pathways via which exercise can benefit cognition, such as stimulating hippocampal neurogenesis[10], [11]. In non-cancer populations, most studies, but not all[12] report an association between higher levels of physical activity[13], [14] or exercise interventions[15], [16] and better cognitive outcomes. In cancer patients, most trials studied the effect of an exercise intervention after treatment (*i.e.,* in survivors), with most of them reporting positive effects on perceived cognition and not on tested cognition[17]–[20]. One small, randomized study (N=25 per study arm) suggests that an unsupervised, home-based walking intervention during chemotherapy might mitigate self-reported CRCI directly after treatment[21]. Evidence from larger, well-conducted trials with longer follow-up times is lacking.

In this study, we evaluated the effect of an aerobic and resistance exercise intervention during adjuvant chemotherapy for breast cancer on cognitive testing and self-reported cognitive complaints measured, on average, 8.5 years after treatment. We hypothesized that exercise during chemotherapy, relative to usual care control, results in less CRCI years after treatment.

METHODS

Setting and participants

The current analysis is part of the Pact-Paces-Heart study, a follow-up investigation of two previously performed randomized controlled trials (RCTs): the Physical Activity during Cancer Treatment (PACT) study and the Physical exercise during Adjuvant Chemotherapy Effectiveness Study (PACES). The design and results of the Pact-Paces-Heart study on cardiovascular outcomes (submitted), as well as results of the original studies, have been published elsewhere[22]–[24]. In brief, the PACT and PACT studies were conducted between 2009-2013 and included 204 and 230 non-metastasized breast cancer patients, respectively. In the PACT study, participants were randomized to either a supervised, moderate-to high-intensity exercise intervention or a control group. The intervention started six weeks after diagnosis with a fixed duration of 18 weeks. PACES' design was comparable, except that there was a second intervention arm (a home-based, low-intensity exercise program), and both interventions of PACES started with the first cycle of chemotherapy and continued until three weeks post-treatment. Both studies collected data (e.g., physical fitness, muscle strength, and patient-related outcomes, including quality of life) at baseline, at the end of chemotherapy, and approximately six months after baseline. In PACT, physical activity levels were recorded by the Short Questionnaire to assess Health-enhancing physical activity (SQUASH)[25]. PACES used the Physical Activity Scale for Elderly[26]. In the follow-up study, physical activity was assessed via the SQUASH. Information on the exercise intervention is provided in Appendix A.

The parent study included 185 breast cancer survivors free of recurrent or metastasized cancer. Participants underwent physical measurements (*i.e.,* cardiac MRI, cardiopulmonary exercise test) and completed questionnaires. Participation in additional cognitive testing was optional. A detailed description of the flow of participants through the studies is provided in Figure 1. The study was approved by the UMC Utrecht institutional review board and was registered with the International Clinical Trial Registry Platform (identifier NTR7247). All patients provided written informed consent.

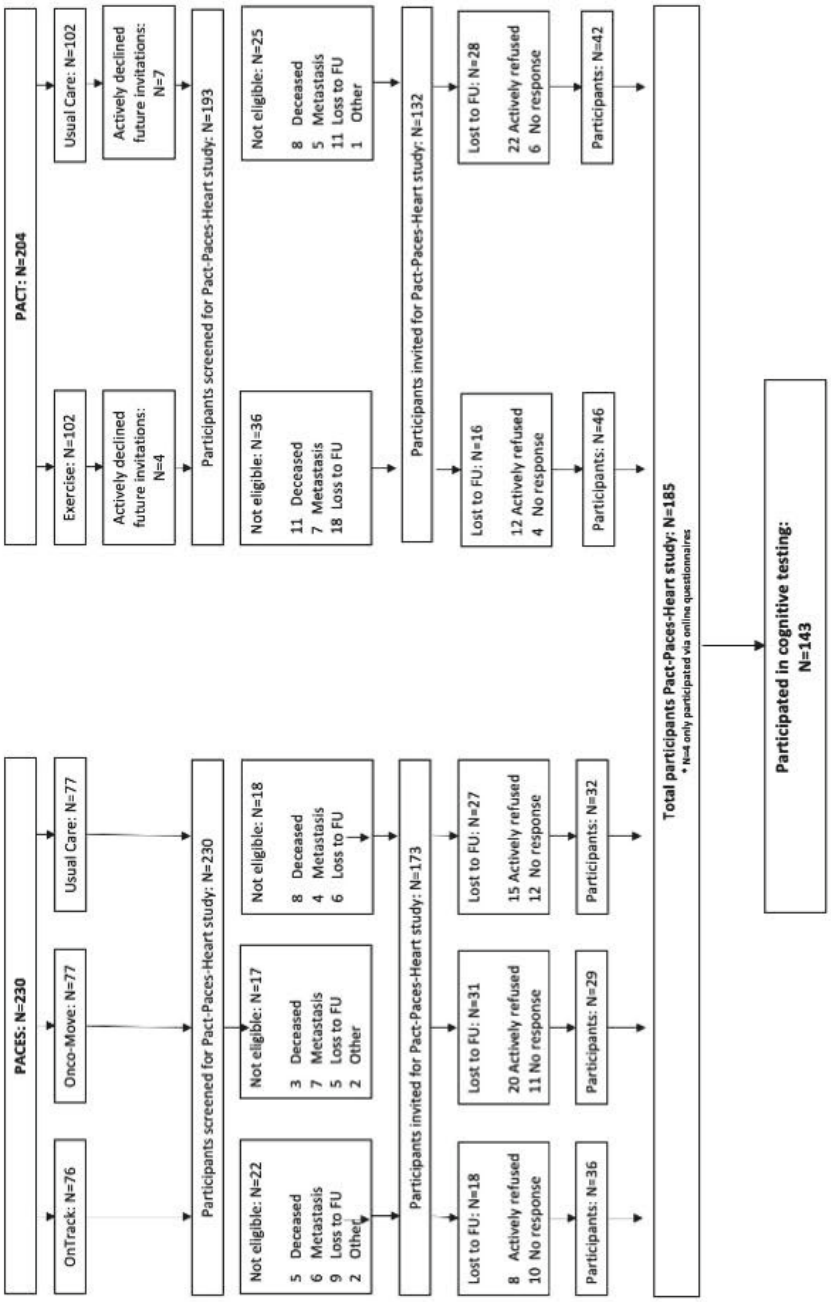

Figure 1. Flowchart of participants in the original PACT and PACES studies, and in the Pact-Paces-Heart study with cognitive testing.

Cognitive outcomes

Objective cognitive testing was performed using the online Amsterdam Cognition Scan (ACS). The ACS is a recently developed, self-administrated neuropsychological test battery that includes 11 computerized tests, based on traditional neuropsychological tests, in the following five cognitive domains: (1) learning and memory; (2) attention and working memory; (3) processing speed; (4) executive functioning; and (5) motor functioning[27]. Reliability and validity to traditional neuropsychological tests of the ACS have been previously described[27], and other oncology studies have used this tool to assess cognitive performance[28], [29].

Subjective cognitive complaints were assessed with the M.D. Anderson Symptom Inventory (MDASI) questionnaire[30], with additional questions from the MDASI multiple myeloma module [27]. The cognitive questions of this module are not specific to multiple myeloma patients and have been previously related to tested cognition[31]. We included two questions on the severity of memory and attention problems and four questions on interference with daily life. Response options were on a 0-10 numeric scale, ranging from "not present" to "as bad as you can imagine" and "did not interfere" to "interfered completely" for the questions on severity and interference, respectively. From these raw scores, a mean subscale score for severity and interference was derived [27]. A previous study reported good-to-excellent reliability, with Cronbach α coefficient values of 0.88 for the severity subscale and 0.91 for the interference subscale[32]. Also, in both the original studies and the follow-up study, all participants of the Pact-Paces-Heart study completed questionnaires on patient-reported outcomes, including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[33]. We calculated the cognitive functioning scale score from this questionnaire, where higher scores (range 0-100) corresponded with better functioning.

Statistical analysis

Numerical data are presented as mean ± standard deviation, and ordinal data or numerical data violating normality assumptions as median [min-max]. Using pre-defined criteria, all ACS entries indicative of poor test understanding, periods of participant distraction, or computer/network problems were identified and excluded. For those tests where higher scores corresponded with worse cognitive performance, we calculated the absolute median deviation per age category (≤40, 41-59, ≥59 years), and all entries >3.5 units were considered outliers and removed

from the database[34]. ACS scores in our sample were compared to normative data (based on 248 healthy adult controls)[35], and expressed as age-adjusted Z-scores. For the cognitive functioning scale of EORTC QLQ-C30, we interpreted our results compared to previously described normative data[36] and used a score of <75 as the threshold for clinically relevant cognitive impairment[37].

We used intention-to-treat regression models with treatment allocation (moderate-to high-intensity exercise versus control) and cognitive outcomes as independent and dependent variables, respectively. All outcomes were modeled linearly, except for those expressed on an ordinal scale (i.e., the correct number of words or sequences), which were modeled via a modified Poisson regression (with a log-link) and expressed as relative differences with robust standard errors (sandwich estimates)[38]For the linear models with non-normally distributed residuals (e.g., the MDASI questionnaire data where most participants reported near-zero scores), estimates and bias-corrected confidence intervals (CIs) were calculated using a bootstrapped distribution based on 10,000 replications[39], [40]

All models were adjusted for age, education (low versus middle or high), study (PACT versus PACES), currently receiving endocrine treatment, and cumulative doxorubicin equivalent dosage (with ratio doxorubicin: epirubicin = 1: 0.7[41]). We additionally adjusted these models for baseline EORTC QLQ C30 scores. Analyses were repeated with changes in self-reported physical activity during chemotherapy, independent of treatment allocation, as the main independent variable. Change in physical activity was defined as the level of physical activity after the intervention (T1) minus the level of physical activity at baseline (T0) and expressed as a z-score, given that the two original studies used different physical activity questionnaires. Restricted cubic splines were used to evaluate the potential nonlinearity of the latter models. We considered a p-value >0.05 as no indication of nonlinearity. Last, we repeated the analyses with physical activity levels at follow-up, expressed as minutes/week as the primary independent variable. As a sensitivity analysis, we added data from participants of the low-intensity exercise program from the PACES trial (N=20) to the exercise group.
All analyses were performed with R studio software (version 4.3.0, Rstudio Inc., Boston, MA).

RESULTS

Of the 185 Pact-Paces-Heart study participants, 143 (N=143/185; 77.3%) participated in the optional cognitive testing. The demographic characteristics of those who completed the cognitive testing were comparable to those who did not participate in the cognitive testing and the original study sample (Supplementary Table 1).

Descriptive results

Of the 143 participants, 66 had been allocated to the moderate-to high-intensity exercise program, 20 to the low-intensity program, and 57 to the control arm. These groups were comparable in most characteristics (Table 1). The average age at the time of cognitive testing was 58.8 ±7.3 years, and the vast majority (>90%) of the participants were post-menopausal. Half of the participants in the control and low-intensity exercise arm and 56% of the women in the moderate-to high-intensity exercise group were highly educated. All participants, except one, received treatment with anthracyclines, with median doxorubicin (equivalent) dosages of 241 [91-420] mg/m2, 235 [0-420] mg/m2, and 292 [196-431] mg/m2 in the control, moderate-to high-intensity exercise, and low-intensity exercise group, respectively. At the time of cognitive testing, 11 (N=11/57; 19.6%) control participants, 7 participants of the moderate-to high-intensity exercise program (N=7/66; 10.8%), and 1 participant of the low-intensity exercise program (N=1/20; 5.0%) received endocrine therapy. Comorbidities were reported in 21 (N=21/57; 37.5%), 22 (N=22/77; 33.8%), and 5 participants (N=5/20; 25.0%), respectively.

Self-reported QLQ-C30 cognitive functioning scores are presented in Table 2. The median score before treatment was 83.3 [0-100.0] in the control and 83.3 [16.7-100.0] in the moderate-to high-intensity group, with self-reported impaired cognitive functioning in 24.6% (N=14/57) and 39.4% (N=26/66), respectively. After chemotherapy treatment, these percentages increased to 50.0%(N=24/48) in the control arm and 53.0% (N=35/66) in the moderate-to high-intensity exercise arm directly after the intervention. At the six-month follow-up, 40.4% (N=21/52) of the control participants and 41.3% (N=26/62) of the moderate-to high-intensity exercise group participants reported impaired cognitive function. At 8.5 years post-treatment, median scores were comparable between study arms; 83.3 [0-100.0] and 83.3 [16.7-100.0], respectively. However, at follow-up, more patients in the exercise group reached the threshold for cognitive impairment (N=31/66; 47.0%) compared to control participants (N=20/56; 35.7%).

Table 1. Characteristics of Pact-Paces-Heart participants who completed the cognitive testing (N=143).
Presented as mean ± SD, median [min-max] or number (percentages)

	Control N=57	**Exercise N=66**	**Low-int. exercise N=20**
Age, years	58.3 ± 7.6	58.9 ± 6.4	59.8 ± 9.3
Original study			
PACT, %	31 (54.3)	39 (59.0)	0 (0.0)
PACES, %	26 (45.6)	27 (40.9)	20 (100.0)
Follow-up time, years	8.6 ±1.2	8.4 ± 1.2	9.2 ± 0.8
Education, %			
Low	6 (10.7)	2 (3.0)	1 (5.0)
Middle	22 (39.3)	27 (40.9)	9 (45.0)
High	28 (50.0)	37 (56.1)	10 (50.0)
Menopausal status, %			
Premenopausal	4 (7.0)	5 (7.6)	2 (10.0)
Postmenopausal	52 (91.2)	61 (92.4)	18 (90.0)
Unknown	1 (1.8)	0 (0.0)	0 (0.0)
Receptor status			
Triple negative	8 (14.0)	12 (18.2)	3 (15.0)
ER/PR+, HER2+	8 (14.0)	11 (16.7)	4 (20.0)
ER/PR-, HER+	2 (3.5)	5 (7.6)	1 (5.0)
ER/PR+, HER-	39 (68.4)	38 (57.6)	12 (60.0)
Radiotherapy, %			
No RT	13 (22.8)	17 (26.2)	8 (40.0)
Left-sided	21 (36.8)	26 (40.0)	5 (25.0)
Right-sided	21 (36.8)	22 (33.8)	5 (25.0)
Unknown	2 (3.5)	0 (0.0)	2 (10.0)
Anthracyclines, %			
No anthracyclines	0 (0.0)	1 (1.5)	0 (0.0)
Doxorubicin	34 (60.7)	30 (46.2)	15 (78.9)
Epirubicin	22 (39.3)	34 (52.3)	4 (21.1)
Unknown	1 (1.8)	1 (1.5)	1 (5.0)
Cumulative dose AC, mg/m^{2*}	241 (91-420)	235 (0-420)	292 (196-431)
Medication use, %			
Cardiovascular	9 (16.1)	15 (23.1)	4 (20.0)
Anti-diabetic	0 (0.0)	1 (1.5)	1 (5.0)
Statins	3 (5.4)	3 (4.6)	2 (10.0)

Table 1. (Continued)

	Control N=57	Exercise N=66	Low-int. exercise N=20
Endocrine treatment	11 (19.6)	7 (10.8)	1 (5.0)
Other	22 (39.3)	17 (26.2)	1 (5.0)
Any comorbidity, %	21 (37.5)	22 (33.8)	5 (25.0)

* Calculated using Doxorubicin : Epirubicin ratio = 1 : 0.
Abbreviations:
AC = anthracycline (equivalent0, ER = estrogen, HER = human epidermal growth factor receptor, int. = intensity, PR = progesterone, RT = radiotherapy.

Scores on the ACS and the MDASI 8.5 years post-treatment are presented in Table 3. Based on the age-adjusted z-scores, participants in our study tended to score lower than healthy controls on the tests assessing learning and memory, attention and working memory, and motor functioning. Above average, although with wide/ non-significant confidence intervals, z-scores were observed for tests of the domain's processing speed and executive functioning.

Table 2. Cognitive functioning based on the EORTC QLQ C-30 in the original studies, and at follow-up.
Presented as median [min-max] or number (percentages)

	Control (N=57)		Exercise (N=66)	
	Data missing (N, %)	Cognitive functioning	Data missing (N, %)	Cognitive functioning
Cognitive functioning				
Before treatment	0 (0)	83.3 [0-100.0]	0 (0)	83.3 [16.7-100.0]
End of chemotherapy	9 (15.8)	75.0 [16.7-100.0]	0 (0)	66.7 [16.7-100.0]
6-months after baseline	5 (8.8)	83.3 [16.7-100.0]	4 (4.5)	83.3 [0-100.0]
8.5-years after baseline	1 (1.8)	83.3 [0-100.0]	0 (0)	83.3 [16.7-100.0]
Cognitive functioning <75, (%)				
Before treatment	0 (0)	14 (24.6)	0 (0)	26 (39.4)
End of chemotherapy	9 (15.8)	24 (50.0)	0 (0)	35 (53.0)
6-months after baseline	5 (8.8)	21 (40.4)	4 (4.5)	26 (41.3)
8.5-years after baseline	1 (1.8)	20 (35.7)	0 (0)	31 (47.0)

Table 3. Cognitive outcomes and corresponding age-corrected Z-scores per study arm. Presented as mean ± SD or median [min-max].

	Control (N=57)		Exercise (N=66)	
	Raw score	**Age-adjusted Z-score* Beta (95% CI)**	**Raw score**	**Age-adjusted Z-score* Beta (95% CI)**
Objective cognitive functioning (ACS)				
Learning and memory				
Wordlist Learning (words, N)	47.0 [27-74]	-0.37 (-0.63, -0.10)	47.0 [13-68]	-0.41 (-0.70, -0.12)
Wordlist Delayed Recall (words, N)	11.0 [6-15]	-0.17 (-0.43, 0.10)	10.0 [4-15]	-0.25 (-0.52, 0.02)
Wordlist Recognition (words, N)	29.0 [26-30]	NA**	29.0 [23-30]	NA**
Attention and working memory				
Box Tapping (correct sequences, N)	9.0 [5-12]	0.17 (-0.02, 0.17)	9.0 [6-12]	0.18 (0.03, 0.33)
Digit Sequences I (correct sequences, N)	10.0 [4-15]	-0.39 (-0.68, -0.10)	10.0 [6-16]	-0.13 (-0.38, 0.13)
Digit Sequences II (correct sequences, N)	8.0 [3-13]	0.11 (-0.35, 0.12)	8.0 [3-14]	-0.18 (-0.05, 0.42)
Processing speed				
Reaction Time (completion time, 10-ms)	31.6 ± 4.1	0.10 (-0.14, 0.35)	34.0 ± 5.3	0.25 (-0.53, -0.02)
Connecting the Dots I (completion time, ms)	37.5 ± 7.8	0.35 (-0.18, 0.51)	35.6 ± 6.7	0.57 (-0.74, 0.40)
Executive functioning				
Connecting the Dots II (completion time, ms)	62.0 ± 15.5	0.34 (0.10, 0.57)	61.1 ± 16.2	0.42 (-0.18, 0.67
Place the Beads (required moves, N)	27.5 [7-64]	0.17 (-0.08, 0.42)	23.5 [4-74]	0.39 (-0.16, 0.62)
Motor functioning				
Fill the Grid (completion time, ms)	68.3 ± 13.4	-0.02 (-0.32, 0.27)	70.7 ± 15.3	-0.20 (-0.51, 0.19)

Table 3. (Continued)

	Control (N=57)		Exercise (N=66)	
	Raw score	**Age-adjusted Z-score* Beta (95% CI)**	**Raw score**	**Age-adjusted Z-score* Beta (95% CI)**
Self-reported cognitive function (MDASI)				
Severity subscale (mean score)	1.50 [0-10]	NA	2.0 [0-9]	NA
Severity subscale classification (%)				
No symptoms	14 (25.0)	NA	16 (24.2)	NA
Mild symptoms	31 (55.4)	NA	34 (51.5)	NA
Moderate symptoms	6 (10.7)	NA	9 (13.6)	NA
Severe symptoms	5 (8.9)	NA	7 (10.6)	NA
Interference subscale (mean score)	0.33 [0-7]	NA	0.92 [0.00-7.3]	NA

* Compared to normative data of 248 non-cancer controls[35].

** Normative data was not available for this test, since this test has been updated since the original version.

Abbreviations:

ACS = Amsterdam Cognition Scan, CI = confidence interval, MDASI = MD Anderson Index, ms= millisecond, N=number, NA = not applicable.

For self-reported cognitive functioning (MDASI) 8.5 years after treatment, most patients reported none or mild symptoms with median scores of 1.50 [0-10] in control participants and 2.0 [0-9] in participants of the moderate-to high-intensity exercise program. Moderate or severe symptoms were reported by 6 (10.7%) and 5 (8.9%), 9 (13.6%), and 7 (10.6%) participants, respectively. Scores on the interference subscale were 0.33 [0-7] in the control group and 0.92 [0-7.3] in the moderate-to high-intensity exercise group.

