Supervised home-based exercise prehabilitation in unfit patients scheduled for pancreatic surgery: study protocol of a multicenter feasibility study

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Study protocol

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Abstract

**Background:** Morbidity rates in pancreatic surgery are high, and especially frail patients with low aerobic capacity are at risk of complications and require specialized prophylactic interventions. Previous studies of small patient cohorts receiving intra-abdominal surgery have shown that an exercise prehabilitation program increases aerobic capacity, leading to better treatment outcomes. In this study we aim to assess the feasibility of a home-based exercise prehabilitation program in unfit patients scheduled for pancreatic surgery on a larger scale.

**Methods:** In this multicenter study adult patients scheduled for elective pancreatic surgery, with a preoperative oxygen uptake (VO$_2$) at the ventilatory anaerobic threshold $\leq$13 mL/kg/min and/or a VO$_2$ at peak exercise (VO$_2$Peak) $\leq$18 mL/kg/min will be recruited. The study will be conducted in a pretest-posttest design. A total of 30 patients will be included in the four-week home-based, partly supervised exercise prehabilitation program on an advanced cycle ergometer. The program comprises 30-minute high-intensity interval training three times a week. Training intensity will be based on a steep ramp test (i.e., an abbreviated maximum exercise test on the advanced ergometer) performance, aiming to improve aerobic fitness. Twice a week, patients will perform functional task exercises to improve muscle function and functional mobility. Every week, a steep ramp test will be repeated, and training intensity will be adjusted accordingly. Next to assessing feasibility (participation rate, reasons for non-participation, adherence, dropout rate, reasons for dropout, adverse events, and patient and therapist appreciation) of this exercise prehabilitation program, we will evaluate individual patient’s responses to prehabilitation on aerobic capacity, functional mobility, body composition, perceived fatigue, quality of life, muscle function, and immune system factors.

**Discussion:** Results of this study will provide important clinical and scientific knowledge on the feasibility of a partly supervised home-based exercise prehabilitation program in a vulnerable patient population. This might ease the path to implementing prehabilitation programs in unfit patients undergoing complex abdominal surgery, such as pancreatic surgery.

**Trial registration:** This study was approved by the Medical Research Ethics Committee of the Maastricht University Medical Center+ (METC azM/UM), the Netherlands (registration number METC20-090, NL75340.068.20, September 2021) and is registered in the Clinicaltrials.gov register (NCT05496777).

**Introduction**

The incidence of pancreatic malignancies is expected to rise as the ageing population grows [1]. The only curative treatment option remains pancreatic surgery, which is highly complex and known for its high postoperative morbidity [2]. Within this already vulnerable patient group, there are unfit patients with a low aerobic fitness, translating into a limited reserve to withstand stress during surgery [3, 4]. As a consequence, these patients are more prone to postoperative morbidity after pancreatic surgery [5, 6]. To effectively intervene in these unfit patients to reduce perioperative risks, specific preoperative risk
assessment is required. In the search of valid preoperative risk assessments diagnostics, preoperative aerobic fitness has been found to have a persistent relationship with postoperative outcomes in major elective intra-abdominal surgeries [5, 7, 8]. A cardiopulmonary exercise test (CPET), which determines two meaningful risk indicators, explicitly the oxygen uptake (VO$_2$) at the anaerobic threshold (VAT) and VO$_2$ at peak exercise (VO$_2$peak), can be used to acquire an objective representation of a patient’s aerobic capacity [9].

