UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

**PhD thesis**

Nicolai Mikkelsen

# Novel predictors for the effect of cardiac rehabilitation and consequence for long-term outcomes

Results from a cardiac rehabilitation program in Copenhagen

Supervisors: Eva Prescott, Hanne Rasmusen

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U N I V E R S I T Y  O F  C O P E N H A G E N
F A C U L T Y  O F  H E A L T H  A N D  M E D I C A L  S C I E N C E S

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# Novel predictors for the effect of cardiac rehabilitation and consequence for long-term outcomes

## Results from a cardiac rehabilitation program in Copenhagen

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# Table of contents

# Papers included in the thesis

**Depression, Socioeconomic Factors, and Ethnicity as Predictors of Cardiorespiratory Fitness Before and After Cardiac Rehabilitation**. *Mikkelsen N, Dall CH, Frederiksen M, Holdgaard A, Rasmusen H, Prescott E.*. <u>J Cardiopulm Rehabil Prev.</u> 2018 Nov 27. doi: 10.1097/HCR.0000000000000367

**II: The motivation for physical activity is a predictor of $VO_{2peak}$ and is a useful parameter when determining the need for cardiac rehabilitation in an elderly cardiac population**
*Nicolai Mikkelsen, Christian H. Dall, Marianne Frederiksen, Annette Holdgaard, Hanne Rasmusen, Eva Prescott. Not submitted yet.* <u>*Waiting on the main study from the EU-CaRE project to be published before this article can be submitted*</u>

**III: Improvement in $VO_{2peak}$ predicts readmissions for CVD and mortality in patients undergoing cardiac rehabilitation**
*Nicolai Mikkelsen, Carmen Cadarso-Suárez, Oscar Lado-Baleato, Carla Díaz-Louzao, Carlos Peña Gil, Jacob Reeh, Hanne Rasmusen, Eva Prescott.* <u>*Submitted for European Journal of Preventive Cardiology, June 2019*</u>

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*I dedicate this PhD dissertation to my father **Finn Mikkelsen***

Nicolai Mikkelsen
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# Summary

**Background**
Cardiac rehabilitation (CR) is an essential part of recovery for patients with cardiovascular disease (CVD). One of the main components of CR is exercise training which aims at improving $VO_{2peak}$. Unfortunately, not all patients benefit equally from CR, and especially socioeconomic and psychological factors affect participation and adherence to CR. Socioeconomic status and psychological distress, especially depression, are associated with worse health outcomes in cardiac patients. Another important psychological factor in CR is level of motivation, and it is unclear how motivation influences the effects of CR.
Participation in a CR programme is associated with a better prognosis, but whether long-term cardiac outcomes can also be predicted by the short-term effects of CR among participants in a CR programme is uncertain.
**Objectives**
The main objectives of this thesis are:

1. To assess if socioeconomic factors and psychological distress are predictive factors of $VO_{2peak}$ before CR and whether they affect the change in $VO_{2peak}$ after CR;
2. To investigate whether motivation, measured with the Behavioral Regulation in Exercise Questionnaire (BREQ-2), predicts $VO_{2peak}$ and change in $VO_{2peak}$ after CR in elderly patients with CVD or valvular heart disease;
3. To assess whether $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR predicts future readmissions for CVD and all-cause mortality.

**Methods**
The 1st objective was addressed with two retrospective studies using a local clinical database from the CR unit in Copenhagen between 1/1/2011 to 30/12/2015. The 3rd objective was answered using the same database from 1/1/2011 to 30/12/2017. The 2nd objective was answered using data from the Danish part of the prospective EU-CaRE multi-center cohort study (1) on elderly cardiac patients in Europe.
Patients participated in an 8-week exercise-based CR program in Copenhagen with two weekly exercise sessions and weekly group-based patient educations.
Socioeconomic status was measured according to educational attainment and working status. Ethnicity was assessed as Western or non-Western European. Depression was measured with patients' self-reported use of antidepressants (pre-existing) and positive depression score in the beginning of CR (newly developed). Motivation was measured with the BREQ-2 which measures five constructs of motivation from external to internal motivation, complemented with a summed score of the five constructs.
$VO_{2peak}$ was measured with a cardiopulmonary exercise test before and after CR. Risk of CVD readmissions was assessed using the Danish National Patient Register and all-cause mortality was assessed using the Danish Civil registration system.
Multiple adjusted linear regression analyses were applied to evaluate the impact of primary exposures on $VO_{2peak}$.
The risk of suffering a new cardiovascular readmission or all-cause mortality were assessed using Cox-proportional hazards and multi-state models.

**Results**
**Paper I**. During 1/1/2011 and 30/12/2015, 1217 and 861 patients had full data from baseline and follow-up analyses, respectively. Mean age was 61.3 years, $VO_{2peak}$ before CR was 21.8 (SD±6.8)

ml/kg/min, and mean improvement following CR was 2.4 (SD±4.3) ml/kg/min. Educational attainment, working status and ethnicity were highly predictive for both $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR, even after adjustment for age, sex, comorbidities and baseline $VO_{2peak}$. However, depression did not affect either $VO_{2peak}$ before CR or change in $VO_{2peak}$.

**Paper II**. 203 patients were included in the study, and 182 patients completed CR. Mean age was 72 years, $VO_{2peak}$ before CR was 18 ml/kg/min (SD±5.1) and improvement from CR was 2.3 ml/kg/min (SD±4.3). $VO_{2peak}$ increased significantly with a higher summed motivation score of 1.02 (.41 - 1.62) ml/kg/min pr. SD, even after adjustment for age, sex, depression, and comorbidities. Improvement in $VO_{2peak}$ was also associated with increased motivation, .74 (.31 - 1.17) pr. SD.

**Paper III**. During 1/1/2011 and 30/12/2017, 1561 patients completed CR with full data. In Cox regression, higher baseline $VO_{2peak}$, as well as change in $VO_{2peak}$ were highly associated with a decreased risk of MACE and all-cause mortality. Applying a multistate model, both $VO_{2peak}$ before CR and change in $VO_{2peak}$ were associated in a non-linear trend with the risk of readmissions for CVD and all-cause mortality. However, if suffering a new readmission for CVD, $VO_{2peak}$ was no longer a predictor for risk of mortality.

**Conclusions**

Socioeconomic status and ethnicity predict how cardiac patients benefit from CR in terms of improvement in $VO_{2peak}$. Motivation also predicts $VO_{2peak}$ and the BREQ-2 questionnaire can be applied to detect patients with a lower $VO_{2peak}$ and those who increase less in $VO_{2peak}$ after CR. The unequal improvement in $VO_{2peak}$ affects the patients' risks of future MACE, cardiovascular readmissions and all-cause mortality. The protective factor of $VO_{2peak}$ seems to last until the time of a new CVD readmission. This could indicate the need for a new CR intervention.

Our results identify groups of patients that need special attention when attending CR. CR programs should consider the socioeconomic, ethnic and psychological barriers to exercise when including patients in a program.

# Dansk resume (Danish summary)

**Baggrund**

Hjerterehabilitering er en essentiel del af genoptræningen hos patienter med hjerte-kar-sygdomme. Træning med formål at forbedre iltoptagelsen er en af hovedkomponenterne i hjerterehabiliteringen. Det er kendt, at ikke alle hjertepatienter profiterer lige godt af rehabilitering, og at især socioøkonomiske og psykologiske faktorer påvirker både deltagelse og gennemførelse af et rehabiliteringsforløb.

Hjertepatienter med lav socioøkonomisk status og psykiske lidelser, herunder især depression, er forbundet med forværring af fremtidigt helbred sammenlignet med hjertepatienter uden psykiske lidelser og med højere socioøkonomisk status.

Motivation er en anden vigtig psykologisk faktor i rehabilitering. Det vides ikke, hvorvidt motivationsfaktoren påvirker effekten af hjerterehabilitering.

Flere studier har vist, at patienter, der deltager i rehabilitering, har svært ved at vedligeholde effekten heraf, og det er endnu uvist, hvorvidt der er en sammenhæng mellem ændringer i iltoptagelse efter rehabilitering og fremtidig hjerte-kar-sygdom samt dødelighed.

**Formål**

Formålet med denne afhandling er:

1. At undersøge, om der er en sammenhæng mellem socioøkonomisk status, etnicitet og depression ift. iltoptagelse før rehabilitering, samt hvorvidt disse kan påvirke ændring i iltoptagelse efter rehabilitering.

2. At undersøge om motivation, målt med et validereret motivationsspørgeskema (BREQ-2), kan forudsige iltoptagelse før rehabilitering samt ændring i iltoptagelse efter rehabilitering hos ældre patienter med hjerte-kar-sygdom eller hjerteklapsygdom.

3. At undersøge om iltoptagelsen før hjerterehabilitering og ændring i iltoptagelse efter rehabilitering kan prædiktere fremtidige genindlæggelser grundet hjerte-kar-sygdom samt prædiktere dødelighed.

**Metode**
Det første og tredje formål blev besvaret ved to retrospektive studier, hvor data blev ekstraheret i perioden år 2011-2018 fra en klinisk database fra hjerterehabiliteringsenheden på Bispebjerg/Frederiksberg Hospital.
Det andet formål blev besvaret gennem en prospektiv kohorteundersøgelse, den danske kohorte i EU-CaRE- et multi-center studie om ældre hjertepatienter i Europa. I den danske kohorte deltog alle patienter i et otte ugers hjerterehabiliteringsprogram på Bispebjerg/Frederiksberg hospital med to ugentlige træningssessioner og ugentlige gruppebaserede patientuddannelsessessioner.
I denne afhandling er betegnelsen socioøkonomisk status anvendt som surrogat for uddannelsesniveau og arbejdsstatus. Etnicitet er defineret som vesteuropæisk etnicitet eller ikke vesteuropæisk etnicitet. Forudgående depression samt nyudviklet depression blev hhv. målt ved data over brug af antidepressiv medicin (forudgående depression) samt ved en positiv score på et modificeret spørgeskema til vurdering af depression (nyudviklet depression). Motivation blev målt med et motivationsspørgeskema (BREQ-2), der måler fem typer af motivation fra ekstern til intern motivation, komplimenteret med en samlet score af de fem motivationstyper.
Iltoptagelsen blev målt, jf. gold standard, med en maksimal iltoptagelsestest før og efter rehabilitering. Oplysninger om indlæggelse med hjerte-kar-sygdom samt død efter rehabilitering blev indhentet fra nationale registre.

**Resultater**
**Artikel I.** Fra d. 1/1/2011 til d. 30/12/2015 gennemførte henholdsvis 1217 og 861 patienter opstart og afslutningen af deres rehabiliteringsprogram. Den gennemsnitlige alder var 61,3 år, iltoptagelsen før rehabilitering var 21,8 (SD ± 6,8) ml/kg/min, og patienterne forbedrede sig 2,4 (SD ± 4,3) ml/kg/min i gennemsnit. Uddannelsesniveau, arbejdsstatus og etnicitet havde en signifikant sammenhæng med iltoptagelsen før og efter rehabilitering, også efter der var justeret for alder, køn, komorbiditet og iltoptagelsen før rehabilitering. Depression var imidlertid ikke associeret med iltoptagelsen, hverken før eller efter hjerterehabiliteringsprogrammet.
**Artikel II.** 203 patienter blev inkluderet i undersøgelsen og 182 patienter gennemførte rehabiliteringsprogrammet. Den gennemsnitlige alder var 72 år, iltoptagelsen før rehabilitering var 18 ml/kg/min (SD ± 5,1), og forbedringen efter rehabilitering var 2,3 ml/kg/min (SD ± 4,3). Der var en positiv sammenhæng mellem iltoptagelse og motivationsscore, 1,02 (.41-1,62) ml/kg/min pr. SD, selv efter justering for alder, køn, depression og komorbiditeter. Der var også en positiv sammenhæng mellem iltoptagelse og højere motivationsscore, .74 (.31 - 1.17) pr. SD.
**Artikel III.** I perioden fra 1/1/2011 til 30/12/2017 var der 1561 patienter, der gennemførte hjerterehabilitering. Højere iltoptagelse, både før og efter rehabilitering, var associeret med lavere risiko for MACE og risiko for død. Ved anvendelse af en multi-state-model var iltoptagelsen, både

før og efter rehabilitering, forbundet med en ikke-lineær sammenhæng med risiko for genindlæggelser med hjertekarsygdom og risiko for død. Hvis patienter blev genindlagt med hjertekarsygdom, var iltoptagelsen ikke længere en prædiktor for risiko for død.

**Konklusioner**

Socioøkonomisk status og etnicitet prædikterer, hvordan hjertepatienter formår at forbedre iltoptagelsen i et rehabiliteringsforløb. Motivation kan ligeledes prædiktere ændring i iltoptagelse, og BREQ-2 spørgeskemaet kan anvendes som et redskab til at detektere patienter med lavere iltoptagelse, både før og efter rehabilitering.

Forskelle, både i iltoptagelsen før opstart i rehabilitering samt ændring i iltoptagelse efter rehabilitering, påvirker patienternes risici for fremtidig kardiovaskulær genindlæggelse og risiko for død. Iltoptagelsens beskyttende faktor synes at vare indtil tidspunktet for en ny kardiovaskulær genindlæggelse, hvorefter det ikke længere prædikterer risiko for død. Dette kunne indikere et fornyet behov for rehabilitering.

Vi har identificeret patientgrupper, der har et særlig behov for opmærksomhed, når de henvender sig i hjerterehabilitering. De socioøkonomiske, etniske og psykologiske barrierer for fysisk aktivitet og rehabilitering bør blive identificeret og behandlet, når patienterne møder til rehabilitering.

# Abbreviations

| | |
|---|---|
| BMI | Body mass index |
| CAD | Coronary artery disease |
| CHF | Chronic heart failure |
| CPET | Cardiopulmonary exercise test |
| CR | Cardiac rehabilitation |
| CVD | Cardiovascular disease |
| CABG | Coronary artery bypass grafting |
| PCI | Percutaneous coronary intervention |
| SES | Socioeconomic status |
| $VO_{2peak}$ | Peak oxygen uptake per kilogram per minute (ml/kg/min) |

# Background

## Cardiovascular disease

Cardiovascular disease (CVD) is accountable for nearly 4 million deaths in Europe each year, equivalent to approximately 45% of all deaths (2). More people die from CVD than any other disease. Ischemic heart disease is the most common CVD and is the single leading cause of mortality, as it is responsible for 19% of all deaths (3).

The risk of developing CVD stems from an interplay between genetics and lifestyle factors (4), and lifestyle factors are estimated to account for approximately 50% of the total risk (5).

Age-adjusted CVD mortality rates have been decreasing recent decades. The decrease in mortality rates can be attributed to a combination of preventive interventions to avoid diseases, early treatment to prevent death during acute events (heart attacks and strokes), and treatment to prevent recurring events and prolong the lives of people with prior CVD. Reductions in modifiable CVD risk factors are estimated to contribute as much as 50% to an observed decrease in mortality from CVDs, reflecting a combined impact of population interventions to reduce risk factors and clinical treatments (3, 6). This shift also means that the prevalence of patients living with CVDs is increasing (7).

Secondary CVD prevention is an organized process, where cardiac rehabilitation (CR) is included, which aims to minimize the impact of CVD and related impairments (8, 9). Secondary prevention should begin when patients are still admitted to the hospital; however, most patients are not referred and do not participate in secondary prevention (10, 11).

One major component of secondary prevention is CR. Most studies show that participating in a CR program decreases the risk of future cardiovascular events, cardiovascular mortality and all-cause mortality in patients with CVD. A Cochrane review from 2016 investigating the effects of CR was able to include 63 studies and 14,486 patients with CVD (12). During 12 months of follow-up, the risk of cardiovascular mortality decreased by 0.74 (95% CI: 0.64 - 0.86) and hospital readmission for CVD of 0.82 (95% CI: 0.70 - 0.96) in patients participating in CR (12). No effect was seen on all-cause mortality. The majority of the included patients were low-risk and younger males. Therefore, the decreased risks observed may not be generalizable to all patients with CVD. It should also be stressed that a follow-up time of 12 months depicts a rather short-term effect on the future risk of mortality and morbidity.

Patients with CHF also seem to benefit from CR. A recent systematic review and meta-analysis of 33 studies and 4740 patients with CHF found that patients that participated in improved significantly on clinical outcomes. At 12 months of follow-up, there was a reduction in heart failure-related readmissions in patients who participated in CR, and health-related quality of life was significantly better (13). Despite the effects in clinical outcomes, CHF patients participating in CR did not have a decreased risk of mortality.

In patients with valvular heart disease, CR has been shown to improve $VO_{2peak}$. However, further studies on clinical outcomes and quality of life need to be performed (14).

## Cardiac rehabilitation (CR)

CR falls into three phases: Phase I: during hospitalization, Phase II: outpatient CR in the hospital and local management, and Phase III: follow-up and maintenance in the primary sector (15). In this thesis, the focus is on Phase II CR.

CR is a multidisciplinary and multifaceted intervention for patients with heart disease. CR aims to improve physical fitness, recovery and psychological health (16) and is recommended by the European Society of Cardiology and the American Association of Cardiology as a Class 1 level of evidence A recommendation in treatment and as secondary prevention of CVDs (17, 18). Rehabilitation of cardiac patients aims to improve the patient's functional level, remove or reduce activity-related symptoms, minimize the degree of disability and allow the heart patient to return to a personally satisfactory role in society (19, 20).

*A CR program should include the following (21-23):*

- Patient assessment
- Counselling on physical activity
- Exercise training
- Strength training
- Nutritional counselling
- Risk factor assessment
- Education
- Management of psychological distress

## $VO_{2peak}$ and health prognosis

A key component of CR is exercise training with the purpose of increasing exercise capacity. Maximum exercise capacity is defined as the maximum amount of physical effort a person can perform, and is measured as $VO_{2peak}$, which indicates physical cardiorespiratory fitness (24).
The association between $VO_{2peak}$ and health outcomes was studied for decades. In 1989, in a study performed by Blair et al. on healthy individuals, they discovered a strong association between the level of $VO_{2peak}$ and all-cause mortality (25) (see figure 1). $VO_{2peak}$ has since been shown to be one the leading risk factors for CVD and a significant prognostic marker (26-28).
The inverse association between $VO_{2peak}$ and risk of mortality appears in populations with and without CVD (29), and is supported by a recent meta-analysis that compiled more than 30 randomized trials (30).

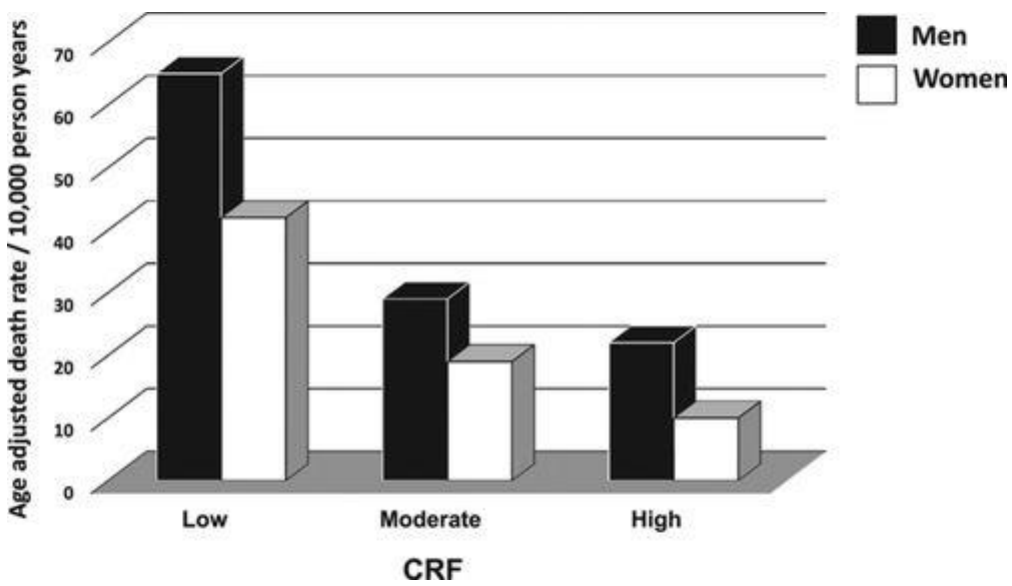


**Figure 1: All-cause death rates across categories of cardio-respiratory fitness (CRF) in 3120 women and 10 224 men. Blair et al (1989)**

## Assessing $VO_{2peak}$ in CR

The "gold standard" of measuring $VO_{2peak}$ is a symptom-limited cardiopulmonary exercise test (CPET), and this test is recommended both for safety and to measure the effect of CR (15, 31-33). It is appropriate to measure $VO_{2peak}$ with a CPET because of its precision, and because $VO_{2peak}$ is a reliable individual predictor of future health outcomes such as CVD and mortality (30, 34-36).
Due to the precision and high predictive value of the CPET, it is frequently applied to assess the individual level of $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR as a parameter of the effectiveness of a CR program. The precision of the test also makes it a recommendable test for clinical research on exercise capacity.
Little research has investigated the long-term prognosis of patients participating in and completing a CR program in relation to how they benefit during CR in, terms of improvement in $VO_{2peak}$. Persistence of exercise training has been shown to decrease significantly following CR, and up to 80% of cardiac patients fail to maintain their physical activity level after CR (37, 38). The variability of sustained improvement in $VO_{2peak}$ makes it unclear whether a stronger effect of exercise training during CR affects the long-term health prognosis.

