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Cardiac and intramuscular adaptations following short-term exercise prehabilitation in unfit patients scheduled to undergo hepatic or pancreatic surgery: study protocol of a multinuclear MRI study

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ABSTRACT

Introduction Short-term exercise prehabilitation programmes have demonstrated promising results in improving aerobic capacity of unfit patients prior to major abdominal surgery. However, little is known about the cardiac and skeletal muscle adaptations explaining the improvement in aerobic capacity following short-term exercise prehabilitation.

Methods and analysis In this single-centre study with a pretest–post-test design, 12 unfit patients with a preoperative oxygen uptake (VO_2) at the ventilatory anaerobic threshold ≤13 mL/kg/min and/or VO_2 at peak exercise ≤18 mL/kg/min, who are scheduled to undergo hepatopancreatobiliary surgery at the University Medical Center Groningen (UMCG), the Netherlands, will be recruited. As part of standard care, unfit patients are advised to participate in a home-based exercise prehabilitation programme, comprising high-intensity interval training and functional exercises three times per week, combined with nutritional support, during a 4-week period. Pre-intervention and post-intervention, patients will complete a cardiopulmonary exercise test. Next to this, study participants will perform additional in-vivo exercise cardiac magnetic resonance (MR) imaging and phosphorus 31-MR spectroscopy of the quadriceps femoris muscle before and after the intervention to assess the effect on respectively cardiac and skeletal muscle function.

Ethics and dissemination This study was approved in May 2023 by the Medical Research Ethics Committee of the UMCG (registration number NL83611.042.23, March 2023) and is registered in the ClinicalTrials.gov register. Results of this study will be submitted for presentation at (inter)national congresses and publication in peer-reviewed journals.

Trial registration number NCT05772819.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Short-term exercise prehabilitation programmes comprising high-intensity interval training can improve preoperative aerobic capacity in unfit patients scheduled to undergo major abdominal surgery.

WHAT THIS STUDY ADDS

⇒ This study will evaluate the physiological adaptations in cardiac and skeletal muscle function in response to short-term exercise prehabilitation using exercise MRI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Insights into the physiological adaptations that contribute to an improved aerobic capacity following short-term exercise prehabilitation may lead to enhanced implementation and adherence due to better understanding and further optimisation of prehabilitation programmes, as well as improved adoption of the prehabilitation concept by healthcare professionals.

INTRODUCTION

Surgery remains the cornerstone in the treatment of hepatopancreatobiliary (HPB) malignancies. However, surgical-induced trauma triggers a systemic stress response characterised by sterile inflammation preceding neuroendocrine and metabolic deregulation, with the magnitude, invasiveness and duration of surgery being directly related to the degree of the systemic stress response in patients.[1 2] Meanwhile, age-related and disease-related pathophysiological alterations and a patient's comorbidities result in decreased physiological reserves and resultant vulnerability, thereby adversely affecting a patient's tolerance to surgery.[3 4] Previous studies report on a clear association

between a low preoperative aerobic capacity (ie, low physiological reserve) and an increased risk of postoperative morbidity and mortality.[5–7] Hence, aerobic capacity is regarded as by far the greatest modifiable patient-related risk factor in major abdominal surgery, and prehabilitation programmes focusing on optimising aerobic capacity are gaining interest as an effective means to reduce the risk of postoperative complications in high-risk patients with a low aerobic capacity.[4 8]

Short-term exercise prehabilitation programmes with a duration of 4–6 weeks have been reported to substantially increase the preoperative aerobic capacity of patients scheduled to undergo major abdominal surgery.[9–12] Moreover, these prehabilitation programmes also demonstrated a reduction in postoperative complication rate, which is highly relevant since postoperative complications are strongly associated with a lower quality of life, delayed postoperative recovery and a detrimental increase in hospital costs.[13 14] Cardiopulmonary exercise testing (CPET) is commonly used to objectively assess aerobic capacity, and select high-risk patients who benefit the most from prehabilitation.[4 6 15] The CPET yields several indicators for a patient's aerobic capacity, of which the oxygen uptake (VO_2) at the ventilatory anaerobic threshold (VAT) and the VO_2 at peak exercise (VO_2peak) are consistently reported as valid indicators for aerobic capacity in surgical patients.[5–7]

