UiT The Arctic University of Norway

Faculty of Health Sciences

Coronary heart disease and cardiac rehabilitation

Participation rate, predictors and effects on symptoms of anxiety and depression, and employment status of patients following percutaneous coronary intervention - A nationwide prospective cohort study

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Table of Contents

List of tables

List of figures

"*If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health."*

— Hippocrates

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List of abbreviations

ACS	acute coronary syndrome
AMI	acute myocardial infarction
BMI	body mass index
BMS	bare-metal stent
CR	cardiac rehabilitation
CABG	coronary artery bypass graft surgery
CHD	coronary heart disease
CI	confidence interval
DBT	diastolic blood pressure
LVEF	left ventricular ejection fraction
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS anxiety subscale
HADS-D	HADS depression subscale
HUNT	Nord-Trøndelag health study
MI	myocardial infarction
NORSTENT	Norwegian Coronary Stent Trial
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
RR	risk ratio
SBP	systolic blood pressure
SD	standard deviation
STEMI	ST-segment elevation myocardial infarction
WHO	World Health Organization

List of papers

The following papers form part of this thesis:

Olsen SJS, Schirmer H, Bønaa KH, Hanssen TA. Cardiac rehabilitation after percutaneous coronary intervention: results from a nationwide survey. *Eur J Cardiovasc Nurs* 2018; 17. 3: 273-279.

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Summary

Background: Improved medical treatment and therapeutic procedures coupled with an ageing population have increased the numbers of people living with coronary heart disease (CHD). This chronic condition has implications for patients' everyday lives, including their physical, physiological and social well-being. According to international guidelines, cardiac rehabilitation (CR) is an integral component of secondary prevention and a recommended form of aftercare for patients with established cardiovascular disease. The key elements of CR consist of lifestyle interventions, risk factor management, and physiological and vocational support. No national estimates exist on the proportion of patients participating in CR programmes in Norway. In addition, the new era of revascularization and advances in secondary prevention therapy call for updated knowledge of the impact of CR programmes on patients' mental health and vocational reintegration.

Aim: The aims of this thesis were to study the CR participation rate, clinically relevant anxiety and depression and employment status of patients following percutaneous coronary intervention (PCI), and the long-term effect of participation in a CR programme on patients' symptoms of anxiety and depression and their employment status.

Methods: Using a prospective observational design, we included data from the Norwegian Coronary Stent trial (NorStent) from baseline and 36 months in the present thesis. NorStent was an all-comer study with broad inclusion criteria and few exclusion criteria, conducted at all centres in Norway that perform PCI during 2008 and 2011. A total of 9013 participants were included in NorStent. Clinical data at the time of PCI were retrieved from the patients' electronic medical records. Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) in a representative sample of 775 patients at baseline. At three years follow-up, 7068 patients (82%) responded to a postal survey that included the HADS and questions on CR participation and employment status.

Results: Twenty-eight per cent of the participants reported having participated in a CR programme. The participation rate differed among the four regional health authorities in Norway (20%-31%). A multivariate statistical model revealed that men had a 28% lower probability of participating in CR, and the likelihood of attending CR decreased with increasing age. Contributors to a higher probability of CR participation were patients having

undergone PCI for an acute coronary syndrome, educational level >12 years, and overweight. Prior coronary artery bypass graft was associated with lower CR participation. CR participants had higher levels of symptoms of anxiety and depression than non-participants at baseline, and both groups had higher levels than the general population. The levels of anxiety and depression had fallen significantly at three years follow-up. In the propensity-matched cohort, CR participants had more clinically relevant symptoms of anxiety, but not depression. Female gender and younger age were associated with higher probability of clinically relevant symptoms of anxiety, whereas older age, lower levels of education and cardiovascular morbidity were associated with higher probability of clinically relevant symptoms of depression. Seventy per cent of participants who were <60 years of age at the index event were employed at three-year follow-up. In the propensity-matched cohort, employment status did not differ between CR participants and non-participants. Being male, living with a partner, and attaining higher levels of education were associated with a higher chance of being employed, while being older, prior cardiovascular morbidity, and former smoking were associated with a lower chance of being employed three years after PCI.

Conclusion: This thesis suggests that few patients with established CHD participate in a CR programme, with certain geographical differences. A significant number of patients who have undergone PCI report symptoms of anxiety and depression, with the highest levels found in those participating in a CR programme. After three years, both the CR participants and non-participants had a higher level of anxiety, but not depression, than the general Norwegian population. A significant number of working-age CHD patients were unemployed three years after PCI and CR appeared to have no beneficial effect on clinically relevant symptoms of anxiety and depression or employment status. The present thesis suggest that the patients most in need, i.e. those who are overweight, smokers, and have the highest levels of anxiety and depression, are identified and encouraged to participate in CR programmes

Summary in Norwegian

Bakgrunn: Antallet som lever med hjerte- og kar sykdommer øker på grunn av bedre medikamentell- og invasiv behandling. Å leve med kronisk hjertesykdom påvirker pasientens hverdag og den fysiske, fysiologiske og sosiale velvære. I henhold til internasjonale retningslinjer er hjerterehabilitering en integrert del av den sekundærforebyggende behandlingen og anbefalt i oppfølgingen av pasienter med etablert hjerte- og karsykdom. De sentrale elementene i hjerterehabilitering består av optimalisering av livsstilsfaktorer, kartlegging av risikofaktorer, fysisk trening og arbeidsveiledning. I dag finnes det ikke nasjonale data på andelen pasienter som deltar på hjerterehabilitering i Norge. I tillegg krever de nye fremskrittene innen invasiv behandling og sekundærforebygging, oppdatert kunnskap om effekten av hjerterehabilitering på pasienters mentale helse og integrering i arbeidslivet.

Hensikt: Hensikten med denne avhandlingen var å estimere omfanget av deltagelse på hjerterehabilitering, klinisk relevant angst og depresjon og ansettelsesstatus hos pasienter som har gjennomgått perkutan koronar intervensjon (PCI), og den langsiktige effekten av deltakelse på hjerterehabilitering på pasientens symptomer på angst og depresjon og ansettelsesstatus.

Metoder: Ved bruk av et prospektiv observasjonelt design brukte vi i denne avhandlingen baseline og 36 måneder data fra Norwegian Coronary Stent-studien (NorStent). NorStent var en studie med få restriksjoner for inklusjon og ble utført i tidsrommet 2008 til 2011 ved alle sentre i Norge som utførte PCI. Totalt ble 9 013 deltakere inkludert i NorStent. Kliniske data på tidspunktet for PCI ble hentet fra den elektroniske pasient journalen. Symptomer på angst og depresjon ble kartlagt ved bruk av Hospital Anxiety and Depression Scale (HADS) i et representativ utvalg på 775 pasienter ved baseline. Etter tre års oppfølging svarte 7 068 pasienter (82%) på et spørreskjema som inkluderte HADS og spørsmål om deltakelse på hjerterehabilitering og ansettelsesstatus.

Resultater: Tjueåtte prosent av studiedeltakerne rapporterte å ha deltatt på et hjerterehabiliterings program. Deltakelsesgraden var forskjellig mellom de fire regionale helseforetakene i Norge (20%-31%). En multivariat statistisk modell avdekket at menn hadde 28% lavere sannsynlighet for å delta på hjerterehabilitering, og oddsen for å delta ble lavere med økende alder. Faktorene for høyere odds for deltakelse på hjerterehabilitering var

pasienter som gjennomgikk PCI på grunn av akutt koronart syndrom, utdanning mer enn 12 år og overvekt. Tidligere koronar bypassoperasjon var assosiert med lavere odds for deltagelse på hjerterehabilitering. De som deltok på hjerterehabilitering rapporterte høyere nivåer av symptomer på angst og depresjon enn de som ikke deltok ved inklusjon, og begge gruppene rapporterte høyere nivåer enn den generelle befolkningen. Nivået av angst og depresjon falt betydelig i løpet av tre års oppfølging. I den propensity-matchede kohorten var det flere med klinisk relevante symptomer på angst, men ikke depresjon, hos de som hadde deltatt på hjerterehabilitering. Kvinner og yngre hadde større sannsynlighet for klinisk relevante symptomer på angst, mens eldre, de med lavere utdannelsesnivå og de med tidligere hjerte- og karsykdom hadde høyere sannsynlighet for klinisk relevante symptomer på depresjon. Sytti prosent av deltakerne som var <60 år ved inklusjon var i arbeid etter 3 år. I den propensity-matchede kohorten skilte ikke ansettelsesstatusen til de som hadde deltatt på hjerterehabilitering seg fra de som ikke hadde deltatt. Menn, samboende og de med høyere utdanningsnivå hadde større sannsynlighet for å være i arbeid, mens eldre, de med tidligere hjerte- og karsykdom og de som hadde tidligere røykt hadde lavere sannsynlighet for å være i arbeid tre år etter PCI.

Konklusjon: Funnene i avhandlingen indikerer at få pasienter med etablert hjertesykdom deltar på et hjerterehabiliteringsprogram, og at det er visse geografiske forskjeller i andel deltagelse. Et betydelig antall pasienter som gjennomgår PCI rapporterer symptomer på angst og depresjon, og de med høyest nivå deltar på hjerterehabilitering. Etter tre år hadde både hjerterehabiliterings deltakerne og de som ikke deltok et høyere angstnivå, men ikke depresjonsnivå, sammenlignet med resultater fra den generelle norske befolkningen. Et betydelig antall hjertepasienter i arbeidsfør alder var arbeidsledige og hjerterehabilitering syntes ikke å ha gunstig effekt på klinisk relevante symptomer på angst og depresjon eller ansettelsesstatus tre år etter PCI. Denne avhandlingen indikerer at pasientene som har særlig behov, overvektige, røykere og pasienter med mest symptomer på angst og depresjon, identifiseres og oppfordres til å delta på hjerterehabilitering.

1 Introduction

One-fifth of the Norwegian population are living with cardiovascular disease; every year, about 40 000 coronary heart disease (CHD) patients have an outpatient consultation or hospital admission. Improved medical treatment and therapeutic procedures coupled with an ageing population have increased the numbers of people living with CHD in Norway (1). This chronic condition has implications for patients' everyday lives, including physical, physiological and social wellbeing. Patients diagnosed with CHD, especially those that have experienced a life-threatening event, are in a situation where they try to accept the potential consequences the disease has on their daily life and future. Mental health and social and vocational reintegration are therefore of importance, and patient-reported outcomes can complement the understanding of the burden of the disease.

According to international guidelines, cardiac rehabilitation (CR) should be a core component of the care received by patients with established CHD (2-4). The key elements of CR consist of lifestyle interventions, risk factor management, and physiological and vocational support (5). Studies have shown great variation in the content of CR programmes and participation rates across Europe and worldwide (6-9). In Norway, there are no uniform national standards and guidelines for CR, and there is a lack of knowledge of participation rates.