Physical exercise training before surgery has been reported to effectively increase the aerobic capacity of patients scheduled for major abdominal surgery [10–17]. In the trial of Barberan-Garcia et al., high-risk patients scheduled for major abdominal surgery were subjected to a multimodal prehabilitation program consisting of (i) motivational interviewing, (ii) a personalized program to promote daily physical activity, and (iii) a supervised high-intensity endurance exercise training program [18]. The mean duration of their program was 6 weeks, and it did not only improve preoperative aerobic capacity, but also resulted in a 51% reduction of postoperative complications [18]. Regarding prehabilitation programs in pancreatic surgery, Ausania et al. subjected patients with a pancreatic or peripancreatic malignancy, regardless of their physical fitness, to a multimodal prehabilitation program consisting of five daily sessions of supervised high-intensity endurance training in the outpatient clinic [14]. Furthermore, patients were trained to perform unsupervised home-based functional and breathing exercises, and nutritional support as well as pancreatic exocrine insufficiency was taken care of [14]. Although the authors report an improvement in physical fitness, as determined by the 10-meter walk test, no differences in postoperative outcomes were observed [14]. However, since high-risk patients are regarded to benefit the most from exercise prehabilitation, adequate patient selection seems essential and greatly influences the effect of an exercise prehabilitation program on improving a patient’s aerobic capacity [11, 12]. Another important factor influencing the feasibility and effect of a prehabilitation exercise program is the setting in which it takes place. Most reported prehabilitation programs have been carried out in an outpatient clinic. However, as pointed out by Ferreira et al., patients prefer a home-based prehabilitation program for reasons such as traveling issues or because a hospital- or community-based exercise program is regarded as too much time-consuming [19]. These perceived barriers will negatively influence a patient’s adherence to a physical exercise training program, likely resulting in a suboptimal training effect [19]. On the other hand, a possible disadvantage of unsupervised home-based exercise training could be lack of adherence of the patient, lack of appropriate exercise intensity, and therefore lack of benefit [4]. It is therefore important to provide adequate supervision, preferably by an experienced physical therapist.

In exercise prehabilitation programs within a limited preoperative time window of four to six weeks, the most efficient training modality to increase aerobic capacity seems to be high-intensity interval training (HIIT) [17, 20]. In the study of van Wijk et al., high-risk patients scheduled for liver- or pancreatic surgery received a partly supervised home-based bimodal prehabilitation program, consisting of HIIT and high-intensity endurance training combined with nutritional support. Their four-week prehabilitation program was shown to be feasible, and improved aerobic capacity by 17%, as determined by performing a CPET pre- and post-intervention [17].
Although several studies investigated the effect of exercise prehabilitation in major abdominal surgery, there is a large heterogeneity in patient selection and prehabilitation program setting, which notably influences its effectiveness and adequate interpretation of results. Therefore, the primary aim of this study is to determine the feasibility of a four-week, home-based, partly supervised, exercise prehabilitation program in unfit patients scheduled for pancreatic surgery. Secondary aims of the study are to evaluate the individual responses to the program on aerobic capacity, functional mobility, muscle strength, body composition, level of perceived fatigue, quality of life, and immune system factors.

Methods

Study design

The described study is a multicenter feasibility study and the study will have a pretest-posttest design. Inclusions have started in January 2022 and will run until patient inclusion is completed (expected in summer 2023) at the Maastricht University Medical Center+, the Netherlands, and at the University Medical Center Groningen, the Netherlands. The latest version of the study protocol (version 7, May 2022) is presented in this manuscript. This study is approved by the Medical Research Ethics Committee of the Maastricht University Medical Center + and Maastricht University (METC azM/UM, registration number METC20-090, NL75340.068.20, September 2021), and is registered in the ClinicalTrials.gov register (NCT05496777). Protocol amendments will have to be approved by the METC azM/UM.

Eligibility criteria

In order to be eligible to participate in this study, patients must meet all of the following criteria: (i) age ≥ 18 years, (ii) planned for elective pancreatic surgery at Maastricht University Medical Center + or at the University Medical Center Groningen, and (iii) providing informed consent to participate. Patients are considered eligible (iv) if they have a VO\(_2\) at the VAT \(\leq 13\) mL/kg/min and/or a VO\(_2\) peak \(\leq 18\) mL/kg/min. A patient who meets any of the following criteria will be excluded from participation in this study: (i) requiring acute surgery, (ii) surgery in another hospital, (iii) not able to cycle on a cycle ergometer, (iv) identified contra-indication(s) for physical exercise training, (v) unable to cooperate during the testing procedures (e.g., insufficient understanding of the Dutch language) and (vi) no available certified physical therapist in the living area of the patient.

