Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

Lars Tung Dyrendahl

Can peer-support improve adherence to exercise training and lead to improved cardiorespiratory fitness in secondary prevention after myocardial infarction?

A randomized sub-trial of The Norwegian Trial of Physical Exercise After Myocardial Infarction

Master's thesis in Physical Activity and Health – Exercise Physiology
Supervisor: Ulrik Wisløff
Co-supervisor: Alexander Robert Gran Svenningsen
May 2023

NTNU
Norwegian University of
Science and Technology

Lars Tung Dyrendahl

Can peer-support improve adherence to exercise training and lead to improved cardiorespiratory fitness in secondary prevention after myocardial infarction?

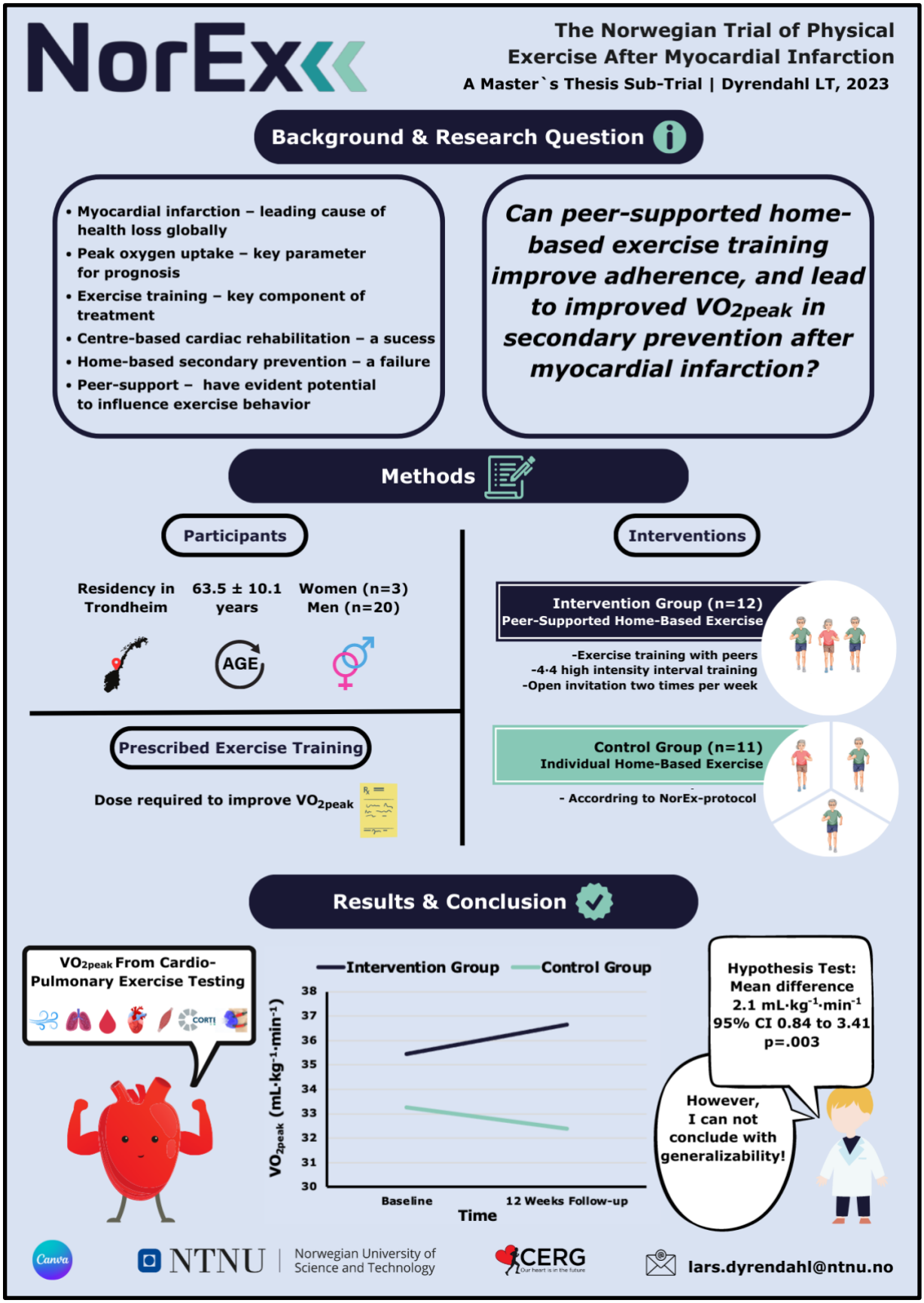
A randomized sub-trial of The Norwegian Trial of Physical Exercise After Myocardial Infarction

Master's thesis in Physical Activity and Health – Exercise Physiology
Supervisor: Ulrik Wisløff
Co-supervisor: Alexander Robert Gran Svenningsen
May 2023

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

NTNU
Norwegian University of
Science and Technology

Infographic



Abstract

Background: Physical exercise training is a key component of treatment after myocardial infarction, but survivors usually fail to maintain prescribed exercise training in daily life. Peer-support have evident potential to promote motivating and facilitating factors to exercise behavior in patients with myocardial infarction. Our objective was to compare the effect of home-based exercise training with peer-support to individual home-based exercise training, on change in cardiorespiratory fitness in secondary prevention after myocardial infarction.

Methods: This study is a sub-trial of NorEx (The Norwegian Trial of Physical Exercise After Myocardial Infarction). NorEx is initiated to determine the efficacy of four years of supervised home-based exercise training, with a dose required to increase cardiorespiratory fitness, on mortality and cardiovascular morbidity in survivors of myocardial infarction. We enrolled 23 participants from the exercise group in with low adherence to the prescribed exercise training, randomly allocated to 12 weeks peer-supported home-based exercise training (intervention group, n=12) or individual home-based exercise training according to the protocol of NorEx (control group, n=11). Cardiorespiratory fitness was measured with gold standard cardiopulmonary exercise testing as peak oxygen uptake at baseline and follow-up.

Results: Six participants in the intervention group and nine participants in the control group completed the intervention and follow-up testing of the primary outcome. Mean difference of change in peak oxygen uptake between groups at follow-up were 2.1 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI 0.84 to 3.41, p=.003).

Conclusion: Peer-supported home-based exercise training can be more effective to maintain or improve peak oxygen uptake compared to individual home-based exercise training according to NorEx-protocol. Large dropout and risk of various bias makes generalizability impossible.

Abstrakt

Bakgrunn: Fysisk trening er en nøkkelfaktor i behandling av hjerteinfarkt, men pasienter mislykkes i å opprettholde en treningsatferd i det dagligdagse. Sosial støtte fra medpasienter har beviselig potensialet til å motivere og fasilitere treningsatferd hos pasienter med hjerteinfarkt. Hensikten med denne studien var å sammenligne effekten av hjemmebasert trening med sosial støtte fra medpasienter, mot individuell hjemmebasert trening på kondisjon i sekundærforebygging etter hjerteinfarkt.

Metode: Denne studien er en substudie av NorEx (The Norwegian Trial of Physical Exercise After Myocardial Infarction). NorEx er igangsatt for å fastslå effekten av fire års supervisert, hjemmebasert trening, med et treningsvolum som er nødvendig for å forbedre kondisjon, på dødelighet og kardiovaskulær sykdom etter hjerteinfarkt. Vi inkluderte 23 deltakere med lav måloppnåelse av foreskrevet trening fra treningsgruppen i NorEx, og fordelte de tilfeldig til enten en intervensjonsgruppe (n=12) med hjemmebasert trening med sosial støtte fra medpasienter eller en kontrollgruppe (n=11) med individuell hjemmebasert trening i henhold til NorEx-protokollen. Kondisjon ble målt som oksygenopptak med ergospirometri, gullstandarden for måling av kondisjon, ved studiestart og studieslutt etter 12 uker.

Resultater: Seks deltakere i intervensjonsgruppen, og ni deltakere i kontrollgruppen fullførte intervensjonen og oppfølgingstesten av oksygenopptak. Estimert forskjell i forandring i oksygenopptak mellom gruppene var 2.1 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% KI 0.84 to 3.41, p=.003).

Konklusjon: Hjemmebasert trening med sosial støtte fra medpasienter kan være mer effektivt for å vedlikeholde eller forbedre oksygenopptak sammenlignet med individuell hjemmebasert trening i henhold til NorEx-protokoll. Stort frafall og risiko for ulike bias gjør generalisering av resultatene umulig.

Acknowledgements

I thank my supervisor, professor Ulrik Wisløff, for great help, for encouraging me to work hard, and for letting me take part in The Cardiac Exercise Research Group and The Norwegian Trial of Physical Exercise After Myocardial Infarction. I also thank my co-supervisor, Alexander Robert Gran Svenningsen, for providing me help with everything between heaven and earth. Thank you to professor Stian Lydersen for educating me in medical statistics, and for providing help with statistical analysis.

Thank you to the whole project group in NorEx for taking me in as a college, and thank you to the engineers in the exercise laboratories at the Next Move Core Facility for discussing exercise physiology with me, and for educating me in cardiopulmonary exercise testing.

Lastly, thank you to Ida Ormstad Nilsen for carrying out the sub-trial project with me.

Table of Contents

Definitions

Pathology

Ischemic heart disease, also called coronary heart disease or coronary artery disease, is the term given to heart problems caused by narrowed coronary arteries leading to ischemia (inadequate circulation, blood and oxygen supply of an organ due to blockage of blood supplying vessels) (3). The term includes myocardial infarction, chronic stable angina pectoris, chronic ischemic heart disease and heart failure due to ischemic heart disease (2). Narrowed vessels are most often caused by buildup of plaque, called atherosclerosis (3). **Myocardial infarction** occurs when the heart muscles blood flow is completely blocked, and the heart muscle cells die (3).

