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Karolinska Institutet, Stockholm, Sweden

HIGH-INTENSITY INTERVAL TRAINING IN COMBINATION WITH AEROBIC OR RESISTANCE TRAINING FOR PATIENTS WITH BREAST CANCER
- A HIIT TO COUNTERACT DETRIMENTAL EFFECTS OF CHEMOTHERAPY

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Stockholm 2018

Published by Karolinska Institutet.
Printed by Eprint AB 2018
Cover illustration: *Mattias Karlén*

ISBN 978-91-7549-978-9

High-intensity interval training in combination with aerobic or resistance training for patients with breast cancer - a HIIT to counteract detrimental effects of chemotherapy

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To all of those who have been afflicted by breast cancer

"I have a personal trainer twice a week that drives me to exercise on a high level ... more a focus on exercise and not a focus on illness and treatment"

Participant from the OptiTrain study

ABSTRACT

With the increasing number of individuals that enter cancer survivorship there is a growing need for interventions that can alleviate treatment-related adverse effects such as fatigue, and that can improve and restore physical functioning and health-related quality of life during and after treatment. After a breast cancer diagnosis, patients with breast cancer show significantly reduced physical activity levels, especially during the adjuvant treatment phase. Today, there is evidence supporting the efficacy of exercise, particularly combined resistance and aerobic training, to improve physiological and health-related outcomes in patients with breast cancer. However, most evidence is based on findings from studies conducted after chemotherapy. The training modality high-intensity interval training (HIIT) has been proven time effective and beneficial for various physiological outcomes. Despite this, data on the effects of HIIT during chemotherapy is limited. Moreover, few of the trials that have assessed exercise training during chemotherapy have included longer follow-ups, especially on objectively measured physiological outcomes, and no trials for patients with breast cancer during chemotherapy have evaluated the effects of exercise on objectively measured pain sensitivity or molecular outcomes in skeletal muscle. To meet the needs that follow the increasingly aggressive treatments for patients with breast cancer, equally progressive countermeasures are needed. Therefore, assessment of the influence of HIIT is highly justified. In this thesis, the aim was to examine and compare the effects of two different supervised exercise programs that included the training modality HIIT with focus on objectively measured physiological and self-reported health-related outcomes over the course of chemotherapy, and 12 months into survivorship. Two hundred and forty women with early stage breast cancer were randomized to 16 weeks of twice weekly supervised resistance combined with high-intensity interval training (RT-HIIT), moderate-intensity continuous aerobic training (AT-HIIT), or usual care (UC).

The results of this thesis showed that compared to the deteriorations found in the UC group over the 16-week intervention, RT-HIIT was effective to counteract fatigue and pain sensitivity and showed improvements in muscle strength, while both exercise groups were effective to prevent declines in cardiorespiratory fitness, gains in body mass, and were effective to alleviate symptom burden. Moreover, exercise-induced specific morphological and functional improvements were found in skeletal muscle. At 12 months, both exercise groups were effective to counteract fatigue, and displayed improved muscle strength compared to deteriorations in the UC group. Additionally, AT-HIIT was effective to maintain body mass, and displayed lower symptom burden, as well as lower sick leave rates compared to the UC group.

Taken together, this thesis shows that adding high-intensity interval training to resistance or aerobic training during chemotherapy in women with breast cancer was feasible, and was shown to be a powerful strategy to manage or prevent many of the short-and long-term adverse effects of treatment and inactivity, as well as to potentially minimize significant societal costs associated with high sick leave rates.

SVENSK SAMMANFATTNING

Cytostatika är ofta en viktig del av behandlingen vid bröstcancer, dock kan behandlingen ha biverkningar som negativt påverkar en persons fysiska och psykiska funktion, och kan leda till lägre nivåer av fysisk aktivitet. Det finns ett behov av interventioner som positivt påverkar patienters funktionsförmåga, livskvalitet, hälsostatus och återhämtning efter en behandling. Högintensiv träning har visat sig vara en effektiv träningsmodell hos friska individer och hos individer med hjärt- och kärlsjukdom. Inom cancervården råder en brist på träningsstudier under pågående cytostatikabehandling, och studier som jämför effekten av olika träningsprogram, som kan ge kunskap om både kort- och långvariga effekter av högintensiv träning på fysisk funktion och livskvalitet hos patienter med bröstcancer.

Huvudsyftet med denna randomiserade kontrollerade studie var att, hos patienter med bröstcancer undersöka effekten av två träningsprogram innehållande högintensiv konditions- och styrketräning vad gäller, påverkan på trötthet, fysisk kapacitet, cancerspecifika symptom, fysisk funktion, muskelstruktur och muskelfunktion både före och direkt efter behandlingen och 12 månader senare.

I OptiTrain studien randomiserades 240 patienter med bröstcancer till en av tre grupper. En grupp deltog under den 16 veckor långa cytostatikabehandlingen i ett strukturerat träningsprogram som kombinerade styrketräning med högintensiv intervallträning. Den andra gruppen genomförde ett strukturerat träningsprogram som innehöll måttligt ansträngande konditionsträning samt högintensiv intervallträning. Kontrollgruppen fick standardråd om fysisk aktivitet.

Resultaten visade att kvinnorna som tränade kombinerad styrke- och högintensiv intervallträning blev mindre trötta, mindre smärtkänsliga och starkare. Båda träningsprogrammen medförde positiva effekter på kondition, kroppsvikt, symptombörda och medförde träningsspecifika anpassningar på muskelnivå jämfört med generella försämringar hos kontrollgruppen. Resultaten från uppföljningsstudien vid 12 månader visade att båda träningsgrupperna minskade den cancerrelaterade trötttheten, och förbättrade muskelstyrkan jämfört med en fortsatt försämrad muskelstyrka hos kontrollgruppen. Gruppen som endast tränade konditionsträning hade en fortsatt bibehållen kroppsvikt och en minskad symptombörda. Dessutom var denna grupp mindre sjukskrivna jämfört med kontrollgruppen 12 månader efter cytostatikabehandlingen.

Sammantaget visar denna avhandling att det kan vara av stort värde av att inom cancervården implementera strukturerad, övervakad fysisk träning för patienter med bröstcancer under pågående cytostatikabehandling för att motverka många av de negativa effekterna av cytostatika och inaktivitet på både muskelstyrka, muskelfunktion, samt för att förbättra livskvaliteten.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers:

I. **Mijwel S**, Backman M, Bolam KA, Olofsson E, Norrbom J, Bergh J, Sundberg CJ, Wengström Y, Rundqvist H. *Highly favorable physiological responses to concurrent resistance and high-intensity interval training during chemotherapy: the OptiTrain breast cancer trial.* Breast Cancer Res Treat. 2018;169(1):93-103.

II. **Mijwel S**, Cardinale D, Ekblom-Bak E, Sundberg CJ, Wengström Y, Rundqvist H. *Validation of 2 Submaximal Cardiorespiratory Fitness Tests in Patients With Breast Cancer Undergoing Chemotherapy.* Rehabil Onc (American Physical Therapy Association Oncology Section). 2016;34(4):137-43.

III. **Mijwel S***, Cardinale DA*, Norrbom J, Chapman M, Ivarsson N, Wengström Y, Sundberg CJ, Rundqvist H. *Exercise training during chemotherapy preserves skeletal muscle fiber area, capillarization, and mitochondrial content in patients with breast cancer.* Faseb j. 2018:fj201700968R.

IV. **Mijwel S**, Jervaeus A, Bolam KA, Norrbom J, Bergh J, Rundqvist H, Wengström Y. *High-intensity exercise during chemotherapy induces beneficial effects on fatigue, muscle strength, and return to work 12 months into breast cancer survivorship.* Manuscript submitted.

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LIST OF SCIENTIFIC PAPERS NOT INCLUDED IN THIS THESIS

Mijwel S, Backman M, Bolam KA, Jervaeus A, Sundberg CJ, Margolin S, Browall M, Rundqvist H, Wengström Y. *Adding high-intensity interval training to conventional training modalities: optimizing health-related outcomes during chemotherapy for breast cancer: the OptiTrain randomized controlled trial.* Breast Cancer Res Treat. 2018;168(1):79-93.

Wengström Y, Bolam KA*, **Mijwel S***, Sundberg CJ, Backman M, Browall M, Norrbom J, Rundqvist H. *Optitrain: a randomised controlled exercise trial for women with breast cancer undergoing chemotherapy.* BMC Cancer. 2017;17(1):100.

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TABLE OF CONTENTS

1 BACKGROUND 1
1.1 Breast cancer incidence 1
1.2 Breast cancer treatment 2
1.2.1 Chemotherapy for breast cancer 2
1.3 Immediate, long-term, and late adverse effects of chemotherapy 3
1.3.1 Cancer-related fatigue and pain 3
1.3.2 Health-related quality of life and symptom burden 4
1.3.3 The cardiovascular system 4
1.3.4 Skeletal muscle 5
1.3.5 Body mass 6
1.4 Physical inactivity 6
1.5 Defining cancer survivorship 6
1.6 Benefits of exercise training 7
1.6.1 Exercise for patients with breast cancer 8
1.7 Exercise recommendations for individuals with cancer 9
2 Hypotheses and aims 10
3 Results and discussion 11
3.1 Attendance to the exercise intervention and patient characteristics 11
3.2 Exercise training durng chemotherapy is effective to counteract increases in cancer-related fatigue 14
3.3 Pressure-pain threshold and pain 18
3.4 Validation of submaximal exercise tests for assessment of cardiorespiratory fitness in patients with breast cancer 20
3.5 Mitochondrial content and capillarization may explain maintained cardiorespiratory fitness with exercise despite declines in blood hemoglobin concentrations 22
3.6 Declines in Skeletal muscle strength, cross-sectional area, and satellite cells were counteracted by exercise 27
3.7 A shift in muscle fiber type – toxicity or disuse? 31
3.8 Body mass gains were counteracted with aerobic training 34
3.9 Acute and persistent symptom burden was alleviated with exercise 36
3.10 Effects of exercise on return to work 37
3.11 Associations between physiological outcomes and fatigue 39
3.12 Statistical considerations 42
3.13 Study design considerations 43
4 Conclusions 44
5 Implications, future perspectives and recommendations 45
5.1.1 The importance of supervised exercise 45
5.1.2 Is exercise during chemotherapy important? 45
5.1.3 Are we treating physical inactivity or chemotherapy-related symptoms? 46

6 Acknowledgments 48
7 References 50

LIST OF ABBREVIATIONS

UC	Usual care
AT-HIIT	Moderate-intensity aerobic combined with high-intensity interval training
RT-HIIT	Resistance- combined with high-intensity interval training
ITT	Intention to treat
VO_{2peak}	Peak oxygen uptake
IMTP	Isometric mid-thigh pull
PPT	Pressure-pain threshold
CRF	Cancer-related fatigue
HRQoL	Health-related quality of life
QoL	Quality of life
PFS	Piper fatigue scale
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
MSAS	Memorial symptom assessment scale
E-B	Ekblom-Bak
A-R	Åstrand-Rhyming
HR	Heart rate
Bpm	Beats per minute
ES	Effect size
CS	Citrate synthase
CSA	Cross-sectional area
MHC	Myosin heavy chain
PA	Physical activity
RPE	Rating of perceived exertion
ER+	Estrogen receptor positive
PR+	Progesterone receptor positive
HER2+	Human epidermal growth factor receptor 2 positive
ANCOVA	Analysis of covariance
LMM	Linear mixed models
EM	Expectation maximization
ES	Effect size

1 BACKGROUND

With the increasing number of individuals that enter cancer survivorship there is a growing need for interventions that alleviate treatment-related adverse effects such as fatigue and that can improve and restore physical functioning during and after treatment. Moreover, after a breast cancer diagnosis, patients with breast cancer show significantly reduced physical activity (PA) levels, especially during the adjuvant treatment phase. Today, there is evidence supporting the efficacy of exercise, particularly combined resistance and aerobic training, to improve physiological and health-related outcomes; although, most evidence is based on findings from studies conducted after chemotherapy (Furmaniak et al., 2016). Moreover, supervised exercise trials with sufficient sample sizes are few and the number of trials that have compared two exercise programs with an appropriate control group is limited.

The training modality high-intensity interval training (HIIT) has been proven time effective and beneficial for various physiological outcomes (MacInnis and Gibala, 2017). Despite this, data on the effects of HIIT during chemotherapy is limited to one pilot study with a mixed cancer population (Schulz et al., 2017). Few trials that have assessed exercise during chemotherapy have included longer follow-ups, especially on objectively measured physiological outcomes, and no trials for patients with breast cancer during chemotherapy have evaluated the effects of exercise on objectively measured pain sensitivity or molecular outcomes in skeletal muscle. To meet the needs that follow the increasingly aggressive treatments for patients with breast cancer, equally progressive countermeasures are needed; therefore, assessment of the incorporation of HIIT is highly justified. In this thesis, the effects of two different supervised exercise programs that included the training modality HIIT were investigated with focus on objectively measured physiological and self-reported health-related outcomes over the course of chemotherapy, and 12 months into survivorship. An effort was also made to support the participants to maintain physical exercise after completion of the intervention. To gain benefits from both resistance and aerobic training in the most time-efficient manner, HIIT was combined with resistance training in one exercise session (RT-HIIT). The second exercise program consisted of endurance training only, where HIIT was combined with moderate-intensity continuous aerobic training (AT-HIIT) in an effort to target and counteract the detrimental effects of chemotherapy.

1.1 BREAST CANCER INCIDENCE

Breast cancer is the most commonly diagnosed type of cancer among women. In 2015, 9 382 new cases of breast cancer were reported in Sweden and 1 431 individuals died from breast cancer the same year (Nationellt vårdprogram, 2018). This is a remarkable increase since 1960 when 2 000 individuals were diagnosed with breast cancer in Sweden, and 641 000 individuals worldwide, in comparison to 2.4 million in 2015 (Fitzmaurice et al., 2017). The risk of getting breast cancer before the age of 75 is 10.3%. Besides genetic factors, there is strong evidence for lifestyle related factors such as being overweight, poor diet, alcohol consumption, smoking, and physical inactivity being major risk factors associated with breast cancer (Cancerfondsrapporten 2018).

1.2 BREAST CANCER TREATMENT

Advances in cancer therapy have contributed to improvements in breast cancer survival (Anampa et al., 2015). The combination of surgery and adjuvant treatment for early stage breast cancer is associated with a 90% cure rate, defined as 5-year survival (Cancerfondsrapporten 2018). Most women with breast cancer in stages I to III receive drug therapy as part of their treatment which may include: chemotherapy, hormone therapy, human epidermal growth factor receptor 2 protein (HER2) targeted drugs, such as trastuzumab (Herceptin), or a combination of these (Nationellt vårdprogram, 2018).

1.2.1 Chemotherapy for breast cancer

The use of chemotherapy depends on a variety of factors including overall health, menopausal status, tolerance for specific medications, and tumor receptor status (Nationellt vårdprogram, 2018). Approximately 80% of breast cancers are estrogen-positive (ER+) and progesterone-positive (PR+) cancers, while 15% are human epidermal growth factor receptor 2 protein positive (HER2+) breast cancers. The type of chemotherapy being administered depends on the classification of the hormone receptor type. A summary of current adjuvant therapy options for four intrinsic subtypes summarized based on ER, PR, and HER2 expression can be found in the table below:

Table 1. "Systemic adjuvant therapy options for operable breast cancer". Reprinted from Anampa et al. (2015) licensed under CC BY 4.0.

Systemic adjuvant therapy options for operable breast cancer

Breast cancer subtype/classification			**Adjuvant systemic therapy**		
Phenotypic subtype		**Intrinsic subtype**	**Endocrine therapy**	**Anti-HER2 therapy**	**Chemotherapy**
Hormone receptors	HER2 overexpresion				
+	-	Luminal A or B	Yes	No	Yes (if high risk)
+	+	Lumonal B or HER2 enriched	Yes	Yes	Yes
-	-	Basal	No	No	Yes
-	+	HER2 enriched	No	Yes	Yes

The most commonly used chemotherapeutic agents used to inhibit cancer cell proliferation include anthracyclines and taxanes, which often are given in cycles with a recovery period in between (Andreopoulou and Sparano, 2013). The main cytotoxic action of anthracyclines involve inhibition of DNA, RNA, and protein synthesis, ultimately leading to cell death (Mordente et al., 2012, Szulawska and Czyz, 2006). The mechanism by which cellular uptake of anthracyclines occurs is not well understood, but is believed to occur through passive diffusion (Mordente et al., 2012). The sequential addition of taxane cycles to anthracycline cycles has been found to improve survival (Peto et al., 2012). Taxanes inhibit tumor growth through targeting microtubule function and thus promoting apoptosis resulting in nonfunctional microtubule synthesis (Abal et al., 2003).

1.3 IMMEDIATE, LONG-TERM, AND LATE ADVERSE EFFECTS OF CHEMOTHERAPY

Despite the therapeutic benefits, chemotherapy is associated with detrimental adverse effects. These may be immediate, resolving after a few days or weeks, or persistent lasting years after completion of treatment (Carelle et al., 2002). Long-term adverse effects are those that begin during treatment or shortly thereafter and persist for a longer period after completion of chemotherapy, while late adverse effects include comorbidities that first appear months or years after completion of chemotherapy such as cardiomyopathies, metabolic syndrome, and type II diabetes (Ewertz and Jensen, 2011). In this thesis, the focus will be on short- and long-term adverse effects.

1.3.1 Cancer-related fatigue and pain

It is well known that patients undergoing active treatment for cancer experience multiple symptoms, and symptoms such as fatigue and pain usually co-occur (Langford et al., 2016). Symptoms are subjective reports by patients that indicate a change in normal functioning due to disease or treatment.

Cancer-related fatigue (CRF) is one of the most debilitating and one of the most commonly reported immediate and persistent symptoms across the breast cancer continuum, that has a negative impact on quality of life (QOL) both during and after treatment (Bower, 2014). Despite this, the underlying pathophysiology is still largely unidentified (Davis and Walsh, 2010); however, it seems that CRF is of multifactorial origin (Stone and Minton, 2008). In contrast to typical fatigue, CRF is not relieved by rest or sleep and does not reflect an individual's exertion level (Stone and Minton, 2008). It has been defined as a "persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning", and consists of physiological, affective, cognitive, and behavioral aspects (Piper et al., 1998). The majority of patients with breast cancer develop fatigue sometime during the course of chemotherapy (Abrahams et al., 2016), especially women that receive taxane-based treatment (Ho and Mackey, 2014). A longitudinal study in patients with early stage breast cancer showed that fatigue levels were low after surgery (9%), and increased during and at the end of chemotherapy (47%-49%), persisting one year later (33%), and then slowly declined until the ten-year follow-up (5%) (Fabi et al., 2017). The impact that CRF has on patients' lives is substantial. It has been reported to be the most significant barrier to functional recovery in patients with early stage breast cancer, preventing patients from conducting their daily routine (Blaney et al., 2010).

The mechanisms behind this complex condition remain unclear. Whether CRF is due to central or peripheral factors or a combination of both remains unknown; however, in patients with advanced breast cancer, evidence has pointed towards fatigue being centrally mediated, although no associations were found between subjective CRF and objectively measured time to fatigue (Kisiel-Sajewicz et al., 2012). Proposed mechanisms behind CRF include nerve damage, mitochondrial dysfunction, hypothalamic-pituitary-adrenal axis dysfunction, circadian rhythm disruption, an increase in systemic inflammation, a decline in

cardiorespiratory fitness, anemia, and pain (LaVoy et al., 2016). Several of the same proposed mechanisms behind CRF have also been shown to be associated with pain such as neural damage and systemic inflammation which can further induce peripheral neuropathy, and pain has been shown to be a predictor of long-term CRF (Schmidt et al., 2015a). Moreover, patients with breast cancer display hypersensitivity to pressure pain compared with healthy individuals (Caro-Moran et al., 2016).

1.3.2 Health-related quality of life and symptom burden

The term health-related quality of life (HRQoL), being distinct from QoL which is a broader concept covering all aspects of life including non-health related features of life, has a focus on the effects of illness and specifically on the impact treatment may have on a person's well-being. HRQoL is therefore thought of as a person's subjective perception of the impact the illness has on physical, psychological and social functioning (Karimi and Brazier, 2016).

Patients with cancer often experience multiple symptoms related to the disease and its treatment (Gapstur, 2007). In contrast to HRQOL which provides information about the impact of symptoms on general aspects of an individual's health, symptom burden is a more disease-specific measurement and is an indicator of the severity of the symptoms that are most associated with a disease or treatment (Kenne Sarenmalm et al., 2014). This self-reported measure has been shown to be more sensitive to the changes in symptoms experienced by individuals with cancer (Burkett and Cleeland, 2007), and includes the presence, frequency, and severity of multiple symptoms, and the level of distress caused by symptoms (Molassiotis et al., 2010). A measure of symptom burden can enhance the understanding of a patients' physiological and psychological functioning during diagnosis and treatment of cancer and is therefore of major relevance for practice and clinical research (Burkett and Cleeland, 2007).