Effect of moderate-to high-intensity exercise on long-term tested and perceived cognition

We did not find any significant effect of moderate-to high-intensity exercise during chemotherapy on objective cognitive testing 8.5 years after treatment (Table 4). The result for the test Reaction Time significantly favored the control group (β per 10-ms=1.87, 95%CI: 0.06; 3.69). Estimates for self-reported cognitive functioning (MDASI) tended to favor control participants, although the results were not statistically significant. The models with additional correction for baseline EORTC QLQ-C30 cognitive functioning scores yielded comparable results, except for the results for the Reaction Time test (β per 10-ms=1.83, 95%CI: -0.01; 3.67). In the sensitivity analysis, where data of participants of the low-intensity exercise program were added to the intervention group, the result on the test Reaction was not significant anymore; β per 10-ms=1.70, 95%CI: -0.03; 3.43, while the test on Digit Sequence II now significantly favored the exercise arm (relative difference per number of sequences of 1.14, 95%CI: 1.02, 1.26). The other models generated similar conclusions to those presented in Table 4 (data not shown).

Association between physical activity levels and long-term cognition

An increase in physical activity level during chemotherapy was not associated significantly with objectively assessed or self-reported cognitive functioning years after treatment (Table 5). Similarly, physical activity levels at follow-up were not associated significantly with cognitive outcomes (relative differences range from 0.99 to 1.01, and beta coefficients per 0 to 0.07 per 10-minute difference in reported physical activity, data not shown).

Table 4. Effect of an exercise intervention during chemotherapy on tested and perceived cognitive functioning 8.5 years post-treatment.

	Regression model	Estimate	Unadjusted (95%CI)*	Fully adjusted 95%CI)**
Objective cognitive testing (ACS)				
Learning and memory				
Wordlist Learning (words, N)	Poisson	Relative difference	0.99 (0.91, 1.07)	0.98 [0.91, 1.06]
Wordlist Delayed Recall (words, N)	Poisson	Relative difference	0.98 [0.89, 1.07]	0.97 [0.90, 1.06]
Wordlist Recognition (words, N)	Poisson***	Relative difference	1.00 [0.98, 1.01]	1.00 [0.99, 1.0
Attention and working memory				
Box Tapping (correct sequences, N)	Poisson	Relative difference	1.00 [0.93, 1.07]	0.99 [0.93, 1.04]
Digit Sequences I (correct sequences, N)	Poisson	Relative difference	1.06 [0.97, 1.16]	1.06 [0.96, 1.17]
Digit Sequences II (correct sequences, N)	Poisson	Relative difference	1.10 [0.98, 1.23]	1.11 [0.99, 1.24]
Processing speed				
Reaction Time (completion time, 10-ms)	Linear	Beta-coefficient	1.75 [0.01, 3.50]	**1.87 [0.06, 3.69]**
Connecting the Dots I (completion time, ms)	Linear	Beta-coefficient	-1.85 [-4.49, 0.79]	-2.00 [-4.36, 0.36]
Executive functioning				
Connecting the Dots II (completion time, ms)	Linear	Beta-coefficient	-0.85 [-6.74, 5.05]	-0.90 [-6.46, 4.67]
Place the Beads (required moves, N)	Poisson	Relative difference	0.90 [0.75, 1.08]	0.91 [0.76, 1.10]
Motor functioning				
Fill the Grid (completion time, ms)	Linear	Beta-coefficient	2.48 [-2.78, 7.73]	2.86 [-2.35, 8.06]

Self-reported cognitive function (MDASI)				
Severity subscale	Linear***	Beta-coefficient	0.32 [-0.61, 1.24]	0.39 [-0.57, 1.34]
Interference subscale	Linear***	Beta-coefficient	0.34 [-0.33, 1.01]	0.55 [-0.14, 1.24]

* High-intensity, supervised exercise versus control (ref), Onco-Move left out.

** Adjusted for age, education level, study (PACT vs PACES), AC dose and current endocrine treatment (yes/no).

*** Using a Bootstrapping distribution.

Abbreviations:

ACS = Amsterdam Cognition Scan, CI = confidence interval, MDASI = MD Anderson Index, ms= millisecond, N=number.

Table 5. Association between change in self-reported physical activity* during chemotherapy and tested and perceived cognitive functioning 8.5 years post-treatment.

	Regression model	Estimate	Unadjusted (95%CI)	Fully adjusted 95%CI)**
Objective cognitive testing (ACS)				
Learning and memory				
Wordlist Learning (words, N)	Poisson	Relative difference	0.99 [0.94, 1.04]	0.99 [0.95, 1.02]
Wordlist Delayed Recall (words, N)	Poisson	Relative difference	0.99 [0.96, 1.03]	0.99 [0.95, 1.02]
Wordlist Recognition (words, N)	Poisson***	Relative difference	0.99 [0.98, 1.00]	0.99 [0.98, 1.00]
Attention and working memory				
Box Tapping (correct sequences, N)	Poisson	Relative difference	1.00 [0.97, 1.03]	1.00 [0.97, 1.03]
Digit Sequences I (correct sequences, N)	Poisson	Relative difference	1.01 [0.96, 1.06]	1.00 [0.96, 1.05]
Digit Sequences II (correct sequences, N)	Poisson	Relative difference	1.01 [0.96, 1.07]	1.01 [0.96, 1.06]
Processing speed				
Reaction Time (completion time, 10-ms)	Linear	Beta-coefficient	-0.31 [-1.23, 0.61]	-0.47 [-1.40, 0.46]
Connecting the Dots I (completion time, ms)	Linear	Beta-coefficient	1.02 [-0.42, 2.46]	1.14 [-0.05, 2.33]
Executive functioning				
Connecting the Dots II (completion time, ms)	Linear	Beta-coefficient	-0.67 [-3.99, 2.65]	-0.33 [-3.29, 2.63]
Place the Beads (completion time, ms)	Poisson	Relative difference	1.02 [0.95, 1.10]	1.00 [0.93, 1.08]
Motor functioning				
Fill the Grid (completion time, ms)	Linear	Beta-coefficient	1.27 [-1.27, 3.80]	1.42 [-0.90, 3.73]

Subjective cognitive complaints (MDASI)				
Severity of symptoms	Linear***	Beta-coefficient	0.09 [-0.34, 0.53]	0.11 [-0.34, 0.55]
Interference with daily living	Linear***	Beta-coefficient	-0.07 [-0.40, 0.25]	-0.09 [-0.42, 0.24]

* Change is defined as the sum of physical activity at the end of chemotherapy minus the sum of physical activity at baseline.

** Adjusted for age, education level, study (PACT vs PACES), AC dose and current endocrine treatment (yes/no).

*** Using a Bootstrapping distribution.

Abbreviations:

ACS = Amsterdam Cognition Scan, CI = confidence interval, MDASI = MD Anderson Index, ms= millisecond, N=number.

DISCUSSION

In this follow-up study, we investigated the effect of exercise and physical activity on tested cognitive functioning and self-reported cognitive complaints in patients with breast cancer who had participated in one of two randomized clinical trials of exercise programs during their primary chemotherapy treatment approximately 8.5 years earlier. Overall, cognitive performance in some domains (particularly learning and memory) was mildly impaired compared to normative data. Most, but not all, participants reported low levels of perceived cognitive symptoms, with less interference in daily life. We observed no significant effects of moderate-to high-intensity exercise or being more physically active during chemotherapy on tested or perceived cognitive functioning years later, compared to non-exercise controls. Moreover, regardless of randomization, we found no significant association between those who reported higher physical activity levels at follow-up and (better) cognitive outcomes.

Most previous studies that have investigated the effects of exercise performed after the treatment of breast cancer on CRCI reported positive effects on (self-reported) cognitive outcomes[17]–[19] However, minimal evidence is available on the efficacy of exercise during chemotherapy on CRCI. From a mechanistic point of view, multiple pathways support the hypothesis of exercise-mediated neuroprotection, including increased resting brain-derived neurotrophic factor (important for various cellular processes such as neurogenesis), local changes in vascularization, and less neuroinflammation[42]–[44]. This biological rationale is supported by the results of a recent, large observational study of breast cancer patients undergoing adjuvant chemotherapy (N=580), that found that higher self-reported physical activity levels before and during chemotherapy were associated with better perceived and objectively measured cognitive function after chemotherapy completion[45]. The two currently available trials that report on the efficacy of exercise during chemotherapy generated inconclusive results. The first study randomized breast cancer patients to either an unsupervised, home-based walking intervention during chemotherapy (N=25) or usual care (N=25) and found significantly higher levels of perceived cognitive complaints in the latter group but not in the exercise group[21]. There was evidence for between-group differences (p interaction for study group x time: 0.05). Nevertheless, given the limited sample size and that objective cognitive functioning appeared to be unaffected, limited conclusions for clinical practice can be made from these results, and thus more robust evidence is needed.

Our results indicate that exercise during chemotherapy did not have (positive) effects on tested CRCI years after treatment. This finding does not necessarily mean that there were no exercise effects directly after treatment, given that cognitive performance may change over time. The original PACES study reported an effect of exercise on self-reported cognitive complaints, based on the EORTC QLQ C-30, with an effect size of 0.33 [23]. In a longitudinal, randomized study among breast cancer patients that studied the effects of self-affirmation(N=160), perceived cognitive symptoms also varied over time. While the MDASI scores initially increased from baseline to the end of chemotherapy, at six months after chemotherapy, scores on the symptom subscale gradually decreased to an average of 2.10±2.01 for patients in the control arm[46]. These findings have been corroborated by longitudinal neuroimaging studies documenting decreased cognitive performance during chemotherapy, with partial recovery[47] or even increased performance years after treatment in some patients[48]. Our study also observed above-average test scores in the domains of Processing Speed and Executive Functioning, but confidence intervals were wide. The current prevailing hypothesis is that the adult brain, although to a lesser extent than during childhood/adolescence, has the capacity to adapt to environmental changes and recover after disease by, for example, recruiting alternative neuronal circuits[49]–[51]. These neural plasticity processes are likely susceptible to cognitive training, such as memory training or speed tasks [52], [53]. If and to what extent participants compensated for cognitive impairments over time (with or without exercise) is an interesting topic for future research.

Based on the MDASI questionnaire, more than three-quarters of our study participants reported no or mild cognitive symptoms. Scores on the interference subscale were also low. Nevertheless, these results also indicate that a substantial proportion has moderate, or even severe, cognitive complaints years after treatment. The latter aligns with the findings on the EORTC QLQ-C30 questionnaire, in which 40% of the participants reached the threshold for clinically relevant cognitive impairment. The MDASI questionnaire assesses cognitive symptoms and their interference in the past 24 hours, while the EORTC QLQ-C30 cognitive functioning is based on the past week. Subscales on the former instrument are also based on more questions with more extensive scoring ranges, which might have allowed for reporting more details on cognitive complaints. Prior research has reported a good (ρ=0.69) and a moderate correlation (ρ=0.49) between the MDASI symptom and interference subscale and the EORTC QLQ-C30 cognitive functioning scale, respectively[32].

Our current study was designed as a post-hoc, post-trial follow-up (FU) investigation of two original randomized trials (*i.e.,* the PACT and PACES study). This post-trial FU design allowed for pragmatically investigating the effect of exercise and physical activity on long-term CRCI in a relatively large sample of breast cancer survivors. Post-trial FU studies can effectively detect persistent or even enhanced treatment effects years after completion of the original trials, sometimes referred to as the 'legacy effect' [54], [55]. Also, delayed adverse effects, which take years or even decades to become clinically apparent, can be detected by PTFU[56], as exemplified by former studies documenting the cardiotoxic properties of high-dose thoracic radiotherapy[57]–[59]. However, by design, post-trial FU studies may be susceptible to selective response/drop-out, especially with more extended periods of FU. In the context of our research, it is conceivable that breast cancer survivors who were originally randomized to the intervention program, or controls which are currently relatively fit and free of symptoms, were more willing to participate in our follow-up trial (and especially in additional, optional cognitive tests). Indeed, we included slightly more participants who were originally randomized to the exercise arm than to the control arm; 46% (n=66/143) versus 40% (n=57/143), respectively. The proportion of control participants in this follow-up study with cognitive impairment before treatment was lower (n=14/57; 24.6%) than the proportion in the exercise group (n=26/66; 39.4%). Thus, a selective response may have dilated our results to a certain extent, although we observed no significant difference in demographic characteristics between those who participated in our FU study and those who did not. A recently published systematic review recommended using registries and data linkage as the most effective approach for post-trial FU studies[56]. Given that such an approach is not possible for endpoints such as patient-reported outcome measures, we suggest, as we did in the first follow-up of PACT[24], that future randomized studies embed a question in the informed consent that allows for potential future data linkage and study invitation to facilitate future post-trial FU investigations.

Our study has several strengths and limitations in addition to those related to the post-trial FU design. A strength is the combination of objectively tested and self-reported cognitive outcomes in our study, given that these outcomes often are not highly correlated and might measure different constructs of CRCI[60], [61]. An additional limitation is that, apart from the EORTC QLQ-C30 questionnaire, cognitive outcomes were not included in the original trials, and thus we cannot

correct for baseline values of the outcome. Also, not all participants experienced cognitive impairment prior to the intervention, with half of them reaching the threshold for clinically impaired cognitive functioning (Table 2). This means that the other half was unlikely to benefit from the intervention, which presumably limited our ability to study the effectiveness of the exercise program on cognitive functioning. Last, our exercise program was not tailored specifically to address cognitive complaints and was perhaps not the most optimal program for that purpose. A previous meta-analysis indicated that, in addition to aerobic and resistance exercise, non-western traditional modes of exercise, such as Tai Chi or yoga, are at least equally effective in improving cognitive functioning[62]. Thus, a multicomponent exercise program incorporating more holistic exercises might confer greater improvement in cognition functioning.

In conclusion, in this pragmatic follow-up study, we observed no significant effect of exercising or being more physically active during chemotherapy on tested and perceived cognitive functioning years after treatment for breast cancer. Similarly, higher levels of reported physical activity at follow-up were not associated with better cognitive outcomes. Future prospective studies are warranted to investigate the complex relationship between exercise and enhanced physical activity among breast cancer patients who have experienced treatment-related impairment in their cognitive functioning.

REFERENCES

[1] K. D. Miller et al., "Cancer treatment and survivorship statistics, 2016.," CA Cancer J Clin, vol. 66, no. 4, pp. 271–289, Jul. 2016, doi: 10.3322/caac.21349.

[2] H. Sung et al., "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.," CA Cancer J Clin, vol. 71, no. 3, pp. 209–249, May 2021, doi: 10.3322/caac.21660.

[3] J. M. Kocarnik et al., "Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019.," JAMA Oncol, vol. 8, no. 3, pp. 420–444, Mar. 2022, doi: 10.1001/jamaoncol.2021.6987.

[4] "Cancer Treatment | Survivor Facts & Figures." https://www.cancer.org/research/cancer-facts-statistics/survivor-facts-figures.html (accessed Mar. 21, 2023).

[5] A. L. Whittaker, R. P. George, and L. O'Malley, "Prevalence of cognitive impairment following chemotherapy treatment for breast cancer: a systematic review and meta-analysis," Sci Rep, vol. 12, no. 1, Dec. 2022, doi: 10.1038/S41598-022-05682-1.

[6] K. D. Van Der Willik, V. Koppelmans, M. Hauptmann, A. Compter, M. A. Ikram, and S. B. Schagen, "Inflammation markers and cognitive performance in breast cancer survivors 20 years after completion of chemotherapy: a cohort study," Breast Cancer Res, vol. 20, no. 1, Nov. 2018, doi: 10.1186/S13058-018-1062-3.

[7] J. S. Wefel, S. R. Kesler, K. R. Noll, and S. B. Schagen, "Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults," CA Cancer J Clin, vol. 65, no. 2, pp. 123–138, Mar. 2015, doi: 10.3322/CAAC.21258.

[8] T. A. Ahles and J. C. Root, "Cognitive Effects of Cancer and Cancer Treatments," Annu Rev Clin Psychol, vol. 14, pp. 425–451, May 2018, doi: 10.1146/ANNUREV-CLINPSY-050817-084903.

[9] S. B. Schagen, A. S. Tsvetkov, A. Compter, and J. S. Wefel, "Cognitive adverse effects of chemotherapy and immunotherapy: are interventions within reach?," Nat Rev Neurol, vol. 18, no. 3, pp. 173–185, Mar. 2022, doi: 10.1038/S41582-021-00617-2.

[10] P. Z. Liu and R. Nusslock, "Exercise-Mediated Neurogenesis in the Hippocampus via BDNF," Front Neurosci, vol. 12, no. FEB, Feb. 2018, doi: 10.3389/FNINS.2018.00052.

[11] T. Kobilo, Q. R. Liu, K. Gandhi, M. Mughal, Y. Shaham, and H. van Praag, "Running is the neurogenic and neurotrophic stimulus in environmental enrichment," Learn Mem, vol. 18, no. 9, pp. 605–609, 2011, doi: 10.1101/LM.2283011.

[12] E. J. Lenze et al., "Effects of Mindfulness Training and Exercise on Cognitive Function in Older Adults: A Randomized Clinical Trial," JAMA, vol. 328, no. 22, pp. 2218–2229, Dec. 2022, doi: 10.1001/JAMA.2022.21680.

[13] K. I. Erickson et al., "Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines," Med Sci Sports Exerc, vol. 51, no. 6, pp. 1242–1251, Jun. 2019, doi: 10.1249/MSS.0000000000001936.

[14] R. S. Prakash, M. W. Voss, K. I. Erickson, and A. F. Kramer, "Physical activity and cognitive vitality," Annu Rev Psychol, vol. 66, pp. 769–797, Jan. 2015, doi: 10.1146/ANNUREV-PSYCH-010814-015249.

[15] R. S. Falck, J. C. Davis, J. R. Best, R. A. Crockett, and T. Liu-Ambrose, "Impact of exercise training on physical and cognitive function among older adults: a systematic review and meta-analysis," Neurobiol Aging, vol. 79, pp. 119–130, Jul. 2019, doi: 10.1016/J.NEUROBIOLAGING.2019.03.007.

[16] L. F. Biazus-Sehn, F. B. Schuch, J. Firth, and F. de S. Stigger, "Effects of physical exercise on cognitive function of older adults with mild cognitive impairment: A systematic review and meta-analysis," Arch Gerontol Geriatr, vol. 89, Jul. 2020, doi: 10.1016/J.ARCHGER.2020.104048.

[17] K. L. Campbell, K. Zadravec, K. A. Bland, E. Chesley, F. Wolf, and M. C. Janelsins, "The Effect of Exercise on Cancer-Related Cognitive Impairment and Applications for Physical Therapy: Systematic Review of Randomized Controlled Trials," Phys Ther, vol. 100, no. 3, pp. 523–542, Mar. 2020, doi: 10.1093/PTJ/PZZ090.

[18] X. Ren et al., "Effects of physical exercise on cognitive function of breast cancer survivors receiving chemotherapy: A systematic review of randomized controlled trials," The Breast : Official Journal of the European Society of Mastology, vol. 63, p. 113, Jun. 2022, doi: 10.1016/J.BREAST.2022.03.014.

[19] E. W. Koevoets et al., "Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer: a randomized controlled trial (PAM study)," Breast Cancer Res, vol. 24, no. 1, Dec. 2022, doi: 10.1186/S13058-022-01530-2.

[20] K. Gehring et al., "A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept," Neuro Oncol, vol. 22, no. 1, pp. 103–115, Jan. 2020, doi: 10.1093/NEUONC/NOZ178.

[21] K. Gokal, F. Munir, S. Ahmed, K. Kancherla, and D. Wallis, "Does walking protect against decline in cognitive functioning among breast cancer patients undergoing chemotherapy? Results from a small randomised controlled trial," PLoS One, vol. 13, no. 11, Nov. 2018, doi: 10.1371/JOURNAL.PONE.0206874.

[22] N. Travier et al., "Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial.," BMC Med, vol. 13, p. 121, Jun. 2015, doi: 10.1186/s12916-015-0362-z.

[23] H. van Waart et al., "Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial.," J Clin Oncol, vol. 33, no. 17, pp. 1918–1927, Jun. 2015, doi: 10.1200/JCO.2014.59.1081.

[24] L. Witlox et al., "Four-year effects of exercise on fatigue and physical activity in patients with cancer.," BMC Med, vol. 16, no. 1, p. 86, Jun. 2018, doi: 10.1186/s12916-018-1075-x.

[25] G. C. W. Wendel-Vos, A. J. Schuit, W. H. M. Saris, and D. Kromhout, "Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity.," J Clin Epidemiol, vol. 56, no. 12, pp. 1163–1169, Dec. 2003, doi: 10.1016/s0895-4356(03)00220-8.