Although an increase in aerobic capacity following short-term prehabilitation, as assessed by CPET, is reported in previous studies, little is known about the exact role of adaptations in cardiac function versus skeletal muscle function contributing to the improvement in aerobic capacity. Impaired cardiorespiratory functioning is typically seen as the cause of a low aerobic capacity in patients. However, peripheral haemodynamic and muscular changes such as sarcopenia and myosteatosis, morphological, vascular or metabolic changes may also contribute to a low aerobic capacity in patients. Moreover, not all patients demonstrate improved aerobic capacity following a prehabilitation programme.[9 10] Next to inadequate training adherence, this might also be explained by individual differences in cardiac and/or skeletal muscle function adaptations to prehabilitation.

Using in vivo exercise cardiac MRI (exCMRI) and musculoskeletal phosphorus 31 exercise multinuclear magnetic resonance spectroscopy (^{31}P-exMMRS) of the quadriceps femoris muscle, it is possible to interrogate the cardiac and skeletal muscle function.[16–18] Therefore, in the current explorative study with a pretest–post-test design, unfit patients approaching HPB surgery will undergo magnetic resonance (MR) measurements next to CPET before and after a 4-week prehabilitation programme. The primary aim of this study is to assess the central (cardiac function) and peripheral (skeletal muscle function) physiological adaptations in response to short-term exercise prehabilitation. To the best of our knowledge, no similar study has been conducted before.

METHODS

Study objective

The primary aim of this study is to assess adaptations in cardiac and skeletal muscle function in response to short-term exercise prehabilitation in individual patients. In this regard, individual differences in the outcomes of the exCMRI and ^{31}P-exMMRS before and after the exercise prehabilitation programme will be compared. For the exCMRI, differences in resting global longitudinal strain (GLS), resting and peak exercise left ventricular ejection fraction and right ventricular ejection fraction, stroke volume index, heart rate and cardiac index will be compared. For the ^{31}P-exMMRS, differences in phosphocreatine (PCr), inorganic phosphorus (Pi) and pH in the quadriceps femoris muscle during rest, exercise and recovery will be compared.

Study design and setting

This study is a single-centre prospective pilot study with a pretest–post-test design that will take place at the University Medical Center Groningen (UMCG). The study will start in September 2023 and run until all 12 intended participants are included (expected in September 2024). In this article, the latest version of the study protocol (V.2, April 2023) will be discussed. The study is approved by the Medical Ethics Committee Groningen, the Netherlands (registration number NL83611.042.23, March 2023), and is registered at ClinicalTrials.gov. Any protocol amendments need to be reviewed and approved by the Medical Ethics Committee Groningen.

Inclusion and exclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following inclusion criteria: (1) aged ≥18 years, (2) diagnosed with a (suspected) liver, pancreatic or biliary (pre)malignancy, (3) scheduled for elective liver or pancreatic resection at the UMCG, (4) having a VO_2 at the VAT ≤13 mL/kg/min and/or a VO_2peak ≤18 mL/kg/min, as determined during baseline CPET, (5) participating in a home-based exercise prehabilitation programme because of their low aerobic capacity and (6) provided informed consent to participate in the study. The CPET cut-off points used in this study protocol were determined based on previous literature suggesting risk stratification based on CPET reports should not rely on specific binary cut-off points, but should be instead focused on strata or zones along a spectrum of fitness in patients.[19 20] Potential participants who meet any of the following criteria will be excluded from participation in this study: (1) requiring acute (emergency) surgery, (2) observed atrial fibrillation or other significant arrhythmias during baseline CPET, (3) history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft <3 months, or untreated severe obstructive coronary artery stenosis, (4) history of more than moderate left-sided valve disease, (5) history of a complex congenital heart disease, (6) receiving neoadjuvant chemotherapy, (7) contraindications for MR (eg,