Recruitment

All patients eligible for pancreatic surgery will be identified at the multi-disciplinary team meetings and evaluated by the surgeon at the outpatient clinic. During the outpatient clinic visit, patients will be given full details of the study, and after a few days, patients from the Maastricht University Medical Center + will be contacted by telephone by a designated investigator to provide extensive information about the study. If patients are interested in participating in the study, a CPET to check whether the patient fulfils the inclusion criteria will be carried out, after which an appointment will be planned to perform baseline assessments and to retrieve written informed consent. At the University Medical Center Groningen, all
patients scheduled for pancreatic surgery perform a CPET as part of usual care. Based on the CPET results, patients will be asked to participate in this study, and an appointment will be planned to perform the remaining baseline assessments and receive written informed consent.

**Interventions**

**Preoperative home-based physical exercise training program**

Participating patients will engage in a home-based, partly supervised exercise prehabilitation program before elective pancreatic surgery. The physical exercise training program will consist of HIIT on an advanced cycle ergometer that is placed at the patient’s home (Lode Corival Home+, Lode BV, Groningen, the Netherlands: see Fig. 1), with the goal to improve a patient’s preoperative aerobic fitness. A certified community physical therapist in the living area of the patient will be asked to partly supervise the physical exercise training program. The community physiotherapist will receive verbal and written instructions on the use of the cycle ergometer, and goals and content of the program.

The duration of the exercise program is four weeks, and the training frequency will be three sessions per week. The supervising community physiotherapist will visit the patient three times during the first week, and once in the weeks thereafter to monitor training progression and provide additional instructions if needed. Patients are encouraged to find a training buddy (e.g., their partner or a close relative) to help and motivate them for the unsupervised training sessions. Each first training session of the week will be preceded by a modified steep ramp rest (SRT) [21], executed under supervision of the community physical therapist. The SRT, a short-time maximal exercise test on a cycle ergometer, has been proven to be a valid tool to estimate aerobic capacity and allows for individual optimization and progress monitoring of the HIIT program [22, 23]. The training program on the cycle ergometer will be personalized weekly to each participant based on their performance during the SRT. Based on SRT performance, the consecutive training sessions comprise HIIT, consisting of a 3-min warm-up at 20 W, 14 high-intensity intervals of 30 seconds at 60% of the peak work rate achieved at the SRT interspersed with 14 low-intensity intervals of 60 seconds at 20 W, and a cool-down of at least 1 min, thereby taking at least 25 minutes to execute (Table 1). Directly after each HIIT session, the patient is asked by the program installed on the cycle ergometer to fill out the 6–20 Borg scale for rating of perceived exertion. Data about the duration, intensity (work rate), heart rate, pedaling frequency, and rating of perceived exertion of each SRT and HIIT session at the cycle ergometer will be automatically recorded by the cycle ergometer at the end of each SRT and HIIT session and uploaded to an online platform (Fig. 2). As such, community physical therapists and the local investigators are able to remotely supervise and monitor training progression and adherence. Once a week, during the supervised SRT and HIIT session, the physical therapist will discuss these findings with the patient. In case of unexpected problems, the community physical therapist can consult the local investigator of the study.
Table 1
High-intensity interval training structure.

<table>
<thead>
<tr>
<th>Exercise phase</th>
<th>Exercise duration</th>
<th>Exercise intensity</th>
<th>Pedaling frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm-up</td>
<td>3 minutes</td>
<td>20 W</td>
<td>40–80 rotations/min</td>
</tr>
<tr>
<td>Interval training</td>
<td>21 minutes</td>
<td>Work interval intensity (n = 14)</td>
<td>60–100 rotations/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 seconds at 60% of WR&lt;sub&gt;peak&lt;/sub&gt; of the steep ramp test</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rest interval intensity (n = 14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 seconds at 20 W</td>
<td>40–60 rotations/min</td>
</tr>
<tr>
<td>Cool-down</td>
<td>1 minute&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20 W</td>
<td>40–80 rotations/min</td>
</tr>
</tbody>
</table>

<sup>a</sup>: duration of the cool-down can be extended when preferred.

Abbreviation: WR<sub>peak</sub> = work rate at peak exercise.