Cardiorespiratory fitness

Cardiorespiratory fitness is the ability of the respiratory, circulatory and muscular systems to consume, distribute and utilize oxygen during maximal exertion involving large muscle groups (33). It is also defined by the Fick equation, as the volume of blood in cardiac output (heart rate · stroke volume) multiplied with the volume of oxygen extracted from circulating blood (arteriovenous oxygen difference) (33). **Cardiopulmonary exercise testing** is the gold standard for measuring cardiorespiratory fitness (31). **Maximal oxygen uptake** refers to the highest rate in which an individual can transport and utilize oxygen during maximal exertion involving large muscle groups. To reach the true maximal oxygen uptake, the oxygen uptake must level off and reach a plateau despite increased workload during a cardiopulmonary exercise test (33). **Peak oxygen uptake** is a term used instead of maximal oxygen uptake when a cardiopulmonary exercise test in an individual does not meet the criteria to be evaluated as the true maximal value. Maximal efforts do not always lead to a plateau in oxygen uptake (e.g. due to lack of motivation or disability of maximal exertion) (33). **Respiratory exchange ratio** is a parameter in cardiopulmonary exercise testing, and refers to the ratio of carbon dioxide produced to oxygen consumed during physical activity (33). **Breathing frequency** is a parameter in cardiopulmonary exercise testing, and refers to the number of breaths per minute (33).

Exercise training principles

Physical activity is defined as any bodily movement, produced by skeletal muscles, that requires energy expenditure above resting metabolism (10). **Exercise training** refers to planned, repetitive structured and purposeful physical activity with the objective to improve or maintain cardiorespiratory fitness (10). **External load** (work) can be explained as the physical activity conducted e.g. distance covered in a fixed time (33). **Internal load** can be explained as the physiological response and energy expenditure to perform the external work (33). **Exercise training intensities** from % of peak heart rate are used to prescribe internal load as heart rate and oxygen consumption, and thus aerobic energy expenditure, relate linearly (33). The terms high-, moderate and low intensity refers to >85%-, 70-84%-, and <70% of peak heart rate respectively.

Exercise-based cardiac rehabilitation

Cardiac rehabilitation is defined as "the coordinated sum of activities required to influence favorably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts preserve or resume optimal function in their community and through improved behavior, slow or reverse progression of disease" (8). Exercise training is a central

component in cardiac rehabilitation and has a Class I recommendation from the European Society of Cardiology and the American College of Cardiology/American Heart Association (8). **Centre-based** cardiac rehabilitation is the traditional form of supervised rehabilitation programs. Centre-based refers to a variety of settings e.g. hospital, physiotherapy department, university gymnasium or community sports centre (9). **Home-based** cardiac rehabilitation refers to a setting from home, and is defined as a structured program, that includes exercise training, with clear objectives for the participants, including monitoring, follow-up visits, letters or telephone calls from staff or at least self-monitoring diaries (9).

Peer-support and peer-instruction

Peer-support refers to social support from peers, which for a patient with myocardial infarction in this in this context, is a fellow patient with myocardial infarction. Peer-support has, to the best of our knowledge, no specific definition, but occurs when peers are sharing experience, knowledge and support with each other from a common perspective (24-28). **Peer-instruction** origins from educational settings, and is a well-researched active-learning technique, generally defined as "an opportunity for peers to discuss ideas or to share answers to questions in an in-class environment, where they also have opportunities for further interactions with their instructor" (29).

Methodological terms and expressions

The Norwegian Trial of Physical Exercise after Myocardial Infarction (NorEx) is a health registry-based randomized control trial, and a Norwegian, national multicenter study with the objective to determine the efficacy of four years of supervised home-based exercise training, with a dose required to increase cardiorespiratory fitness, on mortality and cardiovascular morbidity in survivors of myocardial infarction. The hypothesis is that exercise training, reduces the primary composite endpoint by 20% compared to standard care. **The Hawthorne effect** is a consequent awareness of being studied, with possible impact on behavior in research participation. It refers to a phenomenon, for example in exercise trials, in which participants increase their physical activity level as a result of being evaluated (36).

Statistical terms and expressions

The 95% confidence interval is an estimated interval of a population parameter from observed data. If an experiment were repeated over and over, then 95% of the time, the confidence intervals contain the true population mean (34). **The probability value** is defined as the probability under the assumption of no effect or no difference (null hypothesis), of obtaining a result equal to or more extreme than what was observed if the null hypothesis is true (35).

Abbreviations

95% CI	95% confidence interval
BMI	Body mass index
CRF	Cardiorespiratory fitness
f_B	Breathing frequency
HIIT	High intensity interval training
IHD	Ischemic heart disease
MI	Myocardial infarction
MICT	Moderate intensity continuous training
NorEx	The Norwegian Trial of Physical Exercise after Myocardial Infarction
p	Probability value
PA	Physical activity
RER	Respiratory exchange ratio
SD	Standard deviation
VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen uptake

Introduction

Ischemic heart disease (IHD) is the leading cause of health loss globally with nearly 200 million prevalent cases annually, including more than 7 million acute myocardial infarctions (MI) and over 9 million deaths (1-3). Physical activity (PA) is associated with lower mortality, and cardiorespiratory fitness (CRF) predicts survival in IHD patients (4, 5). It is well documented that exercise training can improve CRF (6), and for inactive people, even as little as 3 minutes of vigorous intermittent lifestyle PA reduces health risk (7). Consequently, treatment guidelines for IHD patients includes PA and exercise training as a central component of cardiac rehabilitation, risk factor modification and secondary prevention (8-10).

Several studies suggests that high intensity interval training (HIIT) at 85-95% of peak heart rate is more effective than lower intensities to improve CRF, both in healthy individuals and in cardiac rehabilitation (11-14). These data are convincing, but largely emanate from exercise trials conducted in laboratory conditions (15). Likewise, traditional centre-based cardiac rehabilitation normally improves PA-levels, CRF and other health related outcomes effectively (8, 9, 16). However, neither laboratory conditions or centre-based facilities reflects what patients face in daily life (15, 17, 18), and it is well known that patients fail to maintain exercise behavior when rehabilitation programs are over (17, 19).

The Generation 100 Study, a five-year exercise trial without laboratory conditions in older adults aged 70-77 years at baseline, reported that nearby outdoor areas and nature were the most frequently used locations for exercise training (18). They also observed an equal split of exercise sessions performed alone and together with others (18). Of interest, they found both moderate intensity continuous training (MICT) and HIIT without strict supervision feasible for older adults (18). HIIT is also found feasible without supervision in home-based cardiac rehabilitation (9).

Home-based cardiac rehabilitation has been introduced as an alternative, since one of the main reasons for not attending traditional rehabilitation programs is difficulty with attending regularly (9). Importantly, home-based cardiac rehabilitation is found to be similarly effective as traditional rehabilitation in improving clinical-, and health related outcomes such as CRF (9). However, it is suggested that high motivation for exercise training should be present for home-based cardiac rehabilitation to work (20).

Motivation is a key factor, in a complex interaction with capability and opportunity, to explain a behavior, such as exercise training (21). Various social factors as social support, positive reinforcement, affiliation, commitment and sharing experience have been identified as facilitators and motivators for exercise training (17, 22, 23). Peer-support interventions have been carried out in various research and patient groups, and have evident potential to promote motivating and facilitating factors to exercise training in IHD patients (24-28).

Greater understanding of social and cultural determinants from professional practices (19) is suggested as a solution to the need of enhanced adherence to exercise training after completion of cardiac rehabilitation (20). Key data are needed to bridge the gap from exercise laboratories to public health policies (15). Simultaneously, NorEx (The Norwegian Trial of Physical Exercise After Myocardial Infarction) is initiated to determine the efficacy

of four years of home-based exercise training, with a dose required to increase CRF, on mortality and cardiovascular morbidity in survivors of MI. The NorEx-intervention will continuously adapt measures to enhance long term adherence to PA and exercise training. Evaluation of preliminary internal results of NorEx indicate that many participants are struggling with adherence to prescribed exercise training.

The aim of this trial was therefore to compare the effect of peer-supported home-based exercise training on change in CRF to individual home-based exercise training according to the NorEx-protocol, in secondary prevention after MI among NorEx-participants with low adherence to prescribed exercise training. We hypothesized that peer-supported home-based exercise training is more effective to improve CRF because implementing known motivators and facilitators likely leads to better exercise adherence than the standard NorEx-protocol.

Methods

Trial Design

The study was a randomized controlled trial with allocation 1:1 to parallel groups. Participants from the exercise training group in NorEx were randomly allocated to two different modes of intervention for 12 weeks, with instruction to follow the exact same prescribed volume of exercise training. Intervention group: Peer-supported home-based exercise training (n=12). Control group: Individual home-based exercise training according to NorEx-protocol (n=11).

A change in methods occurred after trial commencement regarding a planned key outcome of adherence to exercise training. The outcome was supposed to be measured as weekly time of exercise training with high (>85% of peak heart rate), moderate (70-84% of peak heart rate) and low (<70% of peak heart rate) intensity, objectively measured with an optical heart rate monitor with subsequent data collection from a corresponding web portal. However, too much missing data (completely at random) and poor validity occurred due to severe problems with product function and reliability, both in the optical heart rate monitor and web portal. Thus, these data could not be included in the analysis.

Participants

Participants were recruited from the exercise training group in NorEx. NorEx is a health registry-based randomized control trial, and a Norwegian, national multi-center study. The hypothesis of NorEx is that >4-years supervised home-based physical exercise training, with a dose to increase CRF, reduces the NorEx primary composite endpoint of all-cause mortality and cardiovascular morbidity by 20% compared to standard care. Current NorEx-participants were patients hospitalized with acute MI during 2013-2021.

Eligibility criteria for participation in NorEx are described in the NorEx-protocol (Appendix 1). We used two eligibility criteria for participation in the current sub-trial, before invitations to participate were carried out. Due to ability to complete the sub-trial, eligibility criteria 1 was: Permanent address and resident in Trondheim, Norway. With the aim to include participants with low motivation- and poor adherence to the prescribed exercise training from NorEx, eligibility criteria 2 was: Unknown level of PA or persistent score of the PA-metric Personal Activity Intelligence below 100 the last two months prior to inclusion. Information about address, residency, PA-levels and Personal Activity

Intelligence was obtained from records in NorEx. We used an additional exclusion criteria when we carried out invitations and after baseline testing of the primary outcome: Inability to comply with the exercise training protocol due to any present physical disability, somatic disease, or mental problem.