[26] R. A. Washburn, E. McAuley, J. Katula, S. L. Mihalko, and R. A. Boileau, "The physical activity scale for the elderly (PASE): evidence for validity.," J Clin Epidemiol, vol. 52, no. 7, pp. 643–651, Jul. 1999, doi: 10.1016/s0895-4356(99)00049-9.

[27] H. E. M. Feenstra, J. M. J. Murre, I. E. Vermeulen, J. M. Kieffer, and S. B. Schagen, "Reliability and validity of a self-administered tool for online neuropsychological testing: The Amsterdam Cognition Scan," J Clin Exp Neuropsychol, vol. 40, no. 3, pp. 253–273, Mar. 2018, doi: 10.1080/13803395.2017.1339017.

[28] K. M. Klaver et al., "Neuropsychological test performance and self-reported cognitive functioning associated with work-related outcomes in occupationally active cancer survivors with cognitive complaints," J Cancer Surviv, 2022, doi: 10.1007/S11764-022-01223-X.

[29] E. W. Koevoets et al., "Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer: a randomized controlled trial (PAM study)," Breast Cancer Res, vol. 24, no. 1, Dec. 2022, doi: 10.1186/S13058-022-01530-2.

[30] T. R. M. X. S. W. C. C. M. T. H. M. M. M. C. E. C S Cleeland, "Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory," Cancer , vol. 89(7):1634–46., Oct. 2000.

[31] D. Jones, E. G. Vichaya, X. S. Wang, M. H. Sailors, C. S. Cleeland, and J. S. Wefel, "Acute cognitive impairment in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplant," Cancer, vol. 119, no. 23, pp. 4188–4195, Dec. 2013, doi: 10.1002/CNCR.28323.

[32] D. Jones et al., "Validation of the M. D. Anderson Symptom Inventory multiple myeloma module," J Hematol Oncol, vol. 6, no. 1, 2013, doi: 10.1186/1756-8722-6-13.

[33] N. K. Aaronson et al., "The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology," J Natl Cancer Inst, vol. 85, no. 5, pp. 365–376, Mar. 1993, doi: 10.1093/JNCI/85.5.365.

[34] C. L. O. K. P. B. L. Licata. C Leys, "Detecting outliers: Do not use standard deviations around the mean, do use the median absolute deviation around the median.," J Exp Soc Psychol, vol. 4, pp. 764–766, Jul. 2013.

[35] H. E. M. Feenstra, I. E. Vermeulen, J. M. J. Murre, and S. B. Schagen, "Online Self-Administered Cognitive Testing Using the Amsterdam Cognition Scan: Establishing Psychometric Properties and Normative Data," J Med Internet Res, vol. 20, no. 5, May 2018, doi: 10.2196/JMIR.9298.

[36] K. M. de Ligt, N. K. Aaronson, G. Liegl, and S. Nolte, "Updated normative data for the EORTC QLQ-C30 in the general Dutch population by age and sex: a cross-sectional panel research study," Qual Life Res, 2023, doi: 10.1007/S11136-023-03404-2.

[37] J. M. Giesinger et al., "Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research," J Clin Epidemiol, vol. 118, pp. 1–8, Feb. 2020, doi: 10.1016/J.JCLINEPI.2019.10.003.

[38] G. Zou, "A modified poisson regression approach to prospective studies with binary data.," Am J Epidemiol, vol. 159, no. 7, pp. 702–706, Apr. 2004, doi: 10.1093/aje/kwh090.

[39] J. M. Bland and D. G. Altman, "Statistics Notes: Bootstrap resampling methods," BMJ, vol. 350, Jun. 2015, doi: 10.1136/BMJ.H2622.

[40] A. R. C. to A. R. T. E. S. 2019. Functions to Accompany J. Fox and S. Weisberg, "car: Companion to Applied Regression."

[41] J. L. Zamorano et al., "2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (E," Eur Heart J, vol. 37, no. 36, pp. 2768–2801, Sep. 2016, doi: 10.1093/eurheartj/ehw211.

[42] A. Dinoff et al., "The Effect of Exercise Training on Resting Concentrations of Peripheral Brain-Derived Neurotrophic Factor (BDNF): A Meta-Analysis," PLoS One, vol. 11, no. 9, Sep. 2016, doi: 10.1371/JOURNAL.PONE.0163037.

[43] C. W. Cotman, N. C. Berchtold, and L. A. Christie, "Exercise builds brain health: key roles of growth factor cascades and inflammation," Trends Neurosci, vol. 30, no. 9, pp. 464–472, 2007, doi: 10.1016/J.TINS.2007.06.011.

[44] V. Pialoux, A. D. Brown, R. Leigh, C. M. Friedenreich, and M. J. Poulin, "Effect of cardiorespiratory fitness on vascular regulation and oxidative stress in postmenopausal women," Hypertension, vol. 54, no. 5, pp. 1014–1020, Nov. 2009, doi: 10.1161/HYPERTENSIONAHA.109.138917.

[45] E. A. Salerno et al., "Physical Activity Patterns and Relationships With Cognitive Function in Patients With Breast Cancer Before, During, and After Chemotherapy in a Prospective, Nationwide Study," J Clin Oncol, vol. 39, no. 29, pp. 3283–3292, Oct. 2021, doi: 10.1200/JCO.20.03514.

[46] W. Jacobs et al., "The Effects of Being Informed About Chemotherapy-Related Cognitive Symptoms With And Without Self-Affirmation on Perceived Cognitive Symptoms of Breast Cancer Patients: A Randomized Prospective, Longitudinal Study," Clin Breast Cancer, vol. 22, no. 5, pp. 439–454, Jul. 2022, doi: 10.1016/J.CLBC.2022.03.001.

[47] C. Lepage et al., "A prospective study of grey matter and cognitive function alterations in chemotherapy-treated breast cancer patients," Springerplus, vol. 3, no. 1, 2014, doi: 10.1186/2193-1801-3-444.

[48] T. Billiet et al., "Recovery from chemotherapy-induced white matter changes in young breast cancer survivors?," Brain Imaging Behav, vol. 12, no. 1, pp. 64–77, Feb. 2018, doi: 10.1007/S11682-016-9665-8.

[49] A. Dranovsky et al., "Experience dictates stem cell fate in the adult hippocampus," Neuron, vol. 70, no. 5, pp. 908–923, Jun. 2011, doi: 10.1016/J.NEURON.2011.05.022.

[50] J. Song et al., "Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision," Nature, vol. 489, no. 7414, pp. 150–154, Sep. 2012, doi: 10.1038/NATURE11306.

[51] F. Lourenco and B. J. Casey, "Adjusting Behavior to Changing Environmental Demands with Development," Neurosci Biobehav Rev, vol. 37, no. 9 0 0, pp. 2233–2242, Nov. 2013, doi: 10.1016/J.NEUBIOREV.2013.03.003.

[52] H. Takeuchi et al., "Training of working memory impacts structural connectivity," J Neurosci, vol. 30, no. 9, pp. 3297–3303, Mar. 2010, doi: 10.1523/JNEUROSCI.4611-09.2010.

[53] M. Lövdén et al., "Experience-dependent plasticity of white-matter microstructure extends into old age," Neuropsychologia, vol. 48, no. 13, pp. 3878–3883, Nov. 2010, doi: 10.1016/J.NEUROPSYCHOLOGIA.2010.08.026.

[54] I. Ford, H. Murray, C. McCowan, and C. J. Packard, "Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy 20-year follow-up of west of Scotland coronary prevention study," Circulation, vol. 133, no. 11, pp. 1073–1080, Mar. 2016, doi: 10.1161/CIRCULATIONAHA.115.019014/-/DC1.

[55] G. S. Wander and M. Bansal, "Legacy effect in medicine—the expanding horizon!," Indian Heart J, vol. 70, no. 6, p. 769, Nov. 2018, doi: 10.1016/J.IHJ.2018.12.001.

[56] R. Llewellyn-Bennett, D. Edwards, N. Roberts, A. H. Hainsworth, R. Bulbulia, and L. Bowman, "Post-trial follow-up methodology in large randomised controlled trials: a systematic review," Trials, vol. 19, no. 1, May 2018, doi: 10.1186/S13063-018-2653-0.

[57] D. J. Cutter et al., "Risk of valvular heart disease after treatment for Hodgkin lymphoma," J Natl Cancer Inst, vol. 107, no. 4, Apr. 2015, doi: 10.1093/JNCI/DJV008.

[58] F. A. Van Nimwegen et al., "Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk," JAMA Intern Med, vol. 175, no. 6, pp. 1007–1017, Jun. 2015, doi: 10.1001/JAMAINTERNMED.2015.1180.

[59] B. M. P. Aleman et al., "Late cardiotoxicity after treatment for Hodgkin lymphoma," Blood, vol. 109, no. 5, pp. 1878–1886, Mar. 2007, doi: 10.1182/BLOOD-2006-07-034405.

[60] A. D. Hutchinson, J. R. Hosking, G. Kichenadasse, J. K. Mattiske, and C. Wilson, "Objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review," Cancer Treat Rev, vol. 38, no. 7, pp. 926–934, Nov. 2012, doi: 10.1016/J.CTRV.2012.05.002.

[61] F. S. van D. M. J. M. W. B. J. L. P. F. B. S B Schagen, "Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma," Cancer, vol. 85(3):640–50., 1999.

[62] J. M. Northey, N. Cherbuin, K. L. Pumpa, D. J. Smee, and B. Rattray, "Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis," Br J Sports Med, vol. 52, no. 3, pp. 154–160, Feb. 2018, doi: 10.1136/BJSPORTS-2016-096587.

Supplementary table 1. Demographic characteristics of the original PACT (N=204) and PACES (N=230) participants, and participants in the follow-up study. Presented as mean ± SD, median [min-max] or number (percentages)

	Original PACT and PACES	**Pact-Paces-Heart study (N=185)**	
	N=434	**cognitive testing N=143**	**no cognitive testing N=42**
Age, years	50.1 ± 8.6	50.3 ± 7.2	50.8 ± 9.3
Original study, %			
PACT	204 (47.0)	70 (49.0)	18 (42.9)
PACES	230 (53.0)	73 (51.0)	24 (57.1)
Randomization, %			
Exercise: high-int	178 (41.0)	66 (46.2)	16 (48.5)
Exercise: low-int	77 (17.7)	20 (14.0)	9 (21.4)
Control	179 (41.2)	57 (40.0)	17 (40.4)
Education, %			
Low	40 (9.4)	9 (6.3)	0 (0.0)
Middle	176 (41.4)	58 (40.8)	12 (28.6)
High	209 (49.2)	75 (52.8)	30 (71.4)
Receptor status, %			
Triple negative	78 (18.0)	23 (16.1)	6 (14.3)
ER/PR+, HER2+	73 (16.8)	23 (16.1)	8 (19.0)
ER/PR-, HER+	23 (5.3)	8 (5.6)	4 (9.5)
ER/PR+, HER-	260 (59.9)	89 (62.7)	24 (57.1)
Cumulative dose AC, mg/m^{2*}	240 [0-431]	240 [0-431]	240 [176-420]
Pre-treatment cognitive functioning			
EORTC QLQ-C30	83 [0-100]	83 [0-100]	83 [0-100]
EORTC QLQ-C30<75, %	142 (32.8)	50 (35.0)	13 (31.0)

Abbreviations:
AC = anthracycline (equivalent0, ER = estrogen, EORTC QLQ C-30: European Organization of Research and Treatment of Cancer Quality of Life, HER = human epidermal growth factor receptor, PR = progesterone, RT = radiotherapy.

APPENDIX A: EXERCISE INTERVENTION OF PACT AND PACES

The moderate-to high-intensity exercise programs of the PACT and PACES studies comprised two sessions of aerobic and resistance exercise per week under the supervision of a trained physical therapist. The programs were tailored to the participants' exercise capacity. The attendance rate was 81% and 73% for PACT and PACES, respectively[22], [23]. In addition, participants were encouraged to be physically active for at least 30 minutes per day on the remaining days of the week. Participants allocated to the low-intensity, home-based exercise program of PACES were coached by a trained oncology nurse and received written information on physical activity. PACT and PACES control participants were asked to maintain their pre-treatment physical activity levels.

CHAPTER 8

General Discussion

The short-term effects of exercise during adjuvant chemotherapy on various important health outcomes, including cancer-related fatigue, physical fitness, and quality of life, have been documented over the last year by multiple studies and meta-analyses[1]–[4]. However, less evidence is available on whether exercise during chemotherapy has long-lasting effects and thus translates to fewer or less severe cancer-related sequelae years after treatment. This question is essential for cardiovascular disease (CVD), one of the most common yet burdensome adverse effects of cancer and its treatment. CVD may manifest during cancer treatment or years after that, as a result of both direct and indirect cardiotoxicity[5] and competes with cancer (or, in some patient categories, even surpasses it) as the leading cause of death[6]–[8]. With no other effective pharmacological preventive strategy available, gaining insight into the potential of exercise during chemotherapy to protect against long-term cardiotoxicity is of high clinical importance. To this end, the first aim of this thesis was to expand our knowledge of the role of exercise and physical activity in preventing CVD in long-term cancer survivors. In the second part of this thesis, we evaluated the effects of exercise on two other understudied clinical outcomes; cognitive function and chemotherapy treatment tolerance.
In this chapter, we will first discuss the main findings of this thesis. Then, we will discuss the clinical and methodological considerations, especially the direction for future exercise-cardio-oncology studies.

1. MAIN FINDINGS

1.1 Physical activity and exercise in cardio-oncology

Cancer patients and survivors are at increased risk of CVD as a result of both increased baseline CVD risk and anticancer treatment. Although subclinical cardiac abnormalities are likely detectable within the first year after treatment by active surveillance, first manifestations may take years or even decades after treatment to become clinically apparent. In **Chapter 2**, we aimed to provide an overview of these long-term complications of cancer therapy (radiotherapy and systemic treatment) for adult cancer survivors. The spectrum of CVD in cancer patients, often referred to as cancer therapy-related cardiovascular toxicity (CTR-CVT)[5], is wide and varies from subclinical valvular disease to overt heart failure. Virtually all components of the CV system can be affected by cancer treatment, although some are more prone than others. Thoracic radiotherapy is mainly associated with accelerated coronary artery disease and valvular heart disease and, to a lesser extent, with pericardial disease, conduction

abnormalities, and arrhythmias. The most notorious complication of systemic therapy is left ventricular dysfunction, primarily documented after treatment with anthracyclines or anti-HER2 agents (*i.e.,* trastuzumab). Other CV complications of systemic therapy include myocardial ischemia, peripheral artery disease, and metabolic disorders, including arterial hypertension, dyslipidemia, and insulin resistance.

In **Chapter 3**, we summarized the available evidence on the effect of exercise on doxorubicin-cardiotoxicity in a systematic review and meta-analysis. We found that, in rodent studies, our pooled analyses indicated that both forced and voluntary exercise interventions significantly mitigated in- and ex-vivo doxorubicin-induced cardiotoxicity compared to non-exercise controls. In contrast, in clinical studies, results were indicative of exercise-mediated cardioprotection, but given the small number of studies with limited sample sizes and follow-up, not sufficient to ascertain a protective effect of exercise. As for the underlying mechanisms, we identified oxidative stress and related pathways and less doxorubicin accumulation as mechanisms underlying exercise-induced cardioprotection. We hypothesized that the latter could act as an overarching mechanism, effectively tackling other downstream doxorubicin-induced effects, including oxidative stress.

Up to now, research has been primarily focused on the effects of *exercise* on cardiotoxicity in cancer patients during or shortly after primary treatment. Exercise is any planned, structured, or repetitive physical activity to improve or maintain physical fitness [9]. Whether physical activity in daily life, including recreational and household activities, is associated with cardiac function in breast cancer survivors years after treatment is unknown. Therefore, **in Chapter 4**, we evaluated the association between physical activity and global longitudinal strain (GLS), an early marker of cardiotoxicity, and LVEF. Compared to being inactive, we observed that a modest increase in leisure-time physical activity was associated with a relatively large risk reduction, independent of cardiovascular and treatment-related risk factors. This finding indicates that efforts to increase physical activity, by, for example, physical activity programs, may confer a reduction of CVD risk in breast cancer survivors, particularly among those that are inactive. Last, in **Chapter 5**, we evaluated the effect of exercise and physical activity during chemotherapy for breast cancer on long-term CTR-CVT in the Pact-Paces-Heart study. We found that an exercise program during chemotherapy improved structural, but not functional, cardiac imaging parameters after a mean follow-

up of 8.5 years. Self-reported increase in physical activity during treatment was also associated with better structural cardiac imaging parameters, *i.e.,* indicative of less myocardial fibrosis. Also, we observed a high prevalence of cardiac abnormalities, with more than a quarter of the prior relatively fit and healthy participants having an LVEF below 50% 8.5 years after treatment. This underlines the need to routinely incorporate cardiac screening in the follow-up programs for breast cancer survivors and calls for more research to offset the increased CVD risk in breast cancer survivors.

1.2 Physical exercise and its effect on other cancer-related outcomes

In the second part of this thesis, we gained insight into the role of physical exercise in improving two other clinical outcomes; poor treatment tolerance and cognitive complaints in breast cancer. In **Chapter 6**, we aimed to study the association between pretreatment physical fitness and chemotherapy completion and whether participation in an exercise program modified this association. We used data from the original PACT and PACES studies for these analyses, complemented with medical data on chemotherapy tolerance. We observed that those with lower levels of pretreatment physical fitness are less likely to complete chemotherapy as planned. This association was almost completely mitigated in patients that exercised during chemotherapy, while it was more pronounced in non-exercise controls. These findings indicate that assessing pretreatment physical fitness is important to identify those at risk for not completing chemotherapy and that those patients could potentially benefit from referral to an exercise program as additional care. Last, in **Chapter 7**, we studied the effect of exercise and physical activity during chemotherapy on cognitive function years after treatment. We observed no effect of exercise or physical activity during chemotherapy on both tested and perceived cognition. Also, current levels of physical activity were not associated with cognitive function. Based on these results, we concluded that in our sample of breast cancer survivors, exercise and physical activity during chemotherapy had no beneficial effects on cognitive function years after treatment. The results of the exercise-related studies are summarized in figure 1.

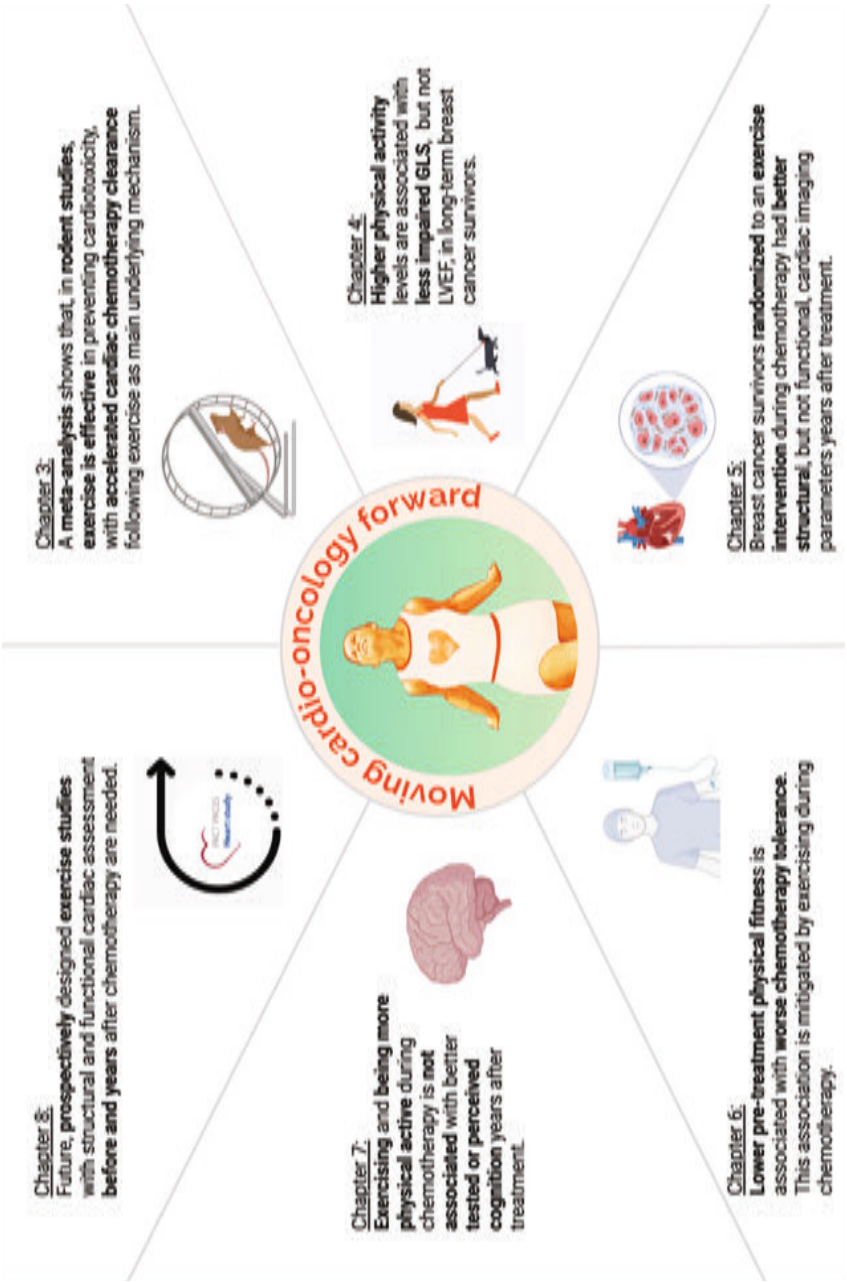

Figure 1: visual summary of the findings of the exercise-related studies in this thesis. Each panel represents a chapter. Note that Chapter 1 (general introduction) and Chapter 2 (overview of long-term cardiovascular disease in adult cancer survivors) are not included, since these chapters generated no new findings related to exercise-cardio-oncology.