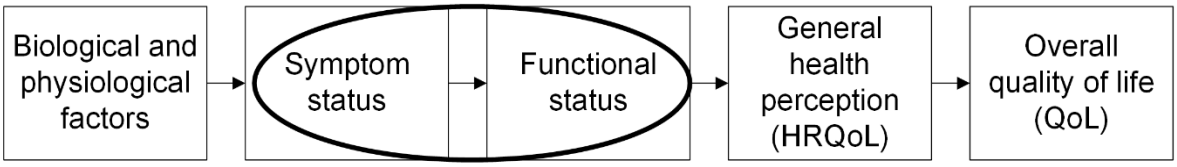

Figure 1. "Symptoms are not synonymous with HRQoL". Symptom burden (circled) is closest to the disease and treatment processes. General HRQOL includes more general aspects of an individual's perception of health-related well-being which is not directly related to treatment, while QoL is the individual's perception of overall well-being. Reprinted with modifications from Burkett and Cleeland (2007) with permission from Springer Nature.

1.3.3 The cardiovascular system

Anthracyclines primarily accumulate in the cell nucleus and mitochondria, which can lead to negative consequences for noncancerous tissues. This chemotherapeutic agent group is known to cause cardiotoxicities including cardiac muscle damage, tachycardia and atrial fibrillation (late effects) (Florescu et al., 2013), and anthracycline-containing chemotherapy can lead to a decline in cardiorespiratory fitness (Peel et al., 2014) (short- and long-term effects). Peak oxygen consumption (VO_{2peak}), which is measured from analysis of expired respiratory gases during a graded exercise test to maximal effort (Hill and Lupton, 1923), is an inversely related

predictor of mortality in the general population (Kodama et al., 2009). It has been shown that patients with breast cancer have a marked impairment in cardiorespiratory fitness across the disease and treatment continuum, with the most pronounced effects in patients that undergo chemotherapy (Klassen et al., 2014). The reductions in VO_{2peak} for patients with breast cancer undergoing chemotherapy typically range from 5% to 10%, and has been found to be approximately 25% lower compared VO_{2peak} values to those of healthy sedentary women after completion of chemotherapy (Peel et al., 2014). Given that cardiovascular disease exceeds breast cancer as the leading cause of death in older women 9 years after their breast cancer diagnosis (Patnaik et al., 2011), and considering that with each metabolic equivalent (resting metabolic rate: 1 MET=3.5 ml/kg/min) increase of cardiorespiratory fitness there is a 24% lower risk of all-cause mortality, and a 24% lower risk of cardiovascular disease mortality in women (Zhang et al., 2017), strategies to maintain VO_{2peak} cannot be emphasized enough. Moreover, poor cardiorespiratory fitness has direct consequences on HRQoL since performance of daily activities is adversely affected (Herrero et al., 2006).

1.3.4 Skeletal muscle

Chemotherapeutic agents have been shown to induce muscle weakness in cancer patients regardless of disease stage or nutritional status (Christensen et al., 2014), as reflected by a slower chair-rise test time (Galvao et al., 2009) and lower handgrip strength (Hayes et al., 2005, Cantarero-Villanueva et al., 2012) compared to healthy controls. In a cross-sectional study, both isokinetic and isometric strength were impaired throughout the breast cancer continuum, with the most detrimental effects for patients who had received chemotherapy (Klassen et al., 2017). Muscle dysfunction and muscle weakness is associated with poorer disease prognosis and is believed to accelerate morbidity and mortality (Dobek et al., 2013).

Preclinical findings in rodents demonstrate that anthracycline-containing chemotherapy induces long-term impairments in muscular mitochondrial respiration and increased release of reactive oxygen species (Gouspillou et al., 2015). In contrast, taxane treatment has, unlike anthracycline-effects, not been shown to impair muscle force production in rodents (Chaillou et al., 2017). Moreover, chemotherapy for breast cancer is often accompanied by prolonged high-dose corticosteroid treatment which can lead to skeletal muscle atrophy and mitochondrial dysfunction (Batchelor et al., 1997). Interest in muscle function has traditionally been confined to cancer cachexia (Christensen et al., 2014), a condition associated with severe body weight, fat, and muscle loss due to underlying disease (Muscaritoli et al., 2010). Loss of skeletal muscle mass with concomitant gains in adiposity (sarcopenic obesity) has clinical implications since it has been linked to increased toxicity (*i.e.* poor tolerance to chemotherapy) leading to a poorer prognosis (Bozzetti, 2017), indicating a need to also assess muscle function in non-cachectic cancer populations. Cytokines have been suggested to play a vital role in promoting skeletal muscle atrophy/sarcopenia (Zhou et al., 2016). With chemotherapy, circulating cytokines are significantly upregulated (van Vulpen et al., 2018), and it is therefore crucial to implement an intervention capable of maintaining or improve muscle mass and reducing the systemic inflammation caused by chemotherapy and physical inactivity.

1.3.5 Body mass

Evidence shows that overweight women and women who gain weight after a breast cancer diagnosis have a doubled risk of recurrence and death from breast cancer at 5 years, as well as 60% higher risk of death over 10 years, when compared to non-overweight breast cancer survivors (Soares Falcetta et al., 2018). Weight gain occurs in most women after breast cancer treatment, especially in those who are younger (Nissen et al., 2011, Harris et al., 2009) and who have been treated with chemotherapy (Demark-Wahnefried et al., 2001). Women with breast cancer gain up to 5 kg body weight during chemotherapy (Makari-Judson et al., 2014), and few return to their pre-diagnosis weight (Irwin et al., 2015). Increases in adiposity may be caused by alterations in metabolic pathways as a result of chemotherapy or drugs taken in combination with chemotherapy such as glucocorticoids which have been shown to induce weight gain (Wung et al., 2008). Moreover, weight gain has an impact on a woman's self-image and QoL (McInnes and Knobf, 2001).

1.4 PHYSICAL INACTIVITY

As defined by the World Health Organization (WHO), "physical activity is any bodily movement produced by skeletal muscle that requires energy expenditure". Physical inactivity, defined as achieving less than 30 minutes of moderate-intensity physical activity per week (World Health Organization 2018) has been shown to be a primary cause of most chronic diseases (Booth et al., 2012), and is estimated to be the main cause for about 21–25% of breast cancers (World Health Organization 2018).

After a breast cancer diagnosis, patients show significantly reduced PA levels, especially during the adjuvant treatment phase, with difficulties returning to pre-diagnosis PA levels one year into survivorship (Huy et al., 2012). Personal and cancer-related characteristics such as age, stage of cancer, and time since treatment have been proposed to be related to physical inactivity (Andrykowski et al., 2007). However, more recent findings have pointed towards fatigue being a more important predictor than the above mentioned factors (Brunet et al., 2013). This is also supported by qualitative study findings showing that fatigue is a significant barrier to maintaining PA levels among active women after treatment (Browall et al., 2016). However, it is not known whether fatigue contributes to and/or is the result of inactivity.

Considering that physical inactivity places adults with a history of cancer at greater risk for morbidity, poorer health outcomes, and mortality (Lynch et al., 2013), women that are consistently inactive is an important target group for exercise interventions.

1.5 DEFINING CANCER SURVIVORSHIP

The Institute of Medicine (IOM) has defined the survivorship time period as "the period following first diagnosis and treatment and prior to the development of a recurrence of cancer or death."(Institute of Medicine, 2006). However, this phase of cancer control continuum has typically not been well described. Courneya and Friedenreich (2007) have proposed a Physical Activity and Cancer Control framework with six cancer-related time periods: two pre-diagnosis

(pre-screening and screening) and four post-diagnosis (pre-treatment, treatment, *survivorship*, and end of life). In this thesis, the term "survivorship" will be used when referring to the time period after completion of chemotherapy. More than 97 000 women in Sweden today have survived breast cancer (Cancerfondsrapporten 2018), and the aging of the population will contribute to an even larger cohort of cancer survivors in the future. As a result, there is an increasing emphasis on providing better support for long-term health promotion and prevention.

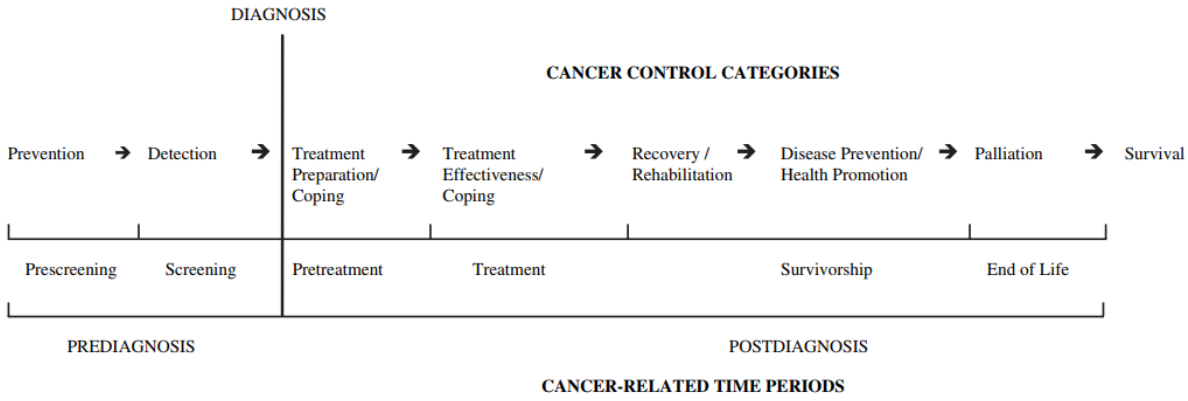

Figure 2. "Physical activity and cancer control framework." Reprinted from Courneya and Friedenreich (2007) with permission from Elsevier.

1.6 BENEFITS OF EXERCISE TRAINING

Exercise training is structured, repetitive, and has as an objective to improve or maintain physical fitness (Caspersen et al., 1985). The biological stress induced by an exercise stimulus, through the perturbation of cellular and systemic environments, results in an adaptation of the body that subsequently withstands future similar challenges (Kraemer, 1988, Goldspink et al., 2002). The pleiotropic effects that exercise induces on the human body are well established in the healthy population (Garber et al., 2011). Endurance training has been shown to result in improved cardiac output (Ekblom et al., 1968), mitochondrial biogenesis (Gollnick et al., 1972), and increased capillarization (Schantz et al., 1983). These adaptations lead to an increased ability to transport and use oxygen to generate energy (Gollnick et al., 1972). The mitochondrion is the main organelle for energy conversion from energy-rich substrates through generation of adenosine triphosphate (ATP) via the electron transport chain. The electron transport chain consists of five protein complexes (complex I, II, III, IV, and V) embedded in the inner mitochondrial membrane, in which the first four complexes transfer electrons by using substrates generated through the tricarboxylic acid (TCA) cycle (Mitchell, 1961). Resistance training on the other hand leads to increases in neural adaptations (Aagaard and Mayer, 2007), muscle size, improved muscle strength (Mangine et al., 2015), and an increase in satellite cell number (Kadi et al., 2005). These classic and well established adaptations to both endurance- and resistance training have been shown in both young and old individuals.

An emerging exercise modality, high-intensity interval training (HIIT), which consists of short bursts of high-intensity exercise interspersed with recovery periods, has been found to be a potent treatment strategy for improving cardiorespiratory fitness (MacInnis and Gibala, 2017, Milanovic et al., 2015) and to induce adaptations of mitochondrial markers (Robinson et al., 2017) in a time efficient manner. The beneficial effects of HIIT are not limited to these physiological factors but have also been shown to induce improvements on HRQoL (Jaureguizar et al., 2016), mood state (Ouerghi et al., 2016), cognitive health (Drigny et al., 2014), systemic inflammation (Munk et al., 2011), neuromuscular adaptations (Buchheit and Laursen, 2013), increases endorphin release in brain areas associated with controlling emotion and pain (Saanijoki et al., 2017), and has also been reported to be a more enjoyable exercise modality compared to low- or moderate-intensity endurance training (Thum et al., 2017).

1.6.1 Exercise for patients with breast cancer

There is a large body of epidemiological evidence showing that individuals that exercise on average have a 25% lower risk of breast cancer, with a stronger effect for moderate to vigorous PA (Friedenreich et al., 2010). Emerging observational data also suggest that regular exercise is associated with a 10-50% reduction in risk of recurrence and cancer specific mortality (Friedenreich et al., 2016). Recently, two randomized controlled trials showed that women that conducted regular aerobic or resistance exercise training had favourable, although non-significant, effects compared to the control group on overall survival (Courneya et al., 2014b, Hayes et al., 2018).

Exercise trials for individuals with breast cancer have primarily been performed in breast cancer survivors after completion of chemotherapy and have shown beneficial effects on cardiorespiratory fitness, muscle strength, HRQoL (Cramp et al., 2010), and fatigue (Cramp and Byron-Daniel, 2012, Meneses-Echavez et al., 2015). Few supervised exercise trials have been conducted during chemotherapy, and most of these have small sample sizes (Juvet et al., 2017). A recent systematic review by Furmaniak et al. (2016) showed that both aerobic and resistance training alone or in combination were effective to attenuate fatigue. Aerobic exercise has been shown to have the most positive effect on cardiorespiratory fitness although effect sizes have on average been small, while resistance training has been shown to induce improvements in muscle strength, lean body mass, and self-esteem. The effects of aerobic and/or resistance training on HRQoL are less convincing showing no or small effects (Furmaniak et al., 2016). Studies have also assessed home based walking interventions; however, there is a lack of intention-to-treat analyses in these studies, and the more recent home-based walking intervention studies have shown negligible to no effects on CRF and VO_{2peak} (Fairman et al., 2016).

HIIT alone in breast cancer survivors after completion of chemotherapy has been shown to be safe and tolerable (Dolan et al., 2016, De Backer et al., 2007b, Kampshoff et al., 2015), inducing slightly more beneficial effects compared to moderate-intensity endurance exercise on cardiorespiratory fitness and cancer-related fatigue (Kampshoff et al., 2015). In patients with breast cancer undergoing chemotherapy, the incorporation of HIIT is limited to one pilot

study in which HIIT was combined with resistance training and included a mix of cancer diagnoses (Schulz et al., 2017). Findings from this pilot study demonstrated favorable effects on cardiorespiratory fitness, muscle strength, and QoL.

1.7 EXERCISE RECOMMENDATIONS FOR INDIVIDUALS WITH CANCER

The American College of Sports Medicine (ACSM) organized a roundtable on exercise prescription guidelines in 2010 (Schmitz et al., 2010). They reported that few randomized controlled trials existed, mainly with small sample sizes and showed contradictory results. However, findings regarding safety was consistent across studies. Since then, an increasing number of trials have been published showing that exercise induces favourable effects on physical function and self-reported outcomes, although the larger bulk of studies included cancer survivors rather than women undergoing chemotherapy, as previously mentioned. The Swedish up-to date clinical handbook on how to prevent and treat diagnoses using PA includes a chapter on PA guidelines for individuals with cancer (Johnsson et al., 2017). These guidelines suggest to engage in both aerobic and resistance based exercise. Recommendations for aerobic exercise are the same as for guidelines for the general population: at least 150 min of moderate intensity (3-7 days/week), at least 75 min of vigorous intensity aerobic exercise (3-5 days/week), or a combination of these. For resistance exercise, the Swedish guidelines recommend including 12 exercises, performed at a moderate intensity at least 1x8-12 repetitions performed 2-3 times/week. Caution is advised for those during chemotherapy: the intensity should be based on the day-to-day state which can be influenced by various degrees of symptoms.

2 HYPOTHESES AND AIMS

It was hypothesized that adding high-intensity interval training (HIIT) to conventional resistance training (RT) or aerobic training (AT) during chemotherapy for patients with breast cancer would be increasingly beneficial in counteracting increases in fatigue and symptom burden, as well as declines in skeletal muscle structural and functional properties. At 12 months, compared to baseline, it was hypothesized that both exercise groups would display sustained levels for physiological and self-reported health-related outcomes compared to deteriorated levels in the control group.

The specific aims of this thesis were to examine and compare the effects of a 16-week RT-HIIT and AT-HIIT intervention during chemotherapy for patients with breast cancer over the intervention period, and 12 months following commencement of chemotherapy compared to usual care (UC) on:

1) Physiological outcomes: cardiorespiratory fitness, muscle strength, body mass, hemoglobin concentration, pain sensitivity, muscle morphology and mitochondrial markers
2) Self-reported health-related outcomes; cancer-related fatigue, pain, symptom burden, and sick leave rates

3 RESULTS AND DISCUSSION

3.1 ATTENDANCE TO THE EXERCISE INTERVENTION AND PATIENT CHARACTERISTICS

The four studies that are included in this thesis are based on the OptiTrain trial (see Wengström et al. (2017) for the study protocol). From March 2013 to July 2016, two hundred and forty participants were included in the OptiTrain trial (papers I-IV). In July 2017 the 12-month follow-up was completed. The participant flow is shown in Figure 3 (papers I, III, & IV).

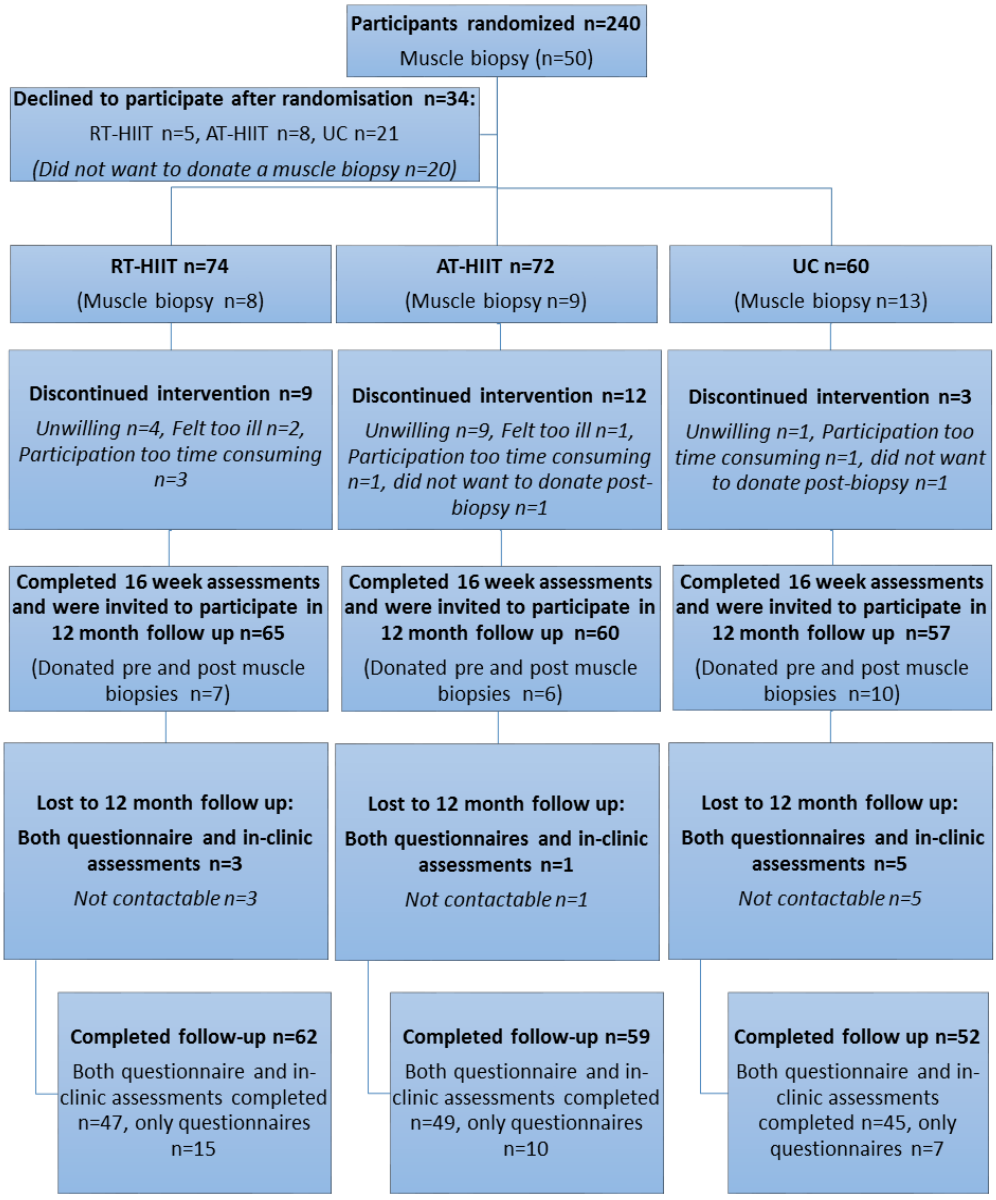

Figure 3. CONSORT diagram of the participant flow (papers I, III, and IV). RT–HIIT, resistance and high-intensity interval training; AT–HIIT, moderate-intensity aerobic and high-intensity interval training; UC, usual care.