## Socioeconomic status, CVD and CR

Lower socioeconomic status (SES) is associated with a higher risk of CVD and premature mortality (39-41).
SES is often defined according to levels of income, educational attainment, or employment status (42). There are advantages and disadvantages to using any of these parameters. In cardiac patients, income may not the optimal parameter, as many cardiac patients are retired, which likely changes income significantly. It can also be problematic to determine causality between income and disease; low income can cause a disease, and low income can be caused *by* a disease (43). Employment status also carries important information in terms of being a part of the labour market, on sick leave or unemployed. However, it carries the same causality paradox. In contrast, educational attainment is only marginally influenced by reverse causality. Education is furthermore likely to influence the type of employment and thereby the level of income, augmenting the reason for applying educational attainment (42) (see figure 2).

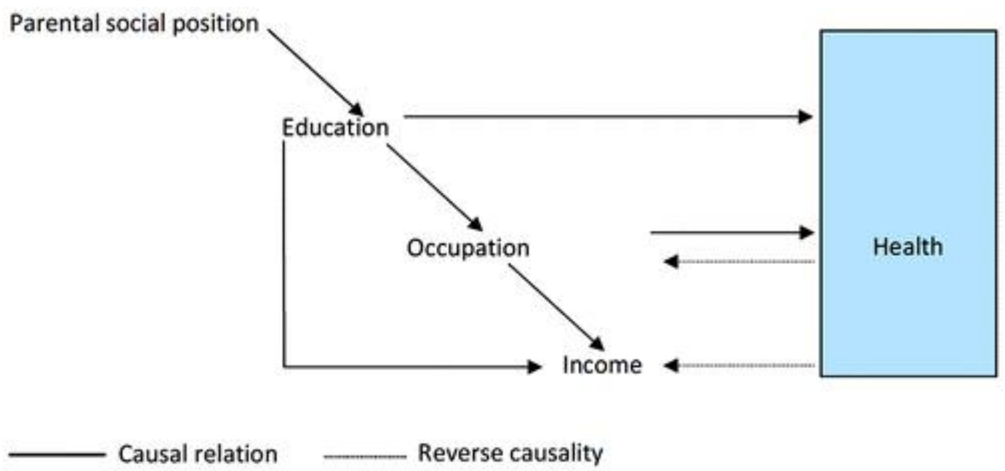


**Figure 2** Social position and health and relevant causal mechanisms (from Yngve et al, 2005 (43))

Diderichsen et al. (2001) proposed a model describing how socially deprived populations are at an increased risk of disease (see figure 3). The model defines five causal mechanisms between social positions and skewed health outcomes (44). The arrows in this figure indicate causal pathways. Elements such as heritage, ethnicity and education affect social positions, leading to adverse health behaviors and a skewed risk of disease.
Educational attainment is the predominant indicator of SES in cardiovascular research (45), and there is extensive evidence linking lower levels of education with higher CVD risk and mortality (46-48).

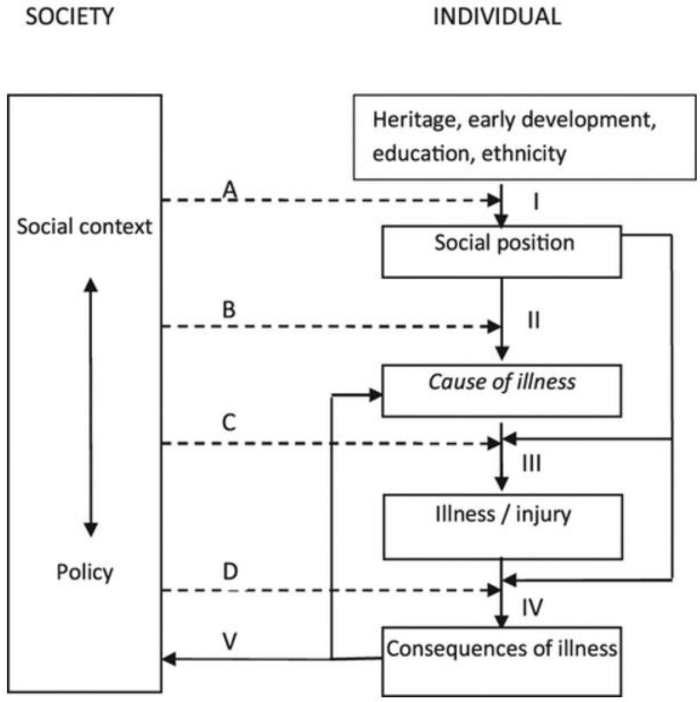


**Figure 3: The social basis of disparities in health. Diderichsen et al (2001)**

The EUROpean Action on Secondary Prevention by Intervention to Reduce Events recently confirmed that cardiac patients with lower educational attainment are at greater risk of unhealthy behavior (EUROASPIRE IV study) (49, 50). This socioeconomic gradient in cardiac risk factors (and $VO_{2peak}$) indicates a greater need for secondary prevention including CR among the socioeconomically deprived. Despite the greater need for secondary prevention, several studies have found that patients with lower SES tend to participate less in CR (51-53).
In the face of the well-known socioeconomic disparities that exist up until CR, it is unknown whether these influences how patients benefit from a CR intervention in terms of the ability to increase their $VO_{2peak}$.

## Depression in cardiac patients

The importance of psychological health for both primary and secondary risk of CVD has gained attention in recent decades, primarily due to emerging evidence of the association between psychological distress and risk of cardiovascular disease (54, 55). Depression is an important psychological parameter that has been shown to alter the risk of incident and secondary risk of CVD (54, 55). Approximately 20% of patients with CVD have symptoms of depression, and in cardiac patients, depression is associated with progression of CVD (54, 56). Moreover, depression

developed due to CVD is associated with poor health-related quality of life and recurrent cardiac events and mortality, independent of other medical and demographic characteristics (56).
The evidence is conflicting regarding how depression affects participation in CR (57-59). It is of concern that patients with depression who do participate in CR have a lower adherence and are more likely to drop out of the CR program (59, 60).
The higher risk of recurrent events and lower quality of life provides evidence that cardiac patients with symptoms of depression are in particular need of CR. CR has indeed been shown to have a positive effect on symptoms of depression, and a reduction in depression has been shown to be associated with improvement in $VO_{2peak}$ (61). As it is a demonstrated inequality for depressive cardiac patients attending CR, there is a need to address whether depression has an influence on how cardiac patients benefit from CR in terms of improving $VO_{2peak}$.

## Motivation to do exercise in cardiac patients

Motivation to be physically active is a key concept in several theories and models that explain healthy behaviors (62-65). One of these theories is the Self Determination Theory. The Self Determination Theory concerns levels of motivation and applies an appropriate framework when studying exercise behaviour (66). According to the Self Determination Theory, there are two major psychological forces that motivate a person to do exercise: intrinsic and extrinsic motivation (66). Intrinsic motivation means engaging in an activity due to the inherent pleasure and satisfaction that it provides. In contrast, extrinsic motivation concerns activities that are performed to receive an award, avoid punishment, or to please somebody else. The type of motivation a patient is guided by prior to a CR program may have an influence on how successful the rehabilitation will be, both in the short and long term.
Motivation in cardiac patients is a relevant and sparsely studied psychological aspect in relation to CR, and it is plausible that lack of motivation partly explains poor compliance and adherence in some cardiac patients.
It is yet to be examined whether level of motivation to do exercise prior to CR has an impact on cardiac patients' physical capacity following rehabilitation.
If a screening of level of motivation to exercise can predict the outcome of CR, it will be possible to detect patients that have a lack of motivation, allowing for differentiation of treatment for these patients.

## Rationale for conducting this thesis

As mentioned in the introduction, CR is an important part of secondary prevention in cardiac patients. CR improves health prognosis and increases quality of life for patients living with CVD. However, there are socioeconomic and psychological factors that influence cardiac patients' health behaviour and thus their future health. Most outpatient CR programs are group-based interventions where patients are offered approximately the same intervention. It is plausible that patients who have different points of departure in terms of SES, different ethnicities and different levels of motivation will experience an unequal benefit of participating in CR. Since exercise training is a main component of CR, it is relevant to examine whether there is an unequal effect of CR in terms of $VO_{2peak}$ between the aforementioned patient groups.
The prognostic value of $VO_{2peak}$ in terms of future risk of mortality and morbidity is well documented; however, it is still unclear whether the ability to change $VO_{2peak}$ during CR is only an immediate effect, or whether this change also affects future risk of mortality and morbidity, in which case inequalities in the effects of CR are even more important to address.

# Aims

**Paper I**

- To investigate if depression, socioeconomic factors and ethnicity influenced $VO_{2peak}$ before CR
- To investigate if depression, socioeconomic factors and ethnicity influenced change in $VO_{2peak}$ following CR

**Paper II**

- To investigate the association between level and type of motivation and level of $VO_{2peak}$ before and after CR

**Paper III**

- To examine the predictive value of $VO_{2peak}$ measured before CR in terms of risk of future cardiovascular readmissions and all-cause mortality
- To examine whether a successful CR, measured as change in $VO_{2peak}$, was a predictor of future cardiovascular readmissions and all-cause mortality

# Methods and design

## Study setting

The CR intervention about which the studies were performed was located at the CR unit at Bispebjerg/Frederiksberg Hospital in Copenhagen.

## Cardiac rehabilitation program at Bispebjerg/Frederiksberg Hospital

Cardiac patients were examined by a rehabilitation cardiologist when they attended the CR unit and the cardiologist evaluated whether the patient could participate in rehabilitation. The patients were also consulted by a nurse, a dietitian and a physiotherapist before rehabilitation was initiated.
The patients then participated in a group-based 8-week outpatient intervention consisting of two weekly exercise sessions of 1.5 hours and one weekly group-based education session. The exercise training consisted of high intensity interval training and strength training.

## Cardiopulmonary exercise test

Cardiorespiratory fitness was assessed using a cardiopulmonary exercise test (CPET) with measurement of $VO_{2peak}$ using a maximal symptom limited bicycle ergometer test (Via Sprint 150P, Ergoline, Germany). Breathing gases were collected and analysed (Jaeger, Master Screen CPX vers.5.21, Cardinal Health, Germany).
The CPET is the “gold standard” within physical capacity testing, and it is a valid and reliable exercise test to measure physical capacity (67). The CPETs were performed with a ramp protocol and patients were tested with the same ramp before and after CR. The patients were encouraged to continue until exhaustion and all tests aimed for a respiratory exchange ratio of > 1.1 and BORG scale of (6-20) > 17 to ensure the validity of the tests (33).

## EU-CaRE study

My colleague Annette Holdgaard and I conducted the Danish part of the EU-CaRE study. EU-CaRE was a multicentre cohort study and a multicentre tele-monitored RCT study (1). We included 239 cardiac patients in the cohort study and tested them pre- and post-rehabilitation. We then performed monthly telephone calls to collect data on care consumption and adverse events. Lastly, we performed a one-year follow-up test. In the RCT study, we included 43 patients who were randomized to controls with no intervention or a six-month tele-monitored intervention consisting of exercise training of their own choice where the training data was uploaded to us. This was supplemented by telephone-based motivational calls. The RCT is not included in this thesis.

## Study populations

#### Paper I and III

Data on the patients who were offered CR at the rehabilitation center at Bispebjerg/Frederiksberg hospital in the period 2011-2018 was entered in a clinical data registry. The registry includes patients diagnosed with STEMI, NSTEMI, unstable or stable angina pectoris, as well as patients who have been revascularized (PCI or CABG), and who have chronic heart failure or intervention for valvular heart disease (TAVI or open surgery).
Data was collected consecutively during visitations and consultations by cardiologists, nurses and physiotherapists. The registry contains clinical and demographic data, including: cardiac diagnosis, $VO_{2peak}$, demographic information, ethnicity, working status at time of cardiac event, educational attainment, living situation (alone or with a spouse), psychological status, co-morbidities, medicine, and blood samples.

**Table 1: Cardiac patients that accepted and completed CR from 2011-2018**

| *Cardiac diagnosis* | *Accepted CR* | *Completed CR* |
|---|---|---|
| *STEMI* | 571 (24%) | 381 (24%) |
| *N-STEMI* | 554 (23%) | 376 (24%) |
| *Unstable angina pectoris* | 201 (8%) | 166 (10%) |
| *Stable angina pectoris* | 557 (23%) | 381 (25%) |
| *CHF* | 156 (8%) | 91 (6%) |
| *Valvular heart disease* | 341 (14%) | 166 (10%) |
| *Total* | 2380 | 1561 |

*Abbreviations: STEMI: ST-segment elevation. N-STEMI: Non-segment elevation. CHF: Chronic heart failure.*

#### Paper II

Paper II was a sub-study on the Danish population that participated in the EU-CaRE project (1). The patients included were aged 65 years or older, had accepted CR and met one of the following criteria within 3 months prior to the start of CR program: 1) acute coronary syndrome (ACS), including myocardial infarction (MI) and/or revascularization, 2) underwent PCI, 3) received CABG, or 4) had undergone an intervention for valvular heart disease.
Exclusion criteria were: patients with a contraindication to CR, mental impairment leading to inability to cooperate, severely impaired ability to exercise, signs of severe cardiac ischemia and/or a positive exercise testing on severe cardiac ischemia, insufficient knowledge of the native language, and an implanted cardiac device (CRT-P, ICD).

## Study designs

### Paper I

Paper I was a retrospective cohort study.
**Primary outcome:** The primary outcome was $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR and was measured before and after CR using CPET.
**Primary exposures:** Primary exposures were *depression*, *socioeconomic status* and *ethnicity,* and were assessed initially at CR. Depression was described as: no depression, depression before cardiac event (self-reported prescription of antidepressants), or newly developed depression measured using a modified depression scale of three questions (PRIME-MD questionnaire) during patient interviews with the rehabilitation nurse. Socioeconomic factors were defined as educational attainment (no education, short term-, medium- or higher education) and working status (employed, unemployed, retired, disability pension). Ethnicity was defined as Western European origin or non-Western origin.
**Explanatory variables:** Explanatory variables included age, sex, cardiac diagnosis (STEMI, N-STEMI, unstable angina pectoris, stable angina, chronic heart failure and valvular heart disease), medication (beta-blockers and statins), and ejection fraction (as a percentage). Comorbidities included diabetes, kidney disease, cancer, chronic obstructive pulmonary disease, and peripheral artery disease. Smoking status was measured as smoker, former smoker, or never smoker.

### Paper II

The study in paper II was performed on the Danish cohort from the EU-CaRE study, which was a prospective multicentre cohort study (1). This study investigated whether level of motivation measured with the Behavioural Regulation in Exercise Questionnaire (BREQ-2) was a predictor of both baseline $VO_{2peak}$ and change in $VO_{2peak}$ following CR.
**Primary outcome:** The primary outcomes were $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR.
**Primary exposure:** Motivation: the level and type of motivation was measured using BREQ-2 (see appendix in paper II).
**Explanatory variables:** The same explanatory variables were used as in paper I. Cardiac diagnosis was defined as acute coronary syndrome, stable coronary artery disease, and valvular heart disease. Questionnaires on depression (PHQ-9), anxiety (GAD-7) and vital exhaustion were gathered along with the BREQ-2.
Data was collected three times: at baseline, at the end of CR, and at a one-year follow-up. This paper does not include data from the one-year follow-up.

### Paper III

Paper III was a retrospective cohort study investigating the prognostic value of baseline $VO_{2peak}$ as well as change in $VO_{2peak}$ following CR.
**Primary outcomes:** Primary outcome variables were *all-cause mortality* and *new readmissions for CVD*, which was a composite of myocardial infarction, unstable angina pectoris, heart failure, and cerebral infarction. Major Adverse Cardiovascular Events (MACE) was also an outcome and was defined as a composite of all-cause mortality and new readmissions for CVD.
Information on all-cause mortality was extracted from the Danish Civil Registration System (68), which, among other things, contains information on name, sex, date of birth, and individuals' vital status and emigration. Information on readmissions for CVD were extracted from the National Patient Register, which holds patient information on all hospital activities (69), and any contact a patient has with the hospital is documented under their social security number (CPR-number). The registry records patient information on admissions and discharge dates, and diagnoses that are

classified according to the International Classification of Diseases (ICD-10). All hospitals are obliged to report to the National Patient Register.
**Primary exposure:** The exposures were $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR.
**Explanatory variables** were the same as for the previous papers.
Exposure and explanatory variables were extracted from the local clinical database at the CR unit at Bispebjerg/Frederiksberg Hospital. The primary explanatory variable was $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR.

## Statistical analyses

Continuous variables are presented as mean ±SD and categorical variables as numbers and percentages. Level of significance was set at <0.05. Normally distributed variables were compared across groups using the students' t-test or a one-way analysis of variance. Non-normally distributed variables were tested using Mann-Whitney and Kruskal-Wallis tests, and categorical variables were tested with a Chi-2 test. Inferential statistics for each paper will be addressed in the following section.

### Paper I

Inferential statistics for predictions of $VO_{2peak}$ were completed using multivariable linear regression analyses.
Potential confounding factors were identified according to previous literature, and whether these factors were associated with $VO_{2peak}$ and the socioeconomic status, depression or ethnicity.
A loss to follow-up analysis was performed using multivariable logistic regression (attending second $VO_{2peak}$ test or not attending). See paper I, figure 1. All statistical analyses were carried out using STATA IC 13.1

### Paper II

Paper II applied BREQ-2, which measures five different constructs of motivation, as well as a summed score of motivation derived from the five subscales which together are called the Relative Autonomy Index (RAI). Correlation analyses were performed between $VO_{2peak}$ and the six different measures of motivation (see paper II, figure 2). The motivation construct with the highest correlation was used to predict $VO_{2peak}$ in multivariable linear regression analyses. We also adjusted for depressive symptoms, measured using a different continuous scale. To compare the different continuous scales (motivation, depression, age, etc.), we performed a standardized adjusted regression analysis. All statistical analyses were carried out using STATA IC 13.1.

### Paper III

In paper III, baseline $VO_{2peak}$ and change in $VO_{2peak}$ were the primary exposure variables and future readmissions for CVD and all-cause mortality were the primary outcomes.
Cox-regression analyses were used to analyse the risk of all-cause mortality and the combined endpoint of readmissions for CVD and all-cause mortality.
Multi-state models were also applied, using the risk of future readmissions for CVD and all-cause mortality as a semi-competing risk scenario (see figure 4). In this multi-state model, the patients who complete CR are at risk of being readmitted for CVD (transition 1). If suffering a new readmission, the patients were still at risk of dying from all-cause mortality (transition 2). The patients who did not suffer an intermediate readmission were also at risk of dying from all-cause mortality (transition 3).
All statistical analyses for paper III were performed during an exchange visit in Santiago De Compostela in collaboration with the Department of Biostatistics at the University of Santiago De

Compostela. We used R (package mgcv) to complete Cox proportional hazards models, and Bayes X to perform the multi-state models.

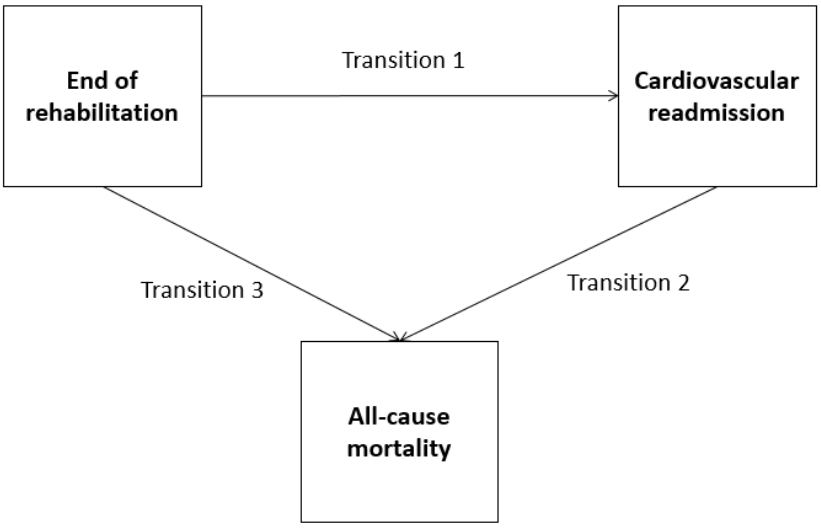


**Figure 4:** Multistate model illustrating the three possible transitions after rehabilitation. Transition 1: risk of suffering a new cardiovascular readmission. Transition 2: Risk of dying from all-cause mortality after suffering a new cardiovascular readmission. Transition 3: Risk of dying without suffering an intermediate cardiovascular event.

### Approval and ethics

Paper I and III were registry-based studies which were approved by the Danish Data Protection Agency. The registry number for paper I is *BFH-2017-071; 05678*; and for paper III *BFH-2017-117; 06028*.According to Danish legislation, no ethical approval was needed for paper I and III. Paper II was approved by Regional Scientific Ethical Committee for Copenhagen, Denmark. The registry number for paper II is *H-15011913*. The study was conducted in accordance with the Declaration of Helsinki and written informed consent was obtained.

# Results

## Paper I

#### Patient characteristics

From 2011 to 2016, a total 1217 patients with a mean age of 61.3 ±10 years performed a baseline CPET and were included in the baseline analyses. 78% were males and more than 90% were patients with IHD. 861 completed both the baseline and the second CPET after CR and were included in the follow-up.
Women, having chronic heart failure, low ejection fraction, living alone, current smokers, and being off the labour market were associated with pre-existing depression (see table 2). New onset depression was associated with being younger, a woman, a current smoker, having non-Western European ethnicity, and living with a partner.

Lower educational attainment was associated with the female sex, being a current smoker, having a lower $VO_{2peak}$, and having non-Western European ethnicity. See baseline characteristics by educational attainment (table 3) and ethnicity (table 4).