Table 1 Questionnaire used to screen for risk of a low aerobic capacity

Question	Answer according to the norm
Does the patient **not** comply with the WHO recommendations for physical activity*? (>150 min of moderate or >75 min of vigorous physical activity per week)	No
Does the patient have a poorly regulated comorbidity?	No
Is preoperative chemotherapy and/or radiotherapy scheduled?	No
Is the patient aged ≥80 years?	No

*WHO recommendations for physical activity.[41]

claustrophobia, implanted cardiac devices), (8) body mass >140 kg or body height >190 cm (due to MR scanner ergonomic limitations) and/or (9) physically incapable of cycling on a cycle ergometer.

Recruitment

All patients referred for HPB-surgery are discussed at a weekly multidisciplinary oncology meeting and will subsequently be evaluated at the outpatient clinic by the surgeon and specialised oncology nurse practitioner. As part of standard care at the UMCG, patients scheduled to undergo elective resection of a (suspected) HPB (pre) malignancy will be screened for a low aerobic capacity. A four-question questionnaire is used to screen for risk of low aerobic capacity (table 1). Patients are considered at risk for low aerobic capacity when at least one of these questions is answered affirmatively. Consequently, patients considered at risk will be referred to a certified sports physician to perform a CPET and objectively assess their aerobic capacity. Based on the CPET results (ie, VO_2 at the VAT and VO_2peak), patients will be asked to participate in a 4-week home-based prehabilitation programme. If so, patients will be screened for potential eligibility for the current study and eligible patients will be contacted by telephone by an appointed clinical research coordinator to give full details on the study. If patients give verbal consent to participate, a research appointment will be planned to retrieve written consent and perform the baseline assessments.

Multimodal prehabilitation program

At the UMCG, a multimodal prehabilitation programme is integrated as standard care in the preoperative care pathway, meaning all patients scheduled to undergo HPB-surgery are referred to the outpatient prehabilitation clinic to be assessed on six patient-related modifiable risk factors: (1) low aerobic capacity, (2) malnutrition, (3) low psychological resilience, (4) iron deficiency (anaemia) and hyperglycaemia, (5) frailty and (6) substance abuse (ie, tobacco use and/or alcohol consumption).[21] Based on assessment results, interventions are deployed as appropriate. For clarity reasons this study protocol will focus only on the physical exercise intervention for patients with a low aerobic capacity.

Patients with a low aerobic capacity (ie, VO_2 at the VAT ≤13 mL/kg/min and/or VO_2peak ≤18 mL/kg/min) as determined during the preoperative CPET are strongly advised to participate in a 4-week home-based physical exercise programme prior to surgery. For the physical exercise programme, an advanced cycle ergometer (Lode Corival Home+, Lode BV, Groningen, the Netherlands) will be placed at the patient's home and a certified community physical therapist will be asked to supervise the programme. The programme comprises 25-min high-intensity interval training (HIIT) sessions, three times a week. Training intensity will be adjusted based on a weekly executed steep ramp test.[22] Hence, the programme is personalised and progression is carefully monitored. In table 2 the structure and training intensity of the HIIT training is provided. Next, patients are instructed to perform functional task exercises twice a week in order to improve muscle function and functional mobility.[9] Training results are recorded by the cycle ergometer and uploaded to an online platform, which also enables the physical therapist and clinical research coordinator to monitor training progression and protocol adherence (ie, frequency, intensity and time). Lastly, after completing the programme, patients will perform a second CPET to determine whether their aerobic capacity has improved.

