

Ingrid Haagenrud Langmo

# Change in peak oxygen uptake after eight-month exercise intervention in post-myocardial infarction men and women

A randomized pre-post substudy of The Norwegian Trial of Physical Exercise After Myocardial Infarction (NorEx)

Master's thesis in Physical Activity and Health

Supervisor: Ulrik Wisløff

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





# Infographic

Change in **peak oxygen uptake** after an eight-month exercise intervention in

## POST-MYOCARDIAL INFARCTION MEN AND WOMEN

A randomized pre-post substudy of The Norwegian Trial of Physical Exercise After Myocardial Infarction

### DID YOU KNOW?

- ! Cardiovascular disease is the number 1 cause of death globally. **17.9 million people** died in 2019 for this cause. (1)
- ! Every 1 mL·kg<sup>-1</sup>·min<sup>-1</sup> increase in peak oxygen uptake (VO<sub>2</sub>peak) is associated with an approximate 15% decrease in cardiovascular-specific mortality. (2)
- ! Previous research suggest high intensity exercise training as the best way of improving your cardiorespiratory fitness (CRF). (2)
- ! Personal activity intelligence (PAI) is a new physical activity metric reflecting health benefit of exercise performed. (3)

### METHODS



11 post-myocardial infarction men and women



Exercise measured with Amazefit Health Watch NorEx



Eight-month exercise training intervention. Participants were encouraged to obtain ≥100 PAI per week, preferably by high intensity exercise training.



Baseline and post-test of CRF measured with gold standard cardiopulmonary exercise testing



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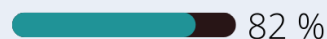


References: 1) Organization WH. Cardiovascular disease (CVDs) [Internet]. 2021 [updated 11.06.2021; cited 2022 23.04]. Available from: <https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-cvds>. 2) Letnes JM, Dalen H, Vesterbekkmo EK, Wisloff U, Nes BM. Peak oxygen uptake and incident coronary heart disease in a healthy population: the HUNT Fitness Study. Eur Heart J. 2019;40(20):1633-9. 3) Health P. Science & research 2022 [cited 2022 11.05.22]. Available from: <https://www.paihealth.com/science-research>.



### RESULTS:

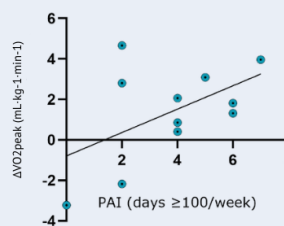
9/11 improved CRF after exercise intervention



Observed increase in VO<sub>2</sub>peak of  $\Delta 1.4 \pm 2.4$  mL·kg<sup>-1</sup>·min<sup>-1</sup> [CI: -3.03 to 0.21]



Increase of VO<sub>2</sub>peak as a function of exercise per week:



PAI:  $\beta=0.58$  [CI: -0.15 to 1.31]

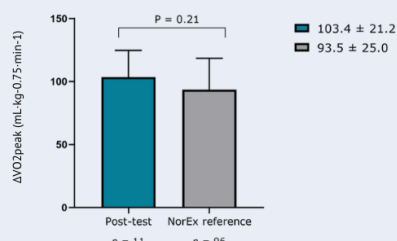
Moderate intensity:  $\beta=0.24$  [CI: -0.19 to 0.66]

High intensity:  $\beta=0.20$  [CI: -1.62 to 2.01]

Low intensity:  $\beta=0.16$  [CI: -0.20 to 0.51]

**Highest increase in VO<sub>2</sub>peak is associated with amount of days ≥100 PAI per week.**

11% higher VO<sub>2</sub>peak after exercise intervention compared to NorEx reference material



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## Acknowledgements

First, I would like to thank my supervisor professor Ulrik Wisløff for sharing his experience and knowledge and giving me the opportunity to be a part of NorEx. I've had a dream of one day could take a part of the Cardiac Exercise Research Group (CERG) and the important work they are doing since I've started my bachelor's degree here at NTNU. I'm proud to be involved in this important study. I would also like to thank my co-supervisor Kaare Harald Bønaa for sharing his experience in research.

Second, I would like to express my appreciation to Arnt Erik Tjønnå, Thomas Fremo and Lisbeth Røe in NeXt Move core facilities for educating me in the performance of cardiopulmonary exercise testing and for always answer the questions and challenges I encountered. A huge thank to Stian Lydersen for helping me with statistical analysis and for the time he spent educating me in statistics.

Furthermore, I'm truly thankful to have been working with my fellow student and friend Sofie Johnsen Lynghaug which made the data collection for this master thesis a great experience. A huge praise to my colleague and friend Alexander Gran Svenningsen for giving me advice and helping me with the writing process. Lastly, I'm very grateful for my mom and sister for always supporting and believing in me through life, especially during my time as a student and this year of hard work.

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## Abbreviations

a- $\dot{V}O_{2\text{diff}}$	Arteriovenous Oxygen Difference
BMI	Body Mass Index
BP	Blood Pressure
CAD	Coronary Artery Disease
CPET	Cardiopulmonary Exercise Testing
CRF	Cardiorespiratory Fitness
CVD	Cardiovascular Disease
ECG	Electrocardiogram
HIIT	High Intensity Interval Training
HR	Heart Rate
HR <sub>peak</sub>	Peak Heart Rate
HR <sub>recovery</sub>	Heart Rate Recovery
MI	Myocardial Infarction
NorEx	The Norwegian Trial of Exercise After Myocardial Infarction
O <sub>2</sub> pulse	Oxygen Pulse
PA	Physical Activity
PAI	Personal Activity Intelligence
Q	Cardiac Output
RER	Respiratory Exchange Ratio
SD	Standard Deviation
SV	Stroke Volume
$\dot{V}O_2$	Oxygen Uptake
$\dot{V}O_{2\text{max}}$	Maximal Oxygen Uptake
$\dot{V}O_{2\text{peak}}$	Peak Oxygen Uptake
$\Delta$	Delta
$\beta$	Beta, Linear regression coefficient

## Definitions

**Allometry:** Allometry is the study of the relationship of body size to shape, anatomy, physiology, and behavior (1). Allometric scaling is among other used to calculate relative values of  $\dot{V}O_{2peak}$  with regards to body mass (2).

**Cardiovascular disease (CVD):** CVD is a group of disorders of the heart and blood vessels including cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism, and coronary heart disease (CHD). CHD includes stable angina, unstable angina, sudden cardiac death, and myocardial infarction (MI) (3).

**Cardiorespiratory fitness (CRF):** CRF is defined as a component of physiologic fitness that relates to the ability of the circulatory and respiratory systems to supply oxygen during activity (4). The gold standard of measuring CRF is cardiopulmonary exercise test (CPET) (5).

**Cardiopulmonary exercise test:** CPET is a clinical procedure evaluating mechanisms and limitations of exercise tolerance for the assessment of cardiopulmonary health usually performed on treadmill or ergometer cycle (5).

**Heart rate recovery (HR<sub>recovery</sub>):** HR<sub>recovery</sub> is defined as the rate HR declines from either submaximal or maximal exercise to rest and are usually measured 1 minute after ended exercise (6). It has been identified as a powerful predictor of cardiovascular and all-cause mortality where a decrease of 15-20 beats per min (bpm) is expected among healthy individuals and <12 bpm represents an unfavorable prognosis for relative risk of cardiovascular mortality (6).

**Intensity zones:** Intensity zones are target ranges used to prescribe workout intensities based on HR, in the literature usually categorized as low intensity (<65%HR<sub>peak</sub>), moderate intensity (65-79%HR<sub>peak</sub>), and high intensity (80-95%HR<sub>peak</sub>) (4). 2021 European Society of Cardiology's Guidelines on cardiovascular disease prevention (7) uses the categories low (57-63%HR<sub>peak</sub>), moderate (64-76%HR<sub>peak</sub>) and high (77-95%HR<sub>peak</sub>). Manufacturer of the Norwegian trial of exercise after myocardial infarction activity watch, Huami, categorizes intensity zones as low intensity (<65%HR<sub>peak</sub>), moderate intensity (65-79%HR<sub>peak</sub>), and high intensity (>80%HR<sub>peak</sub>).

**Myocardial infarction:** MI is a CVD categorized as CHD. MI is usually an acute event, where the major vessels supplying the heart get occluded with deposits of cholesterol blocking the blood supply to the heart (8, 9).

**Personal Activity Intelligence (PAI):** PAI is a new physical activity metric which reflects the health benefit of exercise performed. It can be incorporated in wearable technology and the algorithm considers age, sex, resting HR and maximal HR (10). According to PAI health (2022) "maintaining  $\geq 100$  PAI is strongly associated with adding on average five years to your life and reducing the risk of cardiovascular disease mortality by an average of 25%" (11).

**Peak oxygen pulse ( $O_{2\text{pulse}}$ ):** Left ventricular stroke volume (SV) is the volume of blood pumped out of the left ventricle of the heart per heart beat (12).  $O_{2\text{pulse}}$  is an indirect reflection of SV, measured as oxygen uptake per heartbeat (12).

**Peak oxygen uptake ( $\dot{V}O_{2\text{peak}}$ ):**  $\dot{V}O_{2\text{peak}}$  is the highest measured uptake of  $O_2$  per minute and reflects overall physical health (4).

**Physical activity (PA):** PA is defined as any bodily movement produced by skeletal muscles that requires energy expenditure and includes among other walking, running, cycling, and sports (4). 2021 European Society of Cardiology's Guidelines on cardiovascular disease prevention suggest at least 150-300 minutes a week of moderate intensity or 75-150 min a week of high intensity for cardiovascular disease prevention (7). Aerobic exercise means *with oxygen* and is any type of cardiovascular conditioning such as walking, running, and cycling (7). Unlike aerobic, anaerobic exercise means *without oxygen*, includes sprints, weightlifting, and other conditions involving quick burst of energy (7).

## Abstract

**Purpose:** To investigate the change in peak oxygen uptake ( $\dot{V}O_{2peak}$ ) after eight-month exercise intervention in post-myocardial infarction (MI) men and women.