Functional task exercises

Next to HITT on the cycle ergometer, patients will be instructed to carry out functional task exercises two times a week on training days at which the HIIT session is not preceded by an SRT, thereby practicing activities relevant to the patient (e.g., elastic band exercises, stair-climbing, brisk walking) [24]. An overview of the structure of the overall training program can be found in Table 2. The patient will be instructed to perform 15 exercises of about 30 seconds, with 30 seconds of rest in between. The intensity and complexity of exercises will be individually reviewed weekly by the physical therapist. Next to an increasing exercise intensity or frequency, functional task exercises can also progress in difficulty in terms of making exercises more complex and by adding variation.

Table 2. Overall training program structure.
Abbreviations: HIIT=high-intensity interval training; SRT=steep ramp test; \( \text{WR}_{\text{peak}} \)=work rate at peak exercise.

**Usual care**

As part of usual care, all patients are preoperatively screened for risk factors associated with postoperative complications and are treated accordingly. This includes screening for nutritional deficits, mental resilience, anemia, and iron deficiency, hyperglycemia, and substance abuse (e.g., smoking, alcohol consumption).

**Measurements**

Before, during, and after the preoperative home-based physical exercise training program, all patients will undergo a series of outcome measurements (Table 3).

**Program feasibility**

Feasibility will be determined by (i) monitoring the participation rate of this study, as well as reasons for non-participation, (ii) evaluating adherence of patients to the physical exercise training program as objectively recorded by the cycle ergometer, which provides insight into training session content (e.g., frequency, intensity, duration, premature termination of a training session), (iii) dropout rate and reasons for dropout; (iv) number and severity of adverse events; and (v) patient and therapist appreciation after completing the program by filling out a short questionnaire based on a previous study [25].

**Aerobic capacity – cardiopulmonary exercise test**

For all patients, a pre-intervention CPET will be performed to assess baseline aerobic capacity, which will be used to make a selection of eligible unfit patients and thereupon invite them to participate in the study (\( \text{VO}_2 \) at the VAT \( \leq 13 \text{ mL/kg/min} \) and/or \( \text{VO}_2 \text{peak} \leq 18 \text{ mL/kg/min} \)). After completion of the program, a post-intervention CPET will be performed. The outcome thereof will be used to assess the effectiveness of the home-based physical exercise training program to improve aerobic capacity.

The CPET will be executed under controlled conditions, using a calibrated electronically braked cycle ergometer in an upright position (Lode Corival CPET, Lode BV, Groningen, the Netherlands at Maastricht University Medical Center, and Lode Excalibur Sport, Lode BV, Groningen, the Netherlands at the University Medical Center Groningen). Patients will be fitted with a twelve-lead electrocardiogram to rule out strain-related cardiac ischemia, arrhythmias, and other contraindications for intense physical exercise training during the consecutive exercise program. During the test, patients will breathe through a facemask connected to a metabolic cart (Vynthus CPX, Vyaire Medical, Höchberg, Germany at the Maastricht University Medical Center and Quark CPET, Cosmed, Roma, Italy at the University Medical Center Groningen) for measurements of breath-by-breath \( \text{VO}_2 \), minute ventilation, and carbon dioxide production throughout the CPET. Finally, heart rate and blood pressure will be monitored, and peripherally measured oxygen saturation will be measured at the index finger. After two minutes of rest measurements, the
patient is asked to start cycling. The first two minutes consist of unloaded cycling. Thereafter, the work rate will be linearly incremented with a 5, 10, 15, or 20 W/min ramp protocol (depending on the patient’s self-reported physical fitness) to ensure a test duration between eight and twelve minutes. Patients will be instructed to maintain a pedaling frequency around 80/min. The test effort will be considered maximal when the patient shows objective (i.e., heart rate at peak exercise >95% of predicted and/or a respiratory exchange ratio at peak exercise >1.10) and/or subjective signs (e.g., unsteady biking, sweating, clear unwillingness to continue exercising despite strong encouragement) of maximal effort. CPET interpretation will be performed according to international guidelines by an experienced sports physician or medical physiologist. The last 30 seconds before termination of the test will be used to calculate absolute values at peak exercise. Peak heart rate is the highest heart rate achieved throughout the test. The VAT is described as the point at which the partial end-tidal oxygen tension and the ventilatory equivalent for oxygen reached a minimum and thereafter began to rise in a consistent manner, corresponding with an unchanged ventilatory equivalent for partial end-tidal carbon dioxide tension and carbon dioxide [26]. If this method provides unreliable results, the V-slope method will be applied instead [27].