**Table 2**

Characteristics of the study population by depression

| | *Level* | *Depression* | | | *P-value* |
|---|---|---|---|---|---|
| | | No | New onset depression | Pre-existing depression | |
| ***N*** | | 1034 (85%) | 89 (7%) | 94 (8%) | |
| ***Age*** | Mean (SD), years | 61.7±11 | 56.6±9 | 61.4±9 | ***<0.001*** |
| ***Sex*** | Male | 830 (80%) | 60 (67%) | 60 (64%) | ***<0.001*** |
| ***BMI*** | Mean (SD) | 27.8 (4.6) | 28.3 (4.7) | 27.9 (4.8) | 0.566 |
| ***Living status*** | Not alone | 641 (63%) | 59 (70%) | 46 (50%) | ***0.013*** |
| ***Ethnicity*** | Non- Western European | 149 (14%) | 31 (35%) | 10 (11%) | ***<0.001*** |
| ***Smoking status*** | Never smoked (>1year) | 650 (63%) | 37 (42%) | 47 (50%) | ***<0.001*** |
| | Former smoker (<1year) | 229 (22%) | 21 (34%) | 18 (19%) | |
| | Smoker | 153 (15%) | 20 (23%) | 28 30%) | |
| ***Index event*** | STEMI | 274 (27%) | 34 (29%) | 17 (18%) | ***<0.001*** |
| | N-STEMI | 267(26%) | 30 (25%) | 21 (22%) | |
| | Unstable angina pectoris | 125(12%) | 18 (17%) | 11 (12%) | |
| | Stable angina | 267(26%) | 29 (26%) | 27 (29% | |
| | CHF | 6 (1%) | 0 | 10 (11%) | |
| | Valvular heart disease | 94 (9%) | 0 | 8 (9%) | |
| ***Educational attainment*** | No education | 164 (16%) | 20 (22%) | 21 (22%) | ***0.006*** |
| | Short term education | 255 (25%) | 33 (37%) | 20 (21%) | |
| | Medium education | 145 (14%) | 5 (6%) | 19 (20%) | |
| | Higher education | 229 (22%) | 19 (21%) | 20 (21%) | |
| ***Working status before index event*** | Working | 400 (39%) | 36(40%) | 19 (20%) | ***<0.001*** |
| | Unemployed | 69 (7%) | 15(17%) | 15 (16%) | |
| | Retirement | 497 (48%) | 23(26%) | 46 (49%) | |
| | Disability pension | 56 (5%) | 12(13%) | 14 (15%) | |
| ***Hypertension*** | Yes | 551 (53%) | 50 (56%) | 55 (59%) | 0.491 |
| ***Hypercholesterolemia*** | Yes | 643 (62%) | 66 (68%) | 66 (70%) | 0.163 |
| ***Ejection fraction*** | Percentage | 52% | 52% | 48% | ***0.005*** |
| ***Baseline $VO_{2peak}$*** | VO2/kg/min (SD) | 22.0 (6.8) | 22.0 (6.9) | 20.1 (5.5) | ***0.038*** |
| ***Medicine*** | Beta blockers | 802 (78%) | 75 (84%) | 65 (69%) | ***0.012*** |
| | Statins | 920 (89%) | 85 (96%) | 81 (86%) | ***0.015*** |
| ***Charlson Comorbidity Index*** | 0-9 comorbidities | 2.3 (1.4) | 1.7 (1.3) | 2.5 (1.5) | ***0.002*** |

*Abbreviations: STEMI: ST-segment elevation. N-STEMI: Non-segment elevation. CHF: Chronic heart failure. SD: Standard deviation*

**Table 3**
Characteristics of the study population by educational attainment

| | *Educational attainment* | | | | *P-value* |
|---|---|---|---|---|---|
| | No education | Short term education | Medium education | Higher education | |
| *N* | 205 (18%) | 481 (43%) | 169 (15%) | 268 (24%) | |
| ***Age*** *(years)* | 58±10 | 62.3±10 | 60.6±11 | 61.2±11 | 0.528 |
| ***Sex*** *(male)* | 82% | 75% | 75% | 86% | ***<0.001*** |
| ***Body mass index*** *(kg/m²)* | 28.9 (4.7) | 27.9 (4.6) | 27.2 (5.2) | 27.3 (4.2) | ***0.032*** |
| ***Living status*** *(not alone)* | 56% | 60% | 63% | 74% | ***<0.001*** |
| ***Ethnicity*** *(Non-Western European)* | 34% | 11% | 10% | 12% | |
| ***Smoking status*** | | | | | |
| *Never smoked (>1year)* | 46% | 57% | 67% | 73% | ***<0.001*** |
| *Former smoker (<1year)* | 25% | 26% | 21% | 18% | |
| *Smoker* | 29% | 18% | 12% | 9% | |
| ***Index event*** | | | | | 0.240 |
| *STEMI* | 30% | 25% | 28% | 26% | |
| *N-STEMI* | 25% | 25% | 24% | 27% | |
| *Unstable angina pectoris* | 13% | 12% | 19% | 14% | |
| *Stable angina* | 25% | 29% | 25% | 22% | |
| *Chronic heart failure* | 2% | 1% | 2% | 2% | |
| *Valvular heart disease* | 5% | 5% | 12% | 10% | |
| ***Working status before index event*** | | | | | |
| *Working* | 36% | 33% | 48% | 47% | ***<0.001*** |
| *Unemployed* | 18% | 8% | 5% | 4% | |
| *Retirement* | 37% | 51% | 44% | 44% | |
| *Disability pension* | 9% | 8% | 4% | 5% | |
| ***Hypertension*** *(Yes)* | 55% | 56% | 49% | 51% | 0.419 |
| ***Hypercholesterolemia*** *(Yes)* | 67% | 66% | 62% | 59% | 0.263 |
| ***Ejection fraction*** *(%)* | 51% | 52% | 52% | 53% | 0.528 |
| ***$VO_{2peak}$*** *(mL/kg/min)* | 21.0 (5.6) | 20.8 (6.2) | 23.4 (8) | 24.0 (7.4) | ***<0.001*** |
| ***Beta blockers (****Yes)* | 82% | 79% | 74% | 78% | 0.247 |
| ***Statins*** *(Yes)* | 95% | 91% | 87% | 88% | ***0.019*** |
| ***Charlson Comorbidity Index (****0-9 comorbidities)* | 2.1 (1.5) | 2.4 (1.5) | 2.1 (1.4) | 2.1 (1.3) | ***0.009*** |

*Abbreviations: N-STEMI, Non-segment elevation; STEMI; ST-segment elevation. Data are reported as mean ± SD or number (%)*

**Table 4**
Characteristics of the study population by ethnicity

| | Ethnicity | | |
|---|---|---|---|
| | Western European | Non-Western European | P-value |
| ***N*** | 1027 (84%) | 190 (16%) | |
| ***Age*** *(years)* | 62.3±10 | 55.5±11 | ***<0.001*** |
| ***Sex*** *(male)* | 76% | 88% | ***<0.001*** |
| ***Body mass index*** *(kg/m²)* | 28.8 (4.7) | 28.9 (4.0) | 0.887 |
| ***Living status*** *(not alone)* | 61% | 74% | ***0.001*** |
| ***Smoking status*** | | | |
| *Never smoked (>1year)* | 62% | 54% | ***0.008*** |
| *Former smoker (<1year)* | 22% | 25% | |
| *Smoker* | 16% | 21% | |
| ***Index event*** | | | |
| *STEMI* | 26% | 26% | 0.323 |
| *N-STEMI* | 260 (25%) | 26% | |
| *Unstable angina pectoris* | 12% | 13% | |
| *Stable angina* | 25% | 29% | |
| *CHF* | 1% | 1% | |
| *Valvular heart disease* | 9% | 5% | |
| ***Educational attainment*** | | | |
| *No education* | 14% | 40% | ***<0.001*** |
| *Short term education* | 45% | 31% | |
| *Medium education* | 16% | 10% | |
| *Higher education* | 25% | 19% | |
| ***Working status before index event*** | | | |
| *Working* | 38% | 39% | ***<0.001*** |
| *Unemployed* | 6% | 18% | |
| *Retirement* | 50% | 28% | |
| *Disability pension* | 5% | 15% | |
| ***Hypertension*** *(Yes)* | 56% | 45% | ***0.005*** |
| ***Hypercholesterolemia*** *(Yes)* | 63% | 66% | 0.480 |
| ***Ejection fraction*** *(%)* | 52% | 52% | 0.616 |
| ***$VO_{2peak}$*** *(mL/kg/min)* | 21.9 (6.8) | 21.5 (6.3) | 0.589 |
| ***Beta blockers (****Yes)* | 78% | 82% | 0.195 |
| ***Statins*** *(Yes)* | 90% | 93% | 0.285 |
| ***Charlson Comorbidity Index*** *(0-9 comorbidities)* | 2.3 (1.4) | 1.84 (1.5) | ***<0.001*** |

*Abbreviations: N-STEMI, Non-segment elevation; STEMI; ST-segment elevation. Data are reported as mean ± SD or number (%)*

#### Impact of depression, socioeconomic factors and ethnicity on baseline $VO_{2peak}$.

Mean $VO_{2peak}$ before CR was 21.8 (6.7) ml/kg/min and higher $VO_{2peak}$ was associated with the male sex, younger age, higher ejection fraction, less comorbidity and not using beta-blockers. $VO_{2peak}$ was not associated with cardiac diagnosis or cardiovascular risk factors.

Educational attainment, working status and ethnicity remained associated with $VO_{2peak}$ after full adjustment, while the effect of pre-existing depression was not (see figure 5).

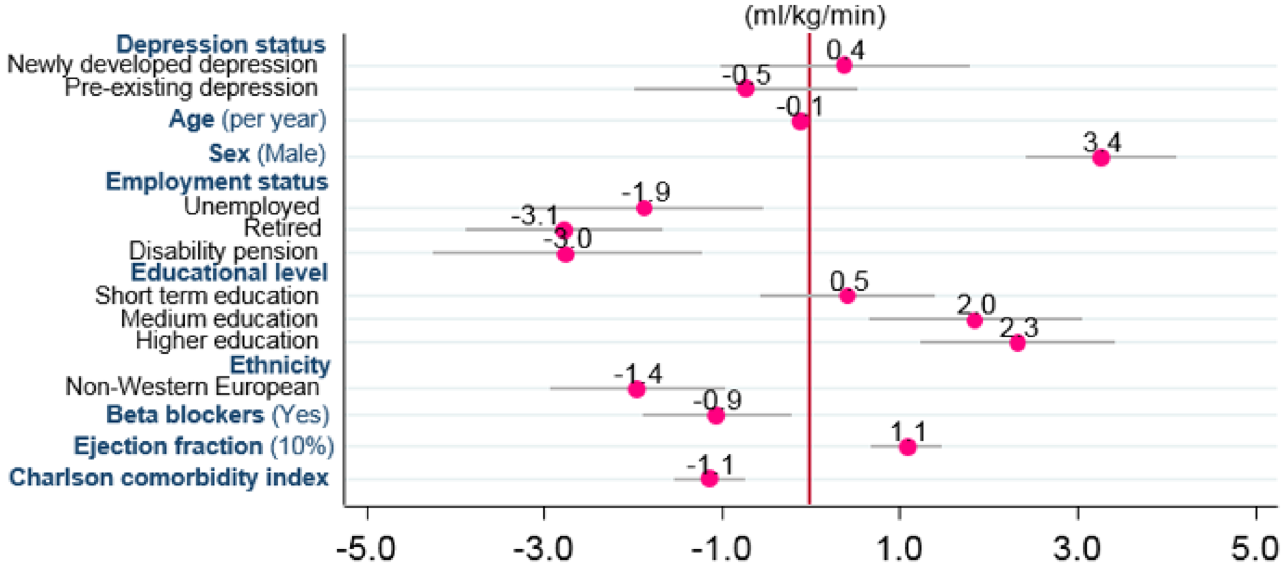


**Figure 5:** Forest plot: beta coefficients from multivariable adjust regression analyses before cardiac rehabilitation. Results are shown as difference in $VO_{2peak}$ pr. ml/kg/min

#### Improvement of cardiorespiratory fitness following CR

Mean improvement in $VO_{2peak}$ after CR was 2.4 (4.3) ml/kg/min equivalent to an 11% increase. Working status, educational attainment, ethnicity and less comorbidity was associated with improvement in $VO_{2peak}$, even after a full multivariable adjustment (see figure 6). Patients who had valvular heart disease had a 2.2 ml/kg/min (CI 1.4 - 3.3) higher improvement of $VO_{2peak}$ than STEMI patients. Unadjusted values are given in paper I, table 2.

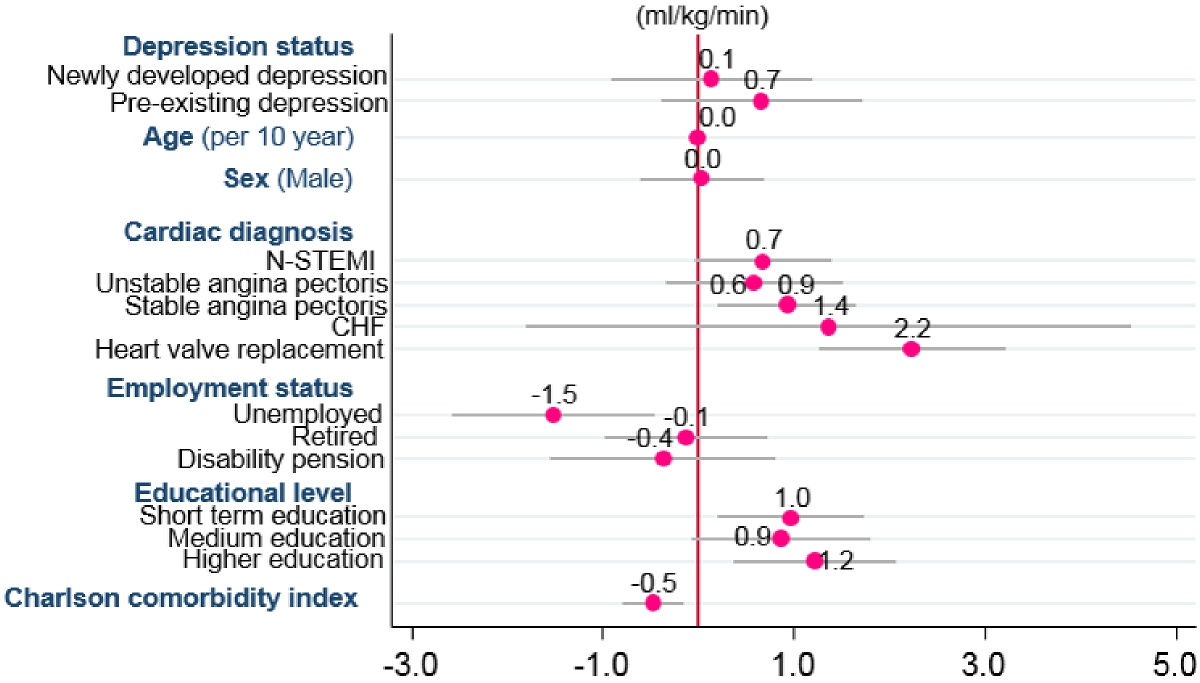


**Figure 6:** Forest plot: beta coefficients from multivariable adjust regression analyses after cardiac rehabilitation. Results are shown as difference in $VO_{2peak}$ pr. ml/kg/min

## Paper II

The baseline analyses comprised 203 patient who both completed the baseline CPET and the BREQ-2 questionnaire. 182 patients finished the CR program and a second CPET. These comprised the follow-up analyses (see paper II, figure 1).

### Patient characteristics

Characteristics of the study population are presented in paper II, table 2 with a categorized RAI score (low, medium and high).
The patients had a mean age of 72 (±5) years and 73% were males. Most of the patients were Western European and living with a partner. Nearly half the population had higher educational attainment. Only 9% were current smokers. $VO_{2peak}$ before CR was 18.2 (±5.0) and the mean RAI motivation score was 5 (±7) with a range from -14 to 19.
Patients with a low level of motivation had a higher prevalence of risk factors: higher BMI, higher prevalence of both diabetes and hypertension, and a lower ejection fraction. Having a low level of motivation was also associated with living alone and scoring higher on vital exhaustion compared to patients with both medium and high levels of motivation.
There were only slight differences between patients with high and medium level of motivation. Having a high level of motivation was associated with a lower prevalence of hypercholesteremia and hypertension, as well as a lower vital exhaustion score.
There was a positive linear association between $VO_{2peak}$ and motivation ($p<0.001$).

### Five constructs of motivation and a composite score (RAI)

Pairwise correlations between $VO_{2peak}$ and all the constructs of motivation were performed with scatterplots and linear prediction. Scatterplots and Spearman correlations are given in paper II, figure 2. The highest correlation was found between $VO_{2peak}$ and RAI ($r= 0.30$, $p< 0.01$), and to avoid multicollinearity between the constructs of motivation, the RAI was used as the primary exposure variable for the baseline predictor analyses.

### $VO_{2peak}$ and motivation before CR

In unadjusted analyses, $VO_{2peak}$ was associated with sex, daily physical activity level (0-7 days), revascularization procedure, comorbidities and vital exhaustion. However, $VO_{2peak}$ was not associated with age, ejection fraction or beta-blockers. The positive association between higher motivation and higher $VO_{2peak}$ remained significant after full, multiple adjustments for age, sex, index diagnosis, physical activity level, kidney disease, COPD, diabetes, ejection fraction and depression (see figure 7). Unadjusted and adjusted results are given in paper II, table 2A. Motivation, depression, age, and ejection fraction were standardized in the multiple adjusted model. This was done to compare the individual continuous covariates on a comparable scale. After standardization, motivation had a slightly higher association with $VO_{2peak}$ than depression.

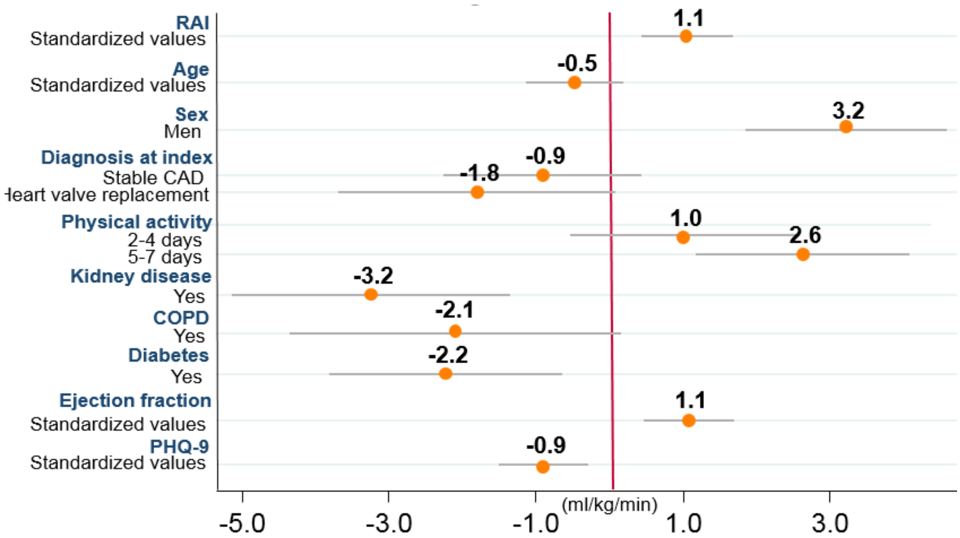


Figure 7: Forest plot: beta coefficients from standardized multivariable adjust regression analyses before cardiac rehabilitation. Results are shown as difference in $VO_{2peak}$ pr. ml/kg/min

### Change in $VO_{2peak}$ after CR

A mean improvement of 2.27 ml/kg/min (SD±4.3) after participating in CR, which was equivalent to a 12% increase, was observed.

After multivariable adjustment, motivation remained statistically associated with change in $VO_{2peak}$, whereas depression did not (see figure 8). There was an inverse association between higher baseline $VO_{2peak}$ and change in $VO_{2peak}$ after CR. There was less improvement with older age and there were no gender differences. Smokers improved less than former smokers and non-smokers. Having diabetes or kidney disease had a negative association with change in $VO_{2peak}$. Unadjusted and adjusted results are given in paper II, table 2B.

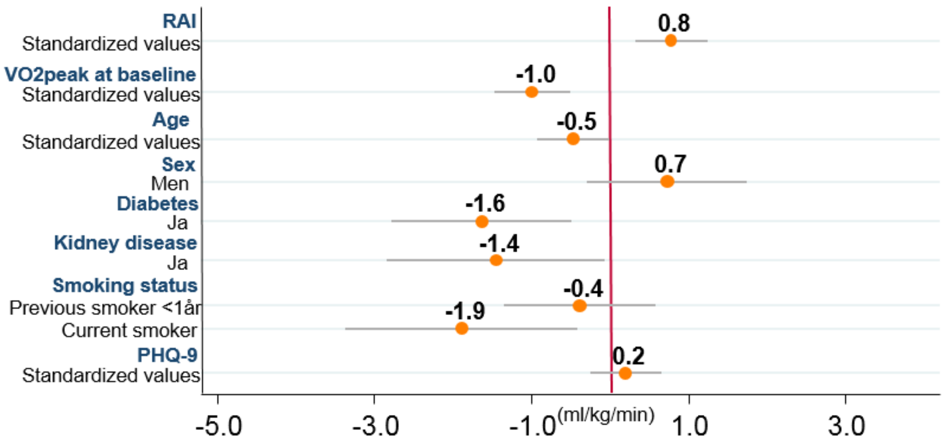


Figure 8: Forest plot: beta coefficients from standardized multivariable adjust regression analyses after cardiac rehabilitation. Results are shown as difference in $VO_{2peak}$ pr. ml/kg/min

## Paper III

### Patient characteristics

1561 patients participated in CR and performed both the first and second CPET. The mean age of the population was 63.6 (±11), 74% were male, 84% had coronary artery disease, 6% had chronic heart failure, and 10% had valvular heart disease.
During a median follow-up time of 2.3 years (IQR 1.3 – 4.1 years), there were 77 deaths and 167 readmissions for CVD. 25 deaths occurred after the patients had suffered a hospital readmission. The patients who died were older, more likely to be retired, living alone, had lower educational attainment, suffered from more comorbidity and had lower baseline $VO_{2peak}$. Demographics for the population are given in paper III, table 1.