2. CLINICAL CONSIDERATIONS ON THE FINDINGS IN THIS THESIS

This thesis aimed to investigate the long-term effects of exercise and physical activity on (cardiovascular) side effects in breast cancer survivors. Here, clinical considerations on the main findings are discussed.

First, our results provide, in general, **additional support for the role of exercise as supportive care** during cancer therapy. A large body of scientific evidence already supports the proposition that exercise should be an integral part of cancer care. Clinical data demonstrate that higher physical activity levels are associated with better survival outcomes for at least the most prevalent cancer subtypes [1]. Also, exercise can mitigate many cancer-related adverse effects, including fatigue, reduced physical fitness, mood disorders, and impaired health-related quality of life [3]. It may also improve bone health and sleep quality[3]. Preclinical evidence indicates that exercise may also directly affect tumor progression (*i.e.,* growth, latency, and metastasis)[10] as well as enhance the effect of an existing anticancer treatment[2]. However, despite all this, exercise is currently not routinely incorporated in all clinical care pathways, and most cancer patients and survivors still fail to meet the physical activity guidelines[11], [12]. For oncologists and other healthcare providers, limited knowledge of the beneficial effects of exercise for cancer patients is considered as one of the barriers that hinders them from exercise prescription[13]. Increasing efforts to create awareness of these effects might help to overcome this barrier. More research, especially on health outcomes that previously received little attention (including CTR-CVT, cognition, and treatment tolerance), on the role of exercise and how this translates to clinical practice for cancer patients could aid in creating additional support and awareness.

In the studies in this thesis, we observed no direct long-term beneficial clinical effect of exercise in terms of, for example, lower symptom burden. This contrasts with the short-term effects of the PACT and PACES studies, which both report positive effects of exercise on cancer-related symptoms[14], [15]. As for the studies in the first (cardio-oncology) part of the thesis, we did, however, observe that exercise and higher levels of physical activity correspond with better markers of subclinical cardiotoxicity, *i.e.,* lower ECV and Native T1 and more negative GLS. Also, survivors with higher self-reported physical activity levels had fewer CVD risk factors, such as hypertension or diabetes.

The clinical significance of subclinical cardiac parameters, as well as improvements in the CVD risk profile, lies in the ability of these parameters to predict future CVD events. Native T1, ECV, and GLS are independent prognostic factors for all-cause mortality and heart failure hospitalization[16]–[20]. A healthier CVD risk profile is associated with lower all-cause and CVD mortality [21], [22]. In a cardio-oncology context, it is assumed that CTR-CVT is a gradual phenomenon where subclinical disease precedes symptomatic disease[23]. The latter occurs when cardiac compensatory mechanisms fail, indicating the progression of the disease to the next phase, which corresponds with an increased risk of adverse clinical events (Figure 2). In this regard, our results could indicate that exercise during chemotherapy prevents early cardiac remodeling, which might translate to better long-term clinical outcomes. Such findings would be consistent with other cardiac populations in which exercise programs have been demonstrated to improve short-term cardiac function and morphology[24] and, in the long term, reduce the risk of myocardial infarction and, eventually, cardiac mortality [25]. Whether less subclinical cardiotoxicity translates to better long-term clinical outcomes must be confirmed by longitudinal follow-up of the Pact-Paces-Heart and HARBOR cohort. However, while awaiting this confirmatory data, with no other effective strategy available, exercise during cancer could be considered a strategy to mitigate CTR-CVT.

In the second part of this thesis, in Chapter 6, we found that breast cancer patients with lower pretreatment physical fitness were less likely to complete chemotherapy as planned. In an explorative analysis, participation in an exercise program almost entirely mitigated this association. Poor chemotherapy tolerance is associated with less optimal disease-free survival[31]. Physical fitness is, in brief, the capacity of the heart, lungs, vascular system, and skeletal muscles to generate energy for physical activity[9]. It is the net result of a combination of non-modifiable factors, such as age and genetics, and modifiable factors, of which physical activity, sedentary time, and a nutritious diet are among the most important[32]. To this end, it can be theorized that sufficient pretreatment physical fitness, or following an exercise program to improve physical fitness, increases the likelihood of chemotherapy tolerance and thus can be related to better survival outcomes. This aligns with former studies[33], [34]. Here, a paradox could occur. If indeed better (maintained) physical fitness translates into lower levels of acute toxicity, and thereby to increased achieved chemotherapy tolerance, the long-term toxicity related to higher doses of received chemotherapy might also be increased. Our results as reported in part one of the thesis show mixed results in

this regard. On the one hand, although not statistically significant and with wide 95%CIs low LVEF was more common in the exercise groups. On the other hand, subclinical parameters of cardiotoxicity significantly *favored* the exercise group. Clearly, whether the cardioprotective effect of exercise offsets the increased chemotherapy burden resulting from higher chemotherapy tolerance requires more research. However, given the lack of other options to improve pretreatment physical fitness and considering that exercise is associated with less symptom burden in cancer patients, we believe that overall, our results do support for the role of exercise as supportive care for oncology outcomes, especially for those with low pretreatment physical fitness.

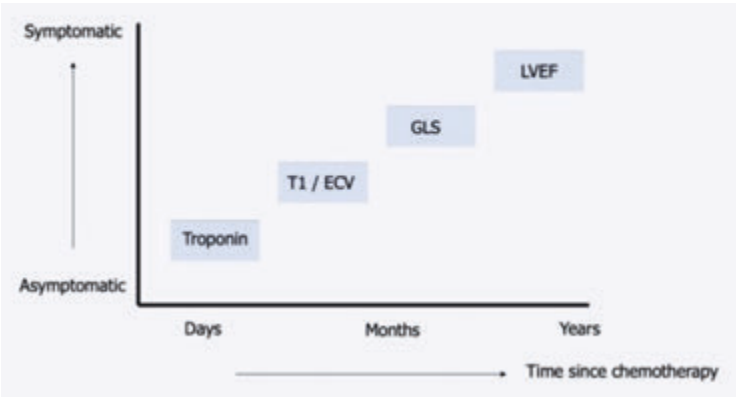

Figure 2. Timeframe of detection of cancer-therapy related cardiac dysfunction in most patients. Troponins can be useful to detect future CTRCD but require repeated sampling to detect a clinically significant rise and the optimal timing with respect to chemotherapy must be established[26]. Increase in T1 mapping indices (i.e., T1 relaxation time and ECV) are reported within weeks following chemotherapy by some, but not all, studies[27]–[29]. A (relative) decline in GLS is considered a strong predictor for subsequent CTRCD[20]. A decline in LVEF is considered a rather late sign of CTRCD and treatment response, if any at that stage, is highly dependent on prompt initiation of heart failure treatment[30].

As a second clinical consideration, we observed a **high prevalence of CV abnormalities** in two clinical cohorts of breast cancer survivors described in this thesis, especially in the Pact-Paces-Heart study (Chapter 5), regardless of allocation to exercise of control conditions during chemotherapy. In a previously described meta-analysis of nearly 50,000 cancer survivors (of whom half were treated with anthracyclines), cumulative incidence for clinically overt and subclinical cardiotoxicity after a median follow-up of nine years was 6%

(95%CI: 3%-9%) and 18% (95%CI: 12%-24%), respectively[35]. In a more recent, prospective cohort study of 2635 patients with various malignancies scheduled for anthracycline-based chemotherapy, 266 (~9%) survivors developed cardiotoxicity (defined as a reduction in LVEF > 10 percentage points to <50%) after a mean follow-up of 5.2 In years [36]. In the HARBOR cohort, abnormal LVEF prevalence was 11% in breast cancer survivors nine years post-treatment[37]. However, subclinical cardiotoxicity, defined as having a GLS>-17%, was prevalent in more than 40% of all study participants[38]. In the Pact-Paces-Heart study, we observed an LVEF<50% prevalence as high as 24% (n=43/179) 8 years post-treatment. Compared to other studies, our study population was relatively old at the time of cardiac imaging and received, especially for a cohort of breast cancer survivors, a high cumulative dose of anthracyclines. Given that these variables are considered among the most important risk factors for CTR-CVT[39], this might account, at least in part, for the discrepancy in proportions. Also, in Pact-Paces-Heart, participants were included before treatment and followed till years after treatment. This contrasts with the HARBOR study, in which survivors were included years after treatment. Thus, those who developed or died of CVD before inclusion might have been underrepresented. Nevertheless, the HARBOR cohort was embedded in a larger cohort of breast cancer survivors with comparable CVD incidence and mortality, making survivor bias unlikely. For the Pact-Paces-Heart study, it can be theorized that we only selected those with (or with interest in) CVD for the follow-up cardiac assessment, which might have resulted in a high proportion of abnormal LVEF. However, the baseline characteristics of participants are comparable to non-participants in the follow-up study. No cardiac deaths were reported during follow-up, and some of our primary outcome parameters were related to subclinical (i.e., asymptomatic) CVD. Also, our Pact-Paces-Heart study population was, apart from having breast cancer, a relatively healthy and fit study population with few clinically documented comorbidities and an interest in participating in an exercise trial. Thus, even if selection bias has occurred and the Pact-Paces-Heart data reflects a subpopulation with (an interest in) CVD, it remains worrisome that such high proportions of LVEF abnormalities can occur in a relatively healthy breast cancer population. Prior research described that having an LVEF in the range of 40% to 50%, regardless of experiencing symptoms, corresponds with a five-fold increased risk of developing heart failure and a 60% increased risk of CV mortality within 12 years [40]. Thus, active follow-up of those with impaired LVEF in our study seems necessary, as well as the need to include regular, long-term cardiac assessment in follow-up programs for newly diagnosed breast cancer patients.

3. METHODOLOGICAL CONSIDERATIONS OF THE PACT-PACES-HEART STUDY

The Pact-Paces-Heart study was designed as an a-priori unplanned, **post-trial follow-up (FU) investigation** of two former randomized controlled trials; the PACT and PACES study. These two studies were both conducted in The Netherlands between 2010-2013 and included participants with non-metastasized breast cancer (and colon patients[41], [42]) scheduled for adjuvant chemotherapy. PACT and PACES randomized participants to a moderate-to high-intensity exercise arm supervised by a physiotherapist or a usual care group. PACES had a second intervention arm comprising a low-intensity, home-based exercise program. In PACES, the exercise interventions started at the first cycle of chemotherapy and continued three weeks after that. The median duration was 19 weeks, coinciding with the fixed intervention period of 18 weeks in PACT. Given these similarities, we assumed that participants could be effectively combined in a pooled follow-up study.

This pragmatic post-trial FU study design yielded a relatively large sample of breast cancer survivors; N=185. This is, compared to former exercise-cardio-oncology studies, with distance the largest study. Also, survivors in our study were, on average, 8.5 ± 1.1 years after treatment. A new randomized exercise study with such a follow-up duration, especially in combination with 185 participants undergoing extensive CV screening, would be (exceptionally) costly and time-consuming. Thus, the post-trial FU design enabled us to effectively study a large sample of breast cancer survivors years after treatment. However, this design also has limitations, of which the possibility of selective response is the most important. The original studies included 434 breast cancer patients (PACT: N=204, PACES: N=230), of whom 185 participated in the follow-up trial. This 43% (n=185/434) is comparable to non-participants for most original PACT and PACES baseline characteristics, including age and cumulative anthracycline dosage. Also, ineligible participants (*i.e.,* those that died during follow-up or were treated for recurrent or metastasized cancer) were generally evenly distributed across the intervention and control arm, with no cardiac-related deaths recorded. As such, it can be hypothesized that the influence of selective response is limited. However, in the context of an exercise trial, it is also conceivable that those who were originally randomized to the intervention arm or those controls who are relatively fit and healthy were more willing to participate in the follow-up investigation. Indeed, we observed slightly higher participation rates in the

moderate-to high-intensity exercise arm than in the control group; 45.0% versus 40.2%, relatively. Also, in Chapter 5, we observed more symptomatic heart disease (cardiac comorbidities) in the exercise group. An impaired LVEF below 50% was also more common in the exercise group, with the regression estimates for this parameter also favoring the control group, although confidence intervals were wide. For the structural parameters ECV and native T1, which likely reflect an asymptomatic disease stage, results favored the exercise arm. These results could support the hypothesis that we mainly selected the healthy controls free of cardiac symptoms for this follow-up investigation.
Another perhaps contradictory explanation for our trend of worse cardiac function in the exercise arm is that breast cancer patients could better tolerate their chemotherapy regime by following the exercise program and thus receive higher cumulative anthracycline dosages. Prior research describes an inverse relationship between anthracycline dosage and LVEF[37], [43]. We observed no difference in median anthracycline dosage between the moderate-to high-intensity exercise and control group. Nevertheless, the potential paradox, with less acute toxicity and better chemotherapy tolerance on the one hand, and increased risk of long-term (cardiovascular) sequelae on the other hand, is a topic worthy of future research.

A second yet related methodological consideration is that our Pact-Paces-Heart study was an **unplanned** post-trial FU investigation. This means that, when designing and conducting the original PACT and PACES studies, participants were not asked, for example, whether they allowed to be approached for future studies during the information consent procedure. This complicated the accrual process for the follow-up study, especially in the current era of privacy regulations. In addition, no baseline cardiac or cognitive measurements were included in the original studies. This limited our ability to establish, at follow-up, if the groups were genuinely comparable at baseline or correct for any baseline values of the outcomes. A recent systematic review recommends using data linkage or access to medical records over clinical-based approaches as the most cost-effective approach for post-trial FU studies, thereby limiting the proportion lost to FU [44]. We suggest that all future randomized studies include a question in the informed consent that allows for potential future study invitations and data linkage with registries to overcome logistical barriers and (selective) loss-to-follow-up.

Last, participants in our study are presumably **not fully representative of the entire population of interest**. Prior exercise-oncology studies, including PACT

and PACES, report participation rates between 11% and 45%[14], [15], [45]–[48]. Participants were, compared to non-participants, more often highly educated, younger, more active, and more likely to be working[48], [49]. In Chapter 7, we describe the results of exercise during chemotherapy on long-term tested and perceived cognition in 143 breast cancer survivors, of whom approximately 50% reported cognitive impairment after chemotherapy. The other half reported no cognitive impairment before or after chemotherapy; thus, this group is unlikely to experience any beneficial effects of exercise. This might explain, among others, the null effects of these analyses. Different recruitment strategies are needed to include more high-risk patients in future studies. Herein, the involvement of the oncologist and radiotherapist seems crucial, given that most patients want to receive information on physical activity and prefer their medical specialist as the primary information source[50], [51].

4. FUTURE STEPS; MOVING EXERCISE-CARDIO-ONCOLOGY STUDIES FORWARD

Evidence from the current available exercise-cardio-oncology studies is, as a whole, indicative that exercise during chemotherapy could yield some cardioprotection in cancer patients and survivors. However, specific knowledge gaps must be addressed to move this field of research forward. These knowledge gaps, grouped by those related to (i) study population, (ii) study design, and (iii) outcome assessment, are discussed below.

As for the **study population**, all currently available evidence is derived from patients with non-metastasized breast cancer. From a cardio-oncology perspective, this group is of high clinical importance, given the high incidence rate of breast cancer, the increased a-priori risk of CVD (most breast cancer diagnoses are in post-menopausal women) and the high 10-year survival rates[52]. However, more research is needed on **other populations**. Of particular interest are the (long-term) survivors of Hodgkin lymphoma and the increasing populations of the other most common malignancies; lung cancer, colorectal carcinoma, melanoma, and prostate cancer[53]. Since these patients differ substantially in terms of baseline CVD risk, type of treatment, and prognosis, results cannot necessarily be extrapolated from one population to another. Also, more research is needed on patients with **advanced cancer**. With the advent of new (immunotherapeutic) agents, the landscape for some types of advanced cancer has changed dramatically. For patients with metastasized

melanoma, for example, immunotherapy improved median survival from a few months[54] to more than five years[55]. Compared to chemotherapy and radiotherapy, immunotherapeutic agents induce a different spectrum of CV side effects, such as myocarditis[56]. Also, as a result of overall muscle wasting (*i.e.,* sarcopenia), patients with advanced cancer are at risk for a degenerative form of cardiomyopathy, which predisposes them even further to heart failure and (ventricular) arrhythmias[57]. Since exercise is currently recommended as first-line therapy for sarcopenia in cancer patients[58], this could be a promising strategy to enhance CVD risk in patients with advanced care.

A second important knowledge gap relating to the study population is the **lack of evidence on high-risk patients**. As described earlier, presumably, a healthy subset of breast cancer patients self-selected to participate in the original PACT and PACES trials. Considering the low incidence rate of LV decline during anthracycline-based chemotherapy for breast cancer[59], with most cases occurring in the elderly or those with pre-existent CVD or predisposing comorbidities (i.e., hypertension, diabetes mellitus, obesity, hypercholesterolemia) [36], [39], the selection of low-risk participants could account, in part, for the lack of intervention effect in most current studies. Also, based on our systematic review in Chapter 6, we observed that animal trials used chemotherapy dosages that were, on average, 2-5 times higher than those used in clinical studies. In our explorative analysis of the Pact-Paces-Heart study, in which we stratified women according to their cumulative anthracycline dosage, we also found the highest intervention effect among those treated with more than 300mg/m^2 of anthracyclines. This dosage coincidence with the only currently registered pharmacotherapeutic therapy for cardioprotection, dexrazoxane. This agent is only recommended in patients with metastatic disease who have already received 300mg/m^2 of anthracyclines and are scheduled for additional anthracycline-based chemotherapy[60], [61]. For dosages <300mg/m^2, no favorable risk/benefit ratio for dexrazoxane has been established[60]. Although overall risk-benefit ratios for exercise are likely different (and more favorable), a future study focusing specifically on those scheduled for high-dose chemotherapy is of clinical interest for this (increasing) patient category.

In terms of **study design**, there is a need for large trials that are **prospectively designed** to analyze cardiac parameters as a response to exercise during and years after chemotherapy treatment. Recently, another post-hoc PTFU analysis of the previously performed OptiTrain study was published[62]. In the per-protocol follow-up analysis, which included 88 of the original 240 participants (36.7%), the

cardiac biomarker NTproBNP was lower in the two exercise groups than in the usual care group after one year of follow-up. Also, those with an increase of this biomarker at 1-year follow-up had a significant drop in VO_2peak at two years, indicating that higher levels of NTproBNP are likely indicative of compromised long-term cardiopulmonary fitness. This study could be, similar to our Pact-Paces-Heart trial, susceptible to attrition bias by design, and thus results need to be confirmed by a prospectively designed study. From a scientific point of view, such a study is best designed as a randomized controlled trial. However, with the growing body of evidence documenting the beneficial effects of exercise during chemotherapy on other health outcomes, randomization to a usual care (*i.e.*, non-exercise) arm seems to challenge the concept of clinical equipoise. Alternative study designs can be considered without the involvement of a non-exercise control group or a wait-list control group. Also, former RCTs in exercise-oncology, including the PACT study, have suffered from contamination, meaning that non-exercise controls also substantially increase their physical activity levels. Recently, an alternative design to the conventional RCT was proposed; the Trials Within Cohorts (TWiCs), in which the intervention study is performed within a longitudinal, observational cohort[63]. The TWiCs design was found to prevent contamination yet increases noncompliance in the intervention group, thereby requiring a larger sample size[64]. Currently, various initiatives are ongoing that are routinely collecting cardiac outcome data in cancer patients undergoing treatment, including the Dutch cardio-oncology registry (ONCOR) [65], which could be candidates for a future (pilot) cardio-oncology exercise TWiC study.