Interventions

Prescribed exercise training was identical to NorEx: A volume of intensity, duration and frequency that accumulates to a minimum of 115 minutes of weekly exercise training, divided into a minimum of 20 minutes exercise training with high intensity (>85% of peak heart rate), and the rest at moderate intensity (70-84 of peak heart rate). Low intensity was considered <70% of peak heart rate. Participants were supervised by various measures in NorEx with the aim of consistent adherence to the exercise protocol. The applied supervision tools (personnel, resources and behavior change techniques) are described in the NorEx-protocol (Appendix 2). Both the intervention- and the control group received the same supervision from the NorEx measures during the trial period.

Intervention Group

The participants in the intervention group in this sub-trial were invited to participate in regular peer-supported home-based exercise sessions, two times per week (24 exercise sessions over 12 weeks) at a fixed time and location outdoors in Trondheim, decided by the participants. We (authors and study personnel) attended 50% of the exercise sessions (the first four, six sporadically, and the last two exercise sessions).

In the first four exercise sessions, we instructed the participants to perform HIIT designed as 4·4 minutes interval training. Firstly, participants warmed up for at least 15 minutes with increasing intensity from low to moderate. Secondly, we transferred practical knowledge about 1: Different modalities to conduct 4·4 HIIT e.g. fixed time or fixed distance. 2: Training principles about individuality and intensity e.g. a) How to conduct high impact external work by walking, jogging and running. b) How heart rate reflects internal load and reaches target zones after about two to three minutes in the first interval, and then increasingly sooner in the second, third and fourth interval, c) How to control effort thereafter, and d) How to control intensity with the rule that breathing (ventilation) should be so strenuous during each interval, that it is only possible to speak a few words or very short sentences. Thirdly, each interval was separated by approximately three minutes, or a fixed distance, active recovery with moderate to low intensity, and lastly, after the last interval, the exercise sessions were terminated with about 5 minutes cool down with moderate to low intensity and rest.

After the first four exercise sessions, we no longer attended regularly, but encouraged the participants to mainly perform 4·4 HIIT. In our absence, exercise sessions were peer-instructed (i.e. Active learning with peers (29)). We attended six sporadically and then the last two exercise sessions, in a passive roll to overlook and assist the peer-instructed exercise training. Other contact with participants was done by text messages, to give weekly reminders of exercise sessions or important information (e.g. if changing time and place).

Control Group

Control group participants received only the supervision described in the NorEx-protocol, summarized as individual home-based exercise training. We had no contact with the control group during the trial period.

Outcomes

The primary outcome was change in CRF. Exploratory descriptive statistics are presented for exercise attendance in the intervention group.

Cardiorespiratory Fitness

CRF was measured as peak oxygen uptake (VO_{2peak}) with gold standard cardiopulmonary exercise testing on a treadmill at the Next Move Core Facility at The Norwegian University of Technology and Science and St. Olav's Hospital, Trondheim, Norway. Peak heart rate was measured and determined simultaneously (H10, Polar, Kempele, Finland).

Ventilatory gas analyzes was done by an ergospirometry system (Metalyzer II, Cortex Biophysik GmbH, Leipzig, Germany), connected to a face mask (Hans Rudolph, Kansas, MO, USA) of appropriate size. The ergospirometry system at Next Move have been validated against Douglas bag and iron lung (Metabolic Calibration System, VacuMed, Ventura, CA, USA). It was calibrated prior to the first test each day, using a standard two-point gas calibration procedure including barometric pressure control, measurements of ambient air and a gas mix of known content (15% O_2 and 5% CO_2, HIQ Center, AGA HIGH Q A/S, Oslo, Norway). Calibration of the volume transducer (Triple-V, Cortex Biophysik GmbH, Leipzig, Germany) was done with a calibration syringe (Calibration Syringe 3000mL, Cortex Biophysik GmbH, Leipzig, Germany). Ambient air was measured before each test, accompanied by volume transducer calibration. Two-point gas calibration took place every fifth test. Height was measured with a stadiometer (Seca, Hamburg, Germany) and weight was measured using a weighing scale (Arctic Heating AS, Nøtterøy, Norway). The treadmill (PPS Med 55, Woodway, Waukesha, WI, USA) at Next Move are calibrated several times per year to ensure correct velocity and inclination.

We used an individualized graded test protocol (30). Participants performed a 10-minute combined warm up and treadmill familiarization phase without ergospirometry measurements. A detailed explanation of the test protocol was given, and participants were instructed to avoid grabbing the handrails if not absolute necessary. Warm up was based on our evaluation of participant`s fitness level, participant`s subjective rate of perceived exertion and heart rate monitoring. The individualized warm up workload determined the initial velocity/inclination on the subsequent treadmill test. The graded test protocol consisted of 3 levels. Two submaximal levels of three minutes with fixed workload and the last level with increasingly workload. Level 1: The individual initial workload was determined during warm up, and stable oxygen uptake and heart rate were reached after approximately 3 minutes. Level 2: Speed increased 1 $km \cdot h^{-1}$ or treadmill gradient was increased by 2% from level 1, with steady state obtained after 2-3 minutes. Level 3: Speed increased 1 $km \cdot h^{-1}$ or treadmill gradient was increased by 2% from level 2. Then, approximately every minute when participants maintained a stable oxygen uptake for >30 seconds, velocity (0.5-1.0 $km \cdot h^{-1}$), inclination (1-2%) or a combination of velocity and inclination was increased. Increased workload was, if possible, obtained with increased speed and keeping a fixed treadmill gradient. If a participant was unable to increase speed, the treadmill gradient was increased instead. Tests ended when participants reached volitional exhaustion (e.g. shortness of breath and leg fatigue) or if any indications for test termination were observed.

Current guidelines for exercise testing of patients with MI were followed (31). Indications for test termination was general pain, symptoms of cardiac events (e.g. chest pain, nausea, dizziness) and occurrence of symptoms from the electrocardiography (Custo Med GmbH,

Ottobrunn, Germany). The test was stopped if any ST depression >2 mm (>1 mm if chest pain at the same time), ST elevation >1 mm, arrhythmias; persistent supraventricular tachycardia (including atrial fibrillation not present in the beginning of the test), ventricular tachycardia (>2 ventricular extra heartbeats in series) or increasing ventricular extrasystoles occurred during workload (31). Testing was not initiated with blood pressure values above 200/110 mmHg before the warm up. Blood pressure was measured on the dominant upper arm, standing, with an automatic blood pressure monitor (SunTech Medical, Morrisville, NC, USA). By occurrence of obvious incorrect measurement, remeasurement was performed after five-minute rest, seated.

Maximal oxygen uptake (VO_{2max}) was considered achieved if subjects reached an oxygen uptake plateau that remained stable despite increased workload (i.e. oxygen uptake did not increase more than 2 $mL \cdot kg^{-1} \cdot min^{-1}$ despite increased workload) and respiratory exchange ratio ≥1.05 (30, 32). Breathing frequency (f_B) >42 was a supplementary measure of maximal effort (33). Since VO_{2max} was not achieved in all tests, CRF are expressed as VO_{2peak} (30). VO_{2peak} was calculated as the mean of the three highest consecutive 10 second measurements.

Of practical reasons (personnel and funding) we were not able to perform testing in a blinded manner in this sub-trial.

Exercise Attendance

Attendance at exercise sessions was defined and measured as number of attended exercise sessions for participants in the intervention group. Attendance lists were logged by participants. Individual text messages from participants were used to record reasons for absence.

Sample Size

Sample size estimation was calculated with a statistical power of 0.8 and significance level of 0.05 (34, 35). A hypothesis of a possible clinically significant group difference in VO_{2peak} change (3 $mL \cdot kg^{-1} \cdot min^{-1}$ (13)) and assumption of a standard deviation of 2 $mL \cdot kg^{-1} \cdot min^{-1}$ was taken into the calculation. We estimated that the trial required 14 participants, 7 in each group. With uncertainty about possible dropout (illness, injury, withdrawal, lost to follow-up) we aimed to include 24 participants, 12 in each group.

Randomization and Inclusion Procedure

Randomization was done by a syntax in IBM SPSS Statistics (Statistical Package for Social Science Version 28, Chicago, IL, USA). Because the trial was a sub-trial utilizing exercise training group participants from NorEx, randomization was done prior to baseline testing of the primary outcome. The purpose was to be able to adjust the information given about the sub-trial between the two groups, and thereby allow blinded participation and avoidance of the Hawthorne effect (36) in the control group. The intervention group received information about the explained intervention, while the control group only was invited to cardiopulmonary exercise testing.

After assessing the exercise training group in NorEx for eligibility, 71 participants were found eligible. We randomly drew 36 participants to receive a telephone invitation to participate in the trial, allocated 18/18 to be invited to the intervention- and the control group. The last 35 participants were first disregarded as surplus.

As many participants were found non-eligible during the telephone conversation, we randomly drew 18 more participants from the remaining 35 eligible participants. They were randomly allocated 6/12 to the intervention- and the control group. In total, 54 eligible participants received a telephone invitation, randomly allocated 24/30 to the intervention- and the control group. The remaining 17 participants were then disregarded as surplus.

Statistical Analysis

IBM SPSS Statistics was used to analyze data. Due to continuous data and normally distributed residuals (confirmed by visually inspection of quantile-quantile plots), a linear mixed effect model was used to analyze and compare change in VO_{2peak} between the intervention- and the control group (37, 38). VO_{2peak} was dependent variable, person was random effect and intercept, time and interaction between time and intervention were fixed effects.