### Influence of $VO_{2peak}$ on MACE

There was a linear association between $VO_{2peak}$ before CR and risk of MACE, even after full adjustment. See paper III, table 2A and figure 1. The hazard rate for MACE was 0.94 (0.91-0.97) for each ml/kg/min in baseline $VO_{2peak}$. Change in $VO_{2peak}$ after CR had a significant curvi-linear association with risk of MACE. Males had a higher risk of suffering a MACE than females (HR 1.98, p=0.003). Having chronic heart failure before CR, having been revascularized with PCI, and suffering from peripheral artery disease were also associated with risk of MACE.

### Influence of $VO_{2peak}$ on all-cause mortality

$VO_{2peak}$ before CR had a linear association with risk of all-cause mortality of HR 0.89 (0.83 - 0.95) per ml/kg/min. See paper III, table 2A and figure 2. Change in $VO_{2peak}$ after CR was also associated with risk of all-cause mortality after full adjustment, HR 0.87 (0.80 - 0.96). Having chronic heart failure or peripheral artery disease was also associated with higher mortality.

### Influence of $VO_{2peak}$ on new readmissions for CVD and all-cause mortality applying a Multi-state model:

*Transition 1: Risk of being readmitted for CVD*

167 patients were readmitted for CVD. There was a significant non-linear association between baseline $VO_{2peak}$ and readmission, whereas there was a linear association (from -2ml/kg/min to 2ml/kg/min) between change in $VO_{2peak}$ and readmission.

*Transition 2: Risk of dying after a readmission for CVD*

25 patients died after a hospital readmission for CVD. The risk of dying after being readmitted for CVD was not associated with either baseline $VO_{2peak}$ nor change in $VO_{2peak}$. Chronic heart failure at baseline was the single significant predictor of mortality in transition 2.

*Transition 3: Risk of dying without an intermediate readmission for CVD*

52 patients died without an intermittent hospital readmission. Both baseline and change in $VO_{2peak}$ had linear associations with risk of all-cause mortality, even after a full adjustment. Males had a higher risk of dying (HR 3.85, P=0.031).

Results from the multi-state model are given in paper III, table 3 and figure 4.

# Discussion

## Principal findings

This thesis consists of three explorative cohort studies investigating socioeconomic and psychological disparities in relation to $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR.
In paper I, we found that patients with lower SES and another ethnicity than Western European had a lower $VO_{2peak}$ before CR and a decreased change in $VO_{2peak}$ after CR. Surprisingly, depression did not affect $VO_{2peak}$ either before or after CR.
In paper II, we identified that a lower degree of motivation for physical activity among older patients with IHD was negatively associated with $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR. Motivation was the strongest psychological predictor of change in $VO_{2peak}$ after CR, stronger than signs of depression, anxiety and vital exhaustion.
$VO_{2peak}$ was also significantly associated with age, sex, cardiac diagnosis and comorbidities, both in paper I and II.
In paper III, we found that risk of MACE, readmissions for CVD, and all-cause mortality were inversely associated with $VO_{2peak}$ before CR and change in $VO_{2peak}$ after CR, confirming that improvement in $VO_{2peak}$ is a protective factor for cardiac patients participating in CR. Once readmitted for CVD, $VO_{2peak}$ was no longer associated with risk of mortality indicating that it was no longer a protective factor for future risk of mortality.

## Effect of CR – what to expect

This thesis discusses the effect of CR in terms of change in $VO_{2peak}$ measured before and after rehabilitation. We found a relative increase in $VO_{2peak}$ of 11% and 12% in paper I and II, respectively. This improvement in $VO_{2peak}$ is similar to recent CR programs with comparable patient populations (70, 71). The heterogeneity between CR programs makes it difficult to locate exact CR program comparisons.
Parameters that affect the extent to which a patient improves in $VO_{2peak}$ during CR are multifactorial and include patient characteristics, CR structure, and genetics (72-74).
In line with other CR research, we found that age, sex and comorbidities were predictive of change in $VO_{2peak}$ after CR (75-78).
Sandercock et al. (2013) performed a meta-analysis on parameters that affect changes in $VO_{2peak}$ following CR (72). With 31 cohorts and RCT studies on CR, they compared patient and program characteristics that affected how patients improved in $VO_{2peak}$. First, they investigated the patients' starting point before CR, in terms of baseline $VO_{2peak}$, as this is often mentioned as a parameter that determines the extent to which a patient can improve their $VO_{2peak}$. Sandercock dichotomized baseline $VO_{2peak}$ to >/<23 ml/kg/min and surprisingly found no influence on change in $VO_{2peak}$ (72). However, this cut-off value was clinically arbitrary, as it was determined statistically based on the median value and not on clinical relevance. The meta-analysis also found that younger patients and males improved more than their counterparts. In paper I, we also found an inverse association between age and change in $VO_{2peak}$, but no effect of sex. This discrepancy between gender effect may be explained by a difference in the time when CR was performed. The meta-analyses included studies from 1970, when most patients included were middle-aged males, and when gender differences were not an issue that was addressed in CR programs.
Approximately 30% of the population in our study (paper III) did not improve in $VO_{2peak}$ after rehabilitation. This result has been found in several studies (70, 79), and most recently by Willams et al. (2019) in a study on 677 patients comparing change in $VO_{2peak}$ in different training modalities

(80). Between 35-52% of the patients were classified as likely non-responders, meaning that, independent of training intensity and/or volume, they did not improve in $VO_{2peak}$ from baseline. They found that age, sex, the individual study, program duration, the number of sessions each week, the patient group, and the average between pre- and post-test scores predicted 17.3% of the variance in training response, suggesting that there were other uncontrolled factors that affected the patients' ability to increase in $VO_{2peak}$. In paper I and II, the predictors of CR effect were highly related to patient characteristics, SES and psychological factors, suggesting that the effect of CR really is multifactorial and dependent on much more than CR program characteristics. This also strongly suggests that these predictors should be accounted for on an individual level when patients attend rehabilitation.

### Socioeconomic differences

SES was assessed using educational attainment and working status in all three papers. The application of these factors is consistent with previous cardiovascular research (39, 81, 82). SES was an important factor when assessing the effect of CR, which confirms Diderichsen's model (2001) on socioeconomic inequality (figure 3), and adds to the evidence on skewed health outcomes in CVD research, even among selected patients participating in CR. In paper I, we found that patients on disability pension was almost twice as likely to drop out of CR compared with patients still working. Previous literature is inconsistent regarding risk of dropout and employment status, both being on the labour market (83) and being unemployed (84) has been associated with risk of dropout indicating predictions on working status and risk of dropout not being generalizable to all CR programs.

The issue of health inequality in relation to SES is also observed in terms of participation in CR (85), which in general is very low. In a comprehensive survey from 2010 including 28 European countries, all but one site had a participation rate lower than 50% (86). A Danish study on 5455 cardiac patients admitted due to myocardial infarction showed that patients with lower education received less information and were less willing to participate in CR (87).

There can be several reasons for both unequal participation and unequal benefit. Patients with lower SES have been shown to have more risk factors when entering the program, including smoking status and depression (88). They are more likely to have high blood pressure and diabetes and to be obese, all variables of clinical relevance (89, 90). Same characteristics as we found in paper I. Taking the patients' perspective, a qualitative study on socioeconomically deprived cardiac patients found that these patients felt excluded from CR during the program: *"they did not feel like they fit in"* in the standard CR. The patients argued there was a need for an individualized tailor-based approach to CR that paid attention to individual needs and preferences (91).

It is necessary to understand how these personal and clinical parameters differ within subgroups of cardiac patients in order to be able to tailor each CR program in the best way to suit the specific needs of patients with lower SES.

### Impact of depression

In paper I, depression was not associated with either lower $VO_{2peak}$ at baseline nor less improvement after CR. In paper II, however, depression was associated with lower baseline $VO_{2peak}$. Paper II included a group of selected elderly patients (>64years) who participated in the EU-CaRE study and can therefore not be compared directly with patients from paper I.

One important difference between paper I and II was the assessment of depression. Paper I used patient-reported use of antidepressants and/or a modified depression questionnaire (PRIME-MD), whereas paper II assessed symptoms of depression using the validated Patient Health Questionnaire

(PHQ-9). PHQ-9 seems to a better screening tool for prediction of $VO_{2peak}$ before CR, but it also could not predict change in $VO_{2peak}$ after CR. Neither paper I or II found any association between depression and change in $VO_{2peak}$, which is in line with previous studies (92). One explanation could be that psychological distress in cardiac patient is a recognized concern in CR and is thus successfully addressed in the program.

### Motivation in cardiac patients

We assessed motivation before the patients began CR using a quantitative questionnaire that measured constructs of motivation for physical activity as well as a summed score.
The positive association between higher motivation for physical activity and $VO_{2peak}$ before and after CR relates to previous studies. One Canadian study (93) measured motivation with BREQ-2 and RAI in partients participating in CR and found a positive association between motivation and exercise behaviour three and six weeks post CR. Slovinec et al (2014) on 801 patients also found that higher intrinsic motivation was positively related with both short- (six months) and long-term (twelve months) exercise behaviour after CR (94).
The association between constructs of motivation and physical activity outcomes was also investigated in a recent review, supporting the influence of intrinsic regulations regarding adherence to physical activity (95). However, there seems to be a discrepancy between the intention to be physically active and being physically active. Almost half of the people who intend to be physically active according to the guideline recommendation are not (96). In accordance with this, less than 50% of cardiac patients maintain their physical activity levels 3 to 6 months after CR, and even fewer at 12 months (97). Based on this evidence, it is relevant to investigate whether BREQ-2 can predict a long-term positive association between motivation and improvement in $VO_{2peak}$.
Degree of motivation is dynamic and is likely to change when a person is exposed to a shift in the environment, such as entering into a CR program. Extrinsic motivation for physical activity, e.g. increased physical fitness, having better health, or losing weight can, over time, lead to an intrinsic interest in exercise and thereby increase patients' adherence in the longer term (98, 99). One of the purposes of CR is patient education and behavior change, and it is likely that some patients will experience a shift from extrinsic to intrinsic motivation during a CR intervention. It is relevant to measure change in patient motivation from pre- to post-CR, as this would make it possible to assess if there are individual patient or CR program differences in how CR increases motivation.
Important motivational factors for physical activity include advice from health professionals, family pressure, improvement in physical fitness, general health benefits, and social reasons such as enjoying group interaction and meeting with friends (100). An approach aiming to increase intrinsic motivation and self-efficacy for physical activity is to individualize CR based on specific needs instead of exclusively offering standard outpatient programs (101). An alternative to outpatient CR is to offer parallel programs at home and, for some patients, include tele-medicine. Offering alternative programs may remove barriers that many patients experience with regard to rehabilitation and physical activity (102), as patients have different preferences for CR delivery. Some prefer a program that fits into their daily life, while others prefer to participate in a social and supervised context, like the traditional outpatient program (103, 104). Alternative CR programs have shown to perform equally to supervised outpatient CR in terms of improvement in cardiovascular risk factors, increase in physical capacity, cardiac events, mortality, or quality of life (105, 106).

## Prognosis after CR

In paper III, we found that change in $VO_{2peak}$ was strongly related to both MACE, all-cause mortality and readmission for CVD.

A recent study from 2018, published by Schutter et al. (107), followed 1171 patients with CVD after CR for a median follow-up time of 6.4 years and found that change in $VO_{2peak}$ was inversely associated with risk of all-cause mortality, in agreement with paper III. This result confirms that the predictive value of change in $VO_{2peak}$ lies in its bearing on health prognosis, even in a longer period than the 2.3 years we investigated. Like paper III, Shutter et al. found that higher age, male sex and lower baseline $VO_{2peak}$ were associated with a higher risk of mortality. Some important differences between our study and Schutter et al.'s were that we included patients with valvular heart disease and patients with CHF who had more than five-fold risk of mortality. Furthermore, Schutter et al. did not have information on comorbidities (except for diabetes), which was an important limitation. We had information on several relevant comorbidities, and peripheral artery disease was significantly predictive both for future risk of MACE and mortality.

A study by Martin et al. (2013) found an inverse association between improvement in $VO_{2peak}$ and risk of mortality in 5641 patients with CVD. They also investigated the prognostic value of change in $VO_{2peak}$ after one year and found that a 3.5ml/kg/min improvement was associated with a 25% risk reduction in all-cause mortality.

As far as we are aware, paper III is the first study to apply a multi-state model to predict outcomes after CR. We found that change in $VO_{2peak}$ after CR was associated both with readmissions for CVD and all-cause mortality. Once being readmitted for CVD, $VO_{2peak}$ was no longer predictive for mortality, reflecting the extent to which it can be applied as a predictor. Being readmitted for CVD will likely change a patients' $VO_{2peak}$, and it could thus be argued that, following this, the patient is in need of a new CR intervention.

Multi-state models are applied in cardiology to predict hospital readmissions in heart failure patients (108-110). One of the strengths of applying this model is the possibility of investigating multiple non-fatal events, such as readmissions, without censoring the patients. It may thus have great potential for investigating future health after CR.

## Defining a successful CR

In our studies, we defined successful CR according to the patients' ability to improve in $VO_{2peak}$. We found that all-cause mortality decreased approximately 20% for each 1 ml/kg/min improvement in $VO_{2peak}$. The risk of being readmitted for CVD had a corresponding decrease with a non-linear trend, which provides support for the use of $VO_{2peak}$ as a parameter to assess the effectiveness of CR.

However, the multifactorial and multidisciplinary approach in CR means that there are several relevant outcomes that must be considered when discussing the effectiveness of rehabilitation. Other important factors are: risk factor control, behavior change, and psychosocial management. CR has been shown to successfully handle important risk factors. Several studies have shown that a decrease especially in smoking, hypertension, and hypercholesteremia led to decreased risk of mortality after CR (111, 112). These factors were highly related to patient education and behavior change. SES has proven to be an important predictor for success in risk factor management. The EUROASPIRE III (113) that was conducted in 22 European countries found that achieving secondary prevention targets was associated with increasing levels of education. Compared to patients with university education, those with primary education were 44% less likely to achieve their targets. In contrast, depression and anxiety did not affect whether risk factor targets were achieved or not.

From the patients' point of view, it is important to investigate whether CR affects psychological status. There is evidence that quality of life increases both for patients living with CVD and for heart failure patients when participating in CR (13, 114). A review from 2019 of CR in patients with CVD showed that patient education and psychological interventions did not consistently improve quality of life, whereas exercise-based CR did in 7 out of 10 studies (114).
A review of 13 RCTs in CR for patients with heart failure found a significant and clinically relevant improvement in quality of life, measured using the validated Minnesota Living with Heart Failure questionnaire (mean difference 5.8 points (CI 2.4 to 9.2) (13).

## Limitations

A limitation of the retrospective design of paper I and III was variable selection. The variables in the database were not chosen for these research questions. In paper I, the consequence of this was especially seen in the measurement of depression. The database had data from an abbreviated depression questionnaire. This resulted in a loss of precision that potentially led to misclassification of patients. Information on the number of training sessions was missing at large, making it unfeasible to adjust for adherence to the CR program. Paper I is likely prone to selection bias, since 600 patients were excluded at baseline because of missing data on the CPET (n = 289) and depression (n = 319). There was also a higher number of drop-outs among patients with depression and patients receiving disability.
In Paper III, we only included patients who completed CR, introducing the risk of selection bias and decreasing the generalizability of the findings to patients not attending CR.
Another limitation of paper III is that we did not have enough data to investigate the risk of cardiovascular mortality. This is due to a delay in the data release of at least one year on cause-specific mortality in the Cause of Death Register. An analysis among the same population on $VO_{2peak}$ and risk of cardiovascular mortality will be possible in two years.
A limitation for all three papers was the low number of patients of non-Western origin. This selection occurred because the patients who did not understand Danish or English were offered rehabilitation in a local setting. For study II, where the number of participants with non-European ethnicity was lowest, the patients had to be able to speak and read Danish to answer the questionnaires.
Additionally, some patients who participated in CR declined to enroll in the study in paper II.
As paper I and III were retrospective studies, it was not possible to determine the causal factors for participation and completion of the rehabilitation program.

## Conclusions

The aim of this thesis was to identify socioeconomic and psychological parameters that altered the effect of CR, and whether this effect influenced the future risk of mortality and readmissions for CVD.
We found that lower socioeconomic status and non-Western ethnicity, but not depression, predicted both lower $VO_{2peak}$ before CR and less benefit from CR in terms of improvement in $VO_{2peak}$.
Motivation was positively associated, both with $VO_{2peak}$ before CR and improvement in $VO_{2peak}$ after CR, even after adjusting for other important psychological parameters, and BREQ-2 is a useful questionnaire to detect these differences.
Both the different levels of $VO_{2peak}$ before CR and the difference in improvement of $VO_{2peak}$ affects the patients' risks of future MACE, cardiovascular readmissions and all-cause mortality. However,

the protective factor of $VO_{2peak}$ seems to last only until the time of a new CVD readmission. This could indicate the need for a new CR intervention.
Our results identify vulnerable subgroups of patients that need special attention when attending CR. There is a need to act on these results and identify barriers and potential solutions to counteract these skewed health outcomes, and CR programs should consider the socioeconomic, ethnic, and psychological barriers to exercise when including patients in a program.

## Perspective and future research

The identification of socioeconomically and motivationally vulnerable patient groups in CR has given rise to several additional research questions that should be addressed.
Initiatives to counteract inequality could be based on patient opinions, meaning that performing structured interviews on this subgroup of patients could identify whether the patients prefer alternative interventions or delivery models. This may lead to new interventional studies that counteract inequalities.
Motivation in cardiac patients predicted the effectives of CR in terms of change in $VO_{2peak}$ in our population. This makes it relevant to investigate whether and how CR can effect a positive change in motivation, as this may increase long-term adherence to physical activity after CR. Motivation could likewise be applied to investigate whether different deliveries of CR can cause changes in motivation. For example, is home-based or tele-monitored CR more likely to affect motivation than center-based CR?
It would be similarly interesting to capture patients while they are still admitted in the hospital. This would make it possible to locate patients who lack motivation and, based on patient responses, address possible motivational barriers to participating in CR.
In general, there should also be a focus on the high percentage of non-participation. Reasons for non-participation should be mapped out and act as the basis for interventions to increase participation.

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# Appendices

- Paper I
- Paper II
- Paper III

# Depression, Socioeconomic Factors, and Ethnicity as Predictors of Cardiorespiratory Fitness Before and After Cardiac Rehabilitation

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**Purpose:** To determine whether cardiac patients with psychosocial or socioeconomic problems have lower peak oxygen uptake ($\dot{V}O_{2peak}$) and whether these factors modify the effect of cardiac rehabilitation (CR).

**Methods:** A retrospective cohort study of patients with ischemic heart disease, valvular heart disease, or heart failure referred for CR. $\dot{V}O_{2peak}$ was assessed by a maximal cardiopulmonary exercise test. Pre-existing depression was defined by use of antidepressants and new-onset depression by a modified Primary Care Evaluation of Mental Disorders (PRIME-MD) questionnaire at CR intake. Socioeconomic status was defined by educational attainment and working status; ethnicity as Western European or non-Western European. Full data from baseline assessment were available on 1217 patients and follow-up on 861 patients.

**Results:** Mean ± SD $\dot{V}O_{2peak}$ before CR was 21.8 ± 6.8 mL/kg/min. After multivariable adjustment, lower $\dot{V}O_{2peak}$ was associated with lower educational attainment, not working, and non-Western ethnicity but not with depression. Mean improvement of $\dot{V}O_{2peak}$ following CR was 2.4 ± 4.3 mL/kg/min. After multivariable adjustment educational attainment, employment status and ethnicity were significant predictors of improvement of $\dot{V}O_{2peak}$ while depression was not.

**Conclusion:** Education, attachment to the workforce, and ethnicity were all associated with lower $\dot{V}O_{2peak}$ before CR, and the disparity was increased following CR. Having pre-existing depression and new-onset depression did not influence $\dot{V}O_{2peak}$ either before or after CR. These results point to important subgroups in need of specially-tailored rehabilitation programs.

**Key Words:** cardiac rehabilitation • cardiorespiratory fitness • depression • ethnicity • socioeconomic status

Cardiorespiratory fitness (CRF) is an individual predictor of life expectancy and morbidity in both the general population and in cardiac patients.[1,2] Cardiac rehabilitation (CR) improves CRF and may reduce cardiovascular mortality up to 25%.[3,4] Therefore, CR is pivotal in secondary prevention of cardiovascular diseases. However, not all cardiac patients benefit equally from CR.[5] Individual characteristics as well as characteristics of the CR program offered are important predictors of improvement in CRF following CR.[5,6] The impact of psychosocial and socioeconomic variables is less well described.

Depression is very common in cardiac patients and is associated with an increased recurrence of disease and higher all-cause mortality.[7-9] Compliance and adherence to CR are also lower in cardiac patients with depressive symptoms.[7-9] Some studies have shown that depression may influence CRF before and following CR.[9,10] However, these studies are based on relatively small study populations.

Like depression, lower socioeconomic status is associated with increased risk of cardiovascular disease and worse health outcomes for cardiac patients[11-14] and has been linked to poorer participation rates in CR.[15,16] Differences in cardiovascular risk factors, CR intake, and cardiovascular prognosis have also been shown in relation to ethnicity.[17-19]

Data suggest, rather than one-size-fits-all, CR should be modified to the individual needs of the patient. We investigated whether depression, socioeconomic status, and/or ethnicity were associated with impaired CRF in a large group of cardiac patients attending CR, and whether these factors attenuated the effect of CR.