**Methods:**  $\dot{V}O_{2peak}$  was measured in 11 post-MI men and women ( $63.4 \pm 9.6$  years,  $178 \pm 10$  cm,  $90 \pm 14$  kg) at baseline and after eight-month exercise intervention, performed on a treadmill or cycle ergometer by cardiopulmonary exercise test (CPET). Physical activity and exercise were monitored continuously with an *Amazfit Health Watch NorEx* during the intervention. Participants were encouraged to obtain  $\geq 100$  PAI per week, preferably by high intensity exercise training.

**Results:** An improvement in  $\dot{V}O_{2peak}$  of  $1.4 \pm 2.4$  mL·kg<sup>-1</sup>·min<sup>-1</sup> ( $p=0.08$  [CI: -3.03 to 0.21]) was observed at group level. The increase of  $\dot{V}O_{2peak}$  as a function of total time, high-, moderate-, and low- intensity exercise training per week performed and amount of days obtaining  $\geq 100$  PAI per week was  $\beta=0.09$  ( $p=0.29$ , [CI: -0.10 to 0.28]),  $\beta=0.20$  ( $p=0.81$ , [CI: -1.62 to 2.01]),  $\beta=0.24$  ( $p=0.24$ , [CI: -0.19 to 0.66]),  $\beta=0.16$  ( $p=0.35$ , [CI: -0.20 to 0.51]), and  $\beta=0.58$  ( $p=0.10$ , [CI: -0.15 to 1.31]), respectively. Participants demonstrated a  $9.9$  mL·kg<sup>-0.75</sup>·min<sup>-1</sup> greater  $\dot{V}O_{2peak}$  compared to reference material from The Norwegian Trial of Exercise after Myocardial Infarction ( $p=0.21$ , [CI: -25.20 to 5.59]).

**Conclusion:** Exercise positively influences cardiorespiratory fitness after eight-month exercise intervention, where weekly days  $\geq 100$  PAI seems to demonstrate the greatest association. A larger sample size is crucial to determine the actual effect as results are not statistically significant. Further research on post-MI patients is necessary to improve clinical decisions and raise awareness of the importance of exercise as secondary prevention after MI.



## Abstrakt

**Hensikt:** Studere endringen i oksygenopptak etter åtte måneders treningsintervensjon blant menn og kvinner som tidligere har vært utsatt for hjerteinfarkt.

**Metode:** Oksygenopptak ble målt ved oppstart og slutten av intervensjonen hos elleve menn og kvinner som tidligere har vært utsatt for hjerteinfarkt ( $63.4 \pm 9.6$  år,  $178 \pm 10$  cm,  $90 \pm 14$  kg). Målingene ble gjennomført på tredemølle eller ergometersykel gjennom en kardiopulmonær belastningstest (CPET). Fysisk aktivitet og trening ble målt kontinuerlig med en *Amazfit NorEx* treningsklokke gjennom hele intervensjonsperioden. Deltakerne ble oppfordret til å opprettholde  $\geq 100$  PAI per uke, foretrukket gjennom trening i høy intensitet.

**Resultater:** En økning i oksygenopptak på  $1.4 \pm 2.4$  mL $\cdot$ kg $^{-1}\cdot$ min $^{-1}$  ( $p=0.08$  [CI: -3.03 til 0.21]) ble observert på gruppenivå. Økning i oksygenopptak som en funksjon av gjennomsnittlig total tid, tid i de ulike intensitetssonene høy, moderat og lav samt antall dager med oppnådd  $\geq 100$  PAI per uke var henholdsvis  $\beta=0.09$  ( $p=0.29$ , [CI: -0.10 to 0.28]),  $\beta=0.20$  ( $p=0.81$  [CI: -1.62 til 2.01]),  $\beta=0.24$  ( $p=0.24$  [CI: -0.19 til 0.66]),  $\beta=0.16$  ( $p=0.35$  [CI: -0.20 til 0.51]) og  $\beta=0.58$  ( $p=0.10$  [CI: -0.15 to 1.31]). Deltakerne hadde et  $9.9$  mL $\cdot$ kg $^{-0.75}\cdot$ min $^{-1}$  høyere oksygenopptak etter treningsintervensjonen sammenliknet med referansematerialet fra NorEx ( $p=0.21$  [CI: -25.20 to 5.59]).

**Konklusjon:** Trening viser å ha en positiv innflytelse på kardiorespiratorisk form etter åtte måneders treningsintervensjon, hvor ukentlig dager  $\geq 100$  PAI viser å ha sterkest sammenheng med økning i oksygenopptak. En større studiepopulasjon er nødvendig for å fastslå den faktiske effekten av trening da ingen av resultatene viser å være statistisk signifikante. Videre forskning på denne pasientgruppen er nødvendig for å bedre kliniske beslutninger og belyse viktigheten av trening som sekundærforebygging etter hjerteinfarkt.

# 1 Introduction

Cardiovascular diseases (CVD) are the number 1 cause of death globally (3). An estimate of 17.9 million people died from CVD in 2019, which represented 32% of all global deaths (3). Eighty five percent of these deaths were due to stroke and myocardial infarction (MI) (3). Statistics state that  $\geq 74.4\%$  of patients with a history of coronary heart disease are likely to experience a secondary event of MI (13). Evidence shows that lifestyle modifications including regular physical activity (PA), have a favorable effect on blood coagulation, fibrinolysis and platelet reactivity, which are all related to reduced incidence of a cardiac event (9). PA may reduce CVD related symptoms and improve immediate CVD risk factors such as elevated blood pressure (BP), blood glucose and blood lipids (14). In addition, PA is shown to increase one's cardiorespiratory fitness (CRF) (9).

## 1.1 Cardiorespiratory Fitness and Cardiopulmonary Exercise Testing

Cardiorespiratory fitness (CRF) is defined as a component of physiologic fitness that relates to the ability of the circulatory and respiratory systems to supply oxygen during activity (4). It reflects overall physical health and is usually measured as maximal oxygen ( $O_2$ ) uptake ( $\dot{V}O_{2max}$ ), or peak oxygen uptake ( $\dot{V}O_{2peak}$ ), which is the highest measured uptake of  $O_2$  per minute ( $mL \cdot kg^{-1} \cdot min^{-1}$ ) during dynamically work with large muscle mass (5). Measuring CRF objectively with the direct method cardiopulmonary exercise test (CPET) is considered the gold standard (5). CPET gives reliable, highly accurate, and comprehensive assessment of both cardiac, pulmonary, and skeletal muscles involved in the response to aerobic exercise. Applications of CPET include assessment of functional capacity, establishment of exercise parameters for cardiac rehabilitation, and for risk- stratifying post-MI patients according to the likelihood of a subsequent cardiac event (9). As exercise capacity and activity status is known to be an important prognostic factor in patients with CVD and has become a well-established predictor of cardiovascular and overall mortality, CPET is a valuable clinical tool to assess CRF in patients with previous MI (9, 15).

The highest incidence of cardiac events is seen in patients with low exercise capacity. Additionally, all-cause and cardiovascular mortality is shown to decrease with increased  $\dot{V}O_{2peak}$  (16). Literature states that every  $1 mL \cdot kg^{-1} \cdot min^{-1}$  increase in  $\dot{V}O_{2peak}$  is associated with an approximate 15% decrease in all-cause or cardiovascular-specific mortality independent of sex (17). However due to the nature of observational studies, they are unable to prove causality between exercise and mortality. Therefore, the Norwegian Trail of Physical Exercise After Myocardial Infarction (NorEx) aims to close this knowledge gap. Additionally, NorEx will create a valid reference material including normal values for the key physiological factors on post MI patients. This may improve diagnostics and be an important tool for cardiac rehabilitation. The present study is a substudy of NorEx and will contribute to research on exercise on this specific patient group.

## 1.2 Physical Activity Targeting Post-Myocardial Infarction Patients

2021 European Society of Cardiology's Guidelines on cardiovascular disease prevention (7) suggest "at least 150-300 min a week of moderate-intensity or 75-150 min a week of vigorous intensity aerobic PA, or an equivalent combination, to reduce all-cause mortality, cardiovascular mortality, and morbidity". According to the guidelines both walking, running, and cycling are suggested as appropriate exercise modalities (7). Tracking PA is becoming more popular than ever, and the technological community is rapidly developing.

Wearable health technology, like wrist activity trackers, is trending among the public and simultaneously becoming more integrated in health care systems (18).

Wrist activity trackers can be incorporated with the new PA metric Personal activity intelligence (PAI) (11). The PAI algorithm considers age, sex, resting heart rate (HR) and maximal HR reflecting the health benefit of the exercise performed (11). Research shows that by achieving and maintaining  $\geq 100$  PAI, risk of CVD- and all-cause mortality is reduced in patients with CVD (10, 19-22). Recent studies found that obtaining  $\geq 100$  PAI was associated with 24-36% significantly lower risk of CVD mortality in participants with known CVD risk factors (21, 22). Additionally, research states that participants who do not obtain  $\geq 100$  PAI have an increased risk of mortality, regardless of meeting the physical activity recommendations (10, 19, 20). The benefits of maintaining  $\geq 100$  PAI also yield for apparently healthy individuals (23, 24). With all these findings, it is interesting to investigate the impact on CRF studying both the new standard of activity tracking, PAI, and different exercise intensities.

### 1.3 Aim

The aim of this study was to investigate the change in  $\dot{V}O_{2peak}$  after eight-month exercise intervention in post-MI men and women. This includes exploring how high, moderate, and low exercise intensity, days  $\geq$ PAI, and individual exercise habits influence CRF. Additionally, the present study will compare the participants  $\dot{V}O_{2peak}$  after exercise intervention to the so far collected normal values on  $\dot{V}O_{2peak}$  for participants of the main study, NorEx. An improved CRF among participants after the exercise intervention is the hypothesis of the present study.

## 2 Material and methods

The current paper is a substudy of NorEx, which is the largest global exercise intervention study ever conducted, with the aim of investigating if three and a half years of supervised exercise prescription prolongs lives and prevents subsequent severe CVD among post-MI patients (25). This substudy aimed to investigate the change in CRF after eight-month exercise intervention, and which exercise intensity provided the greatest improvement in  $\dot{V}O_{2peak}$ . This included exploring how high, moderate, and low exercise intensity, days  $\geq 100$  PAI, and individual exercise habits influence CRF. The present study also compared the participants'  $\dot{V}O_{2peak}$  to the  $\dot{V}O_{2peak}$  of NorEx reference material. The study design is a randomized pre-post intervention study, with the primary outcome being  $\dot{V}O_{2peak}$  ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and  $\text{mL}\cdot\text{kg}^{-0.75}\cdot\text{min}^{-1}$ ). The effect measure for primary outcome is linear regression coefficient ( $\beta$ ). Arithmetic mean and standard deviation (SD) are presented for primary outcomes, if not otherwise stated.