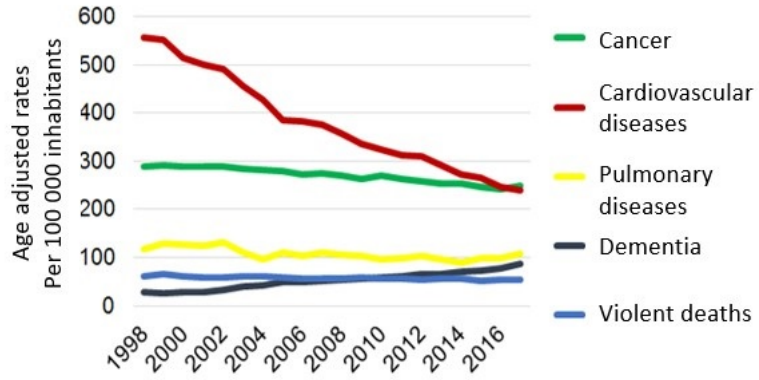
The aim of this thesis is to enhance understanding of CR. Specifically, we wanted to study the CR participation rate, clinically relevant anxiety and depression and employment status in patients having undergone percutaneous coronary intervention (PCI), and the long-term effect of participation in a CR programme on patients' mental health and vocational reintegration.

2 Background

2.1 Coronary heart disease

Cardiovascular disease (CVD), in addition to stroke, has remained the top cause of death worldwide in the last 15 years, and resulted in the death of 15 million people in 2015 (10). In Europe, more than 4 million people die from CVD every year and CVD accounts for 45% of all deaths. There is also substantial variance in the CVD burden across Europe between high- and low-income countries (11). Despite a decrease in mortality over the last fifty years, CVD is still the most common cause of death in Norway along with cancer (Figure 1) (1, 12). In 2017, there were 20 704 hospitalizations for myocardial infarction (MI), representing 12 087 unique persons, according to the Norwegian Myocardial Infarction Register (13). Of these, 30% have had one or more previous MIs, and this figure has remained stable for the last five years (13).

Figure 1. Leading causes of death in Norway 1998-2017 (12)



Development of coronary heart disease

The development of atherosclerosis starts in early life, indicating that CHD develops over the life course (14). The atherosclerotic process is well understood. Studies suggest that atherosclerosis represents a maladaptive chronic vascular immune-inflammatory disease of the medium-sized and large arteries (15). Inside the artery, there is a thin layer of cells, the endothelium. When the endothelium is damaged, monocytes attach to the surface and transmigrate into the sub-intimal space where they transform into macrophages. The macrophages attract and consume fatty low-density lipoproteins (LDL), and turn into large foam cells that cause arterial inflammation when they collapse. The combination of modified LDL particles, macrophages, lymphocytes, and dendritic cells that release several pro-

inflammatory factors such as cytokines and chemokines, describes the atherosclerotic plaque (15, 16). A plaque-affected obstruction of the coronary artery or spasm of normal or plaque-diseased arteries is generally typical of stabile angina (17).

Vulnerable plaques are defined as those with a significant level of inflammation and a thin fibrous collagen cap that is prone to rupture with increased risk of thrombosis. A ruptured plaque is an atherosclerotic vascular lesion with damage that exposes the thrombogenic core of the plaque (16, 18). A ruptured or eroded arteriosclerotic coronary plaque followed by thrombus formation and propagation are the essential elements in the pathophysiology of acute coronary syndrome. Acute coronary syndrome includes unstable angina, non-ST-segment elevation infarction and ST-segment elevation infarction (18).

Risk factors for coronary heart disease

In contrast to a bacterial infection, CVD has no single cause. This makes it possible to develop CVD without the influence of some of the major known risk factors. The presence of co-existing risk factors makes it challenging to explore the direct causal effect because of the high risk of bias. However, international guidelines highlight several factors that can promote CVD (19), which are the same factors used in risk assessment systems to estimate the future risk of fatal CVD (20, 21). In the 1960s, the Framingham study addressed smoking, and raised blood pressure, serum cholesterol and diabetes mellitus as risk factors for CVD (22). Today, obesity, physical inactivity, dietary patterns and alcohol have been added as modifiable risk factors for CVD (23, 24).

Smokers have a tripled risk of non-fatal MI (25), and patients that cease smoking lower their risk of recurrent MI by 43% (26). In addition, second-hand smoke and occasional smoking increase mortality (27, 28). A reduction of one mmol/L in total cholesterol is associated with a reduction in CHD mortality of about 50% in people aged 40-49 years and 17% in those aged 70-79 (29). High diastolic and systolic blood pressure are both associated with increased risk of CVD, and antihypertension treatment reduces CHD mortality by 10-12% (23). Obesity, both in adolescence and adulthood, increases the risk of CVD (30). A body mass index (BMI, kg/m) of 30-35 reduces median survival by 2-4 years and with a BMI of 40-45 the median lifespan is reduced by 8-10 years, comparable with the effect of smoking (31). Observational long-term studies have shown a significant relationship between leisure time activity and

reduced all-cause and cardiovascular mortality (23, 32). Even small doses of physical activity decrease mortality, with the highest effect in the least fit patients (33). Recommended diet and exercise adherence are associated with a decreased risk of MI of almost 50% compared to non-adherence (26).

A meta-analysis of 20 studies found a 28% increased risk of CHD with the presence of anxiety in initially healthy individuals (34). The INTERHEART study comparing 15 152 cases and 14 820 controls found that psychosocial factors, such as depression, anxiety and job stress, increased the risk of MI by 2.67 (24). An additional publication from the INTERHEART study revealed that severe global stress increased the risk of acute MI less than smoking, but comparable to hypertension and obesity (35). A Norwegian population-based study showed that symptoms of anxiety and depression increased the risk of future acute MI by 25% and 31%, respectively (36). In addition to the modifiable risk factors, CVD risk is affected by age, gender and genetic factors (19).

Percutaneous coronary intervention (PCI)

Minimization of residual ischaemia is the goal of revascularization and gives a future benefit of decreased risk of death and myocardial infarction (37). An invasive strategy is the standard of care in patients with suspected coronary heart disease to confirm the diagnosis, identify the culprit lesion, establish the indication for coronary revascularization and stratify the patient's risk (4). In 1977, Andreas Gründzig performed the first PCI with balloon dilatation of the left coronary artery. A high rate of acute closure and restenosis of the treated artery resulted in the introduction of coronary stents (38). Today, pre-dilation followed by implantation of a stent is the established PCI procedure in both acute and elective patients with a significant stenosis in the coronary artery. In 2017, 32 101 invasive procedures were performed in Norway, 41% of which included PCI. Approximately half of the procedures were in relation to an acute coronary event (39).

2.2 Cardiac rehabilitation

In CHD patients, secondary prevention is recommended with the aim of slowing down the progression of the disease and improving the chance of positive health outcomes. Secondary prevention and cardiac rehabilitation are integral components in the comprehensive care of patients with established CHD (5, 40).

History of cardiac rehabilitation

Until the 1950s, strict bed rest was the recommended care after acute MI followed by gradual gentle mobilization. Patients who had an MI were often considered invalid and many were forced into early retirement. Levine and Lowe introduced 'The chair treatment after an acute MI', where patients were mobilized to an armchair, and the term CR was introduced to the literature (41). In the late 1950s, Dr Hellerstein introduced one of the first multidisciplinary approaches to disease with a clinic staffed by physiotherapists, dietitians, vocational counsellors, and psychotherapists. Exercise, diet, and return to work were the main goals in the post-infarct care model (42). During the 1980s, randomized controlled trials (RCTs) showed that structured CR reduced mortality and morbidity and was cost-effective. However, the intensive exercise programme did not show long-term effects, probably because of non-adherence. These findings resulted in more moderate exercise training, which is the basis for current practice in CR in several countries (41-43).

Components of cardiac rehabilitation

The World Health Organization has developed the most quoted definition of CR (44):

> *'The sum of activity required to ensure cardiac patients the best possible physical, mental and social conditions so that they may, by their own effort, regain as normal as possible a place in the community and lead an active life'*

International consensus (guidelines and textbooks) recommends that the core components of today's CR should include lifestyle interventions, risk factor management, and psychosocial and vocational support. The short-term goals for CR are to manage cardiac symptoms, improve functional capacity, limit psychological distress, and give vocational support to the patient. This includes providing education about the condition, optimizing medical treatment and management of blood pressure, cholesterol and blood glucose, and reduction of psychosocial distress and barriers for returning to work (3). The long-term goal is to stabilize or slow the progression of arteriosclerosis, thereby reducing morbidity and mortality, and minimizing the risk of future cardiac events (5, 45, 46). This includes motivating patients to long-term lifestyle changes such as smoking cessation and healthy dietary habits, and promoting medical adherence, physical activity and weight management (3). Several

international guidelines recommend CR as a core component of care for patients with established coronary heart disease (3, 4, 47).

CR programmes are divided into three phases. Phase 1 starts at the hospital immediately after the coronary event. The goal is to promote early mobilization and prevention of complications. Phase 2 can be performed in both inpatient and outpatient settings; here, the aims are clinical stabilization, risk stratification, and the promotion of a long-term healthy lifestyle. Phase 3 is a long-term outpatient CR programme provided in outpatient settings and focusing on physical activity (23).

Over the years, different theoretical perspectives have guided CR, depending on the elements emphasized. The social cognitive theory, introduced by Albert Bandura, has been used to promote lifestyle changes. Self-efficacy is an important aspect of the social cognitive theory, representing the person's belief in her or his ability to succeed in specific situations or accomplish a task (48). Prochaska and DiClemente's transtheoretical, or stages of change, model describes several stages involved in the process of health behaviour change (49). Coping with illness is also a component of CR, theorized by Lazarus and Folkman (50) and Miller (51), as coping can affect mental and physical health. The salutogenic theory of Antonovsky highlights health promotive factors, as opposed to treating illness, and has a component of coping strategies known as the sense of coherence (52, 53).

Today, CR programmes have added theories that emphasize person-centred care. Empowerment focuses on strengthening individuals to allow them to recognize and use their resources and represent their interests in a responsible and self-determined way (54). Motivational interviewing seeks to increase the individual's motivation for change (55). Health literacy is the degree to which a person can access, practice, and understand basic health information and services in order to inform and participate in health decisions (56).

Health literacy is an invisible barrier to healthcare delivery, and limited health literacy is associated with poorer health care and overall health status, increased hospitalizations, and decreased adherence to medications (57, 58). Limited health literacy is more often present among older adults, ethnic minorities, individuals with chronic illness and individuals with low education (57, 58). There is a limited number of studies exploring health literacy among

patients with CHD, but it is suggested that health literacy plays an important part in aftercare for patients with established CHD (57).

Effects of cardiac rehabilitation

A Cochrane systematic review and meta-analysis published in 2011 including 47 studies with 10 794 CHD patients showed that exercise-based CR was associated with a reduction in all-cause mortality (RR 0.87, 95% CI 0.75-0.99), cardiovascular mortality (RR 0.74, 95% CI 0.63-0.87) and hospital admissions (RR 0.69, 95% CI 0.51-0.93), but not total MI and revascularization (59). The updated version of this review from 2016 concluded with similar findings, but no reduction in all-cause mortality. In addition, the authors identified evidence supporting improved health-related quality of life (HQoL), but failed to conduct the meta-analysis needed to establish robust conclusions (60). Notably, a benefit in all-cause mortality was found by Rausch et al., who included both RCTs and prospective cohort studies (61).