In the initial 16-week intervention study (paper I), attendance (calculated as the mean of the individual percentages: attended exercise sessions divided by the total number of sessions) to the exercise sessions was 68% in RT-HIIT and 63% in AT-HIIT groups, while adherence to intensity (calculated as the number of patients who successfully completed 90% of the exercise

sessions according to plan, *i.e.*, intensity and duration, divided by the total number of patients in the intervention groups) was 83% in RT-HIIT and 75% in AT-HIIT. No adverse events occurred during exercise sessions. Moreover, no significant differences were found in attendance rates between those receiving taxane and not receiving taxane treatment. These attendance rates are comparable with other exercise interventions for patients with breast cancer, and a certain amount of contamination and imperfect adherence is to be expected in exercise trials for patients with breast cancer (Furmaniak et al., 2016). Of note, 59% of the participants that dropped out immediately following the randomization were those unwilling to donate a muscle biopsy, indicating that the invasive method rather than unwillingness to participate in the exercise intervention was the reason for this initial dropout.

Patient characteristics from the initial study (paper I) are shown in Table 2. No significant differences were found in patient characteristics between groups, and no significant differences were found between those that dropped out after baseline assessment and those who completed baseline and 16-week post assessments, indicating no systematic drop out during the intervention. Preliminary data analysis (unpublished data) does however suggest that those that dropped out during the study period had a lower sense of coherence, *i.e.* coping worse with stressful situations to maintain and develop health (Olsson et al., 2006).

Table 2. Participant characteristics at baseline

	RT-HIIT n=74	**AT-HIIT n=72**	**UC n=60**
	mean±SD	**mean±SD**	**mean±SD**
Age (years)	52.7±10.3	54.4±10.3	52.6±10.2
Body mass (kg)	68.7±11.3	67.7±13.0	69.1±11.0
Height	165.7±6.7	165.3±6.6	166.4±7.0
SED (% of daily wear time)	63.7±7.7	65.6±6.2	66.6±7.2
MVPA (% of daily wear time)	9.6±2.8	8.3±2.8	8.5±4.3
	n (%)	**n (%)**	**n (%)**
Married or partnered	60.6	59.7	69.5
University completed	67.6	64.7	66.0
Current smokers	4.3	5.9	5.2
Employed	74.6	86.8	79.7
Postmenopausal	51.4	63.9	61.7
Tumour profile			
Triple negative	14.9	11.0	16.7
HER2+, ER+/-	21.6	30.2	20.0
HER2-, ER+	62.2	58.9	61.6
HER2-, ER-	1.4	0.0	1.7
Anthracycline based therapy	40.6	37.0	41.7
Taxane based therapy	59.4	63.0	58.3

SD, standard deviation; RT-HIIT, resistance and high-intensity interval training; AT-HIIT, moderate-intensity aerobic and high-intensity interval training; UC, usual care, MVPA objectively measured moderate- to vigorous intensity physical activity, SED objectively measured sedentary behavior.

When assessing participants with high attendance versus low attendance (cutoff for high attendance was set as over 65%), there was a significant difference in level of education as assessed by an exact χ^2 test (p=0.003), but no differences in other factors such as chemotherapy regimen, menopausal status, PA level, age, or BMI. This is in line with a recent meta-analysis

that suggested an important role for socio-demographic factors, including level of education, in predicting adherence and attendance to exercise in patients with breast cancer (Ormel et al., 2018).

Among the 12-month follow-up completers, no significant differences were found in baseline characteristics between groups. Baseline differences between those that declined to come in for in-clinic follow-up included less moderate-vigorous PA min/day (objectively measured) compared to those that completed 12-month in clinic assessments (p=0.027). Moreover a significantly higher proportion (72%) of participants that did not participate in the in-clinic assessment follow-up had lower attendance levels to the exercise sessions compared to completers (43%) (p=0.005) suggesting a potential selection bias. However no differences were found between RT-HIIT, AT-HIIT and UC groups.

Self-reported PA was assessed through a question whether participants met the PA recommendations of 75 min of vigorous PA or 150 min of moderate intensity PA/week or not. Over the intervention, these results showed a significant decline in the proportion of participants meeting exercise recommendations in the UC group, being significantly different compared to RT-HIIT and AT-HIIT. At the 12–month follow-up, a significantly higher proportion of participants in the UC group met exercise recommendations than at baseline, with no between-group differences (Figure 4). This may be explained by the selection of participants (as indicated by baseline differences in PA levels in the follow-up sample) at the 12-month follow-up being slightly more active compared to those at baseline and at 16 weeks. Similar to our findings, a follow-up study found that patients with breast or colon cancer who previously participated in 18 weeks of combined aerobic and resistance training displayed significantly higher levels of objectively measured moderate-to-vigorous PA levels at 4 years compared to baseline (Witlox et al., 2018). In contrast, a longitudinal study showed significantly reduced levels of PA during cancer treatment, which did not return to baseline PA levels one year later (Huy et al., 2012). Moreover, previous studies have shown that 42% of participants did not meet exercise recommendation guidelines six months after an intervention, regardless if they had taken part in exercise or not (Courneya et al., 2009). Similar findings were also reported by Schmidt et al. (2017).

One limitation in the current study was that objectively measured PA was only measured at baseline, due to practicality issues. It has been shown that in studies using self-reported measures of PA, subjectively assessed PA activity levels are typically higher than objectively measured PA levels (Prince et al., 2008). A preliminary analysis (unpublished data) showed discrepancies with 62% of the participants rating their PA levels according to measured PA. Nevertheless, objectively measured PA will be obtained at the two-year follow-up of the OptiTrain trial which will provide valuable information regarding the participants' PA behavior.

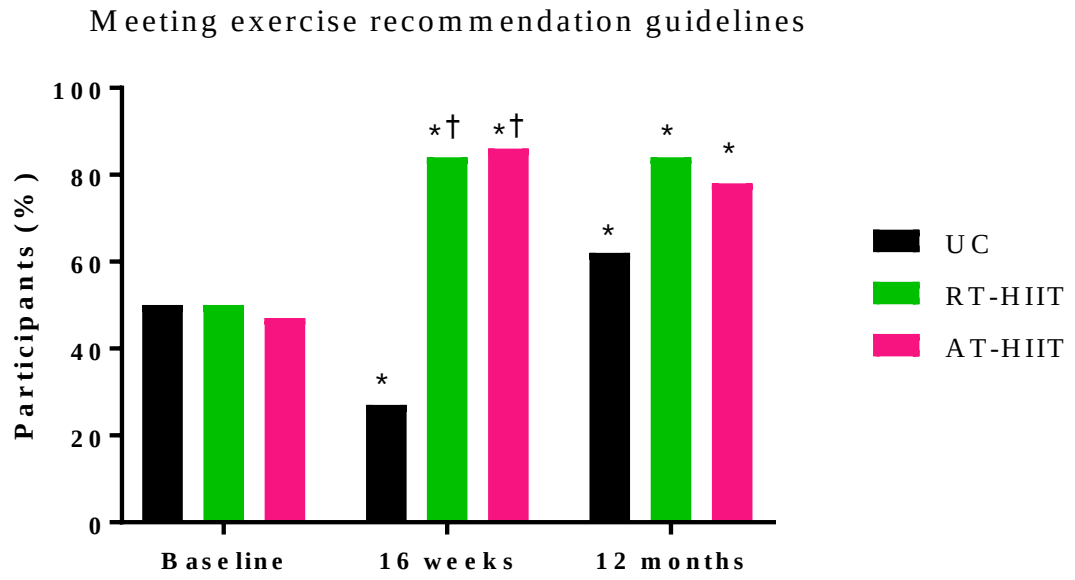

Figure 4. Percentage of participants in each group reporting moderate/high physical activity at baseline, 16 weeks- and 12 months post-baseline. RT-HIIT, resistance and high-intensity interval training group; AT-HIIT, moderate-intensity aerobic and high-intensity interval training group; UC, usual care group; *p<0.05 vs baseline, †p<0.05 vs UC.

When conducting exercise trials, there is a risk of selection bias in which there is a likelihood that a more active and/or healthier sample of patients with breast cancer may accept participation. In the OptiTrain trial, this may also help to explain why a high proportion of participants in the UC group dropped out immediately following randomization. However, compared to objectively measured PA in 508 cancer survivors in the National Health and Nutrition Examination Survey (NHANES) (Thraen-Borowski et al., 2017), as well as 486 healthy middle-aged women from the Swedish CArdioPulmonary bioImage Study (SCAPIS) (Ekblom-Bak et al., 2015), the baseline objectively measured PA data in the OptiTrain trial indicated similar PA patterns as in those studies. Cancer survivors in the NHANES study spent 62% in sedentary time, and 2% in moderate to vigorous PA, while those in the SCAPIS study spent 58% in sedentary time and 4% in moderate to vigorous PA, compared to the OptiTrain participants that spent 63% in sedentary behavior and 9% in moderate to vigorous PA. The slightly higher amount of time spent in moderate to vigorous PA in our sample may be due to the inclusion of younger participants compared to the NHANES and SCAPIS studies, as well as due to the mixed cancer diagnoses in the NHANES study.

3.2 EXERCISE TRAINING DURNG CHEMOTHERAPY IS EFFECTIVE TO COUNTERACT INCREASES IN CANCER-RELATED FATIGUE

Cancer-related fatigue (CRF) has been reported to be one of the most prevalent and debilitating symptoms experienced by patients with breast cancer during chemotherapy and can persist for several years after completion of treatment (Patrick et al., 2003). Besides psychological interventions, exercise training is the only intervention that has the potential to counteract CRF (Mustian et al., 2017). Supervised exercise interventions during chemotherapy have been shown to be effective in relieving CRF (Furmaniak et al., 2016), particularly interventions including both resistance and aerobic training (Meneses-Echavez et al., 2015). However, there

is limited data from studies with sufficient sample sizes that have examined the multiple and different dimensions of fatigue.

In the OptiTrain trial, CRF was the primary outcome and was measured by the validated Swedish version of the 22-item Piper fatigue scale (PFS) (Jakobsson et al., 2013). Data was obtained at baseline, 16 weeks, and 12 months post-intervention. The PFS measures several dimensions of CRF: 1) Behavioral/daily life CRF, 2) Affective/Emotional CRF, 3) Physical/sensory CRF, and 4) Cognitive CRF. The effect of the initial 16-week exercise intervention on CRF have been published in detail elsewhere (findings not included in the thesis) (Mijwel et al., 2018). Findings from this study showed that RT-HIIT counteracted total fatigue (ES=-0.51; p=0.02), behavior/daily life fatigue (ES=-0.62; p<0.001), and physical fatigue (ES=-0.47; p=0.03) compared to the UC group. Moreover, no significant effects on CRF were found in the AT-HIIT group when assessed by the PFS. These findings are similar to those reported by Travier et al. (2015), who also trialed a program of combined aerobic and resistance training, although with lower effect sizes (-0.20), while another trial of resistance training only (BEATE study) showed no beneficial effects on fatigue (Schmidt et al., 2015b). Those findings and the results from this thesis indicate the importance of combined exercise modalities to induce more beneficial effects on CRF. In the current study, fatigue measured by the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C30), showed similar results with the exception that using this assessment tool AT-HIIT also showed favorable effects for countering fatigue compared to UC (ES=-0.47; p=0.01). The EORTC-QLQ-C30 has been shown to be sensitive to change for patients with cancer during chemotherapy (Uwer et al., 2011), but the responsiveness of the PFS has not previously been established (Jakobsson et al., 2013). Preliminary analyzes by our research group to assess the ability of the PFS to detect change over the course of chemotherapy demonstrated that the instrument is indeed sensitive to changes over time in patients with breast cancer (unpublished data). The reason for the different findings between the two assessment tools is unclear. It has been found that for patients with advanced cancer, there is a ceiling effect for assessing fatigue with the EORTC-QLQ-C30 scale. When assessing individual values and histograms for the two scales, there was a normal distribution for the EORTC-QLQ-C30 scale but not for PFS, showing a right skewness of the data. Thus, further analyzes of the PFS will be undertaken.

At 12 months (paper IV), both the RT-HIIT and AT-HIIT groups reported a significant attenuation of total CRF (ES=-0.34; ES=-0.10), behavioral/daily life CRF (ES=-0.76; ES=-0.50), and affective/emotional CRF (ES=-0.60; ES=-0.39), which was significantly different to the UC group. Moreover, cognitive fatigue was also counteracted in the AT-HIIT group (ES=-0.13) (Figure 5A). No significant differences between groups were found for fatigue with the EORTC-QLQ-C30 symptom scale. This is not surprising since the EORTC-QLQ-C30 mainly reflects the physical component of fatigue, and results from this scale align more with results from the physical CRF measured by the PFS (*i.e.* no significant differences between groups). At 12 months, 56% of participants in the UC group were experiencing moderate (score 4-7 out of 10) to severe fatigue (score 7-10 out of 10), while the proportion of participants that

experienced moderate to severe fatigue were 33% and 37% in the RT-HIIT and AT-HIIT groups respectively (Figure 5B-D).

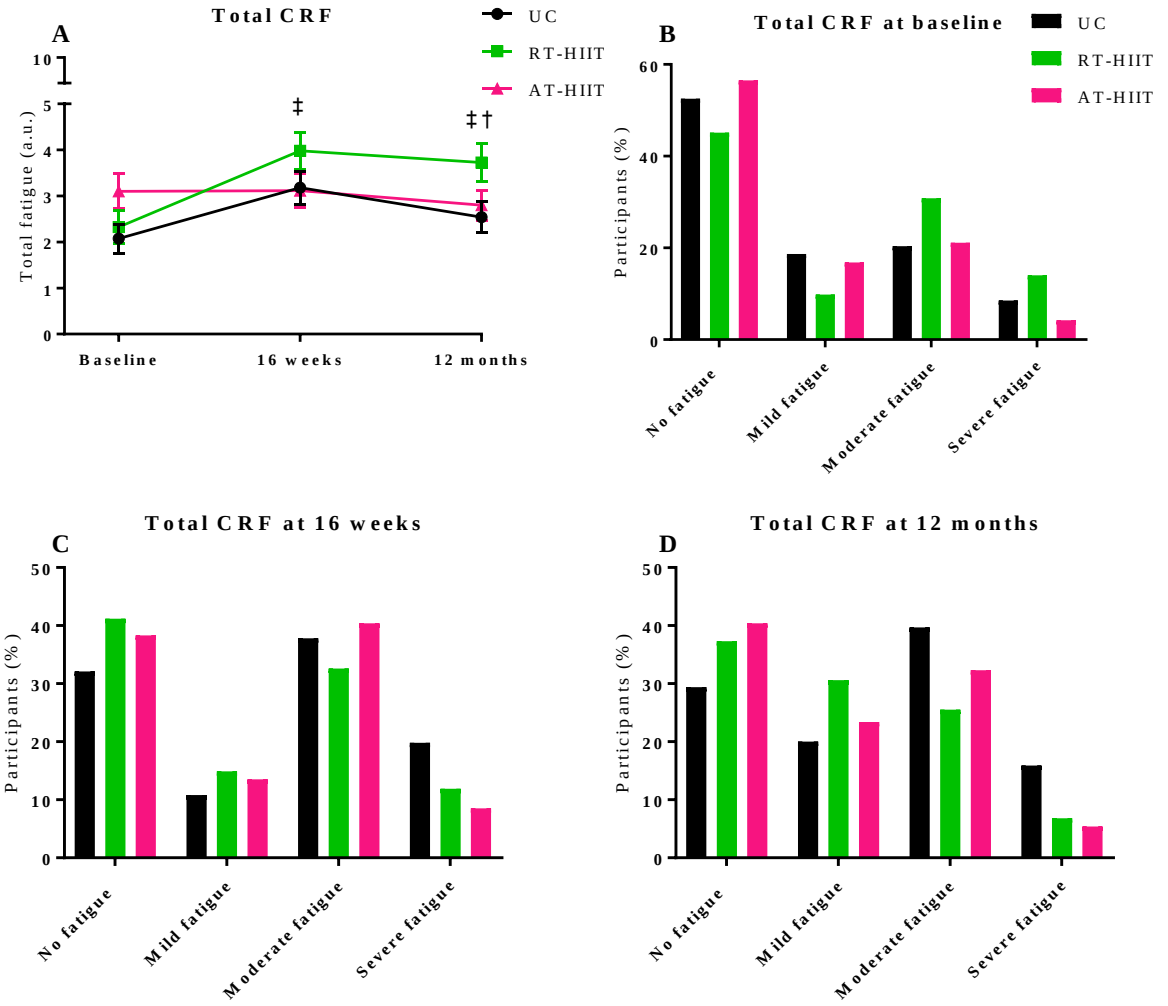

Figure 5. Cancer-related fatigue (CRF) in RT-HIIT (resistance combined with high-intensity interval training), AT-HIIT (moderate-intensity aerobic combined with high-intensity interval training), and UC (usual care) groups A) from baseline to 16 weeks post-intervention and from baseline to 12 months, and Total CRF fatigue levels divided into categories: no fatigue, mild fatigue (score>0), moderate fatigue (score≥4), or severe fatigue (score≥7) at B) baseline, C) 16 weeks- and D) 12 months post-baseline. ‡p<0.05 between RT-HIIT and UC, †p<0.05 between AT-HIIT and UC.

Previous follow-up studies after completion of a supervised exercise intervention during chemotherapy did not find lasting beneficial effects for fatigue either at 4-6 month (Travier et al., 2015, Courneya et al., 2007a, Mutrie et al., 2007) or at 12-month follow-up (Schmidt et al., 2018a). Similar findings, to those from supervised studies, were found for follow-up studies of two home-based exercise interventions during chemotherapy (Eakin et al., 2012, Haines et al., 2010). In the supervised PACT (Travier et al., 2015) and START combined resistance and aerobic exercise trials (Courneya et al., 2007a), the control group had recovered from an increase in CRF to a similar extent as the exercise groups. The reason for the recovery in the control groups was not explained, but could potentially be due to the fact that the control groups in those trials received various types of interventions such as muscle relaxation during

chemotherapy in the PACT trial and a 1-month supervised exercise program post-intervention in the START trial, while in the OptiTrain trial the UC group is strictly treated as a control group until the 5-year follow-up. Alternatively, the control sample in those studies may have been a more motivated group to stay physically active and therefore not being representative of the broader population.

In the current trial, moderate to large effect sizes were found for several dimensions of fatigue, both at 16 weeks and at 12 months following commencement of chemotherapy. Typically small effects sizes have been reported for exercise trials during chemotherapy (-0.18 to -0.35) (van Vulpen et al., 2016). The systematic review conducted by van Vulpen et al. (2016) showed that exercise had the strongest potential to reduce physical fatigue, and the smallest effect on affective and cognitive fatigue. This was also the case for OptiTrain results over the 16-week intervention but not at the 12-month follow-up, where exercise groups were able to counteract affective and cognitive fatigue. The results at 16 weeks and 12 months for the different domains of CRF may be attributable to the fact that the manifestation of acute fatigue during chemotherapy and long-term persisting fatigue have been shown to be predicted by different factors (Schmidt et al., 2015a). Acute fatigue has been found to be caused by chemotherapy, especially physical fatigue, but has not been found to be associated with long-term persisting fatigue, which instead appears to be associated with preexisting depressive or psychological disorders, pain medication, and pre-diagnosis physical inactivity (Schmidt et al., 2015a, Goedendorp et al., 2013). Given that exercise has the potential to alleviate depressive symptoms in patients with breast cancer (Courneya et al., 2007b, Mutrie et al., 2007), as well as in other populations with depressive symptoms (Craft and Perna, 2004), it may have been crucial for the participants that they were able to exercise during chemotherapy to counter the psychological distress associated with finding out about a cancer diagnosis and going through cancer treatment. However, it is unclear whether preexisting depressive disorders were the cause of persistent fatigue in the current trial. Affective fatigue has been shown to be significantly associated with poor social support (Schmidt et al., 2018a). Therefore, in the present study it cannot be ruled out that the motivational support and attention to uphold physical exercise received by the exercise groups after completion of the intervention, although attendance was very low (20%), resulted in favorable effects to relieve affective and/or cognitive fatigue, rather than the exercise *per se*. Nevertheless, in support of exercise inducing these beneficial effects, the BEATE trial by Schmidt et al. (2015b) showed that despite the control group receiving support in the form of a muscle relaxation intervention during chemotherapy, a tendency towards favorable effects were found for the resistance training group to counteract affective fatigue.

There was a significant difference in baseline behavioral/daily life CRF between RT-HIIT and AT-HIIT. The reason for this difference may be attributable to the (non-significant) relatively higher proportion of participants in RT-HIIT being pre-menopausal (47.3%), compared to 36.1% in AT-HIIT and 38.3% in UC. It has been shown that lower age can be a predictor of increased fatigue (Winters-Stone et al., 2008), and this may be due to the distressing premature menopausal symptoms. While these experiences might be more normalized for women in their

50s, for younger women these changes can be exceedingly stressful and can negatively affect QoL (Rosenberg and Partridge, 2013). The blocked randomization did not result in any other differences in patient population characteristics; however, since there is no guarantee of balanced groups with this type of randomization in randomized controlled trials, stratification for important variables may have been able to prevent this randomization issue.

3.3 PRESSURE-PAIN THRESHOLD AND PAIN

Pain is one of the most debilitating symptoms in patients with breast cancer that have undergone chemotherapy and can result in impairments in activities of daily living (Patrick et al., 2003).