Second, there is a need for studies that analyze cardiac parameters as a response to **different exercise regimens**. Currently, studies used exercise regimens that are relatively comparable in terms of frequency, intensity, time, and type of exercise (FITT), meaning that most trials used an aerobic exercise program with an intensity of ~70% of the estimated maximum exercise capacity, with or without additional resistance exercises. On average, the supervised exercise program was 12 weeks, with two to three weekly sessions [66]–[70]. In a recently published meta-analysis, there was some evidence that, when limiting the analyses to only those studies that used ≥36 exercise sessions, an exercise intervention significantly prevented LVEF decline (mean difference of 3.25%, 95%CI 1.2-5.3) compared to non-exercise controls[71]. Results were not statistically significant when studies that used a lower exercise volume were included. In a non-cancer, high-risk population, a combined aerobic and resistance exercise program was superior to aerobic or resistance training in isolation to improve CVD risk

profile, including cardiorespiratory fitness[72]. Also, in a large meta-analysis of 18 trials in patients with clinically stable heart failure (HFrEF), moderate-intensity continuous training with a duration of ≥6 months substantially improved LVEF, while an exercise duration of <6 months was associated with only a modest increase in LVEF (weighted mean difference 6.3%, 95%CI 4.4-8.1% and 3.7%, 95%CI 1.6-5.8%, respectively)[24]. High-intensity aerobic exercise training was not found to be superior compared to moderate-intensity exercise in this pooled analysis. If these results translate to cancer patients is currently unknown, and thus more research is needed to identify the optimal FITT exercise prescription in this patient category.

The third knowledge gap relates to the assessment of CVD in cancer patients. First, more data is needed on the effect of exercise on **structural cardiac parameters**, such as the presence and extent of myocardial edema and fibrosis. All previous studies focused on functional cardiac parameters except for our Pact-Paces-Heart study. The prevailing hypothesis is that CTR-CVT is a gradual phenomenon, where tissue abnormalities precede functional decline (GLS and in a later stadium LVEF, Figure 2). This is supported by observational studies demonstrating that an increase in cardiac troponin I, as a marker for acute myocardial damage, can already be detected after the two first cycles of anthracycline-based chemotherapy[73], [74]. Interestingly, the study by Foulkes et al. reported that post-chemotherapy troponin I release was less increased in the exercise group compared to the usual care group (8-fold versus 16-fold increase, p=0.002, respectively)[75]. In contrast, in the OptiTrain study, no differences in troponin T release were observed among the exercise intervention groups and the control group[62]. Compared to usual care, they reported less of an increase in NTproBNP at one-year follow-up in these exercise groups [62]. This could be interpreted as more cardiac remodeling in the latter group, although an increase in NTproBNP could be related to various factors, including tumor progression[76], age, and comorbidities[77]. The results of the Pact-Paces-Heart study add to the results of these biomarkers studies by describing that exercise and being more physically active during chemotherapy are associated with fewer structural cardiac abnormalities. In a recent cardiac MRI study of 40 patients undergoing anthracycline-based chemotherapy, both native T1 and ECV were significantly increased from baseline to post-chemotherapy[28]. Moreover, a pig study demonstrated that early changes in cardiac tissue composition, e.g., intracardiomyocyte edema, were detected by cardiac MRI within six weeks after the initiation of doxorubicin. Interestingly, stopping doxorubicin upon detecting

these abnormalities prevented LVEF decline, whereas continuation resulted in overt, irreversible cardiotoxicity[78]. Future clinical studies are needed to document longitudinal changes in cardiac MRI parameters as a response to exercise in cancer patients.

In summary, a prospectively designed randomized study that includes pretreatment cardiac measurements and measures after chemotherapy, and, at least the first year after that, could help address these knowledge gaps. Preferably, cardiotoxicity is assessed via a cardiac MRI, given the interest in structural parameters. Consent for linkage with registries or medical records is a-priori obtained to allow for potential future PTFU studies.

CONCLUSION

Exercise during chemotherapy has many positive effects on cancer patients. Preclinical data almost unanimously supports the proposition of exercise-mediated cardioprotection during chemotherapy via, among others, accelerated intracardial chemotherapy clearance. We observed that exercise and higher levels of physical activity during chemotherapy for breast cancer were associated with better structural, but not functional cardiac parameters, years after treatment. Also, breast cancer survivors who were more active had less subclinical cardiotoxicity and better CVD risk profiles. These findings do not necessarily immediately affect cardiac function or complaints. However, given that subclinical parameters are predictive of future adverse clinical events, these findings may translate to better long-term outcomes. Therefore, longitudinal follow-up of these cohorts is necessary. Also, more research on more diverse study populations, different exercise regimens, and more structural cardiac outcomes is warranted to provide more insight into the role of exercise in mitigating CTR-CVT.

REFERENCES

[1] C. M. Friedenreich, C. R. Stone, W. Y. Cheung, and S. C. Hayes, "Physical Activity and Mortality in Cancer Survivors: A Systematic Review and Meta-Analysis," JNCI Cancer Spectr, vol. 4, no. 1, Feb. 2019, doi: 10.1093/JNCICS/PKZ080.

[2] L. Yang et al., "Effects of Exercise on Cancer Treatment Efficacy: A Systematic Review of Preclinical and Clinical Studies," Cancer Res, vol. 81, no. 19, pp. 4889–4895, Oct. 2021, doi: 10.1158/0008-5472.CAN-21-1258.

[3] K. L. Campbell et al., "Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable.," Med Sci Sports Exerc, vol. 51, no. 11, pp. 2375–2390, Nov. 2019, doi: 10.1249/MSS.0000000000002116.

[4] J. A. Ligibel et al., "Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline.," J Clin Oncol, vol. 40, no. 22, pp. 2491–2507, Aug. 2022, doi: 10.1200/JCO.22.00687.

[5] A. R. Lyon et al., "2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS).," Eur Heart J, Aug. 2022, doi: 10.1093/eurheartj/ehac244.

[6] J. L. Patnaik, T. Byers, C. DiGuiseppi, D. Dabelea, and T. D. Denberg, "Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study.," Breast Cancer Res, vol. 13, no. 3, p. R64, Jun. 2011, doi: 10.1186/bcr2901.

[7] H. Abdel-Qadir et al., "A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer.," JAMA Cardiol, vol. 2, no. 1, pp. 88–93, Jan. 2017, doi: 10.1001/jamacardio.2016.3841.

[8] H. Strongman et al., "Does Cardiovascular Mortality Overtake Cancer Mortality During Cancer Survivorship?: An English Retrospective Cohort Study," JACC CardioOncol, vol. 4, no. 1, pp. 113–123, Mar. 2022, doi: 10.1016/J.JACCAO.2022.01.102.

[9] D. S. Siscovick, R. E. Laporte, J. Newman, D. C. Health ; Iverson, and J. E. Fielding, "Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.," Public Health Reports, vol. 100, no. 2, p. 126, 1985, Accessed: Apr. 15, 2023. [Online]. Available: /pmc/articles/PMC1424733/?report=abstract

[10] K. A. Ashcraft, R. M. Peace, A. S. Betof, M. W. Dewhirst, and L. W. Jones, "Efficacy and Mechanisms of Aerobic Exercise on Cancer Initiation, Progression, and Metastasis: A Critical Systematic Review of In Vivo Preclinical Data," Cancer Res, vol. 76, no. 14, pp. 4032–4050, Jul. 2016, doi: 10.1158/0008-5472.CAN-16-0887.

[11] R. Gal et al., "Physical activity levels of women with breast cancer during and after treatment, a comparison with the Dutch female population," Acta Oncol, vol. 58, no. 5, pp. 673–681, May 2019, doi: 10.1080/0284186X.2018.1563712.

[12] C. M. Blanchard, K. S. Courneya, and K. Stein, "Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II," J Clin Oncol, vol. 26, no. 13, pp. 2198–2204, 2008, doi: 10.1200/JCO.2007.14.6217.

[13] S. J. Hardcastle et al., "Knowledge, attitudes, and practice of oncologists and oncology health care providers in promoting physical activity to cancer survivors: an international survey," Support Care Cancer, vol. 26, no. 11, pp. 3711–3719, Nov. 2018, doi: 10.1007/S00520-018-4230-1.

[14] N. Travier et al., "Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial.," BMC Med, vol. 13, p. 121, Jun. 2015, doi: 10.1186/s12916-015-0362-z.

[15] H. van Waart et al., "Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial.," J Clin Oncol, vol. 33, no. 17, pp. 1918–1927, Jun. 2015, doi: 10.1200/JCO.2014.59.1081.

[16] V. O. Puntmann et al., "Native T1 and ECV of Noninfarcted Myocardium and Outcome in Patients With Coronary Artery Disease.," J Am Coll Cardiol, vol. 71, no. 7, pp. 766–778, Feb. 2018, doi: 10.1016/j.jacc.2017.12.020.

[17] A. Kiaos, D. Antonakaki, M.-A. Bazmpani, C. Karvounis, O. Rimoldi, and T. D. Karamitsos, "Prognostic value of cardiovascular magnetic resonance T1 mapping techniques in non-ischemic dilated cardiomyopathy: A systematic review and meta-analysis.," Int J Cardiol, vol. 312, pp. 110–116, Aug. 2020, doi: 10.1016/j.ijcard.2020.04.052.

[18] T. A. Treibel et al., "Extracellular Volume Associates With Outcomes More Strongly Than Native or Post-Contrast Myocardial T1.," JACC Cardiovasc Imaging, vol. 13, no. 1 Pt 1, pp. 44–54, Jan. 2020, doi: 10.1016/j.jcmg.2019.03.017.

[19] E. Y. Yang et al., "Myocardial Extracellular Volume Fraction Adds Prognostic Information Beyond Myocardial Replacement Fibrosis.," Circ Cardiovasc Imaging, vol. 12, no. 12, p. e009535, Dec. 2019, doi: 10.1161/CIRCIMAGING.119.009535.

[20] E. K. Oikonomou et al., "Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis.," JAMA Cardiol, vol. 4, no. 10, pp. 1007–1018, Oct. 2019, doi: 10.1001/jamacardio.2019.2952.

[21] M. F. Piepoli et al., "2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)," Atherosclerosis, vol. 252, pp. 207–274, Sep. 2016, doi: 10.1016/J.ATHEROSCLEROSIS.2016.05.037.

[22] C. Trevisan et al., "Cardiovascular risk profiles and 20-year mortality in older people: gender differences in the Pro.V.A. study," Eur J Ageing, vol. 19, no. 1, pp. 37–47, Mar. 2021, doi: 10.1007/S10433-021-00620-Y.

[23] D. Cardinale, "[A new frontier: cardio-oncology].," Cardiologia, vol. 41, no. 9, pp. 887–891, Sep. 1996.

[24] W. J. Tucker et al., "Meta-analysis of Exercise Training on Left Ventricular Ejection Fraction in Heart Failure with Reduced Ejection Fraction: A 10-year Update.," Prog Cardiovasc Dis, vol. 62, no. 2, pp. 163–171, 2019, doi: 10.1016/j.pcad.2018.08.006.

[25] P. R. Lawler, K. B. Filion, and M. J. Eisenberg, "Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials," Am Heart J, vol. 162, no. 4, 2011, doi: 10.1016/J.AHJ.2011.07.017.

[26] V. Sorodoc et al., "The Value of Troponin as a Biomarker of Chemotherapy-Induced Cardiotoxicity," Life (Basel), vol. 12, no. 8, Aug. 2022, doi: 10.3390/LIFE12081183.

[27] J. H. Jordan et al., "Anthracycline-Associated T1 Mapping Characteristics Are Elevated Independent of the Presence of Cardiovascular Comorbidities in Cancer Survivors.," Circ Cardiovasc Imaging, vol. 9, no. 8, Aug. 2016, doi: 10.1161/CIRCIMAGING.115.004325.

[28] G. C. Meléndez, J. H. Jordan, R. B. D'Agostino, S. Vasu, C. A. Hamilton, and W. G. Hundley, "Progressive 3-Month Increase in LV Myocardial ECV After Anthracycline-Based Chemotherapy," JACC Cardiovasc Imaging, vol. 10, no. 6, pp. 708–709, Jun. 2017, doi: 10.1016/J.JCMG.2016.06.006.

[29] A. Kimball et al., "Late characterisation of cardiac effects following anthracycline and trastuzumab treatment in breast cancer patients.," Int J Cardiol, vol. 261, pp. 159–161, Jun. 2018, doi: 10.1016/j.ijcard.2018.03.025.

[30] D. Cardinale et al., "Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy.," J Am Coll Cardiol, vol. 55, no. 3, pp. 213–220, Jan. 2010, doi: 10.1016/j.jacc.2009.03.095.

[31] L. Rossi et al., "Impact of Adjuvant Chemotherapy on Breast Cancer Survival: A Real-World Population," PLoS One, vol. 10, no. 7, Jul. 2015, doi: 10.1371/JOURNAL.PONE.0132853.

[32] G. Raghuveer et al., "Cardiorespiratory Fitness in Youth: An Important Marker of Health: A Scientific Statement From the American Heart Association," Circulation, vol. 142, no. 7, pp. E101–E118, Aug. 2020, doi: 10.1161/CIR.0000000000000866.

[33] K. S. Courneya et al., "Effects of exercise during adjuvant chemotherapy on breast cancer outcomes," Med Sci Sports Exerc, vol. 46, no. 9, pp. 1744–1751, 2014, doi: 10.1249/MSS.0000000000000297.

[34] S. C. Hayes et al., "Exercise following breast cancer: exploratory survival analyses of two randomised, controlled trials," Breast Cancer Res Treat, vol. 167, no. 2, pp. 505–514, Jan. 2018, doi: 10.1007/S10549-017-4541-9.

[35] M. Lotrionte et al., "Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity.," Am J Cardiol, vol. 112, no. 12, pp. 1980–1984, Dec. 2013, doi: 10.1016/j.amjcard.2013.08.026.

[36] D. Cardinale et al., "Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy.," Circulation, vol. 131, no. 22, pp. 1981–1988, Jun. 2015, doi: 10.1161/CIRCULATIONAHA.114.013777.

[37] J. N. Jacobse et al., "Myocardial dysfunction in long-term breast cancer survivors treated at ages 40-50 years.," Eur J Heart Fail, vol. 22, no. 2, pp. 338–346, Feb. 2020, doi: 10.1002/ejhf.1610.

[38] J. N. Jacobse et al., "Risk of heart failure after systemic treatment for early breast cancer: results of a cohort study.," Breast Cancer Res Treat, vol. 185, no. 1, pp. 205–214, Jan. 2021, doi: 10.1007/s10549-020-05930-w.

[39] J. L. Zamorano et al., "2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (E," Eur Heart J, vol. 37, no. 36, pp. 2768–2801, Sep. 2016, doi: 10.1093/eurheartj/ehw211.

[40] T. J. Wang, J. C. Evans, E. J. Benjamin, D. Levy, E. C. LeRoy, and R. S. Vasan, "Natural history of asymptomatic left ventricular systolic dysfunction in the community.," Circulation, vol. 108, no. 8, pp. 977–982, Aug. 2003, doi: 10.1161/01.CIR.0000085166.44904.79.

[41] J. K. Van Vulpen et al., "Effects of an Exercise Program in Colon Cancer Patients undergoing Chemotherapy," Med Sci Sports Exerc, vol. 48, no. 5, pp. 767–775, May 2016, doi: 10.1249/MSS.0000000000000855.

[42] H. van Waart et al., "Recruitment to and pilot results of the PACES randomized trial of physical exercise during adjuvant chemotherapy for colon cancer," Int J Colorectal Dis, vol. 33, no. 1, pp. 29–40, Jan. 2018, doi: 10.1007/S00384-017-2921-6.

[43] D. D. Von Hoff et al., "Risk factors for doxorubicin-induced congestive heart failure.," Ann Intern Med, vol. 91, no. 5, pp. 710–717, Nov. 1979, doi: 10.7326/0003-4819-91-5-710.

[44] R. Llewellyn-Bennett, D. Edwards, N. Roberts, A. H. Hainsworth, R. Bulbulia, and L. Bowman, "Post-trial follow-up methodology in large randomised controlled trials: a systematic review," Trials, vol. 19, no. 1, May 2018, doi: 10.1186/S13063-018-2653-0.

[45] S. Mijwel, K. A. Bolam, J. Gerrevall, T. Foukakis, Y. Wengström, and H. Rundqvist, "Effects of Exercise on Chemotherapy Completion and Hospitalization Rates: The OptiTrain Breast Cancer Trial," Oncologist, vol. 25, no. 1, pp. 23–32, Jan. 2020, doi: 10.1634/THEONCOLOGIST.2019-0262.

[46] K. S. Courneya et al., "Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial," J Natl Cancer Inst, vol. 105, no. 23, pp. 1821–1832, Dec. 2013, doi: 10.1093/JNCI/DJT297.

[47] C. S. Kampshoff et al., "Participation in and adherence to physical exercise after completion of primary cancer treatment," Int J Behav Nutr Phys Act, vol. 13, no. 1, Sep. 2016, doi: 10.1186/S12966-016-0425-3.

[48] "Recruitment and retention challenges in breast cancer survivorship research: results from a multisite, randomized intervention trial in women with early stage breast cancer - PubMed." https://pubmed.ncbi.nlm.nih.gov/14578147/ (accessed Apr. 18, 2023).

[49] H. van Waart, W. H. van Harten, L. M. Buffart, G. S. Sonke, M. M. Stuiver, and N. K. Aaronson, "Why do patients choose (not) to participate in an exercise trial during adjuvant chemotherapy for breast cancer?," Psychooncology, vol. 25, no. 8, pp. 964–970, Aug. 2016, doi: 10.1002/PON.3936.

[50] K. A. O'Leary, C. A. Estabrooks, K. Olson, and C. Cumming, "Information acquisition for women facing surgical treatment for breast cancer: Influencing factors and selected outcomes," Patient Educ Couns, vol. 69, no. 1–3, pp. 5–19, Dec. 2007, doi: 10.1016/J.PEC.2007.08.002.

[51] S. J. Hardcastle and P. A. Cohen, "Effective Physical Activity Promotion to Survivors of Cancer Is Likely to Be Home Based and to Require Oncologist Participation," J Clin Oncol, vol. 35, no. 32, pp. 3635–3637, Nov. 2017, doi: 10.1200/JCO.2017.74.6032.

[52] H. Sung et al., "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.," CA Cancer J Clin, vol. 71, no. 3, pp. 209–249, May 2021, doi: 10.3322/caac.21660.

[53] IKNL, "Netherlands Cancer Registry: data and figures, most common cancers. ," https://iknl.nl/en/ncr/ncr-data-figures, 2023.

[54] H. Tsao, M. B. Atkins, and A. J. Sober, "Management of cutaneous melanoma," N Engl J Med, vol. 351, no. 10, pp. 998–1012, Sep. 2004, doi: 10.1056/NEJMRA041245.

[55] J. Larkin et al., "Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma," N Engl J Med, vol. 381, no. 16, pp. 1535–1546, Oct. 2019, doi: 10.1056/NEJMOA1910836.

[56] A. R. Lyon et al., "2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)," Eur Heart J, vol. 43, no. 41, pp. 4229–4361, Nov. 2022, doi: 10.1093/EURHEARTJ/EHAC244.

[57] M. S. Anker et al., "Advanced cancer is also a heart failure syndrome: a hypothesis.," J Cachexia Sarcopenia Muscle, vol. 12, no. 3, pp. 533–537, Jun. 2021, doi: 10.1002/jcsm.12694.

[58] E. Dent et al., "International Clinical Practice Guidelines for Sarcopenia (ICFSR): Screening, Diagnosis and Management," J Nutr Health Aging, vol. 22, no. 10, pp. 1148–1161, Dec. 2018, doi: 10.1007/S12603-018-1139-9.

[59] S. L. Heck et al., "Effect of candesartan and metoprolol on myocardial tissue composition during anthracycline treatment: the PRADA trial.," Eur Heart J Cardiovasc Imaging, vol. 19, no. 5, pp. 544–552, May 2018, doi: 10.1093/ehjci/jex159.

[60] "Dexrazoxane | European Medicines Agency." https://www.ema.europa.eu/en/medicines/human/referrals/dexrazoxane (accessed Mar. 06, 2023).

[61] FDA, "Dexrazoxane, ZINECARD." www.fda.gov/medwatch. (accessed Mar. 06, 2023).

[62] J. Ansund et al., "High intensity exercise during breast cancer chemotherapy - effects on long-term myocardial damage and physical capacity - data from the OptiTrain RCT.," Cardiooncology, vol. 7, no. 1, p. 7, Feb. 2021, doi: 10.1186/s40959-021-00091-1.

