Masteroppgave

NTNU
Norges teknisk-naturvitenskapelige universitet
Fakultet for medisin og helsevitenskap
Institutt for sirkulasjon og bildediagnostikk

Sofie Johnsen Lynghaug

Prognostic indicators of cardiac related events and the effect of exercise in Norwegian post-myocardial infarction participants

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

Masteroppgave i Physical Activity and Health
Veileder: Ulrik Wisløff
Medveileder: Kaare Harald Bønaa
August 2022

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Infographic

Prognostic Indicators of Cardiac Related Events and the Effect of Exercise in Norwegian Post-Myocardial Infarction Participants

Did you know?

7 million experience myocardial infarction each year

Survivors are at **high risk** of recurrence, other cardiovascular events or death

Ventilatory efficiency **(VE/VCO2 slope)** and peak oxygen consumption **(VO2peak)** might predict risk of adverse events within a myocardial infarction population

Methods

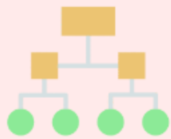
Obtaining values through **cardiopulmonary exercise test (CPET)** on the prognostic indicators VE/VCO2 slope and VO2peak.

109 participants doing CPET at baseline

10 participants doing additional CPET at follow-up after eight months of supervised exercise

Eight month of exercise intervention. Participants were encouraged to maintain **>100 PAI per month**.

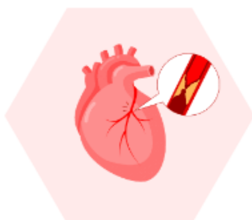
Prognostic indicators were categorized into **Weber** and **ventilatory classifciation systems** to **identify risk** of adverse events



Results

Baseline (n=109)

- **VE/VCO2 slope**: 31.29±4.47 L·min-1. **VO2peak:** 30.9±8.3 mL·kg-1·min-1
- The relationship between VE/VCO2 slope (L·min-1) and VO2peak (mL·kg-1·min-1) showed a **weak negative correlation** (r=-0.093, p=0.336).
- **Distribution** within the Weber and ventilatory classification systems **varied largely** based on **what parameter was set as the prognostic indicator.**



After intervention (n=10)

- **10/10** showed improvements in VE/VCO2 slope (-1.91±1.72 L·min-1[0.67-3.12])
- **8/10** showed improvements in VO2peak (1.35±2.53 mL·kg-1·min-1 [CI: -3.16 to 0.46]).
- **Changes in distribution** within the **ventilatory classification system** were observed, while **no changes** in distribution were seen within the **Weber classification system.**
- **Improvements** in VE/VCO2 slope (r=-0.721, p=<0.05) and VO2peak (r=0.850, p<0.05) had the **strongest correlation** with **type of activity** during the exercise intervention.

Conclusion

- Assumed **risk of cardiac related events** within 12 months **varies largely** based on the prognostic indicator and classification system used among post-MI participants.
- **Eight months of supervised exercise** resulted in **improvements** within the **VE/VCO2 slope** and **VO2peak**, suggesting that **exercise could prevent cardiac related events** by changing assigned risk category to one associated with lower risk.

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CERG
Our heart is in the future

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Abbreviations

MI	Myocardial Infarction
CVD	Cardiovascular Disease
CRF	Cardiorespiratory Fitness
VO_2	Oxygen Consumption
VO_{2peak}	Peak Oxygen Consumption
VO_{2max}	Maximal Oxygen Consumption
V_E/VCO_2	Ventilatory Efficiency
CPET	Cardiopulmonary Exercise Test
AHA	American Heart Association
HF	Heart Failure
PA	Physical Activity
NorEx	The Norwegian Trial of Exercise After Myocardial Infarction
BP	Blood Pressure
ECG	Electrocardiogram
HR	Heart Rate
RER	Respiratory Exchange Ratio
V_E	Minute Ventilation
VCO_2	Carbon Dioxide Output
V_T	Tidal Volume
PAI	Personal Activity Intelligence
BMI	Body Mass Index
SD	Standard Deviation
GA	Goal Achievement
HIIT	High Intensity Interval Training
NS	Non-Significant

Definitions

Cardiovascular Disease: General term for conditions affecting the heart or blood vessels (1). CVD includes coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism (2).

Myocardial Infarction: MI is considered a coronary heart disease and can be caused by sudden insufficiency in myocardial blood flow, usually from coronary artery occlusion (1).

Peak Oxygen Consumption (VO_{2peak}): The highest measured consumption of O2 per minute and is considered a reflection of overall health status (1).

Cardiorespiratory fitness: CRF reflects the ability to take up, transport and utilize oxygen to perform physical work (1). The gold standard for measuring CRF is to directly measure VO_{2max} using cardiopulmonary exercise testing (CPET) (1).

Cardiopulmonary Exercise: Test: A non-invasive, clinical procedure assessing the integrative exercise responses involving the pulmonary, cardiovascular, haematopoietic, neurophysiological, and skeletal muscle systems (3). It involves measurements of respiratory oxygen uptake (VO2), carbon dioxide production (VCO2) and ventilatory measures during a symptom-limited exercise test (3).

Personal Activity Intelligence: PAI is a new personalized metric for PA tracking aiming to make it easier to quantify how much PA is needed to reduce the risk of premature mortality from non-communicable diseases (4). PAI can be integrated in self-assessment heart rate devises and is based on an individual's sex, age, resting heart rate (HR) and maximal HR (4). A PAI score >100 per week at baseline, is found to delay CVD- and all-cause mortality (4).

Abstract

Purpose: To investigate the difference of ventilatory efficiency (V_E/VCO_2 slope) and peak oxygen consumption (VO_{2peak}) as prognostic indicators among Norwegian post-myocardial infarction (MI) men and women at baseline, and study the effect of eight months supervised exercise on prognostic indication within a post-MI population.

Methods: In total, 109 participants (64.2±8.7 years, 176.1±7.9 cm, 87.4±16.8 kg) were randomly selected from the ongoing Norwegian Trial of Physical Exercise After Myocardial Infarction. Baseline prognostic indicator values of V_E/VCO_2 slope and VO_{2peak} were obtained through cardiopulmonary exercise test (CPET), performed on a treadmill or cycle ergometer. Within this population, 10 participants, performed an additional CPET measuring the corresponding prognostic indicator variables after eight months of supervised exercise. Physical activity were measured continuously by an application device during the intervention period. For both groups within the study, the prognostic indicator values were distributed by the Weber and ventilatory classification system identifying risk of cardiac related events within the populations.

Results: At baseline, a mean of 31.29±4.47 and 30.9±8.3 were found in V_E/VCO_2 slope ($L \cdot min^{-1}$) and VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$), respectively. The relationship between V_E/VCO_2 slope ($L \cdot min^{-1}$) and VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) showed a weak negative correlation (r=-0.093, p=0.336). Distribution within the Weber and ventilatory classification systems varied largely based on what parameter was set as the prognostic indicator. After eight months of supervise exercise, the intervention groups showed improvements of -1.91±1.72 [0.67-3.12] and 1.35±2.53 [CI: -3.16 to 0.46] in V_E/VCO_2 slope ($L \cdot min^{-1}$) and VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$), respectively. The improvements within both V_E/VCO_2 slope (r=-0.721, p=<0.05) and VO_{2peak} (r=0.850, p<0.05) had the strongest correlation with type of activity during exercise intervention. Changes in distribution within the ventilatory classification system were observed after exercise intervention, while no changes in distribution were seen within the Weber classification systems.

