

Exercise as Therapy in Oncology

Exploring mechanisms and effects on clinical outcomes



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CHAPTER 1

General introduction and outline of the thesis

CANCER AND ITS TREATMENT

One in two people in the Netherlands are expected to be diagnosed with cancer during their lifetime (1). Currently, cancer is the leading cause of death in the Netherlands, accounting for 47,318 deaths in 2023 (2). The most common cancer types, in order of prevalence, are lung cancer, colorectal cancer, and breast cancer in women, or prostate cancer men (1). As a result of aging and the growing population, the prevalence of cancer is expected to rise both in the Netherlands and worldwide (1, 3). Fortunately, advances in early detection strategies and cancer treatment have significantly improved overall survival rates (1). New developments in chemotherapy, immunotherapy, targeted therapy, radiotherapy, and surgical techniques, either individually or combined, are expected to further improve 5-year and overall survival rates in the coming years (4). Additionally, optimised timing and multimodal treatment combinations of neoadjuvant and/or adjuvant therapies whether or not combined with surgical resection, are anticipated to further enhance clinical outcomes (4).

An example of a multimodal treatment regimen is neoadjuvant chemoradiotherapy (NCRT) for patients with high-risk rectal or oesophageal cancer. This approach combines concurrent chemotherapy and radiotherapy followed by a 6- to 12-week waiting period prior to surgical resection (5, 6). These multimodal treatment strategies aim to reduce tumour size and thereby improve surgical and long-term outcomes or even refrain from surgery in selected cases (5, 6). For oesophageal cancer, NCRT involves the administration of intravenous chemotherapies carboplatin (AUC2) and paclitaxel (50mg/m²) once a week for 5 weeks, along with concurrent radiotherapy (23 fractions of 1.8 Gray) (5). NCRT for rectal cancer typically includes oral capecitabine (825 mg/m² twice a day) in combination with concurrent radiotherapy (25 fractions of 2 Gray) (6). Both therapies can cause severe treatment-related side effects, such as fatigue, diarrhoea, and dermatological problems for rectal cancer, and fatigue, dysphagia, and weight loss for oesophageal cancer (7-9). In addition, cancer treatment can lead to declines in muscle mass, muscle strength and aerobic fitness, limiting a patient's ability to perform daily activities (10, 11). Side effects might occur temporarily during cancer treatment, but can also be long-lasting, such as fatigue, severely impacting quality of life (12). Therefore, strategies aimed to minimise treatment-related side effects, improve physical fitness and thereby enhance quality of life are warranted.

Surgical resection often remains the cornerstone of curative intent multimodal cancer treatment for solid tumours. Surgery for high-risk oesophageal cancer is typically performed by resecting the oesophagus and connecting the gastric tube to the remaining end of the oesophagus by minimally invasive transthoracic (TMIE) or transcervical (MICE) oesophagectomy (13). Surgical treatment for rectal cancer commonly includes total mesorectal excision (TME), in which the entire rectum and surrounding mesorectum is removed (14). Improvements in perioperative care such as the Enhanced Recovery After Surgery (ERAS) and minimally invasive surgical techniques have been implemented to improve postoperative

outcomes (13-16). Despite these innovative developments, postoperative complications occur in a substantial number of patients in both tumour types (approximately 50% in oesophageal cancer and 35% in rectal cancer) (17, 18). Furthermore, both surgical procedures for rectal and oesophageal cancer may have lifelong functional consequences and reduce quality of life (19, 20). Therefore, organ-sparing strategies such as watch-and-wait procedures following clinical complete responses are becoming more popular to avoid unnecessary postoperative morbidity for both tumour types (21, 22). To further enhance perioperative care, there is growing interest in innovative approaches, such as pre-surgical rehabilitation (prehabilitation), which has the potential to reduce complications and augment functional recovery and quality of life (23).

EXERCISE DURING NEOADJUVANT TREATMENT

Strong evidence from randomised controlled trials (RCTs) among various cancer populations showed that physical exercise during adjuvant chemotherapy or radiotherapy can benefit physical fitness, fatigue and health-related quality of life (HRQoL) (24-27). In addition, studies indicate that exercise may limit treatment-related side effects and enhance treatment tolerability, thereby reducing the need for treatment modifications (28, 29). Furthermore, observational studies have demonstrated that higher levels of physical activity and physical functioning during treatment are associated with a reduced risk of cancer recurrence and mortality (30-32). Based on this compelling evidence, the American College of Sports Medicine (ACSM) developed physical activity guidelines for patients with cancer during cancer treatment. These guidelines recommend at least 150 minutes of moderate-to-vigorous physical activity (MVPA) per week, including resistance exercises targeting major muscle groups twice a week (27, 31). However, to date, clinical implementation of these guidelines is limited, largely due to a lack of knowledge on causal effects on clinical outcomes and underlying physiological mechanisms (33).

Several preclinical studies in mice across a wide range of tumour types proposed potential underlying physiological mechanisms by which exercise might reduce tumour growth (34). First, exercise might lead to mobilisation, activation and intratumoural infiltration of natural killer (NK) and cytotoxic T cells, due to an exercise-induced release of epinephrine and interleukin-6 (IL-6) (34-36). Second, studies in mice have shown that exercise might normalise tumour vasculature, which may enhance the accessibility and delivery of cytotoxic chemotherapeutic agents (34). In addition, even a single session of high-intensity aerobic exercise might already modulate tumour perfusion and hypoxia in mice, thereby potentially improving radiotherapy sensitivity (37, 38). Thirdly, exercise may shift glycolytic tumour metabolism towards oxidative phosphorylation, which can potentially affect cancer cell growth (34). Lastly, myokines, such as oncostatin M and SPARC, released by exercising muscles may

have antioncogenic potential (34). However, despite the large number of preclinical studies describing these potential physiological effects of exercise during cancer treatment, clinical evidence and translation to clinical outcomes are lacking.

Recently, clinical pilot studies suggested potential benefits of exercise during neoadjuvant treatment on tumour regression in patients with rectal and oesophageal cancer (39-41). However, sample sizes were small and results were not generalizable to other tumour types and treatment regimens. Furthermore, type, timing and frequency to optimally use the physiological potential of exercise to reduce tumour growth and improve survival, remains to be determined. For instance, timing exercise directly prior to a radiotherapy session and thereby activating the immune system and reducing hypoxia, could enhance the potential of exercise as adjunct radiosensitising therapy in cancer treatment beyond the already proven beneficial effects on physical fitness, treatment-related side effects and quality of life (42).

EXERCISE PRIOR TO SURGICAL RESECTION

Prehabilitation is an increasingly popular strategy to improve postoperative outcomes after surgery. It is often performed in the 3- 6 weeks prior to surgical resection, regardless of preceding neoadjuvant therapy (23). Prehabilitation generally includes an exercise component, but it may also include other modalities such as a nutritional intervention, psychological support and/or a smoking or alcohol cessation program. This multimodal prehabilitation approach has been shown to reduce postoperative complications in patients with colorectal and lung cancer (43, 44), and to decrease the length of hospital stay (44). Furthermore, multimodal prehabilitation has been shown to enhance physical fitness and functional capacity in patients with colorectal cancer prior to surgery (45). Thus, multimodal prehabilitation might be a cost-effective and easily implementable approach to enhance surgical outcomes. However, despite the accumulating evidence in several patient groups, widespread implementation of prehabilitation as part of standard clinical practice remains challenging due to a lack of healthcare insurance coverage (46).

Potential mechanisms underlying the effects of multimodal prehabilitation might be multifactorial, with intervention components acting synergistically. Exercise may enhance cardiopulmonary and muscle function, which is further supported by nutritional interventions including protein supplementation to increase muscle mass and prevent malnutrition (47). Besides, exercise training and a good nutritional status might improve the immune system and promote an anti-inflammatory response, which is advantageous for infection prevention and wound-healing (48, 49). Similarly, improving psychological well-being might positively influence immune status (50). Lastly, smoking cessation programs using nicotine replacement therapy might be effective for reducing wound infections, enhancing wound healing, and improving long-term health (51). Together, these factors may collectively improve the body's

ability to withstand the physiological stress response after surgery and thereby prevent complications, although most important intervention components remain undefined (46).

EXERCISE AND FATIGUE

Fatigue is one of the most common and debilitating side effects during and after cancer treatment, with approximately 25% of cancer survivors experiencing long-term fatigue significantly reducing their quality of life (52, 53). Additionally, it is a frequently reported (patho)physiological symptom in other chronic diseases including chronic obstructive pulmonary disease (COPD), or cardiovascular disease, as well as their associated treatments, like statins (54, 55). Cancer-related fatigue specifically refers to fatigue caused by cancer or its treatment and is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion that is not proportional to recent activities and interferes with daily functioning (56). The pathogenesis of cancer-related fatigue is complex and multifactorial, and might involve physiological, behavioural and psychological factors. Understanding the multifactorial causes of cancer-related fatigue can support the development of more targeted and effective treatment strategies.

Fatigue is generally assessed by distinguishing between perceived fatigue and performance fatigability (57). Perceived fatigue is commonly measured using self-reported questionnaires, whereas performance fatigability can be quantified by the decline in muscle force-producing capacity during a prolonged task (54, 57). This decline in force-production may be related to impaired central activation of α -motor neurons or impaired muscle contractile properties (58). Impairments in muscle contractile properties such as a reduction in the rate of force development or prolonged muscle relaxation times, may manifest as muscle fatigue (59). To assess these muscle contractile properties independently of a patient's motivation or effort, electrical muscle stimulation can be used to bypass central activation (Figure 1; (60)). Altered muscle contractile properties might reflect underlying changes in muscle fiber-type composition, energy metabolism or calcium handling, which can significantly impact exercise performance and contribute to fatigue (61). Further insights into the association between muscle contractile properties and fatigue might facilitate the development of targeted exercise interventions aimed at reducing fatigue.

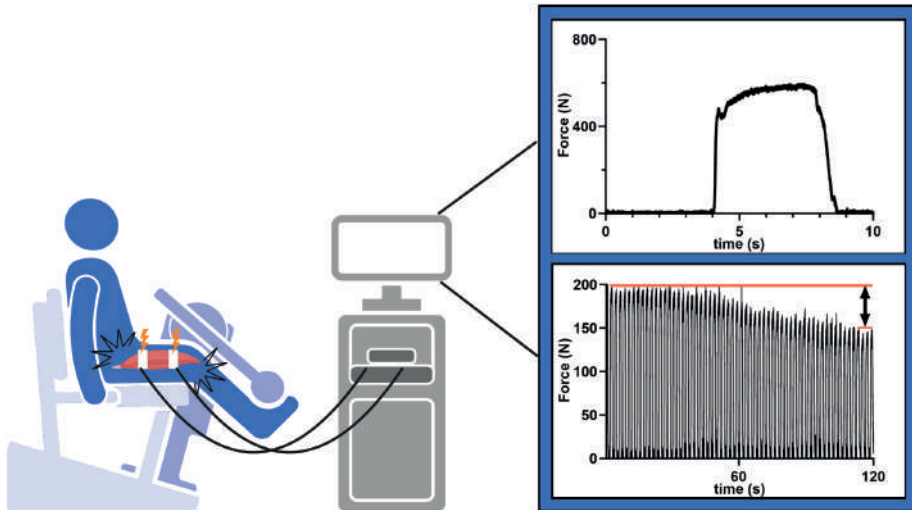


Figure 1. Electrical muscle stimulation setup to measure muscle contractile properties of the *Quadriceps femoris muscle*. The upper panel shows a representation of a maximal voluntary contraction, while the lower panel represents the force decline during repetitive electrical stimulation indicative of fatigue.

Exercise has been identified as an effective nonpharmacological treatment of fatigue in cancer survivors and other patient populations, demonstrating larger effects than pharmacological interventions (54, 62). However, average effect sizes remain small-to-moderate and vary among individuals and patient groups (25, 63). Additionally, fatigue has been identified as a barrier to engage in physical exercise (64). Therefore, exercise targeted at reducing fatigue should be easily accessible, such as walking, which has been identified as the preferred type of exercise for cancer survivors (65). Knowledge on the mechanisms underlying the effects of exercise on cancer-related fatigue might help to improve the efficacy of interventions by identifying and subsequently targeting effective exercise components.

OBJECTIVE AND OUTLINE OF THE THESIS

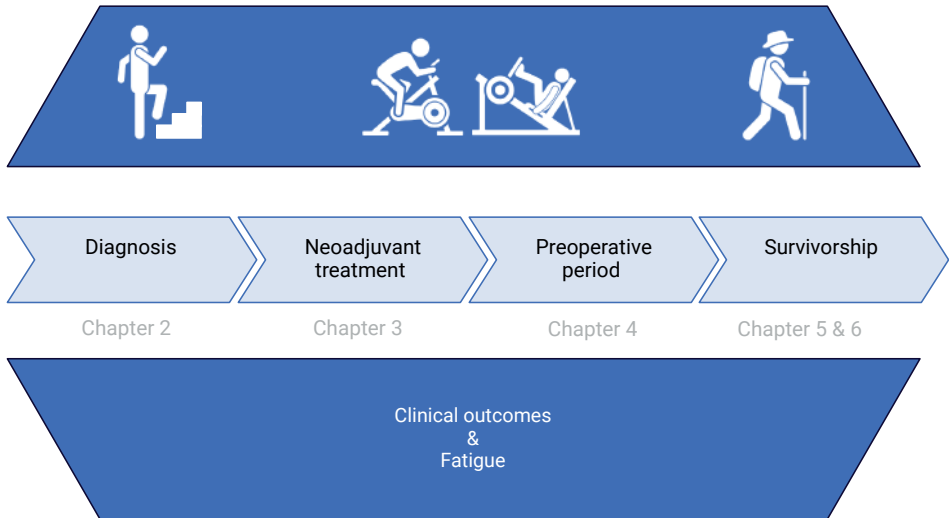


Figure 2. Graphical illustration of the outline of the thesis.

Exercise has potential to act as therapy throughout the cancer continuum, from diagnosis to survivorship. However, to implement exercise as an integral part of cancer care, knowledge of the potential effects on clinical outcomes and underlying physiological mechanisms is essential. Therefore, the aim in the first part of this thesis was to study the potential of exercise during and after neoadjuvant cancer treatment on clinical outcomes. The aim in the second part of this thesis was to explore the mechanisms via which exercise may reduce fatigue (Figure 2).

Part I. Potential of exercise on clinical outcomes

In **Chapter 2**, the association between physical activity levels at the time of rectal cancer diagnosis and tumour downstaging after NCRT is evaluated. This chapter serves as a foundation for the further exploration of the potential of physical activity during the period of NCRT.

In **Chapter 3**, a randomised controlled pilot trial is described aimed to examine the feasibility of two different exercise interventions during NCRT, and further explore the potential effects of exercise on physical fitness, treatment-related toxicity and tumour response.

In **Chapter 4**, the potential effects of multimodal prehabilitation post-NCRT and prior to oesophagectomy on postoperative outcomes and complications in patients with oesophageal cancer are evaluated. Additionally, the potential effects of the prehabilitation intervention

on physical fitness and quality of life, as well as their associations with postoperative complications are examined.

Part II. Exercise and fatigue

To gain further insight into the potential effects of exercise on fatigue, in **Chapter 5**, the effects of a 4-month walking exercise program on cancer-related fatigue in cancer survivors are explored. Furthermore, this chapter evaluates the potential underlying physiological, behavioural and psychological mechanisms of action, complemented by participants' perceptions of how exercise affected their fatigue.

In **Chapter 6**, differences in muscle contractile properties and physical fitness between cancer survivors, patients with chronic myeloid leukaemia on active treatment, statin users, patients with chronic obstructive pulmonary disease and healthy controls are evaluated. In addition, the associations of muscle contractile properties and physical fitness with perceived fatigue in the total group and individual subgroups is explored.

In **Chapter 7**, the main findings of this thesis are summarised and discussed, and clinical implications and methodological considerations are addressed. Furthermore, physiological hypotheses and directions for future research are proposed.

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CHAPTER 2

Physical activity at diagnosis is associated with tumor downstaging after neoadjuvant chemoradiotherapy in patients with rectal cancer

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ABSTRACT

Introduction: Patients with rectal cancer are often treated with neoadjuvant chemoradiotherapy, followed by a waiting period and surgical resection. Good or complete response to neoadjuvant chemoradiotherapy might enable organ preservation, which highlights the need to increase response rates. Pre-clinical studies suggest that physical activity during neoadjuvant chemoradiotherapy may improve tumor downstaging. Therefore, the aim of this study was to investigate whether physical activity and physical functioning of patients with rectal cancer at diagnosis are associated with tumor downstaging after neoadjuvant chemoradiotherapy.

Methods: Patients were included if they participated in the Dutch Prospective ColoRectal Cancer Cohort, a nationwide cohort providing an infrastructure for scientific research, and received neoadjuvant chemoradiotherapy for rectal cancer. Tumor downstaging was dichotomized into good/complete or moderate/poor downstaging. Physical activity (total physical activity, moderate-to-vigorous physical activity (MVPA), and Dutch physical activity guideline adherence) and physical functioning were assessed using questionnaires. Logistic regression analyses were performed to examine associations of physical activity and physical functioning with tumor downstaging, adjusted for relevant confounders.

Results: 268 patients (aged 62 ± 11 years, 33% female) with rectal cancer were included. Patients with moderate (OR = 2.07; 95%CI = 1.07 – 4.07; $p=0.03$) or high (OR = 2.05; 95%CI = 1.05 – 4.07; $p=0.04$) levels of MVPA were more likely to have good/complete tumor downstaging than patients with low levels. No significant associations with tumor downstaging were found for total physical activity, Dutch physical activity guideline adherence, and physical functioning.

Conclusion: We found augmented tumor downstaging in patients with rectal cancer with moderate or high levels of self-reported MVPA before the start of neoadjuvant chemoradiotherapy compared to patients with low levels.

INTRODUCTION

Colorectal cancer is the third most common diagnosed type of cancer worldwide, with rectal cancer accounting for roughly one-third of all colorectal cancer cases (1). In the Netherlands, approximately 3250 patients are diagnosed with rectal cancer each year (2). Patients with rectal cancer are often treated with neoadjuvant chemoradiotherapy (NCRT), followed by a waiting period of 8 – 10 weeks and surgical resection (3). This therapy typically includes radiotherapy of 45-50 Gray delivered in 25 fractions with concurrent oral capecitabine chemotherapy as radiosensitizer (4). NCRT promotes local disease control, tumor regression and clearance of the circumferential resection margin (5). Pathological complete response is associated with excellent long-term disease free and overall survival but only occurs in 15-20% of the patients receiving NCRT (6, 7). Additionally, NCRT may cause severe treatment-related side effects, such as diarrhoea and fatigue, reducing physical functioning (defined as the ability to perform daily physical activities (8)) and health-related quality of life (HRQoL) (9). Consequently, strategies to enhance HRQoL and tumor response rates are needed.

Regular physical activity during chemotherapy or radiotherapy has been shown to limit fatigue, and enhance HRQoL and physical functioning in various cancer populations including rectal cancer (10, 11). Moreover, observational studies showed that higher levels of physical activity and physical functioning, both at diagnosis and during treatment, are associated with a reduced risk of colorectal cancer recurrence and mortality (12). Additionally, results from pilot-studies in patients with locally advanced rectal cancer suggest that physical activity during NCRT might augment tumor response (13, 14). Nevertheless, despite the potentially beneficial effects of physical activity at diagnosis and during treatment, the link between physical activity at diagnosis and tumor downstaging in patients with rectal cancer is largely unknown.

In the Netherlands, the Prospective Dutch ColoRectal Cancer (PLCRC) cohort study collects clinical data and patient-reported outcomes in patients with colorectal cancer, small bowel adenocarcinoma and anal cancer (15). Using data from this unique prospective clinical cohort, we aimed to investigate whether physical activity and physical functioning of patients with rectal cancer prior to the start of NCRT were associated with tumor downstaging. We hypothesize that patients who were physically active and had a good physical function before NCRT have an augmented tumor downstaging compared to patients who were not physically active or had a poor physical function.

METHODS

Study design

We used data from PLCRC, which is a prospective multidisciplinary nationwide observational cohort study in the Netherlands (NCT02070146, ClinicalTrials.gov). All patients with colorectal cancer, small bowel adenocarcinoma and anal cancer are eligible for inclusion. After inclusion, longitudinal clinical data are registered and patient reported outcomes (PROMS) are collected at enrollment and at 3, 6, 12, and 24 months thereafter, followed by an annual questionnaire (15). For the current study, patients with rectal cancer who were treated with NCRT (25 fractions of 2 Gray combined with oral capecitabine) between 2016 and 2021 were eligible. Patients receiving total neoadjuvant therapy (TNT) or short-course radiotherapy were not included in this study. Patients were included for the analyses if they completed questionnaires on physical activity and physical functioning between 1 month prior to and 2 weeks after starting NCRT, reflecting a representative period around diagnosis. Demographics and clinical data on tumor characteristics, tumor downstaging, and treatment details, were retrieved from the Netherlands Cancer Registry (NCR). PLCRC was approved by the Medical Research Ethics Committee of Utrecht, the Netherlands (METC 12-510), and all patients provided informed consent.

Tumor downstaging

Based on clinical TNM stage at diagnosis assessed with magnetic resonance imaging (MRI), we categorized patients into three clinical risk stages: low risk (cT1-3N0), intermediate risk (cT1-3N1, cTxN1), and high risk (cT4 or cN2) tumors (16). Post-NCRT, clinical risk stages were re-evaluated by clinical restaging, generally performed 6-8 weeks after NCRT according to Dutch and European guidelines (17), and pathological restaging performed after surgical resection, if available. After restaging, patients were classified into one of the three before-mentioned risk stages or as having obtained a complete response (yc/ypT0N0M0). Since downstaging from high risk tumors towards a complete response is rare, tumor downstaging was dichotomized based on the defined risk stages into good/complete downstaging versus moderate/poor downstaging. A good/complete tumor downstaging was defined as post-NCRT downstaging to a complete response or downstaging from a high risk stage to a low risk stage. A moderate/poor downstaging was defined as progression, no change in risk stage, or downstaging only one risk stage. Both good and complete downstaging are associated with improved survival compared to patients with moderate or poor downstaging (18).

Physical activity and physical functioning

Physical activity was assessed using the Dutch version of the short questionnaire to assess health-enhancing physical activity (SQUASH) (19). The SQUASH contains 11 items and measures

frequency, duration and intensity of 4 different physical activity domains (actively commuting, physical activities at work or school, household activities, sports and leisure time activities), and asks about physical activities performed in an average week in the past months. Activities were assigned with a Metabolic Equivalent of Task (MET) score, based on the Ainsworth compendium (20) and a total score of MET-hours per week was calculated. Weekly time spent on moderate-to-vigorous intensity physical activity (MVPA; ≥ 3.0 METs) and MVPA during sports and leisure time (MVPA-SL) was calculated. The MVPA-SL variable comprises: gardening, odd jobs, leisure time bicycling, and a maximum of four different sports. The MVPA variable additionally includes: heavy household activities, heavy occupational work and commuting by bike or foot. Lastly, Dutch physical activity guideline adherence was evaluated, which corresponds to the American College of Sports Medicine (ACSM) guidelines for cancer survivors, advising a minimum of 150 minutes MVPA per week combined with at least moderate intensity muscle strengthening exercises twice a week (21, 22).

Information about physical functioning was obtained using the physical functioning subscale of the EORTC QLQ-C30 questionnaire (23). This subscale consists of 5 items about the level of help that is needed or the experienced difficulties during the performance of various daily functions in the past week (24). All items were scored using a four-point scale ranging from 'not at all' to 'very much'. Average scores were calculated from contributing items and linear transformation was used to convert scores ranging from 0 to 100, with higher scores representing higher level of physical functioning (24). Physical functioning is considered 'good' when scored above the Dutch normative value matched for age and sex, and 'poor' when scored below this value (25).

Demographic and clinical factors

Demographic variables age, sex, body height, body weight, and WHO performance status were obtained from the NCR. Body mass index (BMI; kg/m^2) was calculated using NCR reported height and weight, supplemented by self-reported values from questionnaires in case of missing values. Educational level (high, medium, low), living situation (with or without partner), alcohol use, and smoking were obtained from PLCRC questionnaires.

Statistical analysis

Statistical analyses were performed using RStudio (R Core Team). Descriptive statistics were generated for demographic factors, clinical factors, and physical activity and function. Logistic regression analyses were used to examine whether physical activity and physical functioning were associated with tumor downstaging (good/complete vs. moderate/poor). Since physical activity was skewed, it was evaluated using tertiles for weekly MET-hours, MVPA, and MVPA-SL. Dichotomous variables were used for adherence to Dutch physical activity guideline (yes/no) and level of physical functioning (good/poor). Related to the sample size, we selected most important confounders based on literature (26). Hence, logistic regression models were

adjusted for age (continuous), sex (male, female), BMI (continuous), primary risk group (high risk, medium risk, low risk), current smoking (yes, no), and alcohol consumption (yes, no). Given the number of missing values in the WHO performance status variable (Table 1), we performed a sensitivity analysis that included WHO performance status (WHO 0 vs. WHO 1/2) as an additional confounder. Effect modification was explored for age and primary risk group by adding the variable and its interaction term to the regression model, and using the likelihood ratio test. Odds ratios (OR), 95% confidence intervals and corresponding p-value were presented. Statistical significance was set at $p = 0.05$.

Table 1. Demographic and clinical, physical activity, and physical functioning characteristics in tertiles of MVPA.

Characteristics	Total (n = 268)	Low MVPA (n = 88)	Moderate MVPA (n = 88)	High MVPA (n = 88)
MVPA hours/week , median [IQR]	8 [4 - 17]	2 [0 - 4]	8 [6 - 12]	23 [18 - 35]
Sex , n (%)				
male	179 (67)	54 (61)	58 (66)	66 (75)
female	89 (33)	34 (39)	30 (34)	22 (25)
Age , mean \pm sd	62 \pm 11	64 \pm 11	64 \pm 11	60 \pm 10
BMI (kg/m ²), median [IQR]	25.8 [23.9 - 29.0]	26.2 [24.2 - 29.1]	25.4 [23.7 - 28.4]	25.8 [24.1 - 29.4]
WHO performance status , n(%)				
0	181 (68)	49 (56)	63 (72)	66 (75)
1	44 (16)	21 (24)	13 (15)	9 (10)
2	2 (1)	1 (1)	1 (1)	0 (0)
missing	41 (15)	17 (19)	11 (12)	13 (15)
Educational level , n(%)				
high education	87 (32)	26 (30)	26 (30)	34 (39)
medium education	101 (38)	31 (35)	40 (45)	28 (32)
low education	73 (27)	27 (31)	21 (24)	24 (27)
missing	7 (3)	4 (5)	1 (1)	2 (2)
Smoking status , n(%)				
no smoker	235 (88)	74 (84)	80 (91)	77 (88)
current smoker	33 (12)	14 (16)	8 (9)	11 (12)
Alcohol , n(%)				
no drinker	91 (34)	29 (33)	28 (32)	31 (35)
drinker	175 (65)	58 (66)	59 (67)	57 (65)
missing	2 (1)	1 (1)	1 (1)	0 (0)
Living situation , n(%)				
with partner	220 (82)	71 (81)	75 (85)	70 (80)
without partner	43 (16)	16 (18)	13 (15)	14 (16)
other	5 (2)	1 (1)	0 (0)	4 (5)
cT classification , n(%)				
1	2 (1)	1 (1)	0 (0)	1 (1)
2	27 (10)	6 (7)	12 (14)	9 (10)
3	192 (72)	64 (73)	65 (74)	59 (67)
4	46 (17)	17 (19)	10 (11)	19 (22)
X	1 (0)	0 (0)	1 (1)	0 (0)

Characteristics	Total (n = 268)	Low MVPA (n = 88)	Moderate MVPA (n = 88)	High MVPA (n = 88)
cN classification, n(%)				
0	45 (17)	15 (17)	15 (17)	14 (16)
1	86 (32)	22 (25)	26 (30)	36 (41)
2	137 (51)	51 (58)	47 (53)	38 (43)
cM classification, n(%)				
0	261 (97)	86 (98)	86 (98)	85 (97)
1A	7 (3)	2 (2)	2 (2)	3 (3)
Risk stage pre-treatment, n(%)				
high risk	161 (60)	58 (66)	51 (58)	51 (58)
medium risk	70 (26)	19 (22)	24 (27)	25 (28)
low risk	37 (14)	11 (12)	13 (15)	12 (14)
Risk stage post-treatment, n(%)				
high risk	14 (5)	6 (7)	4 (5)	4 (5)
medium risk	45 (17)	20 (23)	10 (11)	14 (16)
low risk	115 (43)	35 (40)	41 (47)	37 (42)
complete response	91 (34)	25 (28)	33 (38)	32 (36)
missing	3 (1)	2 (2)	0 (0)	1 (1)
Completion of Rt dose (>45 Gy), n(%)				
yes	243 (91)	78 (89)	81 (92)	80 (91)
no	5 (2)	2 (2)	3 (3)	0 (0)
missing	20 (7)	8 (9)	4 (5)	8 (9)
Surgical resection, n(%)				
yes	206 (77)	73 (83)	62 (70)	67 (76)
no	62 (23)	15 (17)	26 (30)	21 (24)
Tumor downstaging, n(%)				
good/complete	166 (62)	48 (55)	59 (67)	57 (65)
moderate/poor	102 (38)	40 (45)	29 (33)	31 (35)
Meets Dutch physical functioning norm, n(%)				
yes	58 (22)	20 (23)	26 (30)	12 (14)
no	210 (78)	68 (77)	62 (70)	76 (86)
MET-hours/week, median[IQR]	98 [62 - 146]	50 [30 - 84]	96 [67 - 116]	170 [128 - 218]
MVPA-SL hours/week, median[IQR]	5 [1 - 10]	1 [0 - 3]	6 [4 - 10]	12 [6 - 19]
Dutch physical activity guideline, n(%)				
Adherence	109 (41)	5 (6)	38 (43)	66 (75)
Non-adherence	155 (59)	83 (94)	50 (57)	22 (25)

Abbreviations: BMI, body mass index; WHO, World Health Organization; Rt, radiotherapy; MET, metabolic equivalent of task; IQR, interquartile range; MVPA, moderate and vigorous physical activity; MVPA-SL, moderate and vigorous physical activity in sports and leisure time. 4 patients were excluded from the MVPA tertiles since they missed too much questions in the SQUASH physical activity values.

RESULTS

In total 618 patients with rectal cancer receiving NCRT who completed questionnaires on physical activity and physical functioning were included in the PLCRC cohort between 2016 and 2021. 280 patients had available clinical data and completed the physical activity and physical functioning questionnaire within 1 month prior to and 2 weeks after starting NCRT. Of these patients, 12 patients were excluded due to missing information about tumor downstaging, leading to a total of 268 patients for final analyses.

Patients had a mean (SD) age of 62 (11) years, 33% were female, and 60% of the patients were categorized as high risk at diagnosis (Table 1). Median [IQR] physical activity levels were 98 [62 – 146] MET-hours/week, 8 [4 – 17] hours of MVPA per week and 5 [1 – 10] hours of MVPA in sports and leisure time per week, assessed with the SQUASH questionnaire. The majority of patients (59%) did not meet the Dutch physical activity guideline, and 22% had a good level of physical functioning.

55% of the patients in the low MVPA group had good/complete downstaging, versus 67% in the moderate MVPA group, and 65% in the high MVPA group (Table 1). Patients in the moderate MVPA group (OR = 2.07; 95%CI = 1.07 – 4.07; $p = 0.03$) or high MVPA group (OR = 2.05; 95%CI = 1.05 – 4.07; $p = 0.04$) were more likely to have good/complete tumor downstaging than patients in the low MVPA group (Table 2). The sensitivity analysis showed comparable or even stronger results for patients in the moderate (OR = 3.14; 95%CI = 1.49 – 6.79, $p = 0.003$) and high MVPA group (OR = 2.80; 95%CI = 1.32 – 6.12; $p = 0.008$). Tumor downstaging did not differ significantly between patients in the moderate MVPA group versus the high MVPA group (OR = 0.99; 95%CI = 0.50 – 1.95; $p = 0.97$). No significant associations were found for MET-hours per week, MVPA-SL, Dutch guideline adherence, and physical functioning with tumor downstaging (Table 2). No effect modification was found for primary risk group and age.

Table 2. Associations of physical activity and physical functioning with tumor downstaging.

Variables	Univariable model		Multivariable model ^a	
	OR (95% CI)	p-value	OR (95% CI)	p-value
MET-hours (hours/week)				
Low	Ref.	Ref.	Ref.	Ref.
Moderate	1.16 [0.63 ; 2.13]	0.64	1.35 [0.69 ; 2.68]	0.38
High	1.10 [0.60 ; 2.02]	0.76	1.50 [0.75 ; 3.04]	0.25
MVPA (hours/week)				
Low	Ref.	Ref.	Ref.	Ref.
Moderate	1.70 [0.92 ; 3.14]	0.09	2.07 [1.07 ; 4.07]	0.03*
High	1.53 [0.84 ; 2.82]	0.17	2.05 [1.05 ; 4.07]	0.04*
MVPA-SL (hours/week)				
Low	Ref.	Ref.	Ref.	Ref.
Moderate	0.95 [0.52 ; 1.75]	0.87	1.00 [0.51 ; 1.96]	1.00
High	1.00 [0.54 ; 1.84]	1.00	1.14 [0.59 ; 2.24]	0.69
Dutch physical activity guideline				
Non-adherence	Ref.	Ref.	Ref.	Ref.
Adherence	1.02 [0.62 ; 1.69]	0.94	1.05 [0.61 ; 1.83]	0.86
Physical functioning				
Does not meet the norm	Ref.	Ref.	Ref.	Ref.
Meets the norm	1.11 [0.61 ; 2.05]	0.74	0.95 [0.50 ; 1.84]	0.88

^a Logistic regression model adjusted for baseline characteristics: age (continuous), sex (female, male), BMI (continuous), risk stage at diagnosis (Low risk, medium risk, high risk), alcohol (drinker, no drinker), smoking (smoker, no smoker).

Abbreviations: OR, odds ratio; CI, confidence interval; MET, metabolic equivalent task; IQR, interquartile range; MVPA, moderate-to-vigorous physical activity; MVPA-SL, moderate-to-vigorous physical activity during sport and leisure time. * Statistically significant OR (p-value < 0.05).