Ethical Statement

The trial followed the Consolidated Standards of Reporting Trials, the Vancouver recommendations and was conducted in line with the Declaration of Helsinki. NorEx has been approved by the Regional Committee for Medical Research Ethics (REK 2019/797) and is registered in the ClinicalTrials.gov registry (NCT04617639).

Results

Follow-up

Recruitment and baseline testing of the primary outcome were done ultimo August 2022, and follow-up testing completed in early December 2022. The trial period started in early September 2022 and finished the last week of November 2022. The combined number of enrolled participants in both groups who did not complete the intervention and follow-up testing of the primary outcome per protocol (drop-outs) was 8 (35%). All participants were included for statistical analysis (intention-to-treat approach). Figure 1 outlines randomization, inclusion and exclusion, follow-up, and dropout. Baseline characteristics of the participants are shown in Table 1.

Table 1. Participant characteristics at baseline.

	Intervention group, n=12	**Control group, n=11**
Number of males/females	10/2	10/1
Age, years	61.7 ± 11.2	65.5 ± 8.9
Height, cm	174.6 ± 7.1	176.5 ± 9.3
Weight, kg	83.3 ± 15.6	89.8 ± 18.2
Body mass index, $kg \cdot m^{-2}$	27.3 ± 3.9	28.7 ± 4.3

Values are mean ± standard deviation, unless otherwise stated.

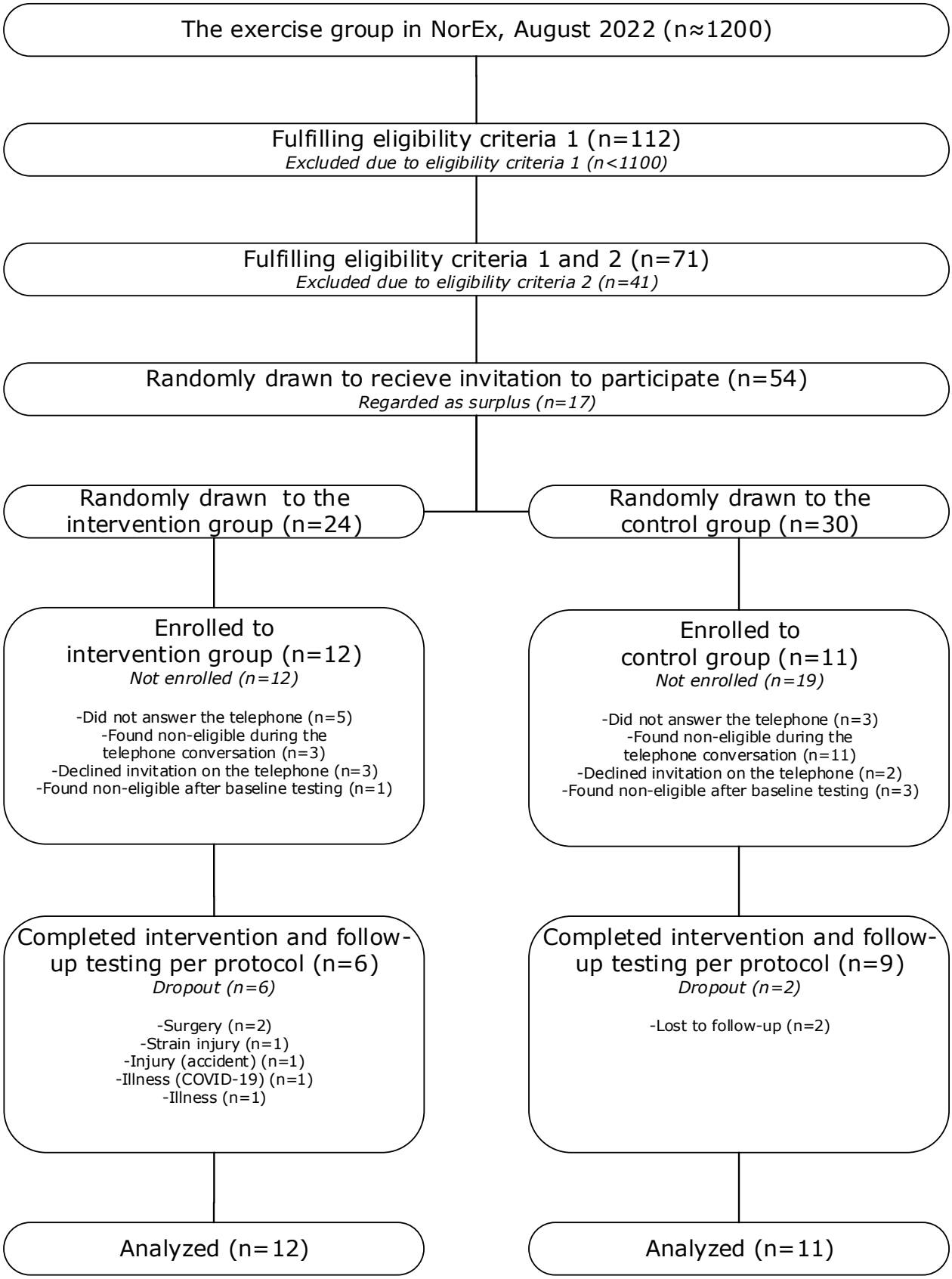


Figure 1. Flow chart of randomization, inclusion, follow-up and dropout.

Cardiorespiratory Fitness

VO_{2peak} improved more in the intervention group compared to the control group (mean difference 2.1 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI 0.84 to 3.41, p=.003). Mean values of VO_{2peak} at baseline (including all participants) and follow-up are shown in Figure 2. Figure 3 shows mean values for participants completing intervention and follow-up testing per protocol (per-protocol participants), while Figure 4 shows individual values at baseline and follow-up for per-protocol participants. Characteristics from cardiopulmonary exercise testing at baseline and follow-up are shown in Table 2.

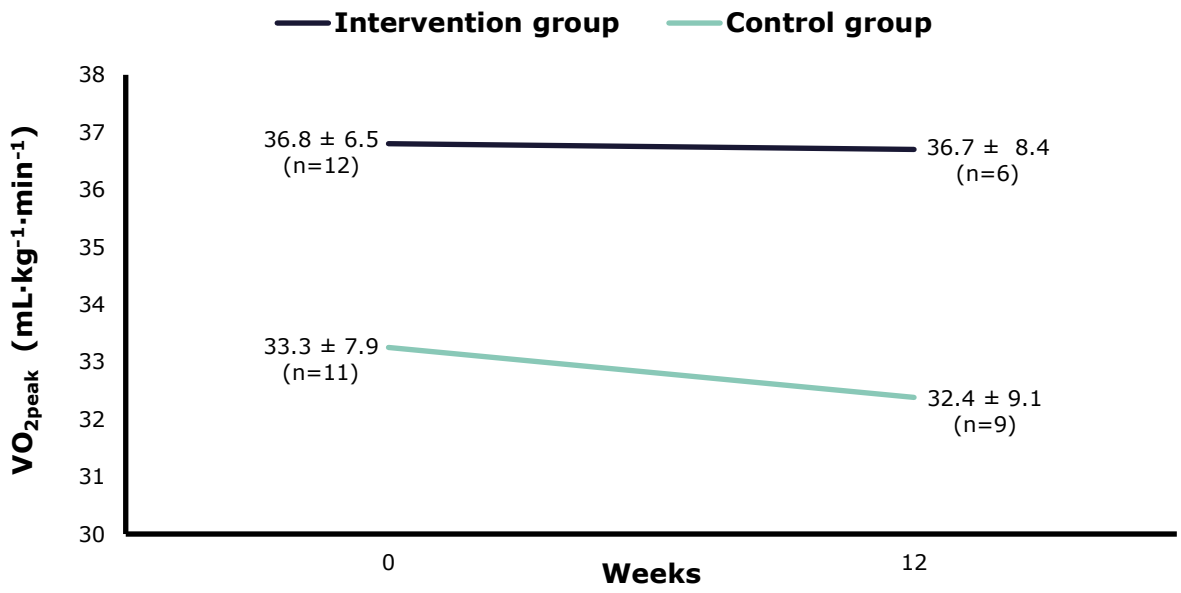


Figure 2. Mean ± standard deviation of VO_{2peak} at baseline and follow-up.

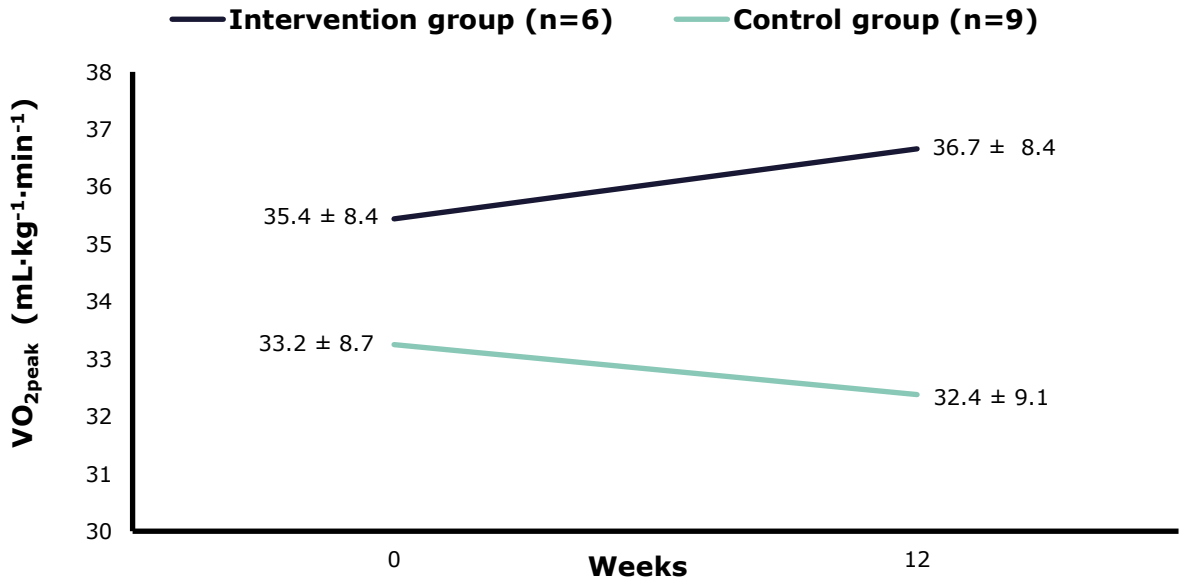


Figure 3. Mean ± standard deviation of VO_{2peak} at baseline and follow-up for per-protocol participants.