### 2.1 Recruitment, Inclusion, and Exclusion Criteria

Recruitment of participants for this substudy is illustrated in Figure 1. An overview of recruitment of NorEx participants is included to understand the perspective of time and why the exact number of 11 post-tests were completed. A total of 58 participants underwent the test protocol described in 2.3 methods in 2021/2022, whereas 12 of these participants underwent pretesting in 2019/2020, 46 participants were random independent sample drawn in 2021/2022. 33 random independent sample drawn participants did not perform CPET due to Covid-19. One NorEx focus intervention participant was excluded from the data material after completing exercise testing due to other diseases. The remaining 11 participants made up the study population that will be further described in the methods section. Due to uneven sex distribution and the limited sample size, results will be presented for both genders combined. The reference material which will be presented in 4.3 Results consists of the 46 random independent sample drawn in 2021/2022 and 50 random independent sample drawn in 2019/2020. Participants for reference material was not exercise monitored or got any specific exercise advice. Additionally, there was no available data on their usual PA level. This was done specific to avoid Hawthorn effect for participants recruited for the NorEx control group. The reference group will therefore only be used as normal values on CRF for this specific population and their characteristics will not be further presented in the methods section.

**Figure 1**

*Flowchart illustrating recruitment of study participants and participants recruited for NorEx*

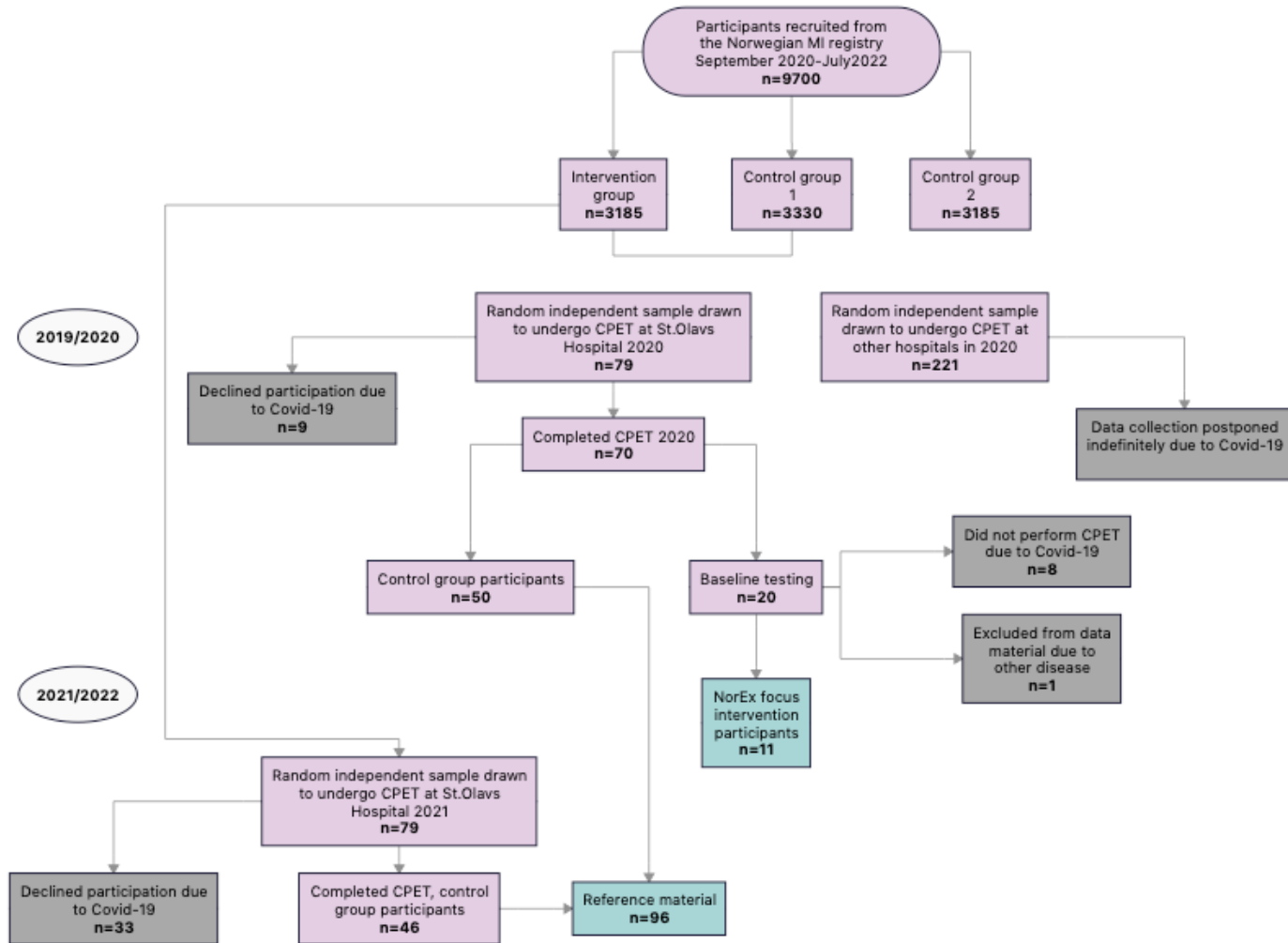


Figure 1: Flowchart illustrating recruitment of NorEx focus intervention participant and control group participants. Color coding: Grey= declined/postponed testing, pink=overview of participants leading to drawn participants used for this substudy, blue= data used for reference values, baseline, and post-test data.

Table 1 demonstrates inclusion and exclusion criteria for the participants included both in the present study and for the establishment of reference values, following NorEx study protocol criteria for recruitment.

**Table 1***Inclusion and Exclusion Criteria for Recruitment of Participants Applied in NorEx.*

<b>Inclusion criteria</b>	<b>Exclusion criteria</b>
<ul style="list-style-type: none"> <li>• &gt;18 years of age</li> <li>• Recruited for NorEx</li> <li>• Non-institutionalized patients</li> <li>• Patients who can perform CPET on treadmill or bicycle.</li> <li>• Situated in the Trondheim area</li> <li>• Hospital admission due to type 1 acute MI by the timeframe 2013-2022</li> <li>• Signed consent form</li> </ul>	<ul style="list-style-type: none"> <li>• Diagnosed dementia</li> <li>• Kidney failure leading to dialysis</li> <li>• Known alcohol or drug abuse</li> <li>• Regular PA level above the exercise intervention</li> <li>• Residing in a nursing home or other institution</li> <li>• Severe psychiatric disorder</li> <li>• Severe illness with reduced life expectancy or which prevents exercise with moderate or high intensity</li> <li>• Participating in endurance sport competitions</li> <li>• Diagnosed heart disease contradicting moderate or high intensity PA</li> <li>• Uncontrolled hypertension (systolic/diastolic BP &gt; 210/ 110 mmHg)</li> <li>• Participate in another intervention study with physical activity / exercise as intervention</li> <li>• Patients with inability to perform CPET on treadmill or ergometer cycle.</li> <li>• Patients with history of exercise syncope or ventricular arrhythmias (1:se3001)</li> </ul>

Abbreviations: NorEx: Norwegian Trial of Exercise after Myocardial Infarction, CPET: cardiopulmonary exercise test, MI: myocardial infarction, PA: physical activity, BP: blood pressure, mmHg: millimeters of mercury.

## 2.2 Study Population

The study population consists of 11 non-institutionalized Norwegian men and women (>18 years of age) situated in the Trondheim area, with medical history of MI, and currently participating in NorEx. Baseline characteristics of the study participants are presented in table 2.

**Table 2***Baseline characteristics of study participants*

<b>Characteristics</b>	<b>All n=11</b>	<b>Women n=2</b>	<b>Men n=9</b>
<b>Age</b> (years)	63.4 ± 9.6 (42-76)	61.5 ± 5.0 (58-65)	63.8 ± 10.6 (42-76)
<b>Height</b> (cm)	178 ± 10 (157-191)	159.5 ± 3.5 (157-162)	181.9 ± 5.1 (174-191)
<b>Body mass</b> (kg)	90 ± 14 (67-109)	77 ± 14 (67-87)	92 ± 13 (69-109)
<b>BMI</b> (Kg·m <sup>2</sup> )	28.4 ± 4.4 (21.9-35.5)	30.4 ± 6.9 (25.5-35.3)	28.0 ± 4.0 (21.9-34.0)

Data are presented as arithmetic mean ± standard deviation, including range. Abbreviations: BMI: body mass index, n: sample size.

### 2.3 Test Protocol

Data collection was performed at St. Olavs Hospital, Emergency and Cardiothoracic Centre, NeXt Move Core facility, Trondheim, Norway from November 1<sup>st</sup> 2021, until March 1<sup>st</sup> 2022. Baseline test data was collected utilizing the same method and location in 2020, by different test personnel. All participants underwent a screening protocol before the baseline tests, performed by nurses, to ensure safe performance of exercise testing. Body mass (kg) was measured before exercise test by weighing scale Model DS-102 (Arctic Heating AS, Notteroy, Norway). Height was obtained from baseline test and controlled before post-test using a standard medical stadiometer. Blood pressure (BP) measurement and Cardiopulmonary exercise test (CPET), including electrocardiography (ECG), was the clinical examination conducted and will be further presented meticulously.

#### 2.3.1 Blood Pressure:

BP was measured before CPET on dominant upper-arm, participant standing on the treadmill, one time only, with an automatic BP monitor (Tango M2, SunTech Medical, Inc., NC, USA). By occurrence of obvious incorrect measurement remeasurement was performed after 5-minute rest, seated. The same procedure was performed immediately after performance of CPET. No performance of CPET was initiated with BP values above 200/110 mmHg in accordance with guidelines of American College of Sports Medicine (4).