Pressure-pain threshold (PPT) is the minimum intensity at which a physical stimulus is perceived as being painful, and is measured and quantified by using algometry (Kinser et al., 2009). A higher PPT has been associated with a higher fitness level (Lemming et al., 2015), as well with higher self-reported PA levels (Andrzejewski et al., 2010). Moreover, resistance exercise training has proven to increase PPT in patients with chronic neck pain (Li et al., 2017), whereas aerobic training has been shown to improve pain tolerance, but not pain threshold in healthy individuals (Jones et al., 2014). To date, no trials have assessed whether exercise has an effect on pressure-pain threshold for patients with cancer.

In paper I, PPT was measured at baseline and at 16 weeks by using a handheld electronic algometer pressed on the mid-trapezius and mid-gluteus muscle bilaterally. RT-HIIT significantly counteracted the hyperalgesia that was found in the UC group for both gluteus (ES=0.53) and trapezius muscles (ES=0.46), and was also superior to AT-HIIT for trapezius PPT (ES=0.30).

Different chemotherapy drugs have been shown to induce pain to various degrees in patients with breast cancer with taxanes being more neurotoxic and associated with higher levels of self-reported pain compared to non-taxane treatments (Majithia et al., 2016). Of note, when performing a subgroup analysis in the current trial, we found that the patients receiving taxanes displayed no hyperalgesia over time and no between group differences. It may be that taxanes cause increased numbness in the acute phase leading to a blunted PPT response. In line with this speculation, taxane-therapies have been shown to cause a loss of vibratory perception (Hilkens et al., 1997). PPT was not assessed at the 12-month follow-up; however, results from the two-year follow up will provide valuable insights into long-term effects of chemotherapy on PPT.

Interestingly, self-reported pain assessed by the EORTC-QLQ-C30 showed that the AT-HIIT group managed to counteract the increase in pain found in the UC group over the intervention (Mijwel et al., 2018). At 12 months, no differences were found for self-reported pain between groups (Figure 6). It has been shown that aerobic training can be more effective compared to resistance training in alleviating pain symptoms over the course of chemotherapy (Schmidt et al., 2015c), while others have found no differences between combined resistance and aerobic training compared to usual care (Travier et al., 2015). Pain symptoms have been shown to

persist one year following completion of chemotherapy (Ganz et al., 2011), and pain has been shown to be one of the major symptoms to impact HRQoL 5 years into survivorship (Schmidt et al., 2018b). A score threshold of 25 for clinically important pain problems has been established for pain for the EORTC-QLQ-C30 questionnaire (Giesinger et al., 2016). This threshold was reached only by the UC group 16 weeks post-intervention. However, a subgroup analysis assessing the proportions of participants below and above the clinically important pain threshold, showed no statistical differences between groups, as assessed by a χ^2 test.

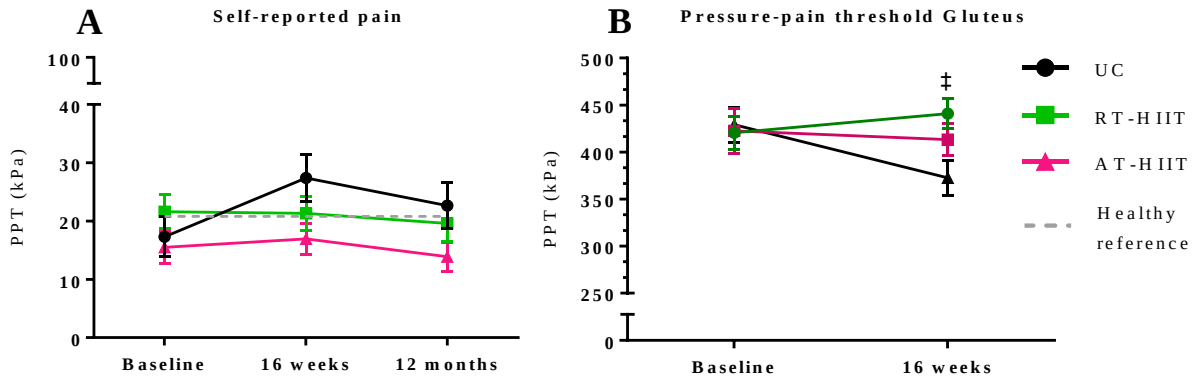

Figure 6. Changes in A) self-reported pain from baseline to 16 weeks (post-intervention) and from baseline to 12 months, and B), pressure-pain threshold (PPT) from baseline to 16 weeks in RT-HIIT (resistance combined with high-intensity interval training), AT-HIIT (moderate-intensity aerobic combined with high-intensity interval training) and UC (usual care) groups. Healthy reference values were obtained from Michelson et al. (2000). ‡p<0.05 between RT-HIIT and UC.

The conflicting findings regarding PPT and self-reported pain could be explained by the lack of relationship between participants' self-report of pain and participants' actual pain threshold (PPT gluteus and self-reported pain, r=-0.02; PPT trapezius and self-reported pain r=0.03). This is in line with a previous study in healthy individuals (Edwards and Fillingim, 2007). In those individuals, it was shown that those with higher self-reported pain were more anxious than those with lower self-reported pain scores, while objectively measured pain thresholds did not follow the same pattern. Another study showed that depression predicted self-reported pain but not cold pain tolerance in patients with opioid dependence (Tsui et al., 2013). Given that a breast cancer diagnosis can be a major psychological stress, associated with depression, fear, and anxiety (Baqutayan, 2012), it may be speculated that the participants were influenced by negative feelings that might have influenced their subjective feeling of pain; in part helping to explain the lack of association with PPT. Indeed, when assessing the association with anxiety from the Memorial Symptom Assessment Scale in the current trial (unpublished data), there was a significant association between self-reported pain and anxiety (r=0.3, p=0.002), but not between measured PPT and anxiety (r=-0.03, p=0.749) at 16 weeks. The implications of self-reported pain and its potential association with important prospective endpoints such as the development of clinical pain conditions remains to be explored.

Evidence suggests an association between muscle strength and PPT in healthy and diseased populations (Henriksen et al., 2013, Hooten et al., 2013). In line with this, we found significant, but weak associations between pre- to post changes in PPT at the gluteus (r=0.16, p<0.05) and

trapezius muscles (r=0.17, p<0.05) and pre- to post changes in lower-limb muscle strength as well as between pre-to post changes in PPT at the trapezius muscle and changes in handgrip strength (r=0.17, p<0.05). These findings could indicate that resistance training may be of particular importance in inducing analgesic effects. In healthy individuals, Henriksen et al. (2013), showed that PPT muscle function was only associated with the pressure pain sensitivity in the local muscle. Therefore, it may be speculated that measuring PPT on more relevant anatomical sites (*i.e. vastus lateralis*) than those measured may have resulted in stronger associations with lower-limb muscle strength in the current study. Despite this, in elderly women, no association between *vastus lateralis* PPT and lower-limb muscle strength (as measured by a chair-stand test) was found (Alfieri et al., 2017). The conflicting findings may be due to differences in populations and differences in assessment techniques of muscle strength as well as anatomical sites of PPT measurement.

PPT reproducibility has been found to be good for the gluteal site (Maquet et al., 2004), and the mean of the bilateral measurements on the same anatomical site have been shown to be valid (Lacourt et al., 2017). However, a limitation here is that only one measurement was performed at each site. To examine the reliability and the absolute agreement of three repeated PPT measurements, a test-retest was performed on 9 individuals by our research group. The findings revealed an excellent reliability of repeated measures (intraclass correlation coefficient=0.83); therefore, any possible error of single measurement is expected to be negligible.

3.4 VALIDATION OF SUBMAXIMAL EXERCISE TESTS FOR ASSESSMENT OF CARDIORESPIRATORY FITNESS IN PATIENTS WITH BREAST CANCER

Patients with breast cancer have considerable impairments in cardiorespiratory fitness that, in part, have been linked to the toxic effects of anticancer therapy. According to a recent systematic review that assessed psychometric properties, safety, and clinical utility of cardiorespiratory fitness in patients with cancer, the "gold standard" for measurement of aerobic fitness, VO_{2peak} (Hill and Lupton, 1923), was not recommended for patients with breast cancer due to clinical efficiency and safety concerns (Drouin and Morris, 2015). Instead, submaximal exercise tests for estimation of cardiorespiratory fitness provide a safer alternative to maximal exercise testing (Drouin and Morris, 2015). There are several valid equations available to estimate VO_{2peak} calculated based on the results of submaximal testing for healthy individuals (Noonan and Dean, 2000). The indirect submaximal exercise tests, the Åstrand-Rhyming (A-R) and Ekblom-Bak (E-B) prediction models have been shown to be valid in healthy individuals (Ekblom-Bak et al., 2014, Åstrand, 1960). Unlike performing a direct VO_{2peak} test, such tests are relatively simple to perform and do not require a maximal effort or as advanced equipment in a laboratory setting (Noonan and Dean, 2000, Drouin and Morris, 2015). The usefulness and simplicity of submaximal exercise tests encourages further research in the field to establish a valid, reliable, and sensitive test for assessment of cardiorespiratory fitness in patients with breast cancer. Furthermore, knowledge of a patient's cardiorespiratory fitness can assist clinicians in accurately and correctly providing an exercise prescription. In

paper II, a validation of A-R and E-B submaximal exercise tests were performed on 8 participants that were part of the larger OptiTrain trial.

All 8 participants underwent a submaximal exercise test on a cycle ergometer prior to an incremental VO_{2peak} test on a cycle ergometer. Findings from the study showed that the single workload stage test A-R was a valid test for patients with breast cancer during chemotherapy. The A-R prediction model overestimated VO_{2peak} by 6%, with a correlation coefficient of 0.9 (p<0.05) between A-R estimated VO_{2peak} and measured VO_{2peak}, and a coefficient of variation of 7%. The E-B prediction model overestimated VO_{2peak} by 42%, and showed a very weak, non-significant correlation with measured VO_{2peak} (r=0.2), and the coefficient of variation was 21%. The individual variation was quite high, although no outliers were found (Figure 7).

It may be speculated that directly measured VO_{2peak} was not reached in all instances during the graded maximal test; however, when assessing the criteria for reaching VO_{2peak}, all participants reached a plateau and the mean respiratory exchange ratio was 1.31.

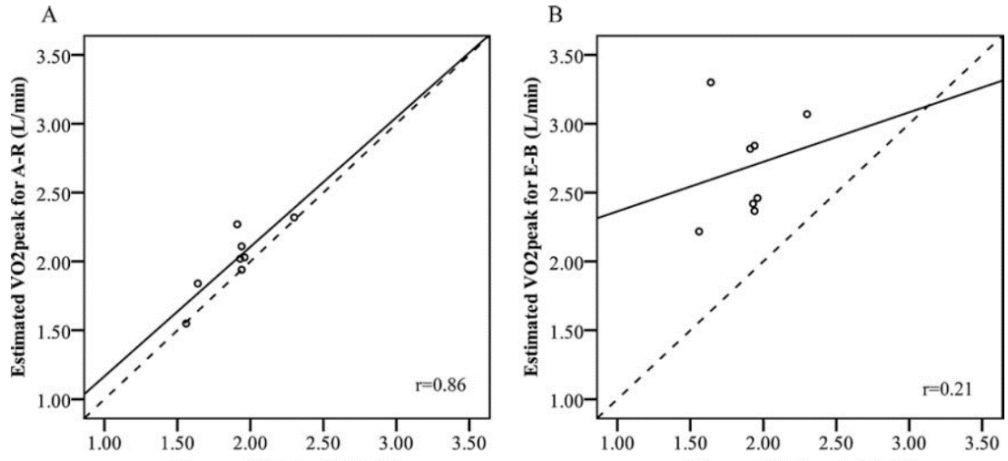

Figure 7. Correlations between measured versus estimated VO_{2peak} for: A) the Åstrand-Rhyming prediction model (A-R) and B) the Ekblom-Bak prediction model (E-B). This work is licensed under CC BY 4.0.

It has been suggested that conducting only one submaximal exercise test, without a familiarization test, is likely to result in an underestimation of VO_{2peak} due to anxiety leading to a higher HR (Åstrand and Ryhming, 1954). However, this was not the case in the current validation study, where both the A-R and E-B tests overestimated VO_{2peak}; thus, one can potentially rule out any anxiety factors that may have influenced the outcomes. An overestimation of both A-R (Siconolfi et al., 1982, Zwiren et al., 1991) and E-B (Ekblom-Bak et al., 2014) has previously been reported in the female population, although the overestimation of E-B was substantially greater in the current study. This may partly be attributed to the fact that VO_{2peak} was performed on a treadmill as opposed to on a cycle ergometer as in the original validation of the E-B test (Ekblom-Bak et al., 2014). VO_{2peak} obtained from treadmill exercise can be 5% to 10% higher. However, given that elderly patients and those with treatment-associated ataxia or peripheral neuropathy were included, cycle ergometry was favored for safety reasons.

The large overestimation of VO_{2peak} by the E-B prediction model seemed to be due to an unusually elevated HR, especially at the lower submaximal workload (30W), likely as a result of chemotherapy making the E-B estimated VO_{2peak} test potentially inappropriate for use in patients with breast cancer while undergoing chemotherapy. Moreover, variations in HR are typically higher at lower intensities compared to higher intensities (Åstrand and Ryhming, 1954). Furthermore, an elevated resting HR was found in women with breast cancer during chemotherapy compared with women with breast cancer who had not yet received chemotherapy or women who had already completed oncologic treatment (Jones et al., 2012). The influence of chemotherapy on HR has previously been suggested to be attributed to chemotherapy-induced autonomic dysfunction in women with early breast cancer treated with chemotherapy, which has been explained by an increased sympathetic activity and decreased cardiac vagal tone (Scott et al., 2014).

As indicated in the current validation study, a single stage test at approximately 70% of the maximal HR seems to accurately predict VO_{2peak}. A study by Evans et al. (2009) showed that women with breast cancer who had completed chemotherapy displayed no difference in HR response at an exercise intensity of 70% of maximal HR compared with healthy women, which may explain why a single stage test at a similar workload generated valid results to predict VO_{2peak}.

The A-R submaximal VO_{2peak} test was valid in patients with breast cancer during chemotherapy. However, sensitivity of the test still remains to be established in this population, as well as in healthy individuals (Noonan and Dean, 2000). Reliability of the A-R prediction model in patients with breast cancer also needs to be further explored. Two previous studies (May et al., 2010, De Backer et al., 2007a) on cancer survivors have established a good test-retest reliability for a submaximal cycle ergometer test, a submaximal test comparable to the A-R predictions model (10 min test at 50% of peak power output). The same studies suggested that the submaximal exercise tests assessed in those studies lacked the ability to detect changes in cardiorespiratory fitness over time. Although, in the study by May et al. (2010), a subgroup analysis revealed that a HR above 140 beats per min (bpm) was associated with changes in directly measured VO_{2peak}, indicating that higher submaximal loads are required during a submaximal cycle test to find reflections of changes in VO_{2peak}.

Besides the importance of establishing an accurate test for evaluation of cardiorespiratory fitness in patients with breast cancer, these findings also supported the use of the A-R prediction model in the larger OptiTrain trial.

3.5 MITOCHONDRIAL CONTENT AND CAPILLARIZATION MAY EXPLAIN MAINTAINED CARDIORESPIRATORY FITNESS WITH EXERCISE DESPITE DECLINES IN BLOOD HEMOGLOBIN CONCENTRATIONS

Current breast cancer treatments can have a negative impact on cardiovascular health (Jones et al., 2012). Exercise for patients with breast cancer has shown short-term beneficial effects on cardiorespiratory fitness, although the long-term effects are less known. Moreover, the effect of exercise during chemotherapy on skeletal muscle mitochondrial content and morphological

adaptations has not been established in patients with breast cancer undergoing chemotherapy. Preclinical reports suggest that anthracyclines can inhibit the complexes of the electron transport chain in skeletal muscle (Gilliam et al., 2013), and reduce mitochondrial respiration (Gouspillou et al., 2015).

Over the intervention (paper I), both RT-HIIT and AT-HIIT showed maintained levels of estimated VO_{2peak}, significantly different from the declines found in the UC group (Figure 8). Similar results were found when only assessing participants with higher attendance levels (over 80% attendance). Interestingly, cardiorespiratory fitness in the RT-HIIT group was maintained despite only a total of 9 min of HIIT per session. This finding contradicts that by Courneya et al. (2013), where only the higher dose (duration) aerobic training at a submaximal constant exercise intensity (50-60 min, 3 days/week, 60-75% of VO_{2peak}) resulted in a maintained cardiorespiratory fitness. This suggests that HIIT provides an effective and time-efficient training strategy resulting in the same beneficial maintenance in cardiorespiratory fitness as high-volume aerobic training, similar to findings in healthy individuals (MacInnis and Gibala, 2017, Milanovic et al., 2015).

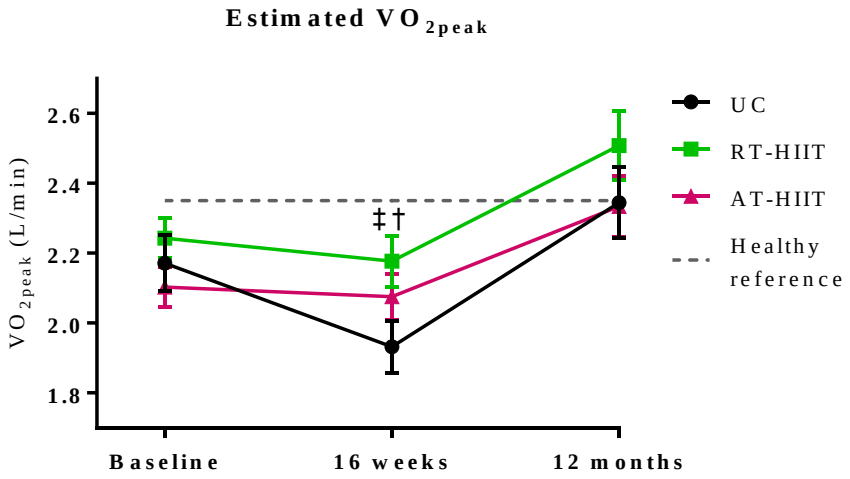

Figure 8. Changes in estimated VO_{2peak} from baseline to 16 weeks and from baseline to 12 months in RT-HIIT (resistance combined with high-intensity interval training), AT-HIIT (moderate-intensity aerobic combined with high-intensity interval training) and UC (usual care) groups. Healthy reference values are obtained from Aspenes et al. (2011). ‡p<0.05 between RT-HIIT and UC, †p<0.05 between AT-HIIT and UC.

In healthy individuals, aerobic training typically results in dose-response improvements in cardiorespiratory fitness over time. Here, the maintained levels of estimated VO_{2peak} in the exercise groups are in line with recent exercise trials (Travier et al., 2015, Schmidt et al., 2015b, Courneya et al., 2013, Dolan et al., 2010). A general increase in the use of taxane-based treatments (Peto et al., 2012) has been suggested to be the cause for the non-improvements in cardiorespiratory fitness (Møller et al., 2015). In paper I, a subgroup analysis was performed on those who had received taxanes compared to those who had not received taxanes. This analysis showed no influence of chemotherapy regimen on cardiorespiratory fitness in the exercise groups. However, the decline in estimated VO_{2peak} in the UC group showed slightly more unfavorable effects for the participants in the UC group that received taxanes (-14%) compared to those who had not received taxanes (-7%), suggesting slightly more toxic effects

of taxanes on the cardiovascular system. It may be that the high-intensity nature of the exercise regimens in the current trial were more effective compared to previous trials to counteract the toxic effects of taxanes on cardiorespiratory fitness.

To assess local skeletal muscle adaptations, muscle biopsies from 23 participants were assessed for muscle morphology and mitochondrial content at baseline and at 16 weeks (paper III). Here, participants in the AT-HIIT group showed significant improvements compared to the declines found in the UC group in capillarization (+33% vs -18%, ES=1.9), citrate synthase activity - a marker for mitochondrial content) (+20% vs -25%, ES=2.2), and protein levels of complex IV (+20% vs -9%, ES=1.3) (Figure 9). These are adaptations that typically take place with aerobic training in healthy individuals (Schantz et al., 1983) showing a trainability in patients with breast cancer receiving chemotherapy.