DISCUSSION

Using data from a large nation-wide cohort study, we found that higher levels of MVPA before starting NCRT were associated with augmented tumor downstaging after NCRT in patients with rectal cancer. Total physical activity, MVPA in sports and leisure time, adherence to the Dutch physical activity guideline and self-reported physical functioning were not associated with tumor downstaging.

Our finding that higher MVPA levels were associated with augmented tumor downstaging strengthens previous results from three exploratory trials reporting an augmented tumor response after a physical activity intervention during NCRT in patients with rectal and esophageal cancer (13, 14, 27). To the best of our knowledge, there are currently no large observational studies on the association between physical activity and tumor response in patients with rectal cancer. In contrast to our findings, large observational studies in patients

with breast cancer receiving neoadjuvant chemotherapy did not show an association between physical activity at diagnosis and tumor response (28, 29). Differences in findings might be explained by the focus on pathological complete response rates rather than tumor downstaging, and the use of different questionnaires to assess physical activity.

Our finding that patients with moderate or high MVPA levels are more likely to have good/complete tumor downstaging after NCRT compared to patients with low MVPA levels highlights the potential importance of promoting MVPA levels directly after rectal cancer diagnosis. In addition, we did not find an association between physical functioning and tumor downstaging, suggesting that the actual performance of MVPA is more important than having sufficient levels of physical functioning to enable MVPA. This is further supported by our finding that total physical activity levels, Dutch guideline adherence and MVPA in sports and leisure time were not associated with tumor downstaging. Since total MET-hours incorporates many light intensity physical activities, the strength of the association between total MET-hours and tumor downstaging may be diluted as compared to MVPA alone. Moreover, the cut-off value for adherence to Dutch guidelines may not provide the sensitivity needed to detect a potential association with tumor downstaging. Furthermore, MVPA-SL includes only sports-related activities, which may not accurately reflect the activity levels of patients who are very active in and around their homes. This discrepancy is evident in the highest tertiles of these measures, where there is a notable difference between total MVPA and MVPA-SL levels. Consequently, our findings suggest that future research on exercise interventions in patients with rectal cancer should focus on increasing MVPA levels, regardless of type and timing, rather than light-intensity physical activity.

The median total physical activity levels of 98 MET-hours/week found in patients with rectal cancer participating in this study were comparable to the median physical activity levels of 90 MET-hours/week reported in patients with metastatic colorectal cancer at diagnosis in the PLCRC cohort (30). Our finding that approximately 60% of the patients with rectal cancer scheduled for NCRT did not adhere to the Dutch physical activity guideline was also comparable to the 61.8% reported for patients with metastatic colorectal cancer in the PLCRC cohort (30) as well as the average Dutch adult population aged 65 years or older (31). These results highlight the room for improvement and the importance to increase physical activity levels in the general Dutch older population.

Previous studies have shown that physical activity levels in patients with colorectal cancer decrease after diagnosis (32). Reduced physical activity levels may impair chemotherapy tolerability and completion (21), increase the risk of surgical complications (33, 34), and reduce survival rates (35). Low MVPA levels at diagnosis and the reduction in physical activity levels of patients during treatment opens a window of opportunity for interventions promoting MVPA directly after diagnosis as well as during NCRT and to study the intervention effects on treatment tolerability and tumor downstaging. Increasing tumor response rates might have important clinical implications as it may increase the number of organ sparing surgeries

or allow more patients to go into an active surveillance program, potentially preventing surgery (36). Interventions promoting MVPA during NCRT in patients with rectal cancer have shown to be feasible and safe in previous pilot studies, however causal mechanisms between physical activity interventions and tumor response have not been elucidated yet (13, 14, 37).

The association between MVPA levels at diagnosis and tumor downstaging provides a valuable starting point to look further into causality of associations and underlying mechanistic effects linking physical activity to clinical outcome. Pre-clinical studies proposed several plausible biological mechanisms which might explain this association (38). In patients with rectal cancer receiving NCRT, physical activity may function as radiosensitizer by reducing tumor hypoxia, which has been identified as a limiting factor for radiotherapy efficacy (39). Additionally, physical activity can improve mobilization and infiltration of natural killer cells and T lymphocytes in patients with cancer (40). Improved lymphocyte count has in turn been associated with downstaging after NCRT in patients with rectal cancer (41). Further insight in mechanisms underlying the effect of physical activity at diagnosis and during NCRT on tumor downstaging might help to explain heterogeneity in tumor response and treatment efficacy in patients with rectal cancer, and subsequently provide leads to optimize exercise prescriptions.

A strength of this study is the use of a large nationwide cohort study aiming for generalizability of findings to other patients with rectal cancer (15, 42). Additionally, the availability of real-world data in a large sample of patients with rectal cancer provided the possibility to evaluate the association between physical activity at diagnosis and tumor downstaging while adjusting for relevant demographic and clinical variables such as pre-treatment risk stage. However, due to patients entering the study at a later moment than at diagnosis, only 284 patients filled in the questionnaire around diagnosis. Furthermore, while neoadjuvant chemoradiotherapy is considered standard of care for patients with rectal cancer in certain countries, such as the Netherlands, the conclusion derived from this real-world dataset might not be directly generalizable to patients receiving TNT or short-course radiotherapy as standard treatment. Another limitation is the use of self-reported physical activity assessed with the SQUASH questionnaire, which is susceptible to overestimation of physical activity levels (43). However, the SQUASH is an extensively used and validated questionnaire, and allows to differentiate between active and less active patients. Therefore, the absolute levels of physical activity should be interpreted with caution, but the associations can be considered valid (30). Additionally, although MRI methods are improving, clinical tumor staging is prone to subjectivity, and differences between clinical and pathological staging remain significant due to a lack of standardization and inter-observer inconsistencies (44). Moreover, tumor response assessed by TNM downstaging does not incorporate heterogeneity in tumor response, which might influence recurrence of disease and survival (44). Nevertheless, supported by the previous reported association between physical activity levels and survival in patients with colorectal cancer, our results provide a valuable starting

point to examine potential causal effects and of physical activity during cancer treatment on clinical outcome and to explore underlying mechanisms of action.

CONCLUSION

Based on a nationwide cohort we demonstrated that moderate to high levels of MVPA at diagnosis are associated with an augmented tumor downstaging after NCRT in patients with rectal cancer, while total physical activity, MVPA in sports and leisure time, and physical functioning are not. These results highlight the need to gain further insight into causality of this association and mechanisms underlying the potential effect of MVPA on tumor response.

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CHAPTER 3

Feasibility and clinical potential of exercise interventions during neoadjuvant chemoradiotherapy in patients with esophageal and rectal cancer

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ABSTRACT

Introduction: Exercise during neoadjuvant chemoradiotherapy (NCRT) has potential to mitigate treatment-related declines in physical fitness, and to improve clinical outcomes, including toxicity and tumor response. However, optimal frequency and timing of exercise remains to be determined. Therefore, this pilot trial aimed to assess feasibility of two different exercise interventions during NCRT in patients with esophageal and rectal cancer and to evaluate potential clinical effects.

Methods: Patients were randomized into one of three study arms during NCRT: 1) 30-min aerobic exercise in-hospital within one hour prior to each radiotherapy fraction (ExPR), 2) two 60-min supervised combined aerobic and resistance exercise sessions per week (AE+RE), and 3) usual care (UC). Feasibility was assessed by examining participation rate and exercise adherence. Intervention effects on physical fitness, health-related quality of life, treatment-related toxicity and tumor response in patients with esophageal cancer were explored using regression analyses and 85% confidence intervals (CI).

Results: 37 patients with esophageal cancer (participation rate: 45%) and 2 patients with rectal cancer (participation rate: 14%) were included. Median session attendance was 98% [IQR=96–100] in the ExPR and 78% [IQR=33-100] in the AE+RE group. We found clinically relevant benefits of exercise on VO_2 max (ExPR: $\beta=9.7$ ml/kg/min, 85%CI=6.9;12.6; AE+RE: $\beta=5.6$ ml/kg/min, 85%CI=2.6;8.5), and treatment-related toxicity (ExPR: $\beta=-2.8$, 85%CI=-5.4;-0.2; AE+RE: $\beta=-2.6$, 85%CI=-5.3;0.0). Additionally, good tumor response was found in 70% in AE+RE and ExPR vs. 55% in UC (OR=1.9, 85%CI=0.5;7.7).

Conclusion: Starting prehabilitation during NCRT is feasible, can increase starting fitness of traditional pre-surgical programs, and has potential to improve clinical outcomes.

INTRODUCTION

Pre-surgical rehabilitation, also known as prehabilitation, is an increasingly implemented strategy to enhance physical fitness and physical function before high-impact surgery, and to improve postoperative outcomes (1-5). Prehabilitation generally includes a physical exercise component and takes place in the weeks prior to surgery, regardless of prior neoadjuvant treatment (1). Previous studies showed that prehabilitation is feasible and beneficial for patients with high-risk esophageal and rectal cancer during the 6-12 week recovery period following neoadjuvant chemoradiotherapy (NCRT)(6, 7). NCRT aims to improve survival by reducing tumor size or achieving a complete pathological response, thereby potentially preventing surgery (8). However, NCRT is associated with severe side-effects including fatigue, dysphagia and weight loss, as well as deteriorations in physical fitness and functioning, and health-related quality of life (HRQoL)(9-12). Preventing these deteriorations during NCRT allows for a higher level of physical fitness at the start of traditional prehabilitation, further enhancing its efficacy (13).

Strong evidence from randomized controlled trials (RCTs) among various cancer populations showed that physical exercise during adjuvant chemotherapy or radiotherapy may counteract treatment-related side effects, and benefit physical fitness, fatigue and HRQoL (14-18). In addition, recent pilot and observational studies suggest potential benefits of exercise during neoadjuvant treatment or pre-surgery on tumor regression in patients with esophageal and rectal cancer (18-21). This is supported by pre-clinical studies in rodents reporting a direct effect of aerobic exercise on tumor growth via several underlying mechanisms (22). First, exercise can result in mobilization, activation and infiltration of natural killer (NK) and T cells (23, 24). Patients with esophageal cancer with a higher number of circulating T cells were more likely to have a pathological complete response (25). Second, preclinical studies in mice showed that a single aerobic exercise session may already modulate tumor perfusion and hypoxia, and thereby potentially function as radiotherapy sensitizer (26, 27). Timing exercise directly prior to a radiotherapy session could therefore enhance the potential of exercise as adjunct therapy in cancer treatment beyond the already proven beneficial effects on treatment-related side effects, physical fitness, and HRQoL (28). Prior to the conduct of a large randomized controlled phase III trial, knowledge on the feasibility and variability in effects on clinical outcome is warranted.

Therefore, the **Exercise during Neoadjuvant chemoradiation Treatment** to improve esophageal and rectal cancer **Outcome** (EXENTRO) pilot trial aimed to assess feasibility of two different exercise programs during NCRT of similar exercise volumes: in-hospital aerobic exercise prior to each radiotherapy fraction, and a twice-weekly combined aerobic and resistance exercise intervention (29), in patients with esophageal and rectal cancer. Second, we aimed to evaluate variability in effects on physical fitness, HRQoL, treatment-related toxicity and tumor response.

MATERIALS AND METHODS

Design and participants

The EXENTRO trial was a multicenter randomized controlled pilot trial comparing two exercise interventions during NCRT with a usual care control group (clinicaltrials.gov identifier: NCT05686213). The study aimed to include a total of 39 patients, based on accrual feasibility and the rule of thumb for pilot studies which recommends 12 patients per arm, accounting for one drop-out per study arm (30). Patients with esophageal cancer were eligible for inclusion if they were scheduled for NCRT according to the CROSS regimen, consisting of a weekly administration of intravenous carboplatin (dose titrated to achieve an area under the curve of 2 mg/ml/min) and paclitaxel (50 mg/m²) with concurrent radiotherapy of 41.1 Gray in 23 fractions for five days a week (31). Patients with rectal cancer were eligible if they were scheduled for NCRT including radiotherapy (25 fractions of 2 Gray) with concurrent oral capecitabine (825 mg/m² twice a day) as chemotherapy (32). Radiotherapy was offered in the closest participating radiotherapy center (Radiotherapiegroep Arnhem, or the internal or external radiotherapy departments of the Radboudumc). Exclusion criteria included disabling comorbidities that could hamper or endanger exercise, cognitive disorders, severe emotional instability, immunodeficiency, or inability to perform basic daily activities such as walking or cycling. Furthermore, patients were excluded if they already engaged in regular (> 2 times a week) and supervised moderate-to-vigorous aerobic and/or resistance exercise and intended to continue this throughout the period of NCRT. The study was conducted in accordance with the declaration of Helsinki and the study protocol was approved by the Medical Ethics Committee Oost Nederland (NL81016.091.22). All patients provided written informed consent before inclusion.

Patients were recruited from the department of Surgery or Radiotherapy in the Radboud University Medical Center (Radboudumc). Patients who did not want to participate in the study were asked to provide a reason if they were willing to give one. After providing written informed consent, all patients underwent baseline measurements. Afterwards, patients were randomized into one of three study arms using Castor electronic data capture (Castor®), using block randomization (blocks of 3 or 6) stratified by age (≤ 70 vs. > 70) and tumor type (rectal vs. esophageal). Study measurements were performed at three timepoints: before the start of NCRT (Baseline; T0), within two weeks after NCRT (T1), and shortly prior to surgery (T2).

Exercise interventions

After randomization, patients were allocated to one of three study arms. The two exercise intervention arms both consisted of 150 minutes of exercise per week during the period of NCRT. Both exercise interventions were tailored to patients' individual fitness levels using

results from baseline testing (Steep Ramp Test (33) to estimate Wmax and indirect 1 repetition maximum (1RM) test (34)).

In the exercise prior to radiotherapy (ExPR) arm, patients performed in-hospital moderate-intensity aerobic cycling exercise for five days a week within one hour prior to the scheduled radiotherapy fractions, supervised by the research team. Cycling exercise was performed on a cycle ergometer (Lode Corival; Lode, Groningen, the Netherlands) placed in proximity to the waiting room of the treating radiotherapy department. Patients performed 5 minutes of warming-up, 20 minutes of moderate-intensity cycling exercise (50-70% of the estimated Wmax, adjusted to Borg 12-14, 'somewhat hard' (35), if needed), and 5 minutes of cooling-down. Heart rate was monitored throughout the exercise session.

In the combined aerobic and resistance exercise (AE + RE) arm, patients performed aerobic and resistance exercise supervised by a local physical therapist specialized in oncology. Patients performed two exercise sessions per week performing 5 minutes warming-up, 20 minutes of resistance exercises targeting 6 large muscle groups in 2 sets of 8-12 repetitions at 70-80% of their estimated 1RM, 30 minutes of moderate-to-high intensity aerobic exercise (50-80% of estimated Wmax, adjusted to Borg 12-15 if needed), and 5 minutes cooling-down (29). Patients were asked to perform a third exercise session per week of 30 minutes moderate-intensity exercise at or from home (e.g., cycling or walking). This program has shown to effectively maintain physical fitness, limit fatigue and enhance HRQoL during treatment in patients with other types of cancer (29), and aligns with the exercise recommendations for patients with cancer (28).

Patients in the usual care control (UC) group did not receive an exercise intervention during NCRT. To assess potential contamination in the control group, patients in the UC group were asked if they attended any supervised exercise sessions during NCRT. Physical therapist, research team members, and patients kept exercise logs to record both supervised and home-based exercise sessions, along with reasons for non-attendance and reasons for exercise dose adjustments. Patients in all groups received dietary counselling during NCRT as part of usual care. After completing NCRT, all patients with esophageal cancer were invited to participate in a multimodal prehabilitation program in the 3-4 weeks prior to surgery (as part of the F4S PREHAB trial, with postoperative complications as primary endpoint (36)), independent of study-arm allocation.

Primary outcome measures

The participation rate of the study was calculated as the number of patients who agreed to participate divided by the total number of approached eligible patients. Reasons for refraining from participation and drop-out were collected, if provided. Information about the feasibility of both exercise interventions was evaluated using exercise-logs registered by physical therapists and the research team.

Exercise session attendance rate was calculated based on the number of attended exercise sessions divided by the total prescribed sessions as collected in the exercise logs, and reasons for non-attendance were evaluated. Compliance was evaluated by the exercise relative dose intensity (ExRDI), calculated as the percentage of exercise dose intensity during the performed exercise sessions relative to the total prescribed exercise dose (37). Reasons for exercise dose adjustments were collected from the exercise-logs and satisfaction with the interventions was assessed on a scale from 0 (not satisfied at all) to 10 (completely satisfied) using a custom-made questionnaire.

Secondary outcome measures

Information on physical fitness, body composition, HRQoL, and physical activity levels were collected at T0, T1, and T2. Patient-reported toxicity was assessed at T1 and T2. Demographic information was evaluated using a custom-made questionnaire and clinical data were retrieved from medical records at T0. After clinical restaging and surgical resection, information about tumor response was collected from medical records.

Aerobic fitness levels were evaluated using the Åstrand-Rhyming submaximal exercise test on a cycle ergometer (38)(Lode Corival; Lode, Groningen, the Netherlands), requiring patients to cycle at a steady-state target heart rate (HR; $180 - \text{age}$) for six minutes. VO_2max was estimated using average workload and the HR of the fifth and sixth minute of the steady state exercise, corrected for age and sex (38). If patients used Beta-blocker medication they were excluded from VO_2max calculations. In addition, maximal short time exercise capacity (MSEC) was determined using the Steep Ramp Test (33). During this short maximal exercise test, workload increases with 25 Watt every 10 seconds until exhaustion, and the MSEC is defined as the highest achieved wattage during the test. Lower body muscle strength (kg) was evaluated using an indirect 1 repetition maximum test (34). Body weight and height were measured and body mass index (BMI; kg/m^2) was calculated. Fat free mass and fat percentage were measured using bioelectric impedance analyses (BodyStat 1500, Bodystat Ltd., Douglas, UK)(39).

HRQoL was evaluated using the subscales from the short-form 36 (SF-36 version 2). Raw scores from this questionnaire were linearly converted to a 0 – 100 scale, with higher scores representing better functioning or well-being (40). Physical activity levels were assessed using the short questionnaire to assess health-enhancing physical activity (SQUASH)(41). This questionnaire contains 11 items and assesses frequency, duration and intensity of 4 different physical activity domains (actively commuting, physical activities at work or school, household activities, sports and leisure time activities). Based on the Ainsworth compendium (42), all activities were assigned a Metabolic Equivalent of Task (MET) score, and total MET-hours per week were calculated. Furthermore, the time spent on moderate-to-vigorous intensity physical activities (MVPA; ≥ 3.0 METs) was calculated.

Patient-reported toxicity was evaluated by a patient-reported version of the common toxicity criteria for adverse events (CTCAE)(43), using items specifically selected for patients with esophageal and rectal cancer by researchers and clinicians (such as items on dysphagia, hoarseness, and nausea for esophageal cancer, and bloating and defecation for rectal cancer). For each item, the scores for frequency, severity and interference with daily activities were asked and combined in a single composite score ranging from 0-3, in which a higher score indicate worse symptoms (44). Total number of moderate-to-severe toxicities (composite scores ≥ 2) were assessed, and composite scores were comprised into a single sum score per patient (45).

Tumor response was evaluated by the tumor regression grade based on pathological restaging after surgery, if available. Mandard tumor regression grade (TRG) was scored on a scale from 1-5, with 1 representing a complete regression and 5 no regression (46), assessed by trained pathologists. TRG was dichotomized into 1-3 (good response) vs. 4-5 (poor response) (20). If patients did not receive surgery following a clinical complete response as assessed by combined positron emission tomography and computed tomography, a good response was assumed, or in case of metastatic disease, a poor response was assumed. A complete response was defined as a clinical complete response without subsequent need for surgery or ypT0N0M0 after pathological restaging.

Statistical analyses

Statistical analyses were performed using RStudio (version 2022.02.01, R Core Team (2020)). Descriptive statistics were used to evaluate feasibility, and results were presented as n (%) for categorical variables, mean \pm standard deviation (SD) or median with interquartile range (IQR) for continuous variables, as appropriate. Linear mixed model analyses were performed to simultaneously assess between-group differences in physical activity and fitness, body composition and HRQoL at T1 and T2. This longitudinal model automatically accounts for missing values under the missing at random assumption. We used logistic regression analyses to examine between-group differences in tumor response and linear regression analyses for treatment-related toxicity. All analyses were performed according to the intention-to-treat principle. As the pilot trial was underpowered by nature, we evaluated the potential clinical relevance of the between-group differences based on the point estimates and measures of variability, with 85% confidence intervals (CI) above or below zero as potentially clinically relevant (47). Additionally, known minimally clinically important differences (MCID) were considered for VO_2 max (3.5 ml/kg/min, corresponding to 1 MET (48)), and for each subscale of HRQoL (40).

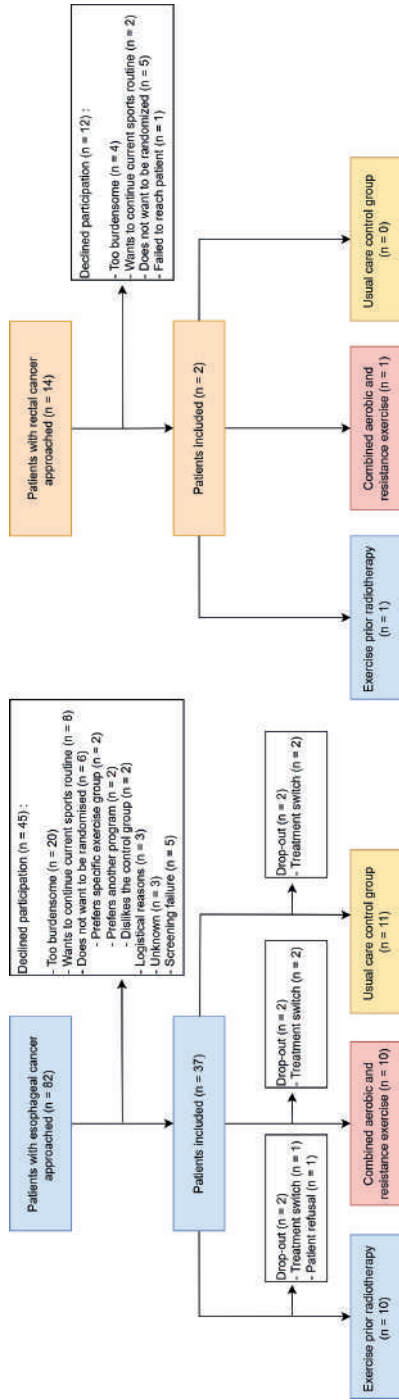


Figure 1. Flowchart of patients with esophageal and rectal cancer included in the EXENTRO trial.

Table 1. Demographic and clinical information of patients with esophageal cancer in the EXENTRO trial.

	Total (n = 31)	UC (n = 11)	AE + RE (n = 10)	ExPR (n = 10)
Gender, n(%)				
Male	26 (84)	9 (82)	9 (90)	8 (80)
Female	5 (16)	2 (18)	1 (10)	2 (20)
Age, years, mean ± sd	65 ± 8	66 ± 7	62 ± 9	68 ± 7
BMI, kg/m², mean ± sd	27.1 ± 4.7	29.0 ± 5.8	27.6 ± 4.0	24.7 ± 3.1
Living situation, n(%)				
Single	6 (19)	5 (45)	0 (0)	1 (10)
Married/living together	25 (81)	6 (55)	10 (100)	9 (90)
Education level, n(%)				
High	7 (23)	3 (27)	1 (10)	3 (30)
Intermediate	10 (32)	4 (36)	4 (40)	2 (20)
Low	14 (45)	4 (36)	5 (50)	5 (50)
Smoking status, n(%)				
Current smoker	12 (39)	6 (55)	4 (40)	2 (20)
Former smoker	13 (42)	2 (18)	5 (50)	6 (60)
Never	6 (19)	3 (27)	1 (10)	2 (20)
Karnofsky performance score, n(%)				
100	13 (42)	5 (45)	4 (40)	4 (40)
90	16 (52)	5 (45)	5 (50)	6 (60)
80	2 (6)	1 (9)	1 (10)	0 (0)
CCI > 1, n(%)				
No	18 (58)	8 (73)	4 (40)	6 (60)
Yes	13 (42)	3 (27)	6 (60)	4 (40)
Tumor location, n(%)				
Middle oesophagus	4 (13)	2 (18)	1 (10)	1 (10)
Distal oesophagus	23 (74)	8 (73)	7 (70)	8 (80)
Oesophagogastric junction	4 (13)	1 (9)	2 (20)	1 (10)
cT classification, n(%)				
2	9 (29)	4 (36)	3 (30)	2 (20)
3	22 (71)	7 (64)	7 (70)	8 (80)
cN classification, n(%)				
0	9 (29)	5 (45)	1 (10)	3 (30)
1	10 (32)	1 (9)	5 (50)	4 (40)
2	10 (32)	5 (45)	3 (30)	2 (20)
3	2 (6)	0 (0)	1 (10)	1 (10)
Histology, n(%)				
Adenocarcinoma	26 (84)	10 (91)	9 (90)	7 (70)
Squamous cell carcinoma	5 (16)	1 (9)	1 (10)	3 (30)
NCRT compliance, n(%)				
Full dose	24 (77)	8 (73)	9 (90)	7 (70)
Dose adjusted	7 (23)	3 (27)	1 (10)	3 (30)
Complete response, n(%)				
No	27 (87)	9 (82)	9 (90)	9 (90)
Yes	4 (13)	2 (18)	1 (10)	1 (10)

	Total (n = 31)	UC = (n = 11)	AE + RE (n = 10)	ExPR (n = 10)
Mandard TRG, n(%)				
1	3 (10)	2 (18)	1 (10)	0 (0)
2	6 (19)	1 (9)	2 (20)	3 (30)
3	10 (32)	3 (27)	4 (40)	3 (30)
4	9 (29)	3 (27)	3 (30)	3 (30)
5	1 (3)	1 (9)	0 (0)	0 (0)
Unknown*	2 (6)	1 (9)	0 (0)	1 (10)

Abbreviations: BMI; body mass index, CCI; Charlson comorbidity index, NCRT; neoadjuvant chemoradiotherapy, TRG; tumor regression grade, ExPR; exercise prior radiotherapy, AE + RE, aerobic exercise and resistance exercise, UC; usual care.

*One patient in the UC group did not receive surgery due to metastatic disease, and one patient in the ExPR group did not receive surgery following a clinical complete response.

RESULTS

Demographic and clinical information

In total, 82 patients with esophageal cancer were approached for participation between September 2022 and July 2024, of whom 37 patients were included in the study (participation rate: 45%, Figure 1). Fourteen patients with rectal cancer were approached for participation, of whom 2 were included in the study (participation rate: 14%, Figure 1). Most common reason for refusal was that patients felt participating was too burdensome (Figure 1). After randomization, 6 patients with esophageal cancer dropped out of the study of which 5 due to a treatment switch to proton beam therapy which was not available in the participating centers (n = 4) or the TRAP-2 trial shortly after study inclusion (n = 1, clinicaltrials.gov ID: NCT05188313), and 1 patient did not want to perform the ExPR intervention (Figure 1). Due to the small number of patients with rectal cancer included in the study, they were excluded from statistical analyses. Patients with esophageal cancer were on average 65 ± 8 years old, had a BMI of 27.1 ± 4.7 kg/m² and 84% was male (Table 1). The two patients with rectal cancer were both male, < 40 years old, and had a BMI between 20- 25 kg/m².

Exercise attendance, compliance and satisfaction

Patients with esophageal cancer in the ExPR group attended 98% [IQR = 96 – 100] of the sessions, and patients in the AE + RE group attended 78% [IQR = 33 – 100] of the sessions (Figure 2). Reasons for non-attendance in the ExPR group were, treatment-related toxicities (constipation, fever; 25%), COVID-19 infection (25%), hospital appointments (25%), and unknown reasons (25%). Reasons for non-attendance in the AE + RE group included illness (e.g. nausea, abdominal complaints; 79%), unavailability of the physical therapist (6.9%), miscommunication between patient and physical therapist (3.4%), patient wanted to train only 1 time per week (3.4%), hospital appointments (3.4%), and unknown reasons (3.4%).

Median ExRDI was 97% [IQR = 91 – 99] for patients with esophageal cancer in the ExPR group and 53% [IQR = 28 – 84] for those in the AE + RE group. In the ExPR group, exercise dose was adjusted in 18 (8%) sessions. Reasons for dose adjustments included: other hospital appointments reducing available exercise time (39%), physical complaints during exercise (back pain, saddle pain; 33%), fatigue (22%), and unknown reasons (6%). In the AE + RE group, dose was adjusted in 40 (44%) sessions, due to fatigue (60%), time constraints (30%), physical complaints during exercise (back pain, muscle pain; 7.5%), and unknown reasons (2.5%). There were no (serious) adverse events related to the training interventions. Two patients (AE + RE, n = 2) did not enroll in the F4S PREHAB intervention.

Satisfaction of patients with esophageal cancer with the exercise intervention was 8.2 ± 0.7 out of 10 for the ExPR group and 7.6 ± 0.7 out of 10 for the AE + RE group.

Patients with rectal cancer attended all exercise sessions in the ExPR group (n = 1, ExRDI = 99%, satisfaction = 9 out of 10) and the AE + RE group (n = 1, ExRDI = 98%, satisfaction = 10 out of 10).

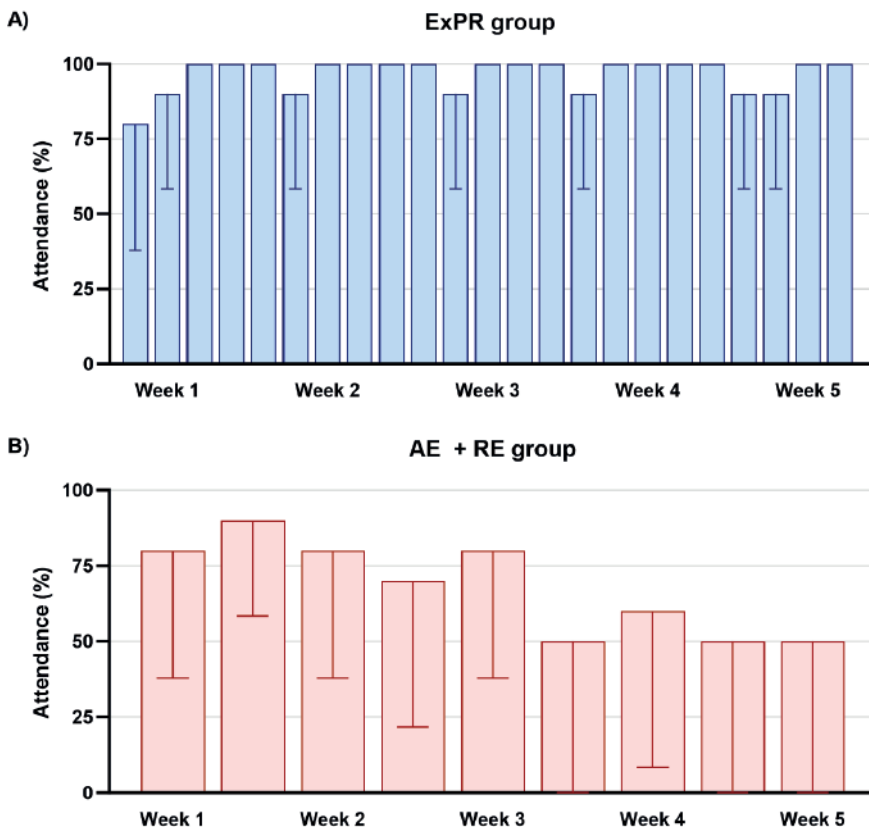


Figure 2. Attendance to exercise sessions of patients with esophageal cancer displayed as mean and standard deviation for A) the exercise prior radiotherapy (ExPR) group and B) the combined aerobic and resistance exercise (AE + RE) group during the five weeks of neoadjuvant chemoradiotherapy.

Potential clinical effects

One patient did not attend study measurements directly post-NCRT resulting in missing physical tests. The median interval between NCRT termination and the post-NCRT study measurements was 14 [IQR = 13 – 19] days, with ten patients unable to attend study measurements within two weeks (UC, n = 3; AE + RE, n = 4; ExPR, n = 3). Details on intervention outcomes are displayed in Table 2. Directly post-NCRT, estimated VO_2max was superior in the ExPR group ($\beta = 9.7$ ml/kg/min, 85%CI = 6.9 ; 12.6) and the AE + RE ($\beta = 5.6$ ml/kg/min, 85%CI = 2.6 ; 8.5) compared to the UC group. Additionally, in the ExPR group, BMI was improved compared to the UC group directly after NCRT ($\beta = 0.7$ kg/m², 85%CI = 0.1 ; 1.2). Between the exercise groups, aerobic fitness was superior in the ExPR group (estimated VO_2max ; $\beta = 4.1$ ml/kg/min, 85%CI = 1.2 ; 7.1, and MSEC; $\beta = 35.0$ W, 85%CI= 12.4 ; 57.6), compared to the AE + RE group directly after NCRT (Figure 3). On the other hand, we found larger effects on role functioning due to physical health ($\beta = 21.1$, 85%CI = 39.4 ; 2.8) and pain ($\beta = 18.1$, 85%CI = 33.1 ; 3.0) in the AE + RE group compared to the ExPR group directly after NCRT.

Nine patients did not attend physical tests shortly before surgery (UC, n = 2; AE + RE, n = 4; ExPR, n = 3) and median interval between study measurements and surgical resection was 3 [IQR = 1 – 5] days. We found that VO_2max was superior in both the ExPR group ($\beta = 6.8$ ml/kg/min, 85%CI = 3.5 ; 10.1) and the AE + RE group ($\beta = 7.8$ ml/min/kg, 85%CI = 4.6 ; 11.0) compared to the UC group, shortly before surgery (Figure 3). Additionally, in the ExPR group, mental health was improved compared with the UC group ($\beta = 12.3$, 85%CI = 1.8 ; 22.9) shortly before surgery. There were no differences between exercise groups shortly before surgery.

Clinical information after NCRT is displayed in Table 1. Evaluation of patients-reported treatment related toxicity showed that patients in the ExPR ($\beta = -2.8$, 85%CI = -5.4 ; -0.2) and the AE + RE group ($\beta = -2.6$, 85%CI = -5.3 ; 0.0) had fewer moderate-to-severe toxicities (Table 3). Furthermore, we found a lower toxicity sum score in the ExPR group ($\beta = -7.3$, 85%CI = -14.3 ; -0.3) and the AE + RE group ($\beta = -7.2$, 85%CI = -14.5 ; 0.0) compared to the UC group directly after NCRT (Figure 3; Table 3). There was no difference in treatment-related toxicities between the groups shortly before surgery. Furthermore, 70% of patients in the ExPR and 70% of patients in the AE+RE group had a good tumor response compared to 55% in the control group (risk difference = -15%, 85%CI = -45 ; 15; OR = 1.9, 85%CI = 0.5 ; 7.7, Figure 3; Table 3).