Since reviews and meta-analyses including studies before the new era of revascularization and advances in secondary prevention therapy may have overestimated the effect of exercise-based CR, Powell et al. performed a systematic review and meta-analysis of only studies including patients after the year 2000 (62). Including 22 studies with 4834 participants, Powell et al. did not find any effect of exercise-based CR on all-cause mortality or cardiovascular mortality, but a small reduction in hospital admission that were unlikely to be of clinical significance (62). In patients with stable angina, the effect of exercise-based CR on all-cause mortality, cardiovascular mortality, MI and cardiovascular hospital admissions is uncertain due to few studies with low quality (63).

Halewijn et al. included not only exercise-based CR but also lifestyle-based programmes in their review and meta-analysis of studies published in 2010-2015 (64). When adding rehabilitation programmes addressing six or more risk factors or prescribing and monitoring of cardioprotective medication, they found a reduction in all-cause mortality, cardiovascular mortality, MI and cerebrovascular events (64). The comprehensive approach has also been shown to be beneficial by Kabboul et al. (65). There is no strong evidence that patient education alone reduces all-cause mortality, cardiac mortality, revascularization or hospitalizations (66), but attending a group-based educational intervention is associated with almost halved all-cause and cardiovascular mortality after first-time MI (67). Exploring the

effect of CR on HQoL, two recent meta-analyses support the findings of Shepherd and While that CR may lead to a clinically meaningful improvement in HQoL (68-70). Evidence also suggests that CR is cost-effective (71, 72).

Several of the previously mentioned meta-analyses report that the included studies come from a wide variety of clinical environments, and that the CR intervention ranged greatly in quality, as also noted by the European cardiac rehabilitation registry (73). Caution is therefore advised when reading the findings. However, a systematic review of recent CR meta-analyses concludes that the results are sufficiently robust in favour of CR that strategies to improve referral rates should be promoted (74).

Participation rate

Participation in CR programmes after an acute coronary event varies widely across Europe, from 0% to 91% (6, 9, 75). Barriers to participation can be categorized as patient-related, provider-related and system-related barriers (76). Patient-related barriers are lack of awareness and perceived need, lack of social support, poor physical wellbeing, living at a distance from the CR, competing work commitments and financial costs. Provider-related barriers are lack of knowledge of the benefits of CR, lack of knowledge on how to refer, the site location or perceptions that patients lack motivation to participate in CR. System-related barriers are capacity constraints, lack of reimbursement by the government and lack of national standards (5, 76-78). The typical non-participant is an older woman, living at some distance from the nearest CR, with a low educational level, living alone and having comorbidities (79). There is a lack of knowledge on interventions to promote CR adherence, but interventions targeting patient-related barriers may increase the possibility of success (9).

Cardiac rehabilitation in Norway

Several studies have found poor risk factor control in patients with established CHD in Norway (80-83). Today, there is a lack of uniform national standards and guidelines for CR and no national secondary prevention register. A report from 2018 on rehabilitation in specialist health services in Norway showed a reduction in numbers of patients receiving rehabilitation and wide geographical differences in the use of rehabilitation (84).

There is also great variation in the duration and content of the different CR programmes in Norway. Some hospitals offer a one- to three-day course with a focus on educational programmes to increase knowledge of the disease and coping skills (the 'Heart School'). Others have an outpatient programme, focusing solely on exercise training or with a comprehensive approach lasting for 2-6 months. The National Association for Heart and Lung Disease (LHL), a wholly patient-owned non-profit organization, offers in-hospital comprehensive CR over four weeks. Different private CR centres offer in-hospital or outpatient CR programmes lasting for three to four weeks. Finally, municipalities with Healthy Life Centres offer exercise training and different courses to optimize a healthy lifestyle, such as smoking cessation. Unpublished data from a national survey conducted by Sverre and Peersen showed that 85% of Norwegian hospitals have a systematic referral to CR for MI patients, 24% offer an outpatient follow-up consultation, 22% offer comprehensive CR, 45% offer 'Heart School' and outpatient exercise training, 24% offer 'Heart School' only and 10% have no CR programme to offer (85). As in Norway, Sweden has variation in length and content of CR between hospitals (86). However, Sweden has systematic follow-up of acute MI patients monitored by the SWEDEHEART registry for quality control and improvement (86).

In Norway, those offered CR are primarily MI patients. A study comparing CR in two neighbouring hospitals in Norway revealed a large difference in participation rates (75% vs. 18%) (87). In the future, the Norwegian Myocardial Infarction Register will publish data on CR participation rates.

2.3 Anxiety and depression

Definition and prevalence

Occasional anxiety is an expected part of life and is an emotion that occurs when an individual faces potentially harmful or worrying triggers. Anxiety increases psychological activity of the body such as rapid heart rate and increased blood pressure. People with anxiety disorders have recurring intrusive thoughts or concerns and typically avoid certain situations out of worry (88, 89). Depression generally involves symptoms such as a feeling of depressed mood, a loss of interest or pleasure in activities, sleep disturbance, fatigue, or impaired concentration. Symptoms must last at least two weeks for establishing a diagnosis of

depression (89-92). Depending on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate or severe (89-93).

Anxiety and depression are common during a lifetime. Epidemiological studies, using the Diagnostic and Statistical Manual of Mental Disorders (90), have showed a lifetime prevalence of anxiety- and depressive disorders of 14%-50% and 14%-21%, respectively (94). Notably, comorbidity between anxiety and depression is strong, and as many as 40%-50% have both conditions (95).

Aetiology

Several idioms describe the connection between the heart and emotion, such as heartbroken, cold-hearted, heartless and stony-hearted. As early as in the 1930s, clinical scientists documented an association between late-life depression and elevated rates of cardiovascular deaths (96). The link between mental illness and CHD is not fully understood, but there is a consensus among scientists that the association is driven through pathways of biological and behavioural mechanisms with bidirectional influences (97-100). The biological mechanism is explained by an autonomic nervous dysfunction with a reduction in catecholamine spillover, pre-ejection period, heart rate variability, baroreflex sensitivity, heart rate recovery after exercise and an increased heart rate. In addition, there is a dysfunction in the hypothalamic-pituitary adrenal axis influencing the levels of cortisol leading to increased free fatty acids. There is also an endothelial dysfunction, higher levels of fibrinogen and other clotting factors and elevated inflammatory biomarkers. Overall, these factors contribute to more rapid progression of atherosclerosis, higher risk of vulnerable plaque and higher risk of atherothrombosis (97-103). Psychological factors are associated with adverse lifestyle behaviours related to smoking, physical activity, diet, alcohol consumption and sleep health. Patients with mental illness are also less likely to adhere to medication, lifestyle changes and cardiac rehabilitation (93, 97-99, 104).

Prevalence of anxiety and depression in CHD patients

The prevalence of anxiety among CHD patients is reported to be 13%-60% (104-107), while of whom only 15-20% meet the criteria for major depression, while the rest are suggested to have clinically relevant depression (93, 104, 108). Several factors can contribute to the differences in prevalence. Changes over time in the detection, prevention and treatment of

CHD complicate the interpretation of this literature. Furthermore, the studies are characterized by several methodological differences, such as differences in instruments measuring symptoms of anxiety and depression, categorical variables versus continuous scores, time from index event to assessment, repeated measuring and differences in cut-off score. Studies have shown that symptoms of anxiety in CHD patients were more prevalent in women, younger patients and patients with a low education level (104, 109). Old age, low level of education and presence of smoking, obesity and diabetes were more prevalent in CHD patients with symptoms of depression (104, 109).

Anxiety and depression and cardiac outcomes

Meta-analyses suggest that anxiety is associated with a slightly increased risk of mortality and poor cardiac outcomes in patients with CHD (106, 110). A systematic review found an increased risk of major adverse cardiac events in patients with general anxiety disorder (107). The association between anxiety and cardiac outcomes seems less strong than it is for depression. A systematic review of 54 studies by Lichtman et al. concluded that comorbid depression increases the risk of all-cause mortality, cardiac mortality, and composite outcomes comprising mortality and nonfatal cardiac events (108). In a PCI population, symptoms of depression were associated with an almost two-fold greater risk of mortality at 10 years follow-up, and symptoms of anxiety were associated with a 50% higher risk of 10-year mortality (111). However, anxiety disappears as a predictor of mortality when adjusting for depression (111).

Effect of cardiac rehabilitation on anxiety and depression

Exercise-based CR has been shown to reduce anxiety (112) and depression (112, 113) and psychological support as stress management, relaxing techniques or individual counselling, is thus recommended as a component of CR (91, 102, 114). However, the scientific evidence for this recommendation was challenged by a Cochrane review that did not find any effect on total mortality, need for revascularization, or the risk of non-fatal myocardial infarction of adding psychological interventions to traditional CR (115). However, cardiac mortality was reduced, and symptoms of anxiety, depression and stress were improved (115). A recent review and meta-analysis including randomized controlled trials and controlled cohort trials published between 1995 and 2017 found similar findings to the Cochrane review with regard to the effect on cardiovascular events, revascularization procedures and risk reduction for

non-fatal MI (116). The findings also suggested that specific psychological interventions may reduce depressive symptoms, but they had no effect on anxiety and quality of life (116). Furthermore, no effects of antidepressant treatment on cardiac outcomes have been observed (117). Notably, reviews on the effectiveness of psychological interventions have been criticized for including studies of moderate to low quality and with heterogeneity in terms of interventions, outcomes and follow-up period (118). The findings should therefore be interpreted with caution. Nevertheless, international guidelines emphasize that CR is a multicomponent intervention that includes screening for anxiety and depression and giving psychological support to those in need (19, 46).

2.4 Employment status

Remaining in the workforce despite having a chronic disease holds important socioeconomic consequences for the patient and society. There is strong evidence of the protective effect of employment, especially on depression and general mental health (107). Today, 79% of Norwegians aged 25 to 66 years are employed, while 10% of those aged 18 to 67 receive a disability pension, about 5% because of cardiovascular diseases (119). In the 1950s, numerous CHD patients failed to return to work after weeks of immobilization. CR started as an initiative to improve the chances for returning to work after MI (41, 43).

Employment status in CHD patients

The heterogeneity of prior studies on employment status and CHD, such as differences in severity of the coronary disease, definition of return to work, state of employment at inclusion and follow-up time complicate the interpretation of this literature. In previous international studies of employed patients, 76%-93% of the patients were found to have returned to work one year after acute MI or coronary artery bypass graft surgery (CABG) (120-124). However, subsequent detachment from employment is common; almost a quarter of MI patients of working age were detached from employment and received social benefit one year after they successfully returned to work (121). A population-based Danish study of 21 926 patients showed that five years after first-time hospitalization for acute coronary syndrome, 88% were still part of the workforce, and of these, 65% were in work, 19% were unemployed and 16% were on sick leave (125). Warraich et al. found that half of the job losses after MI were involuntary and patients who experienced an unfavourable change in employment status reported decreased quality of life, increased depression and less financial means to buy medications (126).