#### 2.3.2 Electrocardiography:

A standard 12-lead ECG (Custo Cardio 100 BT, Custo Med GmbH, Ottobrunn, Germany) was recorded during rest, warm up and CPET. The test was stopped if any occurrence of ST depression >2mm (>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 during workload (26).

#### 2.3.3 Cardiopulmonary Exercise Test:

Participants performed CPET on a Woodway treadmill 3 (serial no. 411120617, Weil am Rhein, Germany). Performance on stationary cycle ergometer (Lode B.V Medical Technology, Groningen, Netherlands) was conducted if participants had reduced

functionality, or if the baseline test was performed on stationary cycle ergometer. Treadmill control of inclination with a digital level (Bosch DNM 60 L, Professional) and velocity by applying the formula  $v = s/t$  was conducted prior to testing to remove source of error related to  $\dot{V}O_{2peak}$  and watt calculations.

Gas calibrations followed the same protocol as Loe and colleagues (27), with following modifications following the NorEx protocol: 1) calibration included measurement of ambient air and a gas mix of known content (15.0 % O<sub>2</sub> and 5.00 % CO<sub>2</sub> in N<sub>2</sub>) (AGA, hiq center, Oslo, Norway), calibration of the Triple-V volume transducer with a calibrated 3 L syringe (Calibration syringe C, Medikro Oy, Model: M9474-C, Kuopio, Finland) and barometric pressure control. 2) Volume calibration before each test. 3) Gas calibration after every third test.

An individualized 10-minute warm up was performed to prepare for testing in addition to determine workload for CPET. A detailed explanation of the test protocol was given during warm up. Participants were encouraged to avoid excessive hand grip on the safety rails, other than what was required for maintaining balance. The warm up was based on HR monitoring, evaluation of PA fitness level, and rate of perceived exertion (moderate intensity), corresponding to 11-13 on BORG scale (Appendix 1.). BORG scale is a subjective rating of perceived exertion. After warm up, participants were fitted with a face mask (Hans Rudolph, Germany) of appropriate size, linked to the spiroergometry system Metalyzer II (Cortex, Leipzig, Germany) for medical, functional analysis of the subject's lung, heart, and metabolism under stress. Polar S610i (Polar Electro Oy Kempele, Finland) was used during CPET as an additional measure of HR and heart rate recovery (HR<sub>recovery</sub>).

In accordance with the NorEx protocol, an individualized testing protocol was used during CPET which included two submaximal steady state measurements of 3 minutes each: 1) performed at warm up workload, and 2) workload increased 1 km/h or 2% incline (treadmill)/25 watt (ergometer cycle). Steady state measures were performed to measure submaximal values of  $\dot{V}O_{2peak}$ . Accordingly, workload progressively increased approximately every 60 seconds (treadmill)/every 30 seconds (ergometer cycle) with regards of an expected response of 3-5 mL·kg<sup>-1</sup>·min<sup>-1</sup> in  $\dot{V}O_2$  and 6-10 beats·min<sup>-1</sup> increased HR. The procedure continued until voluntarily exhaustion and the preset criteria for  $\dot{V}O_{2max}$  were accomplished: 1)  $\dot{V}O_2$  leveling off despite increasing workload, 2) 2 mL·kg<sup>-1</sup>·min<sup>-1</sup> between two 30-second epochs combined with respiratory exchange ratio (RER) of 1.05 or higher (4). Since 7 out of 22 tests (11 pre- and 11 post-test) did not meet these criteria and thereby failed to reach  $\dot{V}O_{2max}$ , the term  $\dot{V}O_{2peak}$  was used.

#### 2.4 Activity Tracker and PAI

Participants received an *Amazfit Health Watch NorEx* (Model A2012. Anhui Huami Information Technology Co., Ltd., Hefei, China) tracking among other HR and PAI. Activity data, such as minutes in different intensity zones and amount of PAI earned, was calculated, and collected from the corresponding web-portal developed for exercise monitoring and data storage *Midong Health Platform*. Time spent in respective intensity zones was calculated following manufacturers standard intensity zones (high: >80%HR<sub>peak</sub>, moderate: 65-79%HR<sub>peak</sub>, low: <65% HR<sub>peak</sub>). With regards to PAI, only days above or below 100 PAI were available for export as the web-portal is currently under development. Average days  $\geq 100$  PAI per week during the intervention period was therefore used as a



measure of participants PA level. Participants were encouraged to obtain  $\geq 100$  PAI per week, preferably by high intensity exercise.

## 2.5 Allometric Scaling

Absolute  $\dot{V}O_{2peak}$  level ( $L \cdot \text{min}^{-1}$ ) is mainly dependent on genetic contribution, moderate-to-vigorous intensity levels of physical activity, and body size (28). Traditionally,  $\dot{V}O_{2peak}$  is scaled for body size differences using ratio scaling ( $Y=bX$ ) and commonly expressed as  $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  using body mass in kg (28). Research states that the oxygen cost of running at a standard velocity does not increase in direct proportion to body mass (2). When comparing  $\dot{V}O_{2peak}$  across individuals, studies suggest a raised  $\dot{V}O_{2peak}$  to the power of 0.75 to exclude several types of errors and misinterpretations including lighter subjects being favored and heavier subjects being penalized (2). In this thesis, when comparing individuals at baseline and post-test, the most common way of expressing  $\dot{V}O_{2peak}$  is used ( $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ ), because in this case body mass does not change considerably. The raised  $\dot{V}O_{2peak}$  to the power of 0.75 is not as frequently used in the literature yet and expressing  $\dot{V}O_{2peak}$  this way may make results more intelligible. However, when comparing post-test values to reference material (4.3), the body mass influences the results at a greater level, and appropriate allometric scaling must be interpreted and raised to the power of 0.75. Results 3.4 were thereby expressed as  $\dot{V}O_{2peak}$  as  $\text{mL} \cdot \text{kg}^{-0.75} \cdot \text{min}^{-1}$

## 2.6 Data Analysis

BMI ( $\text{Kg} \cdot \text{m}^2$ ), Peak  $O_{2pulse}$  ( $\text{mL} \cdot \text{beat}^{-1}$ ), and  $\dot{V}O_{2peak}$  ( $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and  $\text{mL} \cdot \text{kg}^{-0.75} \cdot \text{min}^{-1}$ ) were calculated in Microsoft excel version 16. Additionally, workload (Watts) was calculated by the formula  $\text{Nm/s}$ . Nm, also known as Joule, corresponds to total work which was calculated by the formula: *velocity* · *%incline* · *time*, then divided by time to provide workload in watts.

## 2.7 Statistical Analysis and Data Visualization

IBM SPSS, version 26 (Statistical Package for Social Science, Chicago, IL) was used for descriptive and statistical analyses. The data set was examined for errors and each variable was tested for normality of the residuals (QQ-plot and histograms). Parametric analyses were performed due to normally distributed data. Paired-sample t-test was performed to investigate the increase at baseline and post-test individually and at group level. Analysis of variance (ANOVA) was performed to investigate the difference between time in high, moderate, and low intensity zones. Linear regression was performed to predict the value of different exercise intensities and PAI associated with  $\dot{V}O_{2peak}$ . Independent-sample t-test was performed when comparing participants of the present study to the NorEx reference material. All tests were two-tailed, applied with 95% confidence interval, and a considered statistically significant p-value of  $<0.05$ .

Canva 1.42.0 (App, Perth, Australia) was used for infographic visualization. Mind manager 22.1.159 (Software, ©1994-2022 Corel Corporation) was used for illustrating the study population in figure 1. GraphPad Prism 9.1.0 (Software, San Diego, California, USA) was used for graphic presentation of figures 2-8.

## 2.8 Ethical Statement

The current substudy was carried out according to the Declaration of Helsinki, Vancouver rules for authorship. Additionally, NorEx has been approved by the Regional Committee for Medical Research Ethics (REK 2019/797) and is registered in the ClinicalTrials.gov registry (NCT04617639).

## 3 Results

### 3.1 Physical Responses of Exercise Intervention

Table 3 demonstrates an improved  $\dot{V}O_{2peak}$  after the intervention looking at both absolute value ( $L \cdot min^{-1}$ ), scaled by  $mL \cdot kg^{-1} \cdot min^{-1}$  and scaled by  $mL \cdot kg^{-0.75} \cdot min^{-1}$  at group level.  $HR_{peak}$ ,  $HR_{recovery}$ , body mass and BMI were slightly reduced.  $O_{2pulse}$  remained unchanged. Overall, the participants were able to work at a higher workload with a higher RER value after the exercise intervention compared to baseline. Results are not statistically significant and the change in  $\dot{V}O_{2peak}$  cannot be determined.