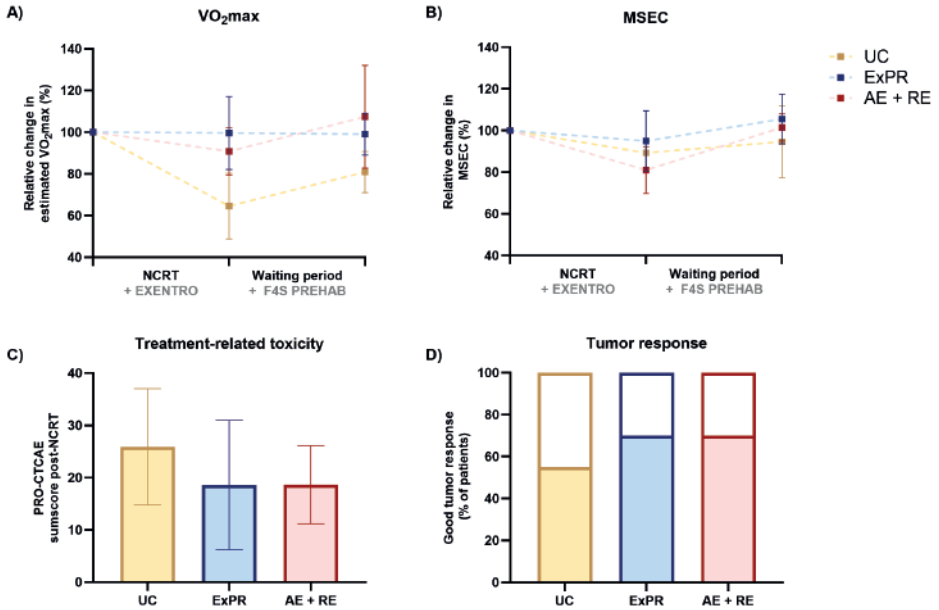


Figure 3. Results of A) Estimated VO₂max, B) Maximal short-time exercise capacity (MSEC), C) Treatment-related toxicity assessed by PRO-CTCAE (Patient-reported version of the Common Terminology Criteria for Adverse Events), and D) tumor response, displayed for patients with esophageal cancer in the usual care group (UC; green), the exercise prior radiotherapy group (ExPR; blue), and the aerobic exercise + resistance exercise group (AE + RE; red).

Table 2. Descriptives and between-group differences in outcome parameters of patients with esophageal cancer.

	T0	T1	T2	Between group difference directly after NCRT β (85% CI)	Between group difference pre-surgery β (85% CI)
Physical fitness					
1RM (kg), mean \pm sd					
Control	156.3 \pm 53.9	139.8 \pm 56.2	171.3 \pm 65.9	Ref.	Ref.
AE + RE	121.5 \pm 52.2	101.5 \pm 60.6	172.5 \pm 63.0	0.1 (-17.0 ; 17.3)	11.3 (-8.1 ; 30.7)
EXPR	137.9 \pm 31.2	106.8 \pm 32.1	150.5 \pm 35.3	-14.6 (-32.4 ; 3.2)	-5.0 (-24.6 ; 14.6)
Estimated VO ₂ max (ml/kg/min), mean \pm sd					
Control	29.1 \pm 7.7	20.6 \pm 7.8	23.0 \pm 7.5	Ref.	Ref.
AE + RE	26.9 \pm 12.2	22.2 \pm 9.2	31.6 \pm 10.0	5.6 (2.6 ; 8.5)	7.8 (4.6 ; 11.0)
EXPR	25.3 \pm 9.1	25.4 \pm 10.3	28.9 \pm 10.6	9.7 (6.9 ; 12.6)	6.8 (3.5 ; 10.1)
MSEC steep ramp test (W), mean \pm sd					
Control	284.1 \pm 72.3	239.1 \pm 67.3	275.4 \pm 90.6	Ref.	Ref.
AE + RE	254.2 \pm 81.3	204.1 \pm 85.0	310.0 \pm 75.5	-13.4 (-36.4 ; 9.6)	19.3 (-6.3 ; 44.9)
EXPR	226.9 \pm 69.0	216.1 \pm 66.8	250.7 \pm 79.3	21.6 (-1.0 ; 44.2)	24.4 (-0.2 ; 49.1)
Body composition					
BMI (kg/m ²), mean \pm sd					
Control	29.0 \pm 5.8	27.9 \pm 5.7	28.6 \pm 6.5	Ref.	Ref.
AE + RE	27.6 \pm 4.0	26.2 \pm 3.9	29.8 \pm 4.0	0.2 (-0.3 ; 0.7)	-0.2 (-0.8 ; 0.4)
EXPR	24.7 \pm 3.1	24.2 \pm 3.2	25.6 \pm 3.2	0.7 (0.1 ; 1.2)	0.3 (-0.3 ; 0.9)
Fat free mass (kg), mean \pm sd					
Control	59.8 \pm 9.5	59.1 \pm 10.6	62.1 \pm 8.2	Ref.	Ref.
AE + RE	58.5 \pm 7.6	58.2 \pm 7.8	63.1 \pm 5.1	1.2 (-0.9 ; 3.4)	-0.3 (-2.8 ; 2.1)
EXPR	52.8 \pm 10.9	52.3 \pm 10.4	55.6 \pm 13.0	0.1 (-2.0 ; 2.3)	0.4 (-2.1 ; 2.9)
Percentage body fat (%), mean \pm sd					
Control	16.9 \pm 7.0	15.6 \pm 6.0	15.7 \pm 7.8	Ref.	Ref.
AE + RE	16.7 \pm 4.9	14.3 \pm 4.9	18.2 \pm 6.6	-0.5 (-1.8 ; 0.8)	0.0 (-1.5 ; 1.4)
EXPR	12.6 \pm 3.8	12.0 \pm 4.2	13.1 \pm 4.8	0.7 (-0.6 ; 2.0)	0.4 (-1.1 ; 1.9)
Health related quality of life					
Physical functioning, mean \pm sd					
Control	88.2 \pm 17.9	65.6 \pm 16.1	80.0 \pm 20.8	Ref.	Ref.
AE + RE	88.0 \pm 13.2	69.4 \pm 16.8	80.6 \pm 28.6	4.3 (-8.9 ; 17.5)	-1.0 (-13.9 ; 12.1)
EXPR	93.0 \pm 11.1	77.5 \pm 25.4	85.8 \pm 15.9	4.8 (-8.4 ; 18.1)	1.1 (-12.7 ; 14.9)
Social functioning, mean \pm sd					
Control	75.0 \pm 17.7	58.8 \pm 22.9	84.1 \pm 22.4	Ref.	Ref.
AE + RE	73.8 \pm 26.6	58.3 \pm 30.6	80.6 \pm 31.9	0.3 (-14.2 ; 14.8)	-4.0 (-18.3 ; 10.4)
EXPR	77.5 \pm 19.4	66.2 \pm 22.1	84.4 \pm 11.1	3.6 (-10.6 ; 17.9)	-1.7 (-16.3 ; 12.9)

	T0	T1	T2	Between group difference directly after NCRT β (85% CI)	Between group difference pre-surgery β (85% CI)
Role limitations physical problems, mean \pm sd	59.1 \pm 21.5	34.4 \pm 16.7	51.7 \pm 23.6	Ref.	Ref.
AE + RE	66.2 \pm 38.2	47.2 \pm 26.5	67.4 \pm 35.6	5.1 (-12.7; 23.0)	7.8 (-9.7; 25.4)
ExPR	75.6 \pm 26.3	35.4 \pm 20.0	73.4 \pm 22.6	-16.0 (-33.8; 1.9)	5.2 (-12.7; 23.2)
Role limitations emotional problems, mean \pm sd	65.9 \pm 23.7	55.8 \pm 36.7	74.2 \pm 20.6	Ref.	Ref.
AE + RE	79.2 \pm 24.9	67.6 \pm 32.9	81.2 \pm 16.5	-1.7 (-23.5; 20.2)	-7.3 (-29.3; 14.9)
ExPR	80.8 \pm 16.7	65.7 \pm 34.7	83.3 \pm 24.0	-5.5 (-27.4; 16.4)	-6.1 (-28.1; 16.0)
Mental health, mean \pm sd	76.8 \pm 12.9	74.5 \pm 17.4	82.3 \pm 14.7	Ref.	Ref.
AE + RE	74.5 \pm 19.5	79.4 \pm 10.5	82.8 \pm 15.4	6.3 (-4.1; 16.8)	2.5 (-7.5; 12.6)
ExPR	64.5 \pm 10.9	67.8 \pm 19.4	82.9 \pm 15.2	6.0 (-4.2; 16.2)	12.3 (1.8; 22.9)
Vitality, mean \pm sd	70.5 \pm 17.7	50.0 \pm 20.0	64.8 \pm 21.0	Ref.	Ref.
AE + RE	66.9 \pm 20.8	48.4 \pm 18.2	63.2 \pm 17.2	2.7 (-9.8; 15.2)	2.6 (-9.3; 14.4)
ExPR	65.6 \pm 17.7	45.1 \pm 17.9	68.8 \pm 13.0	1.8 (-10.5; 14.0)	10.4 (-2.1; 22.8)
Bodily pain, mean \pm sd	83.3 \pm 18.3	62.9 \pm 18.7	83.3 \pm 21.2	Ref.	Ref.
AE + RE	89.1 \pm 14.5	80.5 \pm 21.1	76.9 \pm 30.6	14.0 (-1.0; 28.8)	-9.2 (-24.1; 5.4)
ExPR	90.2 \pm 11.4	66.3 \pm 20.1	90.8 \pm 12.0	-4.2 (-18.5; 10.2)	0.9 (-13.8; 15.6)
General health, mean \pm sd	63.6 \pm 21.5	58.0 \pm 22.4	57.7 \pm 17.9	Ref.	Ref.
AE + RE	61.0 \pm 12.2	53.9 \pm 18.7	56.7 \pm 15.2	-2.2 (-14.2; 9.9)	2.1 (-9.8; 13.9)
ExPR	55.5 \pm 15.5	55.5 \pm 16.9	61.9 \pm 21.9	5.2 (-6.6; 17.1)	12.0 (-0.1; 24.2)
Physical activity					
MET-hours/week, median (IQR)	63.3 (29.7, 128.6)	29.7 (20.8, 42.2)	46.8 (32.6, 63.8)	Ref.	Ref.
AE + RE	66.6 (46.6, 130.9)	22.6 (15.0, 35.0)	51.2 (37.6, 69.4)	0.3 (-45.9; 46.8)	-13.6 (-59.8; 32.8)
ExPR	104.4 (96.8, 116.8)	77.7 (40.2, 112.4)	55.8 (41.6, 72.9)	9.3 (-36.0; 54.9)	-6.2 (-53.5; 41.2)
MVPA (hours/week), median (IQR)	9.5 (2.5, 13.5)	2.8 (1.4, 4.9)	5.0 (1.4, 6.2)	Ref.	Ref.
AE + RE	4.5 (2.2, 8.4)	1.5 (0.3, 4.2)	4.5 (3.1, 7.5)	5.8 (-4.2; 15.8)	4.6 (-5.2; 14.4)
ExPR	13.1 (10.1, 19.4)	11.1 (3.0, 21.1)	9.4 (2.2, 11.4)	2.2 (-7.5; 12.0)	3.7 (-6.4; 13.7)

Abbreviations: IRM; repetition maximum, VO2max; maximal oxygen uptake, MSEC; maximal short-time exercise capacity, BMI; body mass index, MET; metabolic equivalent of task, MVPA; moderate-to-vigorous physical activity, NCRT; neoadjuvant chemoradiotherapy, ExPR, exercise prior radiotherapy, AE + RE; aerobic exercise + resistance exercise. IQR; interquartile range, sd; standard deviation, CI; confidence interval.

Bold values represent statistical significance.

Table 3. Descriptives and between-group differences in treatment outcomes in patients with esophageal cancer.

		mean ± sd	β (85% CI)
Sum score treatment-related toxicity post-NCRT	Control	25.9 ± 11.1	Ref.
	AE + RE	18.7 ± 7.5	-7.2 (-14.5 ; 0.0)
	ExPR	18.6 ± 12.4	-7.3 (-14.3 ; -0.3)
Number of moderate or severe toxicities post-NCRT	Control	7.3 ± 3.9	Ref.
	AE + RE	4.7 ± 3.6	-2.6 (-5.3 ; 0.0)
	ExPR	4.5 ± 4.2	-2.8 (-5.4 ; -0.2)
Sum score treatment-related toxicity pre-surgery	Control	13.1 ± 10.0	Ref.
	AE + RE	11.6 ± 7.1	-1.5 (-7.4 ; 4.3)
	ExPR	10.6 ± 8.6	-2.5 (-8.4 ; 3.3)
Number of moderate or severe toxicities post-NCRT	Control	2.5 ± 4.1	Ref.
	AE + RE	2.2 ± 1.9	-0.2 (-2.2 ; 1.7)
	ExPR	1.2 ± 2.1	-3.2 (-3.2 ; 0.7)
		n (%)	OR (85% CI)
NCRT full dose, n(%)	Control	8 (73)	Ref.
	AE + RE	9 (90)	0.3 (0.0 ; 1.6)
	ExPR	7 (70)	1.1 (0.3 ; 4.7)
Good response TRG, n(%)[†]	Control	6 (55)	Ref.
	AE + RE	7 (70)	1.9 (0.5 ; 7.7)
	ExPR	7 (70)	1.9 (0.5 ; 7.7)

Abbreviations: NCRT; neoadjuvant chemoradiotherapy, TRG; tumor regression grade; ExPR, exercise prior radiotherapy, AE + RE; aerobic exercise + resistance exercise, sd; standard deviation, CI; confidence interval, OR; odds ratio.

Bold values represent statistical significance.

DISCUSSION

In this study, we demonstrated the feasibility of two different exercise interventions during neoadjuvant chemoradiotherapy among patients with esophageal cancer. We found that exercise adherence was substantially higher in the in-hospital daily ExPR exercise intervention compared to the twice weekly AE + RE group. We found promising effects in both groups on aerobic fitness and on BMI in the ExPR group. Furthermore, we found beneficial effects on treatment-related toxicity in both exercise groups compared to UC, and a 15% difference in the proportion of patients with good tumor response. Feasibility for patients with rectal cancer could not be demonstrated due to the low number of eligible patients and the low participation rate.

The participation rate of 45% we found in patients with esophageal cancer can be considered good for exercise oncology trials, and might reflect a good motivation to exercise during the neoadjuvant period (49). Nonetheless, a substantial proportion of patients did not want to participate in the EXENTRO study due to high burden or reluctance to randomization. The excellent adherence to a novel exercise intervention consisting of daily aerobic exercise during NCRT is remarkably higher than previously reported trials on supervised exercise during NCRT and the AE + RE intervention (50). Furthermore, the lower ExRDI in the AE + RE intervention, suggests that the combined aerobic and resistance exercise intervention might impose a significant burden on patients during NCRT. These results highlight that in-hospital exercise during this intensive chemoradiotherapy period minimizes logistical challenges and reduces patient burden compared to attending exercise sessions at a physical therapist, even if the practice is close to patient's home.

Inclusion rate of only 14% for patients in the rectal cancer group was low compared to other studies (49). In contrast to patients with esophageal cancer, surgical resection for patients with rectal cancer is not centralized in our region, hampering the ability to approach patients by clinicians from the recruiting hospitals. Furthermore, during our study period, short-course radiotherapy followed by chemotherapy instead of NCRT became a more popular choice of treatment after publication of the RAPIDO trial (51), reducing the number of eligible patients. The scarcity of data in patients with rectal cancer hampered us to evaluate feasibility of exercise during NCRT in this population. Previous studies, however, demonstrated feasibility of exercise during NCRT in patients with rectal cancer (7), although recruitment difficulties have been reported (52). Future studies should focus on including community hospitals, ensuring efficient logistics and collaboration between recruiting centers and local hospitals to improve patient participation and recruitment.

Both exercise groups improved in aerobic fitness after NCRT compared to the control group, although patients in the ExPR group had a better aerobic fitness than patients in the AE + RE group. This is in line with results from previous prehabilitation trials during neoadjuvant chemoradiotherapy reporting beneficial effects on physiological reserve (6, 7). Larger aerobic

fitness benefit in the ExPR group is most likely related to the larger volume of aerobic training or the higher adherence. Furthermore, despite the increased energy expenditure due to the exercise sessions, patients in the ExPR group effectively maintained their BMI during NCRT. Results on most HRQoL domains were heterogeneous and inconsistent over time. However, our results highlight that resistance exercise, for example through an improved daily functioning, may enhance role functioning and reduce pain, while the improvements in mental health in the ExPR group underscore the potential psychological benefit of aerobic exercise (53).

Shortly before surgery, when all groups had received the multimodal prehabilitation program in the waiting period, both exercise interventions showed a favourable effect on aerobic fitness compared with the control group, demonstrating an elevated starting level of traditional prehabilitation. This may further reduce postoperative complications and enhance surgical recovery (1, 5). The superiority in aerobic fitness found in the ExPR group compared to the AE+RE group directly post NCRT diluted during the waiting period, most likely because the AE+RE group could continue exercising under the supervision of the same physical therapist, facilitating a smooth transition. In contrast, patients from the ExPR group had to transfer from in-hospital exercise to exercising at a local physical therapy practice. Hence, as both exercise interventions appear to offer a significant benefit in aerobic fitness, likely determined by adequate exercise adherence, program choices should take into account individual patients' preference and motivation for optimal benefit.

Our results showed that exercise during NCRT has clinical potential in terms of reducing treatment-related toxicity. A reduction in toxicity might lead to a reduced treatment burden and can enhance tolerability (44). Furthermore, our results showed a 15% difference in the proportion of patients having a good tumor response, which is associated with a better survival (46, 54). Supported by previous explorative studies among patient with esophageal and rectal cancer reporting effects of prehabilitation on tumor response (18-20), our findings highlight the need for future sufficiently powered trials using tumor response as primary endpoint, which has been recognized as a clinically relevant surrogate endpoint in trials in the neoadjuvant setting (46, 54). Additionally, the lack of notable differences between the exercise interventions suggests that most gain could be expected from an intervention that patient can adhere to independent of type or timing. However, future studies with larger sample sizes should reveal the potential impact of exercise type and timing. Additionally, mechanistic studies are needed to examine whether the exercise effect on tumor response is mediated by exercise-induced activation, mobilization, and infiltration of NK and T cells, or by a reduced intratumoral hypoxia, as reported in pre-clinical studies in rodents (55).

Strengths of this study are the three-arm randomized controlled exercise trial design allowing for a comparison between different exercise programs and a control group. Although the sample size of this pilot study is insufficient to demonstrate efficacy of the interventions, we were able to present point estimates and measures of variability on clinically relevant

endpoints useful to inform the design of future trials examining effects of exercise on clinical outcome. Hence, our results should be interpreted as hypothesis generating rather than hypothesis-testing. Moreover, we did not evaluate effects on surgical outcomes in this trial, as all patients received pre-surgical prehabilitation post-NCRT as part of the F4S PREHAB trial, that focuses on postoperative outcomes (36). Additionally, the use of a control group receiving pre-surgical prehabilitation may have underestimated the effects compared to a fully non-exercise control group. Lastly, not all patients felt physically able to attend the follow-up meeting within the first two weeks post-NCRT, which may have impacted their fitness levels after a more extended recovery period, however, these patients were evenly distributed across the study arms. In conclusion, our results show clearly that introducing prehabilitation already during the period of NCRT is an effective way to prevent a decline in physiological reserve during NCRT, potentially favouring treatment outcomes.

CONCLUSION

Exercise interventions during NCRT for patients with esophageal cancer are feasible and help to maintain fitness levels, providing a better starting point for pre-surgical prehabilitation. Daily in-hospital aerobic exercise yields excellent adherence and is beneficial for maintaining physical fitness levels. For patients committed to attending exercise sessions at a physical therapist practice, combined aerobic and resistance exercise offers an effective alternative. Both exercise programs showed clinical potential by reducing treatment-related toxicity and potentially enhancing tumor response. In conclusion, extending prehabilitation to the period during NCRT is a valuable addition to the current prehabilitation programs, usually starting during the waiting period prior to surgical resection.

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CHAPTER 4

The effects of a multimodal prehabilitation program on postoperative complications in patients with oesophageal cancer

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ABSTRACT

Introduction: Postoperative complications after oesophagectomy occur in approximately 50% of patients, severely impacting quality of life and survival. Multimodal prehabilitation is a promising strategy to enhance physiological capacity and reduce postoperative complications. Therefore, the primary aim of this study was to evaluate the effects of a multimodal prehabilitation program on postoperative complication rates after minimally invasive oesophagectomy.

Methods: This study compares data from the F4S PREHAB multimodal prehabilitation intervention (n = 148) with a historical control cohort (n = 230) of patients undergoing minimally invasive oesophagectomy. After propensity score matching, differences in postoperative complications and length of hospital stay between groups were evaluated using logistic regression analyses. Furthermore, changes in intervention targets (e.g., physical fitness, body composition, health-related quality of life) and associations thereof with postoperative complications were evaluated using linear and logistic regression models.

Results: In the prehabilitation group, 20% of patients experienced a severe complication versus 30% in the control group (risk difference 10%, 95%CI=0;19%; OR=0.60, 95%CI=0.36;1.00), and 19% of patients experienced a pulmonary complication versus 29% in the control group (risk difference 11%, 95%CI=2;20%; OR=0.55, 95%CI=0.33;0.94) after oesophagectomy. After prehabilitation, the intervention cohort improved in muscle strength ($\beta=24.9$ kg, 95%CI=14.2;35.6), handgrip strength ($\beta=2.1$ kg, 95%CI=0.3;4.0), maximal short-time exercise capacity ($\beta=29.2$ W, 95%CI=16.5;42.0), 5-times sit-to-stand time ($\beta=-1.0$ s, 95%CI=-1.8;-0.2), body mass index ($\beta=1.0$ kg/m², 95%CI=0.0;1.9), and vitality ($\beta=9.9$, 95%CI=4.8;15.0). We found that patients who experienced a decrease in percentage body fat (OR=1.2, 95%CI=1.0;1.4) or an improvement in mental health (OR=0.9, 95%CI=0.9;1.0) were less likely to have severe complications.

Conclusion: Patients in the prehabilitation group were less likely to experience severe complications and pulmonary complications. Prehabilitation improved physiological capacity of patients. Favourable changes after prehabilitation in percentage body fat and mental health may have contributed to a reduction in severe complications.

INTRODUCTION

Oesophageal cancer is the seventh most common cancer worldwide and has a poor prognosis with 5-year survival rates under 50% (1). Curative treatment for oesophageal cancer often includes neoadjuvant treatment with chemoradiotherapy or chemotherapy prior to oncological resection (2). Patients with oesophageal cancer experience physical deterioration due to both disease-related and neoadjuvant treatment-related side effects, such as dysphagia, weight loss, sarcopenia, malnutrition, and a decline in physical fitness and physical function impacting postoperative outcomes (3-7). Novel developments in perioperative care such as Enhanced Recovery After Surgery (ERAS) programs and minimally invasive surgical techniques have improved postoperative outcomes (2, 8). Nevertheless, postoperative complications after oesophagectomy, including anastomotic leakage and pneumonia, occur in approximately 50% of patients, severely reducing health-related quality of life (HRQoL), and survival (9, 10).

Multimodal prehabilitation including physical exercise, nutritional support, psychological support and smoking cessation, is a promising strategy to enhance preoperative physiological capacity and reduce surgical complications in patients undergoing major surgery (11-15). Studies evaluating prehabilitation prior to an oesophagectomy have demonstrated improvements in postoperative functional recovery, a reduction in length of hospital stay (LoS) (16), and a decrease in pulmonary complication rates (17). However, current evidence on the effects of prehabilitation on postoperative complications in patients with oesophageal cancer is limited due to small sample sizes or unimodal prehabilitation programs, and the most important contributing intervention components remain to be determined (11, 17).

Radboud University Medical Center (Radboudumc) has implemented a multimodal prehabilitation program in routine preoperative care as part of a stepped-wedge clinical trial for patients undergoing major surgery, including oesophagectomy for oesophageal cancer. The primary aim of this study was to evaluate the effects of this multimodal prehabilitation program on postoperative outcomes after a minimally invasive oesophagectomy in a large sample of patients with oesophageal cancer compared with a matched historical control cohort. The secondary aim was to evaluate which intervention parameters (e.g., changes in physical fitness, body composition, or health-related quality of life) may explain effects on occurrence of postoperative complications.

METHODS

Participants and study design

This study used data from patients with oesophageal cancer who participated in the F4S PREHAB trial, which is a single centre stepped-wedge trial, designed and powered to investigate the effect of a multimodal prehabilitation program in patients undergoing high-impact surgery

across various surgical specialties (18). The intervention cohort of the present study comprised patients who underwent minimally invasive oesophagectomy between June 2021 and April 2024 in the Radboudumc and participated in a multimodal prehabilitation program as part of the F4S PREHAB trial. In this cohort of patients, multimodal prehabilitation was introduced shortly after the F4S PREHAB trial commenced, resulting in a small control group and a large intervention group within this patient population (18). Therefore, in the current study, the data of the control group of the F4S PREHAB trial was complemented with data from patients who underwent a minimally invasive oesophagectomy between 2017 and 2021 prior to the start of the F4S PREHAB trial. The study protocol of the F4S PREHAB trial was approved by the regional ethical review board (METC Oost-Nederland; NL73777.091.20).

Patients were included in this study if they underwent minimally invasive oesophagectomy, either through a transthoracic approach (TMIE) with intrathoracic or cervical anastomosis, or a transcervical approach with cervical anastomosis (MICE) in the Radboudumc, with or without neoadjuvant treatment. Exclusion criteria included an American Society of Anesthesiologists (ASA) score ≥ 4 , transhiatal oesophagectomy, and absence of available data on surgical outcomes or performance scores. Exclusion criteria for participation in the F4S PREHAB trial included contraindications for high-intensity exercise and protein supplementation, cognitive disabilities or illiteracy (18).

Prehabilitation program

The multimodal prehabilitation program consisted of four modalities including an exercise intervention, a nutritional intervention, psychological support and smoking and alcohol cessation if indicated. The prehabilitation protocol and screening methods were extensively described elsewhere (18). In short, the exercise intervention entailed a minimum of three weeks of supervised exercise at a local physiotherapist three times per week. The exercise sessions were tailored to individual fitness levels and included both high-intensity interval training (HIIT) and resistance exercise. The HIIT consisted of 4 high-intensity intervals of 4 minutes (at 90% of peak workload, as assessed by the Steep Ramp Test), alternated with 4 moderate-intensity intervals of 3 minutes (at 30% of peak workload). The resistance training consisted of 6 exercises including 2 sets of 10 repetitions (at 65–80% of 1 repetition maximum) targeting all major muscle groups. Additionally, patients were instructed to perform low-intensity aerobic exercise for 60 minutes on the days without supervised training. The nutritional intervention included 1–3 counselling sessions by a dietitian aimed to optimise nutritional intake, focusing on daily protein intake (1.5 g/kg bodyweight), energy, and micronutrients. Furthermore, patients received high-quality protein shakes (30 g of whey protein) and vitamin D as daily supplementation. If indicated, psychological support focused on reducing anxiety and improving coping strategies regarding diagnosis and upcoming surgery. Lastly, patients were instructed to refrain from alcohol consumption and patients

who were actively smoking were referred to an external smoking cessation program (SineFuma, Breda, The Netherlands) (18).

Patients in the control group of the F4S PREHAB trial and the retrospective historical cohort received usual preoperative care according to Dutch guidelines, not including multimodal prehabilitation.

Primary outcomes

The primary outcomes included the total number of patients with a complication and the number of severe complications, represented by a Clavien-Dindo (CD) grade of 3a or higher (19). Complications were categorised into pulmonary complications and anastomotic leakage (20). In addition, the comprehensive complication index (CCI) was calculated by the sum of all complications weighted for severity, ranging from 0 'no complications' to 100 'death' (21). Other clinical outcomes included length of hospital stay (using a cutoff of > 8 days based on the standard postoperative protocol) and readmission at intensive or medium care unit (ICU/MCU). The number of days at the ICU or MCU could not be evaluated due to changes in the standard of care from 2 days to 1 day. Data on surgical outcomes were derived from the Dutch Upper Gastrointestinal Cancer Audit (DUCA) registration, containing data until 30 days post-surgery (22). Missing or incomplete data in the DUCA registry was complemented with data from electronic patient records.

Demographic data such as age, sex, and smoking status were collected from the DUCA registry and electronic patient records. Clinical data such as Karnofsky performance score, treatment type, tumour histology, tumour stage according to the TNM classification, tumour location, ASA score and type of surgery were collected from the DUCA registry. Missing or incomplete data in the DUCA registry was complemented with data from electronic patient records.

Secondary outcomes

In the intervention cohort, measurements were performed after neoadjuvant treatment and prior to surgery, both before and after the prehabilitation program. Body height and weight were measured and body mass index (BMI; kg/m²) was calculated. Furthermore, fat free mass (kg) and percentage body fat (%) were calculated using bioelectrical impedance analyses (Bodystat 1500). Aerobic fitness was evaluated using the estimated VO₂max and maximal short-time exercise capacity (MSEC) based on the steep ramp test performed on a cycle ergometer (Lode, Groningen, the Netherlands) (23). Leg muscle strength was evaluated using an indirect 1 repetition maximum (1RM) protocol on a leg-press machine (24). Handgrip strength of the dominant hand was evaluated using a hydraulic handgrip dynamometer (Jamar, Sammons Preston, Bolingbrook, USA). The 5-times sit-to-stand time was assessed by asking patients to stand up from a chair for 5 consecutive times as fast as possible (25). We assessed physical functioning, mental health and vitality using the Rand-36 questionnaire

(version 1), which contains 36 questions divided in eight subscales, with raw scores linearly converted to a 0–100 scale, and higher scores representing better functioning or well-being (26).

Attendance to the exercise intervention was evaluated by the number of attended exercise sessions. To evaluate adherence to the nutritional intervention it was registered whether patients used protein and vitamin supplementation or not. For the psychological and smoking and alcohol cessation intervention, it was evaluated whether or not a patient was referred to a psychologist or the smoking cessation program.

Statistical analyses

Statistical analysis was performed according to the intention-to-treat principle and analyses were performed using R Studio (R Core Team). Propensity score matching (PSM) was performed to match patients in the intervention cohort with patients in the control cohort to minimise confounding bias. Propensity scores were calculated using multivariable logistic regression including the following confounders: age, sex, BMI, smoking status (never, current, former), ASA score (1/ 2 versus 3), tumour histology (adenocarcinoma versus squamous carcinoma/ other types), tumour location (distal oesophagus/oesophagogastric junction versus proximal/ middle oesophagus), neoadjuvant treatment (chemoradiotherapy versus chemotherapy versus no treatment), clinical T-stage (cT1-2 versus cT3-4/x), clinical N-stage (cN0-1/x versus cN2-3) and Karnofsky performance status (100 versus <100). Cases were matched at a 2:1 ratio using nearest neighbour matching with a calliper of 0.2. Standardised mean differences (SMD) were calculated to assess covariate balance between groups before and after PSM. A SMD < 0.1 was considered sufficient balance between groups.

Differences in postoperative complications were assessed using risk differences, and univariable logistic and linear regression analyses for binary outcomes and continuous outcomes, respectively. Since the introduction of the new MICE technique might impact post-operative complications (27), sensitivity analyses were performed by excluding patients who underwent a MICE procedure from the dataset after PSM. After removal of MICE procedures, PSM was conducted again to ensure adequate matching in this dataset.

To examine whether the intervention cohort improved in physical fitness, body composition, or health-related quality of life, we compared post-intervention values with pre-intervention values of this cohort using linear regression analyses corrected for age, sex, Karnofsky performance status, smoking status, ASA score, type of neoadjuvant treatment and type of surgical procedure. Subsequently, we performed logistic regression analyses to examine whether changes in physical fitness, body composition and HRQoL were associated with surgical outcomes, using the measurement post-intervention (T1) as independent variable adjusted for the baseline value (T0) and previously-mentioned covariables in the models. Missing values were imputed by multiple imputation based on the missing at random assumption using the R package MICE generating 20 datasets with imputed values for the

physical fitness tests and 45 datasets for the questionnaires, based on the proportion of missing values. Risk differences, regression coefficients or odds ratios and corresponding 95%CI were reported, and statistical significance was set at $p \leq 0.05$. Additionally, known minimally clinically important differences (MCID) were considered for each subscale of HRQoL (28, 29).

RESULTS

A total of 433 patients underwent a minimally invasive oesophagectomy in the Radboudumc. 184 patients were eligible for the F4S PREHAB trial, of which 13 patients were not included because the time to oesophagectomy was shorter than 3 weeks, and 22 patients were allocated to the control group (Figure 1). The historical control cohort included 249 patients who underwent an oesophagectomy between 2017 and the start of the F4S PREHAB trial. After exclusions of patients with an ASA score ≥ 4 ($n = 2$) or missing Karnofsky scores ($n = 40$), the final intervention cohort comprised 148 patients and the control cohort included 230 patients (Figure 1). Following PSM, 134 patients who participated in the F4S PREHAB trial were matched to 205 patients in the control cohort (Figure 1). After removal of MICE procedures for sensitivity analyses, the intervention cohort comprised 80 patients and the historical control cohort 144 patients.