With regard to early retirement, a nationwide cohort study from Sweden found that approximately one-third of patients were granted a disability pension within five years after CABG or PCI (127). The reasons for work disability also seemed to change from musculoskeletal disorders and mental disorders before an ischaemic heart disease event to diseases of the circulatory system after such an event (128). A history of long-term sickness absence prior to revascularization is a strong predictor of long-term sickness absence following PCI, followed by disability pension (127, 129). In addition, disability pension at the time of coronary revascularization is associated with higher five-year mortality (130).

Predictors for employment after a coronary event

Previous studies suggest that younger CHD patients have a higher chance of returning to work (121, 123-125, 131), and the EUROASPIRE IV survey revealed that CHD patients younger than 50 years old were three times more likely to be employed (124). Some studies have shown that women are less likely to return to work (121, 123, 125, 131), while others found no gender differences (120, 124). There seems to be a beneficial association between being employed and higher educational level, higher socioeconomic status and living with a partner (120, 121, 124, 125, 131). Barriers to employment are higher rates of symptoms of depression (121, 124), having a manual job (124) and the presence of comorbidities (120, 121, 124, 125).

Effect of cardiac rehabilitation on employment status

The Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology (EAPC) suggests dividing actions that lead to successful return to work after acute treatment for CHD into human and work-related parameters. These parameters should depend on cardiac-related, psychosocial and work-related factors to determine the employability of the patient (132), such as assessment of medical contraindications, capacity building and re-training (114). However, the benefit of CR on employment status is unclear. A Cochrane review that examined interventions to support return to work for people with CHD concluded, with low certainty of evidence, that comprehensive CR may promote return to work within the first six months following CHD. There was little to no evidence that CR promotes return to work between six and twelve months after a CHD event, and no evidence that CR promotes return to work after one year of follow-up (133). These findings concur with recent studies showing no association of CR or psychosocial and vocational interventions with return to work (124, 134). In a survey of CR programmes worldwide, more consistent delivery of return to work counselling was promoted (8).

2.5 Aims of the thesis

The overall aim of this thesis is to provide updated knowledge on aftercare for patients with established CHD. Specifically, we wanted to study the prevalence of CR participation, clinically relevant anxiety and depression and employment status, and the long-term effects of participation in a CR programme on patients' mental health and vocational reintegration. In order to fulfil the overall aim, three different studies were planned:

I. To determine the approximate proportion of Norwegian CHD patients participating in CR programmes after PCI, and to determine predictors of CR participation.

II. To compare levels of anxiety and depression among patients who did and did not participate in a CR programme after PCI, to compare the findings with the levels in the general population, and to assess predictors of clinically relevant anxiety and depression three years after PCI.

III. To determine employment status three years after PCI, compare differences between CR participants and non-participants, and assess predictors of employment.

3 Material and methods

3.1 Study population - The Norwegian Coronary Stent Trial

The Norwegian Coronary Stent Trial (NorStent) was an all-comer study with broad inclusion criteria and few exclusion criteria which was conducted at all centres in Norway that perform PCI, thus covering the total Norwegian population of more than 5 million inhabitants (Table 1). NorStent was a randomized controlled trial comparing long-term health effects of drug-eluting and bare-metal stents. Participants were included from September 2008 to February 2011 with five years follow-up.

Table 1. Inclusion and exclusion criteria for the Norwegian Coronary Stent Trial (135).

The inclusion criteria were:

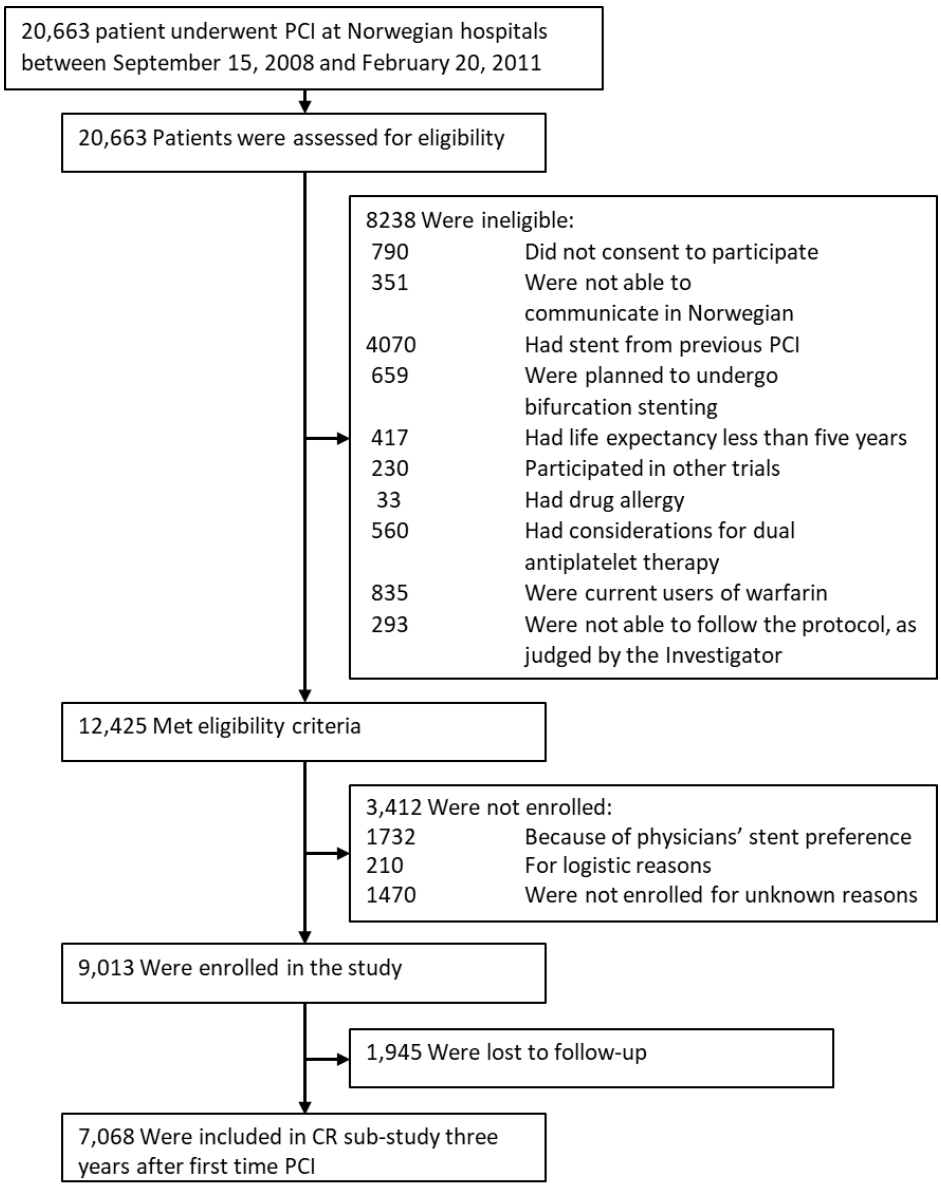
1. Men and women >18 years of age with stable angina pectoris or acute coronary syndrome.
2. The patient has consented to participate and has signed the patient informed consent form.
3. All lesions requiring interventions in one or more native coronary arteries/coronary artery by-pass graft are amendable for implantation of drug-eluting stents only or bare-metal stents only.
4. The patient has a Norwegian ID number, is able to communicate in Norwegian, and is not expected to emigrate during study follow-up.

The exclusion criteria were:

1. Previous implantation of bare-metal or drug-eluting coronary stent(s).
2. Planned intervention for a bifurcation lesion with 2-stent technique.
3. The patient has a serious medical condition (other than coronary artery disease) with a life expectancy of less than 5 years (such as very severe chronic airway disease or cancer).
4. The patient is currently participating in another randomized trial that clinically interferes with the present trial, or requires angiography or other coronary artery imaging procedures.
5. Patients with hypersensitivity or allergy to one of the drugs or components in use with PCI.
6. Contraindications for treatment with clopidogrel/ticlid for 9-12 months.
7. Long-term warfarin use.

A total of 9014 participants were included in the study (Figure 2) (135). Baseline characteristics are shown in Table 2. Using a prospective observational design, we included NorStent data from baseline and 36 months in the present thesis.

Figure 2. Flow diagram demonstrating inclusion and exclusion of participants at baseline and at three years follow-up in NorStent



Papers I and II were based on the 7068 participants with complete status on CR participation at three years follow-up. In addition, Paper II was based on data from a representative subgroup of 775 participants with complete status on CR and self-reported symptoms of anxiety and depression at baseline and at three years follow-up. Paper III was based on the 2488 participants younger than 60 years at baseline with complete status on CR participation and employment status at three years follow-up. Table 2 shows baseline characteristics of

participants with complete data at three years follow-up with comparisons to baseline characteristics of the 1945 participants lost to follow-up.

Table 2. Baseline characteristics of total population and differences between study participants and those lost to follow-up

Characteristic	(n=9013)	(n=7068)	(n=1945)	p-value
Age (years ± SD)	63 ± 10.9	63.1 ± 10.2	60.8 ± 12.9	<0.001
Male gender, n (%)	6757 (75.0)	5321 (75.3)	1436 (73.8)	0.194
Living alone, n (%)	1557 (21.1)	1406 (20.8)	151 (25.1)	0.015
Educational level ≤12 years, n (%)	5575 (69.9)	4683 (68.9)	892 (75.4)	<0.001
Current smoker, n (%)	3147 (34.9)	2226 (31.5)	921 (47.4)	<0.001
Body mass index >25 kg/m^2, n (%)	5067 (64.9)	3979 (64.9)	1088 (64.8)	0.272
Medical history, n (%)				
Prior myocardial infarction	912 (10.1)	664 (9.4)	248 (12.8)	<0.001
Diabetes mellitus	1123 (12.5)	801 (11.3)	322 (16.6)	<0.001
Prior CABG surgery	593 (6.6)	443 (6.3)	150 (7.7)	0.026
Prior stroke	346 (3.8)	260 (3.7)	86 (4.4)	0.320
Prior lipid-lowering treatment	4868 (54.0)	3872 (54.8)	996 (51.2)	0.018
Prior HT treatment	3791 (42.1)	3003 (42.5)	788 (40.5)	0.295
Left ventricular EF ≤40%, n (%)	303 (8.4)	194 (6.9%)	109 (13.9)	<0.001
Indication for PCI, n (%)				
Stable angina	2636 (29.4)	2124 (30.2)	512 (26.5)	0.012
Acute coronary syndrome	6319 (70.6)	4901 (69.8)	1418 (73.5)	-

Values are means (SD) or n (%).