Table 3: Schedule of enrollment, intervention, and assessments.
<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Pre-intervention</th>
<th>Home-based exercise prehabilitation</th>
<th>Post-intervention</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week</td>
<td></td>
<td></td>
<td>30 days postoperative</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Enrolment**

- Eligibility screening
- Informed consent

**Intervention**

- Home-based exercise prehabilitation

**Assessments**

- Baseline characteristics
- Feasibility
- Aerobic capacity
  - CPET
  - SRT
- Muscle strength
  - Handgrip strength
- Body composition
  - Anthropometry
  - L3-index
- Functional mobility
  - 30-sec chair-stand test
  - 2-minute walk test
- Immunological phenotyping
- Questionnaires
  - MFI
  - EORTC QLQ-C30
  - SARC-F
Program appreciation

Postoperative outcomes

<table>
<thead>
<tr>
<th>Surgical complications</th>
<th>●</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay</td>
<td>●</td>
</tr>
<tr>
<td>30-day readmission</td>
<td>●</td>
</tr>
</tbody>
</table>

*a*: patient and community physical therapist appreciation.

Abbreviations: CPET=cardiopulmonary exercise test; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; L3=third lumbar vertebra; MFI=multidimensional fatigue index; SARC-F=strength, assistance with walking, rising from a chair, climbing stairs, and falls; SRT=steep ramp test.

*Aerobic capacity* – *modified steep ramp test*

During the physical exercise training program at the patient’s home, the physiotherapist will assess and monitor aerobic fitness by performing a modified SRT [21] on a weekly base on the advanced cycle ergometer (Lode Corival Home+, Lode BV, Groningen the Netherlands) in an upright position. Training intensity will be adjusted based on SRT performance, which is expected to maintain sufficient training stimulus. A heart rate belt will be fitted around the patient’s chest (Xand cycling, Apeldoorn, the Netherlands) during the test. The steep ramp test starts with three minutes of unloaded cycling. Next, the work rate will be increased in a ramp-like manner by a constant increment of 10 W/10 s. The total test duration is estimated to be four to seven minutes. The patient is instructed to keep the pedaling frequency constant between 60 and 80 revolutions/minute. The main outcome of the SRT is the achieved peak work rate (WR<sub>peak</sub>), defined as the point at which there is a sustained drop in pedaling frequency from 60 revolutions/min, despite strong verbal encouragement. After attaining their WR<sub>peak</sub>, patients will be asked their level of perceived exertion by filling out the 6-20 Borg scale for rating of perceived exertion. They will conclude the SRT with a two-minute cool-down phase consisting of unloaded cycling at a pedaling frequency of about 40 revolutions/min.

*Muscle strength*

To assess the effect of the exercise prehabilitation program on muscle strength, handgrip strength (in kilograms) will be measured in patients before and after the program using the Jamar dynamometer (Sammons Preston, Rolyon, Bolingbrook, IL, USA) [28]. Muscle strength, as measured by handgrip dynamometry, is seen as an indicator of frailty and an independent predictor of complications after surgery [29, 30]. Patients will be asked to sit in upright position with the elbows stretched in a straight line downwards. Patients will be asked to squeeze the handle as forcefully as possible for about two seconds,
starting with the dominant hand. A total of three grip measurements per hand will be performed, with a 15- to 20-second pause between each measurement.

**Body composition**

The patient’s body height (determined to the nearest 0.5 cm) and body mass (determined to the nearest 0.1 kg) will be measured with a metric measuring tape with a wall stop, and an electronic scale (Seca 803, Seca, Hamburg, Germany), respectively, pre- and post-intervention. During the prehabilitation program, the community physiotherapist will measure the patient’s body mass weekly.