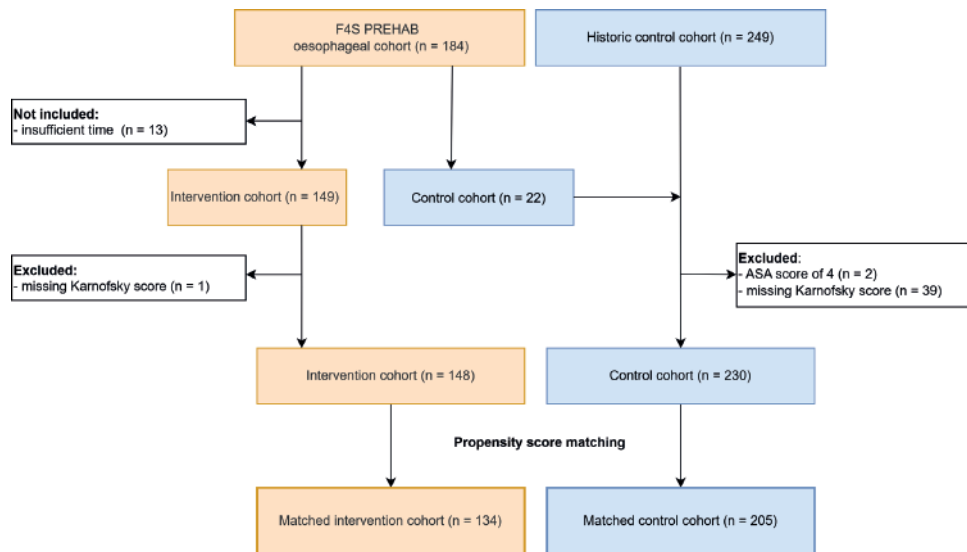


Figure 1. Flowchart of patient inclusion and group allocation before and after propensity score matching.

Baseline descriptives

In the total cohort of patients in this study, patients were on average 66 ± 9 years old, 74% of the patients were men and average BMI was 26.1 ± 4.5 kg/m². MICE procedures were performed in 72 (19%) patients (Table 1). After PSM a good balance in matching variables was achieved between the intervention and control cohort (Table 1). Additional demographical and clinical details before and after PSM and after exclusion of MICE procedures can be found in Supplementary Table 1.

Table 1. Clinical characteristics before and after propensity score matching

	Before matching			After matching		
	F4S PREHAB (n = 148)	Historical control (n = 230)	SMD	F4S PREHAB (n = 134)	Historical control (n = 205)	SMD
Gender, n(%)						
Male	113 (76)	166 (72)	0.10	100 (75)	155 (76)	-0.04
Female	35 (24)	64 (28)		34 (25)	50 (24)	
Age, years, mean ± sd	66 ± 8	65 ± 9	0.13	66 ± 8	65 ± 8	-0.04
BMI, kg/m², mean ± sd	25.7 ± 4.6	26.4 ± 4.5	-0.15	25.9 ± 4.6	26.1 ± 4.1	-0.01
Smoking status, n(%)						
Never	32 (22)	57 (25)	-0.08	31 (23)	47 (23)	0.04
Current smoker	23 (16)	51 (22)	-0.18	21 (16)	42 (20)	-0.03
Former smoker	93 (63)	122 (53)	0.20	82 (61)	116 (57)	-0.01
Karnofsky performance score, n(%)						
70 / 80 / 90	66 (45)	124 (54)	0.19	63 (47)	104 (51)	0.05
100	82 (55)	106 (46)		71 (53)	101 (49)	
ASA score, n(%)						
1 / 2	98 (66)	148 (64)	0.04	89 (66)	136 (66)	-0.01
3	50 (34)	82 (36)		45 (34)	69 (34)	
Tumour location, n(%)						
Distal / Oesophagegastric junction	128 (86)	214 (93)	-0.19	119 (89)	189 (92)	-0.07
Middle / Proximal	20 (14)	16 (7)		15 (11)	16 (8)	
cT classification, n(%)						
1 / 2	36 (24)	37 (16)	0.19	27 (20)	36 (18)	-0.01
3 / 4 / X	112 (76)	193 (84)		107 (80)	169 (82)	
cN classification, n(%)						
0 / 1 / X	101 (68)	181 (79)	-0.22	92 (69)	157 (77)	-0.06
2 / 3	47 (32)	49 (21)		42 (31)	48 (23)	
Neoadjuvant treatment, n(%)						
Chemoradiotherapy	124 (84)	196 (85)	-0.04	114 (85)	175 (85)	0.02
Chemotherapy	19 (13)	24 (10)	0.07	17 (13)	24 (12)	-0.01
No neoadjuvant treatment	5 (3)	10 (4)	-0.05	3 (2)	6 (3)	-0.02
Histology, n(%)						
Adenocarcinoma	115 (78)	189 (82)	-0.11	107 (80)	170 (83)	-0.06
Squamous cell carcinoma / Other	33 (22)	41 (18)		27 (20)	35 (17)	
Type of oesophagectomy, n(%)*						
MICE	66 (45)	6 (3)		60 (45)	6 (3)	
TMIE	82 (55)	224 (97)		74 (55)	199 (97)	

Abbreviations: BMI; body mass index, ASA; American Society of Anesthesiologists, MICE; minimally invasive transcervical oesophagectomy, TMIE; transthoracic minimally invasive oesophagectomy, SMD; standardised mean difference.

*Type of oesophagectomy is not included in the propensity score matching.

Primary outcomes

Postoperative outcomes before and after PSM and after exclusion of MICE procedures can be found in Supplementary Table 2. In the prehabilitation group, 51% of patients experienced a complication versus 59% in the historical control group (risk difference 8%, 95%CI=-2;19%; OR=0.72, 95%CI=0.46;1.11 Figure 2). In the prehabilitation group, 20% of patients experienced a severe complication versus 30% in the control group (risk difference 10%, 95%CI=0;19%; OR=0.60, 95%CI=0.36;1.00; Figure 2); 19% of patients experienced a pulmonary complication versus 29% in the control group (risk difference 11%, 95%CI=2;20%; OR=0.55, 95%CI=0.33;0.94; Figure 2); and 5% had an anastomotic leakage, compared to 12% in the control group (risk difference 6%, 95%CI = 0 – 12%; OR=0.42, 95%CI=0.17;0.99; Figure 2). There were no differences in comprehensive complication index, LoS and ICU/MCU readmission. Results from the sensitivity analyses were comparable with the intention-to-treat analysis for severe complications (OR=0.39, 95%CI=0.20;0.76), pulmonary complications (OR=0.41, 95%CI=0.21;0.81) and anastomotic leakage (OR=0.20, 95%CI=0.06;0.71), and demonstrated a lower total number of patients with postoperative complications (OR=0.48, 95%CI=0.28;0.84) and an improved comprehensive complication index ($\beta = -8.92$, 95%CI=-14.67;-3.17) in the prehabilitation group compared with the control group (Figure 2).

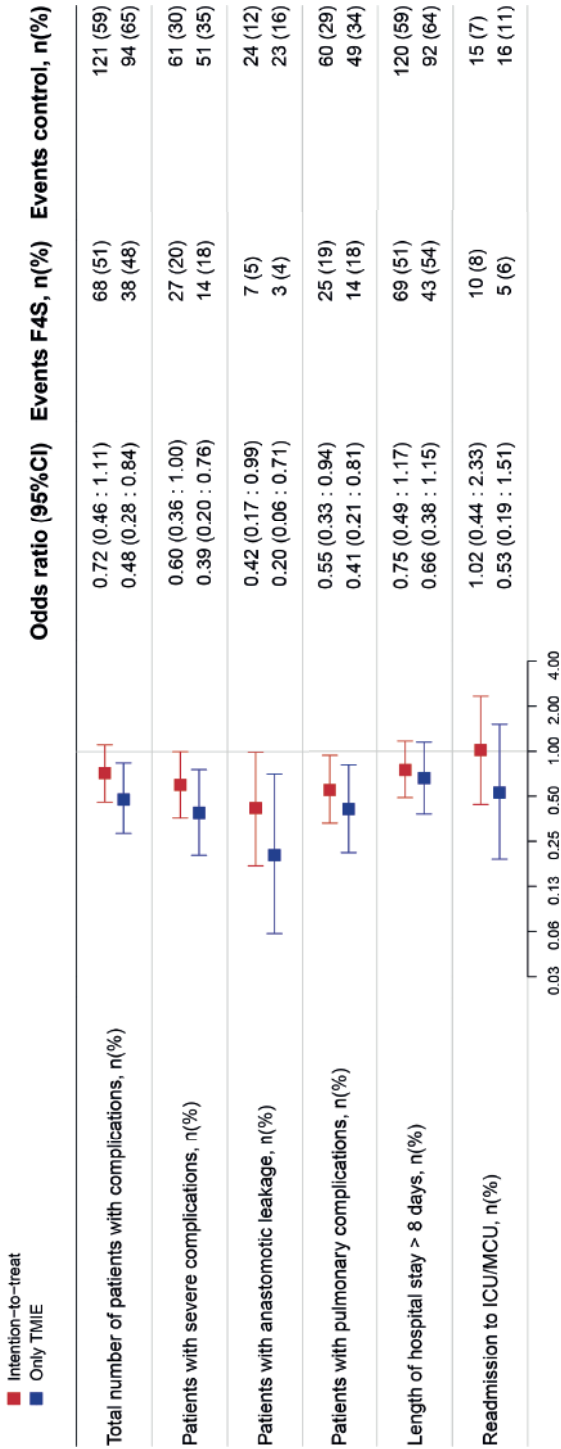


Figure 2. Forest plot for the association of multimodal prehabilitation and postoperative outcomes assessed for the intention-to-treat (red) and sensitivity analysis without minimally invasive transverse oesophagectomy (MICE) procedures (blue). Odds ratio and regression coefficient presented for the multimodal prehabilitation group versus usual care.

Abbreviations: TMIE; transthoracic minimally invasive oesophagectomy, ICU; intensive care unit, MCU; medium care unit, F4S; fit4surgery prehabilitation program.

Secondary outcomes

In total, 135 of 149 patients from the PREHAB cohort participated in any of the prehabilitation modalities. On average patients attended 9 ± 5 exercise sessions at the physiotherapy practice, 106 (71%) patients used protein and vitamin supplementation during the intervention period, 15 (10%) patients had one or more sessions with a medical psychologist, and 9 (6%) patients joined the smoking cessation program.

The proportion missing values at pre-operative follow-up ranged between 10-18% in physical tests and 24-45% in the questionnaires. We found significant improvements from pre to post intervention in leg muscle strength ($\beta=24.9$ kg, 95%CI=14.2;35.6), handgrip strength ($\beta=2.1$ kg, 95%CI=0.3;4.0), MSEC ($\beta=29.2$ W, 95%CI=16.5;42.0) and the 5-times sit-to-stand test ($\beta = -1.0$ s, 95%CI=-1.8;-0.2, Table 2). Furthermore, we found an increased BMI and ($\beta = 1.0$ kg/m², 95%CI = 0.0 ; 1.9) and vitality ($\beta=9.9$, 95%CI=4.8;15.0, Table 2). After imputation, BMI did not show a significant increase ($\beta=0.9$, 95%CI=-0.0;1.8), while physical function did increase ($\beta=7.8$, 95%CI=1.8;13.8)(Supplementary Table 3).

Patients who reduced in percentage body fat (OR=1.2, 95%CI=1.0;1.4) and improved in mental health (OR=0.9, 95%CI=0.9;1.0) were less likely to experience severe complications (Table 2). There were no significant associations between individual intervention parameters and the number of patients with pulmonary complications (Table 2).

Table 2. Intervention data of 135 patients in the intervention cohort.

	Changes in intervention components			Associations with surgical complications	
	T0	T1	Within group change*	Severe complications	Pulmonary complications
			β (95% CI)	OR (95% CI)	OR (95% CI)
Body composition					
BMI (kg/m ²)	25.9 \pm 3.9	26.8 \pm 4.0	1.0 (0.0 ; 1.9)	1.1 (0.6 ; 2.2)	0.9 (0.4 ; 1.8)
Fat free mass (kg)	57.0 \pm 9.8	58.7 \pm 10.1	1.6 (-0.1 ; 3.3)	0.9 (0.7 ; 1.0)	0.9 (0.7 ; 1.0)
Percentage body fat (%)	28.2 \pm 7.8	29.1 \pm 7.4	1.1 (-0.5 ; 2.7)	1.2 (1.0 ; 1.4)	1.2 (1.0 ; 1.4)
Physical fitness					
1RM leg muscle strength (kg)	111.3 \pm 47.8	136.8 \pm 52.9	24.9 (14.2 ; 35.6)	1.0 (1.0 ; 1.0)	1.0 (1.0 ; 1.0)
Handgrip strength (kg)	38.6 \pm 9.9	40.9 \pm 9.7	2.1 (0.3 ; 4.0)	1.1 (1.0 ; 1.3)	1.1 (1.0 ; 1.3)
Estimated VO ₂ max (ml/kg/min)	23.0 \pm 4.3	23.7 \pm 4.2	0.7 (-0.2 ; 1.5)	1.0 (0.7 ; 1.4)	1.0 (0.7 ; 1.5)
MSEC (W)	208.3 \pm 63.1	237.9 \pm 69.9	29.2 (16.5 ; 42.0)	1.0 (1.0 ; 1.0)	1.0 (1.0 ; 1.0)
5STS (s)	9.5 \pm 4.1	8.5 \pm 2.4	-1.0 (-1.8 ; -0.2)	0.9 (0.6 ; 1.2)	0.9 (0.7 ; 1.3)
Health-related quality of life					
Physical functioning score	77.0 \pm 19.7	82.8 \pm 22.6	5.5 (-1.2 ; 12.1)	1.0 (1.0 ; 1.0)	1.0 (0.9 ; 1.0)
Mental health index	75.8 \pm 16.0	77.7 \pm 17.8	1.9 (-2.5 ; 6.3)	0.9 (0.9 ; 1.0)	1.0 (0.9 ; 1.0)
Vitality	58.5 \pm 17.9	68.4 \pm 20.1	9.9 (4.8 ; 15.0)	1.0 (1.0 ; 1.0)	1.0 (1.0 ; 1.0)

*Models are adjusted age, sex, smoking status, ASA score, Karnofsky performance status, tumour location, clinical T-stage, neoadjuvant treatment, and surgical technique. Models on associations with severe complications and pulmonary complications are additionally adjusted for baseline values of each intervention parameter.

Abbreviations: BMI; body mass index, 1RM; 1 repetition maximum, VO₂max; maximal oxygen uptake, MSEC; maximal short-time exercise capacity; 5STS; 5-times sit-to-stand test, OR; odds ratio, CI; confidence interval.

Bold values represent statistical significance.

DISCUSSION

This study evaluated the impact of a multimodal prehabilitation program on surgical outcomes in patients with oesophageal cancer compared to a propensity score matched control cohort. The primary finding of this study is that the number of patients experiencing severe complications and pulmonary complications was 10% lower after prehabilitation compared to the control group. Second, the multimodal prehabilitation program significantly improved leg muscle strength, handgrip strength, maximal short-time exercise capacity, 5-times sit-to-stand time, BMI, and vitality scores. Additionally, patients with a decrease in percentage body fat or an improvement in mental health were less likely to experience severe complications.

Our finding that less patients in the prehabilitation group experienced severe complications strengthens the non-significant yet potentially clinically relevant results from previous smaller RCTs, which reported reductions in postoperative complications following prehabilitation prior to oesophagectomy (16, 30). Furthermore, the 10% difference in severe complications results aligns with outcomes from larger prehabilitation trials in patients with colorectal and lung cancer (14, 15). Moreover, the observed 11% difference in pulmonary complications following prehabilitation further supports results from a meta-analysis on prehabilitation in oesophageal cancer (17). Although we found a decrease in anastomotic leakage in the prehabilitation group, these results have to be interpreted with caution due to the low number of events. Furthermore, sensitivity analyses presented even stronger effects of the prehabilitation program on postoperative complications in a homogeneous group of patients undergoing a TMIE. Thus, our findings highlight the significant clinical impact of multimodal prehabilitation in reducing postoperative morbidity.

Our results showed a significant increase in physical fitness parameters, BMI and vitality after the prehabilitation, including improvements of > 10% in muscle strength, MSEC, 5-STS time, and a clinically relevant increase in vitality, suggesting an enhanced physiological capacity and HRQoL. These results are comparable to previous prehabilitation trials (14). We did not find any associations between the intervention-related change in body composition, physical fitness, and health-related quality of life and postoperative outcomes. Therefore, our results indicate that the prehabilitation-induced reduction in postoperative complications can probably not be attributed to a single intervention-related component but, as proposed by Janssen et al. (16) might rather be a combination of marginal gains. However, our results demonstrated that patients with a decrease in percentage body fat or an improvement in mental health after prehabilitation were less likely to experience severe complications. Potential mechanisms underlying these associations might be an increased inflammation or immune suppression due to higher body fat and poor mental health, contributing to worse postoperative outcomes (31, 32).

A strength of this study is the large sample size with a large intervention cohort of patients with oesophageal cancer. Furthermore, the large historical control cohort allowed for 2:1 propensity score matching. Although a priori differences between the intervention and control cohort were minimised by PSM, residual confounding might have influenced our results. The introduction of the MICE procedure early 2021 coincided with the start of the F4S prehab trial and interferes with the data on postoperative complications, due to a learning curve and learning-associated morbidity (27). We addressed this issue by performing a sensitivity analysis restricted to TMIE procedures, and observed even stronger results. Nevertheless, given the non-randomised nature of this study, it is important to keep in mind the potential impact of small longitudinal improvements in perioperative care on outcomes.

The results in our study have important clinical potential to reduce postoperative complications and morbidity. However, our results warrant further confirmation through large randomised controlled trials, such as the PRESET_RCT (ClinicalTrials.gov: NCT03490565). Additionally, future studies should aim to explore the underlying physiological and psychological mechanisms that contribute to the reduction of severe complications and pulmonary complications after oesophagectomy, whereafter prehabilitation interventions can be targeted and optimised to include the most effective intervention components (33).

CONCLUSION

The results of this study demonstrated that patients with oesophageal cancer who participated in a multimodal prehabilitation program were less likely to experience severe complications and pulmonary complications. The multimodal prehabilitation program enhanced physiological capacity by increasing muscle strength and function, body composition, and vitality. Additionally, patients who decreased in percentage body fat and improved in mental health were less likely to experience severe complications. These results highlight the important clinical implications of multimodal prehabilitation by reducing postoperative complications and morbidity.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Demographic and clinical characteristics before and after propensity score matching, and without MICE procedures.

	Before matching		After matching		Without MICE	
	F4S PREHAB (n = 148)	Historical control (n = 230)	F4S PREHAB (n = 134)	Historical control (n = 205)	F4S PREHAB (n = 80)	Historical control (n = 144)
Gender, n(%)						
Male	113 (76)	166 (72)	100 (75)	155 (76)	64 (80)	116 (81)
Female	35 (24)	64 (28)	34 (25)	50 (24)	16 (20)	28 (19)
Age, years, mean ± sd	66 ± 8	65 ± 9	66 ± 8	65 ± 8	66 ± 8	66 ± 8
BMI, kg/m², mean ± sd	25.7 ± 4.6	26.4 ± 4.5	25.9 ± 4.6	26.1 ± 4.1	26.3 ± 5.0	26.2 ± 4.2
Underweight (< 18.5)	3 (2)	4 (2)	2 (1)	2 (1)	1 (1)	2 (1)
Healthy weight (18.5 – 25.0)	61 (41)	91 (40)	54 (40)	81 (40)	30 (38)	58 (40)
Overweight (25.0 – 29.9)	65 (44)	87 (38)	60 (45)	85 (41)	37 (46)	57 (40)
Obesity (> 29.9)	19 (13)	48 (21)	18 (13)	37 (18)	12 (15)	27 (19)
Smoking status, n(%)						
Never	32 (22)	57 (25)	31 (23)	47 (23)	16 (20)	32 (22)
Current smoker	23 (16)	51 (22)	21 (16)	42 (20)	16 (20)	32 (22)
Former smoker	93 (63)	122 (53)	82 (61)	116 (57)	48 (60)	80 (56)
Karnofsky performance score, n(%)						
70	0 (0)	4 (2)	0 (0)	4 (2)	0 (0)	4 (3)
80	6 (4)	15 (7)	6 (4)	10 (5)	5 (6)	8 (6)
90	60 (41)	105 (46)	57 (43)	90 (44)	34 (42)	64 (44)
100	82 (55)	106 (46)	71 (53)	101 (49)	41 (51)	68 (47)
ASA score, n(%)						
1	4 (3)	16 (7)	3 (2)	16 (8)	2 (2)	11 (8)
2	94 (64)	132 (57)	86 (64)	120 (59)	49 (61)	82 (57)
3	50 (34)	82 (36)	45 (34)	69 (34)	29 (36)	51 (35)
Tumour location, n(%)						
Proximal Thoracic	1 (1)	1 (0)	0 (0)	1 (0)	1 (1)	0 (0)
Middle thoracic	19 (13)	15 (7)	15 (11)	15 (7)	4 (5)	8 (6)
Distal thoracic	108 (73)	188 (82)	101 (75)	163 (80)	60 (75)	117 (81)
Oesophagastric junction	20 (14)	26 (11)	18 (13)	26 (13)	15 (19)	19 (13)
cT classification, n(%)						
1	7 (5)	2 (1)	3 (2)	2 (1)	3 (4)	2 (1)
2	29 (20)	35 (15)	24 (18)	34 (17)	15 (19)	30 (21)
3	108 (73)	187 (81)	103 (77)	166 (81)	59 (74)	110 (76)
4	4 (3)	2 (1)	4 (3)	2 (1)	3 (4)	1 (1)
X	0 (0)	4 (2)	0 (0)	1 (0)	0 (0)	1 (1)
cN classification, n(%)						
0	50 (34)	78 (34)	42 (31)	68 (33)	29 (36)	49 (34)
1	50 (34)	99 (43)	49 (37)	87 (42)	29 (36)	57 (40)
2	40 (27)	47 (20)	35 (26)	46 (22)	20 (25)	36 (25)
3	7 (5)	2 (1)	7 (5)	2 (1)	2 (2)	2 (1)
X	1 (1)	4 (2)	1 (1)	2 (1)	0 (0)	0 (0)

	Before matching		After matching		Without MICE	
	F4S PREHAB (n = 148)	Historical control (n = 230)	F4S PREHAB (n = 134)	Historical control (n = 205)	F4S PREHAB (n = 80)	Historical control (n = 144)
Neoadjuvant treatment, n(%)						
Chemoradiotherapy	124 (84)	196 (85)	114 (85)	175 (85)	60 (75)	117 (81)
Chemotherapy	19 (13)	24 (10)	17 (13)	24 (12)	17 (21)	22 (15)
No neoadjuvant treatment	5 (3)	10 (4)	3 (2)	6 (3)	3 (4)	5 (3)
Histology, n(%)						
Adenocarcinoma	115 (78)	189 (82)	107 (80)	170 (83)	65 (81)	118 (82)
Squamous cell carcinoma	22 (15)	31 (13)	18 (13)	27 (13)	9 (11)	18 (12)
Other	6 (4)	7 (3)	6 (4)	5 (2)	4 (5)	5 (3)
Unknown	5 (3)	3 (1)	3 (2)	3 (1)	2 (2)	3 (2)
Type of oesophagectomy, n(%)						
MICE	66 (45)	6 (3)	60 (45)	6 (3)	0 (0)	0 (0)
TMIE	82 (55)	224 (97)	74 (55)	199 (97)	80 (100)	144 (100)

Abbreviations: BMI; body mass index, ASA; American Society of Anesthesiologists, IQR; interquartile range, MICE; minimally invasive transcervical oesophagectomy, TMIE; transthoracic minimally invasive oesophagectomy.

Supplementary Table 2. Postoperative outcomes before and after propensity score matching, and without MICE procedures.

	Before matching		After matching		Without MICE	
	F4S PREHAB (n = 148)	Historical control (n = 230)	F4S PREHAB (n = 134)	Historical control (n = 205)	F4S PREHAB (n = 80)	Historical control (n = 144)
Total number of patients with complications, n(%)	78 (53)	137 (60)	68 (51)	121 (59)	38 (48)	94 (65)
CD 1	25 (17)	30 (13)	24 (18)	28 (14)	5 (6)	21 (15)
CD 2	58 (39)	104 (45)	50 (37)	89 (43)	31 (39)	74 (51)
CD 3a	16 (11)	46 (20)	14 (10)	41 (20)	8 (10)	32 (22)
CD 3b	10 (7)	25 (11)	7 (5)	21 (10)	2 (3)	20 (14)
CD 4a	6 (4)	13 (6)	6 (5)	10 (5)	3 (4)	10 (7)
CD 4b	0 (0)	3 (1)	0 (0)	2 (1)	0 (0)	2 (1)
CD 5	3 (2)	1 (0)	3 (2)	0 (0)	1 (1)	0 (0)
Patients with severe complications, n(%)	31 (21)	70 (30)	27 (20)	61 (30)	14 (18)	51 (35)
Patients with pulmonary complications, n(%)	28 (19)	70 (30)	25 (19)	60 (29)	14 (18)	49 (34)
Patients with anastomotic leakage, n(%)	8 (5)	28 (12)	7 (5)	24 (12)	3 (4)	23 (16)
Length of hospital stay, median [IQR]	9 [7 - 11]	9 [8 - 14]	9 [7 - 11]	9 [8 - 13]	9 [8 - 11]	10 [8 - 14]
Readmission to ICU/MCU, n(%)	11 (7)	19 (8)	10 (8)	15 (7)	5 (6)	16 (11)

Abbreviations: CD; Clavien Dindo, ICU; intensive care unit, MCU; medium care unit, IQR; interquartile range, MICE; minimally invasive transcervical oesophagectomy.

Supplementary Table 3. Imputed intervention data of 135 patients in the intervention cohort.

	Changes in intervention components			Associations with surgical complications	
	T0	T1	Within group change*	Severe complications*	Pulmonary complications*
			β (95% CI)	OR (95% CI)	OR (95% CI)
Body composition					
BMI (kg/m ²)	25.9 ± 3.9	26.8 ± 4.0	0.9 (-0.0 ; 1.8)	1.1 (0.6 ; 2.1)	0.9 (0.5 ; 1.9)
Fat free mass (kg)	57.1 ± 9.7	58.5 ± 9.8	1.3 (-0.4 ; 3.0)	0.9 (0.8 ; 1.0)	0.9 (0.8 ; 1.1)
Fat percentage (%)	28.2 ± 7.9	28.9 ± 7.0	0.8 (-0.9 ; 2.4)	1.1 (1.0 ; 1.2)	1.1 (0.9 ; 1.2)
Physical fitness					
1RM leg muscle strength (kg)	110.2 ± 47.4	132.8 ± 51.8	22.6 (11.5 ; 33.7)	1.0 (1.0 ; 1.0)	1.0 (1.0 ; 1.0)
Handgrip strength (kg)	38.7 ± 9.9	40.7 ± 9.4	2.0 (0.3 ; 3.7)	1.1 (1.0 ; 1.2)	1.1 (1.0 ; 1.2)
Estimated VO ₂ max (ml/kg/min)	23.0 ± 4.3	23.7 ± 3.9	0.7 (-0.1 ; 1.6)	0.9 (0.7 ; 1.2)	1.0 (0.8 ; 1.4)
MSEC (W)	207.3 ± 63.3	234.7 ± 66.8	27.4 (14.7 ; 40.0)	1.0 (1.0 ; 1.0)	1.0 (1.0 ; 1.0)
5STS (s)	9.5 ± 4.1	8.5 ± 2.4	-1.0 (-1.8 ; -0.2)	0.9 (0.7 ; 1.2)	1.0 (0.7 ; 1.3)
Health related quality of life					
Physical functioning score	76.4 ± 17.9	84.3 ± 18.7	7.8 (1.8 ; 13.8)	1.0 (1.0 ; 1.0)	1.0 (1.0 ; 1.0)
Mental health index	76.6 ± 15.1	77.9 ± 16.7	1.3 (-2.8 ; 5.5)	1.0 (0.9 ; 1.0)	1.0 (0.9 ; 1.0)
Vitality	59.0 ± 17.0	69.2 ± 18.2	10.2 (5.5 ; 15.0)	1.0 (1.0 ; 1.0)	1.0 (1.0 ; 1.0)

*Models are adjusted age, sex, smoking status, ASA score, Karnofsky performance status, tumour location, clinical T-stage, neoadjuvant treatment, and surgical technique. Models on associations with severe complications and pulmonary complications are additionally adjusted for baseline values of each intervention parameter. Abbreviations: BMI; body mass index, 1RM; 1 repetition maximum, VO₂max; maximal oxygen uptake, MSEC; maximal short-time exercise capacity; 5STS; 5-times sit-to-stand test, OR; odds ratio, CI; confidence interval. Bold values represent statistical significance.



CHAPTER 5

Potential mechanisms underlying the effect of walking exercise on cancer-related fatigue in cancer survivors

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ABSTRACT

Introduction: Cancer-related fatigue (CRF) is a common and debilitating long-term side effect of cancer and its treatment. While exercise has been shown to effectively reduce CRF, the underlying mechanisms are not fully clear. Therefore, the aim of this study was to explore the effects of a 4-month walking exercise program on fatigue severity and to explore potential underlying physiological, behavioral and psychological mechanisms of action.

Methods: We included 27 cancer survivors (59 ± 15 years, 37% female) with variable cancer diagnoses who were at least moderately fatigued and finished treatment between 6-36 months ago. This study with a quasi-experimental interrupted time-series design compared a 4-month walking intervention period with a 4-month control period. Measurements of fatigue and physiological, behavioral, and psychological factors were performed, supplemented with participants' perceptions on how exercise influenced their fatigue.

Results: A significant and clinically relevant decrease in fatigue severity was found over time ($\beta = -8.1$, 95%CI = -12.1; -4.2), but could not be attributed directly to the walking exercise intervention. Increases in muscle strength ($\beta = -0.07$, 95%CI = -0.12; -0.02), physical activity ($\beta = -0.1$, 95%CI = -0.2; -0.04) and sleep quality ($\beta = 1.1$, 95%CI = 0.3; 1.9), as well as decreases in muscle relaxation times ($\beta = 0.09$, 95%CI = 0.02; 0.16) and psychological distress ($\beta = 1.1$, 95%CI = 0.8; 1.3) were associated with reductions in fatigue severity. Resilience and physical well-being were perceived as most important constructs explaining the walking exercise effects on fatigue.

Conclusion: Our findings reveal potential physiological, behavioral and psychological mechanisms underlying the multidimensional effects of exercise on fatigue severity.

INTRODUCTION

Cancer-related fatigue (CRF) is one of the most prevalent side effects of cancer and its different treatment modalities (1). It is defined as a distressing, persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activities and interferes with usual functioning (2). Fatigue mostly occurs during active cancer treatment, however, one out of four cancer survivors report CRF after completion of treatment, severely impacting quality of life (QoL) (3, 4).

The pathogenesis of CRF is multifactorial and poorly understood. Risk factors such as type of cancer, treatment regimens and patient characteristics can contribute to CRF (3, 5). As such, behavioral and psychological factors including physical (in)activity, sleep quality, anxiety, and depression have been associated to CRF (6). Additionally, proposed pathophysiological mechanisms contributing to CRF include inflammation, reduced aerobic fitness, reduced muscle strength, circadian rhythm disruption, altered heart rate variability, and impaired neuromuscular function (7, 8).

Peripheral muscular fatigue may be an important neuromuscular mechanism related to CRF (7, 8). It is defined as the loss of voluntary force-producing capacity during exercise, and can be determined using electrical stimulations (9). However, muscle fatigue can also be of central origin caused by failure of neural drive from the central nervous system (CNS) leading to a loss in voluntary muscle force production (8, 9). Investigating muscle contractile properties could provide a better understanding of muscular changes in patients with CRF, thereby gaining insight in potential pathophysiological mechanisms contributing to CRF. At present, the contribution of various physiological, behavioral and psychological factors to CRF remain to be elucidated (7).

Exercise has been identified and recommended as an effective non-pharmacological treatment of CRF (6, 10). Meta-analyses indicate a small-to-moderate effect from exercise interventions on CRF with a large heterogeneity in response (11). A more thorough understanding of this heterogeneity can be achieved by identifying the underlying mechanisms of exercise effects on CRF. This knowledge will help to further personalize interventions to improve their effects.

Exercise can affect CRF via physiological, behavioral and psychological pathways. Physiological pathways include improved aerobic fitness, motor neuron firing rate, maximal voluntary muscle activation, and released anti-inflammatory cytokines (12-14). Behavioral pathways include a higher physical activity level and improved sleep quality (11, 15). Psychological pathways include reduced symptoms of anxiety and depression (16). Despite the positive effects of exercise on CRF, fatigue has also been identified as a barrier to exercise (17). Walking exercise is a moderate-intensity exercise type with limited health risks, and has been indicated by cancer survivors as their preferred exercise type (18), reducing the barrier to exercise.

Therefore, we launched the WALKING Exercise Training to reduce fatigue In Cancer Survivors (KINETICS) trial to examine which physiological, behavioral and psychological pathways can explain the effects of a 4-month walking exercise program on self-reported CRF (Figure 1). To allow for a comprehensive assessment of all potential pathways, we also captured cancer survivors' perceptions of how a walking exercise intervention influenced their CRF.

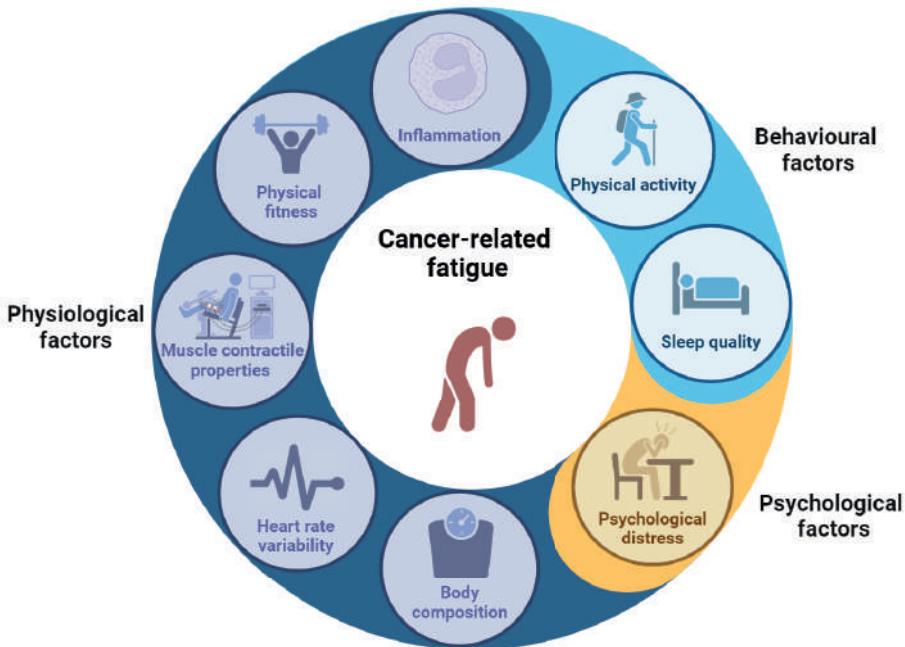


Figure 1. Potential physiological, behavioral and psychological mechanisms underlying cancer-related fatigue investigated in the KINETICS trial.