**Table 3**

*Physiological characteristics of participants at baseline and post-test.*

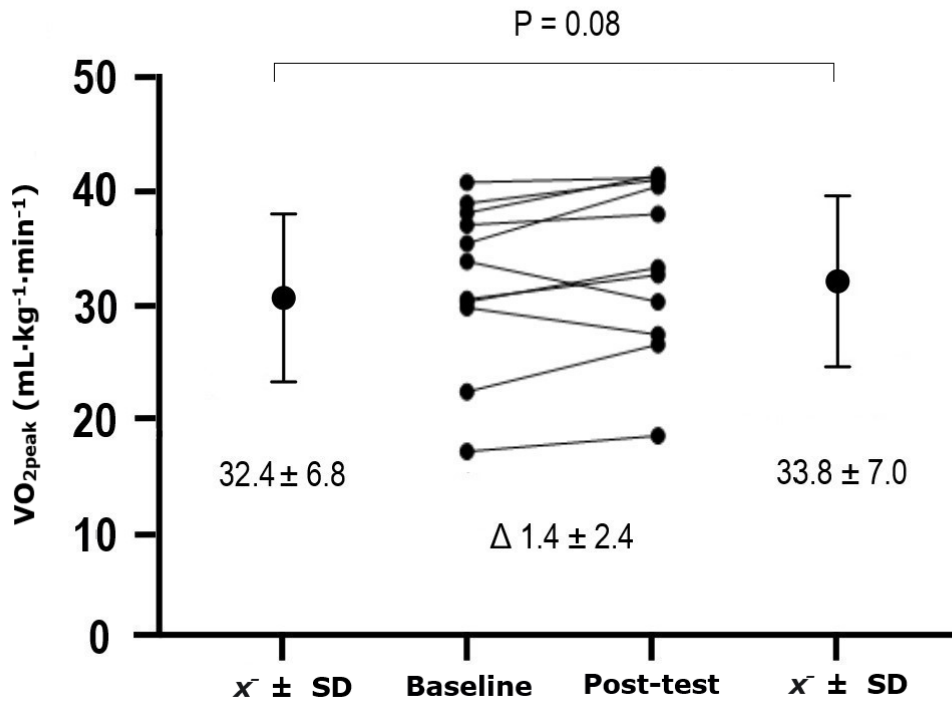
Variables	Baseline	Post-test	$\Delta$ Baseline to Post-test
$\dot{V}O_{2peak}$ ( $L \cdot min^{-1}$ )	2.89 $\pm$ 0.72	2.99 $\pm$ 0.70	0.10 $\pm$ 0.19 [CI: -0.22 to 0.02]
$\dot{V}O_{2peak}$ ( $mL \cdot kg^{-1} \cdot min^{-1}$ )	32.4 $\pm$ 6.8	33.8 $\pm$ 7.0	1.4 $\pm$ 2.4 [CI: -3.03 to 0.21]
$\dot{V}O_{2peak}$ ( $mL \cdot kg^{-0.75} \cdot min^{-1}$ )	99.4 $\pm$ 20.9	103.4 $\pm$ 21.2	4.1 $\pm$ 7.2 [CI: -10.0 – 14.3]
$HR_{peak}$ (beats $\cdot min^{-1}$ )	162 $\pm$ 13	159 $\pm$ 14	2.7 $\pm$ 4.9 [CI: -5.54 to 5.99]
<b>BMI</b> ( $Kg \cdot m^{-2}$ )	28.4 $\pm$ 4.4	28.2 $\pm$ 4.7	-0.2 $\pm$ 0.6 [CI: -0.26 to 0.58]
<b>Body mass</b> (Kg)	89.6 $\pm$ 13.7	88.9 $\pm$ 13.6	-0.6 $\pm$ 1.9 [CI: 0.61 to 1.89]
<b>Peak <math>O_{2pulse}</math></b> ( $mL \cdot beat^{-1}$ )	18 $\pm$ 5	19 $\pm$ 4	0.8 $\pm$ 1.6 [CI: -1.89 to 0.22]
<b>RER</b> ( $CO_2 \cdot VO_2^{-1}$ )	1.08 $\pm$ 0.08	1.09 $\pm$ 0.06	0.02 $\pm$ 0.08 [CI: -0.07 to 0.04]
<b><math>HR_{recovery}</math>, 1 min</b> (beat $\cdot min^{-1}$ )	27 $\pm$ 12	26 $\pm$ 12	-1.1 $\pm$ 6.6 [CI: -3.34 to 5.52]
<b>Workload</b> (Watts)	159 $\pm$ 60	163 $\pm$ 51	4.3 $\pm$ 24.0 [CI: -20.40 to 11.85]

Data are presented as arithmetic mean  $\pm$  standard deviation. Abbreviations:  $\Delta$ : change from baseline to post-test, CI: confidence interval,  $\dot{V}O_{2peak}$ : peak oxygen uptake,  $HR_{peak}$ : peak heart rate, BMI: body mass index, Peak  $O_{2pulse}$ : oxygen uptake per heartbeat, RER: respiratory exchange ratio,  $HR_{recovery}$ : heart rate recovery (1 minute after completed test), workload: peak treadmill/cycle ergometer exercise load calculated in watts.

Figure 2 demonstrates increased  $\dot{V}O_{2peak}$  after the exercise intervention [CI: -3.03 to 0.21]. Results were not statistically significant ( $p=0.08$ ).

**Figure 2**

*Baseline and post-test values of  $\dot{V}O_{2peak}$*



Baseline and post values of  $\dot{V}O_{2peak}$  presented on individual and group level. Data are presented as arithmetic mean  $\pm$  standard deviation. Abbreviations:  $\dot{V}O_{2peak}$ : peak oxygen uptake, P: p-value,  $\bar{x}$ : mean, SD: standard deviation,  $\Delta$ : change from baseline to post-test.

### 3.2 $\dot{V}O_{2peak}$ , Exercise Intensity, and PAI

Table 4 descriptively demonstrates mean time per week  $\pm$  SD and range of exercise performed during the intervention period. Data are categorized as total time, time spent in high, moderate, and low intensity zones, and days  $\geq 100$  PAI per week. Results demonstrate significant more time in moderate ( $p < 0.001$  [CI: 3.43 to 9.84] and low ( $p < 0.001$  [CI: 4.30 to 10.71] intensity zones compared to time in high intensity zone. Difference between low and moderate intensity zone was not statistically significant ( $p = 0.59$  [CI: -2.34 to 4.07]).

**Table 4**

Exercise performed during the intervention period categorized as time per hour performed for total time of exercise, for high, moderate, and low intensity zones, and days  $\geq 100$  PAI a week

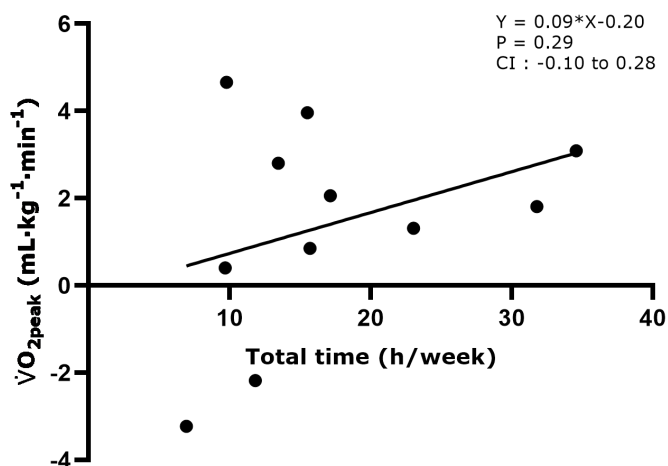
Measure of Exercise	Mean $\pm$ SD (range)
<b>Total time</b> (h/week)	17.2 $\pm$ 9.0 (6.9-34.6)
<b>High intensity</b> (h/week)	1.0 $\pm$ 1.0 (0.1-2.9)
<b>Moderate intensity</b> (h/week)	7.7 $\pm$ 3.9 (2.3-15.7)
<b>Low intensity</b> (h/week)	8.5 $\pm$ 4.9 (2.8-17.2)
<b>Days <math>\geq 100</math> PAI</b> (days/week)	4 $\pm$ 2 (0-7)

Data are presented as arithmetic mean  $\pm$  standard deviation, including range. Exercise intensities are presented as mean hour per week. PAI is presented as days  $\geq 100$  PAI per week. Total time: Includes all intensity zones. High intensity:  $>80\%HR_{peak}$ , moderate intensity:  $65\%-79\%HR_{peak}$ , low intensity:  $<65\%HR_{peak}$ . Abbreviations: h/week: hours per week, PAI: personal activity intelligence, CI: confidence interval, P: p-value.

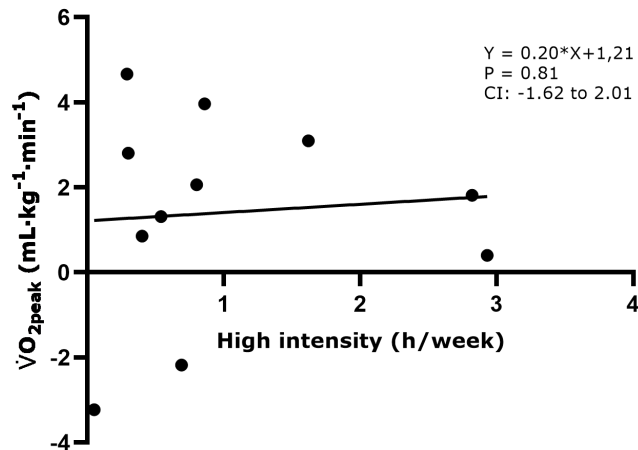
Figure 3 graphically demonstrates the increase of  $\dot{V}O_{2peak}$  as a function of total time per week of exercise performed ( $\beta=0.09$ ,  $p=0.29$ , [CI: -0.10 to 0.28]). This proposes an  $0.09 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  increased  $\dot{V}O_{2peak}$  for every hour exercise performed. Figures 4, 5, and 6 demonstrate the increase of  $\dot{V}O_{2peak}$  as a function of high ( $\beta=0.20$ ,  $p=0.81$  [CI: -1.62 to 2.01]), moderate ( $\beta=0.24$ ,  $p=0.24$  [CI: -0.19 to 0.66]), and low ( $\beta=0.16$ ,  $p=0.35$  [CI: -0.20 to 0.51]) intensity exercise training, respectively. Figure 7, illustrating days  $\geq 100$  PAI, demonstrate the greatest association ( $\beta=0.58$ ,  $p=0.10$  [CI: -0.15 to 1.31]) of change in  $\dot{V}O_{2peak}$ . Adjusting for age did not provide stronger association (total time:  $\beta=0.08$ , high intensity:  $\beta=0.22$ , moderate intensity:  $\beta=0.19$ , days  $\geq 100$  PAI:  $\beta=0.40$ ), except for low intensity ( $\beta=0.17$ ).