[63] S. Y. H. Kim, J. Flory, and C. Relton, "Ethics and practice of Trials within Cohorts: An emerging pragmatic trial design," Clin Trials, vol. 15, no. 1, pp. 9–16, Feb. 2018, doi: 10.1177/1740774517746620.

[64] R. Gal et al., "Effects of exercise in breast cancer patients: implications of the trials within cohorts (TwiCs) design in the UMBRELLA Fit trial," Breast Cancer Res Treat, vol. 190, no. 1, pp. 89–101, Nov. 2021, doi: 10.1007/S10549-021-06363-9.

[65] J. A. M. Kamphuis et al., "ONCOR: design of the Dutch cardio-oncology registry," Neth Heart J, vol. 29, no. 5, pp. 288–294, May 2021, doi: 10.1007/S12471-020-01517-8.

[66] Z. Ma, "Effect of anthracycline combined with aerobic exercise on the treatment of breast cancer.," Pak J Pharm Sci, vol. 31, no. 3(Special), pp. 1125–1129, May 2018.

[67] W. P. Chung et al., "Real-time exercise reduces impaired cardiac function in breast cancer patients undergoing chemotherapy: A randomized controlled trial," Ann Phys Rehabil Med, vol. 65, no. 2, Mar. 2022, doi: 10.1016/J.REHAB.2021.101485.

[68] A. A. Kirkham et al., "Exercise training affects hemodynamics not cardiac function during anthracycline-based chemotherapy.," Breast Cancer Res Treat, vol. 184, no. 1, pp. 75–85, Nov. 2020, doi: 10.1007/s10549-020-05824-x.

[69] A. A. Kirkham et al., "The effect of an aerobic exercise bout 24 h prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: A," Breast Cancer Res Treat, vol. 167, no. 3, pp. 719–729, 2018, doi: 10.1007/s10549-017-4554-4.

[70] W. E. Hornsby et al., "Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial.," Acta Oncol, vol. 53, no. 1, pp. 65–74, Jan. 2014, doi: 10.3109/0284186X.2013.781673.

[71] P. Antunes et al., "Effects of Exercise on Cardiac Function Outcomes in Women Receiving Anthracycline or Trastuzumab Treatment for Breast Cancer: A Systematic Review and Meta-Analysis," Applied Sciences, vol. 11, no. 18. 2021. doi: 10.3390/app11188336.

[72] E. C. Schroeder, W. D. Franke, R. L. Sharp, and D. chul Lee, "Comparative effectiveness of aerobic, resistance, and combined training on cardiovascular disease risk factors: A randomized controlled trial," PLoS One, vol. 14, no. 1, Jan. 2019, doi: 10.1371/JOURNAL.PONE.0210292.

[73] D. Cardinale et al., "Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy," Circulation, vol. 109, no. 22, pp. 2749–2754, Jun. 2004, doi: 10.1161/01.CIR.0000130926.51766.CC.

[74] H. Sawaya et al., "Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab," Circ Cardiovasc Imaging, vol. 5, no. 5, pp. 596–603, 2012, doi: 10.1161/CIRCIMAGING.112.973321.

[75] S. J. Foulkes et al., "Exercise for the Prevention of Anthracycline-Induced Functional Disability and Cardiac Dysfunction: The BREXIT Study," Circulation, vol. 147, no. 7, Feb. 2023, doi: 10.1161/CIRCULATIONAHA.122.062814.

[76] T. Kamai et al., "Elevated serum levels of cardiovascular biomarkers are associated with progression of renal cancer," Open Heart, vol. 5, no. 1, Feb. 2018, doi: 10.1136/OPENHRT-2017-000666.

[77] P. Welsh et al., "Reference Ranges for NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) and Risk Factors for Higher NT-proBNP Concentrations in a Large General Population Cohort," Circ Heart Fail, vol. 15, no. 10, p. E009427, Oct. 2022, doi: 10.1161/CIRCHEARTFAILURE.121.009427.

[78] C. Galán-Arriola et al., "Serial Magnetic Resonance Imaging to Identify Early Stages of Anthracycline-Induced Cardiotoxicity," J Am Coll Cardiol, vol. 73, no. 7, pp. 779–791, Feb. 2019, doi: 10.1016/J.JACC.2018.11.046.

APPENDICES

ENGLISH SUMMARY

Exercise is an increasingly recognized effective strategy to counteract cancer-related symptoms during and shortly after chemotherapy, such as cancer-related fatigue [1]–[4]. However, whether exercise during chemotherapy has lasting effects and thus translates to fewer sequelae years after treatment has received little attention. In the absence of other effective preventive strategies, whether exercise yields long-term benefits is particularly important for cancer therapy-related cardiovascular toxicity (CTR-CVT), one of the most common yet burdensome late effects of cancer and its treatment. In the first part of this thesis, we evaluate the role of exercise and physical activity in mitigating cancer therapy-related cardiovascular toxicity (CTR-CVT) in cancer survivors years after treatment. The (long-term) effects of exercise on two other understudied clinical outcomes, cognitive function, and chemotherapy tolerance, are discussed in the second part of this thesis.

1. PHYSICAL ACTIVITY AND EXERCISE IN CARDIO-ONCOLOGY

Chapter 1 introduced the clinical background of the studies in this thesis. The number of individuals with and beyond a cancer diagnosis has consistently increased over the last decades[5]–[7], and projections forecast that this trend will continue in the future [6]. To adequately address cardiovascular side effects in the increasing population of cancer survivors, the interdisciplinary field of cardio-oncology emerged in the late 1990s [8]. Initially, the scope of cardio-oncology was mainly on treating cardiac side effects, although the emphasis currently shifted more towards early diagnosis and prevention.

Although cancer and CVD are generally considered two different entities, increasing evidence suggests an overlap between these two diseases. Cancer and CVD share common risk factors (such as age and smoking), and multiple biological pathways are common to both disorders[9]–[11]. The anticancer treatment further augments the baseline CVD risk in cancer patients, leading to an almost two-fold increased risk of dying of CVD in breast cancer survivors years after treatment compared to cancer-free age-matched controls[12]. CVD competes with breast cancer itself, or in the elderly or those with pre-existing CVD before cancer treatment even surpasses it as the leading cause of mortality[13]–[15].

Chapter 2 provided an overview of the long-term cardiovascular sequelae of anticancer treatment in adult cancer survivors. Patients treated with thoracic radiotherapy are primarily at risk for accelerated coronary disease and left-sided valvular disease, although virtually all components of the cardiovascular system can be affected by accidental radiotherapy. Radiotherapy-related CVD is primarily reported in patients irradiated with high thoracic dosages, such as the former mantle field radiation for Hodgkin's lymphoma[16]. Nevertheless, radiotherapy-related CVD is also described in patients irradiated with more contemporary radiotherapy techniques[17]. In patients treated with systemic therapy, left ventricular (LV) dysfunction (often referred to as cancer-related cardiac dysfunction; CTRCD) is among the most notorious complications. CTRCD has been predominately reported following treatment with anthracyclines and anti-HER2NEU agents (i.e., trastuzumab). Overt systolic heart failure manifesting years after anthracycline-based chemotherapy is reported in approximately 6% of patients treated with contemporary regimens and is, historically, associated with an adverse prognosis[18], [19].
Nevertheless, with the advent of more advanced cardiac screening methods, the first subclinical abnormalities can now be detected within the year after anthracycline-based chemotherapy. If heart failure medication is prompted, recovery of left ventricular systolic function (LV ejection fraction; LVEF) can be achieved in most patients[20]. Such findings stress the need for routine, clinical implementation of early detection methods, of which echocardiography-derived global longitudinal strain (GLS) seems a particularly promising parameter. Cardiac MRI imaging, if available, can provide additional information, including non-invasive measurements of diffuse myocardial fibrosis by quantifying native T1 relaxation time and extracellular volume fraction (ECV). The current prevailing hypothesis for anthracycline-related CTRCD is that change in cardiac tissue composition precedes functional decline (GLS and a later stadium: LVEF)[21].

In **Chapter 3**, we summarized and quantified the evidence of the effect of exercise during anthracycline-based chemotherapy on in-vivo and ex-vivo parameters of cardiotoxicity and evaluated pathways underlying exercise-mediated cardioprotection. To this end, we included both clinical and preclinical studies. In preclinical studies (N=37), almost all studies report significantly less in-vivo and/or ex-vivo cardiotoxicity in exercising animals than in non-exercise controls. Our pooled analysis, structured around the type of intervention, indicated slightly larger intervention effects for those animal studies treated with forced exercise than voluntary exercise interventions. Accelerated cardiac chemotherapy

clearance, presumably by upregulation of transporting receptor proteins, and less oxidative stress following exercise could underly exercise-mediated cardioprotection. We propose that the former could act as an overarching mechanism, effectively tackling all downstream effects. In the clinical studies (N=3), overall results were indicative that exercise could mitigate anthracycline-related CTRCD to a certain extent. However, given the small sample sizes (N < 30 per study arm) and limited follow-up period, we concluded that evidence was insufficient to confirm the preclinical results in a clinical setting.

Most prior research has focused on exercise's effects on CTR-CVT in cancer patients. Exercise is defined as any planned, structured, or repetitive physical activity to improve or maintain physical fitness [22]. However, whether *daily life physical activity*, including household and recreational activities, is also associated with cardiac outcomes has received little attention. Such an association could stimulate further research with the potential to change physical activity recommendations for cancer survivors. Therefore, in **Chapter 4**, we studied the association between physical activity levels and myocardial function in long-term breast cancer survivors in the HARBOR cohort. The HARBOR cohort (Identifying Subgroups with High Cardiovascular Risk in Breast Cancer Survivors) included 569 female breast cancer survivors treated at ages 40 to 50 years[23]. Based on self-reported physical activity levels, breast cancer survivors were classified into the following four categories of the Cambridge Physical Activity Index; (1) inactive, (2) moderately inactive, (3) moderately active, or (4) active[24]. Echocardiography was performed, on average, ten years after chemotherapy treatment. Compared to inactive survivors, we observed higher physical activity levels were associated with a lower risk of impaired GLS after correction for patient- and treatment-related risk factors. The reduction was most apparent for those that were moderately inactive compared to those who were inactive, with relatively few additional risk reductions in the two most active categories. LVEF was within normal ranges in all physical activity categories and was not associated with physical activity. We concluded that higher physical activity levels were associated with GLS, but not LVEF, independent of CVD risk factors. This finding suggests that physical activity programs may confer CVD benefits in breast cancer survivors, especially those physically inactive. Prospective studies are, however, necessary to confirm the results of our cross-sectional analysis.

In **Chapter 5**, we presented the results of the Pact-Paces-Heart study. We studied the effect of exercise and physical activity during chemotherapy on CTR-CVT

in breast cancer survivors years after treatment. The Pact-Paces-Heart study was designed as a post-trial follow-up (FU) investigation of two previously performed, comparative randomized trials; the PACT (N=204) and PACES (N=230) studies. These two Dutch studies investigated the short-term effect of exercise during adjuvant chemotherapy for breast cancer on various health outcomes, including fatigue, quality of life, and physical fitness[25], [26]. We included 185 (N=185/434; 43%) breast cancer survivors free of recurrent or metastasized breast cancer. The mean time since treatment was 8.5 years. Cardiovascular outcomes were assessed with a cardiac MRI (structural cardiac parameters; extracellular volume fraction (ECV) and native T1 and LVEF), an echocardiogram (GLS), and a cardiopulmonary exercise test (VO_{2peak}).
Compared to those originally randomized to the control arm, we found more favorable ECV and native T1 values, but not LVEF and GLS, in exercising breast cancer survivors. Independent of randomization, higher physical activity during chemotherapy was significantly associated with better ECV and native T1. Those who currently reported higher levels of physical activity had significantly higher VO_{2peak} values, but we found no association with cardiac imaging parameters. In the overall study sample, we observed a high prevalence of cardiac abnormalities, with over a quarter of the prior relatively fit and healthy breast cancer patients having an LVEF below the clinical threshold of 50%. This underlines the need to incorporate cardiac screening in breast cancer follow-up programs routinely and calls for additional research on cardioprotective measures, including alternative exercise regimens.

1.2 Physical exercise and its effect on cancer-related outcomes

Survival rates for most cancers, including breast cancer, have substantially improved over the last years, and ongoing improvements in chemotherapy regimens are considered one of the main drivers for this success[6], [7], [27], [28]. Nevertheless, approximately one-third of the breast cancer patients treated with contemporary chemotherapy regimens fail to adhere to the prescribed treatment schedule [28]. In **Chapter 6**, we studied the association between pre-treatment physical fitness and chemotherapy completion and whether this association was modified by participation in an exercise program during chemotherapy. For these analyses, we complemented the data of the original PACT and PACES studies with medical data on chemotherapy completion. We observed that breast cancer patients with lower pre-treatment physical fitness are less likely to complete chemotherapy as planned. This association was almost completely mitigated in patients allocated to the exercise program, while it was more pronounced in

non-exercise control patients. These results show that pre-treatment physical fitness is vital to identify those at risk for not completing chemotherapy and that this patient group may especially benefit from referral to an exercise program as supportive care during chemotherapy.

Cancer-related cognitive impairment is common in breast cancer survivors treated with chemotherapy; approximately one in three patients report a certain extent of cognitive complaints at some stage of the disease[29]. Cognitive complaints can profoundly impact daily life by, among others, limiting return to work after cancer treatment. In **Chapter 7**, we studied the effect of exercise on cognitive performance and complaints years after chemotherapy in participants in the Pact-Paces-Heart study. Cognitive performance and complaints were assessed via an online, self-administrated test battery of neuropsychological tasks and questionnaires, respectively. A total of 143 participants of the Pact-Paces-Heart parent study (N=143/185; 77%) completed the optional cognitive testing. Half of the participants reported clinically relevant cognitive complaints after chemotherapy in both exercise and the control group. At follow-up, cognitive performance was mildly impaired on some, but not all, cognitive domains in our study sample compared to normative data, with no statistically significant difference between those allocated to the exercise or the control arm. We observed no effect of exercise or being physically active during chemotherapy on long-term tested or perceived cognition. Similarly, higher physical activity levels reported at follow-up were not associated with cognitive outcomes. We concluded that, in our study sample, exercise during chemotherapy was not associated with long-term cognitive outcomes, and future studies should target patients at high risk for developing cognitive impairment.

In **Chapter 9**, we discussed the main results presented in this thesis. Also, we elaborate on the clinical and methodological considerations of the abovementioned studies and suggestions on how the research field of exercise-cardio-oncology can move forward. We concluded that, in general, our results provide additional support for exercise as supportive care during cancer treatment. Also, our clinical studies' high prevalence of cardiac abnormalities stresses the need for long-term cardiac follow-up in this patient category. Our primary methodological consideration relates to the Pact-Paces-Heart study's unplanned, post-trial FU design. Such studies are, by design, susceptible to selective drop-out, although we observed no results indicative of selection bias. Focusing on hard clinical endpoints could limit selective loss-to-follow-up in

future post-trial FU studies[30]. To fully document the role of exercise in mitigating CTR-CVT, a future, large, randomized, prospectively designed study that includes structural and functional cardiac outcomes collected before and directly after treatment and at least one year after chemotherapy is necessary. To adequately allow post-trial FU beyond that period, we suggest including consent for linkage with registries and medical records a-priori in the informed consent procedure.

REFERENCES

[1] C. M. Friedenreich, C. R. Stone, W. Y. Cheung, and S. C. Hayes, "Physical Activity and Mortality in Cancer Survivors: A Systematic Review and Meta-Analysis," JNCI Cancer Spectr, vol. 4, no. 1, Feb. 2019, doi: 10.1093/JNCICS/PKZ080.

[2] L. Yang et al., "Effects of Exercise on Cancer Treatment Efficacy: A Systematic Review of Preclinical and Clinical Studies," Cancer Res, vol. 81, no. 19, pp. 4889–4895, Oct. 2021, doi: 10.1158/0008-5472.CAN-21-1258.

[3] J. A. Ligibel et al., "Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline.," J Clin Oncol, vol. 40, no. 22, pp. 2491–2507, Aug. 2022, doi: 10.1200/JCO.22.00687.

[4] K. L. Campbell et al., "Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable.," Med Sci Sports Exerc, vol. 51, no. 11, pp. 2375–2390, Nov. 2019, doi: 10.1249/MSS.0000000000002116.

[5] K. D. Miller et al., "Cancer treatment and survivorship statistics, 2016.," CA Cancer J Clin, vol. 66, no. 4, pp. 271–289, Jul. 2016, doi: 10.3322/caac.21349.

[6] H. Sung et al., "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.," CA Cancer J Clin, vol. 71, no. 3, pp. 209–249, May 2021, doi: 10.3322/caac.21660.

[7] J. M. Kocarnik et al., "Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019.," JAMA Oncol, vol. 8, no. 3, pp. 420–444, Mar. 2022, doi: 10.1001/jamaoncol.2021.6987.

[8] D. Cardinale, "[A new frontier: cardio-oncology].," Cardiologia, vol. 41, no. 9, pp. 887–891, Sep. 1996.

[9] R. J. Koene, A. E. Prizment, A. Blaes, and S. H. Konety, "Shared Risk Factors in Cardiovascular Disease and Cancer.," Circulation, vol. 133, no. 11, pp. 1104–1114, Mar. 2016, doi: 10.1161/CIRCULATIONAHA.115.020406.

[10] T. J. Pfeffer, S. Pietzsch, and D. Hilfiker-Kleiner, "Common genetic predisposition for heart failure and cancer.," Herz, vol. 45, no. 7, pp. 632–636, Nov. 2020, doi: 10.1007/s00059-020-04953-9.

[11] V. Narayan, E. W. Thompson, B. Demissei, J. E. Ho, J. L. J. Januzzi, and B. Ky, "Mechanistic Biomarkers Informative of Both Cancer and Cardiovascular Disease: JACC State-of-the-Art Review.," J Am Coll Cardiol, vol. 75, no. 21, pp. 2726–2737, Jun. 2020, doi: 10.1016/j.jacc.2020.03.067.

[12] P. T. Bradshaw, J. Stevens, N. Khankari, S. L. Teitelbaum, A. I. Neugut, and M. D. Gammon, "Cardiovascular Disease Mortality Among Breast Cancer Survivors.," Epidemiology, vol. 27, no. 1, pp. 6–13, Jan. 2016, doi: 10.1097/EDE.0000000000000394.

[13] H. Abdel-Qadir et al., "A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer.," JAMA Cardiol, vol. 2, no. 1, pp. 88–93, Jan. 2017, doi: 10.1001/jamacardio.2016.3841.

[14] J. L. Patnaik, T. Byers, C. DiGuiseppi, D. Dabelea, and T. D. Denberg, "Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study.," Breast Cancer Res, vol. 13, no. 3, p. R64, Jun. 2011, doi: 10.1186/bcr2901.

[15] H. Strongman et al., "Does Cardiovascular Mortality Overtake Cancer Mortality During Cancer Survivorship?: An English Retrospective Cohort Study," JACC CardioOncol, vol. 4, no. 1, pp. 113–123, Mar. 2022, doi: 10.1016/J.JACCAO.2022.01.102.

[16] D. B. Hughes et al., "Treatment planning for Hodgkin's disease: A patterns of care study," Int J Radiat Oncol Biol Phys, vol. 33, no. 2, pp. 519–524, Sep. 1995, doi: 10.1016/0360-3016(94)00605-K.

[17] S. C. Darby et al., "Risk of ischemic heart disease in women after radiotherapy for breast cancer.," N Engl J Med, vol. 368, no. 11, pp. 987–998, Mar. 2013, doi: 10.1056/NEJMoa1209825.

[18] M. Lotrionte et al., "Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity.," Am J Cardiol, vol. 112, no. 12, pp. 1980–1984, Dec. 2013, doi: 10.1016/j.amjcard.2013.08.026.

[19] G. M. Felker et al., "Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy.," N Engl J Med, vol. 342, no. 15, pp. 1077–1084, 2000.

[20] D. Cardinale et al., "Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy.," Circulation, vol. 131, no. 22, pp. 1981–1988, Jun. 2015, doi: 10.1161/CIRCULATIONAHA.114.013777.

[21] D. Cardinale, F. Iacopo, and C. M. Cipolla, "Cardiotoxicity of Anthracyclines.," Front Cardiovasc Med, vol. 7, p. 26, 2020, doi: 10.3389/fcvm.2020.00026.

[22] D. S. Siscovick, R. E. Laporte, J. Newman, D. C. Health ; Iverson, and J. E. Fielding, "Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.," Public Health Reports, vol. 100, no. 2, p. 126, 1985, Accessed: Apr. 15, 2023. [Online]. Available: /pmc/articles/PMC1424733/?report=abstract

[23] J. N. Jacobse et al., "Myocardial dysfunction in long-term breast cancer survivors treated at ages 40-50 years.," Eur J Heart Fail, vol. 22, no. 2, pp. 338–346, Feb. 2020, doi: 10.1002/ejhf.1610.