In vivo exercise MR imaging

Study participants will be subjected to two different in-magnet exercise tests at the UMCG before and after the exercise prehabilitation programme: (1) exCMRI imaging of the heart to evaluate alterations in cardiac muscle function, and (2) in-vivo ^{31}P-exMMRS of the quadriceps femoris muscle to evaluate alterations in skeletal muscle function. A study timeline is provided in figure 1. Both exercise tests will be performed in a supine position using a MR-compatible ergometer constructed from non-ferrous components (Lode MR Ergometer Pedal, Lode BV, Groningen, the Netherlands). Data acquired from the CPET will be used to recreate work rate increments on the MR-compatible cycle ergometer resulting in exercise at 40% and 60% of the participants work rate at peak exercise (WR_{peak}) as achieved during the CPET, whereby 60% of the participant's WR_{peak} in upright position corresponds with a near maximum effort in supine position.[23] Also, resting and recovery measurements will be acquired. All in-magnet exercise tests will be conducted inside a multinuclear 1.5T MRI-scanner (MAGNETOM Sola Fit, Siemens, Berlin, Germany; 70 cm

Table 2 HIIT programme structure

Exercise phase	Exercise duration	Exercise intensity	Pedalling frequency
Warm-up	3 min	20 W	40–80 rpm
Interval training (14 intervals)	21 min	**Work interval intensity**	
		30 s at 60% SRT WR_{peak}	60–100 rpm
		Rest interval intensity	
		60 s at 20 W	40–60 rpm
Cool-down	1 min*	20 W	40–80 rpm

*A longer cool-down phase is possible when preferred.
HIIT, high-intensity interval training; SRT, steep ramp test; WR_{peak}, work rate at peak exercise.

bore diameter). Patients will not be exposed to contrast agents. To prevent distortion of imaging results patients are instructed to refrain from vigorous exercise at least 24 hours before the measurements, and caffeine consumption and heavy meals on the day of the measurements.

Exercise cardiac MRI

For this study a previously described exCMRI protocol will be used.[16 24] Patients will be evaluated with resting and exercise CMR to determine resting GLS, resting and peak exercise left ventricular ejection fraction and right ventricular ejection fraction, stroke volume index, heart rate and cardiac index as measures of cardiac function.[24 25] During the test, a series of images are acquired in various planes, including short-axis, long-axis (two-chamber, three-chamber, four-chamber) and additional views to cover the entire heart. These cine images capture the dynamic motion of the heart and allow assessment of cardiac function (eg, ejection fraction, ventricular volumes). The patient will start cycling without resistance (0 Watt) at the advised cadence (60–80 revolutions per minute). Shortly thereafter, the work rate will gradually increase (eg, 10 Watt every 2 min) and MR images will be captured when the patient reaches 40% and subsequently 60% of the patients' CPET WR_{peak}. After patients have reached 60% of their CPET WR_{peak}, patients will stop cycling and after 2 min of rest, a final scout of MR images will be captured (recovery measurements). Importantly, an individualised approach is crucial in exCMRI, as patients may have varying exercise capacities and physiological responses. Therefore, work rate increments will be tailored based on CPET performance. The obtained exCMRI data is compared with the resting CMRI data to identify exercise-induced changes in cardiac function. All exCMRI analyses will be performed offline by dedicated software (CVi42, Circle Cardiovascular Imaging, Calgary, Canada).

Musculoskeletal 31P magnetic resonance spectroscopy

Likewise, a previously described protocol will be used for ^{31}P-exMMRS.[26 27] ^{31}P-exMMRS is a non-invasive imaging technique to study energy metabolism and pH balance of skeletal muscle tissue.[18] Here, it will be used to measure PCr, Pi and pH in the quadriceps femoris muscle at rest, during leg-cycling exercise at 40% and 60% of the patients' CPET WR_{peak} and post-exercise metabolic recovery as described elsewhere.[28] Data will be analysed using AMARAS algorithm in the JMRUI software package.[18] Absolute concentrations will be calculated after correction for partial saturation and assuming adenine nucleotide and creatine pool sizes of 8 and 43 mM, respectively.[26] Intracellular pH will be calculated from the chemical shift difference between the Pi and PCr resonances.[26]

Other study variables

Baseline characteristics will include age, sex, body mass index, intoxications (alcohol and tobacco use), American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index (CCI) and type of HPB tumour requiring surgery. CPET variables will also be recorded (VO_2 at the VAT and VO_2peak). Perioperative variables will include type of surgery, open or minimally invasive surgery, duration of surgery and blood loss during surgery. Postoperative outcomes will include all complications (severity defined by the Clavien-Dindo classification[29]), length of hospital stay in days, readmissions within 30 days after discharge and mortality within 30 days after discharge. Postoperative outcomes are solely collected for explorative purposes.