Conclusion: Assumed risk of cardiac related events within 12 months varies largely based on the prognostic indicator and classification system used among post-MI participants. Eight months of supervised exercise resulted in improvements within the V_E/VCO_2 slope and VO_{2peak}, suggesting that exercise could prevent cardiac related events by changing assigned risk category to one associated with lower risk after exercise intervention.

Sammendrag

Hensikt: Å studere forskjellene mellom V_E/VCO_2 slope og VO_{2peak} som prognostisk indikator blant norske studiedeltakere som har gjennomgått hjerteinfarkt, og å studere effekten av åtte måneder veiledet trening på prognostisk indikasjon i et utvalg av den norske hjerteinfarkt populasjonen.

Metode: Et randomisert utvalg fra det pågående prosjektet Norwegian Trial of Physical Exercise After Myocardial Infarction, resulterte i totalt 109 deltakere (64.2±8.7 år, 176.1±7.9 cm, 87.4±16.8 kg). Utgangsverdiene for de prognostiske indikatorene, V_E/VCO_2 slope og VO_{2peak}, var målt ved hjelp av en kardiopulmonal belastningstest (CPET) på tredemølle eller ergometersykkel. Innenfor de opprinnelige 109 deltakerne, gjennomførte 10 deltakere ytterligere CPET målinger av tilsvarende variabler etter åtte måneder med veiledet trening. Fysisk aktivitet og trening var målt kontinuerlig gjennom intervensjonen ved hjelp av en smartklokke. De prognostiske indikatorverdiene var kategorisert ved bruk av Weber og det ventilatoriske klassifikasjonssystemet for å kartlegge risikoen for hjerterelaterte hendelser innenfor populasjonen.

Resultater: Et gjennomsnitt på 31.29±4.47 and 30.9±8.3 ble observert i henholdsvis V_E/VCO_2 slope ($L \cdot min^{-1}$) og VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$). Forholdet mellom V_E/VCO_2 slope ($L \cdot min^{-1}$) og VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) viste en svak negativ korrelasjon (r=-0.093, p=0.336). Fordeling av variabler ved bruk av Weber- og det ventilatoriske klassifikasjonssystemet viste store variasjoner basert på hvilken variabel som ble brukt som prognostisk indikator. Etter åtte måneder med veiledet trening viste deltakerne forbedringer på henholdsvis -1.91±1.72 [CI: 0.67-3.12] og 1.35±2.53 [CI: -3.16 to 0.46], i V_E/VCO_2 slope ($L \cdot min^{-1}$) og VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$). Forbedringene innen både V_E/VCO_2 slope (r=-0.721, p=<0.05) og VO_{2peak} (r=0.850, p<0.05, korrelerte sterkest med type aktivitet gjennomført i intervensjonsperioden. Fordelingen av deltakere basert på risiko hadde forandret seg innad i det ventilatoriske klassifiseringssystemet, men ikke i Weber klassifiseringssystemet.

Konklusjon: Store variasjoner innen antatt risiko for hjerterelaterte hendelser innen 12 måneder ble funnet basert på hvilken variabel som ble brukt som prognostisk indikator blant deltakere med tidligere hjerteinfarkt. Åtte måneder med veiledet trening resulterte i forbedringer innen V_E/VCO_2 slope og VO_{2peak}, og forslår at trening kan forhindre hjerterelaterte hendelser ved å endre deltakernes tildelte risikokategori til en kategori assosiert med lavere risiko.

Introduction

Acute myocardial infarction (MI) is a major cause of morbidity and mortality worldwide (5). It maintains a substantial footprint on global health, affecting more than 7 million individuals worldwide each year (5). The majority of people experiencing MI survive. However, survivors are at high risk of recurrence, other cardiovascular disease (CVD) events, or death (6). To predict the risk of these outcomes, literature suggests that cardiorespiratory fitness (CRF), in terms of VO_2, is an important prognostic indicator (7, 8). Recently, ventilatory efficiency (V_E/VCO_2) slope has been suggested as an even more powerful predictor of mortality and hospitalization in heart failure patients and likely other CVDs, such as MI (9, 10).

Importance of Prognosis in MI

The prognosis regarding MI plays a central role in associated medical decision making and patient management (11). By determining which variables are prognostic of outcomes we gain insight in the biology of the disease, and are given the opportunity to optimize appropriate treatment strategies based on the prognostic indicators of an individual patient (11). Data indicate that at least one-third of MI patients die before coming to the hospital, and another 40%-50% are dead upon arrival (39). An additional 5%-10% of initial survivors will die within the first 12 months after MI and 20%-50% will be readmitted to hospital due to cardiac related events within the same time period (12, 13). For patients surviving 12 months without subsequent cardiac related events after index MI, the risk remains high, with 20% of patients experiencing an event during subsequent years (13). Prognostic factors regarding similar indications are often used in the design, conduct, and analysis of clinical trials aiming to identify ways to improve the risk of the given outcomes (13).

Classification Systems

In clinical practice today, there exist two major classification systems defining disease severity and prognosis within CVD (14). These systems are based on two different variables obtained from cardiopulmonary exercise testing (CPET): V_E/VCO_2 slope and VO_{2peak}. The Weber classification system, based on VO_{2peak}, paved the way to a large amount of evidence and advancements in the care setting and risk stratification of patients with heart failure (HF) (14). Based on four different categories of VO_{2peak}, the Weber system introduced the use of CPET in daily practice (14). VO_{2peak} became then a measure of standard staging the severity of the disease, unmasking the underlying pathophysiology, and addressing the optimal timing for advanced treatment (14). Directly measured VO_{2peak} has shown to be of considerable influence on prognosis after MI, as it is directly related to the integrated function of numerous physiological support systems, and thus considered a reflection of overall health status

(1). Several prospective cohort studies have reported a consistent, inverse association between VO_{2peak} and CVD events, CVD mortality and all-cause mortality (7, 9, 15).

The Ventilatory classification system is based on ventilatory efficiency, commonly assessed by the minute ventilation-to-carbon dioxide production (V_E/VCO_2) slope. Impaired ventilatory efficiency is indicated within heart disease patients by a growing body of evidence (16). The cause of the increased and inefficient ventilatory response within this population is believed to be multifactorial, involving both peripheral (e.g., locomotor muscle afferents) and central (e.g., ventilation/perfusion mismatch) mechanisms (16). Newer research shows that the ventilatory system may be a better tool for assessing the prognosis of cardiac related events within 12 months compared to the Weber system (9,10). Several studies define a V_E/VCO_2 slope of ≈34 ($L \cdot min^{-1}$) as a threshold value for predicting a poorer prognosis (17). Although this dichotomous threshold has proven to be prognostically significant, a wide range of V_E/VCO_2 slope values are observed within the CVD population (17). This may reflect the need for using the multilevel classification system used within this study instead of a dichotomous or threshold-based system. The specificity gained by using a multilevel classification system makes it easier to identify subgroups within a MI population at increased risk for adverse events across the entire spectrum of clinical severity (17).