METHODS

Participants

This explorative study aimed to include 40 cancer survivors with self-reported CRF. They were recruited by advertisements distributed by patient organizations, local and national media, and via the department of Surgery of the Radboud University Medical Center. Subsequently, they were screened for eligibility via telephone contact. To be eligible for inclusion, cancer survivors needed to be at least moderately fatigued, as indicated with a fatigue score above 27 on the subscale fatigue of the checklist individual strength (CIS; (19)) at the time of screening, and aged 18 years or older. Additionally, oncological treatment needed to be

completed between six months and three years ago, except for hormone therapy, and cancer survivors needed to be in a long-term stable clinical situation. Cancer survivors were not eligible if they had neurological or orthopedic health problems hampering walking exercise, had hemoglobin levels below 6.0 mmol/liter or glucose levels above 8.0 mmol/liter at the time of inclusion. This study was approved by the regional ethical review board (METC Oost-Nederland; #2019-6065), and all participants gave written informed consent before enrollment.

Design and intervention

The study has a quasi-experimental interrupted time-series design, in which participants act as their own controls. All study measurements took place at three timepoints: baseline (T0), pre-intervention (T1) and post-intervention (T2). The 4-month period between baseline and the pre-intervention visit had no study-related activities and served as a control period. After the T1 measurement, cancer survivors received a 4-month home-based walking exercise program. The program was individually tailored and included a detailed description of weekly training goals that gradually increased in training duration, frequency and intensity leading towards a personal walking exercise goal. Three sessions of moderate intensity walking exercise with a individually tailored duration that progressed over time were prescribed per week. Additionally, one weekly session of home-based resistance training consisting of six body weight exercises was added to the walking program. Cancer survivors received exercise counselling by phone or email every other week from the research coordinator to monitor the training program and adjust the program if necessary. During the counselling sessions behavior change techniques including, among others, goal setting, action planning, and problem solving, were applied to support motivation and program adherence (20) (Supplementary material 1).

Cancer-related fatigue

Fatigue severity was assessed using the fatigue subscale of the Checklist Individual Strength (CIS), which consists of 8 items scored on a 7-point Likert scale (19). Scores can be divided in the categories: normal fatigue (score 8 – 26), moderate fatigue (score 27 – 34) and severe fatigue (score 35 – 56). The CIS is a validated questionnaire and has extensively been used in cancer survivors (21, 22). Minimally clinically important difference (MCID) of the fatigue subscale is 8 points (23). Additionally, the Multidimensional Fatigue Inventory (MFI) was included as secondary outcome to evaluate physical and mental fatigue dimensions. MFI scores range between 4 – 20 (24). In addition, vitality was assessed using the RAND-36 health survey (RAND-36), in which raw scores are linearly converted to a 0 and 100 score, and higher scores representing higher vitality (25).

Physiological factors

Height (m), weight (kg), and body composition (skeletal muscle mass and body fat mass in kg) were obtained (InBody 770, Biospace, Seoul, Republic of Korea). Aerobic fitness (maximum oxygen uptake; VO_2max) was estimated using the Åstrand-Rhyming submaximal exercise test on an cycle ergometer (Lode Corival; Lode, Groningen, the Netherlands; (26)). The 1 repetition maximum (1RM) based on the indirect 1 repetition maximum test on a leg press (EN-Dynamic, Enraf-Nonius, Rotterdam, The Netherlands; (27)) was used as indicator for lower body muscle strength. Heart rate variability (HRV) was measured in supine position after 10 minutes of relaxation in supine position. During the HRV measurements, consecutive R-R peak intervals were recorded for 5 minutes (Polar V800, Polar Electro Oy, Kempele, Finland) while breathing frequency was paced by a metronome at a frequency of 12 breaths per minute. R-R intervals were analyzed using Kubios (version 3.5, Biosignal Analysis and Medical Imaging Group, Kuopio, Finland) to determine time domain (SDNN; standard deviation of N-N intervals, RMSSD; root mean square of successive RR interval differences) and frequency domain variables (LF/HF ratio; low frequency/high frequency ratio) (28).

Muscle contractile properties of the dominant *Quadriceps femoris* muscle were determined using an electrical stimulation protocol (29), and included maximal voluntary contraction (MVC), muscle fatigability, early- and half relaxation time (R_t), and maximal force rise (MFR). To evaluate muscle contractile properties, participants were seated in upright position. The lower leg was fixated to a force transducer, and surface electrodes were placed on the distal and proximal part of the anterior thigh (29, 30). MVC was determined by instructing the participants to maximally extend the knee for at least 3 seconds and calculating the mean maximal force over a stable interval of approximately 1 second. Subsequently, the muscle was electrically stimulated inducing a force of least 40% of the MVC. Muscle fatigability was assessed by repetitively stimulating the quadriceps muscle for 2 minutes using 30 Hz bursts with a duration of 1 second every 2 seconds (30).

Force signals were analyzed using Matlab (Version R2022a; The MathWorks Inc, Natick, Massachusetts). Muscle fatigability was evaluated by calculating peak force decline using the percentage force decline between the first and last three bursts of the fatigability protocol. Early- and half relaxation time were calculated, defined as the time needed for the force to decline from 75% to 50% and from 50% to 25% of peak force, respectively. Maximal force rise (MFR) was calculated as the percentage of maximal force incline divided by the peak force (29).

Venous blood was collected and stored in a -80°C freezer. At the end of the study, serum samples were analyzed using an immuno-oncology Luminex assay (Assay HCYTA-60K, Merck-Millipore, Burlington, USA). This panel measures inflammatory markers interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α). Blood plasma samples were analyzed using an immunoturbidimetric assay (Roche diagnostics, Indianapolis, USA) to quantitatively evaluate C-reactive protein (CRP) concentration. Values below limit of quantification were approximated

as 75% of the lowest level of quantification, and values below limit of detection were assigned a placeholder value of 0.01 mg/l for CRP, 0.01 pg/ml for IL-6, and 0.1 pg/ml for TNF- α .

Behavioral and psychological factors

Physical activity was measured objectively using an accelerometer (ActivPAL micro, PAL technologies, Glasgow, UK). The accelerometer was placed on the upper thigh and worn 24 hours a day for at least 7 continuous days. Raw data was converted using PAL Analysis software (PAL Software Suite, version 8, PAL Technologies), analyzed using a script adapted from Winkler et al. (31), and subsequently divided in moderate-to-vigorous physical activity (MVPA; Metabolic equivalent (MET) values ≥ 3) and sedentary behavior (MET-values ≤ 1.5).

The Short Questionnaire to assess health-enhancing physical activity (SQUASH; (32)) was used to evaluate self-reported physical activity. The amount of moderate-to-vigorous physical activity during leisure time, and a total amount of activity during the week was evaluated and converted to MET-values based on the updated compendium of Ainsworth (33).

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). The PSQI can be divided into seven components, which can be summed to a global sleep quality score ranging from 0 to 21 (34).

Symptoms of psychological distress were assessed using the Hospital Anxiety and Depression Scale (HADS), which yields a total score ranging from 0 to 42, with higher scores indicating higher distress (35).

Covariables

Sociodemographic information, clinical information, and smoking behavior were assessed using a custom-made questionnaire. Categorical variables included: marital status (married, divorced, living together, widow), education level (low, medium, high), treatment type and number of treatments (surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy), and smoking status (current, former, never). Comorbidities were assessed using a self-reported version of the Charlson Comorbidity Index (CCI; (36)).

Cancer survivors' perspectives

Cancer survivors' perspectives on how walking exercise influenced their CRF were captured using concept mapping (37). Experiences were collected in response to the focus statement '*How did walking exercise influence your perceived fatigue?*'. Four 1-hour brainstorm sessions were organized in small groups (4 – 6 participants) during the post-intervention study visit, after completion of the intervention and study measurements. During the brainstorm sessions, cancer survivors were asked to write down all their experiences in response to the focus statement. Subsequently, cancer survivors were asked to share their experiences and discuss whether the experiences were defined accurately and unambiguous. After collecting all

experiences researchers removed identical experiences and created a list of all individual experiences. Negatively framed statements were not included in this analysis to prevent indistinct clusters. Following the brainstorm sessions cancer survivors clustered all individual experiences in minimally three clusters of at least two experiences using an online tool (HvA Concept Mapping Tool; Hogeschool van Amsterdam, the Netherlands), and provided all clusters with a corresponding title. Additionally, they rated all individual experiences on a five-point Likert scale from “unimportant” to “very important”. Concept maps were created in R studio (Version 2022.02.1, R Core Team (2022)) using R-CMAP, an open source software for concept mapping (38). This was done by transforming the individual patient data through a multidimensional scaling algorithm, whereafter a 2-dimensional representation of the relative distances between statements was provided. Based on these relative distances, clusters were formed by hierarchical clustering using Ward’s method (38).

Statistical analyses

Demographical and clinical characteristics of cancer survivors were summarized by means and standard deviations (SD) or median and interquartile range for continuous variables, as appropriate, and numbers and proportions for nominal variables. Linear mixed models were used to examine the change in fatigue severity over time. Subsequently, physiological, behavioral and psychological variables were added to the model (separately for each variable) to examine whether changes in these variables were associated with changes in fatigue severity. Assumptions for linearity, normality of residuals, and homoscedasticity were met for all models and models were adjusted for sex. All analyses were conducted in R studio (Version 2022.02.1, R Core Team (2022)).

Table 1. Participant characteristics.

	Participants (n = 27)
Age, mean ± SD (years)	59 ± 15
Gender, n (%) female	10 (37.0)
BMI, mean ± SD (kg/m ₂)	26.9 ± 5.0
Marital status, n (%)	
Married	18 (66.7)
Divorced	3 (11.1)
Living together	4 (14.8)
Widow	2 (7.4)
Education level, n (%)	
Low	4 (14.8)
Middle	13 (48.1)
High	10 (37.0)
Smoking status, n (%)	
Current	2 (7.4)
Former	12 (44.4)
Never	10 (37.0)
Unknown	3 (11.1)
Cancer type, n (%)	
Gastrointestinal cancer	9 (33.3)
Gynecological cancer	6 (22.2)
Urogenital cancer	4 (14.8)
Hematological cancer	3 (11.1)
Breast cancer	2 (7.4)
Lung cancer	1 (3.7)
Brain tumor	1 (3.7)
Melanoma	1 (3.7)
Treatment type, n (%)*	
Surgery	18 (66.7)
Radiotherapy	14 (51.9)
Chemotherapy	18 (66.7)
Hormone therapy	5 (18.5)
Immunotherapy	3 (11.1)
Number of treatments, median [IQR]	2 [2 - 3]
Current hormone therapy, n (%)	5 (18.5)
Self-reported CCI, median [IQR]	3 [2 - 4]
Polypharmacy (>2 medications), n (%)	4 (14.8)
Time between treatment completion and study inclusion (years), median [IQR]	1.5 [1 - 2]

*Participants may have received multiple treatment types. Abbreviations: BMI; body mass index, CCI; Charlson comorbidity index.

RESULTS

Between June 2021 and October 2021, 57 cancer survivors responded to the advertisements and invitations and were subsequently screened for participation. In total, 30 cancer survivors were not eligible due to low fatigue scores ($n = 10$), an inadequate time period after treatment completion ($n = 7$), lack of interest ($n = 7$), already participating in regular physical exercise ($n = 3$), or unknown reasons ($n = 3$). Consequently, 27 cancer survivors were included in the study. Four participants dropped out from the study during the control period, and two participants dropped out during the intervention period. Reasons for dropout were physical complaints hampering walking exercise ($n = 5$) or disease recurrence ($n = 1$). Cancer survivors were on average 59 ± 15 years old, and 37% were female (Table 1).

Fatigue

During the total study period, perceived fatigue severity ($\beta = -8.1$, 95%CI = $-12.1; -4.2$) and physical fatigue ($\beta = -1.7$, 95%CI = $-3.1; -0.3$) decreased, and vitality increased ($\beta = 8.5$, 95%CI = $2.8; 14.2$; Table 2). Fatigue severity decreased significantly during the control period ($\beta = -5.9$, 95%CI = $-9.7; -2.1$), and showed no significant changes during the intervention period (Table 2). During the control period, also mental fatigue decreased ($\beta = -1.5$, 95%CI = $-2.8; -0.2$), and vitality increased ($\beta = 8.8$, 95%CI = $3.2; 14.3$; Table 2), while no significant changes in these outcomes were found during the intervention period.

Table 2. Descriptive information and longitudinal changes in dimensions of fatigue

	T0	T1	T2	Total study period	Control period	Intervention period
				β [95% CI]	β [95% CI]	β [95% CI]
Fatigue severity	35 ± 9	28 ± 13	25 ± 12	-8.1 [-12.1 ; -4.2]*	-5.9 [-9.7 ; -2.1]*	-2.2 [-6.2 ; 1.7]
Mental fatigue	12 ± 5	11 ± 4	11 ± 4	-0.9 [-2.2 ; 0.5]	-1.5 [-2.8 ; -0.2]*	0.6 [-0.8 ; 2]
Physical fatigue	12 ± 4	11 ± 4	10 ± 4	-1.7 [-3.1 ; -0.3]*	-0.8 [-2.2 ; 0.5]	-0.8 [-2.2 ; 0.6]
Vitality	56 [47 - 62]	62 [50 - 75]	62 [56 - 69]	8.5 [2.8 ; 14.2]*	8.8 [3.2 ; 14.3]*	-0.2 [-6 ; 5.5]

Variables are displayed as mean \pm SD or median [IQR]. Regression coefficients (β) and 95% confidence intervals (CI) represent the mean change in the variable over time assessed using unadjusted linear mixed models. Higher scores on the subscale fatigue severity (range: 20 – 140), mental fatigue (range: 4 – 20), and physical fatigue (range: 4 – 20), indicate more fatigue. Higher scores on the subscale vitality (range: 0 – 100) represent higher vitality.

* = p -value < 0.05.

Physiological factors

Descriptive information and changes over time for all physiological factors can be found in Supplementary material 2. During the control period, muscle strength and IL-6 concentration increased significantly. During the intervention period, VO_2 max, early relaxation time, and TNF- α concentration increased significantly. During the total study period, VO_2 max, early

relaxation time, and TNF- α increased significantly, and the decrease in maximal force rise during the fatigability electrical stimulation protocol reduced.

Increases in muscle strength (per 1RM in kg: $\beta=-0.07$, 95%CI=-0.12;-0.02, per 1RM in kg/kg body weight: $\beta=-5.1$, 95%CI=-9.4;-0.8), maximal voluntary contraction (per MVC in N: $\beta=-0.04$, 95%CI=-0.06;-0.01; Figure 2) and reductions in muscle early relaxation time during the fatigability protocol (per %: $\beta=0.09$, 95%CI=0.02;0.16) and muscle half relaxation time (per %: $\beta=0.07$, 95%CI=0.01;0.14) were significantly associated with a decrease in fatigue severity (Figure 3, Table 3). Changes in aerobic fitness, body composition, heart rate variability and concentrations of CRP, TNF-a and IL-6 were not significantly associated with changes in fatigue severity.

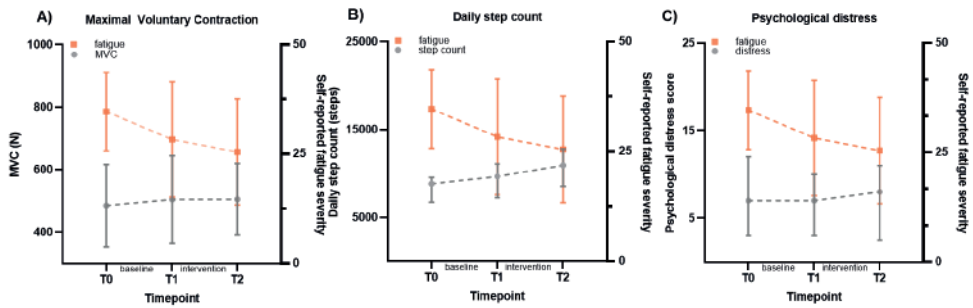


Figure 2. Longitudinal associations with changes in fatigue severity for A) maximal voluntary contraction (MVC) of the quadriceps femoris muscle, B) daily step count, and C) psychological distress. Values are presented as mean \pm standard deviation for fatigue severity and MVC, and median [IQR] for daily step count and psychological distress.

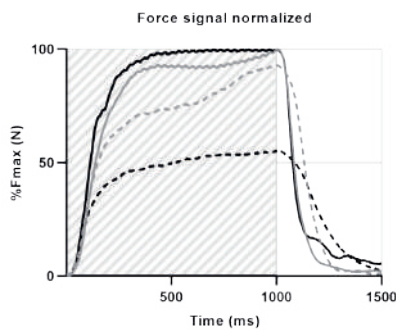


Figure 3. Representative force signals of the first (straight) and last (dashed) electrically stimulated muscle contractions of the fatigability protocol from a severely fatigued (black) and less fatigued (grey) person. The muscle is stimulated for 1 second (striped light grey) and relaxes directly after the electrical pulse.

Table 3. Longitudinal associations of physiological, behavioral and psychological factors with fatigue severity

	β (95% CI) total study period	β (95% CI) total study period [†]
Physiological		
Body composition		
BMI (kg/m ²)	-0.3 (-1 ; 0.4)	
Skeletal muscle mass (kg)	-0.8 (-1.7 ; 0.1)	
Body fat mass (kg)	-0.1 (-0.4 ; 0.2)	
Physical fitness		
Estimated VO ₂ max	-0.2 (-0.5 ; 0.1)	
Estimated 1RM (kg)	-0.07 (-0.12 ; -0.02)*	
Estimated 1RM (kg/kg body weight)	-5.1 (-9.4 ; -0.8)*	
MVC (N)	-0.04 (-0.06 ; -0.01)*	
MVC (N/kg body weight)	-1.7 (-3.5 ; 0.2)	
Muscle contractile properties		
Muscle fatigability (%)	-0.2 (-0.5 ; 0.1)	
Early relaxation time (ms)	0.05 (-0.89 ; 0.99)	
Increase early relaxation time (%)	0.09 (0.02 ; 0.16)*	
Half relaxation time (ms)	0.04 (-0.39 ; 0.45)	
Increase half relaxation time (ms)	0.07 (0.01 ; 0.14)*	
Maximal force rise (%/ms)	11.0 (-4.3 ; 25.8)	
Decrease Maximal force rise (%)	-0.08 (-0.21 ; 0.05)	
Heart rate variability		
SDNN	0.00 (-0.05 ; 0.05)	
RMSSD	-0.01 (-0.06 ; 0.03)	
LF/HF ratio	0.05 (-0.33 ; 0.41)	
Inflammation		
TNF- α (pg/ml) [†]	0.03 (-1.27 ; 1.28)	1.03 (0.28 ; 3.60)
IL-6 (pg/ml) [†]	0.72 (-0.34 ; 1.78)	2.05 (0.71 ; 5.93)
CRP (mg/l) [†]	0.61 (-0.24 ; 1.44)	1.84 (0.79 ; 4.22)
Behavioral		
Objectively assessed behavior		
Daily step count (per 100 steps)	-0.11 (-0.17 ; -0.04)*	
MVPA (hours/week)	-1.21 (-1.95 ; -0.48)*	
Sitting time (hours/day)	0.7 (-0.8 ; 2.2)	
Self-reported behavior		
MVPA leisure time (hours/week)	-0.2 (-0.49 ; 0.09)	
MET-hours/week [†]	-3.1 (-7.1 ; 0.77)	0.04 (0.00 ; 2.16)
Sleep quality		
Total sleep score (PSQI)	1.1 (0.3 ; 1.9)*	
Psychological		
Distress	1.1 (0.8 ; 1.3)*	

Regression coefficients (β) with corresponding 95% confidence intervals (CI) represent the association between the variable and fatigue over time (averaged over all time points), adjusted for sex. Abbreviations: BMI; body mass index, VO₂max; maximum oxygen uptake, 1RM; 1 repetition maximum; SDNN, standard deviation of N-N intervals, RMSSD; root mean square of successive RR interval differences, LF/HF ratio; low frequency/high frequency ratio, MVPA; moderate to vigorous physical activity, MET; metabolic equivalent of task. [†]Values of these variables are log-transformed and are presented in this column after back transformation to original scale, * = p-value < 0.05.

Behavioral and psychological factors

Objectively measured daily step count and weekly MVPA increased during the total study period (Supplementary material 2). Increases in objectively measured daily step count (per 100 steps: $\beta=-0.1$, 95%CI=-0.2;-0.04), weekly MVPA (per hour: $\beta=-1.21$, 95%CI=-1.95;-0.48), sleep quality ($\beta=1.1$, 95%CI=0.3;1.9), and decreases in psychological distress ($\beta=1.1$, 95%CI=0.8;1.3) were significantly associated with decreases in fatigue severity (Table 3; Figure 2).

Cancer survivors' perspectives

In total, 19 cancer survivors generated 111 statements. Removal of 29 duplicates and 19 statements that were not framed positively, resulted in 63 positively framed statements. The 63 statements were clustered in seven clusters, and presented in a concept map (Figure 4). The seven clusters included: *training benefits*, *mental well-being*, *health awareness*, *physical fitness*, *resilience*, *physical well-being* and *daily functioning*. The cluster *resilience* was rated as the most imported cluster with a mean importance of all statements in the cluster of 3.89 ± 0.28 , followed by *physical well-being* (3.88 ± 0.46), and *daily functioning* (3.77 ± 0.48). A description of the individual statements and their importance are provided in Supplementary material 3.

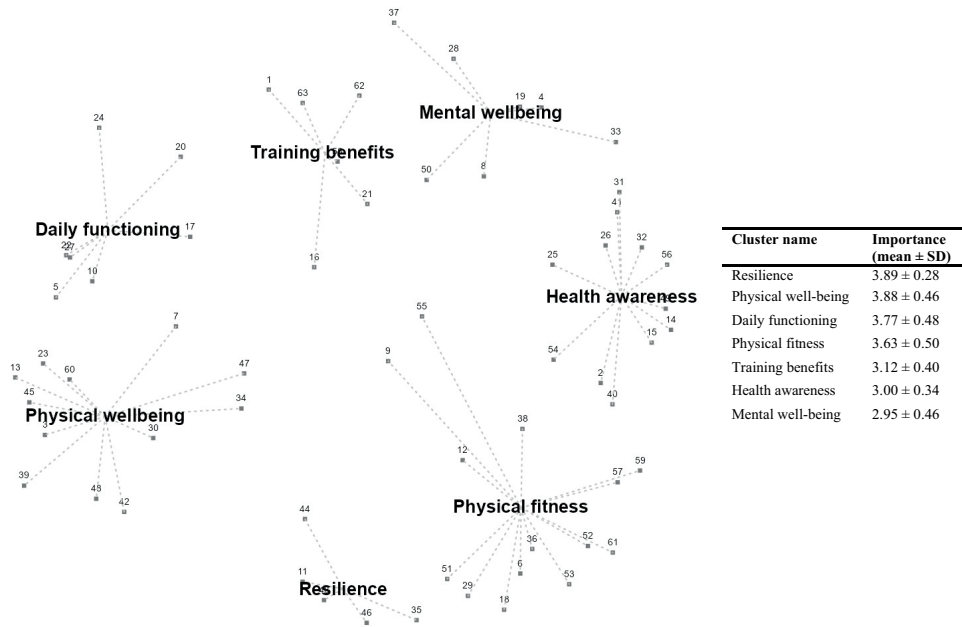


Figure 4. Concept map of patients' experiences of how walking exercise reduces their fatigue severity. Each point corresponds to a statement patients formulated in response to the focus statement (see Supplementary material 3). Statements that are frequently placed in the same cluster are presented closer together in this figure. The dotted lines help to illustrate relative distances. Cluster names of each cluster are presented in the figure. The accompanying table displays the cluster names, as well as the mean and standard deviation of their respective importance scores.

DISCUSSION

This study investigated the effect of a four-month walking intervention on cancer-related fatigue and studied physiological, behavioral and psychological variables associated with these effects. Our results showed that cancer survivors showed a clinically relevant decrease in fatigue severity, however, this effect already started before the walking intervention. Additionally, increases in muscle strength, physical activity, sleep quality, and reductions in muscle relaxation times and psychological distress were associated with reductions in fatigue severity. Furthermore, cancer survivors perceived that improved resilience and physical well-being were the most important benefits of the walking intervention that contributed to reduced perceived fatigue.

Cancer-related fatigue

The present study showed a clinically relevant decrease in fatigue severity over time to below the cut-off value for moderate fatigue (23). Unexpectedly, the largest change was already

found in the control period. Since sudden natural recovery is unlikely in cancer survivors with long-term fatigue, we hypothesize that cancer survivors already started with their walking exercise prior to the start of the intervention period, thereby introducing contamination. This hypothesis is supported by the average increase in step count and MVPA of approximately 10% during the control period. Hence, explaining and participating in the study may already have impacted exercise behavior (39), leaving less room for further changes during the intervention period.

Underlying mechanisms

Our finding that changes in muscle contractile properties (specifically the increase in relaxation times during a fatigability protocol) were associated with reductions in fatigue severity complements results from previous studies showing that increases in rate of force development was correlated with reductions in perceived fatigue in patients with breast or colon cancer undergoing chemotherapy (40), and that decreases in half relaxation time after a fatigability electrical stimulation protocol was associated with decreases in fatigue in patients with chronic myeloid leukemia (41). As skeletal muscle relaxation times are mostly related to Ca^{2+} reuptake into the sarcoplasmic reticulum (42), the increases in relaxation times may suggest sarcoplasmic reticulum dysfunction in cancer survivors with CRF. Additionally, cytostatic agents used in oncological treatment can disrupt muscle relaxation, calcium homeostasis (43), and induce mitochondrial dysfunction. Mitochondrial dysfunction can result in an impaired adenosine triphosphate (ATP) generating capacity (44) which impairs the active reuptake of calcium necessary for muscle relaxation (43). Physical exercise (preferably high intensity interval endurance exercise or resistance exercise (45)) during and after cancer treatment can increase mitochondrial density and function and thereby reducing fatigue (46, 47). However, future studies should reveal whether exercise may improve sarcoplasmic reticulum function in cancer survivors, and thereby reduce fatigue.

Next to muscle relaxation times, we found that a higher quadriceps muscle strength was associated with lower fatigue severity, and that cancer survivors recognized improved fitness and muscle strength as a mechanism through which exercise helped to reduce fatigue. Strikingly, muscle strength from cancer survivors in our study was approximately 30% lower, also after the intervention, compared to values in middle-aged healthy individuals that were assessed using the same protocol (30, 48), and were comparable with patients after chemotherapy treatment (40). The low values of muscle strength and the association with fatigue, suggest that improving muscle strength after treatment could be important to prevent long-term fatigue. On the contrary, neither the increase in aerobic fitness during the intervention period, nor changes in body composition, and heart rate variability were associated with fatigue severity, which indicate that these variables may be a less important intervention target to reduce fatigue. While previous studies have found no differential effect on fatigue across exercise programs (11), results from this study suggest to include resistance

exercises to improve muscle strength combined with progressive muscle relaxation training to improve muscle relaxation times (49). A multimodal exercise intervention including improving physical activity, resistance exercise, and progressive muscle relaxation may therefore be a promising approach to enhance efficacy of exercise interventions in cancer-survivors.

Results of our study also identified several behavioral and psychological pathways via which exercise can reduce fatigue severity, including improved physical activity and sleep, and reduced distress. Our findings demonstrate that an increase in physical activity and sleep quality is associated with reductions in fatigue severity, supporting international physical activity guidelines for cancer survivors (10) and previous literature (11, 15). Also, cancer survivors in our study perceived that exercise helped them to sleep better and improved their well-being, thereby reducing fatigue. Augmenting sleep quality can help maintain a steady circadian rhythm, which is also associated with a reduction in CRF (7, 50). The associations between reduced psychological distress and reduced fatigue severity support results from a previous meta-analysis showing that symptoms of anxiety and depression are associated with fatigue (3, 16), and can be reduced by exercise (10, 51). Resemblance of symptoms of psychological distress and fatigue make it difficult to speculate about causality of this association (16), however exercise clearly benefits both symptoms (10).

Additionally, cancer survivors identified that improved physical and mental resilience (i.e. process of adaptation in response to threats or adversity (52)) and physical well-being were most important mechanisms explaining reductions in fatigue severity after walking exercise. This finding supports a previous cross-sectional study among patients with cancer showing that higher physically activity levels are associated with better resilience (53). Additionally, patients with cancer perceived that exercise provided a means to contribute themselves to recovery, and to improve coping strategies, such as maintaining a positive attitude (54). In our intervention we incorporated several behavior change techniques, including enhancement of self-efficacy, active coping, and social support, which have shown to be important resilience promoting strategies (55). The hypothesis that improved resilience and physical well-being mediate the effects of exercise on cancer-related fatigue should be confirmed in future trials.

Strengths and limitations

The strength of this study is its multifactorial approach, incorporating physiological, behavioral, and psychological factors including detailed measurements of the muscle contractile properties to gain insight into potential mechanisms of a walking exercise intervention on cancer-related fatigue. To ensure comprehensiveness, quantitative measurements were supplemented with cancer survivors' experiences on how exercise helped to reduce fatigue severity. The current knowledge thereby provided useful leads to further improve exercise interventions aiming to reduce fatigue, such as the focus on improving muscle mass and function, and resilience.

A limitation of this study is the relatively small sample size to detect exercise intervention effects on fatigue. However, sample sizes of 27 are well accepted for studies using electrical stimulation (30, 40). Due to the small sample size and the explorative nature of this study, our results should be interpreted as hypothesis-generating rather than hypothesis-testing. Additionally, we used a semi interrupted time-series design instead of a randomized controlled trial in order to prevent unwillingness to participate when risking to be randomized into the control arm. Despite the strength of each person being its own control, it may have introduced contamination in the control period. This may have hampered the detection of significant changes on fatigue severity during the period of the walking intervention. Nevertheless, we were still able to study the factors longitudinally associated with fatigue severity. Another potential limitation of this study was the heterogeneity of the study population in terms of cancer type, treatment and demographics. However, this may improve the generalizability to cancer survivors with cancer-related fatigue.

CONCLUSION

The present study demonstrated that increases in muscle strength, physical activity and sleep quality, and decreases in muscle relaxation times and psychological distress were associated with reductions in fatigue severity in cancer survivors. Although these effects could not be directly attributed to the walking exercise intervention, our findings emphasize the importance of incorporating resistance and progressive muscle relaxation exercises aiming to improve muscle strength and muscle relaxation times, and addressing important constructs such as resilience and physical well-being in a multimodal approach to improve the efficacy of interventions aimed at managing CRF.

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Supplementary material 1. Behavioral change techniques applied during the walking intervention

Intervention phases	Applied behavioral change techniques (20)	Example of application in the KINETICS study	
Preparation	Information about health consequences	Researchers inform participants that scientific evidence indicates that exercise may help to reduce perceived fatigue. Researchers inform participants about the benefits of walking exercise and resistance exercise on fatigue.	
	Goal setting	Researchers discuss with participants the final goal of this walking exercise program.	
	Graded tasks	Researchers discuss with participants that the walking exercise program will be increased in small steps to heavier training sessions.	
	Action planning	Researchers plan the exercise sessions together with the participant.	
	Self-monitoring of behaviour	Participants identify factors that could hamper the planned behaviour. Participants self-monitor their behaviour during the intervention, which is discussed with the researcher.	
	Problem solving	Researchers provide tools how to deal with factors hampering the planned behaviour.	
	Teach to use prompts/cues	Researchers discuss with participants how they can turn the new behaviour into a routine	
	Plan social support	Researchers discuss the possibility to ask for social support during the exercise sessions.	
	Verbal persuasion to boost self-efficacy	Researchers keep in contact with the participant to make sure they set realistic goals.	
	Instruction on how to perform the behaviour	Researchers provide the participant with clear instructions on how to perform the exercise sessions.	
	The exercise program*	Feedback on behaviour	Researchers ask the participants how the exercise sessions are going and give feedback on performance.
		Self-monitoring of behaviour	Participants monitor their behaviour for the past two weeks. Researchers discuss this behaviour with the participants.
		Problem solving	Researchers discuss with participants the encountered problems during the exercise sessions and potential solutions.
		Commitment	Researchers discuss with participants what is needed to complete the next exercise sessions.
Action planning Goal setting		Researchers discuss with participants whether the initial goal seems feasible, or if not what alternative goal participants would want to achieve.	
Focus on past success Anticipation of future rewards		Researchers emphasize previous achievements in the training program. Researchers emphasize that participants are able to reach their final goal.	

*Cancer survivors received counselling every other two weeks to monitor the training program and adjust the program if necessary.

Supplementary material 2. Descriptive information of potential factors underlying cancer-related fatigue.