Safety considerations

For this study MR measurements are used, which are free of ionising radiation. Furthermore, patients will not be exposed to any contrast agents. Importantly, the additional study measurements in this study will not cause a clinical delay in the patient's preoperative period.

Data management plan

All data will be handled confidentially according to the General Data Protection Regulation. The generated data will be collected in an electronic case report form created in Research Electronic Data Capture (REDCap) (REDCap, Vanderbilt University, Nashville, Tennessee, USA), an online database. Imaging data will be stored after de-identification on a secured research drive within the UMCG. Only the principal and coordinating

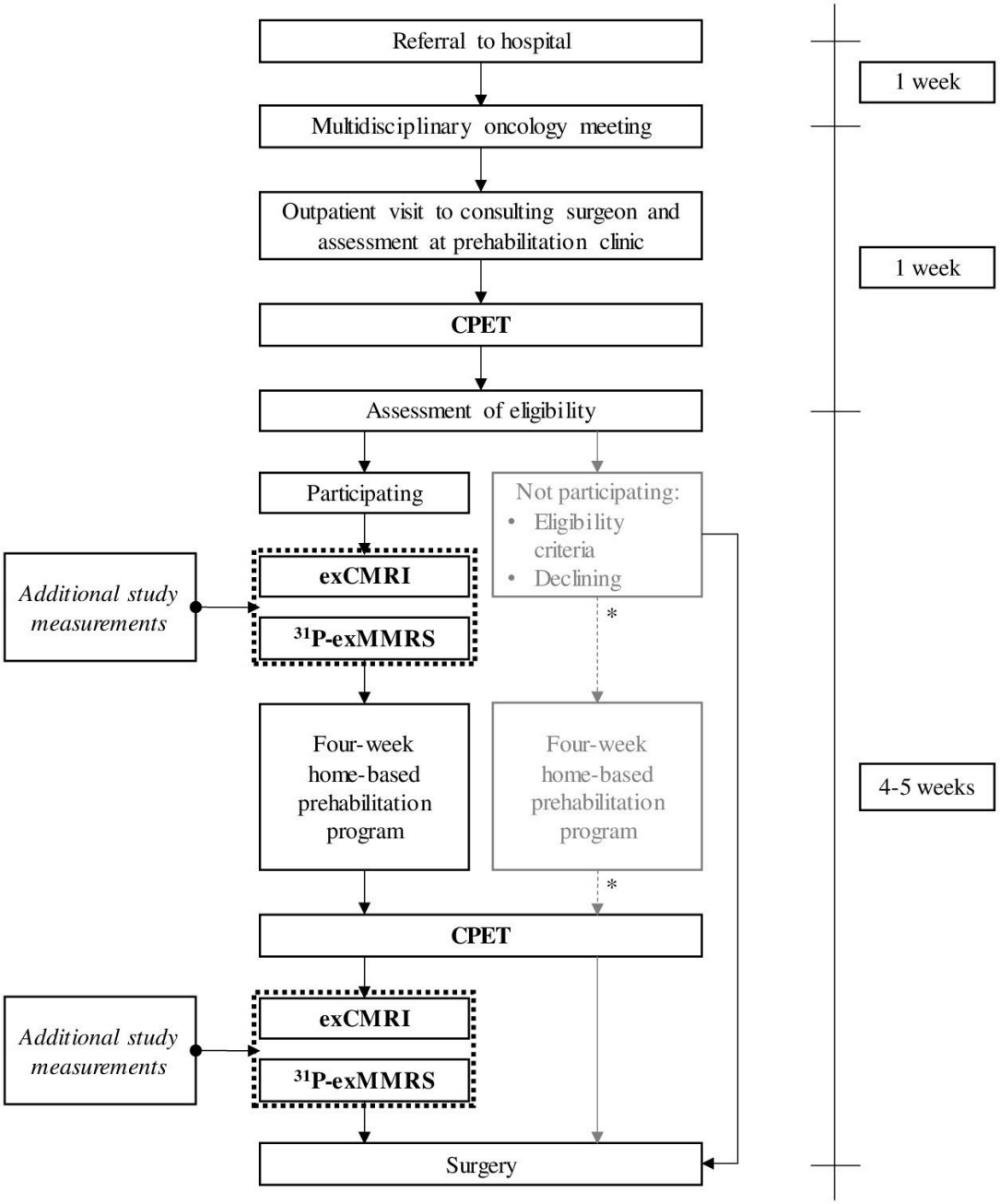

Figure 1 Study timeline. [a]This only applies to patients with a low aerobic capacity based on CPET results, but decided not to participate in the study. CPET, cardiopulmonary exercise test; exCMR, exercise cardiac MR; ^{31}P-MRS, phosphorus 31 magnetic resonance spectroscopy.

investigators will have access to the data. All data will be stored for a maximum of 15 years.

Data analysis

Sample size calculation

Since this study is an explorative study, no sample size analysis has been performed. It is intended to include a total of 12 patients. Results of this study are expected to give insight into the physiological adaptations following an exercise intervention in unfit patients, which might initiate future research.

Statistical analysis

Data will be analysed using the Statistical Package for the Social Sciences for Windows (SPSS, V.25.0, IBM, SPSS, Chicago, Illinois, USA). Data will be presented in tables and figures. Non-parametric data will be presented with median and IQR or mean and SD, as appropriate. Individual differences between continuous variables (ie, CPET (VO_2 at the VAT and VO_2peak), exCMRI (resting GLS, resting and peak exercise left ventricular ejection fraction and right ventricular ejection fraction, stroke volume index, heart rate and cardiac

index), ^{31}P-exMMRS (PCr, Pi and pH in the quadriceps femoris muscle during rest, exercise and recovery) outcomes) before and after the exercise prehabilitation programme will be tested using paired samples t-test or Wilcoxon signed-rank test, as appropriate. The correlation between CPET values and continuous outcome variables of exCMRI and ^{31}P-exMMRS after the exercise prehabilitation programme will be assessed by Pearson's r or Spearman's rho, depending on normality of distribution. A repeated measurements analysis (mixed models in SPSS) will be performed