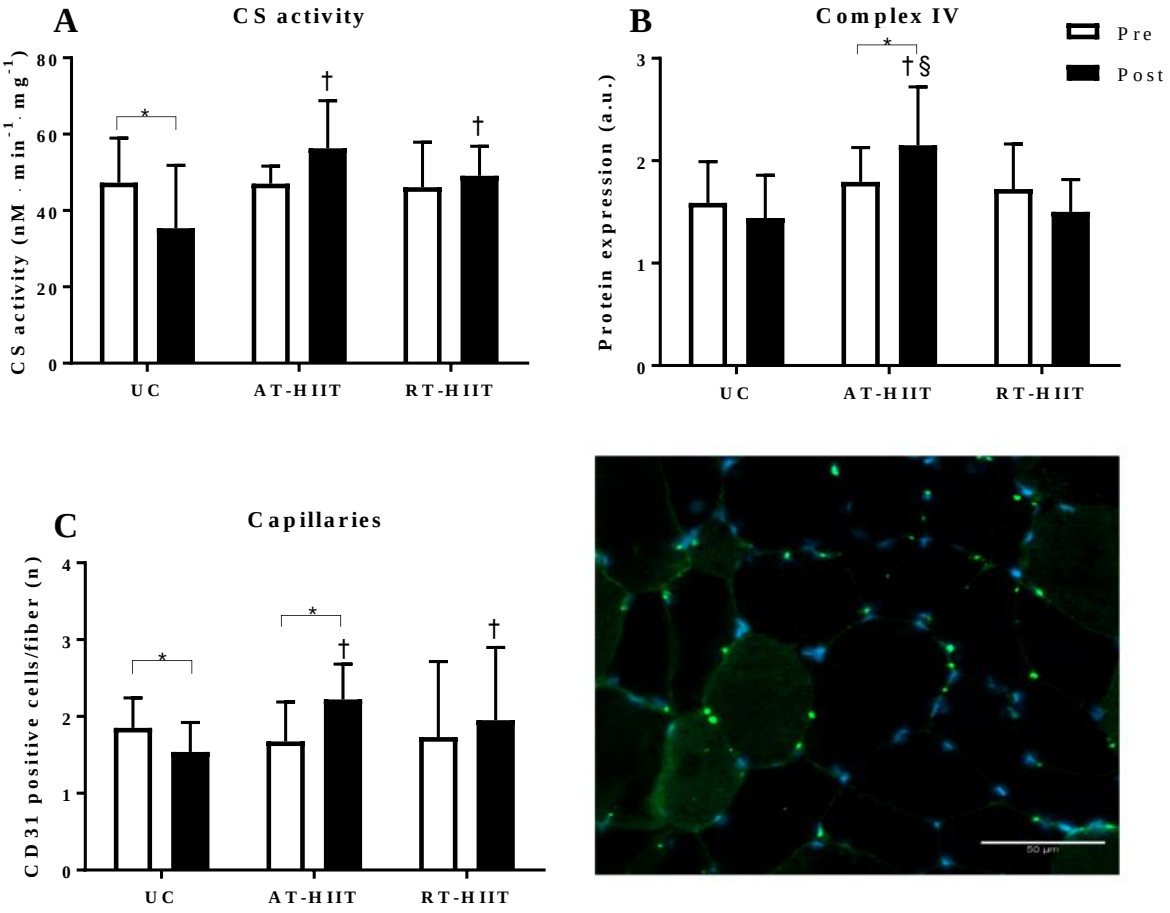

Figure 9. Local skeletal muscle adaptations for A) Citrate synthase activity (CS) ($nM \cdot min^{-1} \cdot mg^{-1}$), B) protein levels of complex IV, and C) immunohistochemical labeling in skeletal muscle for capillaries per fiber pre- to post-intervention in usual care (UC), moderate-intensity aerobic and high-intensity interval training (AT-HIIT), and resistance and high-intensity interval training (RT-HIIT) groups. *$p<0.05$ at post versus pre-measurement; †$p<0.05$ compared to UC; §$p<0.05$ between exercise groups. Image shows immunofluorescent staining of CD31 for capillary analysis stained in green and myonuclei stained in blue. Reprinted with permission from the *Faseb Journal.*

The direct effects of surgery, chemotherapy, and radiotherapy, as well as the secondary effect of these treatments (deconditioning), may cause impairments in one or several steps within the oxygen cascade that consequently leads to a reduction in oxygen delivery (Koelwyn et al., 2014). Despite the declines found in blood hemoglobin concentration in all three groups over the intervention, which plays an important role in the oxygen cascade (Calbet et al., 2006), local skeletal muscle adaptations still took place in the exercise groups in the current trial. Although it cannot be ruled out that the declines in hemoglobin concentration in the exercise groups were partly due to hemodilution through an increase in plasma volume, a training adaptation that usually occurs in healthy individuals (Bonne et al., 2014), it is highly likely that chemotherapy significantly affected blood cell counts negatively despite exercise. This is in line with previous exercise trials that have been conducted during chemotherapy (Dolan et al., 2010).

Mitochondrial oxidative capacity has been reported to be in excess of oxygen delivery in healthy individuals (Boushel et al., 2011). However, recent findings showed that in untrained individuals this mitochondrial oxidative capacity was fully utilized in contrast to the ≈35% excess found in well-trained individuals, which would indicate that an increase in mitochondrial oxidative capacity would lead to an increase in VO_{2peak} only in untrained, but not well-trained individuals (Gifford et al., 2016). In patients with heart failure skeletal muscle diffusion was shown to be a step in the oxygen cascade with the most detrimental effect on VO_{2peak} (Houstis et al., 2018). Although it is largely unknown which steps of the oxygen cascade are primarily affected in patients with breast cancer undergoing chemotherapy (Koelwyn et al., 2014), it can be speculated that an increased oxygen extraction took place through increases in mitochondrial content and capillarization found in the exercise groups compared to the declines in the UC group. This may explain why exercise groups were able to counteract a decline in estimated VO_{2peak} despite declines in oxygen delivery (*i.e.* hemoglobin concentrations). In support of this hypothesis, a recent study showed that the functional role of possessing a mitochondrial oxidative excess capacity was to lower mitochondrial activation while maintaining a high mitochondrial oxygen affinity; thus, optimizing oxygen extraction capacity (Cardinale et al., 2018). However, this remains speculative since the various steps of the oxygen cascade such as total hemoglobin mass, blood volume, and cardiac output were not measured in the current study.

Several associations were found between the various biochemical methods that were used. Outcomes such as changes in capillarization, assessed through immunohistochemistry were associated with changes in CS activity which was assessed spectrophotometrically (r=0.6). Moreover, an association was found between changes in CS activity and changes in complex IV protein levels assessed through immunoblotting (r=0.5), indicating the robustness of the methods despite the low sample size (Figure 10).

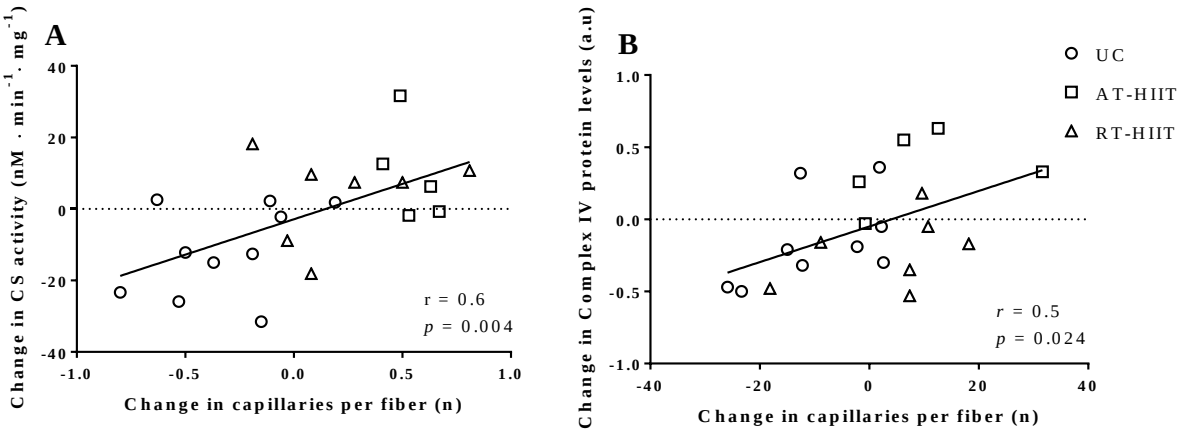

Figure 10. Correlations between changes in A) capillarization and CS activity, and B) capillarization and complex IV protein levels in usual care (UC), moderate-intensity aerobic and high-intensity interval training (AT-HIIT), and resistance and high-intensity interval training (RT-HIIT) groups. *p*, significance level; *r*, correlation coefficient; CS, citrate synthase.

At 12 months (paper IV), all groups had improved estimated VO_{2peak} to a similar extent compared to baseline values (Figure 8). These findings are in line with findings from a previous trial showing a similar recovery at 6 months in all groups versus baseline (van Waart et al., 2015). The self-reported PA data (Figure 4) indicate that the UC group had increased their activity levels during survivorship (from 16 weeks to 12 months), and a higher proportion reported being active compared to baseline. Therefore, it may be that the increase in activity may have protected these individuals from the decline in VO_{2peak} that is commonly found in patients with breast cancer that have undergone chemotherapy (Klassen et al., 2014). Alternatively, the estimated submaximal cardiorespiratory fitness test was not able to detect changes over time (Drouin and Morris, 2015). As discussed previously, a study by May et al. (2010) showed that HR above 140 bpm can provide valid results on changes in VO_{2peak}. To evaluate those findings further, a subgroup analysis was performed to assess whether those reaching 140 bpm or more compared to those below 140 bpm at the higher workload during the A-R test (unpublished data). From pre to post-intervention, the subgroup analysis showed that for those above 140 bpm (50% of the participants), there were significant differences between both RT-HIIT and AT-HIIT versus UC, as demonstrated in the larger OptiTrain trial, while no changes between groups were found for those below 140 bpm (Figure 11). At 12 months, no differences were found between groups for neither above or below 140 bpm subgroup analysis. However, it must be noted that at 12 months, only 30% of the participants reached a HR of at least 140 bpm. In support of previous findings in breast cancer survivors (May et al., 2010), these subgroup analyzes indicate the importance of reaching a higher HR to be able to detect changes in VO_{2peak}. The reason why this was not performed in the current study was due to the workload being initially determined based on rating of perceived exertion (RPE).

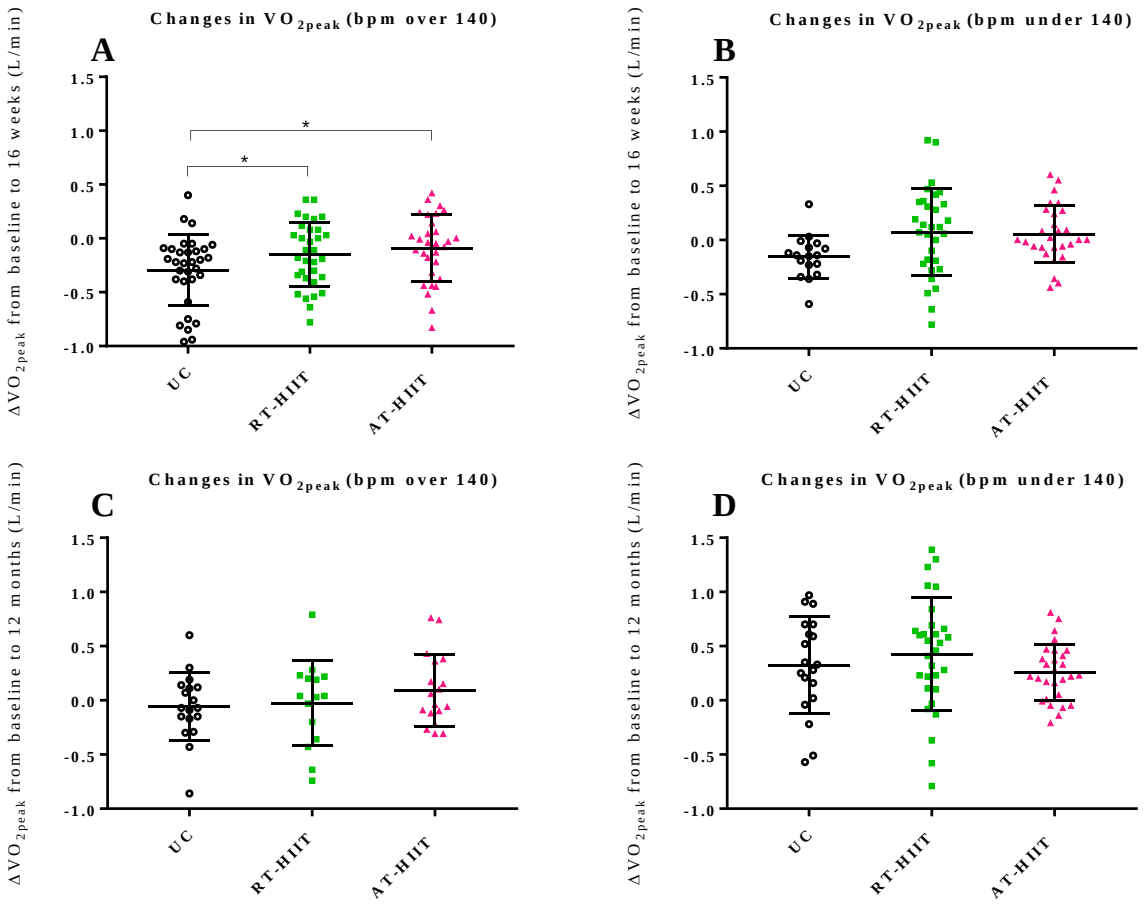

Figure 11. Changes in VO_{2peak} from baseline to 16 weeks for participants with a heart rate A) over 140 beats per min (bpm) and B) under 140 bpm, as well as changes from baseline to 12 months in participants with a heart rate C) over 140 beats per min (bpm) and D) under 140 bpm, in RT-HIIT (resistance combined with high-intensity interval training), AT-HIIT (moderate-intensity aerobic combined with high-intensity interval training) and UC (usual care) groups.

3.6 DECLINES IN SKELETAL MUSCLE STRENGTH, CROSS-SECTIONAL AREA, AND SATELLITE CELLS WERE COUNTERACTED BY EXERCISE

Muscle strength is inversely and independently associated with all-cause mortality (Ruiz et al., 2008), and a reduction in muscle strength has implications for activities of daily living (Hairi Noran et al., 2010). Although most trials have focused on aerobic training for patients with breast cancer, an increasing number of recent trials have incorporated resistance training as a single exercise modality (Schmidt et al., 2015b) or in combination with aerobic training (Travier et al., 2015, Schmidt et al., 2015c), and have shown beneficial effects of resistance training on muscle strength. However, less is known about whether these changes in muscle strength remain into survivorship. Despite observed declines in muscle strength, little is known regarding the effects of chemotherapy *per se* on skeletal muscle in non-cachectic cancer patients. In preclinical models, chemotherapy has been suggested to cause skeletal muscle dysfunction and chemotherapy-induced skeletal muscle atrophy (Gilliam et al., 2009). Muscle fiber CSA and satellite cells have been assessed in a previous exercise trial for patients with

germ cell cancer undergoing chemotherapy (Christensen et al., 2016), but not in patients with breast cancer.

Muscle strength was measured at baseline, 16 weeks, and at 12 months (papers I and IV). Handgrip strength was measured using a hand dynamometer and lower-limb muscle strength through isometric mid-thigh pull. Following the 16-week intervention (paper I) both RT-HIIT and AT-HIIT improved lower-limb muscle strength significantly in comparison to the UC group (ES=0.66, ES=0.48). Similar results were found when analyzing lower-limb muscle strength relative to body mass. Significant handgrip strength gains were found in RT-HIIT compared to both declines in the UC group and maintained levels in the AT-HIIT group (surgery side: RT-HIIT vs. UC: ES=0.41, RT-HIIT vs. AT-HIIT: ES=0.28; non-surgery side: RT-HIIT vs. UC: ES=0.35, RT-HIIT vs. AT-HIIT: ES=0.22) (Figure 12).

The gains in muscle strength over the intervention are in agreement with previous resistance-training interventions for patients with breast cancer (Schwartz et al., 2007, Courneya et al., 2007b, Schmidt et al., 2015b) and mixed cancer diagnoses (Adamsen et al., 2009). Importantly, lower-limb muscle strength also improved in the AT-HIIT group, not a common finding from a conventional aerobic exercise program, possibly indicating a role for HIIT in inducing neuromuscular adaptations. Despite this unexpected finding, a previous trial found that HIIT was able to induce strength improvements in cancer survivors (Dolan et al., 2016). The improvement in handgrip strength that was displayed by the RT-HIIT group offers a prognostic value and is an important correlate of health in survivors of breast cancer (Cantarero-Villanueva et al., 2012).

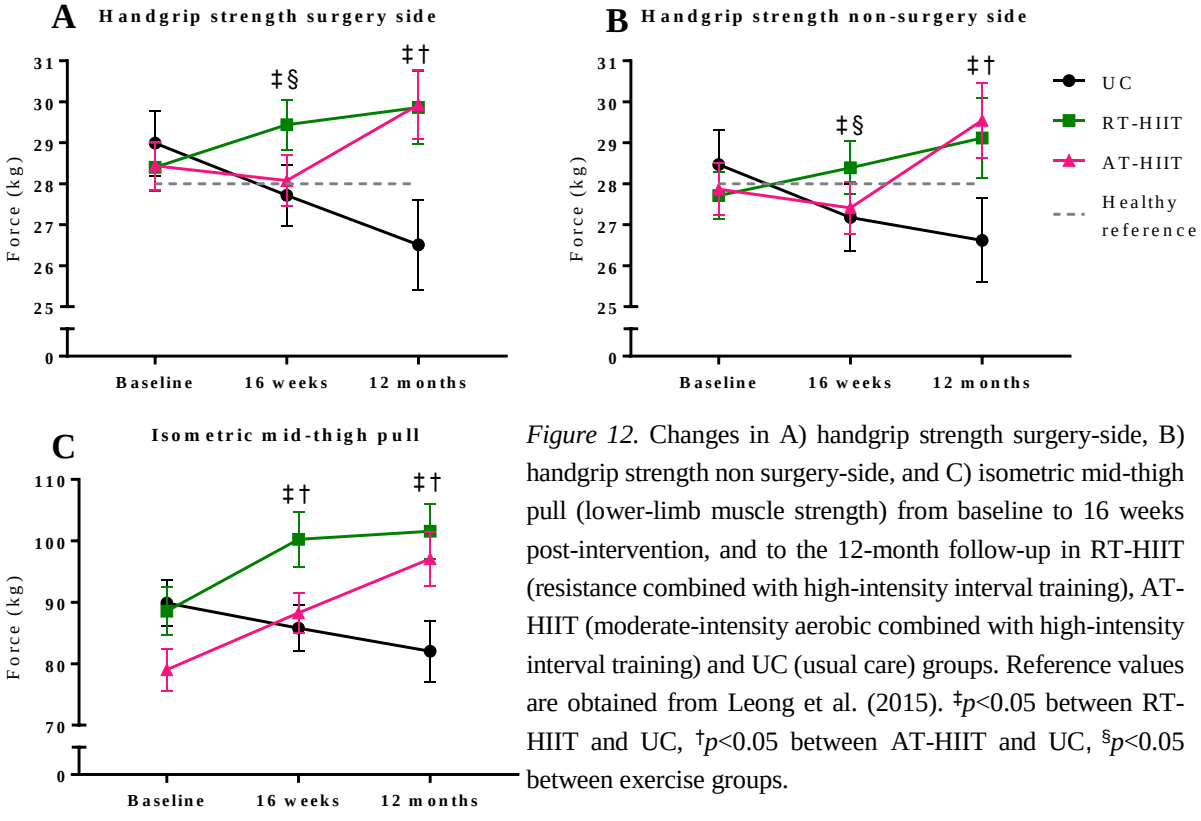

Figure 12. Changes in A) handgrip strength surgery-side, B) handgrip strength non surgery-side, and C) isometric mid-thigh pull (lower-limb muscle strength) from baseline to 16 weeks post-intervention, and to the 12-month follow-up in RT-HIIT (resistance combined with high-intensity interval training), AT-HIIT (moderate-intensity aerobic combined with high-intensity interval training) and UC (usual care) groups. Reference values are obtained from Leong et al. (2015). ‡p<0.05 between RT-HIIT and UC, †p<0.05 between AT-HIIT and UC, §p<0.05 between exercise groups.

In the current study, strength gains were found with RT-HIIT regardless of chemotherapy regimen, and even slightly greater within-group improvements for those receiving taxane-treatment for lower-limb muscle strength (+18.3%) compared to those on taxane-free treatment (+14.2%). In contrast, Courneya et al. (2014a) showed that participants on a taxane-based regimen showed less pronounced strength gains compared to those not receiving taxane-based regimens after combined resistance and aerobic training. This disagreement is unclear; however, despite that taxanes typically induce higher rates of myalgia, arthralgia, and neurosensory effects (Ho and Mackey, 2014), a recent preclinical study, showed no impairments in muscle function in response to taxanes (Chaillou et al., 2017).

In paper III, muscle fiber CSA and satellite cells were measured in skeletal muscle biopsies through immunohistochemistry labelled with laminin and paired-box protein-7 (Pax-7) respectively, at baseline and at 16 weeks (Figure 13). Both RT-HIIT (+29%, ES=2.3) and AT-HIIT (+3%, ES=1.2) significantly counteracted the decline in muscle fiber CSA, found in the UC group (-34%) for type I muscle fibers. Only RT-HIIT significantly counteracted declines in type IIA (+33%) muscle fiber CSA compared to UC (-28%, ES=3.0). In line with this, type I muscle fiber CSA has been shown to increase after HIIT (Simoneau et al., 1985), while resistance training has been shown to induce hypertrophy of type IIA muscle fibers in elderly men (Nilwik et al., 2013) and in men with prostate cancer (Nilsen et al., 2016).

The magnitude of increase in type IIA fibers (34%) is comparable to increases found previously showing a 45% increase in *vastus lateralis* muscle of women after 20 weeks of high-load resistance training (Staron et al., 1994), as well as in healthy elderly after 16 weeks of resistance training (Hikida et al., 2000), indicating a trainability comparable to that seen in healthy individuals.