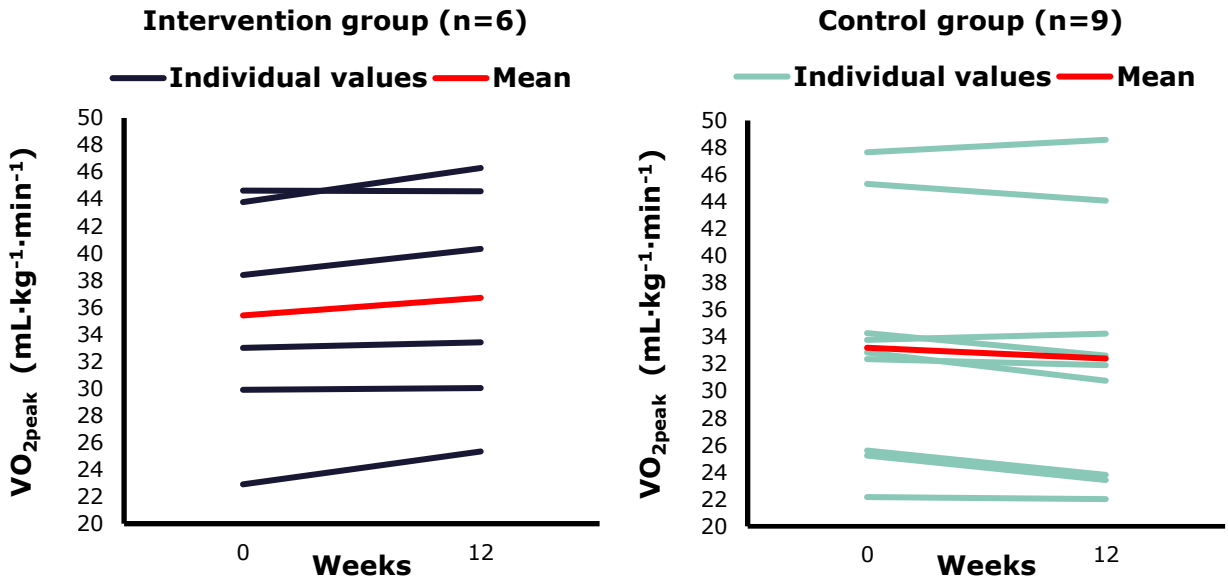


Figure 4. Individual values of VO_{2peak} at baseline and follow-up for per-protocol participants.

Table 2. Characteristics from cardiopulmonary exercise testing at baseline and follow-up.

	Intervention group		**Control group**	
	Baseline (n=12)	Follow-up (n=6)	Baseline (n=11)	Follow-up (n=9)
No. of max-/peak tests	11/1	6/0	8/3	6/3
RER at VO_{2peak}	1.11 ± 0.06	1.13 ± 0.4	1.08 ± 0.06	1.06 ± 0.05
f_B at VO_{2peak}	46 ± 5	47 ± 8	43 ± 8	39 ± 4

Values are mean ± standard deviation, unless otherwise stated. *RER* respiratory exchange ratio, f_B breathing frequency, VO_{2peak} peak oxygen uptake.

Exercise Attendance

Illness was the main reason for absence from exercise sessions. Nine participants (75%) were absent >1 week (2 consecutive sessions in the same calendar week) due to illness. The mean number of attended exercise sessions among participants in the intervention group was 14.4 (60% of all 24 group sessions) (SD 5.6, range 5 to 23), and the mean number of attended participants at each exercise session was 7.2 (58% of all 12 participants) (SD 2.1, range 4 to 11). Per-protocol participants attended more exercise sessions (mean 19.0) compared to drop-outs (mean 9.8). More participants attended exercise sessions with study personnel (mean 8.5) compared to exercise sessions without study personnel (mean 5.9). The mean number of exercise sessions per participants and vice versa are shown in Figure 5. Figure 6 illustrates when dropout occurred.

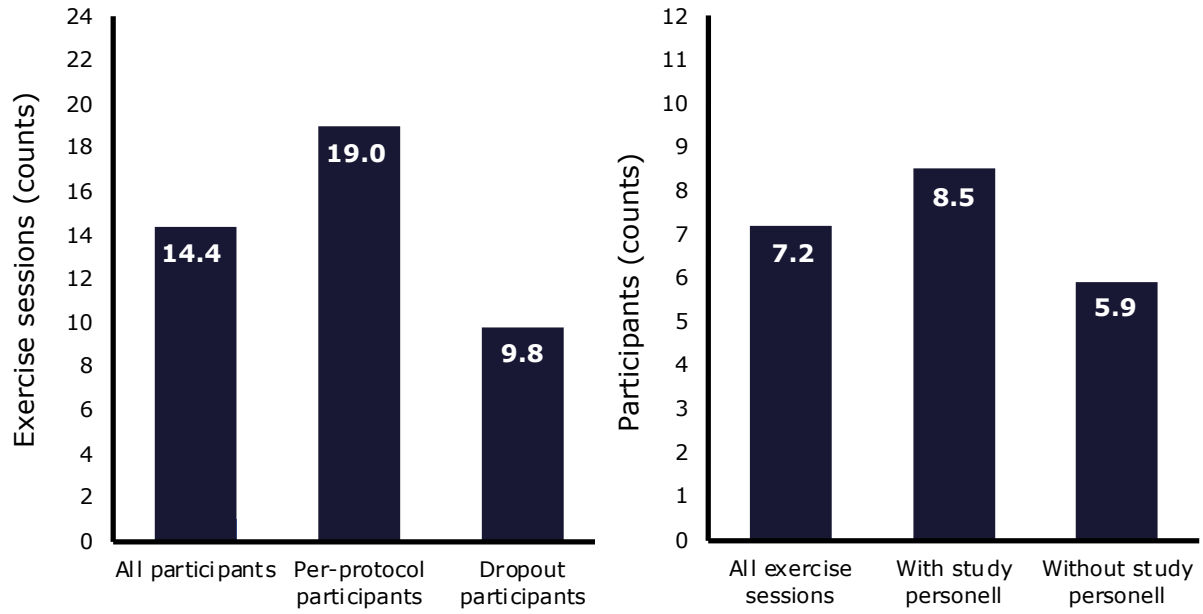


Figure 5. Left: Mean number of attended exercise sessions per participant. Right: Mean number of attended participants per exercise session.

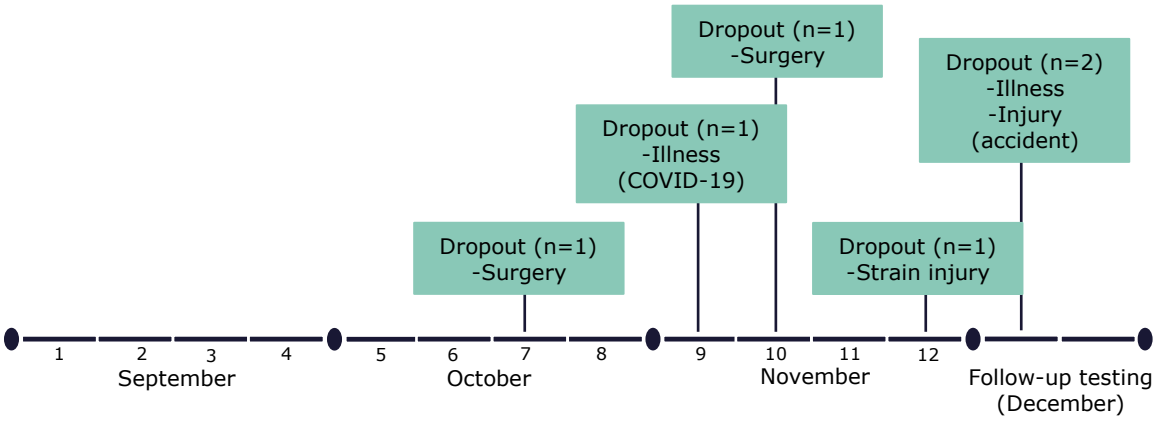


Figure 6. Timing of dropout.

Discussion

The main finding of this trial was that peer-supported home-based exercise training increased CRF more than individual home-based exercise training according to the NorEx-protocol. Exploratory descriptive statistics and ancillary analysis show large variation in exercise attendance in the intervention group.

Strengths and Limitations

This trial has several limitations. Firstly, the change in method after trial commencement regarding the planned outcome of adherence to exercise training left us with an indirect measure of the exercise behavior of interest. It also disallowed us to evaluate change in VO_{2peak} with respect to the prescribed exercise training, and to analyze exercise attendance physiologically, as home-based exercise trials the last decade have been able to (9). Time at target heart rate would allow a more certain discussion about change in VO_{2peak}, and

how participants exercised when they attended peer-supported home-based exercise sessions. Simultaneously, the exercise protocol was a dose required to increase VO_{2peak}. Change in VO_{2peak} indirectly reflect adherence to prescribed exercise training with respect to evidence of higher intensities required to improve VO_{2peak}. Thus, one strength in this trial is the use of the gold standard method to measure CRF which is a clinically important outcome (31). However, since 35% of our participants did not complete the intervention and follow-up testing of the primary outcome per protocol, 12 weeks continuously measured PA would strengthen our data.