SD: standard deviation; CR: cardiac rehabilitation; CABG: coronary artery bypass graft; HT: hypertension; PCI: percutaneous coronary intervention; EF: ejection fraction.

3.2 Data collection

Clinical follow-up of the participants was performed according to routine practise at the intervention centres, and there were no per-protocol follow-up visits. Clinical data were retrieved from the patients' electronic medical records by specially trained registered nurses. A study coordinating centre at the Institute of Clinical Medicine, UiT The Arctic University of Norway, collected the follow-up data using mailed questionnaires. Patients were sent reminders by phone and letter to complete and return their questionnaires.

3.3 Data management

NorStent stores the data in EUTRO, a database developed in 2004 by UiT The Arctic University of Norway. EUTRO ensures the safety, handling and management of sensitive research data and biological material in accordance with Norwegian research legislation and the regulations of The Norwegian Data Protection Authority. We received anonymous and only predefined data from EUTRO approved by the NorStent steering committee. Data management and statistical analyses were performed using IBM SPSS Statistics for Windows, version 23-26. (IBM Corporation, Armonk, New York).

3.4 Study variables

Age, gender, weight, cardiovascular medical history, cardiovascular risk factors and, current cardiac status were collected before the interventional procedure (index event), and medication at discharge was collected from the discharge notes. Educational level was collected 6 months after the index event and living arrangements at two years of follow-up. Age is presented as a categorical variable in the descriptive analyses, while in the regression model age is categorized as ≤59 years, 60-69 years and ≥70 years (Papers I-II) and as <50 years, 50-55 years and 56-59 years (Paper III). Living arrangements are categorized as living alone, living with a spouse/partner or living with others (Paper I), and dichotomized in the regression model as living alone or with a spouse/partner (Papers I-III). Smoking was self-reported and categorized as never smoker, former smoker and current smoker (defined as daily smoker or having stopped smoking less than 30 days ago). Educational level was presented as a dichotomous variable: ≤12 years of education (primary school and/or high school) and >12 years of education (college and / or university degree). BMI (Kg/m^2) was

presented as a categorical variable (Paper I) and as a dichotomous variable (Papers I-III) with a cut-off of >25 Kg/m^2 (overweight). Left ventricular ejection fraction was dichotomized with a cut-off of ≤40%. Geographical affiliation was based on the participants' local hospital and then categorized in one of the four Norwegian Health Authorities.

3.4.1 Cardiac rehabilitation (Papers I-III)

Attendance in a CR programme during the period from baseline to 36 months after the index event was assessed by asking study participants the following questions, representing two possible CR alternatives: (1) Have you participated in a short ambulatory CR programme lasting for hours or days? (2) Have you participated in a hospital- or centre-based in-patient CR programme lasting for one or more weeks? The response options were 'yes', 'no', or 'uncertain'. Participation in CR was coded as "yes" if the patient answered 'yes' to one or both questions, and "no" if the patient answered 'uncertain' or 'no' to both questions. Assessment of CR participation by self-report has been validated in a previous study showing almost perfect agreement between self-reported and site-verified CR participation (136). Table 3 shows differences in baseline characteristics between participants in CR <1 week and CR ≥1 week. The similarities between the groups and content described in these two CR alternatives, allowed us to treat both as one CR variable in our analysis.

Table 3. Baseline characteristics according to duration of cardiac rehabilitation

Characteristic	<1 week (n = 1016)	≥ 1 week (n = 933)	p-value
Age (years ± SD)	61 ± 9.5	59 ± 9.5	<0.001
Male gender, n (%)	763 (75.1)	710 (76.1)	0.635
Living alone, n (%)	168 (17.4)	169 (19.3)	0.305
Educational level ≤12 years, n (%)	603 (61.0)	559 (62.2)	0.636
Current smoker, n (%)	350 (34.4)	349 (37.4)	<0.001
Body mass index >25 kg/m^2, n (%)	578 (66.2)	566 (70.4)	0.064
Medical history, n (%)			
Prior myocardial infarction	59 (5.8)	61 (6.5)	0.109
Diabetes mellitus	82 (8.1)	119 (12.8)	0.002
Prior CABG surgery	22 (2.2)	32 (3.4)	0.098
Prior stroke	17 (1.7)	33 (3.5)	0.023
Prior lipid-lowering treatment	502 (49.4)	470 (50.4)	0.907
Prior HT treatment	351 (34.5)	358 (38.4)	0.206
Left ventricular EF ≤40%, n (%)	33 (12.7)	31 (9.0)	0.181
Indication for PCI, n (%)			
Stable angina	123 (12.2)	174 (18.8)	<0.001
Acute coronary syndrome	891 (87.7)	758 (81.2)	-

Values are means (SD) or n (%).

SD: standard deviation; CR: cardiac rehabilitation; CABG: coronary artery bypass graft; HT: hypertension; PCI: percutaneous coronary intervention; EF: ejection fraction.

3.4.2 The Hospital Anxiety and Depression Scale (Paper II)

Patient-reported symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) in a representative sample of 775 patients at baseline and in all patients at 36 months follow-up (Paper II). HADS was developed by Zigmond and Snaith in 1983 to separate symptoms of anxiety and depression from symptoms caused by physical illness. The HADS therefore systematically excludes physical symptoms that can be mistaken for heart disease (137). For increased sensitivity to mild physiological issues and to avoid underreporting of stigmatized psychological symptoms, linguistic metaphors were used in structuring the questions (137).

The HADS is a self-rating instrument and takes only minutes to complete. It consists of a seven-item subscale for anxiety (HADS-A) and a seven-item subscale for depression (HADS-D). HADS-A reflects symptoms of worry and restlessness, while HADS-D reflects inability to feel pleasure (anhedonia) and covers two of the three diagnostic criteria for depression in the International Classification of Disease (ICD-10).

All questions have four-point response options, ranging from no points for no symptoms to three points for the maximum number of symptoms. The scores on each subscale range from 0 to 21 points. Lower scores reflect a lower symptom presence (137). The HADS has demonstrated good psychometric properties across various patient samples and settings (138, 139). As appropriate in instruments that use unweighted sum scores, simple mean imputation was performed when the respondent had answered at least four of the seven items in each subscale (140). Table 4 shows internal consistency in subscales and missing data before imputing missing items. A Cronbach's alpha of ≥0.8 indicates good overall reliability of the questionnaire (141). A cut-off score of eight on the subscales was used in the analysis and has been found to provide an optimal balance between sensitivity and specificity for identifying possible or probable cases of clinically relevant symptoms of anxiety and depression (138), with scores <8 representing no symptoms of anxiety or depression. The expected HADS-A and HADS-D scores in the general population, presented as a continuous scale, were calculated using previously developed formulas based on the Norwegian general population, controlling for each participant's age, gender, educational level and smoking habit (105).

Table 4. Description of subscales, internal consistency and missing data without and with missing imputation at baseline and three years follow-up[#]

	HADS-Anxiety	HADS-Depression
Items per subscale	7	7
Cronbach's alpha baseline	0.86	0.80
Cronbach's alpha 3 years	0.88	0.84
Missing data without missing imputation baseline, n (%)	10 (1.3)	9 (1.2)
Missing data with missing imputation baseline, n (%)	0 (0)	0 (0)
Missing data without missing imputation 3 years, n (%)	188 (2.7)	111 (1.57)
Missing data with missing imputation 3 years, n (%)	19 (0.3)	14 (0.20)

HADS: The Hospital Anxiety and Depression Scale
[#] This analysis includes 775 patients who were examined with the HADS both at baseline and at three years follow-up

3.4.3 The Norwegian reference population (Paper II)

The Norwegian reference population comprised participants in the second wave of a large population-based general health survey, the 1995-1997 Nord-Trøndelag Health Study (the HUNT 2 Study). A total of 66 140 individuals participated in the study, and 71% of those invited were aged ≥20 years. In Paper II we compared the results on symptoms of anxiety and depression measured with the HADS among PCI patients with the results from 54 867 subjects without previous self-reported cardiovascular disease (142).

3.4.4 Employment status (Paper III)

Employment status 36 months after the index event was ascertained by asking the study participants if they were currently employed full-time or part-time, unemployed, retired on a disability pension, or on sick leave full-time or part-time, or if they were homemakers. Employment status was categorized as 'employed', 'unemployed' or 'retired'. Being employed was classified as employed full-time or part-time. Being unemployed was classified as unemployed or on sick leave full-time or part-time. Retired participants were those that reported receiving a full-time or disability pension. Combinations of the employment status response were categorized as presented in Table 5, showing that most of the responses were in the main categories.

Table 5. Categorization of different combinations of the employment status response in the entire cohort, and numbers of participants in each category (n=7068)

Numbers	Employment status	Category
29	Missing	-
78	Homemaker	0
53	Unemployed	0
2	Unemployed and employed full-time	0
5	Unemployed and employed part-time	0
1	Unemployed and homemaker	0
52	Sick leave part-time	0
7	Sick leave part-time and employed full-time	0
23	Sick leave part-time and employed part-time	0
9	Sick leave part-time and retired	0
3	Sick leave part-time and retired and employed part-time	0
113	Sick leave full-time	0
11	Sick leave full-time and employed full-time	0
3	Sick leave full-time and employed part-time	0
2	Sick leave full-time and homemaker	0
4	Sick leave full-time and unemployed	0
1	Sick leave full-time and part-time and employed full-time	0
1798	Employed full-time	1
339	Employed part-time	1
1	Homemaker and employed part-time and employed full-time	1
13	Retired and employed full-time	1
361	Retired and employed part-time	1
1	Retired and employed full-time and employed part-time	1
4128	Retired	2
6	Retired and homemaker	2
1	Retired and homemaker and employed full-time	2
13	Retired and unemployed	2
10	Retired and sick leave full-time	2
1	Retired and sick leave full-time and employed part-time	2

0: Unemployed, 1: Employed, 2: Retired

3.5 Statistical analysis

3.5.1 Descriptive statistics

Descriptive statistics of continuous variables were performed using interquartile range (Paper I), means and standard deviations (SD) (Papers I-III). Categorical variables were analysed as absolute numbers and percentages (Papers I-III).

3.5.2 Comparisons

Differences in baseline characteristics were assessed using Pearson's chi-square or independent samples Student's t-test, as appropriate (Papers I-III). Between-group comparisons were performed using the independent samples t-test (Papers I-II) or conditional logistic regression (Paper III), and within-group comparisons were performed using paired sample t-tests (Paper II). Differences between the observed scores in the study population and the expected scores in the general population were analysed using the one-sample t-test (Paper II). For all three studies, a two-tailed *p*-value of <0.05 was considered statistically significant.