to assess changes over time in the primary continuous outcome variables (exCMRI and ^{31}P-exMMRS outcomes as described above in the Exercise cardiac MRI and Musculoskeletal 31P magnetic resonance spectroscopy sections). Categorical data (ie, sex, intoxications, ASA score, CCI, type of HPB tumour, type of surgery, severity of complications, readmissions, mortality) will be summarised by frequency and percentage. P values<0.05 will be considered statistically significant.

Ethics and dissemination

Consent

Informed consent will be acquired by the coordinating investigator. Both the patient and investigator must sign the informed consent form with a wet signature, named and dated.

Ethical considerations

This study was approved in May 2023 by the Medical Research Ethics Committee of the UMCG, the Netherlands (registration number NL83611.042.23, March 2023) and is registered in the Clinicaltrials.gov register. This study will be conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Dissemination

Results of this study will be submitted for presentation at (inter)national congresses and publication in a peer-reviewed journal. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. The coordinating investigator will prepare the manuscript and authorship is determined based on individual contribution to the manuscript. A summary of the study findings will also be made available to the website of the funder, 'Stichting Nationaal Fonds Tegen Kanker' (Foundation National Fund against Cancer), The Netherlands. This summary is intended to provide information about the most important study outcomes to the general public.

DISCUSSION

This study will be the first to investigate the adaptations in both cardiac and skeletal muscle function in response to short-term exercise prehabilitation in unfit patients scheduled to undergo HPB surgery. Insights in the physiological adaptations following short-term preoperative exercise prehabilitation that contribute to an improved aerobic capacity might improve further adoption of the prehabilitation concept by healthcare professionals and facilitate a better explanation of the rationale and expectations of prehabilitation to patients, thereby enhancing implementation, protocol adherence and effectiveness. Moreover, this knowledge might enable healthcare professionals to further optimise the prehabilitation programme (eg, by modifying training frequency, intensity, time or type). The clinical relevance is self-evident, the limited 4–6 weeks period before surgery requires a prehabilitation programme with adequate training volume and adherence to achieve optimal results.