The Influence of Exercise on Prognostic Indicators

According to WHO, 30% of deaths caused by MI could be prevented if the population adhered to official guidelines for physical activity (PA) (18). However, the relationship between exercise and prognosis is a broad topic with multiple factors possibly influencing the outcome. Previous research documents improved VO_{2peak} and V_E/VCO_2 slope after exercise interventions within populations with heart disease (16). Investigating the same parameters solely within Norwegian post-MI participants, would be of interest. This investigation could further explore the influence of exercise regimen on the prognostic indicators, V_E/VCO_2 slope and VO_{2peak}, for cardiac related events.

Aim

The aim of the study is to investigate if Norwegian post-MI participants have differences between prognosis when stratified by classification systems, and if exercise influences prognosis within these systems. This involves exploring how exercise regimen, including frequency, activity type, amount, and increased PA levels since pre-trial, are influencing the prognostic indicators value. In addition, secondary CPET baseline data collected from participants was presented to supplement the growing reference material on key cardiorespiratory variables for the Norwegian post-MI population.

Methodology

The Norwegian Trial of Physical Exercise After Myocardial Infarction (NorEx) is a nationwide registry-based prospective, three-arm, randomized multicentre secondary prevention clinical trial aiming to provide conclusive evidence that PA reduces the risk of death or recurrent CVDs. This is done by investigating the effect of approximately three and a half years of supervised exercise on mortality and cardiovascular morbidity among participants who have suffered MI. The current study is a sub study of NorEx aiming to investigate the possible difference in V_E/VCO_2 slope and VO_{2peak} as prognostic indicators of cardiac related events within 12 months, and the influence of exercise on prognostic indicator values among Norwegian post-MI participants.

Recruitment of Participants and Data Collection

Estimated recruitment of participants is illustrated in Figure 1. Data were collected between November 1st 2021 and February 1st 2022 at NeXt Move Core facility, St. Olavs Hospital, Trondheim, Norway. All participants underwent screening according to the screening operational protocol (SOP) performed by nurses to ensure safety regarding inclusion of participants to NorEx. The NorEx protocol included the recruitment of 79 new participants for the current study. However, due to the ongoing COVID-19 pandemic and exclusion criteria, only 49 participants completed a valid CPET as described in *Cardiopulmonary Exercise Testing*. The study population included 39 baseline reference participants tested in 2021/2022, and ten follow-up participants who underwent baseline test in 2020/2021 and follow-up test in 2021/2022 after approximately eight months of supervised exercise. Tests done both in 2020/2021 and 2021/2021 was collected utilising the same method and location, however by different test personnel. The 2020/2021-testing was in conjunction with a part of NorEx called NorEx-focus. NorEx-focus draws a random sample of 300 MI participants for testing cognitive function, and CRF measured with CPET at baseline with a 1- and 3.5-yr-follow-up, respectively. As a result, the follow-up participants within this study are referred to as NorEx-focus participants throughout the paper.

In addition to this study's data collection, data has been extracted and utilised from previous baseline reference material (n=70) within NorEx drawn in 2020/2021. In total, the baseline reference material consists of 109 participants while NorEx-focus consists of ten participants. Due to uneven sex distribution and the limited sample size within NorEx-focus, results regarding this group will be presented for both genders combined.

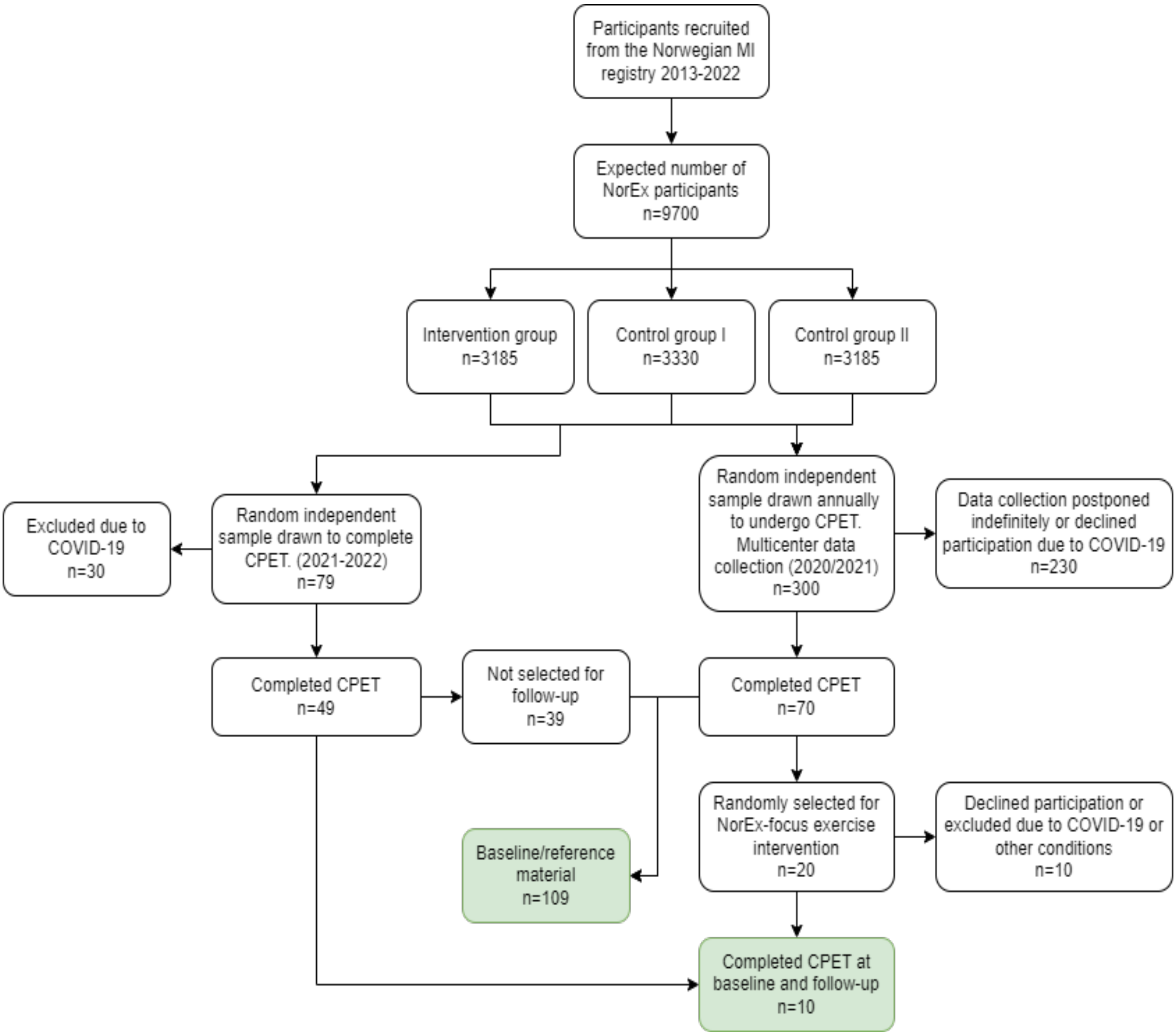

Figure 1: The recruitment process to NorEx and the current sub study. Colour coding: white= overview of participants leading to drawn participants used for this sub study, green= data used for baseline and follow-up.