	T0 (n = 27)	T1 (n = 24)	T2 (n = 21)	Control period β (95% CI)	Intervention period β (95% CI)	Total study period β (95% CI)
Physiological						
BMI (kg/m ²)	26.9 ± 5.0	26.2 ± 3.5	25.9 ± 3.7	0.1 (-0.4; 0.6)	-0.3 (-0.8; 0.2)	-0.2 (-0.7; 0.3)
Skeletal muscle mass (kg)	31.0 ± 5.0	31.3 ± 5.4	32.1 ± 4.8	0 (-0.4; 0.4)	-0.3 (-0.8; 0.1)	-0.3 (-0.7; 0.1)
Body fat mass (kg)	24.4 ± 12.0	22.5 ± 8.5	21.4 ± 8.5	0.2 (-1.1; 1.4)	-0.6 (-1.9; 0.7)	-0.5 (-1.8; 0.8)
Estimated VO ₂ max (ml/kg/min)	27.5 ± 8.1	30.7 ± 11.5	34.0 ± 11.7	1.5 (-1.2; 4.3)	3.3 (0.4; 6.3)*	4.9 (2; 7.7)*
Estimated 1RM (kg)	184.9 ± 57.9	219.2 ± 73.1	205.6 ± 69.3	28.3 (14.4; 42.3)*	-16.4 (-32.6; -0.2)	11.9 (-3.1; 27.1)
Estimated 1RM (kg/kg body weight)	2.3 ± 0.6	2.8 ± 0.9	2.6 ± 0.8	0.4 (0.2; 0.5)*	-0.2 (-0.4; 0)	0.2 (0; 0.4)
MVC (N)	484.9 ± 131.6	504.2 ± 140.3	504.9 ± 114.4	7.8 (-16.7; 32.5)	-25.3 (-51.4; 1.1)	-17.4 (-43.4; 8.9)
MVC (N/kg body weight)	6.1 ± 1.8	6.4 ± 1.6	6.5 ± 1.5	0 (-0.3; 0.4)	-0.2 (-0.5; 0.2)	-0.1 (-0.5; 0.2)
Muscle fatigability (%)	-29.3 ± 12.2	-28.3 ± 12.8	-25.9 ± 13.2	1.2 (-2.8; 5.2)	2.5 (-1.9; 6.8)	3.7 (-0.6; 7.9)
Early relaxation time (ms)	24.0 ± 4.1	22.5 ± 3.1	24.5 ± 3.4	-0.6 (-1.4; 0.3)	1.5 (0.6; 2.4)*	1 (0.1; 1.8)*
Increase early relaxation time (%)	86.4 ± 43.0	90.3 ± 33.7	78.7 ± 41.5	4.1 (-8.9; 17)	-7.8 (-22; 6.2)	-3.7 (-17.5; 9.9)
Half relaxation time (ms)	35.2 ± 7.2	32.6 ± 7.0	36.4 ± 4.4	-1.8 (-5.4; 1.7)	3.6 (-0.2; 7.4)	1.8 (-2; 5.5)
Increase half relaxation time (ms)	78.9 ± 48.2	90.5 ± 42.8	76.3 ± 47.7	11.6 (-7.8; 30.9)	-15.7 (-36.2; 5.2)	-4.1 (-24.5; 16.5)
Maximal force rise (%/ms)	0.8 ± 0.2	0.7 ± 0.1	0.7 ± 0.3	0 (-0.1; 0)	0 (-0.1; 0.1)	0 (-0.1; 0)
Decrease Maximal force rise (%)	-5.6 ± 22.3	-14.7 ± 11.9	-19.2 ± 18.9	-9.7 (-19.3; 0.1)	-3.9 (-14.4; 6.5)	-13.6 (-23.7; -3.4)*
SDNN	25.0 (15.5 - 52.8)	42.1 (27.8 - 70.8)	23.7 (17.5 - 57.8)	15.8 (-4.5; 35.7)	-21.8 (-43.2; -0.2)	-6 (-27.1; 14.9)
RMSSD	26.3 (15.0 - 50.5)	46.9 (20.4 - 77.6)	28.8 (15.1 - 50.5)	17.6 (-3.1; 37.9)	-21.7 (-43.5; 0.2)	-4.1 (-25.7; 17.3)
LF/HF ratio	1.4 (0.7 - 4.4)	1.8 (0.5 - 3.2)	0.6 (0.4 - 1.8)	1.9 (-0.9; 4.7)	-3.1 (-6.2; 0)	-1.2 (-4.2; 1.8)
TNF- α (pg/ml)*	5.0 (0.1 - 12.0)	5.0 (0.1 - 7.6)	5.0 (5.0 - 6.0)	1 (0.45; 2.2)	2.7 (1.1; 6.7)*	2.7 (1.1; 6.0)*
IL-6 (pg/ml)*	0.5 (0.0 - 1.5)	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.2)	0.4 (0.2; 0.9)*	1.6 (0.7; 4.1)	0.7 (0.3; 1.5)
CRP (mg/l)*	2.0 (0.0 - 2.8)	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.5)	0.7 (0.2; 2.2)	0.9 (0.2; 3.3)	0.6 (0.2; 2.2)
Behavioral						
Daily step count	8,812 (6,761 - 9,536)	9,648 (7,643 - 10,899)	10,921 (8,720 - 12,426)	1069.8 (-137.6; 2293.9)	1180.3 (-94; 2456.1)	2250.1 (999.9; 3518.2)*
MVPA (hours/week)	7.6 ± 2.9	8.8 ± 3.7	10.1 ± 3.3	1 (-0.2; 2.2)	1.2 (0; 2.5)	2.2 (1; 3.5)*
Sitting time (hours/day)	10 ± 2	9 ± 1	9 ± 1	0 (-0.5; 0.6)	-0.3 (-0.9; 0.3)	-0.3 (-0.8; 0.3)

	T0 (n = 27)	T1 (n = 24)	T2 (n = 21)	Control period β (95% CI)	Intervention period β (95% CI)	Total study period β (95% CI)
Self-reported MVPA leisure time (hours/week)	7.1 (3.7 - 11.5)	4.8 (1.9 - 10.9)	7.5 (3.1 - 14.6)	-2 (-5.5 ; 1.6)	2.5 (-1.3 ; 6.2)	0.5 (-3.2 ; 4.2)
Self-reported MET-hours/week [†]	92.1 (61.4 - 132.9)	75.0 (62.2 - 107.3)	105.2 (60.0 - 211.4)	0.9 (0.7 ; 1.2)	1.2 (1 ; 1.6)	1.1 (0.9 ; 1.5)
Global sleep quality ^{††}	7 \pm 3	7 \pm 4	6 \pm 3	-0.1 (-1 ; 0.9)	-0.6 (-1.7 ; 0.4)	-0.7 (-1.7 ; 0.3)
Psychological						
Distress [†]	7 (4 - 12)	7 (4 - 10)	8 (3 - 10)	-0.9 (-2.6 ; 0.8)	0.3 (-1.5 ; 2.1)	-0.6 (-2.4 ; 1.2)

Values are presented as mean \pm SD for normally distributed values or median (IQR) for not normally distributed value. Regression coefficients (β) and 95% confidence intervals (CI) represent the mean change in the variable over time assessed using unadjusted linear mixed models. [†] β (95% CI) of these variables were log-transformed and are presented in this column after back transformation to original scale. ^{††}Higher scores represent lower sleep quality and distress. Abbreviations: BMI; body mass index, VO₂max; maximum oxygen uptake, 1RM; 1 repetition maximum; SDNN, standard deviation of NN intervals, RMSSD; root mean square of successive RR interval differences, LF/HF ratio; low frequency/high frequency ratio, MVPA; moderate to vigorous physical activity, MET; metabolic equivalent of task.

* = p-value < 0.05.

Supplementary material 3. Individual statements with mean importance used for concept mapping analysis
Focus statement: *The walking exercise influenced my perceived fatigue because:*

Statement name	Importance \pm SD
Resilience	3.89 \pm 0.28
11 I am more positive in life	4.00 \pm 0.69
35 Over time, I was able to physically recover faster after the exercise training	3.67 \pm 0.69
43 I was able to do more (more kilometres) than I expected	3.67 \pm 0.77
44 I was surprised by the resilience of my body	3.78 \pm 0.81
46 People around me noticed changes in my body	4.33 \pm 0.59
Physical well-being	3.88 \pm 0.46
3 I now have a reason for feeling fatigued	2.89 \pm 1.23
7 I am more active	4.56 \pm 0.51
13 I enjoyed going to places I had never been before/discovering new routes	4.22 \pm 0.73
23 I gained more endurance/fitness	4.33 \pm 0.59
30 I noticed that my boundaries were being pushed	3.61 \pm 1.04
34 I recover faster from fatigue	3.33 \pm 0.84
39 I changed my eating habits (more/larger portions)	4.11 \pm 0.58
42 It promotes my gut recovery	3.78 \pm 0.65
45 I felt that I looked better	4.11 \pm 0.83
47 People around me noticed changes in my appearance	3.72 \pm 0.67
48 I feel healthy	4.11 \pm 0.47
60 I sleep better	3.78 \pm 0.65
Daily functioning	3.77 \pm 0.48
5 I can walk hills and bridges more easily	3.94 \pm 0.73
10 I felt happier	4.06 \pm 0.80
17 I adapted my daily routine to the exercise schedule, and I liked that	3.89 \pm 0.90
20 I felt more energy after the exercise sessions	3.11 \pm 1.02
22 I felt better after a walking exercise session	4.39 \pm 0.61
24 It was nice to walk together	3.11 \pm 1.32
27 I learned to spread my energy throughout the day	3.89 \pm 0.96
Physical fitness	3.63 \pm 0.50
6 I feel physically fitter	4.22 \pm 0.55
9 I have become stronger	3.72 \pm 0.75
12 I noticed that I liked the exercise structure	3.17 \pm 0.99
18 I noticed less mental fatigue	4.00 \pm 0.59
29 I have discovered that there is a limit to what is most enjoyable when it comes to walking	3.78 \pm 0.43
36 The walking training gave me the opportunity to take time for myself	4.06 \pm 1.00
38 I have more interest in doing/room for fun things	2.72 \pm 1.07
51 I noticed that I had to take the fatigue into account during the exercise sessions	4.11 \pm 0.58
52 I used the walking training to stay as fit as possible	4.22 \pm 0.65
53 I found the strength training a pleasant variation because it targets different muscles	4.06 \pm 0.64

Statement name	Importance \pm SD	
55	The moments when I was completely overwhelmed by fatigue disappeared	3.28 \pm 1.23
57	I noticed that it took longer for the fatigue to set in	3.17 \pm 1.10
59	I quickly notice muscle fatigue which can be alleviated by walking	3.22 \pm 1.00
61	I have more leg muscles and less fat mass	3.11 \pm 0.83
Training benefits		3.12 \pm 0.40
1	I felt less fatigued by the training sessions	3.39 \pm 0.85
16	I liked the challenge	3.39 \pm 1.20
21	Walking helps me to worry less	3.33 \pm 1.19
58	I used the training to improve my walking technique	2.72 \pm 1.13
62	I found it important that someone provided guidance during the exercise training	2.50 \pm 1.29
63	I appreciated that the training was easily accessible	3.39 \pm 1.09
Health awareness		3.00 \pm 0.34
2	I have a better insight into the fatigue	3.06 \pm 1.30
14	It felt good to be outside	3.17 \pm 1.04
15	I found it relaxing to be outside	3.33 \pm 1.14
25	I make different social contacts through walking than I normally would	3.39 \pm 0.92
26	I need less planning to have more energy	3.17 \pm 1.04
31	I noticed new or positive things during walking	3.33 \pm 0.84
32	Each time, the training sessions went better and better	2.56 \pm 0.70
40	I am more aware of my dietary intake	2.28 \pm 1.02
41	I can go longer without eating	3.11 \pm 0.90
49	I liked being engaged with my health in a positive way	2.72 \pm 1.07
54	I noticed positive effects on other exercises too	2.78 \pm 1.00
56	Fatigue disappears while walking	3.11 \pm 1.13
Mental well-being		2.95 \pm 0.46
4	Mental fatigue turned into physical fatigue	3.33 \pm 0.91
8	I can do more (daily) activities	3.56 \pm 0.98
19	I noticed positive mental effects	2.72 \pm 1.07
28	I get happy from walking	2.78 \pm 1.17
33	I noticed that I started to walk quicker	2.89 \pm 1.28
37	I noticed that I felt comfortable in my own skin	2.17 \pm 0.92
50	I felt proud after a long walk.	3.22 \pm 0.94



CHAPTER 6

Muscle contractile properties and perceived fatigue in the general and diseased population

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ABSTRACT

Introduction: Knowledge of muscle contractile properties, physical fitness, and their associations with perceived fatigue may provide insights into mechanisms inducing fatigue and treatment targets. We aimed to identify differences in contractile properties and physical fitness between populations, and examine associations with perceived fatigue.

Methods: We pooled data on perceived fatigue, physical fitness, and contractile properties from six studies, including a control group (n=90), cancer survivors (n=27), patients with chronic obstructive pulmonary disease (COPD;n=16), chronic myeloid leukaemia (CML;n=20) and statin users (n=64). We evaluated differences between populations, and associations of contractile properties and physical fitness with perceived fatigue.

Results: Compared with the control group, we found differences in contractile properties of patients with COPD (larger muscle force decline: $\beta=-10.5\%$, 95%CI=-16.7;-4.2, increase in early relaxation time (Rt): $\beta=84.4\%$, 95%CI=51.7;117.0, increase in half Rt: $\beta=83.1\%$, 95%CI=45.5;120.7, muscle force rise (MFR): $\beta=0.2\%/ms$, 95%CI=0.1;0.3, and decrease in MFR: $\beta=-24.3\%$, 95%CI=-35.7;-13.0) and statin users (early Rt: $\beta=-5.4ms$, 95%CI=-10.0;-0.8, increase in early Rt: $\beta=19.8\%$, 95%CI=2.5;37.1). Associations between contractile properties and perceived fatigue varied across populations. Longer relaxation times were associated with higher perceived fatigue in hemato-oncological populations.

Conclusion: Contractile properties were impaired in patients with COPD and statin users. Associations between contractile properties and perceived fatigue varied across populations. In hemato-oncological populations, impaired muscle relaxation was associated with higher perceived fatigue.

INTRODUCTION

Fatigue is a commonly reported (patho)physiological symptom in the general and diseased population (1). Fatigue can be defined as a subjective sense of tiredness, weakness or exhaustion, either physically, mentally, or both (2, 3), and is frequently reported by patients in primary and community care with a prevalence up to 8% (4). Furthermore, fatigue can occur during chronic diseases including cancer, cardiovascular disease, or chronic obstructive pulmonary disease (COPD) and their associated treatments (for example statins, radiotherapy or systemic cancer treatments (2, 5)). It is often reported as one of the most severe and distressing symptoms impairing daily functioning and health-related quality of life (HRQoL) (6, 7).

Assessments of fatigue are often divided into perceived fatigue evaluated by self-reported questionnaires, and performance fatigability (8). Performance fatigability can be quantified by the decline in muscle force-producing capacity during a prolonged task (2, 8), and can be related to impaired central activation of α -motorneurons or impaired muscle contractile properties (9). Electrical stimulation can be used to assess muscle contractile properties independent of a patient's motivation or effort, bypassing central activation (10). The relationship between perceived fatigue and performance fatigability is complex and studies examining this relationship have primarily focussed on homogeneous study populations (8), hampering direct comparisons between populations.

Treatment strategies for perceived fatigue include among others, pharmacological interventions, exercise interventions, and/or psychological interventions (2). However, the effectiveness of these interventions on perceived fatigue is generally small and varies within and between populations (2, 11). Understanding mechanisms underlying fatigue such as physical fitness or muscle contractile properties may help identify targets for therapeutic interventions. Altered muscle contractile properties such as slowed muscle relaxation or maximal force rise might reflect underlying changes in muscle fiber-type composition, energy metabolism, or calcium handling, which can significantly impact exercise performance and contribute to fatigue (12). Knowledge on associations between physiological muscle properties and perceived fatigue across diverse populations might help to advance the understanding of potential differences in the etiology of fatigue and the development of targeted treatment strategies to reduce fatigue.

Hence, in this study, we aimed to identify differences in muscle contractile properties and physical fitness between different patient populations and a control group. Furthermore, we aimed to examine associations of muscle contractile properties and physical fitness with perceived fatigue for the total population and to examine the differences between subgroups.

METHODS

We pooled data on perceived fatigue, physical fitness, and muscle contractile properties from six studies conducted in the Radboud University Medical Center (13-18) using the same electrical stimulation protocol, containing a control group (n = 90) and different patient populations (n = 127), including 27 cancer survivors with cancer-related fatigue, 16 patients with moderate-to-severe chronic pulmonary obstructive disease (COPD), 20 patients with chronic myeloid leukaemia (CML) treated with tyrosine kinase inhibitors (TKI), and 64 patients who use statins for risk reduction of cardiovascular disease (Table 1). Data about muscle contractile properties, questionnaires about perceived fatigue, anthropometrics and aerobic fitness was collected from all six studies, if available (13-18)(Table 1). Details on disease severity and in- and exclusion criteria can be found in the original articles (13-18). All patients provided written informed consent, and all studies have been approved by the local medical ethics committee (METC Oost-Nederland, formerly known as CMO region Arnhem-Nijmegen) (13-18).

Table 1. Descriptive information of studies using electrical muscle stimulation and the included population subgroups.

First author (year)	Study population	N	Sex female, n (%)	Age, mean ± SD (years)	Fatigue questionnaire	Aerobic fitness assessment (PeakVO ₂)
Ten Haaf et al. (2019)	Controls	52	5 (20)	70 ± 4	-	Åstrand-Rhyming test
Allard et al. (2021)	Statin users	32	9 (28)	64 ± 4	BFI	CPET
	Controls	20	10 (50)	63 ± 5		
Allard et al. (2023)	Statin users	32	10 (31)	63 ± 7	BFI	-
	Controls	18	7 (39)	66 ± 6		
Janssen et al. (2019)	Patients with CML	20	6 (30)	54 ± 8	BFI	CPET
Mast et al. (2024)	Cancer survivors	27	10 (37)	59 ± 15	CIS	Åstrand-Rhyming test
Stoffels et al. (2024)	Patients with COPD	16	10 (63)	61 ± 8	CIS	CPET

Abbreviations: BFI; brief fatigue inventory, CIS; checklist individual strength, CML; chronic myeloid leukemia, COPD; chronic obstructive pulmonary disease, CPET; cardiopulmonary exercise test SD; standard deviation.

Perceived fatigue

Perceived fatigue was measured using the checklist individual strength (CIS) (17, 18) or the brief fatigue inventory (BFI), if available (14-16)(Table 1). The subscale fatigue of the CIS questionnaire consists of 8 items scored on a 7-point Likert scale, with scores ranging between 8 and 56 (19). The BFI consists of 9 items scored on an 11-point Likert scale, and yields a total score by averaging all items (20). Higher scores on the CIS and BFI questionnaires correspond to higher levels of perceived fatigue. To allow for pooling of these questionnaires, individual scores were normalized to a 0 to 100 scale by linear transformation.

Muscle contractile properties

Muscle contractile properties of the dominant *Quadriceps femoris* muscle were determined using the same electrical stimulation protocol and same stimulation parameters in all six studies (18, 21). The muscle electrical stimulation protocol is extensively described elsewhere (18, 21). In short, participants were seated in upright position, and surface electrodes were placed on the distal and proximal part of the anterior thigh. The protocol included evaluations of maximal voluntary contraction (MVC) assessed by maximally extending the knee during an isometric contraction for at least 3 seconds and calculating the mean maximal force (N) over a stable interval of approximately 1 second. Subsequently, the muscle was electrically stimulated by inducing a force of at least 40% of the MVC for 1 second with a frequency of 50 Hz. Muscle fatigability was evaluated by a 2-minute protocol repetitively using bursts of 30 Hz of 1 second duration every 2 seconds (18, 21).

Force signals were analyzed using Matlab (Version R2022a; The MathWorks Inc, Natick, Massachusetts). Muscle force decline was used as an indicator for muscle fatigability, and was evaluated as the percentage peak force decline between the first and last three bursts of the fatigability protocol, $Formula\ 1 = \left(\frac{\text{mean last three bursts} - \text{mean first three bursts}}{\text{mean first three bursts}} \right) * 100$. Early- and half relaxation time (Rt) during a single burst were defined as the time needed for the force to decline from 75% to 50% and from 50% to 25% of peak force, respectively, averaged over the first three bursts of the fatigability protocol. Maximal force rise (MFR) was calculated as the percentage of maximal force incline per millisecond divided by the peak force, averaged over the first three bursts of the fatigability protocol. The increase or decrease in relaxation times or MFR was calculated based on the change between the first and last three bursts of the fatigability protocol (Formula 1; (21)). The coefficient of variation (CV) of mean signals during the fatigability protocol was calculated as $CV = \frac{\sigma}{\mu} * 100$, with σ representing the average standard deviation and μ the average mean across all timepoints during the fatigability protocol.

Aerobic fitness

Aerobic fitness was measured using the Åstrand-rhyming test (13, 18) or a cardiopulmonary exercise test (CPET) on a cycle ergometer (14, 16, 17)(Table 1). The Åstrand-rhyming test is a submaximal exercise test including 6-min steady state exercise at a target heart rate of 180 - age. PeakVO₂ was estimated based on the steady-state workload and mean heart rate of the 5th and 6th minute of the test (18). The CPET protocol included ramp-incremental maximal exercise with an increasing workload of 10-15 Watt/min, and peakVO₂ was determined as an average of the highest 30 seconds of VO₂ uptake (21).

Demographic and anthropometric information

Information about age and sex was collected from all studies. In addition, measured body height and weight were collected from all studies and body mass index (BMI) was calculated in kg/m².

Statistical analysis

Statistical analyses were performed using RStudio (R Core Team). Descriptives were generated for anthropometric and demographic variables and parameters of perceived fatigue and performance fatigability. Multiple linear regression models were used to examine differences in contractile properties between populations and to examine the association between muscle contractile properties and perceived fatigue, adjusting for age, sex and study. To explore potential differences in this association between populations, we added an interaction term between muscle property and population subgroup into the model. In case the interaction term significantly improved the model, as determined by the likelihood ratio test, stratified analyses were conducted to explore associations separately within each population subgroup, adjusted for age and sex. Considering the power of our analyses, we did not include multiple measures fitness or muscle contractile properties simultaneously in our models. Assumptions of linearity, normality of residuals, and homoscedasticity were checked for all models. Regression coefficients (β), and 95% confidence intervals (CI) were presented. Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics

Two hundred and seventeen participants were included in the analyses. Mean age of the total sample was 63.7 ± 8.9 years, participants had a mean BMI of 26.4 ± 3.9 kg/m², and 38% was female (Table 2).

Perceived fatigue

Normalized perceived fatigue score of the total population was 25.2 ± 25.3 (Table 2). Perceived fatigue was significantly higher in cancer survivors ($\beta = 37.9$, 95%CI =28.8;46.9) and patients with COPD ($\beta = 34.7$, 95%CI =24.2;45.2), compared to the control group (Table S1).

Physical fitness and muscle contractile properties

(Estimated) PeakVO₂ was 32.3 ± 11.4 ml/kg/min for the total group (Table 2). PeakVO₂ was lower in cancer survivors ($\beta = -9.9$ ml/kg/min, 95%CI =-15.7;-4.1), patients with COPD, ($\beta = -20.9$ ml/kg/min, 95%CI=-27.2;-14.6) and statin users ($\beta = -5.5$ ml/kg/min, 95%CI =-11.0;-0.1) compared to the control group (Table 2; Figure 1; Table S1). Additionally, MVC was lower in cancer survivors (MVC, $\beta = -129.8$ N, 95%CI =-211.9;-47.8, MVC per kg bodyweight, $\beta = -1.8$ N, 95%CI =-2.7;-0.9) and in patients with COPD (MVC, $\beta = -148.3$ N, 95%CI =-243.3;-53.4, MVC per kg bodyweight, $\beta = -1.7$ N, 95%CI =-2.8;-0.7) compared to the control group (Table 2; Table S1).

Muscle contractile properties of the total population and of the subpopulations are presented in Table 2. Patients with COPD showed a larger muscle force decline ($\beta = -10.5\%$, 95%CI =-16.7;-4.2; Figure 1A), larger increase in early Rt ($\beta = 84.4\%$, 95%CI = 51.7;117.0; Figure 1B), larger increase in half Rt ($\beta = 83.1\%$, 95%CI = 45.5;120.7), and a larger decrease in MFR ($\beta = -24.3\%$, 95%CI =-35.7;-13.0; Figure 1C) between the first and last bursts of the fatigability protocol, compared to the control group (Table S1). Additionally, patients with COPD had a faster MFR at onset of the fatigability protocol ($\beta = 0.2$ %/ms, 95%CI = 0.1;0.3; Figure 1C), compared to the control group (Table S1). A smaller early Rt at onset of the fatigability protocol ($\beta = -5.4$ ms, 95%CI =-10.0;-0.8) and larger increase in early Rt between the first and last bursts of the fatigability protocol were found in statin users compared to the control group ($\beta = 26.2\%$, 95%CI = 4.3;48.2; Figure 1B; Table S1).

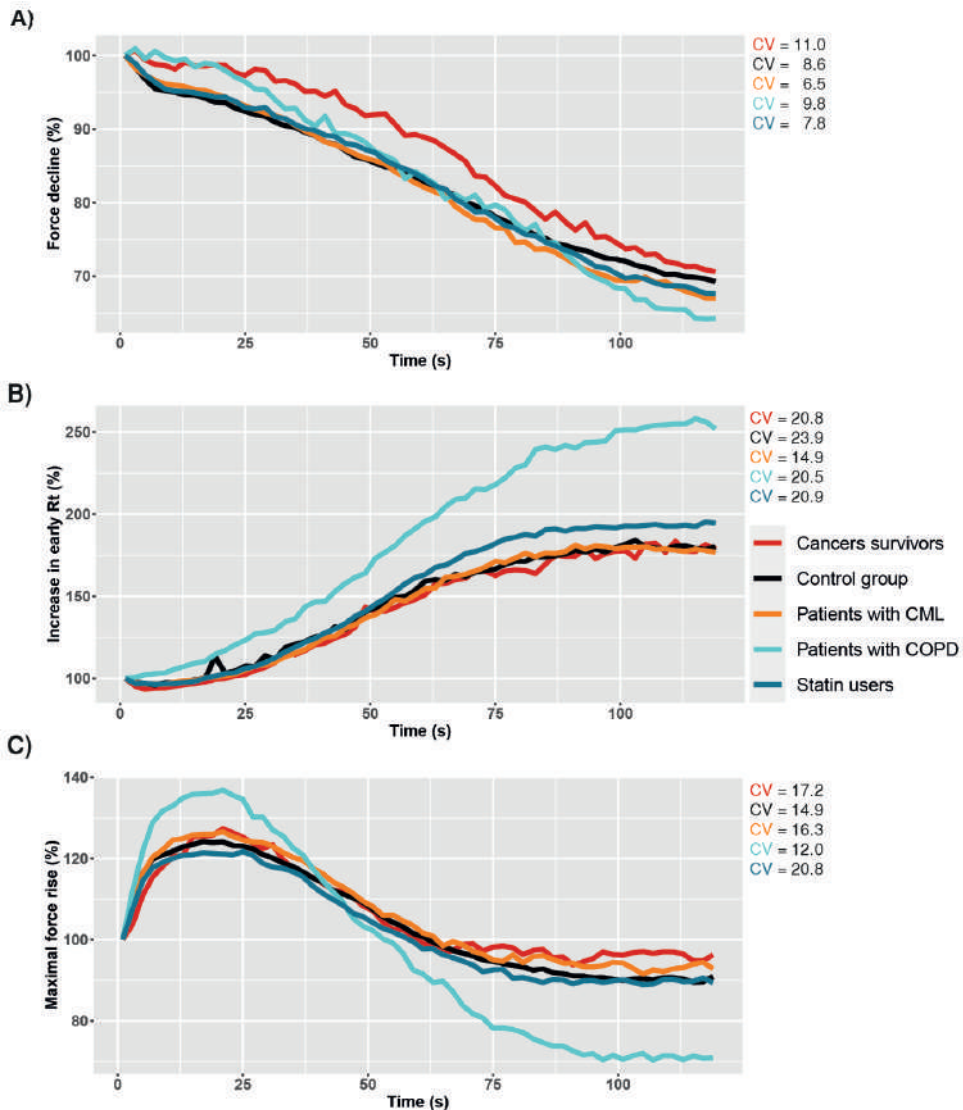


Figure 1. Average signals representing the fatigability protocol in each of the population subgroups, with their coefficient of variation (CV) presented in the legend. Panel A) shows muscle force decline, which presents a larger decline during the fatigability protocol in patients with COPD (light blue) compared to the control group (black). Panel B) shows a larger increase in early relaxation time during the fatigability protocol in statin users (dark blue) and patients with COPD (light blue) compared to the control group (black), Panel C) shows maximal force rise, which shows a larger reduction during the fatigability protocol in patients with COPD (light blue) compared to the control group (black).

Associations of physical fitness and muscle contractile properties with perceived fatigue

For the total population, physical fitness and muscle contractile properties were not significantly associated with perceived fatigue (Table 3). However, the associations of early- and half relaxation times, increase in early relaxation time, and decrease in MFR with perceived fatigue differed between populations (Table 3; Figure 2). In patients with CML, longer early (β per ms = 1.28, 95%CI = 0.10;2.47) and half relaxation times (β per ms = 5.81, 95%CI = 2.39;9.23) were significantly associated with higher perceived fatigue. In cancer survivors, a larger increase early Rt between the first and last bursts of the fatigability protocol was associated with higher perceived fatigue (β per % = 0.23, 95%CI = 0.02;0.44). These associations were not statistically significant in the other populations. The association between MFR and perceived fatigue differed between populations, however, none of the associations within population subgroups reached statistical significance (Table 3).

Table 2. Descriptive information on demographics, perceived fatigue, physical fitness and muscle contractile properties of the total population and population subgroups

	Total population (n = 217)	Control group[†] (n = 90)	Cancer Survivors (n = 27)	Patients with CML (n = 20)	Patients with COPD (n = 16)	Statin users (n = 64)
Sex, female, n(%)	83 (38)	26 (29)	10 (37)	6 (30)	10 (62)	31 (48)
Age, mean ± sd	63.7 ± 8.9	67.6 ± 5.8	59.3 ± 15.0	54.2 ± 8.4	61.2 ± 8.0	63.6 ± 5.7
Body height (cm), mean ± sd	175.1 ± 8.8	176.4 ± 8.1	173.7 ± 6.3	176.5 ± 10.9	170.0 ± 11.0	174.9 ± 9.1
Body weight (kg), mean ± sd	81.3 ± 14.3	82.0 ± 12.6	80.8 ± 14.3	80.2 ± 13.6	73.8 ± 17.4	82.9 ± 15.7
Body Mass Index (kg/m²), mean ± sd	26.4 ± 3.9	26.3 ± 3.2	26.9 ± 5.0	25.8 ± 4.1	25.1 ± 5.3	27.0 ± 3.8
CIS score, mean ± sd	34.3 ± 9.6		34.7 ± 9.0		33.6 ± 10.8	
BFI score, mean ± sd	1.5 ± 1.8	1.0 ± 1.4		2.3 ± 2.2		1.5 ± 1.7
Perceived fatigue (0-100), mean ± sd	25.2 ± 25.3	9.9 ± 14.0	55.6 ± 18.7*	23.3 ± 21.8	53.3 ± 22.6*	15.0 ± 17.4
PeakVO₂ (ml/kg/min), mean ± sd	32.3 ± 11.4	37.6 ± 11.5	27.5 ± 8.1*	34.6 ± 8.4	15.6 ± 3.8*	31.3 ± 7.3*
Maximal MVC (N), mean ± sd	597.0 ± 177.9	637.3 ± 177.2	484.9 ± 131.6*	660.5 ± 189.2	429.3 ± 138.6*	610.7 ± 158.7
MVC per kg bodyweight (N/kg), mean ± sd	7.4 ± 1.9	7.9 ± 1.8	6.1 ± 1.8*	8.3 ± 2.0	5.9 ± 2.0*	7.4 ± 1.7
Muscle force decline (%), mean ± sd	-30.7 ± 10.2	-29.4 ± 10.0	-29.3 ± 12.2	-31.8 ± 8.7	-35.9 ± 11.3*	-31.3 ± 9.4
Half relaxation time (ms), median [IQR]	33.5 [30.2 - 38.1]	33.0 [30.7 - 36.7]	36.0 [28.7 - 39.3]	32.3 [29.0 - 41.2]	32.0 [29.5 - 36.2]	33.7 [31.6 - 37.2]
Increase in half Rt (%), median [IQR]	91.7 [62.2 - 127.5]	87.3 [60.8 - 132.5]	70.2 [41.9 - 109.6]	86.2 [48.0 - 101.9]	151.5 [118.0 - 218.2]*	92.0 [69.3 - 111.4]
Early Rt (ms), median [IQR]	24.0 [22.0 - 26.2]	24.7 [22.7 - 26.7]	23.0 [21.2 - 26.2]	22.5 [20.6 - 24.5]	22.7 [20.5 - 24.3]	24.3 [22.2 - 26.3]*
Increase early Rt (%), median [IQR]	82.4 [57.6 - 115.2]	76.2 [45.1 - 102.4]	77.6 [58.9 - 114.3]	86.3 [53.8 - 100.4]	157.3 [98.6 - 199.8]*	82.8 [57.6 - 118.7]*
MFR (%/ms), mean ± sd	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.1	0.9 ± 0.2*	0.8 ± 0.1
Decrease in MFR (%), median [IQR]	-14.2 [-28.8 - 7.1]	-12.5 [-26.7 - 7.4]	-7.2 [-16.5 - 3.2]	-14.1 [-22.8 - 6.0]	-33.9 [-41.7 - 27.8]*	-18.0 [-29.9 - -9.7]

*statistically significant difference from control group. Differences are tested using linear regression models corrected for age, sex and study allocation.

[†]Fatigue was available for 38 participants in the control group.

Abbreviations: BFI; brief fatigue inventory, CIS; checklist individual strength, CML; chronic myeloid leukemia, COPD; chronic obstructive pulmonary disease, MFR; Maximal Force Rise, MVC; maximal voluntary contraction, Rt; relaxation time, PeakVO₂; maximal oxygen uptake.

Table 3. Associations of physical fitness and contractile properties with perceived fatigue for the total population and population subgroups

	Overall association with perceived fatigue	Differences between groups*	Association with perceived fatigue for the population subgroups			
			Control group (n = 38)	Cancer Survivors (n = 27)	Patients with CML (n = 20)	Patients with COPD (n = 16)
	β (95%CI)	p-value	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
PeakVO ₂ (ml/kg/min)	-0.22 (-0.76;0.32)	0.550				
MVC (N)	-0.01 (-0.03;0.01)	0.158				
MVC per kg bodyweight (N/kg)	-0.90 (-2.51;0.71)	0.554				
Muscle force decline (%)	0.18 (-0.10;0.46)	0.200				
Half relaxation time (ms)	0.25 (-0.11;0.61)	0.037	-0.06 (-0.56;0.45)	0.26 (-2.13;2.65)	1.28 (0.10;2.47)	-0.63 (-2.14;0.88)
Increase in half Rt (%)	0.04 (-0.02;0.09)	0.469				
Early Rt (ms)	0.12 (-0.11;0.34)	0.010	-0.02 (-0.15;0.10)	-0.34 (-3.75;3.08)	5.81 (2.39;9.23)	-1.42 (-4.77;1.94)
Increase early Rt (%)	0.01 (-0.04;0.07)	0.011	0.00 (-0.07;0.06)	0.23 (0.02;0.44)	0.28 (-0.14;0.69)	-0.04 (-0.21;0.13)
MFR (%/ms)	3.69 (-15.21;22.59)	0.643				
Decrease in MFR (%)	-0.13 (-0.28;0.01)	0.014	-0.17 (-0.51;0.17)	-0.22 (-0.65;0.21)	-0.57 (-1.23;0.09)	-0.37 (-1.26;0.51)

Associations are tested using linear regression analyses corrected for age and sex

*p-value of the likelihood ratio test

Abbreviations: BFI; brief fatigue inventory, CIS; checklist individual strength, CML; chronic myeloid leukemia, COPD; chronic obstructive pulmonary disease, MFR; Maximal Force Rise, MVC; maximal voluntary contraction, Rt; relaxation time.
 Bold values represent statistical significance.