The detection of satellite cells were performed by analyzing Pax-7 positive cells. The life-long maintenance of muscle tissue is mediated by satellite cells, lying in close proximity to the muscle fibers (Kadi et al., 2005). Pax-7 has been shown to be frequently expressed in human muscle fibers and has been found to be a reliable marker of human satellite cells (Boldrin and Morgan, 2012). The changes in satellite cell count were significantly associated with changes in muscle CSA and with muscle strength (Figure 14), indicating that the increase in Pax7-positive cells in the RT-HIIT group reflects an activation of skeletal muscle regeneration processes. This increase in satellite cell count was significantly different versus UC (+16% vs -4%, ES=0.9) (Figure 13). Though, it must be noted that the satellite cell acute response has been shown to increase at 24 h and peaking at 72 h following an exercise bout, and thereafter decline (McKay et al., 2009). Therefore, the timing of the biopsies (48-72 h after the last exercise session) may have reflected an acute activation of satellite cells and not chronic training adaptations. In the UC group, the unchanged satellite cell count following the intervention is in accordance with a study conducted on healthy individuals where muscle disuse atrophy did not seem to be accompanied by a decline in satellite cell content (Snijders et al., 2014).

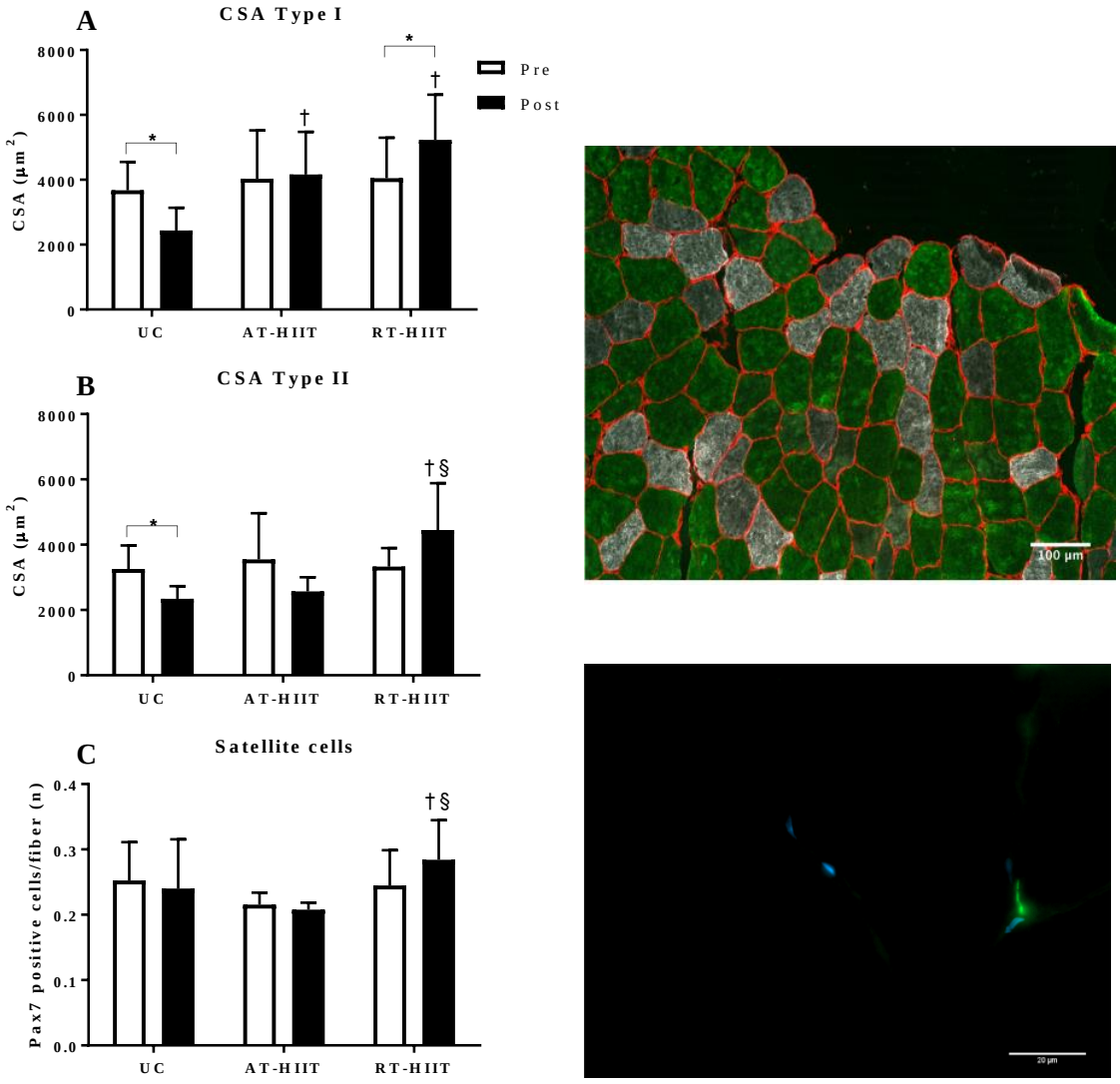

Figure 13. Immunohistochemical labeling in skeletal muscle for A) type I muscle fiber CSA (cross-sectional area), B) type IIA muscle fiber CSA, and C) satellite cells per fiber. *p<0.05 at post versus pre-measurement; †p<0.05 compared to UC; §p<0.05 between exercise groups. Top image shows immunofluorescent staining of myosin type I stained in green, myosin type IIA stained in gray, and basement membrane (laminin) stained in red, and bottom image shows immunofluorescent staining of Pax-7 for satellite cell analysis stained in green and myonuclei stained in blue. Reprinted with permission from the *Faseb Journal.*

It has been suggested that an impaired recovery of skeletal muscle in older adults following exercise may be due to a decline in capillary density, which may result in a greater distance between satellite cells and capillaries. Moreover, a recent study conducted in older men concluded that capillarization was necessary for a muscle hypertrophic response (Snijders et al., 2017). In line with this, in the current study the association between muscle fiber CSA and capillaries per fiber was significant between changes in type I muscle fiber CSA and capillarization (r=0.45, p=0.045), but no associations were found between type II muscle fiber CSA and capillarization.

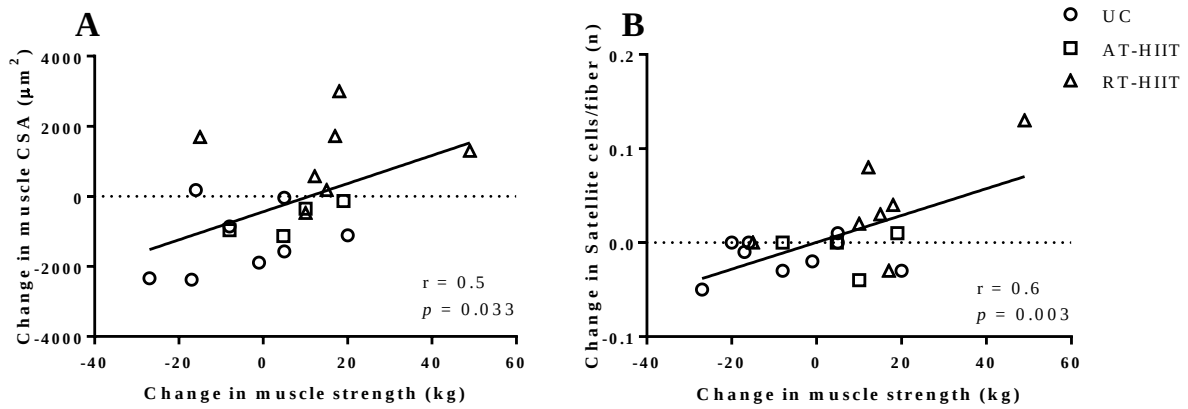

Figure 14. Correlations between changes in A) lower-limb muscle strength and muscle CSA (cross sectional area), and B) lower-limb muscle strength and satellite cell count in usual care (UC), moderate-intensity aerobic and high-intensity interval training (AT-HIIT), and resistance and high-intensity interval training (RT-HIIT) groups. *p*, significance level; *r*, correlation coefficient.

At 12 months (paper IV), both RT-HIIT and AT-HIIT improved lower-limb muscle strength (ES=0.73, ES=1.03) and handgrip strength (surgery side, ES=0.70; ES=0.71; non-surgery side, ES=0.57, ES=0.59) compared to the declines in the UC group. These findings are in contrast with other studies that have included a follow-up after completion of the exercise trial during chemotherapy showing no differences between exercise and control groups for handgrip strength (van Waart et al., 2015, Travier et al., 2015) and other strength measures (van Waart et al., 2015). In the trial by Travier et al. (2015), small effect sizes were found for changes in lower-limb muscle strength favoring exercise 6 months after start of chemotherapy. In those follow-up studies, for many of the muscle strength measures, both the control and exercise groups remained stable/recovered back to baseline levels to the same extent. Similarly, a supervised exercise trial for cancer survivors after chemotherapy showed maintained muscle strength from baseline to the 6-month follow-up in the control group (Rogers et al., 2009). However, it is likely that those individuals had already deteriorated in muscle strength when entering the study showing no further declines at follow-up. In the current study, the motivational support and PA prescriptions for the exercise groups could explain the more positive direction, while the non-existent support for the UC group could explain the continued deteriorations. Moreover, it is unknown whether skeletal muscle atrophy was reversed or not at the 12 month follow-up; however, given the association between muscle strength and muscle CSA in paper III, the declines in muscle strength found at 12 months was likely accompanied by muscle atrophy. Taken together, these findings highlight the importance of the inclusion of high-intensity exercise during chemotherapy to counter the progressive downward spiral in muscle weakness, given its association with therapy complications, lower QoL (Christensen et al., 2014), and its independent association with all-cause mortality (Ruiz et al., 2008).

3.7 A SHIFT IN MUSCLE FIBER TYPE – TOXICITY OR DISUSE?

Skeletal muscle is composed of functionally diverse fiber types (Pette and Staron, 2001). These muscle fiber types are broadly classified as slow-twitch type I fibers, and fast-twitch type II fibers (type IIA and type IIX) (Schiaffino and Reggiani, 2011). Muscle fiber types are capable

of responding to altered functional demands, and changes in the phenotypic profile are dependent on various conditions (Pette and Staron, 2001). With muscle disuse/denervation a slow-to-fast fiber type shift takes place (Jansson et al., 1978, Bagley et al., 2012), while a fast-to-slow muscle fiber shift is evident as a result of cancer cachexia and aging (Ciciliot et al., 2013). No exercise studies in patients with breast cancer have assessed changes is myosin heavy chain (MHC) isoforms; furthermore, the effects of exercise in patients with cancer on MHC isoforms need to be established.

In paper III, separation of MHC isoforms was performed by using a mini-gel electrophoresis system. The results indicated that in the UC group there was a significant reduction in MHC isoform type I (-30%) with a concomitant non-significant increase in type IIA (+25%) and IIX (+24%), indicating a slow-to-fast shift in MHC proportions (Figure 15).

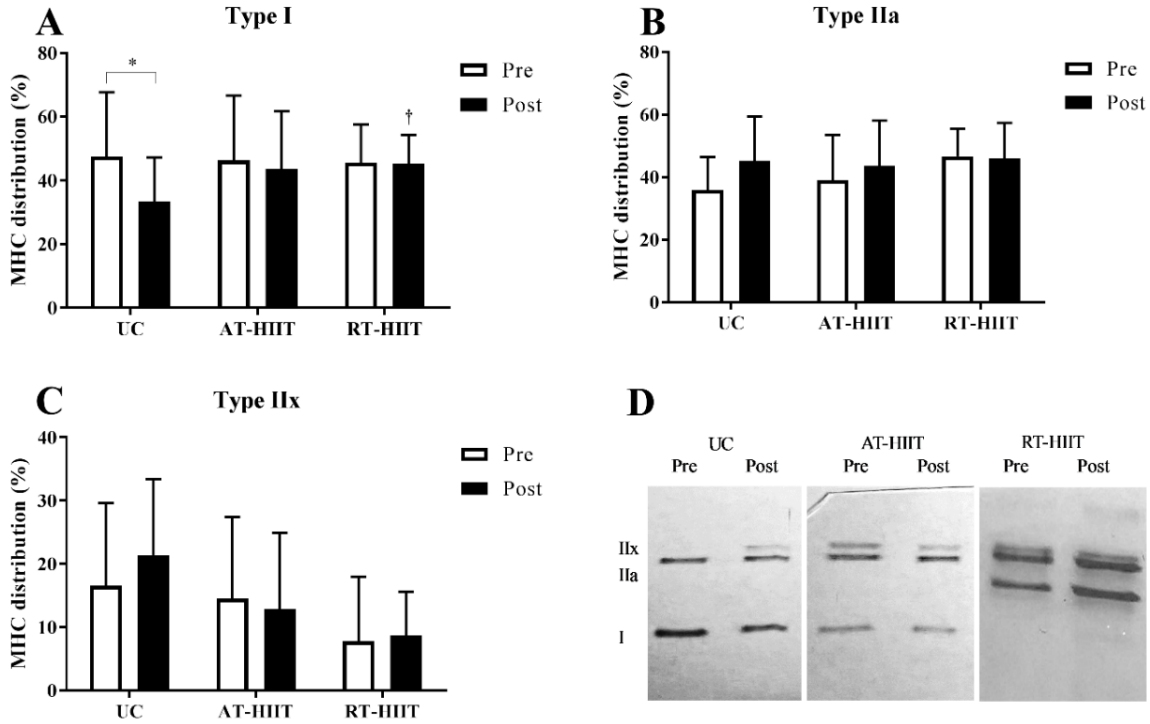

Figure 15. Myosin heavy chain distribution (%) of A) type I, B) type IIa C) type IIx muscle fibers, and D) representative blots pre- to post- intervention in usual care (UC), moderate-intensity aerobic and high-intensity interval training (AT-HIIT), and resistance and high-intensity interval training (RT-HIIT) groups. *p<0.05 at post versus pre-measurement; †p<0.05 compared to UC. Reprinted with permission from the *Faseb Journal.*

These results suggest a muscle disuse phenotype due to loss of mechanical loading and/or neuronal loss, which is typically accompanied by preferential atrophy of type 1 fibers (Wang and Pessin, 2013, Ciciliot et al., 2013). It may be speculated that the significantly lower proportion of participants that reported to meet exercise recommendations (20% in the UC group compared to 80% in exercise groups) was the underlying cause for this finding. Preclinical findings show that cancer cachexia, a muscle wasting condition associated with severe body weight, fat and muscle loss due to underlying disease (Muscaritoli et al., 2010), is associated with fast-to-slow fiber type shift (Ciciliot et al., 2013). However, human data on MHC isoforms suggest that both cachectic and weight stable patients receiving cancer treatment showed a slow- to fast shift in MHC isoforms as well as a reduction in muscle CSA

from the *vastus lateralis* muscle (Toth et al., 2016). Given that muscle CSA was significantly reduced in both type I and type II fibers in the UC group, the shift in proportions did not seem to take place due to alterations in fiber size. A point-biserial correlation analysis (unpublished data) indicated that the participants' self-reported PA levels were significantly associated with the changes in both MHC type I (r=0.6) and MHC type II X (r=-0.6) (Figure 16). These findings support the muscle disuse phenotype shift showing that participants with lower PA levels displayed a reduction in proportions of the oxidative MHC type I muscle fibers, while concomitantly displaying an increase in proportions of MHC type IIX muscle fibers.

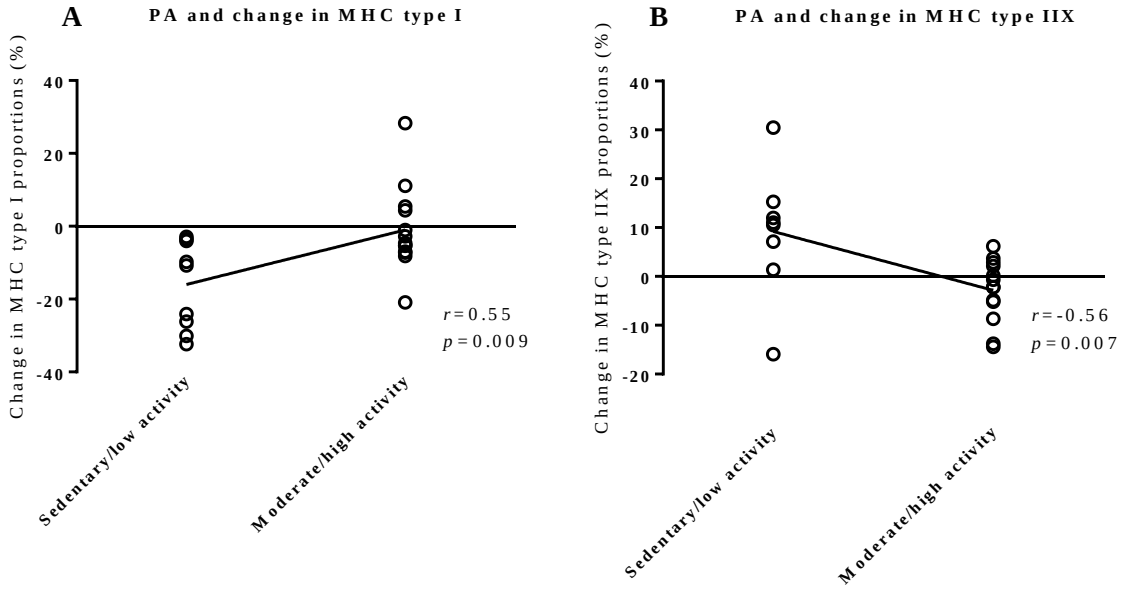

Figure 16. Associations between PA (physical activity) levels at 16 weeks post-intervention and changes in A) type I MHC (myosin heavy chain) isoforms and B) type II MHC isoforms over the 16 week intervention. *p*, significance level; *r*, correlation coefficient.

In addition to denervation, some hormones also appear to affect fiber type composition in a slow-to-fast direction such as thyroid hormone, catecholamines, and insulin (Salvatore et al., 2014, Izumo et al., 1986). Of all the hormones, thyroid hormones appear to have the greatest effect on muscle fiber phenotypes (Pette and Staron, 2001). Of note, thyroid hormones have been shown to increase during chemotherapy in patients with breast cancer (de Groot et al., 2015); thus, it may be speculated that in addition to physical inactivity, alterations in thyroid hormones caused by chemotherapy may have had implications for the altered fiber type proportions in the UC group in the present study. Alternatively it can be speculated that the lower proportion of MHC type I, which are rich in mitochondria, may have been more susceptible to mitochondrial DNA damage caused by anthracyclines (Sorensen et al., 2016). However, a preclinical study suggested otherwise, where no preferential accumulation of anthracyclines was found in any specific fiber type (Fabris and MacLean, 2015).

In paper III, no changes were found in fiber type proportions in participants in either exercise group. These findings are comparable to findings from bedrest studies, which show that resistance and high-intensity aerobic training prevent a deloading-induced slow-to-fast fiber type shift (Bagley et al., 2012, Trappe et al., 2004). In healthy individuals, whether a fiber type

shift takes place with exercise training or not remains disputed (Wilson et al., 2012). However, numerous studies have shown that high load resistance training elicit a maintenance of MHC I, increase in MHC IIa, and decrease in MHC IIx, while HIIT has been shown to lead to an increase in MHC type I and a decrease in MHC type IIX (Simoneau et al., 1985). It may be that lengthier training durations induce increases in MHC I proportions as their transition may take longer to be apparent (Bagley et al., 2012). A limitation with the method used in paper III is that it cannot distinguish between pure and hybrid fibers (I/IIA, IIA/IIX), which are known to be highly plastic; thus, a fiber type shift that was undetected may have occurred with exercise.

3.8 BODY MASS GAINS WERE COUNTERACTED WITH AEROBIC TRAINING

Weight gain related to chemotherapy, steroid medication, hormonal treatment, and physical inactivity is common following a diagnosis of breast cancer (Soares Falcetta et al., 2018), and has been shown to persist several months following chemotherapy (Ganz et al., 2011, McInnes and Knobf, 2001). This can have detrimental implications for developing comorbidities such as diabetes or coronary heart disease (Gross et al., 2015). PA has been shown to be a stronger predictor of weight change during chemotherapy than energy intake (Nissen et al., 2011), indicating the importance of exercise training during chemotherapy for patients with breast cancer.

In papers I and IV, body mass was measured on a scale at baseline, at 16 weeks and at 12 months. From pre to 16 weeks post-intervention (paper I) both RT-HIIT (ES=-0.16) and AT-HIIT (ES=-0.16) did not experience body mass gains that the UC group did. At 12 months, the difference in body mass between AT-HIIT and UC still remained significant (ES=-0.24). Previous findings have shown that 62.5% of cancer survivors that had undergone chemotherapy showed a gain in body mass one year following the start of treatment (McInnes and Knobf, 2001). Similarly, at 12 months (paper IV), 70% of the women in the UC group in the current study displayed gains in body mass, while 56% in the RT-HIIT group and 43% in the AT-HIIT group had gained body weight (Figure 17).