Table 1 demonstrates inclusion and exclusion criteria for all participants associated with NorEx. This includes both the current study and the previous established baseline reference material used supplementary in this paper.

Table 1. Inclusion criteria and exclusion criteria in NorEx

Inclusion criteria	Exclusion criteria
o Men and women with previous hospital admission due to an acute MI (Type I) during 2013-2022. o Minimum 3 months after hospitalization when in a stable condition o Norwegian national identification number o Not expected to emigrate during the study o Age 18-79 years at the time when receiving study invitation o Can communicate in Norwegian or another Scandinavian language o Able to be physically active according to study protocol o Signed consent form	o Regular PA level above the exercise intervention o Participating or plan to participate in endurance sport competitions o Cognitive impairment/dementia o Known alcohol or drug abuse o Severe psychiatric disorder o Known cardiac disease contradicting moderate or high intensity PA o Kidney failure leading to dialysis o Uncontrolled hypertension (systolic / diastolic BP > 210 / 110 mmHg o Severe illness with reduced life expectancy or which prevents training with moderate or high intensity o Residing in a nursing home or other institution o Participating in another research study on physical exercise

Abbreviations: NorEx: Norwegian Trial of Physical Exercise After Myocardial Infarction, PA: physical activity, BP: blood pressure.

Clinical Examinations

Height was measured without shoes (Seca 222, Hamburg, Germany) and was reported in the nearest whole centimetre. Body mass was measured without shoes using a Soehnle weighing scale (Backnang, Germany) and was reported to the nearest kilogram. Electrocardiogram (ECG) was measured with a 12-lead electrocardiograph (Custo Med GmbH, Ottobrunn, Germany). This was used to monitor cardiac response indication of test termination in accordance with AHA's guidelines for exercise testing with CVD patients, such as serious arrhythmias not under control after treatment (19). Heart rate (HR) was measured by radio telemetry (Polar S610i, Polar Electro Oy, Kempele, Finland). Blood pressure (BP) was measured using an automatic BP monitor (Tango M2, SunTech Medical, Morrisville, NC, USA), followed by one repeated measurement immediately post CPET completion. BP was measured in the dominant arm while standing with straight legs and with no talking.

Cardiopulmonary Exercise Testing

An individualized graded protocol was used for testing key cardiorespiratory variables on a treadmill (Woodway, PPS Med, Waukesha, WI, USA) unless there were reasons, such as reduced functionality or leg pain. In these cases, a stationary cycle ergometer (Lode B.V, Medical Technology, Groeningen, Netherlands) was used. The spiroergometric system used (Metalyzer II, Cortex Biophysik GmbH, Leipzig, Germany have previously been tested against the Douglas-bag and iron lung (metabolic Calibration System, VacuMed, Ventura, CA) and has been found reliable and valid (20).

The Metalyzer II was calibrated prior to the first test each day using a standard two-point gas calibration procedure which included the following modifications: 1) measurements of ambient air and a gas mix (15.03% O_2 and 4.98% CO_2 in N2) (Scott Medical Products, Netherlands), 2) calibration on the Triple-V volume transducer with a calibrated 3 L syringe (Cortex Biophysik GmbH, Leipzig, Germany), 3) barometric pressure control. Before each test, the ambient room air was measured in addition to volume calibration, while two-point gas calibration took place every third test. The speed and incline of the test treadmill were calibrated prior to testing.

An individually adjusted 10-minute warm up was performed to prepare for testing and determine initial workload for CPET. The participants were given a detailed explanation of the test protocol and were instructed to avoid grabbing the handrails if not necessary for the duration of the test. Warm up was based on self-reported PA fitness level, HR monitoring, and feedback regarding perceived exertion (corresponding to 11-13 on BORG scale) (D34). After warm-up, participants were fitted an appropriate-sized face mask (Hans Rudolph, Germany) linked to the Metalyzer II before initiating the CPET.

The CPET included two sub maximal steady state measurements of three minutes each: 1) Initial workload determined during warm-up where a stable VO_2 and HR were reached after three minutes, and 2) Increased 1 km/h or 2% incline (treadmill)/25 watt (ergometer cycle) with a steady state obtained after 2-3 minutes. Workload progressively increased approximately every 60 seconds (treadmill)/every 30 seconds (ergometer cycle) with regards of an expected response of 6-10 beats$*$min^{-1} or 3-5 mL·kg^{-1}·min^{-1} in VO_2. The increase of workload continued until voluntarily exhaustion (e.g., shortness of breath or leg fatigue), or stopped prematurely due to safety reasons such as an observation of AHA's indications for test termination (20).

VO_{2max} was considered achieved if participants reached a VO_2 plateau that remained stable even with increased workload (i.e., VO_2 did not increase more than 2 mL·kg^{-1}·min^{-1} between two 30-second epochs), combined with a respiratory exchange ratio (RER) of 1.05 or higher. All other tests were considered VO_{2peak}. As 31% of the participants failed to reach VO_{2max}, the term VO_{2peak} will be used for all participants. Gas exchange variables were reported as 10-s averages. VO_{2peak} was calculated as the mean of the three highest consecutive 10-s measurements. V_E/VCO_2, V_{Epeak}, VCO_{2peak} and V_{Tpeak} were then determined by the three corresponding values.

Classification systems

The Weber (A to D) and ventilatory (VC-I to VC-IV) classification systems were used to present the possible difference in risks of cardiac related events within the same population dependent on which parameter was set as the prognostic marker. This was based on their individual values of either VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) or V_E/VCO_2 slope at baseline. Due to uneven sex distribution and the difference in correlation between age and the prognostic markers V_E/VCO_2 slope (r=0.128, p=0.185) and VO_{2peak} (r=-0.539, <0.001) at baseline, results regarding the classification systems were made without differentiating between sex or age groups. The specific cut off points for each category within the classification system are presented In Table 2.

Table 2: Categories within Weber and Ventilatory classification systems with associated cut-off point variables for VO_{2peak} and V_E/VCO_2.

Disease severity risk	**Weber (VO_{2peak})**		**Ventilatory (V_E/VCO_2)**	
Negligible	A	>20	VC-I	<29.9
Low	B	16-20	VC-II	30.0-35.9
Moderate	C	10-16	VC-III	36.0-44.9
High	D	<10	VC-IV	>45.0

Weber: classification system based on VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) values, Ventilatory: classification system based on V_E/VCO_2 slope ($L \cdot min^{-1}$) values, VO_{2peak}: peak oxygen consumption ($mL \cdot kg^{-1} \cdot min^{-1}$), V_E/VCO_2: minute ventilation-to-carbon dioxide production relationship ($L \cdot min^{-1}$).

Measurements of Supervised Exercise

Participants were encouraged to wear an electronic device (Amazfit Health Watch, Huami Information Technology Co., Ltd., Hefei, China) accompanied by an app (mobile application) for measuring PA. The amount of PA resulted in a Personalized Activity Index (PAI) score, which was based on the individual's age, sex, resting HR and maximal HR (4). This score was recommended to stay >100 throughout the trial. To estimate the effect of the supervised exercise, each participant within NorEx-focus (n=10) had eight months' worth of PAI data extracted from the corresponding web-portal, Midong Health

Platform. This data was analysed according to goal achievement categories set by NorEx: 1) High achievement: 100 PAI >23 days (75% of the time) during a month, 2) Medium achievement: 100 PAI for 15-23 days (50-74% of the time) during a month, 3) Low achievement: 100 PAI for <15 days (<50% of the time) during a month, and 4) Unknown achievement: Wore the watch <15 days during a month. The unknown achievement category was recorded as missing data. Additionally, before initiating the clinical examinations of the follow-up test, test participants filled out a questionnaire regarding their PA during the follow-up period. This was used supplementary to the collected PAI data to get additional information about the participants' exercise habits.