3.5.3 Regression

Univariate and multivariate logistic regression analysis was used to identify predictors of CR participation (Paper I), symptomatic anxiety and depression (Paper II) and for being employed three years after PCI. The multivariate model was built using independent variables that had a statistically significant unadjusted association (Paper I), variables associated with symptoms of anxiety and depression (Paper II) or severity of CHD in previous research (Papers I-III). All models were tested for goodness of fit using the Hosmer-Lemeshow test that compares the prediction model to a hypothetically perfect model. A non-significant difference is desirable as it indicates that the model being tested is not reliably different from the perfect model (141, 143). Interactions are concerned with whether the effect of the independent variable is consistent for all levels of a second independent variable, common for gender and age (141, 143). In Paper I, all significant two-way interactions were tested in the full multivariate model. Only HA×age remained significant and stratified analyses were performed. In Paper II and III, two-way interactions between the independent variables and gender and age were tested. No interactions were found.

3.5.4 Propensity score

An RCT is the gold standard for estimating the effects of treatments on outcomes. In an RCT, patients are randomly assigned to either a treatment or a control group. In observational data, there is a chance of systematic differences between patients receiving and not receiving treatments. These differences are attempted to be controlled for using multiple regression or matching by several baseline characteristics. However, these methods can be less reliable

because the patients are not real candidates for both treatments or they can give a large proportion of unmatched patients (144-147).

Propensity scores (PS) reduce the covariate to a single quantity, and as a result, patients with similar propensity scores in different treatment groups can be compared as they have the same probabilistic distribution (144-147). A patient's propensity score is defined as 'the probability that the patient receives treatment A (instead of B), given all relevant conditions, comorbidities, and other characteristics at the time the treatment decision is made' (145).

We produced a PS to compare CR participants and non-participants on symptoms of anxiety and depression (Paper II) and employment status (Paper III). The PS was calculated for each participant using a logistic regression model with predefined baseline covariates related to the outcome and based on previous literature and scientific understanding. The following variables were included: age, gender, educational level, smoking status, BMI, prior MI or coronary artery bypass graft, diabetes mellitus, prior lipid-lowering treatment, prior hypertension treatment, regional health authority and indication for PCI (Papers II and III), and creatinine concentration and left ventricular ejection fraction (Paper II).

The PS was calculated without replacement and we used one-to-one matching with a calliper of 0.02. Covariate balance was checked as recommended for studies reporting PS analysis using binary statistics and standardized mean difference (145, 147). The analysis was performed using SPSS version 26 with the Statistics Regression module, the Python Essentials and version 1.3.0 of the FUZZY extension command (IBM Corporation, Armonk, New York).

3.6 Ethics

The study conforms with the principles outlined in the Declaration of Helsinki and the UN Declaration of Human Rights (148). All patients gave written informed consent to participate in the study and were informed about the opportunity to withdraw their consent at any time without giving any particular reason. Study participants received the same medical treatment as if they were not participating in the trial and the treatment was performed according to routine hospital practice. NorStent has been reviewed and approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway

(PREKNORD40/2008) and the Norwegian Social Science Data Services (NSD19480) and is registered in ClinicalTrials.gov (NCT00811772).

3.6.1 Funding

The Research Council of Norway and other non-profit organizations founded NorStent, and the Northern Norway Regional Health Authority (Grant number SFP1233-15) founded the PhD project.

3.6.2 User involvement

The idea of this study arose from years of experience working with patients with established CHD. This was in combination with collaboration with health professionals in Norway and abroad. The former patients, i.e. the participants in the clinical NorStent study, are not directly involved. However, the use of patient-reported outcome measures and research topics that are important for the patients' well-being leads us to believe that our research is in line with the patients' preferences.

4 Summary of results

4.1 Paper I

Cardiac rehabilitation after percutaneous coronary intervention: Results from a nationwide study

At three years follow-up, 27.6% of the participants reported having participated in a CR programme. There were geographical differences in participation rates between the health regions in Norway (20%-31%). Compared to non-participants, the typical CR participant was younger, had a higher educational level, currently smoked, had a lesser degree of cardiovascular disease and to a greater extent had acute coronary syndrome as the indication for PCI.

In multivariate adjusted analysis, CR participation was associated with higher levels of education (OR 1.50; 95% CI 1.32-1.71), overweight (OR 1.19; 95% CI 1.05-1.36), an acute coronary event (OR 3.23; 95% CI 2.76-3.79), while the probability of participating in CR decreased with increasing age. Male gender (OR 0.72; 95% CI 0.62-0.83) and prior MI or CABG (OR 0.71; 95% CI 0.55–0.91) were associated with less likelihood of CR participation.

When stratified by regional health authorities, the regression model showed that chronological age was a predictor for non-participation in all regions, and that an acute coronary syndrome was associated with higher odds of participating in a CR programme (Table 6).

Table 6. Odds ratios for participation in cardiac rehabilitation, stratified by regional health authorities in Norway (fully model)

	North (N=1009)				Central (N=969)				South-East (N=3850)				West (N=1240)			
	n (%)	OR	95% CI		n (%)	OR	95% CI		n (%)	OR	95% CI		n (%)	OR	95% CI	
Gender (male)	752 (75)	0.54**	0.37	0.81	739 (76)	0.77	0.54	1.09	2853 (74)	0.73**	0.60	0.88	977 (79)	1.02	0.68	1.53
Age (years)																
≤ 59	345 (34)	1***			356 (37)	1*			1349 (35)	1***			446 (36)	1***		
60-69	373 (37)	0.42	0.29	0.62	385 (40)	0.88	0.63	1.22	1419 (37)	0.63	0.52	0.75	42 (35)	0.59	0.42	0.82
≥ 70	291 (29)	0.18	0.10	0.31	228 (24)	0.54	0.35	0.82	1082 (28)	0.31	0.24	0.39	366 (30)	0.24	0.15	0.39
Education level attained																
> 12 years	240 (25)	1.61**	1.11	2.34	268 (29)	1.58**	1.14	2.19	1227 (33)	1.33**	1.12	1.58	377 (32)	1.83***	1.33	2.50
Smoking status																
Never	298 (30)	1			298 (32)	1			986 (30)	1			378 (31)	1		
Former	367 (37)	0.97	0.64	1.47	294 (32)	1.10	0.76	1.58	1170 (35)	1.13	0.92	1.38	451 (38)	1.12	0.77	1.64
Current	329 (33)	0.84	0.55	1.28	342 (37)	0.98	0.68	1.42	1180 (35)	1.12	0.90	1.38	375 (31)	1.15	0.77	1.69
Prior MI (Yes)	91 (9)	0.37*	0.14	0.99	83 (9)	0.95	0.50	1.79	392 (10)	0.94	0.69	1.29	98 (8)	1.08	0.52	2.25
Prior CABG (Yes)	81 (8)	0.65	0.24	1.76	49 (5)	0.40	0.14	1.09	240 (6)	0.60*	0.38	0.96	73 (6)	0	0	0.0
BMI > 25 (kg/m^2)	711 (71)	1.14	0.78	1.68	538 (56)	1.19	0.88	1.60	2619 (68)	1.17	0.97	1.40	782 (63)	1.19	0.86	1.64
PCI indication (Acute)	663 (66)	1.70**	1.13	2.55	759 (79)	2.85***	1.88	4.33	2515 (66)	3.57***	2.93	4.36	964 (78)	3.09***	1.92	4.95

BMI, Body Mass Index; CABG: coronary artery bypass graft; CI, confidence interval; MI: myocardial infarction; OR: odds ratio; PCI: percutaneous coronary intervention
*, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$.

4.2 Paper II

Cardiac rehabilitation and symptoms of anxiety and depression after percutaneous coronary intervention

We found that 27% and 19% of patients reported clinically relevant symptoms of anxiety and depression, respectively, the week before PCI, with the highest levels found in those participating in a CR programme. After three years, both the CR participants and non-participants had a higher mean level of symptoms of anxiety than the reference population. For symptoms of depression, the CR participants had a higher and the non-participants a lower mean score than the reference population. Changes in HADS-A and HADS-D represent a significant reduction ($p<0.001$) from baseline to three years follow-up.

In a separate analysis of the total cohort of 7068 patients, the HADS-A score after three years of follow-up was significantly higher than that in the reference population (3.92 (SD: ±3.63) vs 3.44 (SD:±0.45), $p<0.001$), while the HADS-D score was significantly lower (3.42 (SD: ±3.44) vs 3.85 (SD: ±0.48), $p<0.001$).

There were no differences in change of symptoms of anxiety and depression between the CR participants and non-participants (HADS-A; p-value= 0.396 and HADS-D; p-value= 0.607). In the propensity-matched cohort, CR participants had more clinically relevant symptoms of anxiety, but not depression (p-value = 0.003 and 0.207, respectively).

Multivariate adjusted analysis showed that male gender (OR 0.45; 95% CI 0.35-0.58) and older age ($p<0.001$) were associated with lower probability of clinically relevant symptoms of anxiety, whereas CR participation was associated with higher probability of clinically relevant symptoms of anxiety (OR 1.47; 95% CI 1.12-1.95). Higher levels of education (OR 0.71; 95% CI 0.53-0.95) and an acute coronary event as the indication for PCI (OR 0.73; 95% CI 0.56-0.95) were associated with lower risk of clinically relevant symptoms of depression. Older age (p-value=0.016), former smoking (p-value=0.012) and prior cardiovascular disease were associated with higher risk of clinically relevant symptoms of depression (prior MI/CABG; p=0.045, prior stroke; p= 0.011).

4.3 Paper III

Employment status three years after percutaneous coronary intervention and predictors for being employed. A nationwide prospective cohort study.

At three years follow-up, 2488 patients were of working age. The majority of these were employed (70.2%), while 11.2% were unemployed and 18.6% were retired. 38.3% of the patients reported having participated in a CR programme at some point during the period from baseline to 36 months.

In the propensity-matched cohort, employment status of the CR participants did not differ from that of the non-participants (p=0.580). The multivariable-adjusted analyses showed that male participants (OR 1.93; 95% CI 1.50-2.50), participants living with a partner (OR 1.40; 95% CI 1.07-1.82), and participants with a high level of education (OR 1.93; 95% CI 1.54-2.42), had a significantly higher chance of being employed three years after PCI. In addition, participants living in western Norway were most likely to be employed, while those in northern Norway had the lowest employment rate (OR 1.89; 95% CI 1.32-2.71). Higher age (p<0.001), former smoking (p=0.01), prior MI or CABG (OR 0.55; 95% CI 0.37-0.81), and prior hypertension treatment (OR 0.69; 95% CI 0.55-0.86) were associated with a lower chance of being employed.

5 Discussion of methodology

5.1 Study design

The present thesis aims to answer the research questions with a prospective observational study design, where we follow a cohort of CHD patients from their first PCI to three years later. A causal relationship exists if the cause comes before the effect, the cause was related to the effect, and we cannot find alternative explanations for the effect other than the cause (149). The papers in this thesis have both a non-experimental and quasi-experimental design with several methods to describe the situation, prove an association or prove a causal relationship, as shown in Table 7.