Myosteatosis (i.e., skeletal muscle fat infiltration) is a biomarker for cancer cachexia (i.e., a multifactorial wasting syndrome leading to loss of skeletal muscle mass with or without loss of fat mass, subsequently inducing progressive functional impairment) and sarcopenia (i.e., loss of skeletal muscle tissue). Myosteatosis alone, but also cancer cachexia and sarcopenia are associated with increased morbidity and mortality [31, 32]. Meanwhile, it has been suggested that physical exercise training improves muscle quality [33]. Therefore, we will evaluate skeletal muscle quantity and quality pre- and post-prehabilitation by analyzing a single slice of a CT-scan at the mid-level of the third lumbar vertebra (L3), which is where both transverse processes are visible. Body composition analysis will be performed using an automated segmentation system developed and validated at Maastricht University [34]. Visceral adipose tissue, subcutaneous adipose tissue, and skeletal muscle tissue will be normalized for the patient’s body height to calculate the L3-index in cm$^2$/m$^2$. Radiation attenuation will be determined by calculating the average Hounsfield-units value of the areas. Low skeletal muscle radiation attenuation is associated with increased myosteatosis [35]. For this study, the CT-scans that are part of the standardized diagnostic work-up of patients will be analyzed. Since CT-imaging prior to oncologic surgery should not be older than six weeks, preoperative CT-scans are performed on a regular basis in patients.

**Functional mobility**

Functional mobility will be assessed using the 2-minute walk test (2MWT) and 30-second chair-stand test pre- and postintervention at the hospital, as well as weekly at the patient’s home. The 30-second chair-stand test evaluates a combination of lower leg muscle strength, balance, and functional mobility by testing the number of repetitions standing up from a sitting position within 30 seconds [36]. The 2MWT is a feasible method to record the distance (in meters) that is walked over a standardized trail in two minutes [37].

**Immunological phenotyping**

As the immune system is highly responsive to physical exercise, it has been suggested that structural physical exercise training can improve overall health and may prolong survival in patients with cancer [38]. To quantify the effect of the preoperative physical exercise training program on the immune system response, blood samples will be taken pre- and post-prehabilitation and analyzed for levels of C-
reactive protein, tumor necrosis factor-α, as well as interleukin-6, interleukin-8, and interleukin-10 by multiplex analysis. Moreover, a separate blood sample for each patient will be drawn for storage at -80 °C for future analysis. Blood samples will be stored in the biobank of the participating hospital, for a maximum of ten years. Future analysis has to be in line with the aims of our ongoing research; if not, informed consent must be retrieved.

Questionnaires

Prior to the start of the exercise program, patients are asked to fill out a perceived fatigue, quality of life, and sarcopenia questionnaire. The level of perceived fatigue is assessed using the multidimensional fatigue index [39], quality of life will be evaluated with the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) questionnaire [40], and finally, the strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire [41] is used to screen for sarcopenia in patients. To check for potential improvements in perceived fatigue, quality of life and sarcopenia, these questionnaires will be repeated after completion of the exercise prehabilitation program.

Study outcomes

Primary outcome

The primary outcome of this study is to assess the feasibility of a four-week home-based, partly supervised exercise prehabilitation program in unfit patients planned for elective pancreatic surgery. Feasibility is assessed via the participation rate, and reasons for non-participation, adherence/compliance to the program, drop-out rate and reasons for dropout, adverse events during the program, and patient and therapist appreciation.

Secondary outcomes

Secondary outcomes are to evaluate the patients’ responses to exercise prehabilitation on aerobic capacity, functional mobility, muscle strength, body composition, perceived fatigue, quality of life, immune system factors, number of overall postoperative complications within 30 days after surgery, and readmissions within 30 days after discharge. Complications will be graded using the Clavien-Dindo classification and divided into surgical and non-surgical complications [42, 43].

Other study outcomes

Data on patient characteristics (e.g., age, sex, nutritional status, Charlson comorbidity index, American Society of Anesthesiologists score, smoking, location and type of the tumor) neoadjuvant therapy, and surgical procedure will also be collected for explorative purposes.

Safety
During and 30 days after the preoperative physical exercise training program, all adverse events observed by the investigator or his staff or reported spontaneously by the participating patients will be recorded.

Data analysis

Sample size calculation

This study will specifically evaluate the feasibility of a home-based, partly supervised prehabilitation program in unfit patients undergoing elective pancreatic surgery. Thus, the study also has a clear explorative character and will at within-subject responses to the program. Based on the number of patients undergoing elective pancreatic surgery annually, and the relatively short study period (<1 year), 15 patients who are willing to participate in the study will be included per hospital, resulting in a total of 30 patients. Results of this exploratory study will provide information on how to proceed in subsequent effect studies and furthermore results can be used to optimize the home-based prehabilitation program in the future.