Statistical Analysis

Microsoft Excel version 16 was used to organize data during data collection and the Software program IBM SPSS, version 27 (Statistical Package for Social Science, Chicago, IL) was used for descriptive and statistical analyses. Both were in addition used for graphical presentation of results. To determine the association between the physiological variables, linear regression was applied with a 95% confidence interval, and a p-value of <0.05 was considered statistically significant. Pearson correlation was used to observe the relationship within variables and Paired Samples T-test was utilised to look at the differences from baseline to follow-up. One-Way ANOVA was used to determine statistically differences between groups. An independent Samples T-test was done to look at the level of significance between sex at baseline. All tests were two-sided. The results are presented as mean ± standard deviations.

Ethical Statement

NorEx was approved by the Regional committee for medical research ethics (REK 2019/797), the Norwegian Data Inspectorate and the National Directorate of Health and is in compliance with the Helsinki declaration. Additionally, NorEx is registered in the ClinicalTrials.gov registry (NCT0417639).

Result

A total of 109 Norwegian post-MI participants, aged 33-78, completed a valid CPET at baseline. Descriptive and physiological data associated with these participants are presented in Table 3-4 and Figure 2. In addition, ten NorEx-focus participants, aged 44-76, completed a valid CPET at follow-up after approximately eight months of supervised exercise. Descriptive, physiological and exercise data associated with NorEx-focus are presented in Table 5-7 and Figure 3-4.

Table 3. Descriptive characteristics of post-MI reference material participants at baseline.

Variables	All (n=109)	Men (n=86)	Women (n=23)
Age (yr.)	64.2±8.7	64.7±8.2	62.4±10.1
Height (cm)	176.1±7.9	178.9±6.0	165.8±5.2
Body mass (kg)	87.4±16.8	90.5±16.1	75.9±14.4
BMI ($kg \cdot m^{-2}$)	28.3±4.3	28.4±4.0	27.7±5.1

Data are presented as arithmetic mean ± SD. Abbreviations: n: sample size, BMI: body mass index.

Table 4. Peak CPET values on prognostic indicators and additional key cardiorespiratory variables in post-MI participants at baseline, stratified by sex.

Variables	All (n=109)	Men (n=86)	Women (n=23)
V_E/VCO_2 slope ($L \cdot min^{-1}$)	31.3±4.5	32.1±4.2	28.2±4.3
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	30.9±8.3	32.1±8.5	26.5±5.8
VO_{2peak} ($L \cdot min^{-1}$)	2.69±0.75	2.88±0.70	2.01±0.51
V_{Epeak} ($L \cdot min^{-1}$)	95.6±28.2	103.4±25.8	66.6±15.1
V_{Tpeak} ($V_E \cdot f_B^{-1}$)	2.28±0.51	2.44±0.42	1.67±0.37
VCO_{2peak} ($L \cdot min^{-1}$)	31.29±4.47	3.05±0.77	2.22±0.65

Data are presented as arithmetic mean ± SD. Abbreviations: n: sample size, V_E/VCO_2 slope: minute ventilation-to-carbon dioxide production relationship, VO_{2peak}: peak oxygen consumption, V_{Epeak}: peak minute ventilation, V_T: peak tidal volume, VCO_2: peak expired carbon dioxide.

Risks of Cardiac Related Events within Post-MI Participants at Baseline

Peak responses of prognostic indicator variables during CPET are presented among other key cardiorespiratory variables in Table 4. The relationship between V_E/VCO_2 slope and VO_{2peak} showed a weak negative non-significant correlation (r= -0.093, p= 0.336). Results showed consequently higher values obtained by men compared to women within both variables ($p<0.001$). Based on the participants' individual peak values at baseline, Figure 2 illustrates the distribution of baseline participants within the Weber and Ventilatory classification systems. Cut-off values within categories are presented in Table 2.

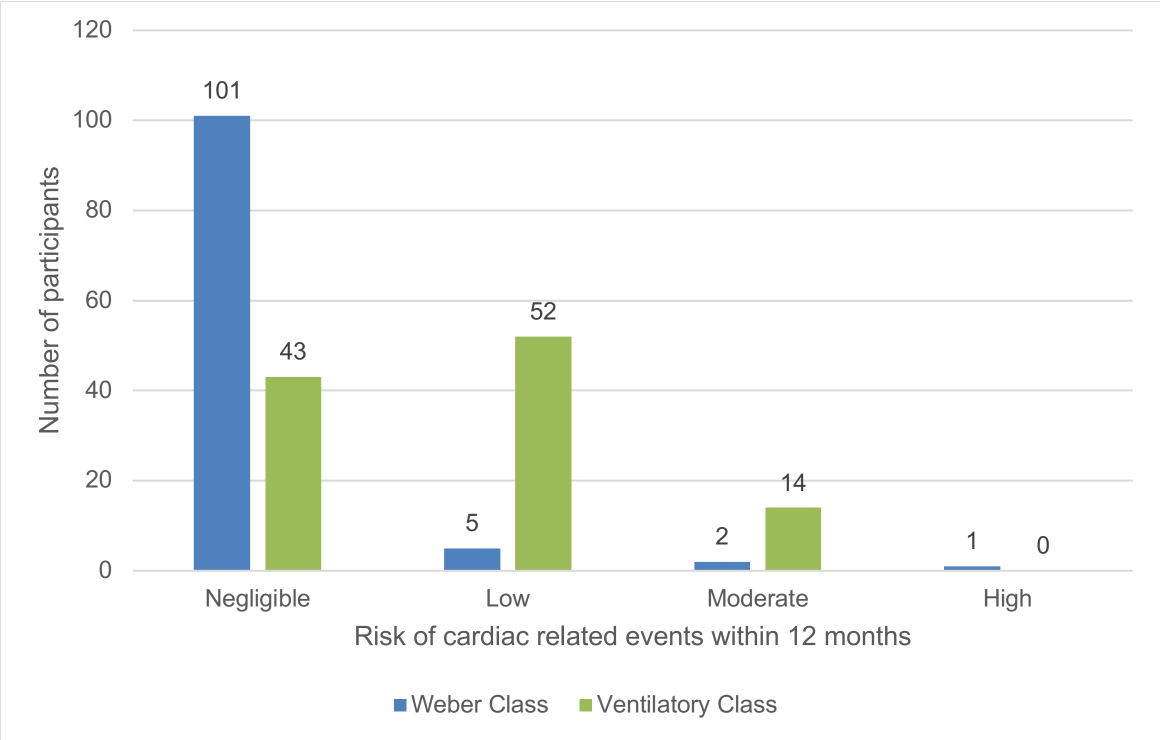

Figure 2: Norwegian post-myocardial infarction participants' risk of cardiac related events within 12 months stratified by Weber and Ventilatory classification systems at baseline. Negligible: Weber Class A with VO_{2peak} >20 $ml·kg^{-1}·min^{-1}$ or Ventilatory Class I with V_E/VCO_2 slope <29.9 $L·min^{-1}$, Low: Weber Class B with VO_{2peak} 16-19.9 $ml·kg^{-1}·min^{-1}$ or Ventilatory Class II with V_E/VCO_2 slope from 30.0 to 35.9 $L·min^{-1}$, Moderate: Weber Class C with VO_{2peak} 10-15.9 $ml·kg^{-1}·min^{-1}$ or Ventilatory Class III with V_E/VCO_2 slope from 36.0 to 44.9 $L·min^{-1}$, High: Weber Class D with VO_{2peak} <10 $L·min^{-1}$ or Ventilatory Class IV with V_E/VCO_2 slope >45.0 $L·min^{-1}$.