In healthy individuals, exercise has been shown to generally have a negligible impact on weight loss (Swift et al., 2014), although a tendency toward aerobic exercise being more effective compared to other exercise modalities in reducing total body mass exists, while resistance exercise is beneficial for increasing lean body mass (Willis et al., 2012). Although a recent systematic review concluded that exercise during survivorship (after chemotherapy) led to an overall weight reduction of 1.4 kg (Soares Falcetta et al., 2018), it remains largely unknown whether aerobic exercise interventions can curb increases in body mass in patients with breast cancer during chemotherapy. A previous trial in patients with breast cancer found a similar follow-up weight gain (+1.6 kg) in both the combined resistance and aerobic training and control group (Travier et al., 2015). Moreover, Haines et al. (2010) did not detect any difference on body composition with combined resistance and aerobic training. No follow-up trials have reported on the effects of aerobic training alone on body mass or body composition outcomes. In the present study, the reason for the effectiveness of the AT-HIIT intervention to

induce a maintenance of participants' body mass directly after chemotherapy and several months later is unclear. A recent systematic review indicated that HIIT was effective in decreasing whole-body fat mass (Maillard et al., 2018). A study by Demark-Wahnefried et al. (2001) suggested that the development of sarcopenic obesity may underlie the weight gain found in patients with breast cancer undergoing chemotherapy. It is difficult to know how much of the reduced body mass in AT-HIIT was fat mass since no measurements of body composition were performed. However, given that skeletal muscle is a major site of insulin-induced glucose uptake, the alterations found in proportions of fiber types in the present study, as well as declines in mitochondrial content indicating a reduced oxidative capacity (as discussed in a previous section), may have had implications for the regulation of metabolic processes, including basal metabolic rate. This may in turn have affected the short and long-term weight gain found in the UC group, and proposing a role for exercise in limiting gains in body mass.

A limitation in the current trial was that there were no measures of body composition. Given that sarcopenia and an increase in total adipose tissue (sarcopenic obesity) have been shown to occur simultaneously in over one third of newly diagnosed patients with early stage breast cancer, body composition measurements provide significant prognostic information that outperform measures of BMI (Caan et al., 2018).

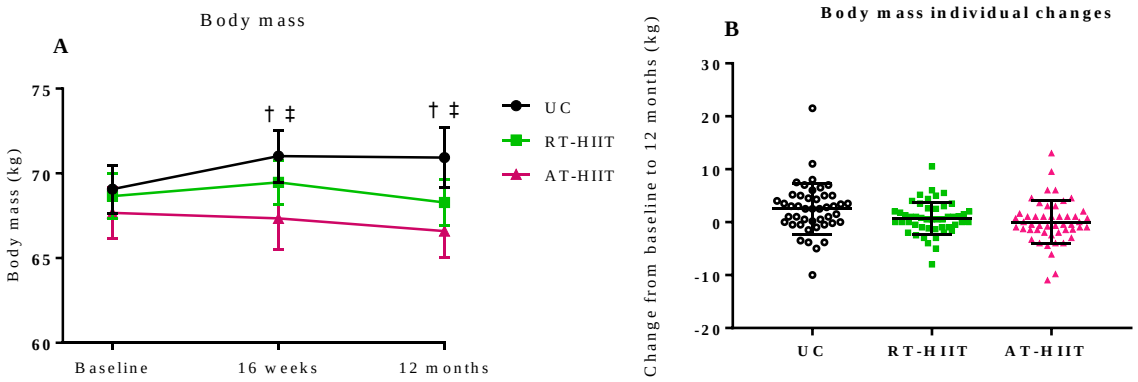

Figure 17. Changes in body mass A) from baseline to 16 weeks post-intervention and to the 12 month follow-up, and B) from baseline to the 12-month follow-up for individual data. ‡p<0.05 between RT-HIIT and UC, †p<0.05 between AT-HIIT and UC.

Moreover, in the current study, there were indirect implications of weight gain on cardiorespiratory fitness. Despite no differences between exercise groups and the UC group in absolute levels of VO_{2peak} (L/min), the UC group displayed 3.8 ml/kg/min lower values compared to a healthy reference group (Loe et al., 2016), while the exercise groups had similar or even slightly higher values compared to this reference group at the follow up. Thus, the weight gain found in the UC group may have clinically meaningful implications since a decline in 1 MET (1 metabolic equivalent=3.5 ml/kg/min) is associated with a significantly increased risk of all-cause and cardiovascular mortality (Barlow et al., 2012).

3.9 ACUTE AND PERSISTENT SYMPTOM BURDEN WAS ALLEVIATED WITH EXERCISE

Symptom burden provides a more comprehensive snapshot of the specific impact of the illness and its treatment than measures of individual symptoms or general HRQoL measures (Burkett and Cleeland, 2007), and can persist despite improvements in HRQoL (Ganz et al., 1998). Given that 1 out of 4 patients with breast cancer report a high symptom burden 12 months after completion of therapy (Molassiotis et al., 2010), finding ways to prevent and alleviate symptoms is of major importance to improve function and decrease the distress experienced by the disease. No randomized controlled exercise trials have measured symptom burden using a symptom specific scale that incorporates both frequency, distress, and burden of breast cancer specific symptoms.

In paper IV, symptom burden was measured by the MSAS which consists of the frequency, severity, and distress of 32 symptoms (Browall et al., 2012, Portenoy et al., 1994). Specifically, findings from the MSAS global distress index subscale (GDI) was reported here. GDI is a measure of overall symptom distress and consists of 10 items: the frequency of 4 psychological symptoms (feeling sad, worrying, feeling irritable, and feeling nervous), and the distress of 6 physical symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth).

Importantly, following the intervention period, symptom burden decreased in both the RT-HIIT (ES=-0.43) and AT-HIIT groups (ES=-0.42) compared to increases in the control group (Mijwel et al., 2018). From baseline to 12 months (paper IV), women in the AT-HIIT group reported significantly reduced symptom burden compared to the unchanged levels UC group (ES=-0.46) (Figure 18).

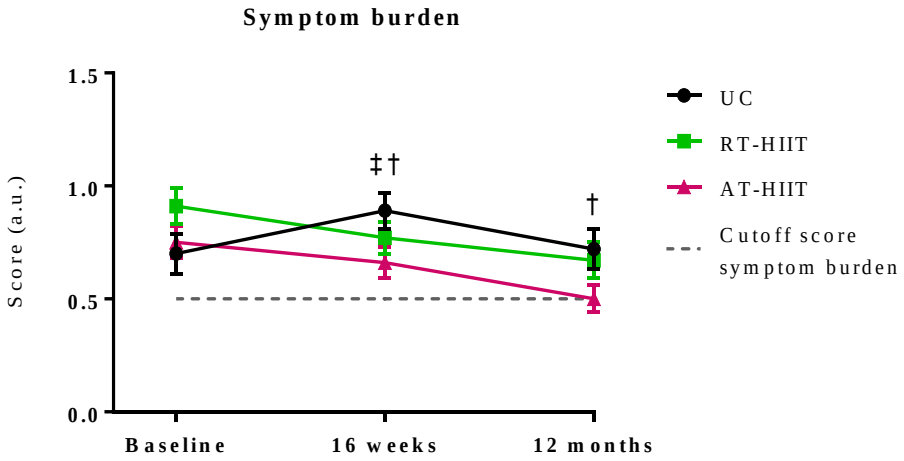

Figure 18. Symptom burden (global distress index scale) from baseline to 16 weeks and to the 12-month follow-up in usual care (UC), moderate-intensity aerobic and high-intensity interval training (AT-HIIT), and resistance and high-intensity interval training (RT-HIIT) groups. The cutoff score is based on a threshold level defining low occurrence in combination with low levels of distress and severity (Browall et al., 2017). ‡p<0.05 between RT-HIIT and UC, †p<0.05 between AT-HIIT and UC.

In the UC group, symptom burden gradually declined following completion of chemotherapy. This is in accordance with a previous longitudinal study showing that the persistence of

symptom burden declined over time in patients with cancer (Deshields et al., 2014). However, the levels did not decline below the "negligible impact threshold levels", indicating that the women in the UC group still suffered from the consequences of elevated chemotherapy-specific symptoms which have implications for survivorship and the patients' QoL (Gapstur, 2007).

The above mentioned results demonstrate that exercise training during chemotherapy was effective to minimize both acute and persistent effects of symptoms related to chemotherapy, indicating that the perception of the illness and limitations by the women in the exercise groups had changed. The current findings are comparable to a study by Mutrie et al. (2007) showing that at the 6-month follow-up, breast cancer symptoms, assessed by the a different questionnaire (FACT-B), had recovered in both exercise and control group, although to a greater extent in the combined aerobic/resistance training group, while a follow-up study of home-based exercise during chemotherapy showed no differences in breast cancer symptoms as assessed by the EORTC-BR23, between exercise and control groups at 6 months (Haines et al., 2010). In the present study, only the AT-HIIT group was effective to induce long-term beneficial effects, reporting levels of symptoms that have a negligible impact on the individuals' well-being (Browall et al., 2017). Interestingly, AT-HIIT was also the only group to significantly counteract cognitive CRF, suggesting that a psychological component was affected in this group. In healthy individuals, both aerobic and resistance training have been found to have positive effects on psychological distress and anxiety, although slightly favoring aerobic training (LeBouthillier and Asmundson, 2017, Khorvash et al., 2012). However, given the increase in muscle strength in the AT-HIIT group following the intervention, this group may have engaged in resistance training following the intervention. Moreover, PA levels indicated that a similar proportion in both RT-HIIT and AT-HIIT reported that they met PA recommendations at 12 months; thus, it is unlikely that the AT-HIIT group was more active. Moreover no significant differences in subject characteristics were found that could explain the more favorable effect in AT-HIIT for alleviating psychological components. Though, as was noted for CRF, participants in the RT-HIIT reported slightly higher symptom burden at baseline. As mentioned previously, there was a slightly higher proportion of participants being premenopausal in the RT-HIIT group. Although this difference was not statistically significant, this may have resulted in the less favorable outcomes for symptom burden at the follow-up. Given that a majority of the women received hormonal therapy after completion of chemotherapy, the symptoms of menopause that tamoxifen and aromatase inhibitors can induce (Garreau et al., 2006) may have exacerbated the experience of symptoms in the premenopausal women at the follow-up.

3.10 EFFECTS OF EXERCISE ON RETURN TO WORK

Studies show that most cancer survivors are able to return to work (de Boer et al., 2009), although a considerable proportion of survivors report a reduced ability to work (Torp et al., 2012a), with cancer survivors 1.37 times more likely to be unemployed than healthy participants (de Boer et al., 2008). The growing number of breast cancer survivors means that

more women may be on sick leave after treatment for breast cancer, ever increasing the burden on the individual and associated societal costs. Emerging evidence highlights the potential for exercise as a potential strategy to decrease sick leave rates (White et al., 2016). However, few trials have investigated if exercise during chemotherapy has an effect on return to work among cancer survivors.

In paper IV, self-reported sick leave rates indicated that a higher proportion of participants in the AT-HIIT group returned to work (from 100% sick leave to 75%, 50%, 25%, or 0%) compared to the UC group (91% vs 69%, respectively; p=0.02) 12 months following the initiation of chemotherapy. In the RT-HIIT group 82% had returned to work at 12 months.

Our findings are in line with a previous exercise trial conducted in cancer survivors showing that those who had performed high-intensity exercise had an increased ability to work (Thijs et al., 2012, van Waart et al., 2015). Additionally, another trial that included a combination of aerobic and resistance training combined with counselling for patients with cancer during chemotherapy showed that 86% of the participants had returned to work at their 12-month follow-up; however, a comparison group was lacking making it difficult to draw any conclusions regarding the effectiveness of their intervention (Leensen et al., 2017). Predictors of a diminished return to work after cancer treatment include fatigue and cognitive symptoms (de Boer et al., 2008). Interestingly, in the current trial, cognitive fatigue in the UC group was still higher than baseline levels at 12 months, while being significantly counteracted in the AT-HIIT group, indicating a possible link between cognitive fatigue and sick leave. In this thesis, a point-biserial correlation analysis was performed to assess whether an association existed between return to work and psychological factors (unpublished data). Results showed that those who had not returned to work had a higher symptom burden (r=0.4) as well as higher cognitive fatigue (r=0.5) at 12 months (Figure 19). However, the causal direction remains unclear. Those that did not return to work may be more psychologically distressed, and since more participants in the AT-HIIT group had returned to work, this may have resulted in a lower psychological burden for these individuals.

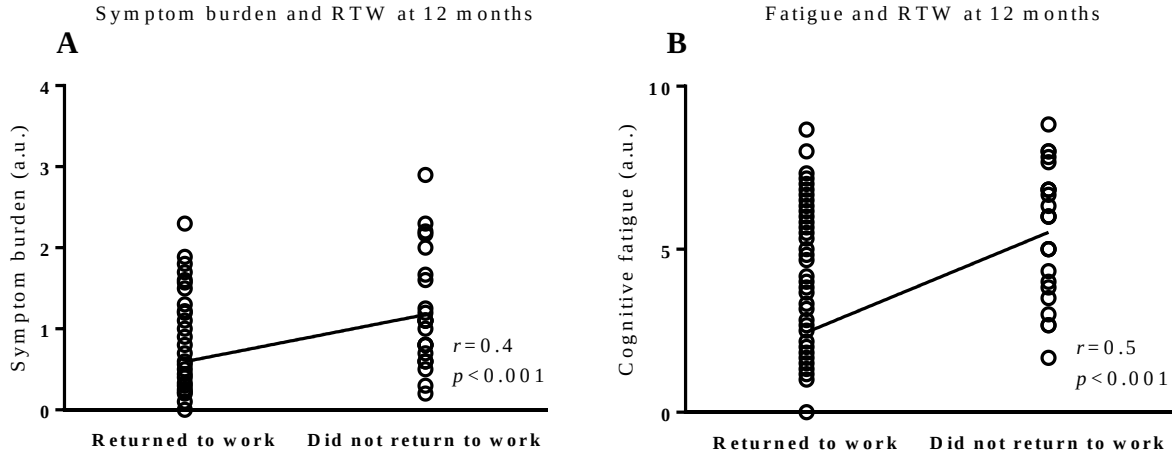

Figure 19. Associations between return to work (RTW) and A) symptom burden B) cognitive fatigue at 12 months after initiation of chemotherapy. *p*, significance level; *r*, correlation coefficient.

Similarly to the sick leave rates in the UC group, a Dutch longitudinal study showed that 37% of women treated for breast cancer were on sick leave for longer than 1 year (Torp et al., 2012b). The same study showed that 12% were on sick leave for longer than 2 years, suggesting the importance of implementing effective countermeasures as early as possible after a cancer diagnosis. The findings from the current study are promising and suggests a role for exercise in improving long-term adverse effects of chemotherapy that affect the ability to work.

3.11 ASSOCIATIONS BETWEEN PHYSIOLOGICAL OUTCOMES AND FATIGUE

As mentioned previously, cancer-related fatigue is one of the most prevalent symptoms experienced by patients with cancer, both during and after treatment. Several mechanisms are proposed for fatigue, both central and peripheral. Among these, reduced physical activity (Goedendorp et al., 2013, Winters-Stone et al., 2008) and loss of muscle mass (Kilgour et al., 2010) or muscle strength (Winters-Stone et al., 2008) may contribute to fatigue. However, although advances are being made, the etiology of CRF is not yet fully understood.

In the OptiTrain study, the change in fatigue from EORTC-QLQ-C30 was used for measuring associations with physiological outcomes. This scale has previously been shown to be responsive to change over the course of chemotherapy and reflects the physical component of fatigue.

A weak inverse association between change in self-reported CRF and change in lower-limb muscle strength was found both over the intervention (r=-0.3; p<0.001) (paper I), and from baseline to 12 months (EORTC-QLQ-C30: r=-0.25; p=0.008) (paper IV). Despite being weak, the sustained association with fatigue at 12 months suggests muscle strength as an important underlying component of the multifactorial symptom CRF. This is in line with a study by Winters-Stone et al. (2008) showing that fatigue was significantly associated with lower-limb muscle strength in breast cancer survivors at least one year after completion of chemotherapy. In patients with advanced breast cancer, evidence points in the direction that CRF is centrally mediated through an inability to voluntarily recruit and activate as much muscle as that in healthy controls (Kisiel-Sajewicz et al., 2012). The reason for the motor unit recruitment and activation dysfunction is unclear. It may be speculated that chemotherapy induces both peripheral and central nerve damage (Dietrich, 2010), which may lead to muscle denervation. Resistance training may be vital to induce central neuromuscular adaptations through increased activation of motor neurons by increasing firing frequencies (Aagaard and Mayer, 2007), as indicated by the more pronounced muscle strength gains in RT-HIIT over the intervention and in the AT-HIIT group following the intervention with subsequent beneficial effects on CRF.

Studies of patients with advanced cancer have shown a weak inverse but significant association between self-reported CRF and handgrip strength (Schvartsman et al., 2017). Moreover, in breast cancer survivors, weak negative associations were found between handgrip strength and self-reported CRF (Cantarero-Villanueva et al., 2012), as well as between changes in 12-min walk test and CRF in patients with breast cancer during chemotherapy (Mock et al., 2005). However, no associations were found between handgrip strength and cardiorespiratory fitness

measures with changes in self-reported CRF, either from baseline to 16 weeks, or from baseline to 12 months. In line with this, no associations were found in a study by Thorsen et al. (2005) between cardiorespiratory fitness (also assessed by a submaximal cycle test) and self-reported CRF. It can be speculated that stronger associations would be found between time to fatigue assessments and CRF than maximal strength assessments. A recent study that measured fatigability by repeated handgrip contractions showed a significant strong association with several dimensions of self-reported fatigue (Veni et al., 2018).

It may seem prudent to assume that the association between muscle strength and CRF, as evident from both the current findings and findings by others, would be accompanied by associations between CRF and muscle fiber size. However, in paper III, no significant association was found between changes in CRF and muscle fiber CSA (r=-0.4) (Figure 20). Previous cross-sectional studies in patients with advanced cancer showed a strong negative association with muscle mass in men but not in women (Neefjes et al., 2017, Kilgour et al., 2010), suggesting a sex-difference with regards to the possible influence of muscle mass on fatigue.

Mitochondria have an essential role in energy conversion through the process of oxidative phosphorylation, and powers most of the cells' activities (Mitchell, 1961). Given that fatigue is a hallmark symptom of mitochondrial disease (Filler et al., 2014), it may be that physical inactivity, in combination with chemotherapy, is detrimental to the function of mitochondria, as evident in paper III, and as a result induces or aggravates symptoms of fatigue. In paper III, a significant and strong association was found between changes in CS activity and changes in fatigue as measured by the EORTC-QLQ-C30 (r=0.7) (Figure 20).

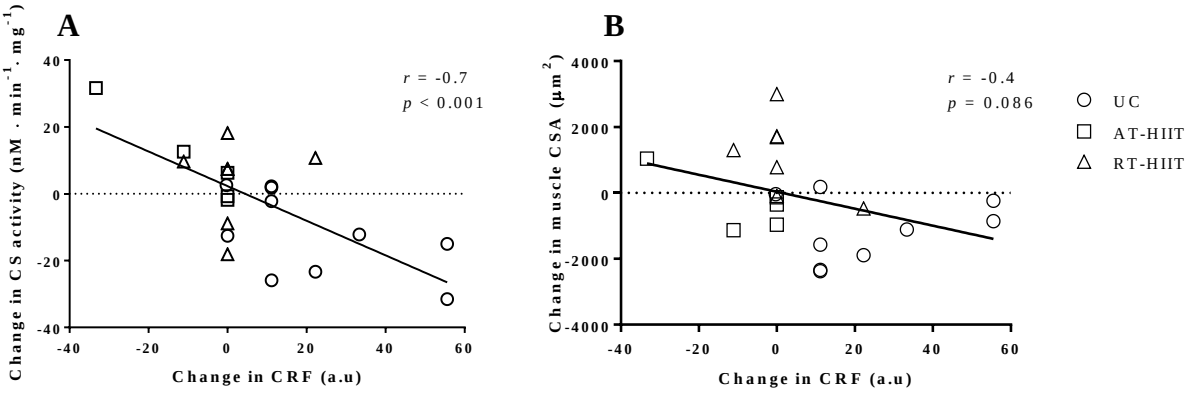

Figure 20. Associations between changes in cancer-related fatigue and A) CS (citrate synthase) activity, B) muscle CSA (cross-sectional area) in usual care (UC), moderate-intensity aerobic and high-intensity interval training (AT-HIIT), and resistance and high-intensity interval training (RT-HIIT) groups. *p*, significance level; *r*, correlation coefficient. Reprinted with permission from the *Faseb journal.*

These findings are in line with findings in individuals with chronic fatigue syndrome showing an impaired oxidative phosphorylation compared with healthy individuals (Filler et al., 2014). Chronic fatigue syndrome which displays many similarities with CRF, is a syndrome speculated to have both central peripheral explanations for the origin of fatigue. In the current study, the strong association between CS activity and CRF indicates a peripheral component

of the physical domain of CRF; however the reduction in CS activity may be an indirect effect of physical inactivity or an originally centrally mediated mechanism.