[24] N. J. Wareham et al., "Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.," Public Health Nutr, vol. 6, no. 4, pp. 407–413, Jun. 2003, doi: 10.1079/PHN2002439.

[25] N. Travier et al., "Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial.," BMC Med, vol. 13, p. 121, Jun. 2015, doi: 10.1186/s12916-015-0362-z.

[26] H. van Waart et al., "Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial.," J Clin Oncol, vol. 33, no. 17, pp. 1918–1927, Jun. 2015, doi: 10.1200/JCO.2014.59.1081.

[27] L. Rossi et al., "Impact of Adjuvant Chemotherapy on Breast Cancer Survival: A Real-World Population," PLoS One, vol. 10, no. 7, Jul. 2015, doi: 10.1371/JOURNAL.PONE.0132853.

[28] G. H. Lyman, "Impact of chemotherapy dose intensity on cancer patient outcomes," J Natl Compr Canc Netw, vol. 7, no. 1, pp. 99–108, 2009, doi: 10.6004/JNCCN.2009.0009.

[29] A. L. Whittaker, R. P. George, and L. O'Malley, "Prevalence of cognitive impairment following chemotherapy treatment for breast cancer: a systematic review and meta-analysis," Sci Rep, vol. 12, no. 1, Dec. 2022, doi: 10.1038/S41598-022-05682-1.

[30] R. Llewellyn-Bennett, D. Edwards, N. Roberts, A. H. Hainsworth, R. Bulbulia, and L. Bowman, "Post-trial follow-up methodology in large randomised controlled trials: a systematic review," Trials, vol. 19, no. 1, May 2018, doi: 10.1186/S13063-018-2653-0.

NEDERLANDSE SAMENVATTING

Fysieke training als ondersteunde therapie gedurende de kankerbehandeling wordt steeds meer bewezen effectief geacht om kanker-gerelateerde symptomen tijdens en direct na de behadeling tegen te gaan. Zo leidt fysieke training tijdens chemotherapie tot minder kanker-gerelateerde vermoeidheidsklachten en zorgt het voor behoud van de fysieke fitheid direct na de behandeling [1]–[4]. Echter, of fysieke training tijdens chemotherapie ook bescherming kan bieden tegen de effecten op *lange termijn* van kanker is nog onduidelijk. Deze vraag is vooral van belang voor hart- en vaatziekten. Hart- en vaatziekten behoren tot de meest voorkomende alsook meest belastende langetermijneffecten van kanker en de daarmee samenhangende behandelingen. Er is op dit moment geen (medicamenteuze) behandeling om dit te voorkomen.
In het eerste deel van dit proefschrift wordt de invloed van fysieke training en lichaamsbeweging tijdens chemotherapie op het voorkomen van hart- en vaatziekten bij kankeroverlevenden jaren na de behandeling geëvalueerd. De (lange termijn) effecten van fysieke training tijdens chemotherapie op twee andere klinisch-relevante uitkomsten; cognitief functioneren en het kunnen volhouden van de chemotherapie, worden besproken in het tweede deel van dit proefschrift.

1. FYSIEKE TRAINING BINNEN DE CARDIO-ONCOLOGIE

In **Hoofdstuk 1** wordt de achtergrond van de in dit proefschrift beschreven studies geschetst. Over de afgelopen decennia neemt het aantal kankerpatiënten toe, onder andere als gevolg van de vergrijzing [5]–[7]. Daarnaast genezen steeds meer patiënten van kanker of leven ze langer door na de behandeling, onder andere als gevolg van steeds beter wordende chemotherapiebehandelingen. Deze twee trends samen resulteren in een continu groeiende groep kankeroverlevenden. Met het toenemen en langer leven van deze groep worden de langetermijneffecten van kanker steeds beter zichtbaar. Dit maakt goede nazorg na kanker van toenemend klinisch belang.
Dat kankerpatiënten en - overlevenden een hogere kans hebben op hart- en vaatziekten werd voor het eerst al beschreven in 1979[8]. Het leidde er, 20 jaar later, toe dat er een nieuw vakgebied werd opgericht dat zich specifiek bezighoudt met het voorkomen en behandelen van hart- en vaatziekten bij kankerpatiënten; de cardio-oncologie[9]. Initieel richtte de cardio-oncologie zich vooral op het behandelen van de (acute) bijwerkingen van de kankerbehandeling,

maar de laatste jaren verschuift de aandacht steeds meer naar vroege detectie van schade aan het hart.

Kanker en hart- en vaatziekten werden jaren gezien als twee verschillende entiteiten en ook op die manier behandeld. Echter, binnen de cardio-oncologie is er toenemend bewijs dat er een overlap is tussen deze twee ziektebeelden. Zo delen ze bepaalde belangrijke risicofactoren, zoals leeftijd en roken. Daarnaast zijn er deels dezelfde biologische mechanismen betrokken bij het ontwikkelen van zowel kanker als hart- en vaatziekten[10]–[12]. Dit leidt ertoe dat kankerpatiënten, nog voorafgaand aan de behandeling voor kanker, al een verhoogd risico hebben op hart- en vaatziekten. Dit risico neemt gedurende de kankerbehandeling verder toe. Overlevenden van kanker hebben een ruim twee keer zo hoge kans om te overlijden aan hart- en vaatziekten ten opzichte van leeftijdsgenoten zonder kanker [13]. Hart- en vaatziekten zijn op dit moment de belangrijkste niet kanker-gerelateerde doodsoorzaak bij kankerpatiënten. Echter, voor een aanzienlijk deel van de kankerpatiënten is inmiddels, als gevolg van de toegenomen overlevingskansen, het risico om te overlijden aan hart- en vaatzieken zelfs groter dan het risico om aan kanker zelf te overlijden [14]–[16]. Daarnaast gaat het ontwikkelen van hart- en vaatziekten na een succesvol geachte kankerbehandeling ook gepaard met verhoogde kans op andere ziektes en aanzienlijk verminderde kwaliteit van leven.

In **Hoofdstuk 2** wordt een overzicht gegeven welke hart- en vaatziekten bij welke type kankerbehandeling kunnen optreden. Bestraling kan nadelige effecten hebben op vrijwel elk binnen het bestralingsveld gelegen onderdeel van hart- en vaatstelsel. Meest voorkomend zijn echter het lekken of vernauwen van de hartkleppen en het versneld dichtslibben van de kransslagaders, met een verhoogd risico op een hartinfarct op relatief jonge leeftijd als gevolg. Deze aandoeningen worden vooral beschreven bij patiënten die bestraald zijn met een hoge dosis radiotherapie op de borstkas, zoals bij de voormalig gebruikte mantelveldbestraling voor lymfeklierkanker[17]. Echter, ook bij patiënten die op dit moment bestraald worden met relatief lage doseringen worden al cardiovasculaire bijwerkingen beschreven [18]. Bij kankerpatiënten die systemische therapie (chemotherapie, immunotherapie of hormonale therapie) ondergaan is het ontwikkelen van verminderde pompkracht van het hart, met hartfalen als gevolg, de meest gevreesde bijwerking. Dit is vooral beschreven bij patiënten die zijn behandeld met anthracycline bevattende chemotherapie en middelen gericht tegen het HER2-eiwit, zoals trastuzumab bij HER2-positieve

borstkanker. Hartfalen jaren na behandeling met anthracyclines is beschreven bij ongeveer 6% van de kankeroverlevenden. Als de eerste tekenen, zoals benauwdheid of enkeloedeem, zichtbaar werden was de prognose lange tijd zeer somber, waarbij het merendeel van de patiënten kwam te overlijden binnen twee jaar [19], [20]. De laatste jaren is echter toenemend aandacht voor het opsporen van de eerste afwijkingen aan het hart, nog voordat dit leidt tot klinische symptomen. Als er wordt gestart met hartfalen medicatie in dit asymptomatische stadium, is bij een aanzienlijk deel van de patiënten herstel van de pompfunctie van het hart mogelijk [21]. Dit illustreert het belang van het routinematig screenen van de hartfunctie van kankerpatiënten. Bij screening met behulp van echocardiografie is de globale longitudinale strain (GLS) een veel belovende parameter, omdat deze eerder afwijkingen laat zien dan de linkerventrikel ejectiefractie (LVEF), de gangbare maat voor de pompfunctie van het hart. Een MRI-scan van het hart, indien beschikbaar, kan aanvullende diagnostische informatie leveren door de weefselsamenstelling van het hart te beschrijven. Dit gebeurt aan de hand van de T1 relaxatietijd (*native* T1) en het extracellulaire volume (ECV). De gedachte hierachter is dat de weefselsamenstelling van het hart al meetbaar afwijkend wordt, voordat de achteruitgang in hoe het hart samenknijpt (GLS en in een later stadium LVEF) meetbaar is [22].

In **Hoofdstuk 3** wordt het effect op het hart beschreven van fysieke training tijdens anthracycline bevattende chemotherapie. Hierbij hebben we al het beschikbare bewijs samengevat van zowel dier- als mensstudies en, indien mogelijk, door middel van een meta-analyse, gekwantificeerd. Daarnaast wordt besproken welke biologische mechanismen betrokken zijn bij het voorkomen van hartschade door fysieke training. Vrijwel alle dierstudies (N=37) beschrijven significant minder hartschade bij de dieren die (bijv. door middel van een looprad) getraind werden tijdens chemotherapie in vergelijking tot de controlegroep (de dieren niet getraind werden). Het effect van training bij de dierstudies die een geforceerde beweeginterventie gebruikten was groter dan in de studies waarbij dieren vrijwillig konden trainen. De onderliggende biologische mechanismen lijken vooral te bestaan uit versnelde klaring van chemotherapie uit het hart, vermoedelijk door een toename van transporter receptoreiwitten, en verminderde oxidatieve stress. Onze hypothese is dat versnelde chemotherapie klaring optreedt als een overkoepelend mechanisme dat alle daaropvolgende mechanismen en effecten positief beïnvloedt. De beschikbare klinische studies bij patiënten met kanker (N=3) beschreven aanwijzingen dat een beweeginterventie tijdens chemotherapie kan leiden tot minder hartschade. Echter, deze studies

waren beperkt tot een kleine groep patiënten (N < 30 per studie arm) en een korte follow-up tijd. We concludeerden daarom dat het klinisch bewijs op dat moment onvoldoende was om de resultaten van de dierstudies te bevestigen bij kankerpatiënten.

Het meeste wetenschappelijke onderzoek heeft zich tot nu toe gericht op het effect van *fysieke training* in het voorkomen van hartschade bij patiënten met kanker. Met fysieke training worden geplande, gestructureerde of repetitieve bewegingen bedoeld die als doel hebben om de fysieke fitheid te verbeteren dan wel te behouden [23]. Het is echter onduidelijk of de mate van bewegen in het dagelijks leven, zoals bij huishoudelijke of recreatieve activiteiten, ook geassocieerd is met cardiovasculaire uitkomsten. Een eventuele associatie zou gevolgen kunnen hebben voor het beweegadvies voor kankerpatiënten. Om die reden hebben we in **Hoofdstuk 4** de associatie tussen het lichamelijk activiteitenniveau en de hartfunctie op lange termijn onderzocht, bij borstkankeroverlevenden binnen het HARBOR-cohort. Dit cohort bestaat uit 569 vrouwen die op de relatief jonge leeftijd van 40-50 jaar voor borstkanker behandeld zijn [24]. Ongeveer 10 jaar na de behandeling werd zowel het fysieke activiteit niveau en de hartfunctie gemeten. Op basis van het niveau van hun zelf-gerapporteerde lichamelijke activiteit werden de vrouwen ingedeeld in één van de vier categorieën van de Cambridge Physical Activity Index; (1) inactief, (2) overwegend inactief, (3) overwegend actief, of (4) actief [25]. Ten opzichte van de inactieve groep bleken hogere fysieke activiteit niveaus geassocieerd te zijn met een lager risico op het hebben van een slechtere hartfunctie (gemeten met GLS). Hierbij hebben we de invloed van andere patiënt- en behandeling-gerelateerde risicofactoren voor hart- en vaatzieken uitgesloten door daarvoor in de analyses te corrigeren. De grootste relatieve afname van risico werd gezien voor de "overwegend inactieve" groep ten opzichte van de "inactieve" groep, met relatief weinig extra risico vermindering voor de twee meest actieve categorieën. LVEF was in alle categorieën binnen de normaalwaarden en niet geassocieerd met fysieke activiteit. We concludeerden dat de hogere fysieke activiteitenniveaus geassocieerd waren met meer gunstigere GLS-waarden, maar niet LVEF, onafhankelijk van risicofactoren voor hart- en vaatziekten. Dit suggereert dat beweeginterventies mogelijke positieve cardiovasculaire gezondheidseffecten kunnen bewerkstelligen, vooral bij de inactieve groep borstkanker overlevenden. Prospectieve studies zijn echter nodig om de bevindingen van deze cross-sectionele analyse te bevestigen.

In **Hoofdstuk 5** worden de resultaten van de Pact-Paces-Heart studie beschreven. In deze studie wordt het effect van een fysiek trainingsprogramma tijdens chemotherapie op hartschade bestudeerd in een groep borstkanker overlevenden, ruim acht jaar na behandeling. De Pact-Paces-Heart studie is een vervolgonderzoek van twee eerder uitgevoerde, gerandomiseerde studies; de PACT (N=204) en de PACES (N=230) studie [26], [27]. Deze twee Nederlandse studies onderzochten het effect van een beweeginterventie tijdens adjuvante chemotherapie voor borstkanker, op verschillende uitkomsten direct na de chemotherapie, zoals vermoeidheidsklachten en kwaliteit van leven. Aan de vervolgstudie deden 185 (N=185/434; 43%) borstkankeroverlevenden mee, die in de tussenliggende periode van 8.5 jaar niet waren behandeld voor een recidief of uitgezaaide borstkanker. Cardiovasculaire uitkomsten werden gemeten met een MRI-scan van het hart (weefselsamenstelling; natieve T1-tijd en het ECV, en de LVEF), een echocardiogram (GLS) en een maximale inspanningstest (piek zuurstofopnamecapaciteit, VO_{2peak}).
In borstkankeroverlevenden die deel hebben genomen aan het trainingsprogramma observeerden we een significant gunstigere samenstelling van het hartweefsel ten opzichte van de controlegroep. Deze resultaten vonden we niet voor LVEF, GLS of de gemeten fysieke fitheid. Ook bleek dat de huidige zelfgerapporteerde fysieke activiteit niveaus waren geassocieerd met gunstigere samenstelling van het hartweefsel, ongeacht of patiënten destijds hadden deelgenomen aan het fysieke trainingsprogramma. Borstkankeroverlevenden die op het moment van deelname aan de vervolgstudie aangaven meer fysiek actief te zijn hadden significant hogere VO_{2peak} waarden, maar geen betere cardiale parameters. In de gehele studiegroep observeerden we relatief veel cardiale afwijkingen, waarbij meer dan een kwart van de – voorafgaand aan de borstkanker relatief gezonde en fitte vrouwen – een verminderde pompfunctie van het hart had. Dit bevestigt het belang van het implementeren van routinematig cardiale screeningsprogramma in borstkanker follow-up programma's. Daarnaast illustreert het ook dat er meer aanvullend onderzoek nodig is naar methodes om het hart te beschermen, zoals mogelijk anders vormgegeven beweegprogramma's.

1.2 Fysieke training en andere kanker-gerelateerde uitkomsten.

Voor de meeste vormen van kanker, inclusief borstkanker, zijn de overlevingskansen de afgelopen decennia aanzienlijk toegenomen. Continue verbeteringen in chemotherapiekuren wordt beschouwd als één van de belangrijkste oorzaken van dit succes [6], [7], [28], [29]. Echter, op dit moment

lukt het ongeveer een derde van de borstkanker patiënten niet om de voorgeschreven chemotherapie vol te houden, veelal als gevolg van bijwerkingen (bijv. misselijkheid en vermoeidheid) [29]. In **Hoofdstuk 6** bestudeerden we de associatie tussen fysieke fitheid bij aanvang van de behandeling en de mate waarin de chemotherapie werd volbracht zoals deze was voorgeschreven. Daarnaast bestudeerden we of een deelname aan een fysiek trainingsprogramma tijdens de chemotherapie hierop van invloed was. Voor deze analyses gebruikten we data van de eerdergenoemde studies PACT en PACES, aangevuld met gegevens over de mate waarin de chemotherapie is getolereerd. We zagen dat voor patiënten met een lagere fysieke fitheid voorafgaand aan de behandeling de kans kleiner is dat zij de chemotherapie zoals voorgeschreven volbrengen. Deze relatie werd echter vrijwel compleet tenietgedaan als patiënten deelnamen aan een fysiek trainingsprogramma tijdens chemotherapie. In de niet-bewegende controlegroep, daarentegen, hing de fysieke fitheid voorafgaand aan de behandeling juist sterker samen met de mate van volbrengen van de chemotherapie. Deze resultaten tonen aan dat het meten van fysieke fitheid voorafgaand aan de behandeling helpt om diegenen met een verhoogd risico op het niet volhouden van de chemotherapie te identificeren. Daarnaast suggereren de resultaten dat vooral de niet fitte patiënten met kanker baat kunnen hebben bij een beweegprogramma als ondersteunde behandeling tijdens de chemotherapie.

Kanker-gerelateerde cognitieve problemen, zoals vergeetachtigheid, zijn op enig moment in het ziekteproces beschreven bij ongeveer een derde van de met chemotherapie behandelde borstkanker patiënten [30]. Deze cognitieve klachten kunnen een grote impact hebben op het dagelijkse leven en bijvoorbeeld door de terugkeer naar werk te bemoeilijken. In **Hoofdstuk 7** onderzochten we het effect van fysieke training op objectieve en subjectieve cognitie uitkomsten bij deelneemsters aan de Pact-Paces-Heart studie. Het cognitief functioneren werd gemeten met online neuropsychologische testen. Cognitieve klachten werden gescoord met vragenlijsten. In totaal namen 143 van de 185 deelneemsters van de Pact-Paces-Heart studie deel aan dit cognitief onderzoek. Ongeveer de helft van de deelneemsters gaf aan direct na de chemotherapie cognitieve klachten te hebben ervaren. Ruim acht jaar na behandeling waren sommige onderdelen van het cognitief functioneren, zoals geheugen en snelheid van informatieverwerking, lager bij borstkankeroverlevenden ten opzichte van de gemiddelde populatie. Dit was zowel in de beweeg- als in de controlegroep het geval. We zagen geen effect van fysieke training tijdens de behandeling of van de mate waarin deelnemers aangaven te hebben bewogen tijdens chemotherapie, op cognitief

functioneren of het ervaren van cognitieve klachten. We concludeerden dat, in onze studiegroep, fysieke training tijdens behandeling niet geassocieerd was met cognitief functioneren of het ervaren van cognitieve klachten op de lange termijn. Onze aanbeveling is dat toekomstige studies zich vooral richten op patiënten met verhoogd risico op cognitieve klachten.

In **Hoofdstuk 8** bediscussieerden we de belangrijkste bevindingen van dit proefschrift. Ook worden hier de meest belangrijkste klinisch en methodologische beperkingen besproken en doen we aanbevelingen voor verder onderzoek naar fysieke activiteit binnen de cardio-oncologie. We concludeerden dat, in het algemeen, de resultaten in dit proefschrift het belang van fysieke training als ondersteunende behandeling tijdens chemotherapie lijken te onderschrijven. Dat cardiale afwijkingen desondanks veelvoorkomend bleken te zijn, impliceert dat het vervolgen van de hartfunctie op lange termijn noodzakelijk is. De belangrijkste methodologische beperking van de Pact-Paces-Heart studie is het feit dat – ten tijde van de originele studies – dit vervolgonderzoek nog niet gepland was. Dit maakt de studie in theorie gevoelig voor selectieve uitval van deelnemers. Dit betekent dat in plaats van de hele studiegroep, er alleen een deel mee doet dat juist wel (of geen) klachten van hart- en vaatziekten ervaart, waardoor de uitkomsten vertekend zouden kunnen zijn. We zagen in onze gegevens echter geen aanwijzingen voor selectieve uitval. Het toespitsen op harde klinische uitkomsten, zoals (cardiovasculair) overlijden, vermindert de kans op selectieve uitval in toekomstige vervolgonderzoeken, omdat dit soort gegevens vaak voor meer mensen beschikbaar zijn [31]. Een grote, prospectieve, gerandomiseerde studie die zich focust op zowel de weefselsamenstelling als de functie van het hart, gemeten voorafgaand aan -, direct en jaren na de behandeling is nodig om de rol van fysieke training definitief te beschrijven in de literatuur. Dit laatste hoofdstuk sluit af met de aanbeveling om tijdens de informed consent procedure van originele studies al toestemming te vragen voor het eventueel toekomstig linken van studiegegevens aan medische databases, om zo toekomstig vervolgonderzoek adequaat te kunnen uitvoeren.