## METHODS

### STUDY POPULATION

We performed a retrospective study using a clinical registry in the CR Unit at Bispebjerg/Frederiksberg Hospital in Copenhagen, Denmark. The registry contained all cardiac patients who participated in CR from 2011 to 2016. We included patients with the following diagnoses: ST-elevation myocardial infarction (STEMI), non-STEMI, unstable angina pectoris, stable coronary artery disease with revascularization (percutaneous coronary intervention or coronary artery bypass grafting), chronic heart failure, or heart valve replacement.

The study was approved by the Danish Data Protection Agency (BFH-2017-071; 05678). According to Danish legislation no ethical approval was required.

### REHABILITATION PROGRAM

The CR program consisted of a supervised 8-wk outpatient exercise intervention at the hospital, with 2 weekly sessions of 1.5 hr with high-intensity interval (80% of peak oxygen uptake [$\dot{V}O_{2peak}$]) and resistance training. The program was complemented with a weekly session of group-based patient education for 1.5 hr on heart disease, psychological issues, and diet counseling. In addition, patients had one or more individual sessions with a cardiologist and a nurse, respectively.

CRF was assessed 6 to 8 wk postsurgery using a cardiopulmonary exercise test (CPX) with measurement of $\dot{V}O_{2peak}$ using a maximal symptom-limited bicycle ergometer

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test (via Sprint 150P, Ergoline). Expired gases were collected and analyzed (Jaeger, Master Screen CPX version 5.21, Cardinal Health). Each test aimed at a respiratory exchange ratio ≥ 1.1 to ensure the validity of the CPX.[20]

### PRIMARY EXPOSURE AND OUTCOME VARIABLES

The primary exposure variables were depression, socioeconomic status, and ethnicity. Depression included pre-existing depression defined as patients receiving antidepressants before their cardiac event, and new-onset depression defined as a sign of depression at the baseline CR visit assessed using a 3-question modified depression questionnaire, the validated Primary Care Evaluation of Mental Disorders (PRIME-MD) score.[21] Patients fulfilling both criteria were classified as pre-existing depression. Socioeconomic factors comprised educational attainment and working status. Educational attainment was grouped in 4 categories: no education, short-term education (eg, craftsman), medium education (bachelor degree or equivalent), and higher education (master degree in university). Working status was also in 4 categories: employed, unemployed, retired, and being on disability pension. Ethnicity was categorized as Western European or non-Western European descent. The majority of the patients of non-Western descent were from the Middle East. No distinction between first- and second-generation immigrants was made. CRF measured at baseline and change following CR were the primary outcomes.

### CONFOUNDING VARIABLES

Age, sex, index event, use of β-blockers, use of statins, left ventricular ejection fraction, and comorbidities were included as potential confounding variables. Comorbidities were assessed using the validated Charlson Comorbidity Index[22] that combines comorbidities (diabetes, kidney diseases, cancer, chronic obstructive pulmonary disease, and age) to estimate disease burden.

### STATISTICAL ANALYSIS

Normally distributed variables were compared across groups using the *t* test or 1-way analysis of variance. Nonnormally distributed variables were tested using Mann-Whitney and Kruskal-Wallis tests while categorical data were tested by the $\chi^2$ test. When statistically significant differences between groups were found, *post hoc* pairwise comparisons were made using the *t* test and $\chi^2$ with no adjustment for multiple comparisons.

Predictors of $\dot{V}O_{2peak}$ at baseline were tested using multiple-adjusted linear regression analyses. Confounders for the baseline analyses were identified according to previous literature[5,6] and whether they were associated with CRF and depression/socioeconomic factors/ethnicity. Follow-up analyses were additionally adjusted for baseline $\dot{V}O_{2peak}$. Identified confounders were tested sequentially against a simple regression model to assess the impact they had on CRF. Confounders that influenced a change in the estimate for the primary exposure variable of >15% were included in the final model.[23]

Loss to follow-up was defined as patients attending a baseline $\dot{V}O_{2peak}$ test and not attending the follow-up $\dot{V}O_{2peak}$ test when completing CR. Predictors of loss to follow-up were tested using a multiple logistic regression. Some patients chose to join a CR program in another unit and were not a part of the loss to follow-up analysis.

A 2-tailed *P* value < .05 was considered as statistically significant. All statistical analyses were carried out using STATA IC 13.1 (StataCorp LP).

## RESULTS

A total of 1780 patients accepted CR during the period. Several patients had missing data on the depression variable and were excluded from the analysis. After excluding patients with missing data on depression or baseline CPX (Figure), 1217 patients comprised the sample for the baseline analyses. For the follow-up analyses, 861 (71%) patients with CPX at baseline and follow-up comprised the study population.

### BASELINE CHARACTERISTICS

The mean age of the study population was 61.3 y, 78% were male, and 92% had coronary heart disease as index event. New-onset or pre-existing depression was present in 15%, 60% were not part of the workforce, and 16% were of non-Western ethnicity.

Baseline characteristics by depression status at baseline are given in Table 1. Patients with pre-existing depression were more likely to be women, to have chronic heart failure and low ejection fraction, live alone, be smokers, and be out of the workforce. Patients with new-onset depression were younger, more likely to be female, smokers, of non-Western ethnicity, and cohabitating. Baseline characteristics by educational attainment and ethnicity are given in the supplementary material (see Supplemental Digital Content 1, available at: http://links.lww.com/JCRP/A86, and Supplemental Digital Content 2, available at: http://links.lww.com/JCRP/A87). Lower educational attainment was associated with female sex, smoking, lower CRF, and non-Western ethnicity.

### CRF BEFORE CR

Mean ± SD $\dot{V}O_{2peak}$ at baseline was 21.8 ± 6.7 mL/kg/min, which was higher with higher educational attainment, in patients who were part of the workforce and in patients of Western ethnicity. $\dot{V}O_{2peak}$ was associated with sex, age, left ventricular ejection fraction, Charlson Comorbidity Index, and use of β-blocker, but not with index event (STEMI, non-STEMI, unstable angina pectoris, stable coronary artery disease with revascularization [percutaneous coronary

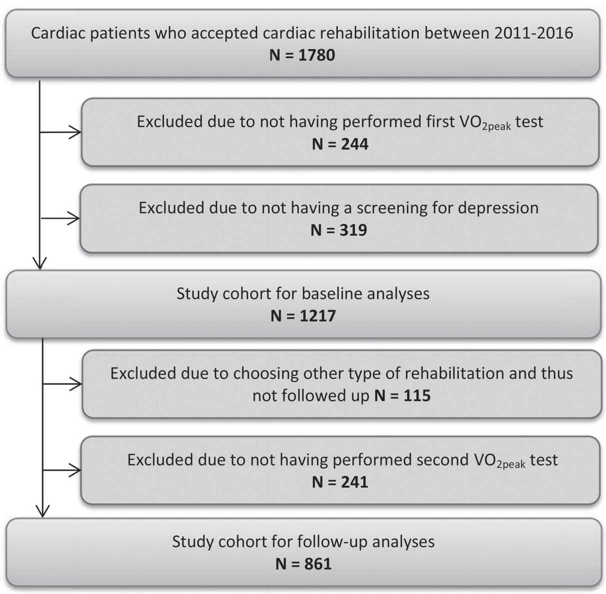


**Figure.** Flowchart of study population with number of patients excluded and reason for exclusion.

**Table 1**

**Characteristics of the Study Population by Depression**

| Characteristics[a] | Depression: No n = 1034 | New-Onset Depression n = 89 | Pre-existing Depression n = 94 | *P* Value |
|---|---|---|---|---|
| Age, yr | 62 ± 11[b] | 57 ± 9[b,c] | 61 ± 9[c] | <.001 |
| Sex, male | 80[b,d] | 67[b] | 64[d] | <.001 |
| Body mass index, kg/m$^2$ | 27.8 ± 4.6 | 28.3 ± 4.7 | 27.9 ± 4.8 | .566 |
| Ejection fraction, % | 52[d] | 52[c] | 48[c,d] | .005 |
| $\dot{V}O_{2peak}$, mL/kg/min | 22.0 ± 6.8[d] | 22.0 ± 6.9[c] | 20.1 ± 5.5[c,d] | .038 |
| Smoking status | | | | |
| Never smoked (>1 yr) | 63[b,d] | 42[b,c] | 51[c,d] | <.001 |
| Former smoker (<1 yr) | 22[b] | 35[b,c] | 19[c] | |
| Current smoker | 15 | 23 | 30 | |
| Hypertension | 53 | 56 | 59 | .491 |
| Hypercholesterolemia | 62[b,d] | 68[b] | 70[d] | .163 |
| β-Blockers | 78[d] | 84[c] | 69[c,d] | .012 |
| Statins | 89[b] | 96[c] | 86[b,c] | .015 |
| Living status (not alone) | 63[b] | 70[b,c] | 50[c] | .013 |
| Ethnicity (Non-Western European) | 14[b] | 35[b,c] | 11[c] | <.001 |
| Index event | | | | |
| STEMI | 27[d] | 29[c] | 18[c,d] | <.001 |
| N-STEMI | 26 | 25 | 22 | |
| Unstable angina pectoris | 12[b] | 17[b,c] | 12[c] | |
| Stable angina | 26 | 26 | 29 | |
| Chronic heart failure | 1[b,d] | 0[b,c] | 11[d,c] | |
| Heart valve replacement | 9[b] | 0[b,c] | 9[c] | |
| Educational attainment | | | | |
| No education | 17[b,d] | 24[b] | 23[d] | .006 |
| Short-term education | 43[d] | 47[c] | 33[c,d] | |
| Medium education | 15[b,d] | 6[b,c] | 21[c,d] | |
| Higher education | 24 | 23 | 22 | |
| Working status before index event | | | | |
| Working | 39[b] | 42[c] | 20[c,d] | <.001 |
| Unemployed | 7[b,d] | 17[b] | 16[d] | |
| Retirement | 48[b] | 27[b,c] | 49[c] | |
| Disability pension | 5[b,d] | 14[b] | 15[d] | |
| Charlson Comorbidity Index (0-9 comorbidities) | 2.3 ± 1.4[b] | 1.7 ± 1.3[b,c] | 2.5 ± 1.5[c] | .002 |

Abbreviations: N-STEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.
[a]Data are reported as mean ± SD or (%).
[b]No depression versus new-onset depression ($P < .05$).
[c]New-onset depression and pre-existing depression ($P < .05$).
[d]No depression and pre-existing depression ($P < .05$).

intervention or coronary artery bypass grafting], chronic heart failure, or heart valve replacement) or cardiovascular risk factors (Table 2A). In an age- and sex-adjusted analysis, education, working status, ethnicity, and pre-existing depression were associated with $\dot{V}O_{2peak}$.

After multivariable adjustment educational attainment, working status and non-western ethnicity remained associated with $\dot{V}O_{2peak}$, while pre-existing depression did not.

### *IMPROVEMENT OF CRF FOLLOWING CR*

Overall improvement of $\dot{V}O_{2peak}$ following CR was 2.4 mL/kg/min ± 4.3 or equivalent of 11% increase. The age- and sex-adjusted improvement of $\dot{V}O_{2peak}$ was similar in men and women and was not related to depression status (Table 2B). Patients with heart valve replacement had a greater improvement in $\dot{V}O_{2peak}$, whereas patients who were unemployed or with lower levels of education seemed to benefit less.

After multivariable adjustment working status, educational attainment and ethnicity remained associated with improvement in $\dot{V}O_{2peak}$. Patients with heart valve replacement had greater improvement in $\dot{V}O_{2peak}$ (2.6 mL/kg/min [1.4-3.8]) compared with STEMI patients.

### *LOSS TO FOLLOW-UP*

A total of 241 (22%) patients were lost to follow-up. In a multivariable-adjusted logistic regression, loss to follow-up was associated with younger age, higher baseline $\dot{V}O_{2peak}$, smoking, comorbidity, and being on disability pension but not with depression, educational attainment, or ethnicity (Table 3).

## DISCUSSION

The aim of this study was to evaluate whether depression, socioeconomic status, and ethnicity affected CRF and effect

**Table 2**

**Predictors of $\dot{V}O_{2peak}$ Before Cardiac Rehabilitation (A) and Change in $\dot{V}O_{2peak}$ Following Cardiac Rehabilitation (B) From Linear Regression Analyses**

| Predictors[a] | Regression Coefficient Adjusted for Age and Sex | Multivariable-Adjusted Regression Coefficient |
|---|---|---|
| ***A. $\dot{V}o_{2peak}$ before CR (number of observations = 1217)*** | | |
| Sex, male | 3.1[b] (2.3 to 3.9) | 3.4[b] (2.6 to 4.2) |
| Age (per 10 yr) | −2.5[b] (−2.8 to −2.3) | 0.1 (−0.7 to 0.8) |
| Depression | No depression | No depression |
| New onset of depression | −0.9 (−2.2 to 0.4) | 0.4 (−1.0 to 1.8) |
| Pre-existing depression | −1.4[c] (−2.7 to −0.1) | −0.5 (−1.89 to 0.68) |
| Educational attainment | No education | No education |
| Short-term education | 1.4[d] (0.4 to 2.4) | 0.5 (−0.5 to 1.4) |
| Medium education | 3.5[b] (2.4 to 4.6) | 2.0[d] (0.8 to 3.2) |
| Higher education | 4.1[b] (3.1 to 5.1) | 2.3[b] (1.2 to 3.4) |
| Working status | Working | Working |
| Unemployed | −3.8[b] (−5.0 to −2.6) | −1.9[d] (−3.2 to −0.6) |
| Retirement | −3.0[b] (−4.0 to −2.0) | −3.1[b] (−4.2 to −2.0) |
| Disability pension | −4.5[b] (−5.7 to −3.2) | −3.0[b] (−4.5 to −1.6) |
| Ethnicity | Western European | Western European |
| Non-Western European | −3.3[b] (−4.1 to −2.4) | −1.4[d] (−2.3 to −0.4) |
| β-Blockers (yes) | −1.4[b] (−2.2 to −0.7) | −0.9[c] (−1.8 to −0.6) |
| Charlson Comorbidity Index | −1.7[b] (−2.0 to −1.3) | −1.5[c] (−2.0 to −1.1) |
| Ejection fraction (per 10%) | 1.3[b] (1.1 to 1.4) | 1.1[c] (0.8 to 1.5) |
| ***B. Change in $\dot{V}o_{2peak}$ after CR (number of observations = 861)*** | | |
| Baseline $\dot{V}O_{2peak}$ | −0.25 (−0.28 to −0.23) | −0.2 (−0.3 to −0.2) |
| Sex, male | 0.1 (−0.7 to 0.7) | 0.5 (−0.2 to 1.3) |
| Age (per 10 yr) | −0.5[b] (−0.7 to −0.2) | −0.4 (−1.1 to 0.2) |
| Depression | No depression | No depression |
| New onset of depression | −0.5 (−1.6 to 0.6) | −0.4 (−1.5 to 0.7) |
| Pre-existing depression | 0.15 (−1.04 to 1.34) | 0.3 (−0.9 to 1.5) |
| Index event | STEMI | STEMI |
| N-STEMI | 0.4 (−0.3 to 1.1) | 0.7 (−0.1 to 1.5) |
| Unstable angina pectoris | 0.4 (−0.5 to 1.2) | 0.4 (−0.6 to 1.4) |
| Stable angina pectoris | 0.8[c] (0.2 to 1.5) | 0.9 (−0.1 to 1.7) |
| Chronic heart failure | 1.3[c] (0.2 to 2.4) | 2.2 (−1.2 to 5.5) |
| Heart valve replacement | 2.3[b] (1.2 to 3.3) | 2.6[b] (1.4 to 3.8) |
| Educational attainment | No education | No education |
| Short-term education | 1.2[d] (0.3 to 2.0) | 1.6[b] (0.7 to 2.5) |
| Medium education | 1.1[c] (0.1 to 2.0) | 1.3[c] (−0.3 to 2.4) |
| Higher education | 1.6[b] (0.7 to 2.5) | 2.0[b] (1.1 to 3.0) |
| Working status | Working | Working |
| Unemployed | −1.4[d] (−2.5 to −0.4) | −1.9[d] (−3.1 to −0.8) |
| Retirement | 0.1 (−0.8 to 0.9) | −0.2 (−1.2 to 0.7) |
| Disability pension | −0.6 (−1.9 to 0.6) | −0.9 (−2.3 to 0.5) |
| Ethnicity | Western European | Western European |
| Non-Western European | −1.3[d] (−2.0 to −0.5) | −0.9[c] (−1.1 to −0.1) |
| β-Blockers (yes) | −0.2 (−0.9 to 0.4) | −0.3 (−1.1 to 0.5) |
| Charlson Comorbidity Index | −0.4[b] (−0.7 to −0.1) | −1.1[b] (−1.1 to −0.3) |
| Ejection fraction (per 10%) | 0.1 (−0.1 to 0.2) | 0.2[c] (0.1 to 0.4) |

Abbreviations: CR, cardiac rehabilitation; N-STEMI, non-ST-segment elevation myocardial infarction; STEMI; ST-segment elevation myocardial infarction.
[a]Values indicate difference in mL/kg/min.
[b]$P < .001$.
[c]$P < .05$.
[d]$P < .01$.

of CR following a cardiac event. The main findings are that, after multivariable adjustment, patients with pre-existing depression and signs of new-onset depression do not have lower CRF than cardiac patients without depression, and both groups benefit equally from CR. However, educational attainment, working status, and ethnicity were all negatively associated with CRF and were also predictors of less improvement in CRF following CR.

### DEPRESSION AS A PREDICTOR OF $\dot{V}O_{2peak}$

To our knowledge, depression has not been investigated as a predictor of CRF before CR in previous studies. Studies

**Table 3**

**Multivariable-Adjusted Logistic Regression of Loss to Follow-up[a]**

| | OR (95% CI) |
|---|---|
| $\dot{V}O_{2peak}$, mL/kg/min | 0.96[b] (0.94 to 0.98) |
| Sex, male | −0.31 (−0.63 to 0.90) |
| Age | 0.97[c] (0.95 to 0.99) |
| Depression status | Not depressed |
| New onset of depression | 0.89 (0.53 to 1.48) |
| Pre-existing depression | 1.55 (0.96 to 2.37) |
| Smoking status | Never smoked (>1 y) |
| Former smoker (<1 yr) | 1.03 (0.74 to 1.43) |
| Smoker | 1.68[c] (1.19 to 2.37) |
| Working status | Working |
| Unemployed | 1.19 (0.73 to 1.92) |
| Retirement | 1.43 (0.75 to 1.75) |
| Disability pension | 1.91[c] (1.50 to 3.16) |
| Educational attainment | Higher education |
| No education | 1.13 (0.74 to 1.71) |
| Short-term education | 0.99 (0.71 to 1.40) |
| Medium education | 0.87 (0.57 to 1.36) |
| Ethnicity (non-Western European) | 1.09 (0.75 to 1.59) |
| Charlson Comorbidity Index (0-9 comorbidities) | 1.17[c] (1.01 to 1.36) |

[a]Adjusted for β-blockers, living status, and ejection fraction. They did not confound the results and were excluded from the analyses.
[b]$P < .001$.
[c]$P < .05$.

of associations between depression symptom severity and CRF in healthy populations were recently summarized in a meta-analysis.[24] A modest correlation ($r = -0.16$, [−0.21 to −0.10]) between depression symptom severity and CRF was found. In our study we did not find a significant association, but the results do not exclude a modest association between both chronic and new-onset depression and $\dot{V}O_{2peak}$.

Depression has previously been suggested as a predictor of lack of improvement of $\dot{V}O_{2peak}$ following CR. This was shown in a cohort study by Egger et al[9] in 2008 on 114 patients with coronary artery disease. Using the Hospital Anxiety and Depression Scale, they found that depression was associated with lower improvement (−0.2 mL/kg/min, $P = .047$) of CRF following CR.[9] We did not observe this finding, which may be related to lack of statistical power. Unlike the aforementioned study, we stratified depression into pre-existing depression and new-onset depression. Stratifying depression is relevant since cardiac patients with pre-existing and new-onset depression have different characteristics, as confirmed in the present and other studies[25] and their psychopathology is likely to have a different time course after myocardial infarction.

The other comparative study found was approximately 10-yr old.[9] CR programs are modified, as new knowledge is gained and the increased awareness on depression in cardiac patients may explain why some patients with depression improve as much as those without depression. Patients in our study received a group-based exercise intervention with a multidisciplinary approach and were closely monitored with patient education and individual counseling with a nurse. Psychosocial issues were also addressed during the individual consultations. There was an increased loss to follow-up among patients with pre-existing depression (non-significant OR =1.51, $P = .072$). An unequal dropout rate among those with and without depression should be expected, as those with depression usually have lower adherence and compliance to CR programs.[10,26,27] This could bias the results and lead us to overestimate the effects of CR in patients with pre-existing depression.

### *SOCIOECONOMIC PREDICTORS OF $\dot{V}O_{2peak}$*

Previous research has focused on identifying physical and exercise-related parameters as predictors of $\dot{V}O_{2peak}$.[5,28,29] In our study, $\dot{V}O_{2peak}$ was dependent on several relevant parameters, both before and after CR. The strongest associations were seen for socioeconomic factors.

Lower educational attainment was associated with lower baseline $\dot{V}O_{2peak}$ as well as smaller improvement following CR. Thus, the disparity present at baseline was increased following CR. Combined, the estimated difference in $\dot{V}O_{2peak}$ between highest and lowest education levels was approximately 4.5 mL/kg/min, a relatively large difference in a population with a mean baseline $\dot{V}O_{2peak}$ of 21.8 mL/kg/min. The impact of educational attainment stands in contrast to a German cohort study by Salzwedel et al[30] from 2015, which reported that being a current smoker and being female, but not socioeconomic status, were associated with less effect following CR. However, the study by Salzwedel et al was based on brief, in-house CR in a more selected population and may not be comparable to results from outpatient CR.