The physical inactivity in the UC group, as reflected by declines in oxidative capacity, was described in a previous section, with a significant association between PA levels and MHC type I and MHC type IIX. The same association was found between changes in PA levels and changes in CS activity (r=0.7; p<0.001) (unpublished data). Moreover, at 16 weeks and at 12 months those reporting being sufficiently physically active displayed lower fatigue levels compared to those that did not meet PA recommendations (p<0.001), emphasizing the important role of PA to counteract CRF directly or indirectly. The causal direction is unclear, but given the numerous detrimental consequences of physical inactivity, a negative spin-off effect may be taking place as a consequence leading to exacerbated fatigue. Both psychological distress (depression and anxiety) that can occur when learning of a cancer diagnosis (Schumacher et al., 2013), and insomnia have been shown to be linked to fatigue (Abrahams et al., 2018), which could lead to reduced PA, even prior to chemotherapy. Further reductions in PA may take place after initiation of chemotherapy through indirect factors such as social barriers (*e.g.* encouragement to rest and not to be active during a cancer treatment and lack of support from health care professionals) (Browall et al., 2016), and symptom burden. A decline in muscle function, as reflected by muscle weakness and contractile dysfunction may take place resulting from either chemotherapy-induced nerve damage and physical inactivity leading to further increases in fatigue. This could in turn lead to reductions in oxidative capacity as demonstrated by a reduction in type I fibers and reduced mitochondrial content, and a decline in cardiorespiratory fitness (Figure 21).

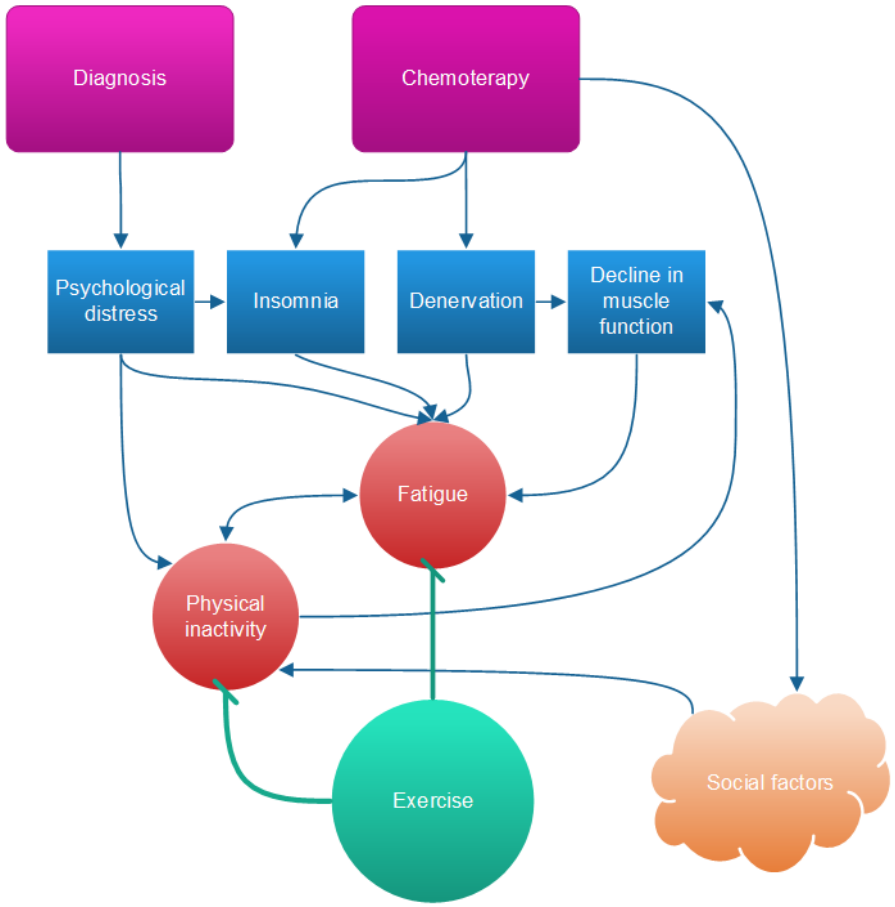

Figure 21. Illustration of the potential links between cancer treatment, physical inactivity, and the complex multifactorial syndrome fatigue, and the role of exercise to directly or indirectly counteract the adverse effects of physical inactivity and chemotherapy on fatigue.

3.12 STATISTICAL CONSIDERATIONS

The strengths of the statistical analysis include the ITT analysis, as well as the adjustment for the pre-test score, both when performing the analysis of covariance (ANCOVA) and linear mixed model (LMM) analysis in order to be certain that any post-test differences truly result from the treatment (Zhang et al., 2014).

In paper I, missing data were imputed using the expectation maximization (EM) method. The EM which is based on a likelihood function has been shown to provide unbiased estimates when missing values do not exceed 10% (Rubin et al., 2007, Dong and Peng, 2013), as was the case in paper I. LMM was chosen in paper IV due to the strengths of LMM in longitudinal designs, and its ability to account for a larger number of missing values (Baayen et al., 2008).

Adjusting for baseline covariates improves the precision of the outcome. However, these covariates need to be carefully chosen and should predict the outcome of interest (Steingrimsson et al., 2017). In paper IV, adjustment for menopausal status and tumor receptor status was performed for the primary outcome. Both of these variables have been shown to influence fatigue levels. Since both chemotherapy and hormonal therapy are typically chosen based on tumor receptor status, and previous findings have shown that fatigue levels can differ depending on these treatment regimens, tumor receptor status was chosen as an appropriate baseline covariate, while menopausal status was chosen as the second appropriate factor given that pre- versus postmenopausal women experience fatigue differently as previously discussed.

Both *p*-values and effect sizes (ES) were reported for results from paper I and paper IV. Reporting the ES, rather than only the statistical significance, provides information regarding the magnitude of difference, and more "true" information about the significance of the difference (Sullivan and Feinn, 2012). In this thesis, the effect size was calculated as the mean pre-post change in the treatment group minus the mean pre-post change in the control group, divided by the pooled pretest standard deviation (Morris, 2007). The reason for pooling only the pretest standard deviation, as opposed to the change in standard deviation which is likely to yield an inflation in ES, was to provide an unbiased estimate of the effect size since pre- and posttest scores are not independent (Morris, 2007).

In paper I, the subgroup analyzes that were performed to assess whether differences in chemotherapy regimen (taxane vs no-taxane) had an impact on physiological outcomes, should be interpreted with caution. Subgroup analyses have been shown to be prone to over interpretation, and although these can provide valuable information, such analyzes are typically underpowered (Assmann et al., 2000).

The correlation analyzes that were performed provided an indication of the relationship between two variables, but does not indicate that one variable *causes* the other. In several cases a spurious relationship may be present, in which the relationship may be induced by a third unseen factor. Therefore, despite providing indications of a link between two sets of variables, those analyzes must be interpreted cautiously.

3.13 STUDY DESIGN CONSIDERATIONS

The rationale for choosing the training modality HIIT in both exercise groups was because of its proven effectiveness in the healthy population and in its ability to provide beneficial effects in a time efficient manner (MacInnis and Gibala, 2017). Given that exercise adherence in patients with cancer is typically low (Furmaniak et al., 2016), the addition of HIIT was hypothesized to maximize health benefits. Resistance exercise was combined with HIIT to target the preservation of muscle mass, while moderate-intensity continuous aerobic training was combined with HIIT (*i.e.* endurance/aerobic exercise only) to match the training duration of RT-HIIT. Concerns have been raised regarding the safety HIIT in clinical populations (Colberg et al., 2010). It can be speculated that its induction of exercise stress could compromise the immune system, especially considering the periods of increased risk of infection (neutropenic periods). However, in healthy individuals, despite that HIIT results in acutely elevated circulating stress hormones such as catecholamines and cortisol, immunity has not been shown to be compromised (Fisher et al., 2011), and HIIT has in sedentary individuals recently been shown to improve neutrophil and monocyte function (Bartlett et al., 2017). Whether this is the case in patients with breast cancer is not known; however, here, the HIIT regimens appeared safe and no adverse events were reported as a result of training sessions. A limitation is the lack of comparison with continuous aerobic training, resistance training, or HIIT alone, which should be addressed in future studies.

The use of rating perceived exertion (RPE) to control exercise intensity has been found to be a valid measure in healthy individuals (Borg, 1982). Data indicate that patients with breast cancer underreport RPE (Drouin et al., 2015); so, at an expected higher RPE these women reported a lower RPE, suggesting that the intensity in the current trial was likely not lower than the intended intensity.

The timing of the baseline assessment, after one chemotherapy session was necessary due to practicality reasons as there was limited time to perform both ECG and baseline measurements before the first chemotherapy session. Although, this does provide some benefit by excluding acute effects of chemotherapy from analyses comparing measurements over the intervention, for the 12 month follow-up, it is not optimal with a baseline that is influenced by chemotherapy. This may have led to an overestimation of the outcome effects at 12 months. However, this was the case for all three groups, and, since this is an issue in several other trials, findings from the current study are still comparable.

In the current study, there was an issue of detection bias – the assessors were not blinded to group allocation. Randomization after baseline assessment would have been optimal. Another aspect that could be improved was the randomization process used to randomize participants to donate muscle biopsies. Given that muscle biopsy sampling is an invasive method, a high dropout rate was expected; thus the nature of the randomization process (1 out of 5 randomized to donate a muscle biopsy) did not allow for the intended number of participants for the biochemical analyzes.

4 CONCLUSIONS

Adding high-intensity interval training to resistance or aerobic training was shown to be feasible and proved to be effective in counteracting fatigue, symptom burden and physiological declines in women with breast cancer undergoing chemotherapy. Participants performing RT-HIIT or AT-HIIT had maintained, or even improved, markers of skeletal muscle function and morphology, which was significantly different from the declines found in the group undergoing usual care. Both high-intensity exercise programs resulted in beneficial effects on fatigue and muscle strength at 12 months, with additional effects for AT-HIIT on symptom burden, body mass, and return to work. Taken together, this thesis shows that it is possible to conduct supervised high-intensity exercise programs for patients with breast cancer during chemotherapy and that this may be a powerful strategy to manage or prevent many of the short-and long-term adverse effects of treatment and inactivity, as well as to potentially minimize significant societal costs associated with high sick leave rates in women with breast cancer.

5 IMPLICATIONS, FUTURE PERSPECTIVES AND RECOMMENDATIONS

5.1.1 The importance of supervised exercise

Here, it was shown that high-intensity exercise training during chemotherapy was effective within a clinical setting. The beneficial effects on several physiological and self-reported health outcomes that were found over the intervention lasting into survivorship justifies high-intensity supervised exercise for patients with breast cancer. In support of this, several studies have demonstrated the importance of supervised exercise not only to provide motivational support to perform exercise (Segal et al., 2017) but also to provide an educational component, which in turn can induce self-efficacy and a sense of mastery (Eakin et al., 2012) and can induce long-term effects on self-esteem (Courneya et al., 2007a). In the current study, the higher self-reported PA levels in the UC group at the follow-up was not enough to counteract the deteriorations found over the course of chemotherapy. Participants in the exercise groups, through probable gains in self-esteem and sense of mastery, were potentially able to carry out exercise at higher intensities after completion of the intervention which led to beneficial effects.

5.1.2 Is exercise during chemotherapy important?

An intriguing question is whether exercise is needed during chemotherapy or if patients are too fatigued to engage in a supervised exercise program, particularly HIIT, during chemotherapy. In the current study, the participants experienced increases in fatigue, symptoms, and body mass, declines in muscle strength accompanied by muscle atrophy and a fiber type shift, declines in cardiorespiratory fitness accompanied by mitochondrial dysfunction and a decline in capillarization in the UC group, with many of these decrements still present in survivorship. This supports the notion of initiating a structured exercise program as soon as possible after a cancer diagnosis, in order for the women to enter the treatment period better equipped to counteract detrimental adverse effects of chemotherapy. Although supervised exercise conducted after completion of chemotherapy tends to show larger improvements in fatigue and physiological outcomes than exercise conducted during chemotherapy (Juvet et al., 2017), this is likely due to the detraining that may have taken place since the time from diagnosis as well as there being no acute influence of chemotherapy.

In healthy and several clinical populations, HIIT has been suggested as a successful strategy that results in quick physiological adaptations and improved health outcomes with benefits for public health (MacInnis and Gibala, 2017). In patients with breast cancer, there is increasing evidence to suggest higher intensity exercise as a more effective training strategy to counteract the adverse effects of chemotherapy. Since there is no innate drive to be physically active, sustaining PA is, and will continue to be a major challenge (Biddle and Batterham, 2015). Therefore, when implementing exercise, focus should lie on types of exercise that will induce the greatest health benefits in a time-efficient manner. Also, given that treatment for patients with breast cancer has become increasingly aggressive, HIIT may be effective as an equally progressive countermeasure to counter the adverse effects of chemotherapy. For certain

individuals that may not be willing or able to perform HIIT at the intended intensity, adjustments in the exercise regimen and intensity is crucial, highlighting the important role of competent staff capable of modifying exercise programs for these individuals. However, given the high adherence to intensity in the current trial, many women with early stage breast cancer should be physically capable of performing HIIT and high-load resistance training, and may only need educational and motivational support initially.

As with all exercise studies, those participating in this exercise study may not be entirely representative of the general breast cancer population. Given that those dropping out from the exercise trial had a lower sense of coherence, highlights the need to target these individuals, as well as those who were eligible but did not choose to participate in the first place. A recent study found a significant difference in socio-economic status between those accepting participation and those that did not in an exercise trial for patients with prostate cancer (Koonj Beharry et al., 2018). Although such information is not available regarding those that declined participation immediately after randomization, the high proportion of highly educated participants in the OptiTrain study adds weight to this issue. Another factor that may significantly influence participation is clinician recruitment, with factors reported to be time constraints, a lack of interest, and not having a strong belief in the efficacy of the trial (Ross et al., 1999). Moreover, recent findings have shown that one factor that affects health-care professionals' promotion of physical exercise is the belief that patients with cancer might suffer from a physical overexertion by doing intense exercise (Haussmann et al., 2018). These factors should be considered and addressed in order to ensure that as many individuals as possible are encouraged to enter exercise intervention trials. In support of this, it has been found that unfit patients can benefit more from exercise than fit patients (Wiskemann et al., 2014). Therefore, it is important to find ways to inform clinicians and health care practitioners of the efficacy and safety of exercise, especially more strenuous exercise, since they play a crucial "gateway" role in providing information on implementation and benefits of physical exercise. To overcome the selective sample in exercise trials, in an ongoing study (Umbrella Fit), patients will be asked if they want to participate in future studies and give consent for collection of patient information, providing self-reported outcomes, and randomization into future intervention studies (Gal et al., 2017). The participants will not know whether they have been part of a control group or not. These types of studies can be a solution to the potential selection bias in randomized controlled trials.

5.1.3 Are we treating physical inactivity or chemotherapy-related symptoms?

The marked deterioration of the individual's physical function, and reduced HRQoL after a cancer diagnosis have been suggested to be due to direct effects of chemotherapy and/or general reductions of PA levels (Patrick et al., 2003).

A challenge is to design studies that can isolate the effects of cancer and its treatment from physical inactivity at baseline as well as increased physical inactivity during treatment. Findings from the OptiTrain trial (not part of this thesis) showed that those who were less

physically active reported greater fatigue and symptoms at baseline, also were those who gained the greatest benefit from exercise (Mijwel et al., 2018). There is a possibility that these women were not physically active because of experiencing fatigue; as discussed previously, the causal direction cannot be established. It may be that exercise has the potential to induce direct beneficial effects on chemotherapy-related symptoms such as fatigue and symptom burden. Keeping symptoms in check could prevent further declines in PA. Findings from paper III indicated that a muscle fiber shift took place that resembled a muscle disuse phenotype, which was accompanied by lower PA levels following the intervention. Therefore, it can be speculated that physiological deteriorations is a secondary cause of chemotherapy which induces increased fatigue and symptoms leading to reduced PA levels.

Another great challenge is to maintain patients' motivation to exercise after the completion of an in-clinic supervised exercise program. Although HIIT seems to be a favorable exercise modality to counter adverse effects of chemotherapy, the effectiveness of unsupervised HIIT in a cancer population after completion of supervised exercise interventions still needs to be established. Future studies also need to delineate if all individuals benefit from these regimens (*i.e.* individual response), and to examine the optimal exercise frequency and duration.

Future studies should aim to identify strategies to motivate patients to engage in physical exercise and maintain lifestyle changes throughout the cancer treatment and survivorship continuum, and to introduce exercise as an integral and continuous part of standard care.

6 ACKNOWLEDGMENTS

I wish to express my sincere gratitude to everyone that contributed to this thesis, you all mean so much more to me than what can be expressed in a few sentences.

First of all, I would like to thank **the participants** in the OptiTrain trial for the immense contribution to the research project during such a challenging period in life. Without them this study would not have been possible.

Thanks to **Karolinska Institutet** for providing me with a supportive research environment during these 4 years. The studies included in this thesis were supported by grants from the Swedish Cancer Society, the Cancer Society of Stockholm, the Swedish Cancer and Traffic Accident Foundation, and the Swedish Society for Medical Research.

Special thanks to *my supervisors;*

Yvonne Wengström, my main supervisor, for introducing me to the clinical world, for being a great leader, for believing in me and for letting me be part of the OptiTrain trial. I couldn't wish for a better supervisor, group, and project to be part of.

Helene Rundqvist, for introducing me to exercise oncology and preclinical research already in 2012, that made me want to undertake a PhD in this field. Thanks for sharing your intellectual ideas and opinions, for believing in my abilities, and for always being there since day one.

Carl Johan Sundberg, for welcoming me to the Molecular Muscle Physiology Lab, and for sharing your vast knowledge, for interesting discussions and your support during these years.

Jessica Norrbom, for your endless support, and for the positive energy you bring to the group.

My mentor; **Eva Jansson,** for sharing your insightful knowledge about exercise physiology, and for your advice on how to cope in the research world.

Other members of the OptiTrain group; **Malin Backman,** for all the hard, but fun years collecting all the OptiTrain data together; **Kate Bolam,** for bringing new ideas to the group, for your touch of Australian humor that always cheers people up, and most of all for all of your support; **Anna Jervaeus,** for your scientific and real life advice, and for always being supportive.

Other people that have been involved in the OptiTrain study; **The Clinical Trial Unit at Karolinska University Hospital (KPE),** for all the assistance with randomization and blood sampling during the OptiTrain study period; **the Oncological rehabilitation center (ORC),** for the use of gym facilities; **Jonas Bergh, Maria Browall, Anouk Hiensch** and **Anne May,** for your inspiring and fruitful collaboration.

Present and former colleagues at;

The Molecular Muscle Physiology Lab, especially my co-author and colleague **Mark Chapman;** my colleagues **Stefan Reitzner, Charlotte Schönbeck, Malene Lindholm, Eva**

Karin Gidlund, Mia Ydfors, Eric Emanuelsson, for all scientific contributions, interesting discussions, and joyful times both during and after working hours.

The Department of Physiology and Pharmacology, especially **Håkan Westerblad, Irene Lund, Sofia Pettersson, Eva Lindgren** and **Manizheh Izadi,** for the support during my PhD; my co-author **Niklas Ivarsson,** for the collaboration; **Michaela Sundberg, Maja Schlittler**, **Arthur Cheng,** and **Rocio Paublete,** for making work and non-work time into such a joy.

The Division of Clinical Physiology, especially **Thomas Gustafsson,** for giving me the opportunity to work in your lab on the Metapredict study; **Rodrigo Fernando Gonzalo** and **Tommy Lundberg,** KI's real exercise physiologists, for interesting discussions about science and life; **Seher Alam,** for your kindness and making me feel welcome in the lab; **Helene Fischer,** for always being helpful and for taking time to teach me about cell culture.

The Department of Oncology and Pathology, especially, **Arne Östman,** for giving me the opportunity to work in your lab on a project that led to my first publication, and for sharing your profound knowledge.

Christoph Siebenmann, for involving me in the hypoxic sensing paper.

Fawzi Kadi, and **Jeffrey Moffitt,** for sharing your knowledge and for inspiring me to pursue a research career in exercise physiology.

All my friends, especially **Pharah, Tina** & **Aram, Therese, Melissa** & **Ken, Dijana** & **Nicolas, Sophia, Mahmoud** & **Lisa, Tom** & **Saara, Fredrik** & **Marielle**, **Dmitry, Gregory** & **Mirjam,** for making life such a joy, and for sharing great moments in life from travels, weddings, parties, sports, to discussions about life.

The Cardinale family, **Sanja** and **Alessandro,** for always being there, and for sharing all joys in life; **Antonietta and Franco** for the amazing son that you brought into this life, and for the support and hospitality.

My grandmother, for always being an inspiration and having a positive attitude in life.

My aunt, for caring and for sharing memorable moments in life.

My sister, for being my best friend, for always being there for me, and for all the great memories that we share.

My mother, for your love and support. Your positive attitude towards life and your strength has made me believe that I can do anything I pursue in life.

Daniele, my soulmate, husband, best friend, colleague, and co-author, for the joy and energy you bring into my life. Thank you for always standing by my side and for making the world a more beautiful place. We started this PhD journey and we will end it together. I can't wait to move on to the next stage in life and explore the rest of the world with you.

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