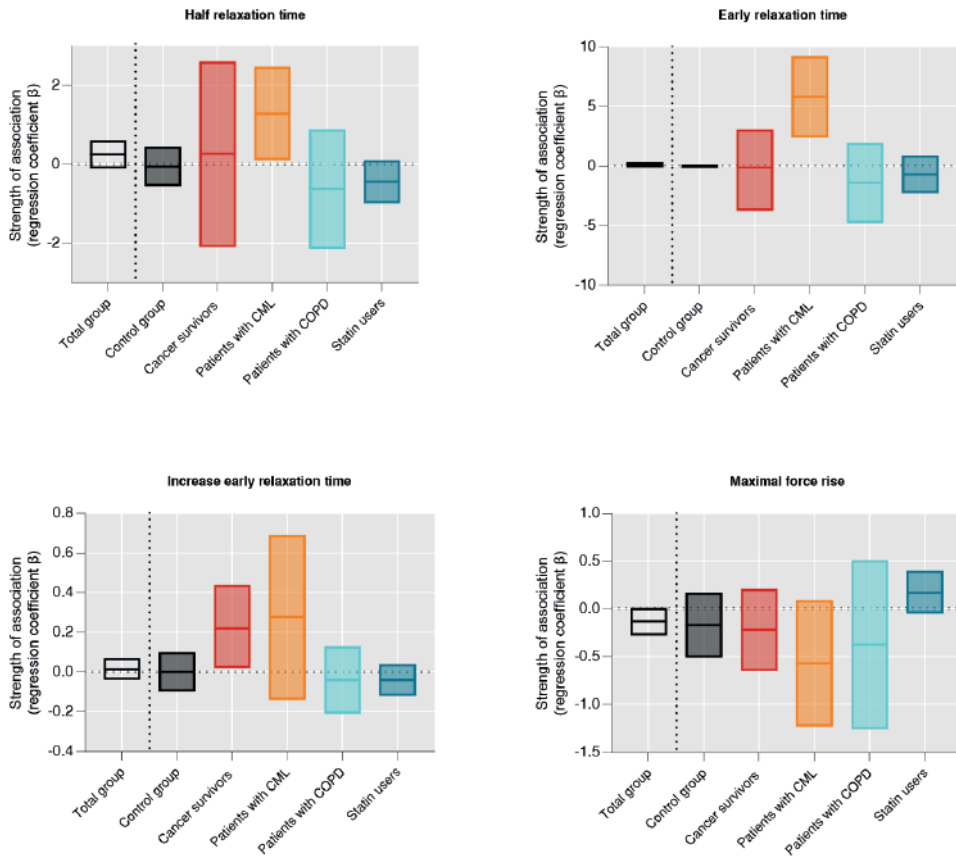


Figure 2. Visual representation of the association represented by the regression coefficient (β) and upper and lower bounds of the 95% confidence interval (CI), between A) half relaxation time, B) early relaxation time, C) increase in early relaxation time, and D) maximal force rise with fatigue across the total population and within population subgroups.

DISCUSSION

Our study evaluated differences in muscle contractile properties, physical fitness and fatigue between specific patient populations and a control group, as well as the association of physical fitness and muscle contractile properties with perceived fatigue. There were three key findings. First, compared with a control group cancer survivors and patients with COPD had a lower muscle strength and aerobic fitness. Second, we found substantial muscle fatigue in patients with COPD and impaired muscle relaxation in statin users compared with a control group. Third, the associations between muscle contractile properties and perceived fatigue were not significant in the total population, and were not uniform across population subgroups. Specifically, impaired muscle relaxation was associated with higher perceived fatigue in hemato-oncological populations, while this was not the case for other subpopulations.

Our findings showed a reduced aerobic fitness and muscle strength in both patients with COPD and cancer survivors. In patients with COPD, a reduced exercise capacity is a frequently reported systemic manifestation of the disease, impacting physical function and quality of life (22). Similarly, in cancer survivors, physical fitness and physical function is often reduced due to the disease or its treatment (23). Patients with CML did not show a reduced physical fitness level in this study, which might be related to treatment or inclusion criteria of the study. In statin users, we found a reduction in aerobic fitness levels but not in muscle strength, which might be related to a reduced level of physical activity or statin associated muscle symptoms, and highlights the importance of aerobic exercise training for this patient population (5, 24). Exercise interventions both incorporating aerobic fitness and muscle strength exercises are recommended in exercise guidelines for patients with COPD and cancer survivors (25, 26) and may help to improve aerobic fitness and muscle strength and thereby physical function and quality of life in these patient populations.

The larger muscle fatigue in patients with COPD as compared with the control group was indicated by the larger muscle force decline and slowing in muscle force development during the fatigability protocol. These changes, as well as the rapid MFR at onset of the fatigability protocol, might be explained by the increased proportion of fast-twitch type II relative to slow-twitch type I muscle fibers, leading to a shift towards a glycolytic muscle metabolism in skeletal muscles of patients with COPD (27). Additionally, the observed slowing in relaxation times during the fatigability protocol in both patients with COPD and statin users might be due to impaired mitochondrial activity or sarcoplasmic reticulum Ca^{2+} handling in skeletal muscles, and might subsequently lead to poor exercise performance we and others found in these populations (21, 28, 29). In statin users, altered early relaxation times compared to the control group might be related to statin-induced myalgia (5, 9, 29). Notably, despite pronounced alterations, muscle contractile properties in these patient populations were not associated with perceived fatigue, suggesting involvement of other mechanisms in the perception of fatigue such as a limited ventilatory capacity, disrupted mechanisms of central

activation or psychosocial factors in patients with COPD (30) or muscle pain and cramps in statin users (5).

Our finding that the association between muscle contractile properties and perceived fatigue was not uniform, suggests differential pathophysiological mechanisms underlying fatigue perception. We found that impaired contractile muscle properties, particularly muscle relaxation, may potentially contribute to perceived fatigue in hemato-oncological populations, while this is less likely in the control group, patients with COPD, and statin users. Slowed relaxation times might be a manifestation of muscle fatigue in these patient populations (31). This suggests that improving muscle relaxation times may potentially be a target to reduce fatigue in the hemato-oncological population (9). For example, moderate-to-high intensity aerobic exercise training has been shown to improve mitochondrial function and aerobic capacity and might thereby have the potential to improve muscle relaxation times (9). Supportively, moderate intensity aerobic exercise alone or combined with resistance exercise has shown to be effective in reducing perceived fatigue in hemato-oncological populations (26). However, it is important to note that exercise is likely to be beneficial for all populations, regardless of the specific role of muscle contractile properties. Furthermore, whether the exercise-induced reduction in fatigue is indeed mediated by muscular mechanisms remains to be elucidated.

A strength of this study is the use of a unique and relatively large dataset containing identical and detailed electrical stimulation measurements in different populations allowing for direct comparison. A limitation of this study is the cross-sectional study design which hampers the ability to draw conclusions on causal mechanisms between muscle contractile properties and perceived fatigue. In addition, the current study setup does not allow for insights into central mechanisms (α -motorneuron activity) or more fundamental muscular mechanisms (muscle fiber type composition, mitochondrial function, or Ca^{2+} handling), which could contribute to fatigue. Additionally, the recordings of perceived fatigue were standardized within studies, but not across studies, potentially introducing variability. However, both fatigue questionnaires have a recall period of at least 24 hours, which might limit within-day variability. Nevertheless, as with any questionnaire, they may have been prone to recall bias. Similarly, not all VO_2max measurements are conducted using gold-standard techniques. The variability introduced by combining maximal and submaximal exercise tests might hamper comparability between groups and detectability of associations. Finally, the small sample size or little variation in perceived fatigue in some subpopulations may have hampered the detection of associations between contractile properties and perceived fatigue in these populations.

Perspective

By presenting detailed information about muscle contractile properties and their association with fatigue in various populations, this study has important clinical implications. Different mechanisms underlying perceived fatigue might be present in these populations,

emphasizing the need for targeted treatment approaches. Future research might focus on causal mechanisms and the optimization of targeted exercise prescriptions in terms exercise type and dosing, to improve exercise capacity and reduce fatigue, across different study populations.

CONCLUSION

The present study demonstrates differences in physical fitness and muscle contractile properties of distinct patient populations and controls. Compared with a control group, patients with COPD and cancer survivors had a lower physical fitness. Also, we demonstrated that muscle contractile properties were not significantly associated with perceived fatigue in the total population of participants, but we found profound differences in associations between population subgroups. Specifically, in hemato-oncological populations we found that impaired muscle relaxation was associated with higher perceived fatigue.

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SUPPLEMENTARY MATERIAL

Table S1. Differences in physical fitness and muscle contractile properties between patient populations and the control group

	Cancer Survivors (n = 27)	Patients with CML (n = 20)	Patients with COPD (n = 16)	Statin users (n = 64)
	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
Body Mass Index (kg/m ²)	1.2 (-0.9;3.3)	0.1 (-2.2;2.5)	-0.3 (-2.7;2.1)	1.0 (-0.6;2.6)
Perceived fatigue (0-100)	37.9 (28.8;46.9)	4.3 (-6.0;14.7)	34.7 (24.2;45.2)	5.7 (-1.1;12.6)
PeakVO₂ (ml/kg/min)	-9.9 (-15.7;-4.1)	-3.6 (-9.8;2.6)	-20.9 (-27.2;-14.6)	-5.5 (-11.0;-0.1)
Maximal MVC (N)	-129.8 (-211.9;-47.8)	16.7 (-75.4;108.8)	-148.3 (-243.3;-53.4)	23.1 (-39.4;85.6)
MVC per kg bodyweight (N/kg)	-1.8 (-2.7;-0.9)	0.0 (-1.0;1.1)	-1.7 (-2.8;-0.7)	-0.1 (-0.8;0.6)
Muscle force decline (%)	-2.7 (-8.4;3.1)	-6.4 (-12.8;0.0)	-10.5 (-16.7;-4.2)	-3.0 (-7.2;1.2)
Half relaxation time (ms)	3.4 (-1.7;8.5)	3.8 (-1.7;9.3)	3.1 (-2.3;8.4)	0.6 (-3.1;4.3)
Increase in half Rt (%)	-13.1 (-49.2;22.9)	-8.6 (-47.4;30.3)	83.1 (45.5;120.7)	14.4 (-11.7;40.5)
Early Rt (ms)	-2.8 (-9.1;3.6)	-3.5 (-10.7;3.6)	-3.1 (-9.9;3.8)	-5.4 (-10.0;-0.8)
Increase early Rt (%)	16.5 (-13.7;46.7)	10.9 (-23.0;44.9)	84.4 (51.7;117.0)	26.2 (4.3;48.2)
MFR (%/ms)	0.0 (-0.1;0.1)	0.0 (-0.1;0.1)	0.2 (0.1;0.3)	0.0 (0.0;0.1)
Decrease in MFR (%)	7.1 (-3.2;17.4)	-0.4 (-12.0;11.1)	-24.3 (-35.7;-13.0)	1.3 (-6.2;8.7)

Differences with the control group are tested using linear regression models corrected for age, sex and study allocation.

Abbreviations: CML; chronic myeloid leukemia, COPD; chronic obstructive pulmonary disease, MFR; Maximal Force Rise, MVC; maximal voluntary contraction, Rt; relaxation time, PeakVO₂; maximal oxygen uptake.

Bold values represent statistical significance.



CHAPTER 7

General discussion

There is a large body of evidence showing that exercise can maintain physical fitness, improve quality of life and limit fatigue during and after cancer treatment (1-4). To optimise the use of exercise as adjunct cancer therapy, knowledge on the potential effects on clinical outcomes and underlying physiological mechanisms is essential (5). Therefore, the aim in the first part of this thesis was to explore the potential of exercise during and after neoadjuvant cancer treatment on clinical outcomes, such as tumour response or surgical complications (**Chapters 2-4**). The aim in the second part of this thesis was to explore the mechanisms via which exercise may reduce fatigue (**Chapters 5-6**)(Figure 1). In this final chapter, we will discuss the main findings of this thesis and address methodological considerations. Furthermore, we propose future research directions and address the clinical implications of the findings of this thesis.

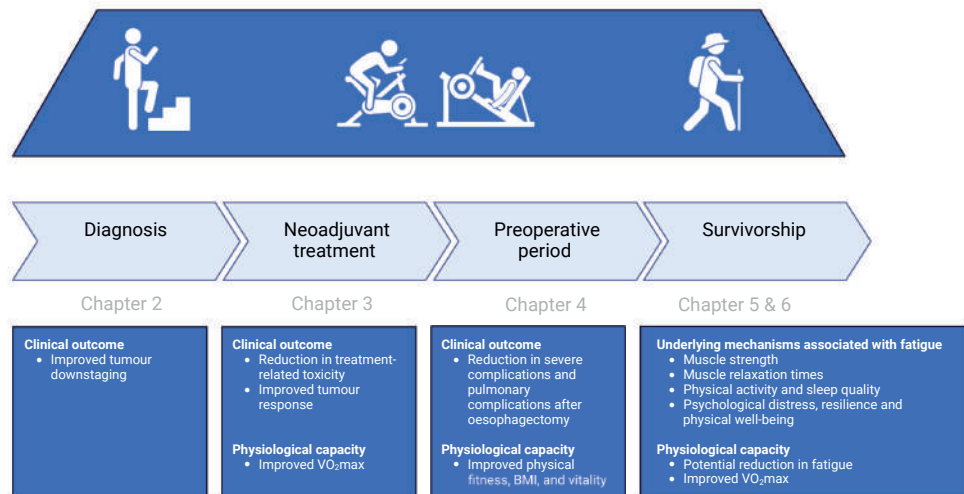


Figure 1. Visualisation of the main findings of this thesis. In this thesis we assessed physical activity levels at the time of diagnosis, and evaluated different exercise programs, including exercise interventions during neoadjuvant treatment, multimodal prehabilitation in the preoperative period, and a walking-exercise intervention in cancer survivorship. Higher physical activity levels and exercise interventions were associated with favourable clinical outcomes (purple boxes), such as an improved tumour response, a reduction in postoperative complications, and potentially contributed to reduced fatigue.

MAIN FINDINGS OF THIS THESIS

Part I. The potential of exercise on clinical outcomes

Higher levels of moderate-to-vigorous physical activity (MVPA) at diagnosis were associated with augmented tumour downstaging after neoadjuvant chemoradiotherapy treatment (NCRT) for rectal cancer (**Chapter 2**). This study used a large dataset with real-world data from a prospective national cohort study of patients with colorectal cancer. In contrast, total physical activity, MVPA in sports and leisure time, adherence to the Dutch physical activity guideline and self-reported physical functioning were not associated with tumour downstaging. Although the results present an association between MVPA at diagnosis and tumour downstaging, causality cannot be determined due to the observational nature of the study. Therefore, future randomised controlled trials are necessary to understand the effects of exercise during NCRT on clinical outcomes, including tumour response. Information on the feasibility of such an exercise trial regarding accrual and exercise adherence is essential prior to the conduct of a large trial.

Therefore, the feasibility and clinical potential of two exercise interventions during NCRT were examined in patients with rectal and oesophageal cancer (**Chapter 3**). In this chapter we demonstrated that both moderate intensity aerobic exercise prior to each radiotherapy fraction (ExPR) and twice-weekly combined moderate-to-high aerobic and resistance exercise (AE + RE) are feasible in patients with oesophageal cancer during NCRT. Feasibility in patients with rectal cancer could not be demonstrated due to the small number of eligible patients and a low participation rate. We found that exercise adherence was substantially higher in the ExPR intervention compared to the AE + RE intervention, highlighting that in-hospital exercise during this intensive chemoradiotherapy period might help to minimise logistical challenges and reduces patient burden. Both the ExPR and the AE + RE interventions yielded significant and clinically relevant effects on aerobic fitness after NCRT compared to the usual care control group. Furthermore, we observed clinically relevant beneficial effects of both exercise interventions on treatment-related toxicity and a 15% higher proportion of patients with a good tumour response compared to a usual care control group. Therefore, starting current prehabilitation programs during neoadjuvant treatment rather than starting in the waiting period prior to surgery, may enhance baseline fitness levels and provide significant clinical benefits for patients with oesophageal cancer. Due to the small sample size, intervention effects on clinical outcomes remain hypothesis-generating, and larger trials on the effects of prehabilitation on clinical outcomes are needed.

To further examine the clinical potential of exercise, the effect of a multimodal prehabilitation program (comprising an exercise, nutritional, psychological and smoking cessation component) during the waiting period prior to surgical resection on postoperative outcomes was evaluated in a large cohort of patients with oesophageal cancer, compared to a propensity score-matched control cohort (**Chapter 4**). The findings of this study showed

that patients who received multimodal prehabilitation were less likely to experience severe complications and pulmonary complications following an oesophagectomy. Furthermore, the multimodal prehabilitation program significantly improved physical fitness, BMI and vitality. These findings have important clinical relevance by reducing postoperative morbidity, enhancing recovery, and potentially improving disease-free survival (6).

Part II. Potential mechanisms by which exercise may reduce fatigue

Fatigue is a prevalent and debilitating side effect during and after cancer treatment, with approximately 25% of cancer survivors experiencing long-term fatigue significantly diminishing their quality of life (7, 8). Exercise has been identified as an effective nonpharmacological treatment of fatigue in cancer survivors and other patient populations (9, 10). However, knowledge on the mechanisms underlying the effects of exercise on fatigue might help to improve the efficacy of interventions by identifying and subsequently targeting effective exercise components. Therefore, the results from the studies in **Chapter 5** and **Chapter 6** present several potential mechanisms associated with fatigue.

We evaluated the effects of a 4-month walking exercise program on cancer-related fatigue (**Chapter 5**). Although the results from this study indicated that cancer survivors had a clinically relevant reduction in fatigue severity during the study, this effect could not be attributed to the walking intervention. Patients had already altered their exercise behaviour during the control period, which might have contributed to the reductions in fatigue. Increases in muscle strength, physical activity, and sleep quality, as well as decreases in psychological distress were associated with reductions in fatigue. Furthermore, cancer survivors perceived that resilience and physical well-being were most important benefits of the walking intervention, contributing to improvements in fatigue. On a muscular level, we found an association between increases in muscle relaxation times, which might be a manifestation of muscle fatigue, and higher perceived fatigue in cancer survivors.

Furthermore, in the study described in **Chapter 6**, we found that muscle relaxation times were associated with fatigue not only in cancer survivors but also in patients with chronic myeloid leukaemia (CML). We also showed that the associations between muscle contractile properties and perceived fatigue were not uniform across patient populations. In addition, we demonstrated that muscle contractile properties were significantly impaired in patients with chronic obstructive pulmonary disease (COPD) and statin users, compared to a control group. These findings suggest that while exercise may be beneficial for all patient groups, it should be tailored to address the specific differences in muscle contractile properties related to fatigue in each population.

DISCUSSION OF MAIN FINDINGS

Methodological considerations

When interpreting the findings of this thesis, some methodological considerations related to the study designs need to be taken into account. Most findings in this thesis are derived from studies with observational and quasi-experimental study designs. In addition, a randomised controlled trial (RCT) was conducted, which is considered the gold standard for assessing intervention effects and establishing causality (11). Despite the strengths of each study design, several limitations associated with the study designs used must be considered.

A main limitation of the observational study designs is the inability to make causal inferences. For example, from the association found between MVPA and tumour downstaging (**Chapter 2**) it is not clear whether improving MVPA could enhance tumour downstaging or whether patients with favourable tumour characteristics are more physically active, as they have less disease burden. Similarly, the association between slower muscle relaxation and higher perceived fatigue (**Chapter 6**) might indicate that patients with lower levels of perceived fatigue are more likely to engage in activities that enhance muscle relaxation. Despite the limitations, observational studies often use large datasets and real-world data which improves generalizability. For example, the study presented in **Chapter 2** has a large sample size and uses nation-wide real-world data, allowing to adjust for relevant confounders. In addition, by pooling data from different study populations, the dataset used in the study in **Chapter 6** facilitated between-group comparisons, thereby strengthening the credibility of our findings.

Although RCTs are the gold-standard study designs to study exercise effects, they are not always feasible. In the KINETICS study in **Chapter 5**, an RCT design was not desired because of the timing of the walking exercise program, which was designed to prepare participants for the Four Days Marches in Nijmegen. Instead, we used a quasi-experimental interrupted time-series design in this trial, starting with a 4-month control period in which each participant acted as their own control. Although this design allowed for potential contamination of the control period, it still enabled a comprehensive evaluation of the effect of the walking-exercise intervention on cancer-related fatigue and the identification of mechanisms associated with changes in fatigue.

The F4S PREHAB trial, described in **Chapter 4**, used a stepped-wedge trial design rather than a randomised design, which is preferred in case of ethical concerns about withholding a potentially beneficial intervention from a particular group of patients. This stepped-wedge trial design resulted in a small number of patients with oesophageal cancer in the control group, as the prehabilitation intervention in this patient cohort was introduced shortly after the trial started. To address this limitation, we supplemented the control group with observational historical data and used a quasi-experimental study design with propensity score matching (PSM) in **Chapter 4**. PSM is a valid and robust method because it controls for confounding and generates similar study cohorts based on baseline characteristics. However,

the potential for residual confounding and the accuracy of PSM, which depends on the quality of historical data and the handling of missing data, remain limitations.

Lastly, as described in **Chapter 3**, the EXENTRO trial had a three-arm pilot RCT design. Although an RCT is the preferred trial design for demonstrating intervention effects, the EXENTRO was underpowered by design hampering statistical power to sufficiently prove effects. Furthermore, as with all exercise trials, there remained a potential risk of contamination in the control group (12). Despite these limitations, the EXENTRO trial demonstrated the feasibility of two exercise interventions and generated important hypotheses for future research.

Altogether, the promising results of exercise during and after cancer treatment on treatment-related toxicity and clinical outcomes presented in this thesis highlight the need for future research on the potential causal effects and underlying mechanisms.

Future perspectives and hypothesised physiological mechanisms explaining exercise effects on clinical outcomes

The studies presented in this thesis show an association between exercise prior to and during NCRT and tumour response (**Chapter 2 and 3**). However, causality needs to be confirmed in future trials powered on tumour response as primary outcome. Furthermore, the relationship between exercise-induced physiological mechanisms during and after exercise and tumour response needs to be explored to understand the potential synergistic effects of exercise and cancer treatment (13). While preclinical studies have investigated potential underlying mechanisms by which exercise might influence clinical outcomes, clinical research in patients is limited (14). Therefore, a secondary and future aim of the EXENTRO trial is to elucidate the potential underlying mechanisms by which exercise influences tumour response after NCRT in patients with oesophageal cancer (clinicaltrials.gov identifier: NCT05686213). The future part of the EXENTRO study will focus on two pathways that might influence the effect of exercise on tumour response: 1) exercise-induced changes in mobilisation, function, and intratumoural infiltration of immune cells, and 2) alterations of intratumoural vasculature and hypoxia (14, 15).

Potential effects of exercise on tumour response

Results from the EXENTRO trial in **Chapter 3** suggest potential beneficial effects of both exercise interventions on tumour response in patients with oesophageal cancer, which is further supported by the association between MVPA and tumour response observed in **Chapter 2**. One mechanism via which exercise might directly impact tumour response is through an improved immune status. Even a single bout of exercise could impact pathways that induce beneficial effects on the immune system. For example, previous research demonstrated that an acute bout of exercise can mobilise lymphocytes, including natural killer (NK) cells and CD8+ T cells, into the bloodstream in both healthy individuals and patients

with cancer (16, 17). This exercise-induced mobilisation of lymphocytes has shown to be dependent on a release of (nor)epinephrine and adrenergic mechanisms combined with a higher shear stress on blood vessels due to an increased mean arterial pressure (18). To investigate whether lymphocytes are mobilised after an exercise bout in patients with oesophageal cancer undergoing NCRT in the EXENTRO trial, blood samples were drawn before and after a 30-minute aerobic exercise session in the ExPR group.

Results demonstrated an increase in circulating white blood cells, lymphocytes, monocytes and neutrophils following 30 minutes of moderate intensity cycling exercise in patients enrolled in the EXENTRO trial (Figure 2). This increase could potentially have clinical implications, as a previous study in patients with oesophageal cancer showed that a higher number of circulating memory T cells was associated with a better tumour response after NCRT (19). Consequently, the increase number of lymphocytes might contribute to the suggested improvement in tumour response we presented in **Chapter 2 and 3**. Given that the mobilisation of lymphocytes is associated with changes in blood pressure and heart rate, exercise-induced immune responses may vary depending on the intensity, duration, and type of exercise (20). Therefore, future research should investigate the optimal FITT principles (frequency, intensity, type, and timing) of exercise during cancer treatment to optimise immune mobilisation and thereby potentially enhance tumour response.

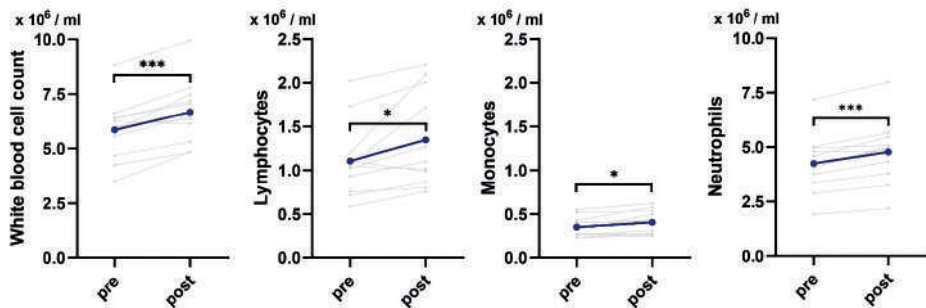


Figure 2. Unpublished results of the EXENTRO study showing an increase in white blood cell count, absolute lymphocytes, monocytes, and neutrophils pre and post 30 minutes of moderate-intensity aerobic cycling exercise in 11 patients included in the EXENTRO study.

Beyond the acute immune mobilisation after an exercise bout, exercise training, which can be considered as repeated bouts of exercise, has been suggested to enhance NK cell and T-cell function and cytotoxicity in patients with cancer (18, 20, 21). An enhanced NK cell and T-cell function is another potential mechanism that could partly explain the link between exercise and tumour response suggested in **Chapters 2 and 3**. This enhancement might be particularly important in patient undergoing NCRT as both chemotherapy and

radiotherapy can impair NK cell viability and function (22, 23). Furthermore, preservation of NK cell function during radiotherapy may synergistically augment the effects of radiotherapy on tumour response (22, 24). Future analyses of the EXENTRO study will assess how exercise affects changes in NK- and T-cell function and cytotoxicity over time, using peripheral blood mononuclear cells (PBMCs) derived from blood samples that were collected before and after NCRT, and prior to surgery, corresponding to the time points of the physical tests.

In addition to exercise-induced mobilisation and enhanced function of immune cells, exercise may also promote increased infiltration of lymphocytes into tumour tissue, as previously demonstrated in rodents (20, 25). In clinical studies, an increased infiltration of NK and T cells into tumour tissue has been demonstrated in patients with prostate cancer who adhered to an exercise intervention (26, 27). Enhanced immune cell infiltration may exert significant antitumour effects and thereby potentially improve tumour response, providing a plausible mechanism for the suggested associations in **Chapters 2 and 3** (19, 28). Thus, investigating the link between exercise-induced immune infiltration in the tumour tissue and tumour response following neoadjuvant therapy represents a crucial area of research, advancing our understanding and clinical application of exercise interventions for patients with cancer. In line, future analyses of the EXENTRO trial will include immunohistochemistry (IHC) to assess the number and subsets of infiltrating lymphocytes in both the diagnostic and resected tumour tissue samples.

Potential of exercise as radiotherapy sensitiser

Another proposed physiological mechanism by which exercise might influence tumour response is through an exercise-induced ‘normalisation’ of intratumoural vasculature and a reduction in hypoxia, which might help explain the suggested link between exercise and tumour response presented in **Chapter 2 and 3**. Intratumoural hypoxia due to functionally abnormal tumour vasculature is one of the main factors hampering radiotherapy efficacy in patients with solid tumours (29). Besides hampering radiotherapy efficacy, an abnormal tumour vasculature might also hamper delivery of chemotherapeutic agents and immune cells. Therefore, normalising intratumoural vasculature and reducing hypoxia might enhance both radiotherapeutic and chemotherapeutic efficacy and antitumour immune response. Pre-clinical studies showed promising results on exercise as a strategy to normalise intratumoural vasculature and reduce hypoxia. However, these results might not be directly translatable to patients and clinical evidence is scarce (30, 31).

An acute exercise bout might improve tumour perfusion and induce mild hyperthermia, potentially reducing hypoxia and thereby improving therapeutic efficacy when timed immediately before a radiotherapy fraction in patients (32). Furthermore, a previous study in patients with pancreatic cancer showed that exercise training could normalise tumour vasculature (33), likely due to mechanisms induced by shear stress (31). However, current clinical evidence is primarily based on *ex vivo* IHC analyses and very small sample sizes (30).

Future analyses of the EXENTRO study will evaluate the potential exercise-induced changes in intratumoural vascularisation and hypoxia using IHC analyses on diagnostic biopsies and surgical resection material. Despite the promising prospects of the EXENTRO analyses, more research is necessary. In particular, future studies using *in vivo* imaging techniques are essential to elucidate both the acute and chronic effects of exercise on tumour perfusion and hypoxia. These insights are crucial for the effective tailoring and timing of exercise as adjunct cancer therapy to optimally utilise its potential beneficial radiosensitising effects.

Potential effects of exercise on postoperative outcomes

The study in **Chapter 4** of this thesis demonstrated beneficial effects of a multimodal prehabilitation program, including a high-intensity exercise modality, on postoperative complications after an oesophagectomy for oesophageal cancer. This type of high-impact surgery can induce a physiological stress response, disrupting endocrine, immune, and haemodynamic homeostasis (34). Exercise may help to manage this stress response by enhancing cardiorespiratory fitness, thereby supporting the body's ability to meet the increased oxygen demands in the perioperative period (35). Furthermore, exercise might enhance the immune system (18), potentially improving the body's ability to withstand the hyperinflammatory state following surgery (36). Other prehabilitation components, such as adequate nutrition and a good mental well-being, might further support the immune system (37). Together, these mechanisms provide a plausible starting point for understanding the reduction in postoperative complications observed after the multimodal prehabilitation intervention.

However, an improved cardiorespiratory fitness and immune status are only two of the many proposed mechanisms by which multimodal prehabilitation might influence postoperative complications (38). The beneficial effects might rather result from an accumulation of marginal gains across various areas such as anaemia, aerobic capacity, inflammation, nutrition, frailty, smoking cessation and medication optimisation (38). In order to optimally tailor multimodal prehabilitation, it is necessary to understand the most important components of the intervention, which may require large clinical trials. Additionally, although prehabilitation may be beneficial for all patients, identifying specific subgroups most in need of these interventions is crucial for effective implementation in clinical practice (39).

Potential of exercise on fatigue and underlying mechanisms

Chapters 5 and 6 of this thesis present potential underlying physiological mechanisms of exercise on fatigue. In cancer survivors, multiple physiological, behavioural and psychological mechanisms were found to be associated with fatigue (**Chapter 5**). Particularly, addressing constructs such as resilience and physical well-being in a multimodal interventional approach has potential to alleviate fatigue. Furthermore, our findings on muscle contractile properties and fatigue in different patient populations demonstrated that exercise prescriptions should

not follow a “one-size-fits-all” approach, as the underlying mechanisms and pathophysiology may vary between populations (**Chapter 6**).

To illustrate, we found an association between muscle relaxation times and perceived fatigue, which was observed in patients with CML and cancer survivors, but not in other populations (**Chapter 6**). Prolonged muscle relaxation times might result from an impaired Ca^{2+} regulation or a disrupted adenosine triphosphate (ATP) homeostasis (40). In patients with CML, the association between early and half relaxation times and perceived fatigue might be linked to the glycolytic pathway disruptions caused by the use of tyrosine kinase inhibitors (TKIs) (41, 42). However, the exact mechanisms underlying the association between relaxation times and perceived fatigue in this patient group remains speculative since mitochondrial function and density did not appear to be affected by TKI use (43). In cancer survivors, the use of chemotherapeutic agents might have led to a reduced mitochondrial biogenesis and function, as well as an altered Ca^{2+} metabolism (44, 45). Furthermore, chemotherapy might lead to muscle atrophy, as seen in muscle biopsies, affecting both slow-twitch muscles fibres and to a greater extent fast-twitch muscle fibres (46). This shift in muscle fibre type expression may be reflected by the increase in relaxation times found in **Chapter 5 and 6** (47). High-intensity aerobic exercise training is a strategy to preserve skeletal muscle fibre area and mitochondrial content in patients with cancer, while resistance exercise may be a beneficial strategy to maintain muscle strength and muscle fibre area (48, 49).

Thus, the underlying muscular mechanisms are critical to consider for healthcare providers when tailoring exercise programs for different patient populations experiencing fatigue. Exercise might provide an effective alternative treatment strategy to pharmaceutical approaches (9). Future research should focus on elucidating the causal mechanisms by which exercise affects fatigue and exploring the potential additional benefits of incorporating psychosocial support, such as cognitive behavioural therapy which has been proven to effectively reduce fatigue. Additionally, future studies should focus on developing targeted exercise prescriptions that specify exercise type, intensity, and duration, and the need for a multidisciplinary approach by adding psychosocial components.

CLINICAL IMPLICATIONS

The results of this thesis suggest that a comprehensive prehabilitation program, already starting during neoadjuvant treatment, has the potential to improve physiological capacity and clinical outcomes in patients undergoing NCRT for oesophageal cancer. Although this thesis focuses on patients with rectal and oesophageal cancer, the potential benefits of prehabilitation starting during neoadjuvant treatment might also be generalisable to other patient populations. These findings may have clinical impact by enhancing physical fitness,

reducing surgical complications, and potentially enhancing treatment efficacy, for the growing number of patients with solid tumours who are treated with neoadjuvant therapy (50). Additionally, this thesis provides suggestions for exercise interventions in cancer survivors to target fatigue, which should incorporate resistance exercise and address the constructs of resilience and physical well-being. Implementing tailored exercise interventions for cancer survivors after treatment could be an effective strategy to alleviate fatigue and thereby improve long-term health-related quality of life. Although the findings of this thesis support existing international guidelines recommending physical activity during and after cancer treatment (4, 51, 52), healthcare providers such as surgeons, radiation oncologists, and medical oncologists often perceive barriers to refer patients to physical therapists, such as the limited capacity for the delivery of physical activity programmes (53).