Procedures for data checking and entering

All data will be handled confidentially according to the General Data Protection Regulation. Signed informed consent forms and other traceable data will be stored on a local server secured with a password. Coded data will be collected in an electronic case report form created in Castor (Castor, New York, USA), a program aimed at clinical trial data recording and monitoring. Only the principal and coordinating investigator of each center will have access to uncoded data. Variables will be checked for the number of missing, improbable, or impossible values, prior to statistical analysis. In case of impossible or improbable values, the patient’s data file will be reviewed.

Statistical analysis

The R software package (R Foundation for Statistical Computing, Vienna, Austria) will be used for statistical analysis. Collected data on patient characteristics will be presented in tables. Continuous variables will be displayed as mean ± standard deviation, while categorical variables will be presented as number (n) and percentage (%). Descriptive statistics will be used to answer the primary study parameter of feasibility. As previously described, feasibility will be presented in tables and based on participation rate (n, %), adherence to the program (%), dropout rates (%), adverse events (n, %, text), patient motivation (scale 0-10), and appreciation (text). The secondary aim is to evaluate the patients’ responses over time in terms of aerobic capacity, muscle function, functional mobility, body composition, perceived fatigue, quality of life, and immune system function. Individual response profiles will be graphically depicted and presented in tables. A repeated measurements analysis will be used to analyze changes over time in continuous variables. P-values <0.05 will be considered statistically significant.

Dissemination policy
Research results will be disclosed and submitted to a peer-reviewed scientific journal, in case of positive as well as negative results. The investigators will prepare the manuscript together. Co-authorship is preserved for all participating investigators and to those who – at discretion of the principal investigator – constructively contributed to the study. Disputes on the interpretation of results will not lead to an unnecessary delay in publication.

Discussion

Results of this study will provide important clinical knowledge on implementing a supervised (partly direct supervision, partly remote supervision) home-based exercise prehabilitation program for unfit patients scheduled for pancreatic surgery. Any potential barriers that hamper effective execution of a physical exercise training program will be identified by thoroughly analyzing feasibility outcomes. This gathered scientific knowledge will fill in gaps in current literature and poses the ability to improve preoperative optimization of unfit patients. Prove of feasibility might ease the path to implementing exercise prehabilitation programs in patients undergoing complex abdominal surgery, such as pancreatic surgery. Ultimately, this may lead to better treatment outcomes in this vulnerable patient population. Apart from future patients being scheduled for pancreatic surgery, we expect participating patients to benefit directly from the physical exercise training program, due to an expected increase in preoperative aerobic capacity, and subsequently better treatment outcomes.

Several studies indicated that a VO$_2$ at the VAT <11 mL/kg/min and/or a VO$_2$peak <18 mL/kg/min, as determined during a CPET, are accurate cut-off points to identify patients that have a higher risk for postoperative morbidity and mortality [5, 8]. Nevertheless, preoperative physical exercise training might also be beneficial for patients with mediocre aerobic capacity undergoing pancreatic surgery. In the Netherlands, the mean waiting time for surgery is four to six weeks, meaning there is sufficient time for patients to participate in physical exercise training programs. Therefore, we have chosen to include all patients with a VO$_2$ at the VAT $\leq$ 13 mL/kg/min and/or a VO$_2$peak $\leq$ 18 mL/kg/min in their waiting period. Previous studies have clearly demonstrated the beneficial effect of exercise prehabilitation on aerobic capacity in patients scheduled for intra-abdominal surgery [13-16, 18]. In high-risk patients scheduled for major abdominal surgery, Barberan-Garcia et al. demonstrated a 35% increase in aerobic endurance time and a 51% reduction of postoperative complications, after a six-week preoperative high-intensity endurance training [18]. More recently, Berkel et al. demonstrated a 10% increase in aerobic capacity (VO$_2$ at the VAT and VO$_2$peak) and an almost 50% decrease in the incidence of postoperative complications in high-risk patients scheduled for colorectal surgery undergoing a three-week community-based and personalized preoperative HIIT program [16]. Despite evidence suggesting that exercise prehabilitation is effective, among the reported prehabilitation programs there is a large heterogeneity in the design and setting. Although most of the reported prehabilitation programs were carried out under supervision in an outpatient clinic, patients clearly prefer a home-based prehabilitation program [19]. Nevertheless, home-based prehabilitation programs should be supervised, since a possible disadvantage of unsupervised home-based exercise training could be lack of adherence of the patient or lack of
appropriate exercise intensity, and therefore lack of benefit [4]. A supervised and personalized exercise program in a home-based setting might enhance the participation rate, adherence, and motivation of (high-risk) patients, and has shown to be the preferred method for a prehabilitation program [4, 17, 44]. To illustrate this, van Wijk et al. recently reported on a 83% adherence rate in their partly supervised home-based training program, which led to an increase of respectively 17.8% and 17.2% in VO$_2$ at the VAT and VO$_2$peak in unfit (VO$_2$ at the VAT <11 mL/kg/min) patients undergoing liver or pancreatic resection [17].