Working status also predicted $\dot{V}O_{2peak}$ both before and after CR, as lower $\dot{V}O_{2peak}$ before CR was strongly associated with patients being on disability pension, pension, or being unemployed. Being unemployed also predicted less improvement in $\dot{V}O_{2peak}$ following CR. Previous studies have found that working status was a predictor of initiation of CR.[16,31] Our study adds to this in identifying work-related subgroups in greater need of CR through poorer CRF. In addition, we found that not only comorbidity but also current working status was associated with more dropout. This result is supported by a study on adherence to CR at the Vermont Medical Center finding that lower socioeconomic status was highly associated with lower adherence to the CR program.[32]

### *ETHNICITY AS A PREDICTOR OF $\dot{V}O_{2peak}$*

Not having a Western European ethnicity was associated with lower $\dot{V}O_{2peak}$ both before and after CR, even after adjusting for socioeconomic factors. Ethnic inequalities in referral and adherence to CR programs have previously been found in several studies, although mainly from the United States.[33-35] It is likely that in Europe having another ethnicity than Western European is associated with cultural barriers, preventing these patients from achieving the most from CR.

### *STRENGTHS AND LIMITATIONS*

This is one of the largest studies to examine how depression, socioeconomic factors, and ethnicity affect CRF both before and after CR. A strength of the study was dividing depression into pre-existing and new-onset of depression. In addition, the high-quality clinical registry comprising unique data on patient characteristics, comorbidities, medicine, and physical examinations is likely to be representative of patients participating in CR.

A limitation of our study was that the patients were screened for depression using an abbreviated depression questionnaire. Simplifying the questionnaire might have led to misclassification and loss of precision. A future study could apply a finer depression scale, which could make it possible to detect smaller and perhaps graded differences. Another limitation was only 16% of the patients were of non-Western origin. As this was a retrospective study, we could not determine causal factors responsible for participation and completion of the CR program. Also, it was not possible to adjust for adherence (number of training sessions attended) in the CR program. Results may also be biased by the marginally higher dropout rate among patients with depression and on disability pension, although this is likely to cause us to underestimate the effect of these factors. Finally, 600 patients were excluded from the baseline analysis due to missing data on the cardiopulmonary exercise test (n = 289) and screening for depression (n = 319). Although this loss is likely to be random, it may increase the risk of a selection bias.

## CONCLUSION

Having pre-existing depression and new-onset depression did not influence $\dot{V}O_{2peak}$ either before or after CR. All subgroups of patients improved in $\dot{V}O_{2peak}$ after CR. Socioeconomic parameters and non-Western ethnicity were associated with impaired $\dot{V}O_{2peak}$ at baseline, and this difference was reinforced by different efficacy of CR across socioeconomic and ethnic subgroups. These results identify important subgroups with particular need of attention, encompassing measures such as supervised CR, extended programs, and programs specifically targeting ethnic barriers to exercise when planning an outpatient CR program.

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# Title

The motivation for physical activity is a predictor of $VO_{2peak}$ and is a useful parameter when determining the need for cardiac rehabilitation in an elderly cardiac population

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# Abstract

**Background:** Exercise-based cardiac rehabilitation (CR) is an essential contributor to a successful recovery for elderly cardiac patients. The motivation for physical activity is a psychological parameter seldom described in secondary prevention, and it is plausible that motivation contributes to the differential effect of CR.

**Purpose:** To investigate if motivation, measured using the behavioral regulation in an exercise questionnaire (BREQ-2), predicts $VO_{2peak}$ in elderly cardiac patients before and after CR.

**Methods:** A prospective cohort study of elderly ischemic cardiac patients and patients with valvular disease participating in cardiac rehabilitation was used. Motivation was measured using BREQ-2, which measures five constructs of motivation and a summed score - the relative autonomy index (RAI). $VO_{2peak}$ was measured before and after CR using a cardiopulmonary exercise test (CPET).

**Results:** Two hundred and three patients performed the baseline tests and initiated CR. One hundred and eighty-two completed CR and comprised the follow-up group. The mean $VO_{2peak}$ was 18 ml/kg/min (SD±5.1). VO2peak increased significantly with increasing motivation, 1.02 (.41 - 1.62) ml/kg/min pr. SD. Mean improvement from CR was 2.3 ml/kg/min (SD±4.3), the equivalent of a 12% increase. A change in $VO_{2peak}$ after CR was likewise positively associated with increased motivation, .74 (.31 - 1.17) pr. SD.

**Conclusion:** The level of motivation predicts $VO_{2peak}$ before CR, and is also able to predict changes in $VO_{2peak}$ following CR. Motivation measured with the BREQ-2 questionnaire can be applied as a screening tool for elderly cardiac patients before they initiate CR to detect patients with low $VO_{2peak}$.


Keywords: Cardiac rehabilitation, cardiac patients, motivation, BREQ-2, Social determination theory, cardiorespiratory fitness, $VO_{2peak}$

# Introduction

Cardiac rehabilitation (CR) is an essential contributor to a successful recovery for cardiac patients. CR improves life expectancy, physical function, and quality of life and patients experience less relapse of the disease compared to non-participants of CR (1-3).

Although the benefits of exercise-based rehabilitation are well studied, compliance and adherence in CR remain low (4). This is especially the case in elderly cardiac patients. Poor compliance and adherence have previously been linked to psychological distress, especially anxiety and depression (5-7). As psychological distress is more prevalent in the younger segment of the cardiac population (8, 9), other psychological factors may determine success in CR in the elderly cardiac patients.

Physical exercise is a primary component in CR. The motivation for physical activity is a parameter seldom described in secondary prevention, and it is plausible that the lack of motivation to be physically active can explain the difference in success rates when participating in CR.

The motivation for physical activity can be measured using the validated "behavioral regulation in exercise questionnaire" (BREQ-2). BREQ-2 is based on the Self Determination Theory, which is used to understand exercise and physical activity patterns (10, 11) and why people adopt and/or maintain a behavior change (12, 13). The BREQ-2 questionnaire measures different constructs of motivation. A summed score of the level of motivation can be derived by combining the constructs of motivation. The summed score is named the Relative Autonomy Index (RAI).

This study aimed to investigate if the constructs of motivation and/or the RAI was associated with $VO_{2peak}$ in elderly cardiac patients before CR and whether motivation would affect a change in $VO_{2peak}$ following CR.

# Methods

## The study population

This is a prospective cohort study of elderly cardiac patients entering a CR program at a Danish cardiac rehabilitation unit at a hospital in Copenhagen from December 2015 to February 2018 (14). Patients were asked to join the study if they were more than 64 years of age and met one of the following criteria within three months of entering the CR program: 1) had acute coronary syndrome, including myocardial infarction 2) underwent percutaneous coronary intervention, 3) received coronary artery bypass grafting or 4) received a heart valve replacement. Exclusion criteria: Patients with a contraindication to CR, mental impairment leading to an inability to cooperate, a severly impaired ability to exercise, signs of severe cardiac ischemia and/or a positive exercise testing on severe cardiac ischemia, insufficient knowledge of the native language and an implanted cardiac device (CRT-P, ICD).

Ethical approval for the study was obtained from the Regional Scientific Ethical Committee for Copenhagen, Denmark (Ref.: H-15011913) and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained.

The study cohort is part of a multi-center/national cohort study, *European Cardiac Rehabilitation in the Elderly* (EU-CaRE, https://eu-care.org/).

## Rehabilitation program

The CR program consisted of a supervised eight-week outpatient exercise intervention at a hospital with two weekly sessions of 1.5 hours with a high-intensity interval (80% of $VO_{2peak}$) and resistance training. The program was complemented with a weekly session of group-based patient education for 1.5 hours on cardiovascular disease, psychological issues, and diet counseling. Additionally, patients had one or more individual sessions with a cardiologist, a dietician, a physiotherapist, and a nurse.

### Primary exposure – the motivation for physical activity

The level and type of motivation were measured using BREQ-2 (see appendix). The BREQ-2 is the second version of the questionnaire and is a validated and useful tool to measure a patient's motivation for exercise (15).

The BREQ-2 inventory comprises 19 items. Each item has five possible answers scored on a scale of 0–4 (0 = Not true for me; 4 = Very true for me). The questionnaire assesses five constructs: *amotivation* – e.g., "I think that exercising is a waste of time"; *external regulation* – e.g., "I exercise because other people tell me I should"; *introjected regulation* – e.g., "I feel guilty when I do not exercise"; *identified regulation* – e.g., "I value the benefits/advantages of exercising"; and *intrinsic motivation* – e.g., "I enjoy my exercise sessions". BREQ-2 was measured as a multidimensional scale, measuring each of the five types of motivation. Additionally, a summed score was derived from the five subscales, the Relative Autonomy Index (RAI). The RAI gives an index of the degree to which respondents are motivated. The RAI is obtained by weighting each subscale and then summing these weighted scores. Each subscale score is multiplied by its weighting, and then the weighted scores are summed. Higher, positive scores indicate greater relative autonomy; lower, negative scores indicate more controlled regulation.

In the descriptive analyses (Table 1) the RAI was categorized into low, medium and high degrees of motivation.

### Study outcome

The primary study outcome was $VO_{2peak}$. $VO_{2peak}$ was assessed before and after CR using a cardiopulmonary exercise test (CPET) using a maximal symptom-limited bicycle ergometer test (Via Sprint 150P, Ergoline). Breathing gases were collected and analyzed (Jaeger, Master Screen, vers.5.21, Cardinal Health). Each test aimed at a respiratory exchange ratio greater than 1.1 to ensure the validity of the CPET tests (16).

### Confounding variables

Other variables of interest included age, sex, revascularization (PCI or CABG), educational attainment (Short or higher education), working status (working or retired), smoking status (never a smoker, former smoker, current smoker), physical activity level during leisure time (>30 minutes, 0-7 days per week) before cardiac event, the use of beta blockers (yes/no), use of statins (yes/no), left ventricular ejection fraction (%), comorbidities. Psychological distress was accounted for with three questionnaires measuring vital exhaustion, depression, and anxiety. Vital exhaustion was assessed using a 17-item questionnaire (17). Depression and anxiety were assessed the validated Patient Health Questionnaire (PHQ-9) (18) and General Anxiety Disorder questionnaire (GAD-7) (19), respectively.

Follow-up analyses were also investigated for the influence of $VO_{2peak}$ at baseline, the premature end of rehabilitation and compliance to the CR program (<50%, 50-75% or >75% attendance).

## Statistical analysis

The summed motivation score, RAI, is a continuous variable. For the descriptive statistics, the RAI was categorized into low (RAI<0, medium (RAI 0-9) and high (RAI>10-20) levels of motivation. For the inferential statistics, the RAI was used as a continuous variable.

Normally distributed variables were compared across the different levels of motivation using one-way ANOVA. Non-normally distributed variables were tested using Mann-Whitney and Kruskal-Wallis tests, while a Chi 2 test tested categorical data. Statistically significant differences between the groups were tested with pairwise comparisons using t test and Chi 2 tests.

Correlation between the constructs of motivation and $VO_{2peak}$ were assessed by scatterplots and tested using Pearson's Correlation.

The influence of motivation on $VO_{2peak}$ was tested using multiple adjusted linear regression analyses. Confounders for both baseline and follow-up analyses were identified according to previous literature (20, 21) and whether they were associated with CRF and motivation. Follow-up analyses were additionally adjusted for $VO_{2peak}$ at baseline and compliance to the CR program. Identified confounders were tested sequentially against a simple regression model, and adjusted for sex and age to assess the impact on CRF. Confounders that influenced a change in the estimate for motivation by more than 15% were included in the final model (22). Due to the different continuous scales of the covariates, a standardized regression model was conducted to compare the strength of the association of different continuous predictors with the outcome within the same model.

A 2-tailed *p* value <0.05 was considered to be statistically significant. All statistical analyses were carried out using STATA IC 13.1 (StataCorp LP).

# Results

Two hundred and thirty-seven patients were initially included in the study. Two hundred and three performed the baseline CPET and completed the BREQ-2 questionnaire. These patients comprised the baseline analyses. One hundred and eighty-two patients performed the second CPET and comprised the follow-up analyses. For a detailed overview of patient exclusion, see Figure 1.

## Baseline characteristics

Baseline characteristics, according to the categorized RAI score (low, medium and high motivation), are presented in Table 1.

The mean age of the population was 72 (±5) years old, and 73% was male. The majority were Western European and living with a spouse. Almost half of the population had a higher educational attainment. Only 9% were current smokers. Half of the population had a PCI, 30 % CABG, 14% heart valve replacement and 5% no revascularization. The mean $VO_{2peak}$ before CR was 18.2 (±5.0). The mean motivation RAI score was 5 (±7) ranging from -14 to 19.

Twenty-three percent of the population had low levels of motivation, while 31% were highly motivated. Patients with a low level of motivation had an overall higher burden of risk factors: higher body mass index, higher prevalence of both diabetes and hypertension, and lower LVEF. Patients with a low level of motivation also tend to live alone more and score higher on vital exhaustion than patients with both medium and high levels of motivation.

Differences between high and medium motivation levels were minor: Patients with a high level of motivation had a lower prevalence of hypercholesteremia, less hypertension, and lower vital exhaustion score.

There was a definite increase in $VO_{2peak}$ with an increasing level of motivation ($p<0.001$).

## Constructs of motivation

A correlation between the five constructs of motivation and $VO_{2peak}$ was tested using pairwise correlations and scatterplots with a linear prediction (Figure 2). Except for introjected regulation, all constructs of motivation were significantly correlated with $VO_{2peak}$ at baseline. $VO_{2peak}$ correlated most with RAI ($r= 0.30$, $p< 0.01$). RAI also correlated with the other constructs of motivation. The highest correlation was observed between RAI and $VO_{2peak}$. Amotivation and external regulation were especially right-skewed, whereas intrinsic regulation had a bimodal distribution.

To avoid multicollinearity between the different constructs of motivation, the RAI was chosen as the primary exposure variable for the baseline analyses.

## $VO_{2peak}$ before CR

$VO_{2peak}$ was associated with sex, activity level, revascularization procedure, comorbidity, and vital exhaustion, but not with age, ejection fraction, or use of beta-blockers. RAI and $VO_{2peak}$ were significantly correlated (Fig. 2). When adjusting for age and sex, the RAI remained significantly associated with $VO_{2peak}$ (Table 3). After multiple adjustments, motivation continued to be associated with $VO_{2peak,}$ even after an adjustment for depression.

Motivation, depression, age and ejection fraction were standardized in the multiple models to compare the importance of the individual covariates on the same scale. After standardization, motivation had a just as high association with $VO_{2peak}$ as depression. Comorbidity also had a high impact on $VO_{2peak}$.

## Change in $VO_{2peak}$ following CR

A mean improvement from CR was 2.27 ml/kg/min (SD±4.3), the equivalent of a 12% increase. In age and sex, an adjustment change in $VO_{2peak}$ was positively associated with motivation score, and negatively associated with comorbidities and having hypertension.

In the multiple-adjusted model, motivation continued to be statistically associated with $VO_{2peak}$, whereas depression was not associated. Age remained insignificant, and males improved more than females. Smokers improve less than previous smokers and non-smokers. Using statins, having hypertension, hypocholesteremia, and comorbidities also had a negative association with a change in $VO_{2peak}$.

In the standardized model, comorbidities had the strongest association. Motivation had a strong association along with a baseline $VO_{2peak}$.

# Discussion

We aimed to investigate whether motivation, measured using BREQ-2, was a predictor of $VO_{2peak}$ before and after CR in an elderly cardiac population. This is the first study to apply BREQ-2 to cardiac patients to predict the success of CR. Using the computed RAI score, there was a significant association between motivation and $VO_{2peak}$, both before and after CR. This was shown in both simple and multiple-adjusted regression analyses.

## Motivation as a predictor of $VO_{2peak}$ before and after CR

Applying the BREQ-2 to measure motivation seems to be a valid tool to predict physical capacity in the elderly cardiac population. Psychological distress, measured using depression, anxiety, and vital exhaustion, does not appear to affect this relationship.

In current CR programs, it is recommended that the patients are screened for psychological distress with, for example, the Hospital Anxiety and Depression Scale (HADS) (23). The prevalence of psychological distress is higher in the younger part of the cardiac population (24).  These results showed that depression is equally important for $VO_{2peak}$ before CR. However, the presence of depression did not affect the impact of motivation on $VO_{2peak}$. Vital exhaustion and anxiety did not have an impact on $VO_{2peak}$ before CR.

Motivation was the only psychological factor that had an impact on change in $VO_{2peak}$ following CR. Neither depression, anxiety, nor vital exhaustion had an impact on change in $VO_{2peak}$. This could suggest that it is more relevant to screen older cardiac patients for motivation rather than other psychological factors, at least if the purpose is to screen for physical condition.

It should be stressed that this is a selected patient group that has accepted CR. Less than 50% of cardiac patients participate in CR (25), and it is uncertain whether these results can be generalized to patients that don't participate in CR, as they may have lower motivation. It is also uncertain whether this can be transferred to younger cardiac patients (<65 years).

## Constructs of motivation

BREQ-2 measured five constructs of motivation. In addition, we calculated the summed score, RAI. Some literature suggests that applying a simple score, e.g., the RAI, is a step backward and a simplification of the SDT (ref).

We tested all possible constructs of motivation against $VO_{2peak}$ in this paper and found that the constructed score was the only score that was normally distributed, and that this score also had the highest correlation with $VO_{2peak}$ (Figure 2).

The skewness of amotivation, external regulation and intrinsic regulation, in particular, might be explained by the selection of patients. The patients participated voluntarily in the CR program, and this suggests that the patients had at least some motivation for exercise. Patients with a high level of amotivation may be prone to reject participation in CR and participation in the study, introducing an increased risk of selection bias. This suggests that not all constructs of motivation fit equally well for patients engaging in exercise-based CR.

For future research, the model fit for amotivation specifically may be better if the BREQ-2 questionnaire is collected while the patients are still hospitalized. Many cardiac patients never initiate CR, and these patients, in particular, could prove to have higher levels of amotivation.

### Strengths and weaknesses

The focus on adapting a simple screening tool for motivation is a new approach in cardiac rehabilitation.

Motivational interviews can be time-consuming, and demand extra resources in a CR unit. Using the BREQ-2 could prove a relevant tool to guide therapists in targeting patients with low levels of motivation before they initiate rehabilitation.

The prospective study design provided the high quality of the data, both with regards to exposures, confounders, and endpoints. Also, given the nature of the prospective design, we could address the issue of causality between exposure and outcome.

A significant limitation to this study is that the patients were required to speak sufficient Danish to participate because they had to fill in Danish questionnaires, introducing a selection bias. Also, some patients who participated in CR declined to enroll in the study.

## Conclusion

Motivation predicted $VO_{2peak}$, both before and after participating in CR. Motivation measured with the BREQ-2 questionnaire can be applied as a screening tool for elderly cardiac patients before they initiate CR, both to detect patients with lower $VO_{2peak}$, and to detect patients that will increase less in $VO_{2peak}$ after CR.

## Table 1

Patient characteristics by level of motivation at the baseline

| | Motivation for physical activity | | | *p* value |
|---|---|---|---|---|
| | **Low** (RAI<0) | **Medium** (RAI 0-9) | **High** (RAI 10-20) | |
| **N** | **46 (23%)** | **94 (46%)** | **63 (31%)** | |
| **Age** (years) | 71.3±5 | 72.2±5 | 72.8±5 | 0.360 |
| **Sex (male)** | 34 (74%) | 69 (73%) | 46 (73%) | 0.995 |
| **Body mass index** ($kg/m^2$) | 29.3 (4.7) | 26.8 (4.0) | 26.3 (4.4) | ***<0.001*** |
| **Living status** (alone) | 21 (46%) | 27 (29%) | 18 (29%) | 0.096 |
| **Ethnicity** (Non- Western European) | 2 (4%) | 4 (4%) | 6 (9%) | 0.342 |
| **Educational attainment** | | | | |
| Short-term education | 26 (57%) | 43 (46%) | 38 (60%) | 0.169 |
| Long-term education | 20 (43%) | 51 (54%) | 25 (40%) | |
| **Index event** | | | | |
| ACS | 17 (37%) | 48 (52%) | 36 (57%) | 0.200 |
| Stable CAD | 22 (48%) | 34 (36%) | 17 (27%) | |
| Heart valve replacement | 7 (15%) | 11 (12%) | 10 (16%) | |
| **Smoking status** | | | | |
| Never smoked (>1year) | 27 (59%) | 58 (62%) | 14 (63%) | 0.094 |
| Former smoker (<1year) | 14 (30%) | 29 (31%) | 17 (27%) | |
| Smoker | 5 (11%) | 7 (7%) | 6 (10%) | |
| **Hypertension** (yes) | 14 (70%) | 32 (66%) | 37 (59%) | 0.468 |
| **Hypercholesterolemia** (yes) | 35 (76%) | 66 (71%) | 35 (55%) | ***0.047*** |
| **Ejection fraction** (%) | 50% | 52% | 53% | ***0.031*** |
| **Diabetes** (yes) | 16 (35%) | 15 (16%) | 8 (13%) | ***0.009*** |
| **Peripheral artery disease** (yes) | 4 (9%) | 11 (12%) | 4 (6%) | 0.485 |
| **COPD** (Yes) | 2 (4%) | 8 (9%) | 5 (8%) | 0.666 |
| **Kidney disease** (yes) | 5 (11%) | 11 (12%) | 8 (13%) | 0.978 |
| **Beta blockers** (yes) | 34 (74%) | 64 (68%) | 44 (70%) | 0.779 |
| **Statins** (yes) | 40 (87%) | 83 (88%) | 55 (87%) | 0.969 |
| **Vital exhaustion** (0-17 score) | 5.6 (4.1) | 4.2 (4.1) | 3.6(3.4) | ***0.027*** |
| **PHQ-9** (0-27 score) | 5.8 (4.6) | 5.2 (4.8) | 4.4 (4.3) | 0.641 |
| **GAD-7** (0-21 score) | 4.1 (4.4) | 3.4 (4.5) | 2.6 (3.4) | 0.607 |
| **$VO_{2peak}$** (mL/kg/min) | 16.1 (3.9) | 17.5 (4.7) | 20.3 (6.0) | ***<0.001*** |

Abbreviations: RAI, relative autonomy index; ACS, acute coronary syndrome; CAD; coronary artery disease; COPD; chronic obstructive pulmonary disease; PHQ-9; patient health questionnaire; GAD-7; generalized anxiety disorder. Data are reported as mean ± SD or number (%).