In addition to a homogenous cohort by selecting solely high-risk unfit patients scheduled to undergo HPB surgery, another strength of the present study is the integrated multimodal prehabilitation programme for all included patients. The multimodal prehabilitation programme is patient-personalised, meaning patients are subjected to specific interventions based on their identified preoperative risk factors.[21] Hence, our multimodal prehabilitation programme has a tailor-made approach and is therefore highly efficient in optimising patient-related preoperative risk factors.[30] Furthermore, the gold standard for assessment of aerobic capacity, the CPET, is used for risk assessment and objectively determine a patient's preoperative aerobic capacity.[6] Risk assessment is an important element of prehabilitation, since high-risk patients seem to benefit the most from prehabilitation.[15] The subsequent home-based exercise prehabilitation programme for patients with a low aerobic capacity is supervised by a community physical therapist, which contributes to an expected overall high compliance rate and adequate training volume. Based on a previous study with the same preoperative home-based HIIT programme in unfit patients approaching HPB surgery, a high adherence rate (83%) and high effectiveness (+17% improvement in aerobic capacity) is expected.[9] Consequently, adaptations in cardiac and skeletal muscle function underlying the improvement in aerobic capacity may become apparent, probably more pronounced than in fit patients and/or exercise prehabilitation programmes with lower compliance rates. Other strengths of this study are the additional pre-intervention and post-intervention in-magnet exercise tests, next to the conventional CPET, to acquire objective information on the adaptations in cardiac and skeletal muscle function. With exCMRI the effective cardiac output can be assessed, as patients reach their near-maximum effort during exercise, magnifying the insights in the physiological process with a non-invasive approach.[17 31] Moreover, due to the precision of exCMRI, it is highly reproducible and therefore only small sample sizes are required to detect small changes over time after short-term exercise interventions.[17 24 32] Also, exCMRI has previously been successfully used to assess cardiac function and determine beneficial effects of exercise training programmes, including in the field of oncology.[33–35] Lastly, ^{31}P-exMMRS during exercise is

widely used in research settings to assess skeletal muscle function.[26 27 36 37] Non-invasive measurements of skeletal muscle function using ^{31}P-exMMRS have been shown to be precise and reproducible, making it a reliable tool to assess adaptations in skeletal muscle function in response to physical exercise training.[38–40]

A limitation of this study is the possibility that patient inclusion might appear to be challenging. Patients participating in this study are subjected to four additional in-magnet exercise tests (pre-intervention and post-intervention exCMRI and ^{31}P-exMMRS). Not all patients may be willing to perform these additional study measurements due to personal, logistical and time limitations (eg, living too far from the hospital, no transport opportunities, becoming too much after being diagnosed with a (pre)malignancy) or able to perform the in-magnet exercise tests due contraindications for exercise MR (eg, claustrophobia, implanted cardiac devices), body mass >140 kg or body height >190 cm). The appointed clinical research coordinator will ensure that everything is as easy as possible for patients to participate in the study (eg, by combining research appointments simultaneously with clinical appointments). Furthermore, the in-magnet exercise tests take little time to execute; this will be clearly explained to eligible patients.

In conclusion, exercise prehabilitation programmes are an important aspect of improving perioperative care for unfit patients undergoing major abdominal surgery. Insights in the physiological adaptations assessed by exercise CMR and ^{31}P-exMMRS following short-term exercise prehabilitation may contribute to enhanced implementation and adherence due to better understanding and further optimisation of prehabilitation programmes. Ultimately, this may lead to higher efficacy of prehabilitation programmes and subsequently better treatment outcomes for unfit patients scheduled to undergo major abdominal surgery.

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Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no data sets generated and/or analysed for this study.

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