Strengths of the present study are its clear study design consisting of a supervised home-based prehabilitation program, the ability to thoroughly assess feasibility in a vulnerable patient population, the use of validated measurement instruments, and the personalized training program based on an individual patient's performance at the weekly executed SRT. This study is aimed to set the standard for home-based exercise prehabilitation programs in pancreatic surgery. Nevertheless, this study will have some limitations. First of all, the physical exercise training program is only partly supervised by a physical therapist. This may lead to a lower patient adherence to the exercise program and subsequently suboptimal training results. However, the advanced cycle ergometer used in this study automatically captures data on training frequency, intensity, and duration. This enables the physical therapist to monitor training progression and compliance in real-time and gives the opportunity to intervene if necessary. Furthermore, as mentioned before, van Wijk et al. have reported an acceptable 83% adherence in their partly supervised exercise program [17]. Also, given that the primary outcome of interest is feasibility of the training program, non-completion of a training adds valuable information to the dataset. Another limitation might be that our study focuses on exercise prehabilitation while most unfit patients might benefit from a multimodal approach, including screening and subsequent treatment of common risk factors associated with postoperative complications. This screening is part of usual care in both centers. If necessary, nutritional support, treatment of modifiable risk factors (e.g., dyslipidemia, smoking, alcohol consumption), and mental support will be implemented within the patient's individual prehabilitation program.

While hospital- and community-based exercise prehabilitation programs encounter significant feasibility issues when enrolling vulnerable unfit patients, this study will offer unfit patients a unique personalized exercise prehabilitation program with adequate supervision in the setting of their own residence. Hence, it is expected that this study will achieve high adherence rates and subsequently high efficacy in improving patients' preoperative aerobic capacity.

**Declarations**

**Ethics approval and consent to participate:** This study was approved by the Medical Research Ethics Committee of the Maastricht University Medical Center+ and Maastricht University (METC azM/UM), the Netherlands (registration number METC20-090, NL75340.068.20, September 2021) and is registered in the Clinicaltrials.gov register (NCT05496777).

Informed consent will be obtained from all participating subjects.

All methods are carried out according to relevant guidelines and regulations.
Consent for publication: Not applicable.

Availability of data and materials: Not applicable.

Competing interests: none declared

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Author’s contributions: N.H. and A.W. prepared the manuscript for publication. B.B., S.R., and M.d.D. performed the ethical approval procedure and communicated with external parties. B.B. prepared figures 1 and 2 and tables 1-3. S.O.D. and J.K. invented and implemented the protocol. All authors read and approved the final manuscript. All authors reviewed the manuscript.

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References


Figures

![Figure 1](image)

*Figure 1*

*The Lode Corival Home+ cycle ergometer used in this study.*
Training results registered by the advanced cycle ergometer and displayed at the online platform. 
a: results of an executed SRT. 
b: results of the consecutive HIIT session at 60% of WR\textsubscript{peak} of the SRT. 
Abbreviations: HR=heart rate, WR=work rate; WR\textsubscript{peak}=work rate at peak exercise.