**Figure 3**

Change in  $\dot{V}O_{2peak}$  as a function of total time of exercise training

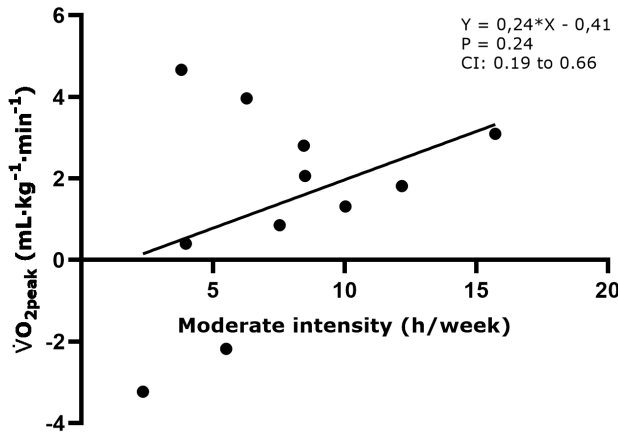
**Figure 4**

Change in  $\dot{V}O_{2peak}$  as a function of high intensity exercise training



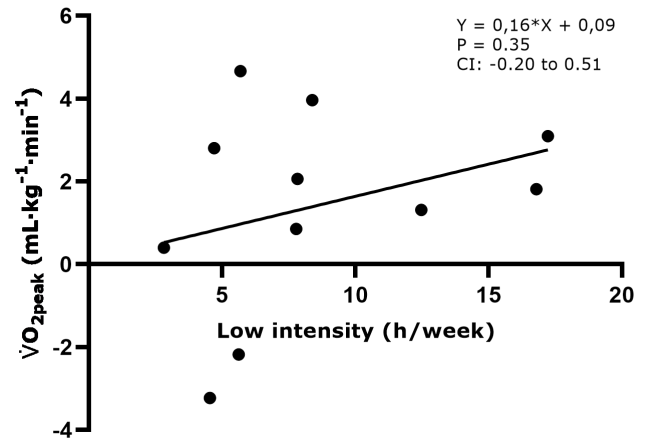
**Figure 5**

*Change in  $\dot{V}O_{2peak}$  as a function of moderate intensity exercise training*



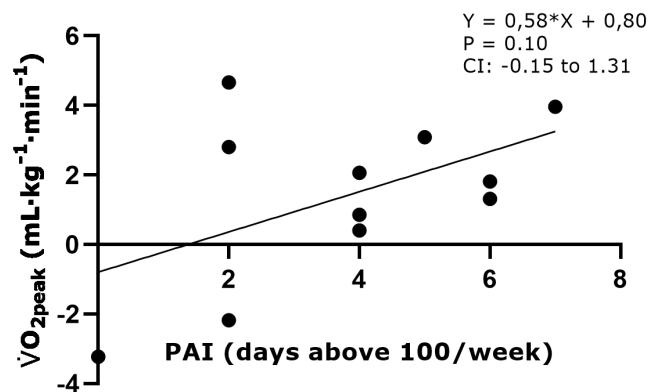
**Figure 6**

*Change in  $\dot{V}O_{2peak}$  as a function of low intensity exercise training*



**Figure 7**

*Change in  $\dot{V}O_{2peak}$  as a function of weekly PAI*



Figures 3-7: Increase of  $\dot{V}O_{2peak}$  as a function of total time, high, moderate, and low intensity exercise training performed per week, and change in  $\dot{V}O_{2peak}$  as a function of days  $\geq 100$  PAI per week. Abbreviations:  $\dot{V}O_{2peak}$ : peak oxygen uptake, h/week: hours per week, Y=slope coefficient, P=p-value. CI: confidence interval, PAI: personal activity intelligence.

### 3.3 Individualized Overview of Exercise Intervention

Table 5 demonstrate an individual overview of study participants, including both objective and subjective measures. An increased  $\dot{V}O_{2peak}$  is observed among 82% (n=9/11) of the participants and a decreased  $\dot{V}O_{2peak}$  among 18% (n=2/11) of the participants after the exercise intervention. An increased  $O_{2pulse}$  is observed among all participants who demonstrate an increased  $\dot{V}O_{2peak}$  (except subject 5 and 10 with no change in  $O_{2pulse}$ ) and decreased  $O_{2pulse}$  corresponding to decreased  $\dot{V}O_{2peak}$ . Participants with the greatest increase in  $\dot{V}O_{2peak}$  reported HIIT as exercise modality while participants with the greatest decrease in  $\dot{V}O_{2peak}$  reported walking as only exercise modality. Participants with increased  $\dot{V}O_{2peak}$  demonstrate decreased  $HR_{peak}$  while participants with decreased  $\dot{V}O_{2peak}$  demonstrate increased  $HR_{peak}$ .

**Table 5**

Individual overview of study participants including measures obtained from both CPET, activity tracker and questionnaire form.

Measure	Subject	1	2	3	4	5	6	7 #	8 #	9	10	11	
	<b>Sex</b>	F	M	M	M	M	M	M	F	M	M	M	
	<b>Age</b> (years)	65	73	69	76	66	63	42	58	55	59	71	
CPET	<b>Baseline <math>\dot{V}O_{2peak}</math></b> (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	23.2	40.4	18.3	30.6	38.7	35.4	33.9	30.1	37.9	36.9	30.8	
	<b>Post-test <math>\dot{V}O_{2peak}</math></b> (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	27.1	40.8	19.6	33.4	40.6	40.1	30.6	27.9	41.0	37.8	32.8	
	<b><math>\Delta \dot{V}O_{2peak}</math></b> (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	↑ 3.96	↑ 0.40	↑ 1.31	↑ 2.80	↑ 1.81	↑ 4.66	↓ 3.23	↓ 2.18	↑ 3.09	↑ 0.85	↑ 2.06	
	<b>Baseline <math>O_{2pulse}</math></b> (mL·beat <sup>-1</sup> )	10	19	11	18	18	21	25	15	19	23	18	
	<b>Post-test <math>O_{2pulse}</math></b> (mL·beat <sup>-1</sup> )	13	20	12	19	18	24	22	14	20	23	20	
	<b><math>\Delta O_{2pulse}</math></b> (mL·beat <sup>-1</sup> )	↑ 3	↑ 1	↑ 1	↑ 1	0	↑ 3	↓ 3	↓ 1	↑ 1	0	↑ 2	
	<b>Baseline <math>HR_{peak}</math></b> (beats·min <sup>-1</sup> )	153	147	168	163	173	166	149	176	185	160	142	
	<b>Post-test <math>HR_{peak}</math></b> (beats·min <sup>-1</sup> )	145	140	158	162	173	163	154	177	179	164	138	
	<b><math>\Delta HR_{peak}</math></b> (beats·min <sup>-1</sup> )	↓ 8	↓ 7	↓ 10	↓ 1	↓ 1	↓ 3	↑ 5	↑ 1	↓ 6	↑ 4	↓ 4	
	<b>Baseline <math>HR_{recovery}</math></b> 1 min (beat·min <sup>-1</sup> )	29	19	21	33	48	22	36	19	24	41	5	
	<b>Post-test <math>HR_{recovery}</math></b> 1 min (beat·min <sup>-1</sup> )	26	10	17	41	36	28	38	21	16	42	10	
	<b><math>\Delta HR_{recovery}</math></b> (beat·min <sup>-1</sup> )	↓ 3	↓ 9	↓ 4	↑ 8	↓ 12	↑ 6	↑ 2	↑ 2	↓ 8	↑ 1	↑ 5	
	<b>Baseline Borg scale</b>	20	18	20	18	19	19	19	19	19	19	19	18
	<b>Post-test Borg scale</b>	19	19	19	19	19	18	19	19	19	18	20	17
<b><math>\Delta</math> Borg scale</b>	↓ 1	↑ 1	↓ 1	↑ 1	0	↓ 1	0	0	↓ 1	↑ 1	↓ 1		

Activity tracker	<b>Total time</b> (h/week)	16	10	23	13	32	10	7	12	35	16	17
	<b>High intensity</b> (h/week)	1	3	1	0	3	0	0	1	2	0	1
	<b>Moderate intensity</b> (h/week)	6	4	10	8	12	4	2	6	16	8	9
	<b>Low intensity</b> (h/week)	8	3	12	5	17	6	5	6	17	8	8
	<b>Days <math>\geq</math> 100 PAI</b> (days/week)	7	4	6	2	6	2	0	2	5	4	4
Questionnaire form	<b>Frequency</b> (times/week)	2-3	$\geq$ 4	$\geq$ 4	2-3	$\geq$ 4	2-3	2-3	2-3	$\geq$ 4	2-3	2-3
	<b>Intensity</b>	Moderate	Moderate	Moderate	Moderate	Moderate	High	Moderate	Moderate	High	High	Moderate
	<b>Duration</b> (min)	>60	>60	30-60	>60	>60	30-60	30-60	>60	30-60	>60	>60
	<b>Exercise modality</b>	HIIT	Ski, cycle	Walk	Walk	Ski, run	HIIT	Walk	Walk	HIIT	HIIT	Walk, run

Abbreviations: CPET: cardiopulmonary exercise test, #: Other morbidity, F=female, M=male,  $\dot{V}O_{2peak}$ : peak oxygen uptake, min: minutes,  $\uparrow$ =increase,  $\downarrow$ =decrease,  $O_{2pulse}$ : oxygen pulse,  $HR_{peak}$ : peak heart rate,  $\Delta$ : delta, h: hours, PAI: personal activity intelligence, HIIT: high intensity interval training.



### 3.4 Study Population Compared to NorEx Reference Material

In comparison across participants, using appropriate scaling procedures explained in 2.5 methods,  $\dot{V}O_{2peak}$  is raised to the power 0.75. Figure 8 demonstrates a  $9.9 \text{ mL}\cdot\text{kg}^{-0.75}\cdot\text{min}^{-1}$  higher  $\dot{V}O_{2peak}$  among the participants at post-test compared to reference material of NorEx [CI: -25.20 to 5.59]. Results were not statistically significant.