Changes in Key Cardiorespiratory Variables within NorEx-Focus Participants

Table 5: Descriptive characteristics of NorEx-focus participants at baseline and follow-up (n=10).

Variables	Baseline	Follow-up
Age (yr.)	62.8±9.8	63.8±9.8
Height (cm)	177.4±10.6	177.7±10.6
Body mass (kg)	90.1±14.3	89.5±14.7
BMI ($kg \cdot m^{-2}$)	28.9±4.4	28.5±4.6

Data are presented as arithmetic mean ± SD. Abbreviations: n: sample size, BMI: body mass index.

Table 6: Peak key cardiorespiratory variable values and prognostic marker values from baseline to follow-up after 8 months of supervised exercise (n=10).

Variables	Baseline	Follow-up	Change in Baseline to Follow-up
V_E/VCO_2 slope ($L \cdot min^{-1}$)	31.88±4.63	29.98±4.34	-1.91±1.72 [0.67-3.12] #
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	32.54±7.15	33.89±7.40	1.35±2.53 [CI: -3.16 to 0.46]
VO_{2peak} ($L \cdot min^{-1}$)	2.92±0.75	3.01±0.73	0.09±0.20 [CI: -0.23 to 0.52]
V_{Epeak} ($L \cdot min^{-1}$)	103.5±24.5	105.0±27.9	1.5±5.1 [CI: -5.1 to 2.2]
V_{Tpeak} ($V_E \cdot f_B^{-1}$)	2.31±0.43	2.41±0.49	0.10±0.15 [CI: -0.21 to 0.01]
VCO_{2peak} ($L \cdot min^{-1}$)	3.10±0.82	3.31±0.85	0.21±0.23 [CI: -0.38 to -0.05] #

Data are presented as arithmetic mean ± SD. Abbreviations: n: sample size, V_{Epeak}: peak minute ventilation, V_{Tpeak}: peak tidal volume, VCO_{2peak}: peak expired carbon dioxide, VO_{2peak}: peak oxygen uptake, V_E/VCO_2 slope: minute ventilation-to-carbon dioxide production relationship, #: Statistical difference of <0.05.

Table 6 demonstrates improvements in all mean values of key cardiorespiratory variables after eight months of supervised exercise. However, results regarding the V_E/VCO_2 slope and VCO_{2peak} were the only ones proved statistically significant ($p<0.05$). Nevertheless, the follow-up CPET showed a 1.4% ($p=0.373$) increase in V_{Epeak} and a 4.3% ($p=0.060$) increase in V_{Tpeak} when compared to baseline. Absolute VO_{2peak} ($L \cdot min^{-1}$) at follow-up showed a 3.1% ($p=0.185$) increase, while relative VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) at follow-up showed a 4.1% ($p=0.127$) increase when compared to baseline. V_E/VCO_2 slope at follow-up had decreased by 6% ($p<0.05$) when compared to baseline.

Changes in Risks of Cardiac Related Events within NorEx-Focus Participants

Due to the observed changes in V_E/VCO_2 slope and $VO2_{peak}$, the distribution of participants within the Weber and Ventilatory classification systems partially changed from baseline to follow-up. This change is illustrated in Figure 3 and 4. Additionally, a strong, negative correlation (r= -0.782, p<0.01) was found between changes in V_E/VCO_2 slope and changes in VO_{2peak} during follow-up.

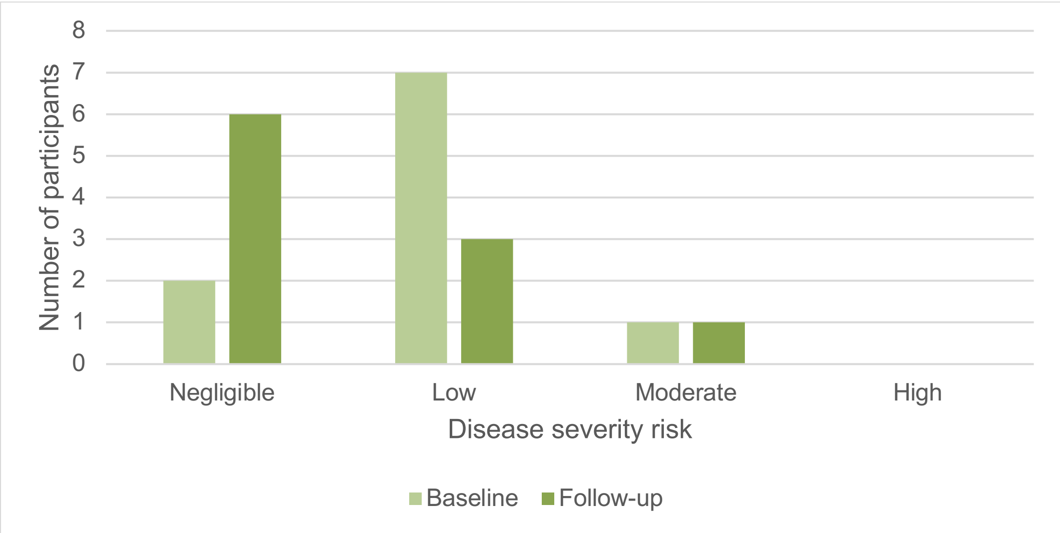

Figure 3: Distribution of NorEx-focus participants at baseline and follow-up after eight months of supervised exercise according to the Ventilatory classification system. Cut-off values within each category are presented in Table 2.

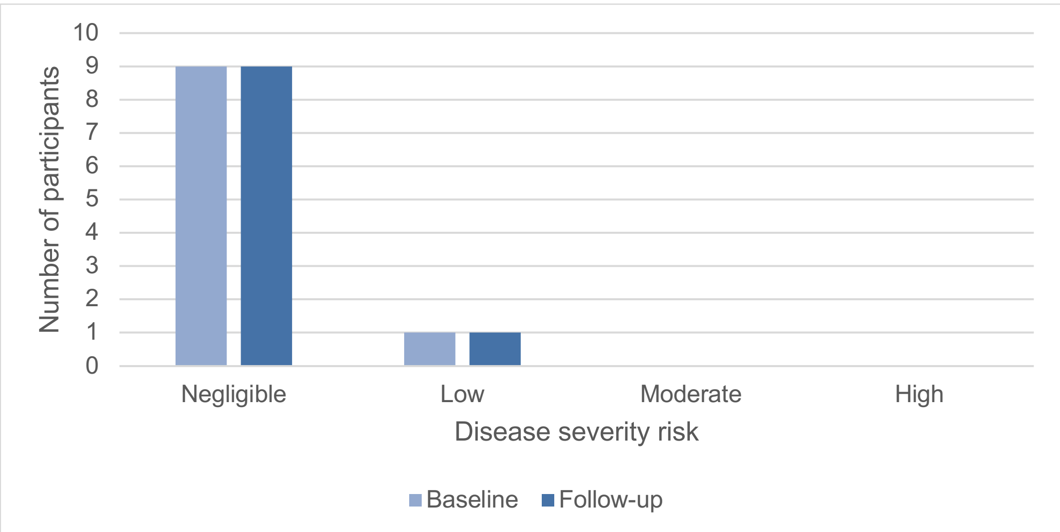

Figure 4. Distribution of NorEx-focus participants at baseline and follow-up after eight months of supervised exercise according to the Weber classification system. Cut-off values within each category are presented in Table 2.