Despite these perceived barriers, the successful execution of the exercise interventions described in **Chapters 3 and 4** demonstrates how the growing availability of resources and physical therapists specialised in oncology can help overcome such barriers. In the Netherlands, there are well-established networks of physical therapists trained in oncology (e.g. Onconet or FyNeOn), that facilitate referral by providing an easily accessible online resource for medical specialists. Specialised physical therapists are available in most areas in the Netherlands, allowing the majority of patients to reach a qualified physical therapist within a 15-minute travel radius. The results from both the EXENTRO (**Chapter 3**) and F4S PREHAB (**Chapter 4**) trials demonstrate the feasibility of prehabilitation interventions supervised by a local physical therapist (54). Furthermore, the F4S PREHAB trial successfully integrated multimodal prehabilitation as part of standard clinical care in the Radboudumc, a large university medical centre. Unfortunately, supervised exercise during or after cancer treatment at a local physical therapy practice are currently not covered by basic healthcare insurance in the Netherlands.

As an alternative to exercise training at a physical therapist practice, the results from the EXENTRO trial (**Chapter 3**) demonstrated the feasibility of an in-hospital daily aerobic exercise intervention during NCRT for oesophageal cancer. A low-burden exercise intervention is essential during the intensive NCRT treatment, as patients have to cope with a demanding treatment schedule that includes daily hospital visits on weekdays for radiotherapy, weekly chemotherapy administrations, consultations with medical oncologists, radiation oncologists, and dietitians, as well as routine blood draws. The in-hospital exercise intervention at the department of radiation oncology minimises logistical challenges and reduces patient burden compared with exercise at a physical therapist's practice. Placing cycle ergometers in or near the waiting room of the radiation oncology department offers a feasible and easily implementable approach. This approach could be efficiently scaled up to provide potential benefits for patients undergoing radiotherapy. Although supervised exercise sessions may be more effective (2), unsupervised training interventions, when combined with strict triage to identify patients at risk and guidance through tailored eHealth devices, could serve as an effective low-cost alternative (55).

The lack of clinical implementation of exercise interventions during and after cancer treatment is often attributed to missing evidence on the effects of exercise on clinical outcomes (56). However, establishing causal effects of exercise on clinical outcomes such as tumour response and disease-free survival requires large, well-powered trials. These trials require extended inclusion periods and long follow-up times, as seen in the CHALLENGE trial (57), which is expected to span approximately 15 years. Given these limitations, there is a growing interest in more innovative and more efficient research designs, such as adaptive trials, as exemplified by the AMICO trial (clinicaltrial.gov ID: NCT04754672). Such adaptive trials require early clinically relevant endpoints (58). In the neoadjuvant setting, tumour response may be such an early observable endpoint, as demonstrated by the EXENTRO trial. Simulation studies have demonstrated that these adaptive trial designs can yield the same conclusions based on a smaller sample size (59). Such novel research designs may help to bridge the existing knowledge gap on the effects of exercise on clinical outcomes. While future research on physiological mechanisms and (long-term) clinical outcomes is warranted, there are no major disadvantages to integrating exercise as part of standard care to improve physical fitness and quality of life (1-4).

CONCLUSIONS

The findings of this thesis demonstrate the potential of exercise on clinical outcomes, including treatment-related toxicity, surgical complications, and tumour response, as well as long term fatigue. Additionally, the results provide insights into potential physiological, psychological and behavioural mechanisms underlying fatigue. Moreover, this thesis offers valuable insights into potential underlying mechanisms linking exercise to clinical outcomes and identifies starting points for future research in the field of exercise oncology. Collectively, this thesis provides valuable evidence for the potential of Exercise as Therapy in Oncology.

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CHAPTER 8

Summary

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A general introduction on the current prevalence of cancer and the recent developments in multimodal treatment strategies was provided in **Chapter 1**. In this chapter, multimodal treatment strategies in patients with oesophageal and rectal cancer, and the potential side effects of these treatments were described. It was highlighted that physical exercise can mitigate side effects of neoadjuvant treatment, enhance physiological capacity prior to surgical resection and enhance recovery after completion of treatment. Additionally, several underlying physiological, psychological, and behavioural mechanisms by which exercise can reduce fatigue were described. We emphasised that there is a gap in knowledge of the potential effects of exercise on clinical outcomes and underlying physiological mechanisms of action, which hampers the implementation of exercise as an integral part of cancer care. Therefore, the aim in the first part of this thesis was to explore the potential of exercise during and after neoadjuvant treatment on clinical outcomes. The aim in the second part of this thesis was to explore the mechanisms via which exercise may reduce fatigue.

In **Chapter 2**, we evaluated whether physical activity and physical functioning at diagnosis were associated with tumour downstaging after neoadjuvant chemoradiotherapy (NCRT), among 268 patients with rectal cancer who participated in the Dutch nationwide Prospective ColoRectal Cancer Cohort. We found that patients with moderate or high levels of self-reported moderate-to-vigorous physical activity (MVPA) before the start of NCRT were twice as likely to have good/complete tumour downstaging compared to patients with low MVPA levels. Although these results suggest a clear link between MVPA at diagnosis and tumour downstaging, causality cannot be determined due to the observational nature of the study. Hence, future randomised controlled trials are necessary to understand the causal effects of exercise during NCRT on clinical outcomes. Prior to the conduct of a large trial, information on the feasibility is warranted.

Therefore, in **Chapter 3**, we assessed feasibility of two different exercise interventions during NCRT in patients with rectal and oesophageal cancer and explored the effects on physical fitness, treatment-related toxicity, and tumour response. In total, 37 patients with oesophageal cancer and 2 patients with rectal cancer were randomised into one of three study arms during NCRT: 1) 30-min in-hospital aerobic exercise within one hour prior to each radiotherapy fraction, 2) two 60-min supervised combined aerobic and resistance exercise sessions per week and a 30-min moderate-intensity home-based exercise session, and 3) usual care. We showed that starting prehabilitation already during NCRT is feasible and can elevate starting fitness levels of traditional 3–4-week pre-surgical prehabilitation programs. The 98% attendance rate and clinically relevant effects on aerobic fitness suggests that in-hospital exercise during the intensive chemoradiotherapy period minimises logistical challenges and reduces patient burden compared to attending exercise sessions at a physical therapist with had an attendance rate of 78%. Both exercise programs had clinical potential by reducing treatment-related toxicity compared with the usual care control group. Furthermore, the percentage of patients with a good tumour response was 15% higher in

both exercise groups compared to the usual care control group. Due to the small sample size, intervention effects on clinical outcomes remain hypothesis-generating, and larger trials on the effects of prehabilitation on clinical outcomes are needed.

Consequently, in **Chapter 4**, we evaluated the effects of a multimodal prehabilitation program on postoperative complication rates after oesophagectomy in a large group of patients with oesophageal cancer. This study compared data from the F4S PREHAB trial with a propensity-score matched historical control cohort of patients undergoing minimally invasive oesophagectomy. We found that prehabilitation was associated with a 10% reduction in both severe complications and pulmonary complications after oesophagectomy. Furthermore, prehabilitation enhanced patients' physiological capacity and yielded clinically relevant effects on vitality prior to surgery. Patients with a reduction in percentage body fat and improvements in mental health were less likely to experience severe complications. These results are of important clinical relevance by reducing postoperative morbidity after oesophagectomy, enhancing recovery, and potentially improving long-term survival.

The aim in the second part of this thesis was to explore the mechanisms via which exercise may reduce fatigue. In **Chapter 5** we explored the effects of a 4-month walking exercise program on fatigue severity and the potential underlying physiological, behavioural, and psychological mechanisms of action, supplemented with participants' perceptions on how exercise influenced their fatigue. We found a significant and clinically relevant decrease in fatigue severity over time, which could not be attributed directly to the walking exercise intervention but could partly be explained by a change in physical activity behaviour during the baseline period. The findings in this chapter showed that increases in muscle strength, physical activity, sleep quality, and reductions in muscle relaxation times and psychological distress were associated with reductions in fatigue severity. Furthermore, cancer survivors identified resilience and physical well-being as most important constructs explaining the walking exercise effects on fatigue.

In **Chapter 6**, we pooled data on perceived fatigue, physical fitness, and muscle contractile properties from six studies, including a control group, cancer survivors, patients with chronic obstructive pulmonary disease, chronic myeloid leukaemia, and statin users. This study aimed to identify differences in contractile properties and physical fitness between populations and examine associations with perceived fatigue. We demonstrated that muscle contractile properties, specifically muscle force decline, relaxation times, and maximal force rise, were impaired in patients with COPD, and that relaxation times were impaired in statin users. Furthermore, we found that associations between contractile properties and perceived fatigue varied across populations. In hemato-oncological populations, impaired muscle relaxation was associated with higher perceived fatigue. These results demonstrated that exercise prescriptions targeting fatigue should not follow a "one-size-fits-all" approach, as the underlying mechanisms and pathophysiology may vary between populations.

In **Chapter 7**, the main findings of this thesis were presented, demonstrating that exercise during and after the neoadjuvant treatment is feasible and can have beneficial effects on physiological capacity and clinical outcomes. Furthermore, the findings of this thesis demonstrated mechanisms via which exercise may reduce fatigue. In addition, methodological considerations of the different study designs used in this thesis were discussed. Subsequently, we highlighted future perspectives for exercise oncology research and emphasised the importance of future clinical trials to investigate the effects on clinical outcomes and to unravel underlying mechanisms of action. Examples of these mechanisms by which exercise might contribute to an improved tumour response in patients are an exercise-induced improvement in immune function, immune cell infiltration in the tumour, and reductions in intratumoural hypoxia. In line with these hypotheses, we described the secondary and future aim of the EXENTRO trial to explore these potential underlying mechanisms in patients with oesophageal cancer during NCRT. In addition, we proposed several underlying physiological mechanisms by which exercise might influence clinical outcome after surgery, potentially resulting from an accumulation of marginal gains in areas such as anemia, aerobic capacity, and inflammation. Furthermore, mechanisms were suggested by which exercise may reduce fatigue, such as improvements in muscle relaxation times. Lastly, we discussed the clinical implications of the potential effects of exercise on clinical outcomes and emphasised the value to incorporate exercise as part of standard clinical practice.

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Hoofdstuk 1 gaf een algemene introductie over het aantal kankerdiagnoses per jaar en de recente ontwikkelingen in behandelstrategieën. In dit hoofdstuk werden voorbeelden van multidisciplinaire kankerbehandelingen voor patiënten met endeldarm- en slokdarmkanker en de mogelijke bijwerkingen van deze behandelingen benoemd. Daarnaast werden de mogelijke positieve effecten van fysieke inspanning als ondersteunende zorg beschreven, zoals het verminderen van bijwerkingen of het verbeteren van de fysiologische capaciteit tijdens de neoadjuvante behandeling, voorafgaand aan een operatie en na afronding van een behandeling. Ook werden de mogelijke fysiologische, psychologische en gedragsmechanismen die ten grondslag kunnen liggen aan vermoeidheid beschreven. We benadrukten dat er kennis ontbreekt over mogelijke effecten van fysieke inspanning op klinische uitkomsten en de mogelijke onderliggende mechanismen, wat eraan bijdraagt dat trainingsprogramma's nog niet als standaardzorg worden geïmplementeerd. Het eerste doel van dit proefschrift was daarom om te onderzoeken wat de mogelijke effecten van fysieke inspanning tijdens en na de neoadjuvante behandeling zijn op de klinische uitkomsten. Het tweede doel van dit proefschrift was om de onderliggende mechanismen in kaart te brengen die effecten van fysieke inspanning op vermoeidheid kunnen verklaren.

In **Hoofdstuk 2** onderzochten we of de mate van fysieke activiteit en het fysiek functioneren rondom de diagnose endeldarmkanker geassocieerd was met het verkleinen van de tumor na neoadjuvante chemoradiotherapie (NCRT). We onderzochten dit in 268 patiënten met endeldarmkanker die behandeld werden met NCRT uit het Prospectief Landelijk Colorectaal Kanker Cohort (PLCRC), een nationaal cohort dat te gebruiken is voor wetenschappelijk onderzoek. We vonden dat patiënten die een matig of hoog niveau van matig-tot-zware fysieke activiteit (MVPA) rapporteerden voor de start van de NCRT, een twee keer zo grote kans hadden op een goede of complete behandelrespons dan patiënten met een laag niveau van MVPA. Hoewel deze resultaten een verband laten zien tussen MVPA bij diagnose en een reductie in het tumor stadium, kon het oorzakelijke verband niet worden bepaald met deze observationele studieopzet. Daarom zijn toekomstige gerandomiseerde studies met een controlegroep nodig om de effecten van fysieke inspanning tijdens NCRT op de klinische uitkomsten te bepalen. Echter, voordat een grote trial naar het effect op klinische uitkomsten opgezet kan worden is inzicht nodig in de haalbaarheid van een dergelijke studie.

Daarom onderzochten we in **Hoofdstuk 3** de haalbaarheid van twee verschillende inspanningsinterventies gedurende de periode van NCRT bij patiënten met endeldarm- en slokdarmkanker, waarbij we ook de potentiële effecten op fysieke fitheid, behandelingsgerelateerde bijwerkingen en tumor respons in kaart brachten. Zevenendertig patiënten met slokdarmkanker en twee patiënten met endeldarmkanker werden gerandomiseerd in een van de drie studie armen gedurende NCRT: 1) 30 minuten fietstraining in het ziekenhuis binnen een uur voorafgaand aan iedere bestraling, 2) twee training sessies van 60 minuten gecombineerde kracht en duurtraining per week en een matig intensieve trainingssessie van 30 minuten vanuit huis, en 3) standaardzorg. We toonden aan dat het

starten van de fysieke training tijdens NCRT haalbaar is en dit het startniveau van de fitheid voor traditionele trainingsprogramma's voorafgaand aan een operatie kan verbeteren. Met name bij de dagelijkse fietstraining voorafgaand aan de bestraling was dit effect zichtbaar. De patiënten konden de dagelijkse fietstrainingen beter volhouden (98%) dan de trainingen bij de lokale fysiotherapeut (78%), wat mogelijk te verklaren is doordat tijdens de intensieve periode van chemoradiotherapie een trainingsprogramma in het ziekenhuis de logistieke uitdagingen vermindert en de last voor de patiënten verlaagt. Beide trainingsprogramma's kunnen behandelingsgerelateerde bijwerkingen verminderen ten opzichte van de controlegroep. Ook was het percentage patiënten met een goede tumor response 15% hoger in de trainingsgroepen in vergelijking met de controlegroep. Door het kleine aantal patiënten blijven de interventie-effecten op klinische uitkomsten vooral hypothese-genererend en zijn er grotere studies naar de effecten van prehabilitatie op klinische uitkomsten nodig.

Daarom evalueerden we in **Hoofdstuk 4** de effecten van een multimodaal programma voorafgaand aan een operatie (een prehabilitatie programma) op postoperatieve complicaties na een slokdarm-verwijderende operatie (oesofagectomie) bij patiënten met slokdarmkanker. In deze studie vergeleken we gegevens van patiënten met slokdarmkanker die een minimaal invasieve oesofagectomie ondergingen uit de F4S PREHAB studie met een gematchte historische controlegroep. We toonden aan dat deelname aan prehabilitatie geassocieerd was met een afname van 10% in ernstige complicaties en pulmonaire complicaties na een oesofagectomie. Daarnaast vonden we dat prehabilitatie de fysiologische capaciteit en de vitaliteit van de patiënten voorafgaand aan een oesofagectomie verhoogt. Patiënten met een daling in vetpercentage of een verbetering in mentale gezondheid na het prehabilitatie programma hadden minder kans op het krijgen van een ernstige complicatie. Deze resultaten zijn relevant voor de klinische praktijk omdat ze laten zien dat prehabilitatie postoperatieve morbiditeit na een oesofagectomie kan verminderen en daarmee mogelijk het herstel kan versnellen en de lange termijn overleving van deze patiënten kan verbeteren.

In het tweede gedeelte van dit proefschrift hebben we ons gericht op het in kaart brengen van de mechanismen onderliggend aan vermoeidheid en de mogelijke effecten van fysieke inspanning op vermoeidheid. Het doel van **Hoofdstuk 5** was daarom om inzicht te krijgen in het effect van een 4 maanden durend wandeltrainingsprogramma op de ernst van vermoeidheid en om de potentiële onderliggende fysiologische, psychologische en gedragsmechanismen in kaart te brengen. Daarbij verzamelden we ook de ervaringen van deelnemers over hoe wandeltraining hun vermoeidheid beïnvloedde. Hoewel er gedurende het project een significante en klinische relevante vermindering in de ernst van vermoeidheid werd waargenomen, kon deze verbetering niet direct aan de wandelinterventie worden toegeschreven. Deze verandering kon waarschijnlijk gedeeltelijk worden verklaard door een verandering in beweeggedrag van de deelnemers gedurende de controle-periode voorafgaand aan de wandeltraining. De bevindingen in dit hoofdstuk lieten zien dat een stijging in spierkracht, fysieke activiteit, slaapkwaliteit en een daling in de spierontspanning en

psychologische belasting mogelijk ten grondslag liggen aan de effecten van inspanning op vermoeidheid. Deelnemers gaven aan dat veerkracht en fysiek welbevinden belangrijke factoren zijn die het effect van wandelen op het verminderen van vermoeidheid verklaarden.

In **Hoofdstuk 6** hebben we gegevens over ervaren vermoeidheid, fysieke fitheid en contractiele spiereigenschappen van zes studies gecombineerd, met als doel om de verschillen tussen deze groepen in kaart te brengen en de associaties van contractiele spiereigenschappen en fysieke fitheid met ervaren vermoeidheid te onderzoeken. Deze studies bevatten gegevens van verschillende patiëntengroepen waaronder een controlegroep, patiënten die behandeld zijn voor kanker, patiënten met chronische obstructieve longziekten (COPD), patiënten met chronische myeloïde leukemie en patiënten die statines gebruikten voor hart- en vaatziekten. Onze bevindingen toonden aan dat contractiele spiereigenschappen, zoals een afname in spierkracht, spierontspanning en een maximale krachtsopbouw, verstoord waren bij patiënten met COPD, en dat spierontspanning verstoord was bij patiënten die statines gebruikten. Ook vonden we dat de verbanden tussen contractiele spiereigenschappen en ervaren vermoeidheid verschilden tussen de groepen. In patiënten met chronische myeloïde leukemie of patiënten die kanker hadden gehad, hing een vertraagde ontspanning van de spier samen met meer ervaren vermoeidheid. Deze resultaten lieten zien dat trainingsvoorschriften niet universeel toepasbaar zijn, aangezien onderliggende mechanismen en pathofysiologie kunnen variëren tussen groepen.

In **Hoofdstuk 7** werden de belangrijkste bevindingen van dit proefschrift bediscussieerd. Deze bevindingen lieten zien dat fysieke inspanning tijdens en na de neoadjuvante behandeling haalbaar is en positieve effecten kan hebben op de fysiologische capaciteit en de klinische uitkomsten bij patiënten met kanker. Daarnaast demonstreerden de resultaten van dit proefschrift mogelijke onderliggende mechanismen die de effecten van fysieke inspanning op vermoeidheid kunnen verklaren. In dit hoofdstuk werden vervolgens de methodologische overwegingen van de verschillende onderzoeksopzetten naast elkaar gezet. Ook beschreven we toekomstperspectieven voor wetenschappelijk onderzoek binnen de inspanningsoncologie en benadrukten het belang van toekomstige klinische studies om de effecten van inspanning op klinische uitkomsten in kaart te brengen en de onderliggende werkingsmechanismen te ontrafelen. Deze onderliggende mechanismen, zoals een verbeterde functie van het immuunsysteem, infiltratie van immuun cellen in de tumor en een vermindering van hypoxie in de tumor, kunnen mogelijk bijdragen aan een verbeterde behandelrespons van de tumor. Dit sluit aan bij de vervolgstappen van de EXENTRO-studie, waarin deze mechanismen van training tijdens NCRT bij patiënten met slokdarmkanker nader zullen worden onderzocht. Daarnaast gingen we in op de onderliggende mechanismen waarbij fysieke inspanning invloed zou kunnen hebben op klinische uitkomsten na een operatie, wat zou kunnen komen door een opeenstapeling van kleine verbeteringen in onder andere de zuurstofvoorziening en ontstekingswaarden. Na afronding van een behandeling zou inspanning kunnen leiden tot een vermindering in vermoeidheid door bijvoorbeeld het verbeteren van

de spierontspanning. Tot slot bediscussieerden we de klinische implicaties van de mogelijke effecten van fysieke inspanning op klinische uitkomsten en benadrukten het belang om fysieke training op te nemen als onderdeel van de oncologische standaardzorg.

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ETHICS AND PRIVACY

The results of this thesis are based on studies involving human participants and research was conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. The recognised Medical Ethics Review Committee 'METC Oost-Nederland' approved the EXENTRO trial in **Chapter 3** (NL81016.091.22), the F4S PREHAB trial in **Chapter 4** (NL73777.091.20), the KINETICS trial in **Chapter 5** (NL72604.091.20), and the pooled studies in **Chapter 6** (NL80842.091.22, NL59390.091.16, NL59192.091.16, NL36743.091.11, and 2007/148). All participants gave written informed consent prior to collecting and processing the data, and the studies complied with the declaration of Helsinki. For the EXENTRO and KINETICS trials, consent was also obtained for sharing the pseudonymised or anonymised data for future research with the goal to answer research questions in the same field of research. The privacy of the participants in these studies was assured using pseudonymisation. The pseudonymisation key was stored in a secured file on a secured network drive that was only accessible to members of the project who needed access to it because of their role within the project. Pseudonymisation was ensured by encrypted and unique individual participant codes. The encrypted participant codes were used in all data files and (electronic) case report forms.

DATA COLLECTION AND STORAGE

The data used in this thesis were collected and stored according to the Findable, Accessible, Interoperable and Reusable (FAIR) principles (1). Appropriate data management is essential for knowledge discovery, innovation, scientific integrity, and the preservation and re-use of data sets. Data described in **Chapter 2** was acquired through a Data Transfer Agreement with the Prospective Dutch ColoRectal Cancer cohort (PLCRC) and were provided as encoded pseudonymised Microsoft Excel Files. Data from the trials in **Chapter 3** and **Chapter 5** have been collected through electronic case report forms using Castor Electronic Data Capture (2021, Ciwit B.V., Amsterdam, NL). Paper (hardcopy) data (e.g. written informed consent forms) of the studies described in **Chapter 3** and **Chapter 5** are stored in closed cabinets at the Department of Medical BioSciences (Radboudumc, Nijmegen). Raw and processed digital data of all studies are stored on the department server of the Radboudumc, which is backed up twice daily to prevent data loss, and are only accessible by project members working at the Radboudumc. These secure storage options safeguard the availability, integrity and confidentiality of the data. Data were converged from Castor EDC to IBM SPSS Statistics 29 or R version 4.2.1 for statistical analyses.

Availability of data

All studies were published open access. Data will be preserved for at least 15 years upon completion of the study. **Chapter 2** is based on existing data from the PLCRC cohort. All relevant summary data are provided in the paper and its supplemental information. The Dutch Colorectal Cancer Group is the formal owner of the research data (www.dccg.nl), data requests should be directed to the study coordinator of PLCRC (www.plcrc.nl). Data from the F4S PREHAB trial in **Chapter 4** are owned and stored at the department of Surgical Oncology from the Radboudumc. Data requests should be directed to Dr. B. van den Heuvel (Baukje.vandenheuvel@radboudumc.nl). Data from the pooled studies in **Chapter 6** are stored and archived at the department of Medical BioSciences or Department of Pulmonary Diseases according to Radboudumc policies, and can be made available upon reasonable request to the corresponding authors. The datasets from **Chapters 3** (<https://doi.org/10.34973/tn8j-xd98>) and **Chapter 5** (<https://doi.org/10.34973/ss3j-vj24>) are published in a Data Sharing Collection at the Radboud Data Repository. The data are published open access and data can be made available for research with similar research questions upon reasonable request.

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Met de afronding van dit proefschrift komt er ook een einde aan mijn periode bij het Radboudumc. Ik heb enorm genoten van de afgelopen vier jaar en ik heb Nijmegen en het Radboudumc in mijn hart gesloten. Ik wil dan ook iedereen die hier aan heeft bijgedragen bedanken.

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Allerliefste **mamsies**, wat een geluksvogel ben ik met zulke lieve moeders. De onvoorwaardelijke basis waar we altijd op kunnen terugvallen hoe woelig de tijden ook zijn. Dankjulliewel voor al jullie support en het eindeloos geïnteresseerd aanhoren van mijn verhalen ook als jullie er eigenlijk niets van snaptten. Lieve **Jennie**, onze rots in de branding die voor ons door het vuur gaat. Ik ben vereerd dat ik de laatste jaren steeds meer van jou in mezelf herken en het was zo ontzettend leuk om samen een weekje aan onze boeken te schrijven. Lieve **Lisette**, ups of downs, het maakt niet uit, want je bent er altijd voor ons! Of het nou is om me weg te brengen naar Schiphol of gezellig een nachtje in Arnhem te komen logeren. Dankjewel voor alle steun en je luisterend oor. Hoe ver ik ook uitvlieg, het is altijd het fijnst om weer bij jullie thuis te komen. To the moon and back!

Met dit dankwoord komt er een einde aan een prachtige periode in mijn leven. Nog eenmaal dank aan iedereen die hierbij betrokken is geweest en ik kan niet wachten wat de toekomst gaat brengen!

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Mast IH, Baas KPA, Jørstad HT, Wood JC, Nederveen AJ, Bakermans AJ. Dynamic MR imaging of cerebral perfusion during bicycling exercise. *Neuroimage*. 2022;250:118961.

Mast IH, Bongers CCWG, Gootjes EC, de Wilt JHW, Hopman MTE, Buffart LM. Potential mechanisms underlying the effect of walking exercise on cancer-related fatigue in cancer survivors. *Journal of Cancer Survivorship*. 2024;Online ahead of print.

Mast IH, de Wilt JHW, Duman B, Smit KC, Gootjes EC, Vissers PAJ, Rütten H, Nagtegaal ID, Hopman MTE, May AM, Buffart LM. Physical activity at diagnosis is associated with tumor downstaging after neoadjuvant chemoradiotherapy in patients with rectal cancer. *Radiotherapy & Oncology*. 2024;200:110523.

Mast IH, Allard NAE, Ten Haaf D, Stoffels AAF, Janssen L, van Hees HWH, Timmers S, Hijmans-Kersten BTP, Hopman MTE, Buffart LM. Muscle contractile properties and perceived fatigue in the general and diseased population. *Physiological Reports*. 2024;12(23):e70134.

Brouwer CG, Tusscher MRT, de Roos BM, Gootjes EC, Buffart TE, Versteeg KS, **Mast IH**, Streppel MM, Werter IM, May AM, Verheul HMW, Buffart LM, & AMICO Consortium (2025). Experiences of patients with metastatic colorectal cancer participating in a supervised exercise intervention during chemotherapy. *Supportive Care in Cancer*. 2025;33(2):82.

Mast IH, Gootjes EC, Rütten H, den Hartogh MD, Brouwer CG, Nagtegaal ID, van der Post RS, Hopman MTE, van den Heuvel B, Rosman C, de Wilt JHW, Klarenbeek BR, Buffart LM. Feasibility and clinical potential of exercise interventions during neoadjuvant chemoradiotherapy in patients with esophageal and rectal cancer. *Journal of Sport and Health Science*. 2025;In press.

van der Sluijs KM, Bakker EA, Kerstens TP, Stens NA, de Koning IA, Thannhauser J, Malik AEF, Reesink KD, Nabeel PM, Raj KV, Joseph J; **Nijmegen Exercise Study collaboration**; Eijsvogels TMH, Thijssen DHJ. Association of Objectively Measured Sedentary Behavior With Arterial Stiffness: Findings From the Nijmegen Exercise Study. *Scandinavian Journal of Medicine & Science in Sports*. 2024;34(11): e14757.*

*Contributed as member of the Nijmegen Exercise Study collaboration.

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Isa Hiske Mast werd geboren op 12 augustus 1997 te Dordrecht en groeide op in Amersfoort. In 2015 behaalde zij haar Gymnasium diploma met Technasiumcertificaat aan het 't Hooghe Landt college in Amersfoort. Daarnaast doorliep ze tijdens de laatste twee jaren van haar middelbare school het U-Talent programma aan de Universiteit van Utrecht. In 2018 voltooide ze de bachelor Medische Natuurwetenschappen aan de Vrije Universiteit Amsterdam, waarna ze startte met de research master Human Movement Sciences aan dezelfde universiteit. Tijdens deze master liep zij stage bij het Kinderbewegingscentrum in het Wilhelmina Kinderziekenhuis en op de afdeling Radiologie en Nucleaire Geneeskunde in het Amsterdam UMC, waarna ze in 2020 afstudeerde. Ook na haar stage op de afdeling Radiologie en Nucleaire Geneeskunde in het Amsterdam UMC werkte ze nog een aantal maanden door als onderzoeksassistent.



Vanaf 2021 begon Isa met haar PhD traject in het Radboudumc bij de onderzoeksgroep Exercise Oncology op de afdeling Fysiologie. Tijdens dit traject werd ze begeleid door dr. Laurien Buffart, prof. dr. Hans de Wilt, prof. dr. Maria Hopman en dr. Elske Gootjes. Gedurende haar promotieonderzoek deed ze onderzoek naar mogelijke effecten van fysieke inspanning tijdens de behandeling van kanker op klinische uitkomsten. Ook onderzocht ze mogelijke onderliggende mechanismen die effecten van fysieke inspanning op vermoeidheid kunnen verklaren. Dit proefschrift is het eindresultaat van haar promotieonderzoek. Naast de onderzoeken beschreven in dit proefschrift, begeleidde ze verschillende stagiaires en gaf ze onderwijs voor de opleidingen Geneeskunde en Biomedische wetenschappen. Ook presenteerde ze de resultaten van haar onderzoeken op meerdere nationale en internationale congressen. Momenteel werkt Isa als postdoctoraal onderzoeker in de onderzoeksgroep Exercise Oncology in het Radboudumc. In Juni 2025 zal ze starten als postdoctoraal onderzoeker op de afdeling Radiologie en Nucleaire Geneeskunde in het Amsterdam UMC.

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PHD PORTFOLIO OF ISA MAST

Department: **Medical BioSciences – research group Exercise Oncology**

PhD period: **01/01/2021 – 31/12/2024**

PhD Supervisor(s): **Dr. L.M. Buffart, Prof. Dr. J.H.W. de Wilt, Prof. Dr. M.T.E.**

Hopman

PhD Co-supervisor(s): **Dr. E.C. Gootjes**

Training activities	Hours
Courses	
- Introduction course for PhD candidates, RIHS (2021)	15.00
- General Radboudumc introduction for research personnel, Radboudumc (2021)	9.00
- eBROK course, Radboudumc (2021)	26.00
- Regressietechnieken (V30), Amsterdam UMC (2021)	36.00
- R Introduction Course, Radboudumc (2021)	12.00
- Projectmanagement voor Promovendi, RU (2021)	45.00
- Basic life support + AED, Radboudumc (2022)	6.00
- Basiscursus oncologie, NVvO (2022)	36.00
- Scientific integrity, Radboudumc (2023)	20.00
- Re-registration eBROK, Radboudumc (2024)	5.00
- The next step in my career, RU (2024)	40.00
Seminars	
- TWGE GE Nijmegen 2022, Comprehensive cancer center (IKNL) (oral presentation) (2022)	4.00
- TWGE GE Nijmegen 2023, Comprehensive cancer center (IKNL) (pitch presentation) (2023)	4.00
- GE Symposium 'Ontwikkelingen bij slokdarm- en maagkanker' 2023, Comprehensive cancer center (IKNL) (oral presentation) (2023)	4.00
- Research Integrity Round (attendee), Radboudumc (2024)	3.00
Conferences	
- Cancer Research Retreat (poster presentation) (2022)	16.00
- American College of Sports Medicine Annual Meeting (poster presentation) (2023)	28.50
- Cancer Research Retreat (laptop presentation) (2023)	16.00
- PhD retreat (oral presentation) (2023)	21.00
- American College of Sports Medicine Annual Meeting (thematic poster presentation & 2-min thesis pitch) (2024)	32.00
- American Society of Colon & Rectal Surgeons (oral presentation) (2024)	28.00

Other

- Member RIHS PhD Council (2021)	26.00
- CRC Clinical Research Meeting (2022)	10.00
- Organising PhD Retreat (2022)	56.00
- Organising PhD Retreat (2022)	56.00
- Chair workshop committee RIHS PhD Council (2023)	42.00
- Colorectal surgery lunch meeting (2023)	3.00
- Colorectal pasta party, hosted by Prof. J.H.W. de Wilt (2022, 2023, 2024)	15.00
- Exercise Oncology meeting (2022, 2023, 2024)	50.00

Teaching activities**Lecturing**

- Lecture honours program (2022)	4.00
- Practicum Steep Ramp Test, minor Clinical Exercise Physiology (2021, 2022, 2023)	4.00
- Meet the PhD (2022, 2023, 2024)	24.00
- Research project, minor Moving Questions (2022, 2023)	20.00
- Guest lecture Exercise and Clinical Immunology (VU) (2023, 2024)	6.00
- Design a training schedule, minor Clinical Exercise Physiology (2021, 2022, 2023, 2024)	60.00

Supervision of internships / other

- Literature Thesis - Bram Schoenmakers (2021)	14.00
- MSc internship Human Biology - Luna van Merkestein (2022)	60.00
- MSc internship Human Movement Sciences - Veerle Muntjewerff (2022)	60.00
- Literature Thesis - Valerie Versteeg (2022)	14.00
- MSc internship Erasmus exchange - Maria Dolores Lopez (2022)	36.00
- BSc internship Medical Biology - Kjelvar Knol (2023)	30.00
- MSc internship Health Sciences - Berfin Duman (2023)	60.00
- MSc internship Biomedical Sciences - Kyra van Keeken (2023)	60.00
- Literature Thesis - Twan Thörig (2024)	14.00
- MSc internship Biomedical Sciences - Lisa van Zuuk (2024)	60.00
- MSc internship Biomedical Sciences - Iris van den Heuvel (2024)	60.00
- MSc internship Medicine - Nina Gerrits van den Ende (2024)	36.00

Total**1286,50**



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