**Figure 8**

*$\dot{V}O_{2peak}$  of study population after exercise intervention and NorEx reference material*

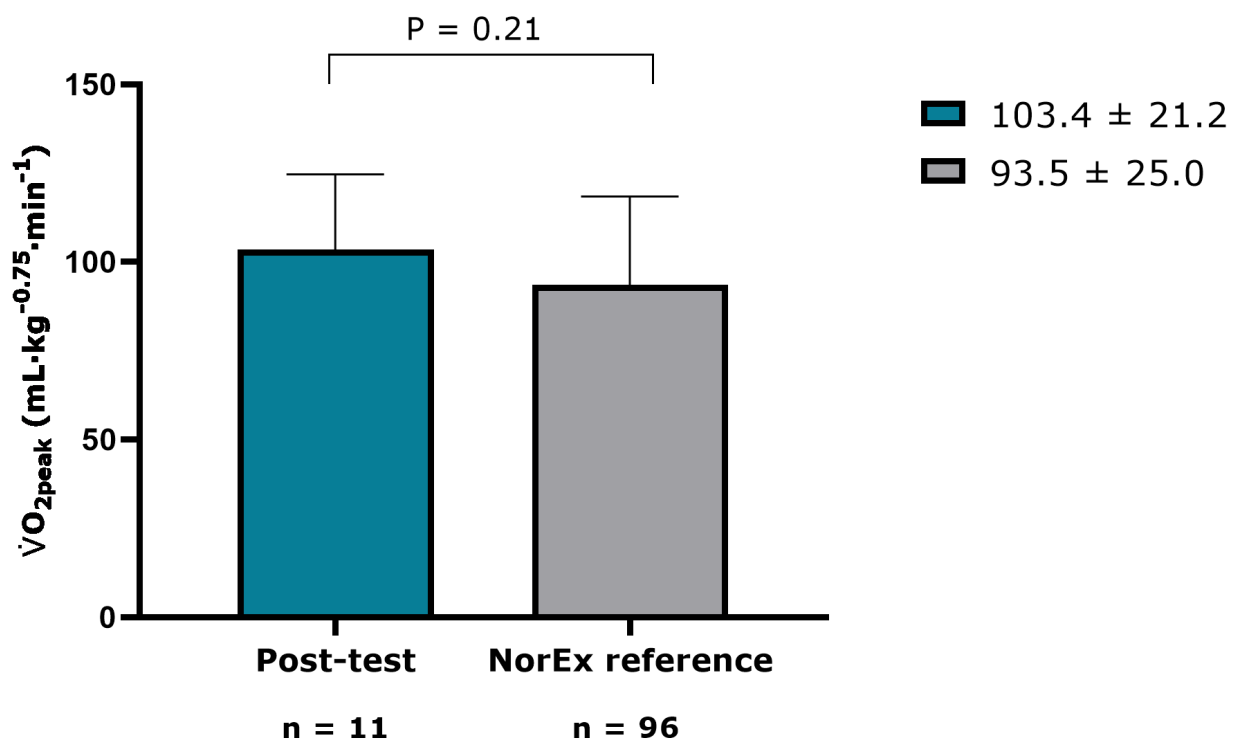


Figure 8: Peak oxygen uptake at post-test and peak oxygen uptake of the reference material of NorEx. Data are presented as arithmetic mean  $\pm$  standard deviation. Abbreviations:  $\dot{V}O_{2peak}$ : peak oxygen uptake, NorEx: The Norwegian Trial of Physical Exercise after Myocardial Infarction, P: p-value, n=sample size.

## 4 Discussion

The main findings of this NorEx substudy are 1) the eight-month exercise intervention improved CRF in terms of  $\dot{V}O_{2peak}$  among 82% (n=9/11) of the participants, while 18% (n=2/11) showed reduced  $\dot{V}O_{2peak}$ , 2) PAI demonstrated the strongest association with increased  $\dot{V}O_{2peak}$  followed by moderate intensity, high intensity, low intensity, and total time, respectively, 3) Participants with the greatest improvement in  $\dot{V}O_{2peak}$  demonstrate an increase or unchanged  $O_{2pulse}$  and reported HIIT as exercise modality. On the contrary, participants with the largest reduction in  $\dot{V}O_{2peak}$  demonstrated a decreased  $O_{2pulse}$  and reported walking as only exercise modality, 4) Participants of the present study had a  $9.9 \text{ mL}\cdot\text{kg}^{-0.75}\cdot\text{min}^{-1}$  higher  $\dot{V}O_{2peak}$  compared to reference material of NorEx. Notably, due to the small sample size, none of the results were statistically significant and the actual effect of exercise intensity cannot be determined. Nevertheless, it is interesting to discuss the possible physiological factors responsible for the response to different exercise intensities and PAI because a bigger sample size on this exact patient group may give different results.

### 4.1 Physiological Responses of Exercise Intervention

Stroke Volume (SV) is the volume of blood pumped out of the left ventricle of the heart during each heartbeat, is a dependent factor determining CRF, and acutely increases in the context of physical exercise. Left ventricular remodeling, which includes pathophysiological changes of the left ventricle in the heart, is a result of MI and may impair the hearts' ability to pump sufficient blood to working muscle (29). The function of  $\dot{V}O_{2peak}$  is  $(HR \times SV) \times a-vO_{2diff}$ , thereby, HR, which also acutely increases during exercise, is another determining factor of CRF. Results show that several of the participants with an increased  $\dot{V}O_{2peak}$  had a lower  $HR_{peak}$  at post-test compared to baseline. This may indicate that the participants did not push themselves as hard at post-test compared to the baseline test. This is also reflected by lower BORG scale values at post-test among several participants. Thereby,  $\dot{V}O_{2peak}$  may be underestimated. However, the overall  $HR_{peak}$  ( $159 \pm 14 \text{ beat}\cdot\text{min}^{-1}$ ) is in line with previous research on post MI patients (range 153-156  $\text{beat}\cdot\text{min}^{-1}$ ) (30, 31). The last aspect of the function of  $\dot{V}O_{2peak}$ ,  $A-vO_{2diff}$ , is the difference in  $O_2$  content of the blood between arterial and venous blood, an indicator of how much  $O_2$  of the blood is removed in the capillaries as the blood circulates in the body.

Another factor which may support the thought of an underestimated  $\dot{V}O_{2peak}$  is workload. Even though the participants fulfilled the criteria of a peak-test, the participants with lower  $HR_{peak}$  at post-test compared to baseline did in fact work at a higher workload with a higher RER. SV and HR determines the  $O_{2pulse}$ , an indirect indicator of cardiac output (Q). An increased  $O_{2pulse}$  reflects increased blood supply from heart to muscle and is a positive response of exercise we wish to determine. For the present study, the  $O_{2pulse}$  did not seem to increase at group level. At an individual level, the participants who increased their  $\dot{V}O_{2peak}$  the most also increased their  $O_{2pulse}$  correspondingly. The mean  $O_{2pulse}$  of the present study indicates a normal SV ( $18.7\pm 4.0 \text{ mL}\cdot\text{beat}^{-1}$ ) and is above average values when compared to studies conducted on similar populations ( $11.0\pm 2.0 \text{ mL}\cdot\text{beat}^{-1}$  to  $16.6\pm 3.5 \text{ mL}\cdot\text{beat}^{-1}$ ) (32, 33). A reason for reported deviations might be age, mixed CVD, or exercise- and lifestyle habits.

Chronic responses to exercise in post-MI patients, includes among other, a faster decrease in  $HR_{recovery}$ , which indicates a faster recovery after maximal effort (6). For the present

study,  $HR_{\text{recovery}}$  remained unchanged at group level. Individually, there was no clear trend between increased or decreased  $\dot{V}O_{2\text{peak}}$  and  $HR_{\text{recovery}}$ . There are several sources of error which can occur when measuring  $HR_{\text{recovery}}$ . Precision of time is crucial in addition to the negative influence of both dehydration, caffeine, and fatigue (6). Average value of  $HR_{\text{recovery}}$  ( $26 \pm 12 \text{ beat}\cdot\text{min}^{-1}$  [CI: -3.34 to 5.52]) is slightly below mean values found in Moholdt et al. (31) ( $32.6 \pm 9.5 \text{ beat}\cdot\text{min}^{-1}$  and  $31.4 \pm 9.4 \text{ beat}\cdot\text{min}^{-1}$ ). A Possible explanation is younger participants with a higher  $\dot{V}O_{2\text{peak}}$  in the study of Moholdt et al. (31), since higher  $HR_{\text{recovery}}$  is associated with higher CRF (6, 31). The Generation 100 study (32), including older CVD patients, presented findings more similar to the present study ( $25 \pm 10 \text{ beat}\cdot\text{min}^{-1}$  (women),  $27 \pm 12 \text{ beat}\cdot\text{min}^{-1}$  in (men) (32). Two participants of the present study had  $HR_{\text{recovery}} < 12 \text{ beat}\cdot\text{min}^{-1}$  prior to the exercise intervention, which is related to increased risk of premature death (6, 32). Still, the mean  $HR_{\text{recovery}}$  indicates that post MI patients in the present study do not have a delayed decrease in HR after exercise (32).

#### 4.2 $\dot{V}O_{2\text{peak}}$ and Exercise Intensity

The majority of the study population increased their  $\dot{V}O_{2\text{peak}}$  during the intervention. Analyses suggest the strongest association between  $\dot{V}O_{2\text{peak}}$  and days  $\geq 100$  PAI, followed by time per hour performed in moderate, high, low intensity zone and total time, respectively.

Multiple studies suggest that HIIT is a powerful exercise modality to positively influence CRF among CVD patients (30, 34-36). Respective studies also show an effect of moderate intensity, however, not as substantial as high intensity. Results of the present study suggests that moderate intensity has a  $0.04 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  larger increase in  $\dot{V}O_{2\text{peak}}$  per hour a week of exercise performed compared to high intensity. Unlike Ramos et al. (34) and Wisløff et al. (35), this present study uses the term high intensity for  $\geq 80\%HR_{\text{peak}}$  and moderate intensity for  $65-79\%HR_{\text{peak}}$  due to the manufacturer of the NorEx watch's definition of standard intensity zones (34, 35). This means that the effect of exercise spent between  $80-85\%HR_{\text{peak}}$  is categorized as high intensity in the present study but moderate intensity in other studies (34, 35). This may affect the outcome by concealing the actual effect of high intensity. Like the present study, Currie et al. (37) did not report any significant difference in CRF improvement between high and moderate intensity exercise but may also be influenced by restricted sample size ( $n=22$ ). Similar to Dun et al. (36), the present study suggests that exercising at high and moderate intensity zones has a better effect on CRF compared to low intensity exercise training. Additional regression analysis was done to investigate the effect of high and moderate intensity zones combined because of the deviation in termination of moderate and high intensity zones. Results did not give any greater significance, or a larger improvement in  $\dot{V}O_{2\text{peak}}$  per hour spent ( $\beta=0.10$   $P=0.49$  [CI: -0.02 to 0.04]), neither when adjusted for age ( $\beta=0.01$ ).