Further, exercise trials are always at risk of bias, since it is the most exercise motivated participants who tend to accept trial invitations. All participants were recruited from the exercise group in NorEx, meaning they are among the Norwegian MI population already participating in an exercise trial. On the other hand, NorEx will enroll nearly 10 thousand MI patients, and one can speculate if such a large selection will be characterized as exercise motivated. Moreover, eligibility criteria 2 was implemented to target low motivated participants, and previous research suggests that it is difficult for MI patients to maintain exercise behavior in secondary prevention (19). However, only five participants declined the invitation to participate, but surprisingly many participants were found non-eligible after during the telephone conversations (n=14). Several NorEx-participants were injured or had recently been through various surgery or treatment for other diseases, which made them unable to comply with the exercise protocol at the current time for this trial. Thus, it is not surprisingly they fulfilled eligibility criteria 2.

The major limitations to this trial are due to participants, the randomization and inclusion procedure, and dropout. Strict eligibility criteria often limits the generalizability in randomized trials (39). In our trial, lack of eligibility criteria with respect to age and a small selection is the probable explanation of large variance in baseline characteristics. It is also an imbalance between males and females, thus the number of females in our trial (n=3) is comparable with the intervention group in NorEx, which consisted of 17% females per November 2022.

The randomization and inclusion procedure are a source of potential selection bias as our selection (n=23) was randomized in advance of baseline testing. This may have contributed to considerable differences in baseline characteristics, VO_{2peak} and ability to reach VO_{2max}. These differences can also be speculated as a reflection of imbalance in exercise motivation. However, notably, the control group had better adherence to follow-up testing despite non-favorable baseline characteristics, VO_{2peak} and ability to reach VO_{2max}. Notwithstanding, differences in background variables do occur in randomized control trials (40). Imbalances from randomization are coincident, and in small studies considerable imbalances can be nonsignificant (40). Importantly, our statistical test of the primary outcome is adjusted for baseline VO_{2peak}, which is a strength despite the randomization and the large dropout.

However, even with adjustment for baseline VO_{2peak} and intention-to-treat approach (41), we regard the dropout as our main limitation, which makes generalization of the abovementioned main findings impossible. Our small sample size was vulnerable to dropout, and thus, more strict eligibility criteria and even a smaller, but more certain selection may have been preferable for external validity, thus in a more specific subpopulation in NorEx. Despite large dropout, we consider that exclusion bias did not

occur, but our statistical analysis is, however, conducted on the principle that data are rarely missing completely at random (42).

Another limitation is the lack of blinded testing of the primary outcome. Possible detection bias follows a total of six cardiopulmonary exercise tests in the control group that failed to reach VO_{2max}. Effort can also be considered with the respiratory exchange ratio and breathing frequency (30-33), and lower values was seen in the control group. However, the six tests were distributed equally between baseline and follow-up testing, and higher values of the mentioned variables can be obtained after oxygen uptake reaches a plateau and the highest values is observed (33). In addition, two control group participants failed to reach VO_{2max} both at baseline- and follow-up testing, and one who failed to reach VO_{2max} in both tests had the highest VO_{2peak} among the control group and improved VO_{2peak} during the trial period. Two control group participants failed to reach VO_{2max} once each during baseline- and follow-up testing respectively.

Cardiorespiratory Fitness

Non-favorable baseline characteristics for the control group may have influenced the change in VO_{2peak}. The control group was almost 4 years older, had 1.4 $kg \cdot m^{-2}$ higher body mass index (BMI) and 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ lower VO_{2peak} compared to the intervention group.

Although older adults and MI patients respond to aerobic endurance exercise training with adaptations similar to younger adults (13, 33), age-related decline in oxygen uptake increases with age (43). The general impression of age-related decline is »10% per decade, but may increase up to 15-20% per decade for women- and 20-25% per decade for men after 70 years of age (43). Annual age-related decline is suggested to be about 0.3 to 0.5 $mL \cdot kg^{-1} \cdot min^{-1}$ per year (43). Thus, with about 4 years age difference, the expected difference in VO_{2peak} between the groups at baseline would be about 1.2 to 2.0 $mL \cdot kg^{-1} \cdot min^{-1}$. This is a smaller difference than the one observed. Simultaneously, preliminary reference values of VO_{2peak} in NorEx from 70 participants with mean years of age 65.0 ± 8.5 is 31.7 $mL \cdot kg^{-1} \cdot min^{-1}$. Per November 2022, median age in the exercise training group of NorEx was 67.0 years. Accordingly, both groups had high initial values of VO_{2peak}, but the intervention group was also younger and had clinically significant, and superiorly higher VO_{2peak} compared to the NorEx-population.

The control group also had higher BMI, compared to preliminary reference values (28.2 ± 3.6). Despite PA, exercise training and HIIT is found feasible in both older adults and IHD patients, high impact activities is more likely to result in injury among overweight or deconditioned adults (31). Obese participants (BMI >30 $kg \cdot m^{-2}$) can have difficulties with gait instability, low functional capacity, risk of- or coexisting orthopedic impairments, and uneven body weight distribution (31, 44).

However, differences in age and BMI are considerable in favor of the intervention group, but mean values do not differentiate between categories as decades in age, and levels of BMI (31, 43). In contrast, the control group had clinical significant lower VO_{2peak} at baseline, and may thus have had better potential to increase VO_{2peak} due to training status compared to the intervention group with surprisingly high VO_{2peak} (45). As discussed, imbalances at baseline may be a result of potential selection bias or coincident from randomization.

A major reason for the significant result in VO_{2peak} change is the decline in VO_{2peak} for the control group, seen in Figure 2 and Figure 3. Mean observed values at baseline and follow-

up in Figure 3 indicates 0.8 mL·kg^{-1}·min^{-1} decline for the controls, around 40% of the observed mean difference between the groups. Again, the general, although simplified suggestion about annual decline in VO_{2peak} with age is about 0.3 to 0.5 mL·kg^{-1}·min^{-1} per year (43). Reasons are uncertain, but age in general and less PA and exercise training as a result of age are likely contributing factors (43). It is noteworthy that the control group had a greater decline in VO_{2peak} in 12 weeks compared to what is suggested as expected annual decline with age. This result indicates that the supervision from NorEx failed to help participants with consistent adherence to the exercise protocol during these 12 weeks. Considering 71 of the 112 participants who fulfilled eligibility criteria 1 also fulfilled eligibility criteria 2 ultimo August 2022, these findings might be an eye opener to the ongoing NorEx-trial.

Conversely, about 60% of the mean difference in VO_{2peak} change is due to improvement in the intervention group. Although our intervention group had high initial $VO_{2peak,}$ change in VO_{2peak} for participants with complete data are lower compared to previous exercise trials emphasizing high intensity exercise training. A systematic review with meta-analysis have reported an increase of 5.5 mL·kg^{-1}·min^{-1} from 52 studies, thus with various duration and exercise session frequency, but intensities corresponding to The American College of Sports Medicine`s vigorous intensity of 77 to 90% of peak heart rate (14). A more comparable, thus centre-based intervention in cardiac rehabilitation, with 12-week duration and two weekly 4·4 HIIT sessions increased VO_{2peak} by 4.6 mL·kg^{-1}·min^{-1} in MI patients specifically (13). The mean number of attended exercise sessions in the 12-week trial period was similar to participants with complete data in our trial, who attended 19.0 exercise sessions compared to 20.4 in the centre-based intervention group (13). Without any possibility to evaluate the intensity and duration of the peer-supported home-based exercise sessions, comparison in VO_{2peak} change indicates that it is challenging to achieve the same effectiveness in home-based exercise training in secondary prevention compared to 4·4 HIIT in centre-based cardiac rehabilitation with laboratory conditions. A trial of centre-based versus home-based cardiac rehabilitation in IHD patients found similar results (20). The centre-based- and home-based intervention groups had both a median number of 24.0 attended exercise sessions, and improved VO_{2peak} by 4.3 and 2.8 mL·kg^{-1}·min^{-1} respectively (20).

Compared to our per-protocol participants in the intervention group, the home-based cardiac rehabilitation group increased VO_{2peak} 1.5 mL·kg^{-1}·min^{-1} more in only five additional exercise sessions (20). The study reported that target heart rate was achieved in all participants and time at target heart rate was high with an average of 12.3 minutes per 4·4 HIIT session (20). The quality and ability to carry out 4·4 HIIT sessions in this home-based intervention, combined with the results from laboratory conditions reflects that there may have been a greater potential of improvement in our intervention group. However, our intervention group participants had a higher initial VO_{2peak}, and were older at baseline compared to intervention groups in both studies (13, 20). These studies are also cardiac rehabilitation conducted shortly after index incidents, and not exercise training in daily life for risk factor modification and secondary prevention (13, 20).

The choice of season for the trial period may have influenced the change in VO_{2peak} in our two groups. The Generation 100 Study found that older adults are more physically active in warmer than colder months (46). Baseline testing was done at the end of the last Norwegian summer month, with increasingly colder weather through the trial period. Follow-up testing was done in the first winter month. We speculate if change in VO_{2peak}

reflects that the intervention group was facilitated to overcome barriers to PA and exercise training from increasingly colder weather, but not the control group. Hence, the intervention may be an effective method to maintain PA and exercise training during a time of the year characterized by less PA and exercise training in older adults. Moreover, the mean decline in the control group and visual inspection of individual change in VO_{2peak} seen in Figure 4, illustrates that peer-supported home-based exercise training also contributed to maintain CRF contrary to individual home-based exercise training. In addition, observational studies have found that even 1 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement in VO_{2peak} have substantial impact on prognosis with IHD (47, 48). Therefore, when emphasizing the known challenge to maintain exercise behavior in MI patients (17, 19), trainability due to high initial VO_{2peak} at baseline for the intervention group (33), and decrease in VO_{2peak} in the control group as well as known annual decline with aging (43), the small improvement in the intervention group may be of great importance.