Table 7. Design used to prove a causal relationship in the present thesis

	Research question	Design	
Paper I	Determine proportions Determine predictors	Descriptive Correlational	Non-experimental
Paper II	Determine proportions Determine predictors	Descriptive correlational	Non-experimental
	Compare proportions between two groups	Post-test with propensity score matching	Quasi-experimental
	Compare levels between two groups	Pre-test and post-test Comparison with general population	Non-experimental
Paper III	Determine proportions Determine predictors	Descriptive Correlational	Non-experimental
	Compare proportions between two groups	Post-test with propensity score matching	Quasi-experimental

A prospective non-experimental design has the benefit that it can be used for large samples, with lower costs and with long-term follow-up, and it is strong in realism (149, 150). When estimating the proportion of patients participating in CR who had symptoms of anxiety and depression or their employment status, we used descriptive methods where the purpose is to observe, describe, and document aspects of a situation (150). Findings from descriptive studies can serve as a starting point for hypothesis generation for use in future research (150). It is also an alternative when it is unethical to offer an intervention to one group, but not the other (149, 150). CR has a Class I recommendation with Level A of evidence for patients

with CHD (37, 151, 152). This would represent an ethical challenge for us in conducting an RCT. We chose to improve the prospective observational study design by adding propensity score matching to our non-equivalent groups (CR yes and CR no). This method strengthens the design and is therefore referred to as quasi-experimental (149, 150).

The validity of the study must be considered in interpreting the results, and possible threats need to be addressed. Validity is not an absolute, but a matter of degree (150). A taxonomy of four types of validity was introduced by Shadish et al.: statistical conclusion validity, internal validity, construct validity and external validity (149). The present study has many strengths, such as a large representative sample, the prospective study design, the long-term follow-up, and the high response rate. We have made efforts to improve the validity of our findings and to reduce the risk of threats. Despite these strengths, there are some limitations to take into consideration. Strengths and limitations are therefore discussed in more detail in the next sections.

5.1.1 Statistical conclusion validity

Statistical conclusion validity concerns the validity of inference that there truly is an association between the assumed cause and effect. Decisions about research design can protect against reaching false statistical conclusions. Type I errors occur when the researcher concludes that there is an association or effect, when there is not (149, 150). A two-tailed *p*-value of <0.05 was considered statistically significant in the present thesis, implying that 5% of the association or effect occurs by chance alone (representing a 5% probability of committing a type I error). A type II error occurs when the researcher concludes that there is no association or effect, when in fact there is (149, 150). The level of statistical significance and the large sample size increase the chances to capture the true differences in the statistical tests, and we believe that there is a good balance between the probabilities of committing a type I and type II error.

The large sample size gives us better precision through powerful statistical methods that attempt to control confounding variables. Confounders are common in observational studies and can suggest that there is an association between the exposure and the outcome where there is none, or mask a true association (150). In Papers I-III, we used multivariable regression analysis and included variables considered most important in relation to the

outcome, as further described in the papers. Notably, because of the high correlation between symptoms of anxiety or depression, we did not control for depression when analysing anxiety or vice versa, as this could cause a disproportionate weakening of the association (Paper II). However, a sub-analysis where we categorized the response >8 in HADS-A, HADS A+D and HADS-D could have given us further information about the presence of the combination of anxiety and depression in our population.

In Paper I, we used stratification when analyses differed between regional health authorities. Both stratification and statistical adjustment can reduce the risk of confounding (150). Unfortunately, we could not control for previously diagnosed anxiety and depression disorders and treatment with antidepressants (Paper II) or employment status at baseline (Paper III). In addition, not knowing the content and level of CR, especially in terms of physical activity and vocational and psychological support, may have influenced our findings.

In Papers II and III we used propensity matching scores, in which potential confounders are used to build a statistical model where we reduce the covariate to a single quantity called the propensity score: the participants with high scores are more likely to have certain confounders, while those with low scores are less likely. The matching allows us to compare participants with the same 'level' of confounders. Nevertheless, despite the use of statistical methods that reduce the chance of confounding, unknown factors may still be significant residual confounding factors and present in all papers.

5.1.2 Internal validity

Internal validity implies the validity of inferences that, given that an empirical association exists, it is the independent variable that caused the outcome. Quasi-experimental and descriptive studies are especially vulnerable to threats to internal validity (149, 150). Bias is a problem that threatens internal validity. Bias is a systematic deviation from the truth that produces a distortion in the study results. Bias can seldom be avoided, but through systematic analysis and careful implementation of findings, bias can be reduced to a minimum (150). In the present thesis, internal validity of our results needs to be seen in light of selection bias, attrition bias, recall bias and instrument bias.

Selection Bias

As NorStent was developed to evaluate the long-term risk and benefits of the use of drug-eluting stents versus bare metal stents in a large, randomized trial, this might have influenced the selection of the patients included in the study. For example, 1732 patients were not enrolled in the study because of physicians' stent preference. This could happen in situations where the patients were diabetic, had long stenosis or small vessels, and were randomized to bare-metal stents. This indicates that selection bias is probably present to some extent, as these patients are often complex CHD patients and women. In addition, patients that refused to participate in the study or were not enrolled for unknown reasons (2260 patients) might have been those with severe presentation of the coronary event. Lack of time to enrol the patient or for the patient to take a decision on participation in the study before the index PCI may have excluded patients eligible for our analysis. However, 73% of patients with protocol eligibility were included, and the large nationwide sample size, reduced the risk of selection bias in our cohort substantially.

Attrition bias

Attrition bias is a possible source of bias in our study, especially given the long follow-up time. Attrition occurs when the characteristics of those who remain in the study differ from those of the drop-outs (150). It is recommended to have <5% attrition as this leads to little bias. The present study had a response-rate of 82% excluding the patients that died during follow-up, giving us less than 20% loss and an intermediate level of threats to validity (153). The study design makes it unlikely that participants left the study for reasons related to the outcome, and this therefore had little impact on the results. However, some differences are present between those lost to follow-up and those participating at three years follow-up. Overall, the participants that dropped out were younger, lived alone, had a lower educational level, were current smokers, had a higher degree of comorbidities and had an acute coronary syndrome at index event (Table 2). These patient characteristics are at some extent typical for non-attendees in CR programmes (79), and the CR participation rate presented in Paper I may therefore be even lower. The prevalence of symptoms of anxiety and depression in Paper II may also be higher, as drop-outs more often have depression, anxiety and negative affectivity than completers (154).

Recall bias

In self-reporting, the respondent must comprehend the question being asked, recall information from memory, make a decision about the accuracy of the information recalled and formulate an answer (155). Recall bias is a problem in studies that have self-reporting and can be greater when the time interval being asked about is longer. Responders tend to under-report the severity of past problems (140). Research has shown that it is less common for a person to wrongly remember an event that did not occur (156). The present thesis assessed CR participation by self-report as there is no national register or standard use of ICD codes in institutions offering CR. Assessment of CR participation by self-report has been validated in a previous study, showing almost perfect agreement between self-report and site-verified CR participation (136), suggesting that recall bias regarding CR participation is less likely in this study. In Paper II, the participants were asked about symptoms of anxiety and depression in the period before hospitalization approximately nine weeks after inclusion. This delay in time could have influenced their answers in a positive direction, but our participants scored worse compared to the general Norwegian population.

Instrument bias

When using self-report instruments, people often tend to present themselves in a favourable light (155). As the present data were collected by mail or phone, there is a smaller risk that the participants modify their answers, compared to having an in-hospital interview. The HADS demonstrated adequate reliability in the present study (Cronbach's alpha >70). The HADS is validated for use in a CHD population and, in contrast to diagnostic interviews and other self-reported instruments regarding mental health, the HADS systematically excludes physical symptoms that can be mistaken for heart disease (137). This, in addition to the use of the recommended cut-off value, strengthens the chance of detecting the true prevalence of clinically relevant symptoms of anxiety and depression.

Regarding employment status, we chose to categorize the variables following Harrison et al. (157). Due to timeline and costs, it was not possible to link our data with the National Insurance Registry. We therefore chose a strict age limit to ensure that the patients included in our analysis were retired because of health issues, and not age.

5.1.3 Construct validity

Construct validity refers to the degree to which inferences can legitimately be made from the operationalizations in the study to the theoretical constructs on which those operationalizations were based (149, 150). Although there is a consensus internationally on what should be the content of CR, there is a great variation in what is being offered (85, 86). The CR variable in this study was merged as we wanted to determine whether there were differences between participants receiving no follow-up care and those receiving some. There is a possibility that participants that answered 'no' to CR participation had received some form of follow-up care that is in the concept of CR, but not named CR. Furthermore, when analysing the effect of CR, there is a risk of contamination as non-participants may also adopt a healthier lifestyle. In addition, both CR participants and non-participants could have been influenced by national campaigns promoting physical activity, a non-smoking environment and healthy dietary habits. Anticipating a threshold in how much people will improve their lifestyle could explain the lack of differences between CR participants and non-participants.

5.1.4 External validity

External validity is the extent to which the results can be generalized to other settings, time, populations or measures of the outcomes (149, 150). The NorStent was performed at all centres in Norway that perform PCI, thus covering the total Norwegian population of more than 5 million inhabitants. The clinical setting and a multi-centre approach strengthen the external validity (149, 150). We believe therefore that the findings of our study are representative of the Norwegian population and applicable to other northern European countries.

6 Discussion of main results

This study has revealed that few patients with established CHD participate in a CR programme, with certain geographical differences. We also found that 27% and 19% of patients who had undergone PCI reported symptoms of anxiety and depression, respectively, with the highest levels found in those participating in a CR programme. There were no differences in changes in symptoms of anxiety and depression between the CR participants and non-participants. After three years, both the CR participants and non-participants had a higher level of anxiety, but not depression, than the general Norwegian population. In addition, we found that 70% of participants aged 62 years and younger reported being employed three years after PCI. These individuals' employment status was not aided by CR participation. Finally, the study reported several patient characteristics related to future likelihood of CR participation, long-term symptoms of anxiety and depression, and being employed after PCI.

6.1 Cardiac rehabilitation participation

Only 28% of the study participants reported having participated in a CR programme, which is lower than the European average (6, 7). In Norway, Peersen et al. found a large difference in participation rates between two nearby hospitals, Drammen and Vestfold (18% vs. 75%, respectively) (87). Vestfold has inpatient referral and start-up after two weeks, while Drammen has suboptimal availability and referral procedures (87). Lack of national standards and guidelines for CR represents a system barrier in Norway and CR delivery varies considerably. We found differences between the four regional health authorities, which may be due to differences in financial support, availability and referral practice. In addition, the scientific doubt as to the effect of CR coupled with the successful effect of medications on coronary risk factors may contribute to barriers to provision and low numbers of referrals.

In a qualitative study from Norway, PCI patients described a stressful hospital environments and little information about their diagnosis and consequences of the disease. They therefore sought information from friends, newspapers and the Internet (158). Patient-related barriers and lack of awareness and perceived need can explain low participation rates. We found less likelihood of CR participation among older patients and patients with a lower educational level, which are known characteristics of people at risk of limited health literacy (57, 58). The fact that many of the CR programmes are named 'Heart School' can act as an barrier to

patients with negative associations to school as they might think that they will be tested or need to prove their knowledge there.