# Table 2

Standardized coefficients of predictors of $VO_{2peak}$ before cardiac rehabilitation (A) and a change in $VO_{2peak}$ following cardiac rehabilitation (B). Values indicate the difference in ml/kg/min.

| A | Age and sex adjusted | Multiple adjusted model |
|---|---|---|
| **Motivation** (RAI pr. SD) | 1.70 (1.04 - 2.37) *** | 1.05 (.43 - 1.69) ** |
| **Age** (pr. SD) | -1.47 (-3.09 - .15) | -1.02 (-2.47 - .42) |
| **Sex** (male) | 2.65 (1.06 - 4.24) *** | 3.23 (1.85 - 4.60) *** |
| **Activity level** (>30 min.) | 0 days | 0 days |
| 2-4 days | 1.71 (-.04 - 3.45) | 1.01 (-.52 - 2.56) |
| 5-7 days | 3.54 (1.93 - 5.15) *** | 2.64 (1.18 - 4.10) *** |
| **Index diagnosis** | ACS | ACS |
| Stable CAD | -1.76 (-3.29 - -.23) * | -.90 (-2.25 - .45) |
| Heart valve replacement | -2.47 (-4.62 - -.32) * | -1.80 (-3.69 - .09) |
| **Ejection fraction** (pr. SD) | 1.28 (.46 - 2.09) * | 1.24 (.54 - 1.94) ** |
| **COPD** (yes) | -2.34 (-5.03 - -.35) | -2.09 (-4.35 - .17) |
| **Diabetes** (yes) | -4.01 (-5.71 - -2.30) *** | -2.22 (-3.81 - -.64) * |
| **Kidney disease** (yes) | -3.98 (-6.14 - -1.82) *** | -3.24 (-5.13 - -1.35) ** |
| **PHQ-9** (pr. SD) | -1.28 (-1.99 - -.58) *** | -.89 (-1.51 - -.28) * |
| **B** | **Age and sex adjusted** | **Multiple adjusted model** |
| **Motivation** (RAI pr. SD) | .57 (.12 - 1.01) * | .78 (.33 - 1.24) ** |
| **Baseline $VO_{2peak}$** (pr. SD) | -.56 (-1.16 - .21) | -1.30 (-1.94 - -.66) *** |
| **Age** (pr. SD) | -.84 (-1.85 - .18) | -1.00 (-2.01 - -0.01) * |
| **Sex** (male) | -.18 (-1.21 - .85) | .74 (-.28 - 1.76) |
| **Smoking status** | Never smoker | Never smoker |
| Previous smoker | -.23 (-1.22 - .77) | -.37 ( -1.34 - .59) |
| Current smoker | -1.43 (-3.00 - .14) | -1.89 (-3.36 - -.40) * |
| **Diabetes** (yes) | -1.37 (-2.50 - -.24) * | -1.62 (-2.78 - -.48) ** |
| **Kidney disease** (yes) | -0.98 (-2.37 – 0.42) | -1.45 (-2.84 - -0.06) * |
| **PHQ-9** (pr. SD) | .22 (-.24 - .69) | .21 (-.24 - .66) |

Significance levels: *p<0.05, **p<0.01, ***p<0.001. Abbreviations: RAI, relative autonomy index; ACS, acute coronary syndrome; CAD; coronary artery disease; COPD; chronic obstructive pulmonary disease; PHQ-9; patient health questionnaire.

# Figure 1

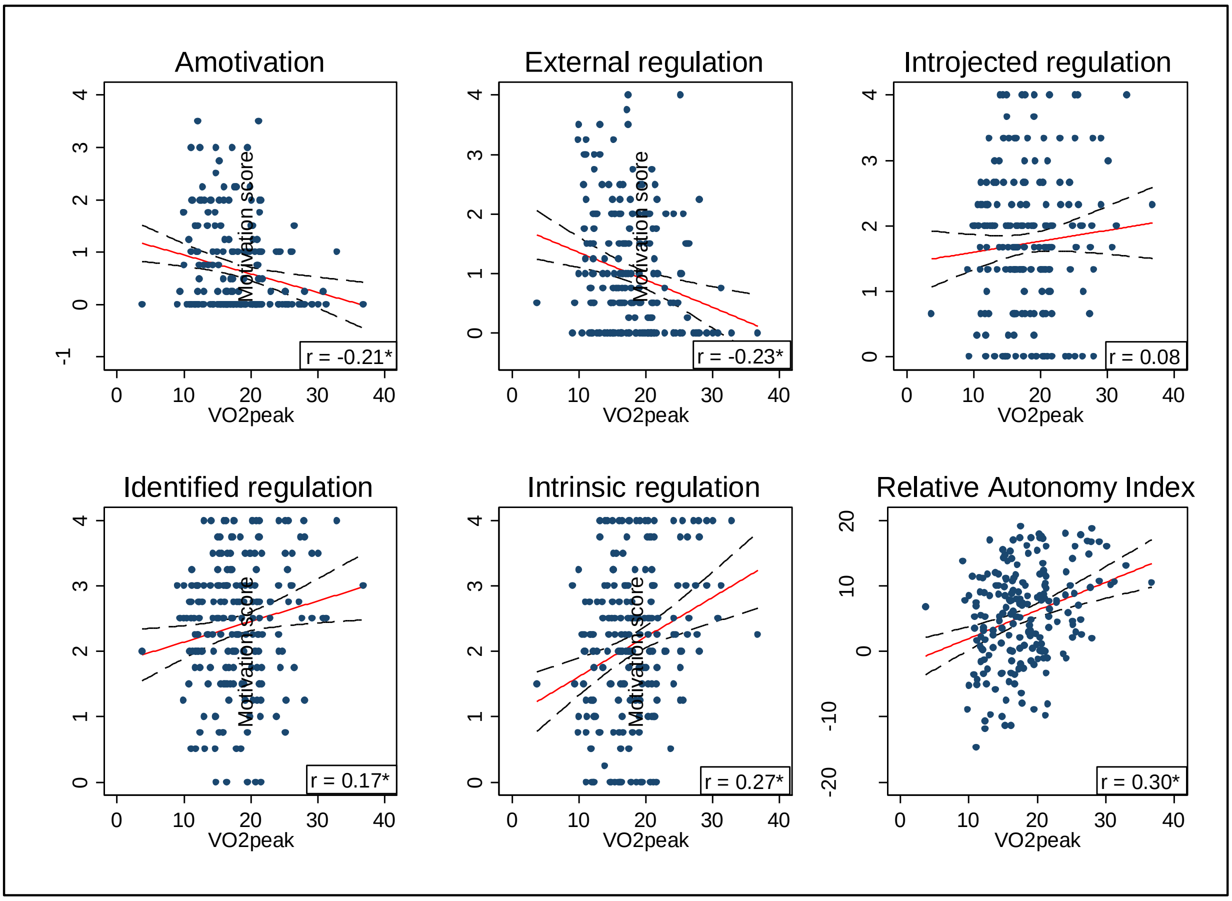
Flowchart of patient exclusion

| | |
|---|---|
| **236** | **signed the informed consent** |
| 14 | were considered ineligible for CPET testing and performed a six-minute walk test |
| 6 | withdrew the informed consent before performing first $VO_{2peak}$ test |
| 13 | did not complete the questionnaires |
| **203** | **performed first CPET and questionnaires and comprised the baseline analyses** |
| 16 | dropped out of rehabilitation |
| **187** | **performed the second CPET and comprised the follow-up analyses** |

Figure 1: Flowchart of the patient population with the number of patients excluded and the reason for exclusion

## Figure 2

Scatterplot and Spearman correlation coefficient (r) of constructs of motivation and $VO_{2peak}$




Significance: *P<0.05

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# Appendix

**EXERCISE REGULATIONS QUESTIONNAIRE (BREQ-2)**

**Age: __________ years** **Sex: male female (please circle)**

***WHY DO YOU ENGAGE IN EXERCISE?***

**We are interested in the reasons underlying peoples' decisions to engage, or not engage in physical exercise. Using the scale below, please indicate to what extent each of the following items is true for you. Please note that there are no right or wrong answers and no trick questions. We simply want to know how you personally feel about exercise. Your responses will be held in confidence and only used for our research purposes.**

| | | Not true for me | | Sometimes true for me | | Very true for me |
|---|---|---|---|---|---|---|
| 1 | I exercise because other people say I should | 0 | 1 | 2 | 3 | 4 |
| 2 | I feel guilty when I don't exercise | 0 | 1 | 2 | 3 | 4 |
| 3 | I value the benefits of exercise | 0 | 1 | 2 | 3 | 4 |
| 4 | I exercise because it's fun | 0 | 1 | 2 | 3 | 4 |
| 5 | I don't see why I should have to exercise | 0 | 1 | 2 | 3 | 4 |
| 6 | I take part in exercise because my friends/family/partner say I should | 0 | 1 | 2 | 3 | 4 |
| 7 | I feel ashamed when I miss an exercise session | 0 | 1 | 2 | 3 | 4 |
| 8 | It's important to me to exercise regularly | 0 | 1 | 2 | 3 | 4 |
| 9 | I can't see why I should bother exercising | 0 | 1 | 2 | 3 | 4 |

## Title page

**Title:** Improvement in $VO_{2peak}$ predicts readmissions for CVD and mortality in patients undergoing cardiac rehabilitation

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## Abstract

**Background:** Improvement in exercise capacity is a main goal of cardiac rehabilitation (CR) but the effects are often lost at long-term follow up and thus also the benefits on prognosis. We assessed whether improvement in $VO_{2peak}$ during a CR program predicts long-term prognosis.

**Methods and results:** We performed a retrospective analysis of 1561 cardiac patients completing CR in 2011- 2017 in Copenhagen. Mean age was 63.6 (11), 74% were male, and 84% had coronary artery disease, 6% chronic heart failure and 10% heart valve replacement. The association between baseline $VO_{2peak}$ and improvement after CR and being readmitted for CVD and/or all-cause mortality was assessed with three different analyses: Cox regression for the combined outcome, for all-cause mortality and a multi-state model. During a median follow-up of 2.3 years, 167 new readmissions for cardiovascular disease and 76 deaths occurred. In adjusted Cox regression there was a non-linear decreasing risk of the combined outcome with higher baseline $VO_{2peak}$ and with improvement of $VO_{2peak}$ after CR. A similar linear association was seen for all-cause mortality. Applying the multi-state model, baseline $VO_{2peak}$ and change in $VO_{2peak}$ were associated with risk of a new CVD admission and with all-cause mortality but not with mortality in those having an intermediate readmission for CVD.

**Conclusion:** $VO_{2peak}$ as well as change in $VO_{2peak}$ were highly predictive of future risk of readmissions for CVD and all-cause mortality. The predictive value did not extend beyond the next admission for a cardiovascular event.



**Keywords:** Cardiac rehabilitation, $VO_{2peak}$, multi-state model, secondary prevention, exercise testing, exercise capacity

## Introduction

Cardiac rehabilitation (CR) increases exercise capacity ($VO_{2peak}$), quality of life and reduces the risk of subsequent cardiovascular mortality and morbidity (1-4). Exercise training is a core component of CR and improvement of $VO_{2peak}$ is a common criterion to measure effect of a CR intervention (5). $VO_{2peak}$ is likewise a strong individual predictor of mortality and morbidity (6).

Improvement in $VO_{2peak}$ after CR differs among patients (7) and both ethnic, psychosocial and physical characteristics such as age, sex and pre-existing fitness level have been shown to predict these differences (7-9). Few studies have addressed whether difference in improvement of $VO_{2peak}$ affects future risk of mortality. The prognostic effect of CR, in terms of future morbidity and mortality, has mainly been investigated comparing participation vs. non-participation in CR (3, 4).

Risk of future readmissions for CVD and mortality (MACE) is commonly used as a composite endpoint for long-term prognosis after CR, as is risk of all-cause mortality (10, 11). Newer statistical methods, multi-state-models, have also made it possible to investigate terminal and non-terminal outcomes separately using a semi-competing risk scenario. Applying such methodology offers a better understanding of the disease process.

We investigated the prognostic value of $VO_{2peak}$ and change in $VO_{2peak}$ after CR on risk of MACE and all-cause mortality, and, in addition applied a multi-state model to investigate risk of future readmissions for CVD and mortality to better understand how $VO_{2peak}$ affects the progression of disease (12).

## Material and methods

### Population

We investigated characteristics and clinical outcomes of cardiac patients diagnosed with coronary artery disease (myocardial infarction and patients undergoing PCI or CABG), chronic heart failure or heart valve replacement, who were referred to- and completed a CR program between 1/1/2011 and 30/12/2017. The patients were identified using a local clinical database from the CR unit at Bispebjerg and Frederiksberg hospitals.

### Rehabilitation program

Patients participated in an eight-week supervised outpatient exercise intervention with two weekly training sessions of 1.5 hours with high intensity interval- (80% of $VO_{2peak}$) and resistance training. The training sessions was complemented with weekly group-based patient education on lifestyle risk factor management, psychological health and diet counselling.

The study was approved by the Danish Data Protection Agency (BFH-2017-117; 06028). According to Danish legislation no ethical approval was required.

### Baseline and explanatory variables

$VO_{2peak}$ was assessed before CR (6-8 weeks post-surgery) and after CR using a cardiopulmonary exercise test (CPET) with a maximal symptom limited bicycle ergometer test (Via Sprint 150P, Ergoline, Germany). Breathing gases were collected and analysed breath-by-breath (Jaeger, Master Screen CPX vers.5.21, Cardinal Health, Germany). Each test aimed at physical exhaustion and a respiratory exchange ratio of more than 1.1 to ensure the validity of the CPET test. (13) The CPET was performed at baseline and after CR. Patient characteristics and explanatory variables were assessed and entered in the local database as the patients entered CR.

## Primary endpoints

With the use of a unique personal identification number the patients were linked to the Danish national registries, which are continuously updated on hospital admission, death and emigration.
Readmissions for CVD were defined as a composite of myocardial infarction (I21), unstable angina pectoris (I20), heart failure (I50) and stroke (I63) and ascertained through linkage with**:** *The Danish National Patient Register* (14) From The Danish *Civil registration system* (15) information on all-cause mortality and emigration was ascertained. We defined MACE as the combination of hospital admission for CVD and all-cause mortality.

## Potential confounders

Age, sex, working status (employed, unemployed, retired, and being on disability pension), educational attainment (no education, short-term education, medium education, and higher education), index diagnosis, medication, tobacco use, chronic obstructive pulmonary disorder, diabetes, kidney disease and peripheral artery disease.

## Statistical analysis

Difference in clinical characteristics were compared with Chi-square test for categorical variables, and t-tests for continuous variables when normally distributed and Mann-Whitney when non-normally distributed.
We used Cox proportional hazards models to determine the associations between $VO_{2peak}$ before CR as well as change after CR, both for risk of MACE and risk of mortality. All models were adjusted for confounding factors. Survival time was calculated from the date of final $VO_{2peak}$ test to first event. Patients were censored at first event or if follow-up ended and patients were still event-free.
Risk of new readmissions and death was also analysed using a semi-competing risk model, the multi state model (16). In the multistate model, patients are not censored if they are readmitted for CVD. When applying the multistate model, all patients completing CR were at risk of being readmitted for CVD (figure 3, transition 1). If readmitted for CVD, patients stayed in the cohort and stayed at risk of dying (transition 2). The patients that were not admitted for CVD were similarly at risk of dying (transition 3).
A 2-tailed *p* value <0.05 was considered as statistically significant. Statistical analyses were carried out using the free statistical software R. (17) R package mgcv was used to perform the fitting of the Cox proportional hazards models (18) including possible non-linear effects of the continuous covariates (i.e. age, baseline $VO_{2peak}$, change in $VO_{2eak}$), while survival (19) and smooth HR (20) packages were used for graphics. Bayes X (21) was used to fit the multistate survival models.

# Results

## Study population

Between 2011 and 2017, 1561 patients participated in- and completed the outpatient CR program. Mean age was 63.6 (11), 74% were male, and 84% had CAD, 6% CHF and

10% heart valve replacement. Distribution of baseline characteristics according to readmissions and mortality are given in table 1.

Median follow-up time was 2.3 years (IQR 1.3 – 4.1 years). There were 167 readmissions for CVD and 77 deaths, of which 25 occurred after suffering a new hospital admission.

The patients that died, whether with or without an intermediate readmission, were older, lived alone, were more likely to be retired, had lower educational attainment more co-morbidity and had lower $VO_{2peak}$ than patients that survived throughout the follow-up.

### Influence of $VO_{2peak}$ on MACE

Baseline $VO_{2peak}$ was highly predictive of suffering a MACE after CR (see figure 1, a) with a linear association which remained statistically significant after full adjustment. The HR for MACE was 0.94 (0.91-0.97) for each ml/kg/min change in baseline $VO_{2peak}$. Change in $VO_{2peak}$ showed a highly significant curvi-linear association with risk of MACE (figure 1 b). Results of the regression analyses are given in table 2. Males were at higher risk than females (HR 1.98, p=0.003). CHF, having been revascularized with PCI and suffering from peripheral artery disease were also associated with risk of MACE. (see table 2)

### Influence of $VO_{2peak}$ on all-cause mortality

Baseline $VO_{2peak}$ was highly predictive of future risk of mortality with a linear association, HR 0.89 (0.83 - 0.95) per ml/kg/min, as was change in $VO_{2peak}$, HR 0.87 (0.80 - 0.96) (figure 2 a and b). Having CHF and peripheral artery disease was also associated with higher mortality risk but the association between $VO_{2peak}$ and outcome remained largely unaffected by adjustment (table 2).

### Multi-state model: Influence of $VO_{2peak}$ on new readmissions for CVD and/or all-cause mortality

*Transition 1: Risk of being readmitted for CVD*

167 patients were readmitted for CVD. There was a significant non-linear association between baseline $VO_{2peak}$ and a linear association between change in $VO_{2peak}$ and readmission for the range of change in $VO_{2peak}$ from -2ml/kg/min to 2ml/kg/min. The hazard did not increase nor decrease significantly with greater changes of $VO_{2peak}$. See figure 4, a+b, transition 1.

*Transition 2: Risk of dying after a readmission for CVD*

25 patients died after a hospital readmission. The risk of dying after readmission was not associated with baseline $VO_{2peak}$ or change in $VO_{2peak}$ (fig 4 c+d). Having CHF at baseline was the only significant predictor of mortality in this transition, although statistical power was limited.

*Transition 3: Risk of dying without an intermediate readmission for CVD*

52 patients died without an intermittent hospital admission. Both baseline and change in $VO_{2peak}$ were highly predictive of all-cause mortality (fig 4 e+f). Males had higher risk of dying (HR 3.85, P=0.031). See table 3

## Discussion

Change in $VO_{2peak}$ following CR was highly predictive for the risk of future readmissions for CVD and all-cause mortality, even after full adjustment for baseline $VO_{2peak}$, cardiac diagnosis and co-morbidities. This result seems to emphasize the importance of achieving significant improvements in $VO_{2peak}$ during a CR program. The results of the multistate model, however, indicate that the mortality benefits of baseline and improvement in $VO_{2peak}$ do not extend beyond the first readmission for CVD.

### Use of $VO_{2peak}$ as endpoint for success in CR

We found that both baseline $VO_{2peak}$ and change in $VO_{2peak}$ after CR were inversely associated with future risk of readmissions for CVD and mortality. Change in $VO_{2peak}$ is the main measure used when evaluating the impact of a CR program both with regards to individual changes, and for comparison with no CR or alternative CR delivery modes such as homebased- or telemonitored CR. To our knowledge, only one previous study has investigated the effect of change in $VO_{2peak}$ on mortality. This was a retrospective study of 5641 patients with coronary artery disease participating in CR with a one year follow-up (22). This study also found an inverse association between change in $VO_{2peak}$ and risk of mortality. There are, however, important methodological differences to our study. We performed a gold standard cardiopulmonary exercise test, whereas the comparative study applied a graded exercise test which is not validated to estimate change in effect over time, something they also pointed out as a limitation in their study. In addition to mortality, the present study addresses CVD outcomes over an extended period (median 2.3 years versus 1-year).

### Application of the multi-state model in a semi-competing risk setting

In addition to the Cox-model we applied a multi-state model to analyse a semi-competing risk scenario of being readmitted for CVD and/or all-cause mortality. This model adds a dimension to the traditional Cox-model. In our study, adding the multi-state model provided information on otherwise censored patients that were readmitted for CVD and then died in the follow-up. This prediction model provides a new dimension to the extent to which $VO_{2peak}$ can predict future outcomes. The model has been applied previously in cardiovascular research (23-25) but not in CR. Upshaw et al. 2016, proposed the use of multi-state models to predict risk of heart failure hospitalizations and all-cause mortality arguing the strength of not censoring patients in case of non-terminal events (25).