REFERENCES

[1] C. M. Friedenreich, C. R. Stone, W. Y. Cheung, and S. C. Hayes, "Physical Activity and Mortality in Cancer Survivors: A Systematic Review and Meta-Analysis," *JNCI Cancer Spectr*, vol. 4, no. 1, Feb. 2019, doi: 10.1093/JNCICS/PKZ080.

[2] L. Yang *et al.*, "Effects of Exercise on Cancer Treatment Efficacy: A Systematic Review of Preclinical and Clinical Studies," *Cancer Res*, vol. 81, no. 19, pp. 4889–4895, Oct. 2021, doi: 10.1158/0008-5472.CAN-21-1258.

[3] J. A. Ligibel *et al.*, "Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline.," *J Clin Oncol*, vol. 40, no. 22, pp. 2491–2507, Aug. 2022, doi: 10.1200/JCO.22.00687.

[4] K. L. Campbell *et al.*, "Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable.," *Med Sci Sports Exerc*, vol. 51, no. 11, pp. 2375–2390, Nov. 2019, doi: 10.1249/MSS.0000000000002116.

[5] K. D. Miller *et al.*, "Cancer treatment and survivorship statistics, 2016.," *CA Cancer J Clin*, vol. 66, no. 4, pp. 271–289, Jul. 2016, doi: 10.3322/caac.21349.

[6] H. Sung *et al.*, "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.," *CA Cancer J Clin*, vol. 71, no. 3, pp. 209–249, May 2021, doi: 10.3322/caac.21660.

[7] J. M. Kocarnik *et al.*, "Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019.," *JAMA Oncol*, vol. 8, no. 3, pp. 420–444, Mar. 2022, doi: 10.1001/jamaoncol.2021.6987.

[8] D. D. Von Hoff *et al.*, "Risk factors for doxorubicin-induced congestive heart failure.," *Ann Intern Med*, vol. 91, no. 5, pp. 710–717, Nov. 1979, doi: 10.7326/0003-4819-91-5-710.

[9] D. Cardinale, "[A new frontier: cardio-oncology].," *Cardiologia*, vol. 41, no. 9, pp. 887–891, Sep. 1996.

[10] R. J. Koene, A. E. Prizment, A. Blaes, and S. H. Konety, "Shared Risk Factors in Cardiovascular Disease and Cancer.," *Circulation*, vol. 133, no. 11, pp. 1104–1114, Mar. 2016, doi: 10.1161/CIRCULATIONAHA.115.020406.

[11] T. J. Pfeffer, S. Pietzsch, and D. Hilfiker-Kleiner, "Common genetic predisposition for heart failure and cancer.," *Herz*, vol. 45, no. 7, pp. 632–636, Nov. 2020, doi: 10.1007/s00059-020-04953-9.

[12] V. Narayan, E. W. Thompson, B. Demissei, J. E. Ho, J. L. J. Januzzi, and B. Ky, "Mechanistic Biomarkers Informative of Both Cancer and Cardiovascular Disease: JACC State-of-the-Art Review.," *J Am Coll Cardiol*, vol. 75, no. 21, pp. 2726–2737, Jun. 2020, doi: 10.1016/j.jacc.2020.03.067.

[13] P. T. Bradshaw, J. Stevens, N. Khankari, S. L. Teitelbaum, A. I. Neugut, and M. D. Gammon, "Cardiovascular Disease Mortality Among Breast Cancer Survivors.," *Epidemiology*, vol. 27, no. 1, pp. 6–13, Jan. 2016, doi: 10.1097/EDE.0000000000000394.

[14] H. Abdel-Qadir *et al.*, "A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer.," *JAMA Cardiol*, vol. 2, no. 1, pp. 88–93, Jan. 2017, doi: 10.1001/jamacardio.2016.3841.

[15] J. L. Patnaik, T. Byers, C. DiGuiseppi, D. Dabelea, and T. D. Denberg, "Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study.," *Breast Cancer Res*, vol. 13, no. 3, p. R64, Jun. 2011, doi: 10.1186/bcr2901.

[16] H. Strongman *et al.*, "Does Cardiovascular Mortality Overtake Cancer Mortality During Cancer Survivorship?: An English Retrospective Cohort Study," *JACC CardioOncol*, vol. 4, no. 1, pp. 113–123, Mar. 2022, doi: 10.1016/J.JACCAO.2022.01.102.

[17] D. B. Hughes *et al.*, "Treatment planning for Hodgkin's disease: A patterns of care study," *Int J Radiat Oncol Biol Phys*, vol. 33, no. 2, pp. 519–524, Sep. 1995, doi: 10.1016/0360-3016(94)00605-K.

[18] S. C. Darby *et al.*, "Risk of ischemic heart disease in women after radiotherapy for breast cancer.," *N Engl J Med*, vol. 368, no. 11, pp. 987–998, Mar. 2013, doi: 10.1056/NEJMoa1209825.

[19] M. Lotrionte *et al.*, "Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity.," *Am J Cardiol*, vol. 112, no. 12, pp. 1980–1984, Dec. 2013, doi: 10.1016/j.amjcard.2013.08.026.

[20] G. M. Felker *et al.*, "Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy.," *N Engl J Med*, vol. 342, no. 15, pp. 1077–1084, 2000.

[21] D. Cardinale *et al.*, "Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy.," *Circulation*, vol. 131, no. 22, pp. 1981–1988, Jun. 2015, doi: 10.1161/CIRCULATIONAHA.114.013777.

[22] D. Cardinale, F. Iacopo, and C. M. Cipolla, "Cardiotoxicity of Anthracyclines.," *Front Cardiovasc Med*, vol. 7, p. 26, 2020, doi: 10.3389/fcvm.2020.00026.

[23] D. S. Siscovick, R. E. Laporte, J. Newman, D. C. Health ; Iverson, and J. E. Fielding, "Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.," *Public Health Reports*, vol. 100, no. 2, p. 126, 1985, Accessed: Apr. 15, 2023. [Online]. Available: /pmc/articles/PMC1424733/?report=abstract

[24] J. N. Jacobse *et al.*, "Myocardial dysfunction in long-term breast cancer survivors treated at ages 40-50 years.," *Eur J Heart Fail*, vol. 22, no. 2, pp. 338–346, Feb. 2020, doi: 10.1002/ejhf.1610.

[25] N. J. Wareham *et al.*, "Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.," *Public Health Nutr*, vol. 6, no. 4, pp. 407–413, Jun. 2003, doi: 10.1079/PHN2002439.

[26] N. Travier *et al.*, "Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial.," *BMC Med*, vol. 13, p. 121, Jun. 2015, doi: 10.1186/s12916-015-0362-z.

[27] H. van Waart *et al.*, "Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial.," *J Clin Oncol*, vol. 33, no. 17, pp. 1918–1927, Jun. 2015, doi: 10.1200/JCO.2014.59.1081.

[28] L. Rossi *et al.*, "Impact of Adjuvant Chemotherapy on Breast Cancer Survival: A Real-World Population," *PLoS One*, vol. 10, no. 7, Jul. 2015, doi: 10.1371/JOURNAL.PONE.0132853.

[29] G. H. Lyman, "Impact of chemotherapy dose intensity on cancer patient outcomes," *J Natl Compr Canc Netw*, vol. 7, no. 1, pp. 99–108, 2009, doi: 10.6004/JNCCN.2009.0009.

[30] A. L. Whittaker, R. P. George, and L. O'Malley, "Prevalence of cognitive impairment following chemotherapy treatment for breast cancer: a systematic review and meta-analysis," *Sci Rep*, vol. 12, no. 1, Dec. 2022, doi: 10.1038/S41598-022-05682-1.

[31] R. Llewellyn-Bennett, D. Edwards, N. Roberts, A. H. Hainsworth, R. Bulbulia, and L. Bowman, "Post-trial follow-up methodology in large randomised controlled trials: a systematic review," *Trials*, vol. 19, no. 1, May 2018, doi: 10.1186/S13063-018-2653-0.

.

LIST OF PUBLICATIONS

This thesis

Naaktgeboren WR, Linschoten MM, de Graeff A, van Rhenen A, Cramer MJM, Asselbergs FW, Maas AHEM, Teske AJ. Long-term cardiovascular health in adult cancer survivors. *Maturitas.* 2017;105:37:45.

Naaktgeboren WR*, Binyam D, Stuiver MM, Aaronson NK, Teske AJ, van Harten WH, Groen WG, May AM. Efficacy of physical exercise to offset anthracycline-induced cardiotoxicity: A systematic review and meta-analysis of clinical and preclinical studies. *Journal of the American Heart Association*. 2021;10(17).

Naaktgeboren WR, Groen WG, Jacobse J, Steggink LC, Walenkamp AME, van Harten WH, Stuiver MM, Aaronson NK, Aleman B, van der Meer PC, Schaapveld M, Sonke GS, Gietema J, van Leeuwen FE, May AM. Physical activity and cardiac dysfunction in long-term breast cancer survivors: A cross-sectional study. *JACC CardioOncology.* 2022;9;4(2):183-191.

Naaktgeboren WR, Stuiver MM, van Harten WH, Aaronson NK, Scott JM, Sonke GS, van der Wall E, Velthuis M, Leiner T, Teske AJ, May AM*, Groen WG*. Effects of exercise during adjuvant chemotherapy for breast cancer on long-term cardiovascular toxicity. *Open Heart*; 2023, in press.

Naaktgeboren WR*, Groen WG*, van Harten WH, van Vulpen JK, Kool N, Sonke GS, van der Wall E, Velthuis M, Aaronson NK, May AM*, Stuiver MM*. Physical fitness and chemotherapy tolerance in patients with early-stage breast cancer. *Medicine of Science, Sports and Exercise*. 2022;54(4):537-542.

Naaktgeboren WR, Koevoets EW, Stuiver MM, van Harten WH, Aaronson NK, van der Wall E, Velthuis M, Sonke GS, Schagen SB, Groen WG*, May AM*. Effect of physical exercise during adjuvant chemotherapy for breast cancer on long-term tested and perceived cognition: Results of a pragmatic follow-up study. *Under review.*

Other publications

Oliveira MF, **Naaktgeboren WR**, Hua AH, Ghosh AK, Oakervee H, Hallam S, Manisty CH. Optimising cardiovascular care of patients with multiple myeloma. *Heart*. 2021;107(22):1774-1782

De Baat EC, **Naaktgeboren WR**, Leiner T, Teske AJ, Habets J, Grotenhuis HB. Update in imaging of cancer-related cardiac toxicity in adults. *Open Heart*. 2018(1):e001506

Teske AJ, Linschoten MM, Kamphuis JAM, **Naaktgeboren WR**, Leiner T, van der Wall E, Kuball J, van Rhenen A, Doevendans PA, Cramer MJM, Asselbergs FW. Cardio-oncology: an overview on outpatient management and future developments. *Netherlands Heart Journal*. 2018: 26(11):521-532

Naaktgeboren WR, Voogel AJ, Spijkerboer AM, Lobatto ME, Bot PTG. A rare case of recent onset Loeffler's endocarditis in the absence of hypereosinophilia. *Submitted*.

Binyam D*, **Naaktgeboren WR***, Groen WG, Aaronson NK, Hiensch AE, van Harten WH, Stuiver MM, May AM. Eight-year follow-up of the effects of exercise during chemotherapy in non-metastatic breast cancer patients op patient-reported outcomes. *Submitted.*

Book chapter

Naaktgeboren WR, Teske AJ. Leerboek cardiac-care verpleegkunde, Hoofdstuk 14: cardiale oncologie. *In press.*

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Ik wil ook alles **deelneemsters aan de Pact-Paces-Heart studie** bedanken voor hun deelname. Het waren intensieve meetdagen, veelal op zaterdag (!), waarbij jullie zowel een MRI-scan, een hartecho, een bloedafname, een fietstest en testje van de vaatfunctie ondergingen. We verzochten jullie ook nog in de vroege ochtend nuchter te arriveren met vaak een flinke reistijd. Fantastisch dat jullie hiertoe bereid waren! Zonder jullie inspanningen was dit proefschrift er simpelweg niet geweest.

Geachte **leden van de leescommissie**; **professor Bots**, **professor Hartgens**, **professor van Leeuwen**, **professor Linn** en **professor Verkooijen**: ik wil jullie hartelijk bedanken voor jullie tijd en bereidheid mijn proefschrift te lezen.

De eerdergenoemde Pact-Paces-Heart studie meetdagen vonden plaats in het UMC Utrecht. Gezien de verscheidenheid aan studiemetingen waren deze dagen niet mogelijk geweest zonder betrokkenheid van veel verschillende disciplines en afdelingen. Ik ben heel dankbaar voor de samenwerking en ook trots dat we deze meetdagen door hebben kunnen zetten tijdens de Coronapandemie. **Tim Leiner**, je hebt me als student wegwijs gemaakt in de wondere wereld van de cardiale MRI en stond aan het begin van mijn wetenschappelijke loopbaan. Ik ben heel blij dat we onze samenwerking ook tijdens mijn promotietraject hebben kunnen voorzetten. **Arco Teske**, jouw cardio-oncologische expertise waren onmisbaar binnen het studieteam. Ik ben heel dankbaar voor je klinische input, maar ook dat je me hebt leren echo-en en alle de studie echo's wilde

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vooral etend, slapend en lezend hebben doorgebracht beschouw ik echt als één van onze hoogtepunten. Lieve **Charisma**, wat ben ik blij dat ik jou heb leren kennen tijdens de Epi master. Je hebt een energie en enthousiasme die maken dat ik je graag om me heen hebt. Dank voor al onze fijne gesprekken. Lieve **Sabine**, in een ander dankwoord werd beschreven dat jij niet half beseft wat voor fantastisch en uniek persoon je bent. Ik neem dit graag over omdat het zo spot-on is. Dank voor alle inzichten de afgelopen jaren. Lieve **Tanneke**, binnen 10 minuten zijn we weer op de hoogte van elkaars leven, ook al zien we elkaar soms maanden niet. Ik bewonder jouw kracht en energie. Dank voor jouw visie op de wereld, daar wil ik meer van horen met meer wijn. Lieve **Elise**, mijn meest recent opgedane vriendin, maar ik zou me geen leven meer zonder jou kunnen en willen voorstellen. Ik ken niemand zo attent en integer als jij. Ook al ben je zelf veelste te vroeg bevallen, presteer je het toch om voor mij een verjaardagscadeautje met handgeschreven kaartje te hebben. Dank voor alle waardevolle gesprekken, yoga sessies en levenslessen. Lieve **Anna**, mijn partner in crime op vele boevenpaden door Cuba, Amsterdam en omstreken. Wat een verrijking zijn al deze avonturen met jou geweest. Je bent echter ook diegene die mijn vriezer van ingevroren maaltijden komt voorzien op het moment dat mijn wereld even stilstond. Ik zou je altijd en voor alles durven te bellen. Dank voor je jarenlange aanvoerderschap van team rosé en nog zoveel meer.

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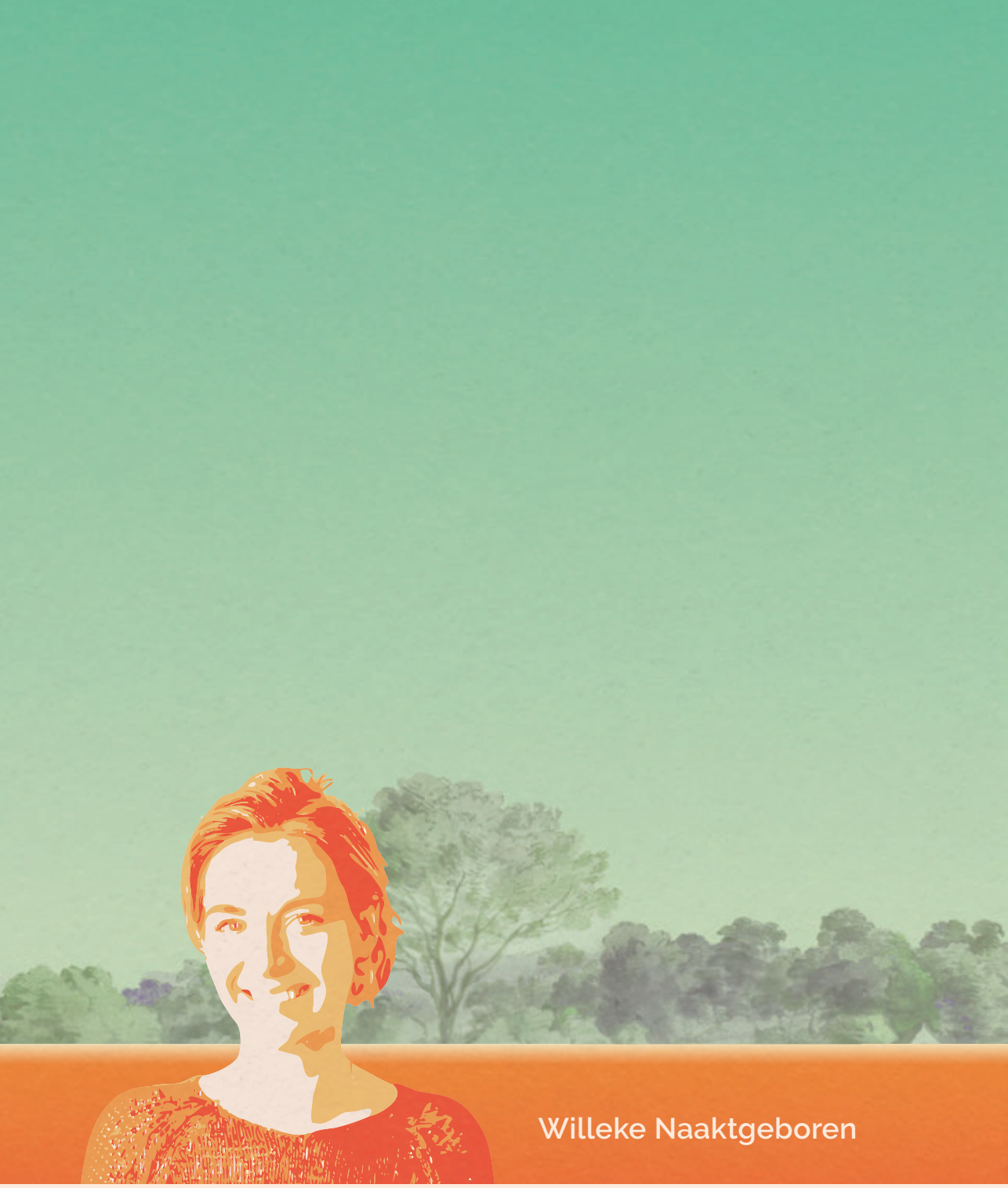
ABOUT THE AUTHOR

Willeke Naaktgeboren was born in Rotterdam, the Netherlands. During childhood, she was interested in being outdoors and various sports, including wakeboarding and field hockey. She played the latter at a competitive level and won the national championship in field hockey five times. After graduating from the Gymnasium at the Montessori Lyceum Rotterdam, she began her Biomedical Sciences studies at Utrecht University in 2009. One year later, she switched to study Medicine at the same university. During her studies, she participated in the Honours Programme, an extracurricular activity program focused on deepening research and academic skills. Willeke also worked as a student-assistant teacher in physiology and anatomy. In 2013, she went abroad for her obstetrics-gynecology internship in rural India. Following this unique experience, she continued her (extracurricular) research, now focusing on cardio-oncology. In her master's thesis, Willeke studied the role of cardiac MRI imaging in diagnosing chemotherapy-induced cardiotoxicity in patients treated for breast cancer and presented the results at the SCMR Congress in Washington, USA. Subsequently, she moved to London for an elective cardio-oncology internship, for which she received funding from, among others, the Nijbakker-Mora Stichting and the Circulatory Health Travel Grant of the UMC Utrecht. In these months, she was mostly focused on the cardiovascular complications of patients with multiple myeloma.

After obtaining her medical degree, she started working on this thesis in 2017 as a Ph.D. candidate at the Netherlands Cancer Institute and the UMC Utrecht. She worked under the supervision of prof. W.H. van Harten, prof. A.M. May, dr. M.M Stuiver and dr. W.G. Groen. During her research, she collaborated closely with various departments, including cardiology, radiology, medical oncology, and sports medicine, in conducting the Pact-Paces-Heart study. In 2021, she received a Master of Science in Clinical Epidemiology from Utrecht University. As of November 2022, Willeke started as a cardiology resident at the Spaarne Gasthuis in Haarlem, the Netherlands. She lives near Haarlem with her partner Geert and their two children, Lot and Chiel, and they are expecting their third child in spring 2024.



Willeke Naaktgeboren