At an individual level, subject 6 ( $+4.7 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and 9 ( $+3.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) demonstrated the greatest improvements in CRF among the participants. Both self-reported HIIT as exercise modality, a frequency of  $\geq 2-3$  exercise sessions per week, and duration of  $\geq 30-60$  min. This type of exercise influences CRF in accordance with previous research (34, 35). On the contrary, subject 7 ( $-3.2 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and subject 8 ( $-2.2 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) had their  $\dot{V}O_{2\text{peak}}$  reduced after the exercise intervention. They both self-reported walking as their sole exercise modality, which makes the findings in CRF not surprising, and are in accordance with previous studies investigating low intensity exercise

and the impact on CRF (36). Notably, these two individuals reported additional comorbidities (fractured shoulder and Covid-19 short time before post-test) which are likely to affect their CRF due to reduced exercise ability. Additionally, it is important to evaluate the limitations related to subjective measurements, as their evaluation of intensity may deviate from the actual intensity based on HR.

Results obtained from subjective measurements, questionnaire form, deviated from the objectively measured results obtained from wrist activity trackers. Subjective measures are usually based on subjective judgements, and questionnaires produce substantially higher estimates of PA participation compared to objective measurement by accelerometer (38). An overestimated PA is seen among people with obesity and low PA levels, which are frequently seen with CVD patients (39). It may explain why the subjects with reduced or marginal increase in CRF self-reported exercising 2-3 or even  $\geq 4$  times a week at moderate and high intensity 30-60 min per session. In general, it is interesting to look at the subjective measurements since the objectively measure obtained from wrist activity trackers may have some limitations regarding measurement accuracy (18). Additionally, objectively measured PA may be underestimated as participants may not always be wearing the activity tracker. Combined, the reason for changed CRF due to exercise may be studied.

Ross et.al (39) state when counselling sedentary people, the importance of emphasizing the gains in health can be achieved with relatively modest increase in PA, as the largest improvement in CRF is seen in subjects progressing from unfit to fit, compared to subjects progressing from fit to more fit. This is noteworthy, as the greatest mortality benefits also occur when progressing from least fit to fit (39). Taking this into consideration when looking at an individual level, it is crucial to look at the actual value of  $\dot{V}O_{2peak}$  at baseline and post-test, not only the amount of increase. Subject 3 ( $\dot{V}O_{2peak}$  post-test:  $19.6 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ,  $\uparrow 1.31$ ) and 6 ( $\dot{V}O_{2peak}$  post-test:  $40.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ,  $\uparrow 4.66$ ) is a great example (both men). Even though the greatest increase is seen in subject 6, the health benefit of subject 3 may still be noteworthy because the physiological values (including  $O_{2pulse}$ ) at baseline is very poor.

With regards to different response in terms of CRF after this exercise intervention, the commonly discussed term *non-responders*, defined as individuals who do not respond to an exercise intervention, may be relevant. While some researches are critical to the term, others claim that 10% of subjects demonstrate an adverse response to exercise (40). Pickering et al. (40) question the methodology of CPET, and suggest that the non-response is due to physical stress, discomfort, and lack of motivation in relation to the performance of the test. Astoriono et al. (41), Ross et al. (42) and Montero et al. (43) all share the findings that the exercise non-responders are dose dependent, and that they occur more frequent in the low-intensity zones rather than in high zones and volume. They also suggest that longer exercise interventions will reduce the occurrence of non-responders. In this sub study, there were two individuals (subject 7 and 8) who did not respond to the exercise intervention which corresponds to 18% of the sample size, close to what evidence suggest to be expected. However, in this case, the non-response is more likely to be a result of the comorbidity they were exposed to during the intervention period. Subject 2 and 10 did have a marginal increase in  $\dot{V}O_{2peak}$  of  $<1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and may be identified as non-responders. However, the discussion regarding the term non-responders should

rather involve how we can facilitate to an actual exercise response, rather than whether the term non-responders exist.

### 4.3 Study Population Compared to NorEx Reference Material

The present study has, in addition to look at the change in  $\dot{V}O_{2peak}$  after an eight-month exercise intervention on eleven men and women, supplemented the collection of the ongoing reference material of NorEx. Normative reference standards are essential to optimize the clinical value of CRF. The reference value on CRF collected in NorEx was used as a tool to see if the participants at post-testing reached values above average for this specific population, which they did ( $\dot{V}O_{2peak} +9.9 \text{ mL}\cdot\text{kg}^{-0.75}\cdot\text{min}^{-1}$  [CI: -25.20 to 5.59]).

The sample size of this sub study's population turned out smaller than expected, due to Covid-19, which restricted the ability of stratifying participants. This made the comparison with other published reference material on this population challenging, as they stratified on both age and sex (44). Research suggests that  $\dot{V}O_{2peak}$  is closely associated with age. The comparison of post-test and reference material of NorEx should therefore preferably be stratified by age (45). However, additional analysis was done with age as covariate in accordance with guidelines (1 covariate per 10 participants, preferably above 20), but did not give any greater association except from low intensity exercise. Decline of  $HR_{peak}$  occurs with increasing age due to intrinsic cardiac changes, rather than to neural influences which makes the declination of  $\dot{V}O_{2peak}$  also to be expected (12). This applies to both post-MI patients and the apparently healthy population (27). After an exercise intervention or exercise program,  $HR_{peak}$  remains unchanged or might be slightly reduced, which is also seen in this present study. Increased age also entails frailty, including among other reduced mobility and sarcopenia, in addition to the reduced  $HR_{peak}$ . This may impact the performance of CPET and explain some of the reason of the expected decline in  $\dot{V}O_{2peak}$  and age.

Sex is another factor greatly impacting  $\dot{V}O_{2peak}$ , mainly due to the physiological differences between genders. For example, men typically have more muscle mass, more bone mass, and a lower percentage of body fat than women. Men also have larger lungs, wider airways, and greater lung diffusion capacity, even when normalized to height, which has important consequences especially considering pulmonary function. An important structural difference between genders is that maximal exercise capacity may be limited to pulmonary capacity in women as they age, in contrast to young men. In terms of cardiovascular function, men have significantly greater left ventricular mass and chamber size than women. Because the left ventricular ejection fraction is the same in both sexes, SV is larger in men than women (12). This explains why women on average show a lower  $\dot{V}O_{2peak}$  compared to men, which also was observed in the present study. Additionally, studies targeting post-MI patients show a majority of men in the study population (34, 35). Men have twice as high risk to be exposed for a MI compared to women (46). This may explain the big gender proportions present in many of the studies targeting MI patients, including this one. Among women it is shown that the risk of MI increases with age (47). A larger sample size would therefore preferably control for sex. Either way, regardless of sex, both genders do have an effect of exercise training, confirmed in the present study.

#### 4.4 Strengths and limitations

The main strength of the present study is the detailed information that is available on an individual level and the duration of the intervention period. This gives valuable information regarding the realistic increase of  $\dot{V}O_{2peak}$  that can be expected if exercising is implemented as an everyday routine. Additionally, all tests were performed in the same lab, using the same equipment. Even though baseline tests were performed by different test personnel, the same protocol was followed. This substudy is also the continuation of establishing a reference material on CRF for MI patients in Norway, which will create normal values for the key physiological factors for these post-MI patients. As CVD is a wide range of diseases, including multiple heart diseases with differing pathologies and corresponding physiological responses, restricting the study to only MI patients improved the validity for this exact patient group. The present study can also lead to more research on MI patients and a better understanding on how PA and exercise impact how the human body translates movement into cardiovascular health. With regards to participants, the study challenges to push them in terms of high intensity exercise. This can lead to more motivation to be physical active, and increase knowledge to reduce insecurity linked to their own health to improve mental health (48).

A major limitation to this study is that there is no control group available for the exercise intervention, which was done intentionally to avoid Hawthorn effect for participants recruited for the NorEx control group. However, comparing post-test results of the present study's population to reference material of NorEx may show trends of improvement in CRF when exercising. Additionally, the sample size in the present study was small due to a large amount of postponed testing due to Covid-19 and subjects were predominantly males. Performance of robust statistical analysis was therefore impossible, restricting internal validity. Consequently, any inference about the safety of this exercise is precluded, making this a «proof of concept» study rather than determining the actual effect of exercise intensity. Even though the small sample size restricts the study's external validity, Trondheim is shown to be representative of the Norway population in general through the HUNT study (27). Also, the categorization of different intensity zones was not consistent with neither guideline's terminology, nor other studies within the research field which makes the generalization of intensities challenging. Furthermore, the study had restricted access to any information about the participant's medical history or medication. This may be an important aspect to consider with regards to their effect on variables of interest such as HR.

## 5 Conclusion

Exercise positively influences CRF after eight-month exercise intervention, which confirms the hypothesis of the present study. Weekly PAI seems to have the greatest association when also investigating the different exercise intensities high, moderate, and low. The study highlights the importance of looking at individuals, as notable effects may be hidden by only analyzing mean values on group level. Participants included for exercise intervention demonstrated a greater CRF compared to NorEx reference material. However, a larger sample size is crucial to determine the actual effect of exercise's influence on CRF, as none of these results demonstrate significant results. Further research on post-MI patients is necessary to improve clinical decisions and raise awareness of the importance of exercise as secondary prevention after MI.

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## 7 Appendices

### Appendix 1.

#### *Borg scale*

<b>Borg scale</b>	
<b>6</b>	
<b>7</b>	Very, very light
<b>8</b>	
<b>9</b>	Very light
<b>10</b>	
<b>11</b>	Fairly light
<b>12</b>	
<b>13</b>	Somewhat hard
<b>14</b>	
<b>15</b>	Hard
<b>16</b>	
<b>17</b>	Very hard
<b>18</b>	
<b>19</b>	Very, very hard
<b>20</b>	

Reference: (49)

### Appendix 2.

#### *Questionnaire form*

<b>How frequently do you exercise</b>	<b>How hard do you push yourself?</b>	<b>How long does each session last?</b>	<b>Exercise modality</b>	<b>Comorbidity?</b>
Never	Take it easy (low intensity)	< 15 min	Walk	No
<1 a week	Heavy breath and sweat (moderate intensity)	16 – 30 min	Cycle	Yes
1 a week	Push near exhaustion (high intensity)	30 – 60 min	Run	Specify: _____
2-3 a week		> 60 min	HIIT	
≥ 4 a week			Other: _____	

Run was defined as continuous running, specified as *not* intervals. Abbreviations: min: minutes, HIIT: high intensity interval training.