The multi-state analysis found the same inverse association between both baseline $VO_{2peak}$ and change in $VO_{2peak}$ and risk of all-cause mortality. In addition, the model added a level to the risk prediction, transition 2; the risk of all-cause mortality after being readmitted for CVD. There was no association between baseline $VO_{2peak}$ and risk of mortality if the patients readmitted for CVD after CR. This result indicates that the protective effect that improved $VO_{2peak}$ is no longer present if a patient is readmitted to hospital. This may imply a need for a new CR intervention. However, only 25 patients died after readmission for CVD, so this result should be confirmed in a larger cohort with a larger number of readmissions.

### Limitations

There are some limitations to this study. One is that we assessed only patients who completed CR, introducing the risk of selection bias. Hence, these results may not be generalizable to cardiac patients not attending CR. Some confounding factors were missing at large, such as left ventricular ejection fraction and cancer making the study prone to some residual confounding. However, this clinical database contained most important clinical variables, so residual confounding was considered to be minimal.

## Conclusion

Both baseline $VO_{2peak}$ and improvement in $VO_{2peak}$ during a CR program are strong predictors of subsequent prognosis in cardiac patients. Patients that are not able to improve their exercise capacity from CR have increased risk of future readmissions for CVD and mortality. Future studies should address how prognosis can be improved in these patients. Also, our results indicate that the protective factor of improved $VO_{2peak}$ is restricted to the time until new CVD admissions occur, and this may indicate the need for repeated participation in CR.

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## Figure 1

Risk of MACE from baseline $VO_{2peak}$ (a) and change in $VO_{2peak}$ (a)

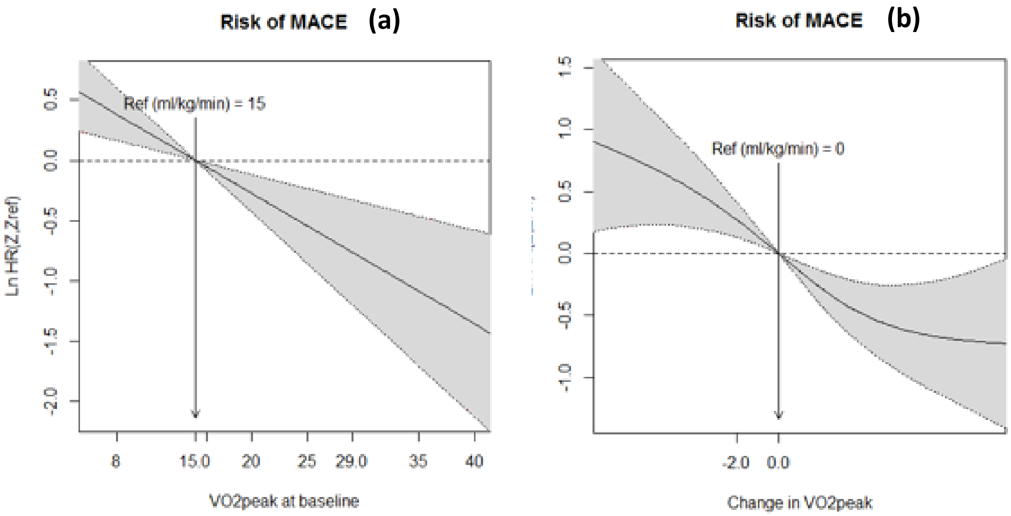


Figure *1*: Smooth log hazard ratio estimates with 95 % pointwise credible bands for baseline $VO_{2peak}$ (taking value 15 as reference) and change in $VO_{2peak}$ (taking 0 as reference) Adjusted for: Age, sex, index diagnosis, revascularization and peripheral artery disease.

**Figure 2**

Risk of death from baseline $VO_{2peak}$ and change in $VO_{2peak}$

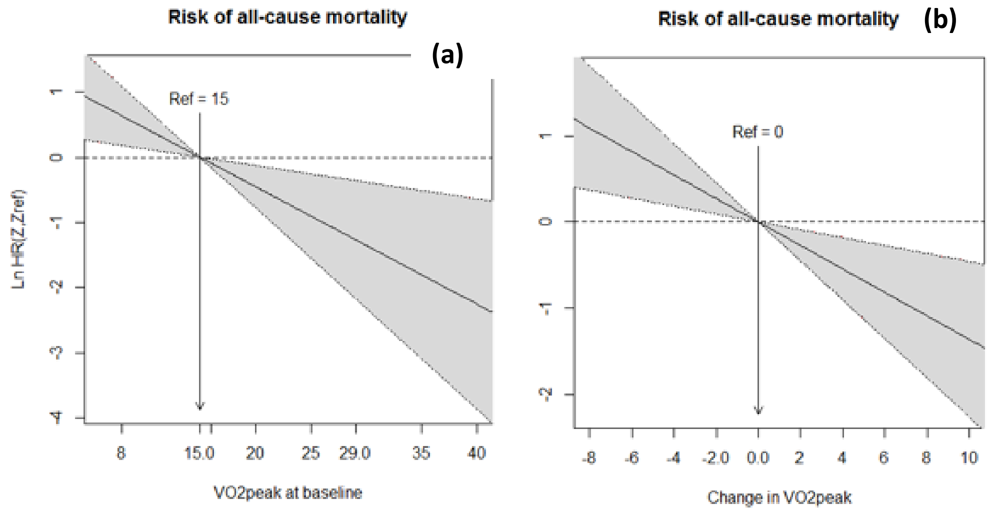


Figure *2*: Adjusted smooth log hazard ratio estimates with 95 % pointwise credible bands for baseline $VO_{2peak}$ (taking value 15 as reference) and change in $VO_{2peak}$ (taking 0 as reference) Adjusted for: Age, sex, index diagnosis, revascularization and peripheral artery disease.

**Figure 3**

Flowchart of the multi-state model transitions

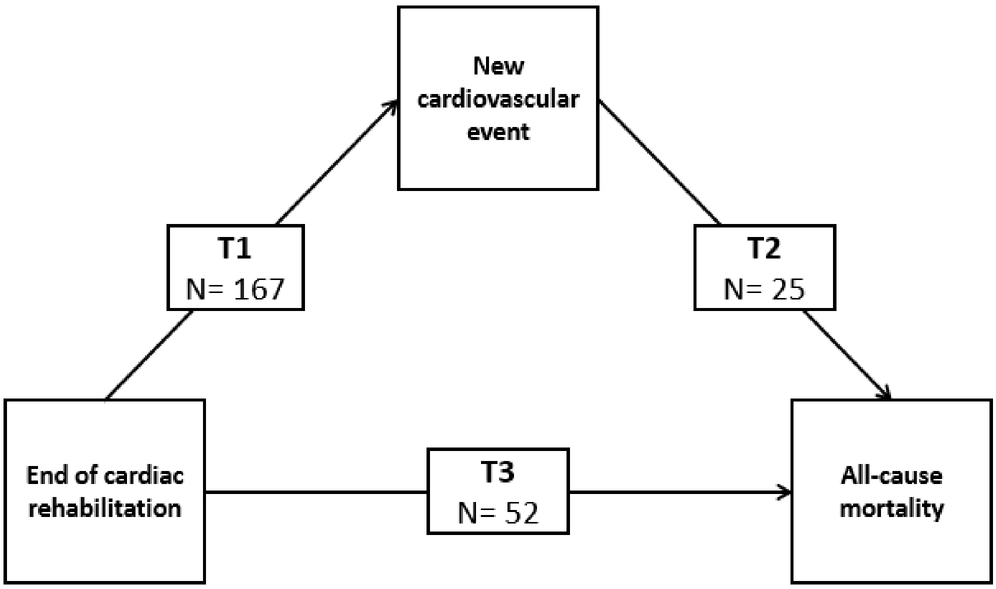


Figure 3 shows the different transitions in the multi-state model. Transition 1(T1) is the risk of readmission for CVD after cardiac rehabilitation. Transition 2(T2) is the risk of mortality after readmission for CVD. Transition 3(T3) is the risk of mortality without suffering an intermediate readmission.

## Figure 4

Multi-state models for baseline $VO_{2peak}$ (a) and change in $VO_{2peak}$ after CR (b) in all three transitions. Transition 1 (risk of readmission) Transition 2(risk of mortality after readmission) Transition 3 (risk of mortality without intermediate readmission)

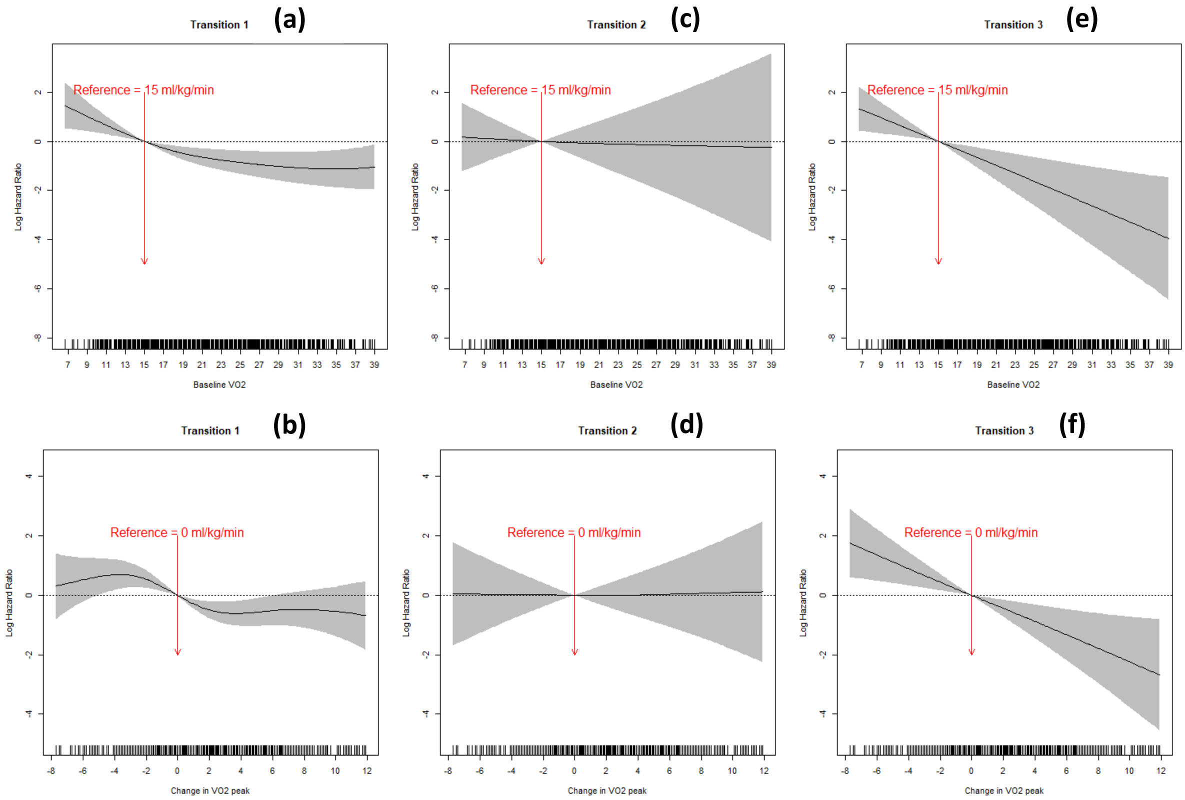

**Table1**

Demographic characteristics of the population. First total population, then the subpopulation of patients readmitted for CVD

| Variables | Level | No events | Death | Readmission | P-value | Readmission N=167 Survived | Died | P-value |
|---|---|---|---|---|---|---|---|---|
| | | N = 1342 | N = 52 | N = 167 | | N = 141 | N = 25 | |
| ***Age (years)*** | Mean (SD) | 63 (11) | 72 (9) | 65 (11) | **<0.001** | 64 (11) | 71 (8) | **<0.001** |
| ***Sex*** | Males | 1002 (75%) | 39 (75%) | 134 (80%) | 0.289 | 114 (81%) | 20 (77%) | 0.846 |
| ***BMI*** | Mean (SD) | 27.5 (5) | 27.5 (5) | 27.8 (4) | 0.513 | 27.8 (5) | 27.9 (4) | 0.980 |
| ***Co-habitant*** | Yes | 809 (60%) | 24 (46%) | 89 (53%) | **0.002** | 79 (56%) | 10 (38%) | 0.101 |
| ***Ethnicity*** | Western European | 1126 (84%) | 46 (88%) | 142 (85%) | 0.827 | 116 (82%) | 26 (100%) | 0.066 |
| ***Index diagnosis*** | ACS | 764 (59%) | 30 (59%) | 96 (59%) | 0.219 | 85 (62%) | 11 (42%) | 0.115 |
| | Stable CAD | 325 (25%) | 11 (22%) | 45 (27%) | | 37 (27%) | 8 (31%) | |
| | CHF | 72 (6%) | 5 (10%) | 14 (9%) | | 9 (7%) | 5 (19%) | |
| | Heart valve replacement | 156 (11%) | 5 (10%) | 9 (5%) | | 7 (5%) | 2 (8%) | |
| ***Revascularization*** | PCI | 767 (59%) | 35 (70%) | 113 (70%) | 0.062 | 98 (72%) | 15 (62%) | 0.330 |
| | CABG | 296 (23%) | 8 (16%) | 29 (18%) | | 25 (18%) | 4 (17%) | |
| | None | 227 (18%) | 7 (14%) | 19 (12%) | | 14 (10%) | 5 (21%) | |
| ***Working status*** | Employed | 460 (35%) | 3 (6%) | 39 (6%) | **<0.001** | 37 (28%) | 2 (8%) | **0.027** |
| | Unemployed | 74 (6%) | 1 (2 %) | 12 (2%) | | 12 (9%) | 0 (0%) | |
| | Retired | 694 (53%) | 46 (92%) | 100 (63%) | | 77 (58%) | 23 (88%) | |
| | Disability | 79 (6%) | 0 (0%) | 7 (4%) | | 6 (5%) | 1 (4%) | |
| ***Educational attainment*** | No education | 187 (16%) | 7 (18%) | 32 (24%) | **<0.001** | 27 (19%) | 5 (19%) | 0.958 |
| | Short term | 502 (37%) | 21 (55%) | 60 (44%) | | 49 (35%) | 11 (42%) | |
| | Medium | 195 (16%) | 5 (13%) | 15 (11%) | | 13 (9%) | 2 (8%) | |
| | Higher | 303 (26%) | 5 (13%) | 29 (21%) | | 25 (18%) | 4 (15%) | |
| ***Smoking status*** | Non-smoker | 835 (62%) | 27 (52%) | 101 (60%) | 0.109 | 84 (60%) | 17 (65%) | 0.615 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Previous smoker | 274 (20%) | 11 (21%) | 31 (19%) | | 28 (20%) | 3 (12%) | |
| | Current smoker | 182 (14%) | 8 (15%) | 24 (14%) | | 19 (13%) | 5 (19%) | |
| ***Diabetes*** | Yes | 205 (16%) | 12 (24%) | 33 (21%) | 0.08 | 26 (20%) | 7 (27%) | 0.585 |
| ***COPD*** | Yes | 120 (9%) | 9 (18%) | 20 (13%) | 0.06 | 13 (10%) | 7 (27%) | **0.044** |
| ***PAD*** | Yes | 79 (6%) | 9 (19%) | 18 (12%) | **<0.001** | 10 (8%) | 8 (31%) | **0.002** |
| ***Kidney disease*** | Yes | 66 (5%) | 8 (19%) | 9 (6%) | **<0.001** | 7 (6%) | 2 (8%) | 0.984 |
| ***Beta blockers*** | Yes | 976 (77%) | 31 (74&) | 123 (82%) | 0.290 | 102 (81%) | 21 (88%) | 0.634 |
| ***Statins*** | Yes | 1103 (87%) | 35 (81%) | 138 (92%) | .009 | 116 (92%) | 22 (92%) | 1 |
| ***$VO_{2peak}$ baseline*** | Median (IQR) | 21.7 (6.8) | 17.8 (4.6) | 20.8 (7.1) | **<0.001** | 21.3 (7) | 17.8 (5) | **0.020** |
| ***Change in $VO_{2peak}$*** | Median (IQR) | 2.6 (3.9) | 1.2 (4.9) | 0.5 (3.1) | **<0.001** | 2.4 (4.1) | 1.2 (3.4) | 0.152 |

Abbreviations: BMI; Body mass index, ACS; acute coronary syndrome, CAD; coronary artery disease, CHF; chronic heart failure, PCI; percutaneous coronary intervention, CABG; coronary artery bypass grafting, COPD, chronic obstructive pulmonary disease, PAD; peripheral artery disease.

**Table 2**

Hazard ratios (and 95% Confidence Intervals) from Cox-regression models for MACE and death of all causes

| | (A) Risk of MACE | | (B) Risk of death | |
|---|---|---|---|---|
| **Variables** | **HR** | **95% CI** | **HR** | **95% CI** |
| **Age** (per year) | 1.01 | (0.99 - 1.03) | 1.06** | (1.02 - 1.10) |
| **Sex** (males) | 1.98** | (1.25 - 3.14) | 2.19 | (0.92 - 5.22) |
| **Index diagnosis** | | | ACS | ACS |
| **ACS** | ref | | | |
| Stable CAD | 0.97 | (0.68 - 1.39) | 1.10 | (0.56 - 2.16) |
| Heart valve disease | 1.56 | (0.57 - 4.23) | 2.19 | (0.38 - 12.68) |
| CHF | 2.71* | (1.13 - 6.49) | 5.39* | (1.37 - 21.15) |
| **Revascularization** | PCI | PCI | PCI | PCI |
| CAGB | 0.59* | (0.38 - 0.90) | 0.68 | (0.31 - 1.49) |
| None | 0.32** | (0.14 - 0.72) | 0.57 | (0.16 - 2.06) |
| **PAD** (yes) | 1.98** | (1.22 - 3.22) | 2.23* | (1.04 - 4.76) |
| **Baseline $VO_{2peak}$** (ml/kg/min) | 0.94*** | (0.91 - 0.97) | 0.89** | (0.83 - 0.95) |
| **Change in $VO_{2peak}$** (ml/kg/min) | - | - | 0.87*** | (0.80 - 0.96) |

*P<0.05, **P<0.01, ***P<0.001. Abbreviations: MACE; major adverse cardiovascular events, ACS; acute coronary syndrome, CAD; coronary artery disease, CHF; chronic heart failure, PCI; percutaneous coronary intervention, CABG; coronary artery bypass grafting, PAD; peripheral artery disease.

**Table 3**

Transitional HRs for Multistate Prediction Model

| | T1: End CR to readmission | | T2: Readmission to death | | T3: End CR to death | |
|---|---|---|---|---|---|---|
| **Variables** | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** |
| **Age** (per year) * | 1.01 | (0.99-1.03) | 1.08* | (1.01-1.17) | 1.05* | (1.00-1.1) |
| **Sex** (males) | 2.01* | (1.24 – 3.26) | 0.54 | (0.12 – 2.31) | 3.85* | (1.12 – 13.15) |
| **Index diagnosis** | ACS | | ACS | | ACS | |
| Stable CAD | 1.07 | (0.72-1.59) | 2.30 | (0.77-6.88) | 0.69 | (0.28-1.72) |
| Heart valve disease | 0.61 | (0.24-1.54) | 5.05 | (0.47-54.44) | 0.67 | (0.08-5.47) |
| CHF | 2.32 | (0.7-7.65) | 18.63 | (0.84-415.1) | 3.82 | (0.6-24.22) |
| **Revascularization** | PCI | | PCI | | PCI | |
| CAGB | 0.53* | (0.33 – 0.84) | 1.78 | (0.41 – 7.65) | 0.47 | (0.17 – 1.31) |
| None | 0.38 | (0.15 – 0.95) | 0.78 | (0.04 – 14.28) | 0.47 | (0.07 – 3.03) |
| **PAD** (yes) | 2.04* | (1.24 – 3.36) | 2.61 | (0.74 – 9.27) | 2.51 | (0.90 – 7.03) |
| **Baseline $VO_{2peak}$** * | 0.95** | (0.92-0.99) | 0.99 | (0.87-1.12) | 0.86*** | (0.79-0.94) |
| **Change in $VO_{2peak}$** | | | | | | |
| -5.00 | 1.87 | (1.02-3.45) | 1.03 | (0.35-3.00) | 3.08 | (1.50-6.31) |
| -4.00 | 2.00 | (1.20-3.34) | 1.03 | (0.44-2.37) | 2.45 | (1.39-4.32) |
| -3.00 | 1.96 | (1.3-2.97) | 1.02 | (0.55-1.89) | 1.95 | (1.28-2.97) |
| -2.00 | 1.72 | (1.27-2.32) | 1.02 | (0.68-1.52) | 1.55 | (1.17-2.06) |
| -1.00 | 1.35 | (1.15-1.58) | 1.01 | (0.83-1.23) | 1.25 | (1.08-1.43) |
| 0.00 (reference) | 1.00 | - | 1.00 | - | 1.00 | - |
| 1.00 | 0.75 | (0.64-0.88) | 0.99 | (0.82-1.20) | 0.80 | (0.70-0.92) |
| 2.00 | 0.61 | (0.46-0.81) | 0.99 | (0.68-1.45) | 0.65 | (0.49-0.85) |
| 3.00 | 0.55 | (0.38-0.8) | 1.00 | (0.57-1.74) | 0.52 | (0.34-0.79) |
| 4.00 | 0.54 | (0.35-0.83) | 1.01 | (0.48-2.10) | 0.42 | (0.24-0.73) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5.00 | 0.56 | (0.35-0.90) | 1.02 | (0.41-2.55) | 0.33 | (0.16-0.67) |

*P<0.05, **P<0.01, ***P<0.001. Abbreviations: CI; confidence intervals, CR; cardiac rehabilitation, ACS; acute coronary syndrome, CAD; coronary artery disease, CHF; chronic heart failure, PCI; percutaneous coronary intervention, CABG; coronary artery bypass grafting, PAD; peripheral artery disease. * Indicates that the presented hazard ratio was calculated considering the variable effect as linear.