Table 7: Individual data of NorEx-participants obtained from questionnaire, electronic device and CPET.

Participant	Frequency (times/wk.)	Intensity	Duration (minutes)	Activity	Amount (since pre-test)	GA	V_E/VCO_2 slope	VO_{2peak} $mL \cdot kg^{-1} \cdot min^{-}$
1	2-3	Low	30-60	Walk	More	Low	↓ 0,47	↓ 3,23
2	2-3	High	30-60	Run	Same	High	↓ 1,6	↑ 3,08
3	2-3	High	>60	Run	More	Low	↓ 0,4	↑ 0,85
4	2-3	High	30-60	HIIT	More	Low	↓ 4,57	↑ 4,66
5	>4	Moderate	30-60	Walk, run	Less	High	↓ 0,87	↑ 1,81
6	>4	Moderate	30-60	Walk, run	More	High	↓ 2,13	↑ 1,31
7	>4	Moderate	>60	Walk, run	Same	Medium	↓ 0,4	↑ 0,4
8	2-3	Moderate	>60	Walk, run	More	Low	↓ 3,27	↑ 2,8
9	2-3	Low	30-60	Walk	Same	Low	↓ 0,57	↓ 2,18
10	2-3	High	>60	HIIT	More	High	↓ 4,77	↑ 3,96

Abbreviations: CPET: cardiopulmonary exercise test, PAI: personal activity intelligence, GA: goal achievement as explained in *Methods*, V_E/VCO_2 slope: change in peak minute ventilation-to-carbon dioxide output ($L \cdot min^{-1}$) from baseline to follow-up, VO_{2peak}: change in peak oxygen consumption ($mL \cdot kg^{-1} \cdot min^{-1}$) from baseline to follow-up, HIIT: high intensity interval training.

Table 8. Correlation between the prognostic indicators, exercise data and goal achievement attained during exercise intervention.

	VE/VCO2 slope		**VO2peak**	
	r	**p**	**r**	**p**
Frequency	0.309	NS	-0.105	NS
Intensity	-0.530	NS	0.796	<0.05
Duration	-0.152	NS	0.228	NS
Activity	-0.721	<0.05	0.850	<.0.05
Amount	-0.475	NS	0.182	NS
GA	-0.177	NS	0.238	NS

Abbreviations: V_E/VCO_2 slope: minute ventilation-to-carbon dioxide production slope, VO_{2peak}: peak oxygen consumption ($mL \cdot kg^{-1} \cdot min^{-1}$), r: measure of strength between the linear relationship done by Pearson's correlation, p: probability, NS: results found non-significant ($p>0.05$).

Effect of Exercise on Prognostic Indicator Values among NorEx-Focus Participants

Table 7 demonstrates individual data obtained from questionnaire, electronic device and CPET. Improved ventilatory efficiency was observed among all (n=10/10) participants within NorEx-focus, while 80% (n=8/10) obtained increased relative VO_{2peak} at follow-up. Participants showing a decrease in VO_{2peak} reported low intensity training and walking as the main activity type in addition to attaining low goal achievement during the eight months of supervised exercise. The participants with the greatest improvements in VO_{2peak} and ventilatory efficiency, reported regular HIIT and an increase in exercise amount since baseline test.

Table 8 demonstrates the relationship between questionnaire data and changes within the prognostic indicators. Type of activity is the only variable found statistically significant within both prognostic indicators (<0.05). Exercise intensity was found statistically significant within the changes in VO_{2peak} ($p<0.05$).

Discussion

The main findings of the current study are 1) alleged risk of cardiac related event varies largely based on the prognostic indicator used among post-MI participants, 2) eight months of supervised exercise improved the mean of key cardiorespiratory variables 3) eight months of supervised exercise could improve prognostic indicator values and likely decrease the risk of cardiac related events within 12 months.

Risks of Cardiac Related Events within Post-MI Participants at Baseline

To the authors knowledge, no comparison has been made between the Weber and Ventilatory classification systems among MI participants. Both variables used within the classification systems have been associated with adverse events among MI populations (8, 15, 21, 22). However, VO_{2peak} seems to be the most studied and used variable within this context (8, 15, 21, 22). Nevertheless, comparisons between the two classification systems are widely explored among the HF population where it is found valuable for prognostic assessment (9, 10, 14, 17, 23). Both MI and HF are considered CVDs, where MI remains the most common cause of HF worldwide (24). Based on this possible connection, it may indicate that the Weber and Ventilatory classification systems could additionally provide prognostic indications on identifying subgroups at increased risk for adverse events among MI participants.

Within HF population, V_E/VCO_2 slope has previously been found to be prognostically superior when compared to VO_{2peak} (10). If the possible connection between HF and MI results in the same prognostic significance of the variables within MI, we could expect V_E/VCO_2 slope to be prognostically superior to VO_{2peak} within the MI population as well. Assuming the Ventilatory classification system has a higher reliability within its distribution, this might explain why when divided by the two systems the distribution within risk categories varies largely based on what parameter is set as the prognostic indicator. As previously demonstrated in Figure 2, division by the Weber system resulted in 93% of the participants risks for major cardiac events to be considered as negligible, while division by Ventilatory system only considered 39% of the same population's risks as negligible. As a result, underestimation of risks done by the Weber classification system could be assumed. This assumption could be further supported by research stating that individuals surviving MI are at high risk for recurrence, cardiac related hospitalisation or death (23, 25). Therefore, it seems counterintuitive to indicate negligible risk of cardiac related events among 93% of the post-MI participants.

The participants within this study experienced MI between 2013-2021. They were included minimum three months after hospitalisation when in stable condition. Other than that, no time frame of inclusion within their associated MI was given. The possible difference of eight years between index MI could have affected the prognostic indication among participants at baseline, and therefore also the distributions presented in this study. One potential factor worth mentioning is the time elapsed from a potential participation in cardiac rehabilitation. Research shows that participants partaking in cardiac rehabilitation 2-12 weeks after MI have an increased level of VO_{2peak} six months after ending the training period compared to baseline (21). However, a decrease in VO_{2peak} was seen among the same population at the 30-month follow-up suggesting discontinued training after ending the supervised training period (21). Considering this, the possibility of difference in time elapsed between initial MI to inclusion within this study may vary among participants and could be a factor influencing the measured variables and distributions within the current study.