An improvement about 1 $mL \cdot kg^{-1} \cdot min^{-1}$ in 12 weeks in secondary prevention may also be a more realistic improvement than the clinical significant 3 $mL \cdot kg^{-1} \cdot min^{-1,}$ (13), and peer-supported home-based exercise training may be an effective method to adhere to prescribed exercise, and maintain or improve $VO_{2peak.}$

Exercise Attendance

It is likely that the Hawthorne effect was avoided in the control group due to covert observation and indirect measurement of adherence to prescribed exercise with directly measured CRF from cardiopulmonary exercise testing. However, although the intervention group underwent an intervention, it is possible that they were affected by awareness of being observed. Conversely, we did not define any per-protocol cut-off due to exercise attendance, and participants received a very open invitation to participate in exercise sessions. If the intervention group was affected by the Hawthorne effect, the exploratory results on exercise attendance suggest it had a stronger effect in per-protocol participants. However, the exercise attendance in per-protocol participants might as well be due to taking known facilitators and motivational factors into consideration when designing the exercise training intervention.

The range of attended exercise sessions per participants illustrates individual variety of capability, opportunity and motivation (21), and probably reflects individuality to exercise barriers. We speculate for example, that fixed time and location for exercise sessions, may have created a barrier as one size does not fit all in a group of 12 participants. Accordingly, barriers of time and distance is documented reasons for difficulty with attending regularly in cardiac rehabilitation (9). Similarly, the highest number of attended participants in an exercise session ranged up to 11, and, again, illustrates how the intervention never was convenient for all 12 participants at once. Furthermore, illness became the most certain barrier to participate, and occurred throughout the trial period. COVID-19 was a frequently reported reason for illness.

Figure 6 indirectly illustrates that participants used the intervention for exercise training throughout the whole trial period. Half of the dropout occurred in the last week of the trial period or during follow-up testing of the primary outcome. Thus, nine participants made use of the intervention over a 12-week period regardless of frequent exercise attendance. This finding may indicate that the participants enjoyed peer-supported home-based exercise training when they were not ill and when it was convenient to participate. Furthermore, similar varying exercise attendance is reported in the abovementioned home-

based cardiac rehabilitation trial (20). Despite the median exercise attendance was 100%, it also ranged down to 10, with four participants not reaching 70% (16.8 exercise sessions) of the exercise sessions (20).

Per-protocol participants had better exercise attendance than drop-outs, illustrated to the left in Figure 5. Timing of dropout partly explains the result, as the first 3 drop-outs dismissed an average of 8.6 exercise sessions due to surgery (n=2) and COVID-19. Per-protocol participants may have been more resistant to illness compared to drop-outs.

Exercise sessions with study personnel present had more attended participants compared to exercise sessions without study personnel, seen to the right in Figure 5. Supervision is emphasized as a factor of great influence to exercise training and might explain the attendance rate in our trial (17). Also the abovementioned trial of centre-based versus home-based cardiac rehabilitation, found significantly better exercise attendance in the supervised centre-based group, compared to the home-based group (20). Professional, holistic rehabilitation including supervision is found to be one of the success factors for general rehabilitation programs (17). Accordingly, the sudden transition to daily life without supervision is highlighted as one of the reasons for failure in maintaining exercise behavior (17).

Figure 5 shows that exercise sessions without study personnel had 5.9 attended participants on average, and the six per-protocol participants had better exercise attendance compared to drop-outs. As exercise sessions with study-personnel had 8.5 attended participants on average, it may indicate that it was drop-outs who tended to be absent in exercise sessions without study personnel. It is possible that supervision from study personnel was more motivating than peer-support for drop-outs. Notably, visual inspection of Figure 2 and Figure 3, reveals that it was participants with higher baseline VO_{2peak} that became drop-outs. Individual tailored exercise training in for patients with individual needs is also addressed as a key component in cardiac rehabilitation (17). For example patients with high PA-levels prior to MI can have different independency to exercise training compared to the more traditional MI patients (17). It is possible that drop-outs, who increased the mean baseline VO_{2peak} from 35.4 $mL \cdot kg^{-1} \cdot min^{-1}$ for per-protocol participants to 36.8 $mL \cdot kg^{-1} \cdot min^{-1}$ for the whole intervention group, had a greater need of individual tailored exercise training from professionals than a need of peer-support. However, as we attended the first four exercise sessions, most of our presence was in the first half of the trial period, before dropout occurred and less participants were available to attend.

Importantly, we did not define or structure our presence, or give any special information prior to the exercise sessions we attended. In combination with a rather short trial period, this challenges the ability to evaluate the feasibility of our intervention.

Conclusion

Peer-supported home-based exercise training is more effective to maintain or increase CRF compared to individual home-based exercise training according to the NorEx-protocol. Risk of various bias makes generalizability impossible and thus there is a demand for further research, in which elements from our intervention group method can be considered implemented. We then suggest a more comprehensive method addressing the issues discussed in this thesis.

References

1. Institute for Health Metrics and Evaluation (IHME). GBD 2019 Cause and Risk Summary: Ischemic Heart Disease Seattle, USA: IHME, University of Washington; 2020 [cited 2023 13. april]. Available from: https://vizhub.healthdata.org/gbd-results/.

2. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25.

3. Institute of Medicine Committee on Social Security Cardiovascular Disability C. Cardiovascular Disability: Updating the Social Security Listings. Washington (DC): National Academies Press (US)

Copyright 2010 by the National Academy of Sciences. All rights reserved.; 2010.

4. Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, et al. Physical Activity and Mortality in Patients With Stable Coronary Heart Disease. J Am Coll Cardiol. 2017;70(14):1689-700.

5. Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. Circulation. 2016;134(24):e653-e99.

6. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, et al. Effects of Exercise Training on Cardiorespiratory Fitness and Biomarkers of Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2015;4(7).

7. Stamatakis E, Ahmadi MN, Gill JMR, Thøgersen-Ntoumani C, Gibala MJ, Doherty A, et al. Association of wearable device-measured vigorous intermittent lifestyle physical activity with mortality. Nat Med. 2022;28(12):2521-9.

8. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2016;2016(1):Cd001800.

9. Anderson L, Sharp GA, Norton RJ, Dalal H, Dean SG, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation. Cochrane Database Syst Rev. 2017;6(6):Cd007130.

10. Dasso NA. How is exercise different from physical activity? A concept analysis. Nurs Forum. 2019;54(1):45-52.

11. Rognmo Ø, Hetland E, Helgerud J, Hoff J, Slørdahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. Eur J Cardiovasc Prev Rehabil. 2004;11(3):216-22.

12. Helgerud J, Høydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. Med Sci Sports Exerc. 2007;39(4):665-71.

13. Moholdt T, Aamot IL, Granøien I, Gjerde L, Myklebust G, Walderhaug L, et al. Aerobic interval training increases peak oxygen uptake more than usual care exercise

training in myocardial infarction patients: a randomized controlled study. Clin Rehabil. 2012;26(1):33-44.

14. Mitchell BL, Lock MJ, Davison K, Parfitt G, Buckley JP, Eston RG. What is the effect of aerobic exercise intensity on cardiorespiratory fitness in those undergoing cardiac rehabilitation? A systematic review with meta-analysis. Br J Sports Med. 2019;53(21):1341-51.

15. Gray SR, Ferguson C, Birch K, Forrest LJ, Gill JM. High-intensity interval training: key data needed to bridge the gap from laboratory to public health policy. Br J Sports Med. 2016;50(20):1231-2.

16. Dibben GO, Dalal HM, Taylor RS, Doherty P, Tang LH, Hillsdon M. Cardiac rehabilitation and physical activity: systematic review and meta-analysis. Heart. 2018;104(17):1394-402.

17. Coull A, Pugh G. Maintaining physical activity following myocardial infarction: a qualitative study. BMC Cardiovasc Disord. 2021;21(1):105.

18. Reitlo LS, Sandbakk SB, Viken H, Aspvik NP, Ingebrigtsen JE, Tan X, et al. Exercise patterns in older adults instructed to follow moderate- or high-intensity exercise protocol - the generation 100 study. BMC Geriatr. 2018;18(1):208.

19. Racodon M, Pezé T, Masson P. Analysis of physical exercise in cardiac patients following cardiovascular rehabilitation. Acta Cardiol. 2020;75(7):598-603.

20. Aamot IL, Forbord SH, Gustad K, Løckra V, Stensen A, Berg AT, et al. Home-based versus hospital-based high-intensity interval training in cardiac rehabilitation: a randomized study. Eur J Prev Cardiol. 2014;21(9):1070-8.

21. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6:42.

22. Costello E, Kafchinski M, Vrazel J, Sullivan P. Motivators, barriers, and beliefs regarding physical activity in an older adult population. J Geriatr Phys Ther. 2011;34(3):138-47.

23. Miller W, Brown PR. Motivators, Facilitators, and Barriers to Physical Activity in Older Adults: A Qualitative Study. Holist Nurs Pract. 2017;31(4):216-24.

24. Dennis CL. Peer support within a health care context: a concept analysis. Int J Nurs Stud. 2003;40(3):321-32.

25. Parry M, Watt-Watson J. Peer support intervention trials for individuals with heart disease: a systematic review. Eur J Cardiovasc Nurs. 2010;9(1):57-67.

26. Clark AM, Munday C, McLaughlin D, Catto S, McLaren A, Macintyre PD. Peer support to promote physical activity after completion of centre-based cardiac rehabilitation: evaluation of access and effects. Eur J Cardiovasc Nurs. 2012;11(4):388-95.

27. Pedersen M, Bennich B, Boateng T, Beck AM, Sibilitz K, Andersen I, et al. Peer-mentor support for older vulnerable myocardial infarction patients referred to cardiac rehabilitation: single-arm feasibility study. Pilot Feasibility Stud. 2022;8(1):172.

28. Burton E, Farrier K, Hill KD, Codde J, Airey P, Hill AM. Effectiveness of peers in delivering programs or motivating older people to increase their participation in physical activity: Systematic review and meta-analysis. J Sports Sci. 2018;36(6):666-78.

29. Knight JK, Brame CJ. Peer Instruction. CBE Life Sci Educ. 2018;17(2):fe5.

30. Loe H, Steinshamn S, Wisløff U. Cardio-respiratory reference data in 4631 healthy men and women 20-90 years: the HUNT 3 fitness study. PLoS One. 2014;9(11):e113884.

31. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873-934.

32. Hermansen L, Saltin B. Oxygen uptake during maximal treadmill and bicycle exercise. J Appl Physiol. 1969;26(1):31-7.

33. McArdle WD, Katch FI, Katch VL. Exercise Physiology. 8. ed2017.

34. Hoekstra R, Morey RD, Rouder JN, Wagenmakers EJ. Robust misinterpretation of confidence intervals. Psychon Bull Rev. 2014;21(5):1157-64.

35. Dahiru T. P - value, a true test of statistical significance? A cautionary note. Ann Ib Postgrad Med. 2008;6(1):21-6.

36. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol. 2014;67(3):267-77.

37. Lydersen S. Analyse av longitudinelle data. Tidsskriftet Den Norske Legeforening. 2022.

38. Lydersen S. Justering av utgangsverdi i longitudinelle randomiserte studier. Tidsskriftet Den Norske Legeforening. 2022.

39. Hjelmesæth J. Randomiserte studier – nyttige for hvem? Tidsskriftet Den Norske Legeforening. 2014.

40. Pripp AH. Randomisering. Tidsskriftet Den Norske Legeforening. 2018.

41. Lindbæk M, Skovlund E. Kontrollerte kliniske forsøk – jakten på sann effekt av behandling. Tidsskriftet Den Norske Legeforening. 2022.

42. Lydersen S. Manglende data – sjelden helt tilfeldig. Tidsskriftet Den Norske Legeforening. 2019.

43. Letnes JM, Nes BM, Wisløff U. Age-related decline in peak oxygen uptake: Cross-sectional vs. longitudinal findings. A review. Int J Cardiol Cardiovasc Risk Prev. 2023;16:200171.

44. Petridou A, Siopi A, Mougios V. Exercise in the management of obesity. Metabolism. 2019;92:163-9.

45. Plowman SA, Smith DL. Exercise Physiology for Health, Fitness and Performance. Fifth Edition ed. Philadelphia: Wolters Kluwer; 2017.

46. Aspvik NP, Viken H, Ingebrigtsen JE, Zisko N, Mehus I, Wisløff U, et al. Do weather changes influence physical activity level among older adults? - The Generation 100 study. PLoS One. 2018;13(7):e0199463.

47. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. Circulation. 2002;106(6):666-71.

48. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J. 2008;156(2):292-300.

Appendices

Appendix 1. Extract from NorEx-protocol: Eligibility criteria

Inclusion Criteria

The subject must meet all of the following inclusion criteria:

- Men and women who were hospitalized in a Norwegian hospital with an acute myocardial infarction (Type I) during 2013-2022. Patients are included minimum 3 months after hospitalization when they are in a stable condition.
- Norwegian national identification number, able to communicate in Norwegian or other Scandinavian language, and not expected to emigrate during the study period.
- Age 18 - 79 years at the time when receiving study invitation.
- Being able perform physical activity at an intensity level as prescribed for the intervention group, as determined by study personnel.
- Signed informed consent.

Exclusion Criteria

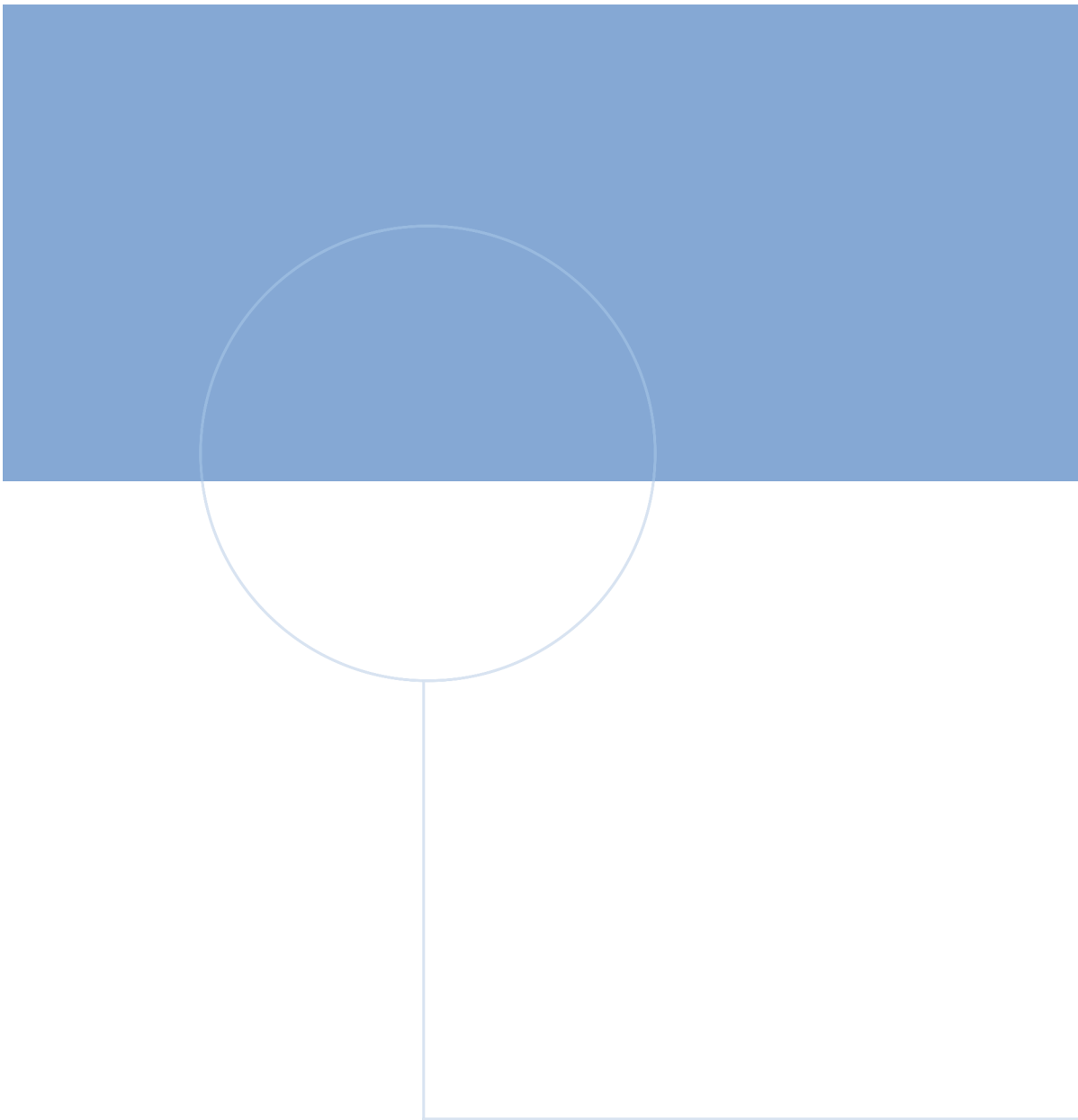
The following must not be present at the time of enrolment:

- Participation in physical activity at a similar or higher intensity level than what is prescribed for the intervention group, as determined by study personnel.
- Participation or planned participation in endurance sport competitions.
- Cognitive impairment / dementia that may interfere with the participants ability to comply with the study protocol.
- Alcohol or drug abuse or serious psychiatric disease.
- Known cardiac disease that may represent a contraindication for moderate or high-intensity physical activity, such as symptomatic valvular heart disease, a diagnose of obstructive hypertrophic cardiomyopathy, uncontrolled hypertension, in-compensated heart failure, serious arrythmia not under control after treatment, pulmonary hypertension, significant angina after revascularization and optimal drug treatment.
- Renal insufficiency requiring dialysis.
- Any end-stage somatic disease with short life expectancy or that is expected to interfere with the participants ability to comply with the study protocol, such as advanced cancer, chronic lung disease with exacerbations requiring hospitalizations, or other serious disease, as determined by study personnel.
- Inability to comply with the study protocol due to any physical disability, somatic disease, or mental problem, as determined by study personnel.
- Residing in a nursing home or other institution.
- Participating in another research study on physical activity.

Appendix 2. Extract from NorEx-protocol: Supervision and follow-up of the exercise group

Participants will be supervised, and their physical activity levels monitored electronically or manually throughout the entire study span. This allows individualized and dynamic participant pathways and continuous adjustment of personalized measures to optimize adherence to the exercise protocol. The overall aim of participant supervision and follow-up is a) consistent adherence to the prescribed exercise dose, and b) consistent collection of data on activity levels and IT usage. To achieve these aims, the following personnel, resources and behavior change techniques will be employed systematically:

1. **Personal supervision and coaching** by personal trainers (PT) and/or online study mentors located at NTNU for direct one-to-one contact and support:
    - Gradual instruction and thorough education at study initiation.
    - Motivation for long-term study commitment.
    - Reengagement of participants in case of non-adherence to exercise protocol.
    - Technical support.
2. **Social support** by involvement of a family member or close friend as co-participant/buddy.
3. **Community-based** initiatives:
    - Facilitation of the use of established exercise groups and facilities (e.g. Healthy Living Centers, LHL and gyms).
    - Competitions, common goals and an award system for individual and team performance.
4. **Self-management** tools for skills development, motivation and empowerment:
    - Self-monitoring of behavior by wearable activity sensors, an app and a web portal.
    - Personalized feedback of behavior.
    - Education and information through various channels.
    - Clear instructions and practical guidance, including gradual introduction to the study, personalized exercise plans, instructional videos and relevant user-experiences.
    - Monitoring and review of outcome: Regular performance assessments to inform participants and supervisors of improvements in aerobic endurance and strength capacities.
5. **eHealth:** A customized IT solution for participants, co-participants, PTs and online mentors to deliver the abovementioned tools, monitor adherence to the exercise protocol and to manage the study workflow. Consists of a wearable activity monitor, an app, and web-based administrator modules.



NTNU

Norwegian University of
Science and Technology