Changes in Key Cardiorespiratory Variables within NorEx-Focus Participants

The heart and the lungs make up an inseparable anatomic and functional unit where changes in one affect the other. As a result, MI may yield several changes within the respiratory system (16). As outlined previously, the inefficient ventilatory response to exercise observed in heart disease is multifactorial (16). Structural changes in the lungs and pulmonary vasoconstriction are suggested responsible for the excessive ventilation observed, while occurrence of alterations in breathing patterns is associated with a lower rate of increase in V_T (16). Previous investigations have demonstrated resistive, elastic and viscoelastic changes among post-MI participants possibly resulted from alveolar, interstitial and intrabronchial oedema (26). However, several studies on MI participants and other CVD populations, have observed improvements in likely affected cardiorespiratory variables, after exercise intervention (16, 25, 27-31)This is in line with the findings of the current study as improvements within the cardiorespiratory variables measured were observed after exercise intervention. This suggest that worsening within cardiorespiratory variables due to MI could be modified with exercise interventions within the post-MI population.

Changes in Risks of Cardiac Related Events within NorEx-Focus Participants

As outlined previously, a strong negative correlation between the observed changes within the prognostic indicators was found. This could explain the decrease in V_E/VCO_2 slope seen in all participants while an increase in VO_{2peak} was seen simultaneously within 80% (n=8/10) of the participants. This is in line with previous observations of a strong relationship between an increase in CRF, defined by VO_{2peak}, and improvements in ventilatory efficiency after exercise interventions (31).

In the current study, eight months of supervised exercise led to partially changes within the distribution of risk due to the demonstrated improvements within the prognostic indicators.

When level of risk was stratified by the Weber Class, 90% (n=9/10) and 10% (n=1/10) of the participants at baseline were distributed in the negligible (A) and low (B) risk category, respectively. This distribution did not change at follow-up. Stratified by Ventilatory Class 20% (n=2/10), 70% (n=7/10) and 10% (n=1/10) of the participants at baseline were distributed in the negligible (VC-I), low (VC-II) and moderate (VC-III) risk category, respectively. At follow-up, 60% (n=6/10) and 30% (n=3/10) were now distributed in VC-I and VC-II, respectively, while VC-III remained the same. As a result, the distribution between the classification systems were more aligned at follow-up compared to baseline. A possible reason could be the previous suggested underestimation of risk among the Weber classification system. At follow-up, this could have resulted in the improved alignment within distribution as the risk of cardiac related events would be expected to decrease after an exercise intervention based on previous findings within HF population (9, 10, 14, 17, 23). Even though the study only observed changes in risk within one classification system, the findings could be of importance to further investigate methods to identify subgroups at increased risk for adverse events among post-MI participants. Considering the statistically prognostic power of the V_E/VCO_2 slope within other CVD populations (6), the positive change within its distribution of post-MI participants could possibly reduce the risk of adverse events occurring.

Effect of Exercise on Prognostic Indicator Values among NorEx-Focus Participants

The majority of the study population improved their prognostic indicator values during the exercise intervention. Analyses suggested the strongest association regarding both V_E/VCO_2 slope and VO_{2peak} was found in exercise modality, partially reflecting intensity. The changes within VO_{2peak} were also found to correlate strongly with exercise intensity. Exercise has previously been shown to improve cardiorespiratory variables and reduce the risk of cardiovascular and all-cause mortality in populations with CVDs (16, 25,29-32). Respective studies also suggest these outcomes particularly in connection with exercise at moderate or high intensities. Analyses done within the current study demonstrated an association between seemingly higher intensity exercise modalities with greater improvements within both prognostic indicators. Based on exercise intensity solely, an association was found between greater improvements of VO_{2peak} and higher intensity during exercise.

Following the exercise intervention within the current study, an increase in VO_{2peak} was observed in 80% (n=8/10) of the participants while all participants improved their ventilatory efficiency. On an individual level, subject 4 (+4.66 $mL \cdot kg^{-1} \cdot min^{-1}$) and subject 10 (+3.93 $mL \cdot kg^{-1} \cdot min^{-1}$) reported HIIT as exercise modality and a frequency of 2-3 exercise sessions per week. These subjects demonstrated the greatest improvements in both VO_{2peak} and V_E/VCO_2 slope among the participants. This type of exercise influences the given variables in accordance with previous research (D17, D25, D26). On the contrary, a decrease in VO_{2peak} was observed among subject 1 (-3.23 $mL \cdot kg^{-1} \cdot min^{-1}$) and subject 9 (-2.18 $mL \cdot kg^{-1} \cdot min^{-1}$). These participants reported low intensity exercise in combination with walking as their sole exercise modality, in addition to obtaining low goal achievement during the intervention period. These results are in accordance with previous studies investigating low intensity exercise and the impact on VO_{2peak} (28, 32).

When looking at the correlation between goal achievement and changes within prognostic indications, it is important to keep in mind that the goal achievements' cut-off value is 100 PAI with goal achievement categories based on PAI scores monthly. This means that if a participant consequently obtains 99 PAI every day throughout a month, he/she will score low goal achievement. On the other hand, if a participant obtains 100 PAI 23 days, and 0 PAI the rest of the month he/she will obtain high goal achievement. Considering this, basing goal achievement on shorter time periods compared to monthly could be of interest and possibly shown more reliable compared to the protocol used within the current study.

Strength and Limitations

The main strength of the current study is the sample size regarding key cardiorespiratory variables at baseline in addition to detailed information available on an individual level among the intervention population. 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. Intraclass correlation coefficient of 0.997 between test personnel was observed regarding height measurements within the same population. This suggest that the measurements done by these specific test personnel are reliable, even though only one variable was tested. Another major strength with the current study is that the changes within cardiorespiratory variables including prognostic indicators after eight months of supervised exercise, are measured directly among the same population. This includes the distribution within classification systems on NorEx-Focus. Another strength was the large amount of CPET variables on key cardiorespiratory variables obtained. This was presented to supplement the growing reference material on key cardiorespiratory variables for the Norwegian post-MI population.

The biggest limitation to the study is the lack of directly explored endpoints related to cardiac related events within 12 months. As a result of this, everything regarding the risk of cardiac related events is based on assumptions and observational data utilized from other populations. Another limitation is the low sample size within NorEx-Focus due to a large amount of postponed testing due to COVID-19. Performance of robust statistical analysis were as a result hard to execute. Additionally, the large representation of males compared to females within the current study is considered a limitation. The sole cut-off value of 100 PAI is considered a limitation as it can underestimate an individual's exercise data. Furthermore, the study had restricted access to any information about the participant's medical history or medication. As previously mentioned, this could e.g., be linked to the participant's potential participation in cardiac rehabilitation, possibly affecting the baseline values and distribution, as this participation is unknown within the population.

Conclusion

Assumed risk of cardiac related events within 12 months varies largely based on the prognostic indicator and classification system used among post-MI participants. Eight months of supervised exercise resulted in improvements within the V_E/VCO_2 slope and VO_{2peak}. The results of the current study therefore suggest that the exercise subscribed through NorEx could prevent cardiac related events within Norwegian post-MI participants by changing assigned risk category to one associated with lower risk. However, a larger sample size is crucial to determine the actual effect of exercise's influence on the cardiorespiratory variables. Further research on post-MI participants and the prognostic indication of V_E/VCO_2 and VO_{2peak} is needed.

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