Compared to northern Norway, patients in central and southern/eastern parts of the country were more likely to participate in a CR programme. In stratified analysis, we found that young age, higher educational level and an acute coronary event as indication for PCI were the strongest predictors of CR participation in all regions. In Norway, patients undergoing planned PCI stay in hospital for one day on average, while those with acute coronary syndrome stay for two to four days. The short hospital stay after PCI with limited time for health information may increase the distinction in CR participation between patients with low and high health literacy. Patients with a higher degree of health literacy tend to seek information about the beneficial effects of CR and to request this kind of treatment.

In contrast to previous research, our multivariate analysis showed that women were more likely to participate in a CR programme than men (79, 159), perhaps because of an increasing focus in recent decade on women's cardiovascular health. Previously, many domestic tasks had been suggested as a barrier for women to participate in CR, but this might be less of an issue today. Overweight patients and those with an acute coronary event were more likely to participate in CR. This may be a combination of individuals' desire to optimize their lifestyle and the fact that clinicians can more easily identify such patients' risk of future CHD events. Prior CR participation may explain why patients with prior MI or CABG less often report engaging in CR.

6.2 Symptoms of anxiety and depression and cardiac rehabilitation

Previous research on the prevalence of symptoms of anxiety and depression both in the general population and in CHD patients has varied in design, measurement methods and accordingly prevalence estimates (93, 94, 104, 107-109). The present study revealed a higher prevalence of symptomatic anxiety and depression at the index event than reported in previous studies of CHD patients from Nordic countries. Our prevalence was consistent with the mean results in Europe (104, 105, 107), and lower than that reported in a PCI population (111). Variation in severity of anxiety and depression over a lifetime and differences in methods to measure symptoms of anxiety and depression may partly explain the dissimilarities.

When investigating levels of symptoms of anxiety and depression in a CHD population, it is interesting to compare the levels with the general population. We found that at the index event, both CR participants and non-participants had higher levels of anxiety than expected in the general population. This may be due to the patients' recent diagnosis of CHD, sometimes presented or perceived as a life-threatening event. At three years follow-up, the levels of symptoms of anxiety had decreased significantly in the study population. This change represents a minimal clinically important difference, as the threshold for CHD patients is reported to be 1.7 points (160). However, it was still higher than expected in the general population, but not statistically significant among the non-participants. We also found a statistically significant higher level of anxiety in the total cohort three years after PCI compared to the general population. These findings may indicate that some of the study participants had a generalized anxiety disorder with more persistent symptoms.

We found no differences in changes in symptoms of anxiety between the CR participants and non-participants, but when we compared the propensity-matched groups, more CR participants reported clinically relevant levels of anxiety three years after PCI. We do not believe that CR promotes anxiety, but that healthcare professionals identify and encourage anxious patients to participate in a CR programme. Furthermore, if there is limited availability on CR programmes, patients in most need are given priority. As previously shown (104, 109), the multivariate analysis revealed that women and younger patients were associated with symptomatic levels of anxiety three years after PCI. Notably, the unadjusted analysis showed that patients living alone, currently smoking, and with a lower educational level, had a higher

risk of clinically relevant symptoms of anxiety three years after PCI, which is characteristic of patients with lower socioeconomic status and limited health literacy (57, 58, 161).

Regarding symptoms of depression, the level of symptoms in both CR participants and non-participants were higher than expected compared to the general population. As depression is a risk factor for CHD, these findings were as expected. Surprisingly, the CR participants had similar levels to the expected score of the general population after three years, and the non-participants had significantly lower levels of symptoms of depression. Also in the total study population, we found lower levels of depression than those expected in the general population. The normal variation in severity of depression can be one explanation, but we cannot exclude the possibility that some patients received treatment for their depression during the follow-up period. The present study suggests that less educated and older patients are at risk of clinically relevant symptoms of depression, as also shown in previous research (104). We also found that patients with cardiovascular diseases, a history of smoking and acute coronary syndrome were at risk of clinically relevant symptoms of depression three years after PCI. This may indicate that these patients are living with an increased burden of the disease that influences the level of depression.

As with symptoms of anxiety, there was no significant change in level of depression between CR participants and non-participants after three years. These findings were confirmed in the propensity-matched analysis, where we found no benefit regarding the level of clinically relevant symptoms of depression in CR participants. Unfortunately, we were unable to control for previously diagnosed anxiety and depression disorders, which may have affected the results. There is no robust evidence of the benefit of psychological interventions on symptoms of anxiety and depression, and reviews and meta-analyses may have been influenced to some extent by historically limited publications with negative findings (publication bias). However, as we have limited information about the content and level of physical and psychological support during CR, this should be taken in account when interpreting the results.

6.3 Employment status and cardiac rehabilitation

We found that 70% of patients 62 years and younger reported being employed three years after PCI, slightly lower than in previous studies of CHD patients (120-122, 126). However, differences between previous studies and the present study regarding study population, severity of the coronary disease, employment status at inclusion and follow-up time make it difficult to compare our findings. Detachment is present in up to 24% of patients one year after return to work (121). This demonstrates the importance of long-term follow-up when measuring employment status after PCI and may explain a lower rate of employed patients in our study at three years follow-up compared to previous findings. In addition, the rate of employed patients in our study is somewhat lower than that reported in the general Norwegian population (119), indicating that our study population has health issues that may act as barriers to employment.

This assumption is strengthened by the fact that about 19% of patients of working age reported that they were retired three years after PCI, demonstrating that approximately twice as many CHD patients leave the workforce early as in the general population (119). We lack information on the reasons for early retirement, but research has demonstrated that the most common reasons seemed to change from musculoskeletal disorders and mental disorders before an ischaemic heart disease event to diseases of the circulatory system after such an event (128). Despite improvements in the prognosis for CHD patients, there may still be a fear of a negative health impact because of the physical or mental stress involved in work. Furthermore, there might be less stigma related to disability due to CHD than musculoskeletal disorders.

We did not have the opportunity to study change in employment status over time, as we lacked information on employment status at the index event and on subsequent morbidity during the three years. A history of long-term sickness absence prior to revascularization is, for example, a strong predictor of long-term sickness absence following PCI, followed by a disability pension (125, 127). We found that being male, living with a partner, and higher levels of educational attainment were associated with a greater chance of being employed three years after PCI. The beneficial association between educational level and return to work has previously been shown (120, 121, 125). Higher educational level may indicate a white-collar job, previously known to facilitate return to work (132). Regarding gender differences,

previous research is more inconclusive, but most studies report that men are more likely to be employed than women are (120, 121, 124, 125, 129). We also found that older patients and those living in northern Norway had less chance of being employed. Fewer opportunities for retraining or changing the type of job can be one explanation, leading to a disability pension after long-term work incapacity.

We did not find any differences in employment status in our propensity-matched comparison between those participating in CR and the non-participants three years after PCI. One limitation is that we could not control for employment status at index event. In addition, we do not know the content of the vocational training in the CR programmes. Differences between CR programmes regarding vocational support may explain some of the difficulty in finding an effect of CR on employment status. However, there appears to be little benefit of CR on employment status and a Cochrane review found no evidence that CR promotes return to work after one year follow-up (133). These findings were supported by two recent studies showing no association between CR or psychosocial and vocational interventions and return to work (124, 134). An ageing population will lead to a future need to keep as many people as possible employed and to stay in their jobs longer; vocational support may thus play a more central role in aftercare for CHD patients in the future.

7 Conclusions and future perspectives

We believe that our findings provide a valid picture of parts of CR provision in Norway, and that our findings can serve as a starting point for future research. The design of this study, however, limits the possibility to find causal effects between CR and participation rate, clinically relevant symptoms of anxiety and depression or employment status.
We found that the estimated CR participation rate in Norway is low. The typical CR participant in Norway is young, overweight, well-educated, and has suffered from an acute coronary event. We also found that the participation rate to some extent varied geographically. Despite a reduction in levels of symptoms of anxiety and depression after three years, we did not identify any beneficial effect of CR participation. However, the CR participants reported a clinically important decrease in symptoms of anxiety. Compared to the reference population, our patients had higher levels of anxiety, but not depression, three years after PCI.

A significant number of working-age patients remain unemployed three years after their first coronary revascularization, indicating that employment status should be an important component of aftercare for PCI patients. However, we did not identify any beneficial effect of CR participation on employment status. Healthcare providers should pay attention to factors associated with clinically relevant levels of anxiety and depression and unemployment in PCI patients, to prevent long-term symptoms of anxiety and depression and future poor vocational outcome. The present study suggests that the patients most in need, i.e. those who are overweight, smokers, and have the highest levels of anxiety and depression, are identified and encouraged to participate in CR programmes.

The beneficial effect of cardio-protective medications may have been at the expense of other initiatives that promote secondary prevention, although those without the strongest evidence on mortality and morbidity. However, from the patients' perspective, mental health and social and vocational reintegration are important and associated with higher levels of medical and healthy lifestyle adherence. Greater acceptance by healthcare providers that CR facilitates secondary prevention may increase the referral and participation rates, which in turn may result in more patients achieving treatment goals in secondary prevention. National standards for secondary prevention goals, how to reach them and the role of CR programmes in secondary prevention therapy seem to be needed. In addition, we need high quality research to

prove the beneficial effect of CR in an era of improved pharmacological and interventional treatments, and to find the most efficient modes of delivery.

The content of future CR must take into account the economic pressure on our health care system and a greater demand for tailored health services, recently mentioned in the Norwegian National Health and Hospital Plan 2020-2023 (162). Today, CR in Norway is practised as “one size fits all”, but with a great variety in the content of CR programmes between hospitals. A first step would be to gain an overview of all the CR programmes in Norway. Secondly, attempts should be made to ascertain the barriers to CR participation and achieving treatment goals in secondary prevention. Thirdly, patients that would benefit from the different modes of delivery must be identified. This should lead to a nationwide randomized controlled trial investigating both the ‘hard’ and ‘soft’ outcomes of CR. Finally, a national CR register should be established to continuously measure predefined quality indicators. All these initiatives should be planned by a multidisciplinary team and involve a mixed interventions approach in order to enhance understanding of all the aspects involved.

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Papers I-III

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Abstract

Aim: The purpose of this study was to estimate the proportion of Norwegian coronary heart disease patients participating in cardiac rehabilitation programmes after percutaneous coronary intervention, and to determine predictors of cardiac rehabilitation participation.

Methods: Participants were patients enrolled in the Norwegian Coronary Stent Trial. We assessed cardiac rehabilitation participation in 9013 of these patients who had undergone their first percutaneous coronary intervention during 2008–2011. Of these, 7068 patients (82%) completed a self-administered questionnaire on cardiac rehabilitation participation within three years after their percutaneous coronary intervention.

Results: Twenty-eight per cent of the participants reported engaging in cardiac rehabilitation. Participation rate differed among the four regional health authorities in Norway, varying from 20%–31%. Patients undergoing percutaneous coronary intervention for an acute coronary syndrome were more likely to participate in cardiac rehabilitation than patients with stable angina (odds ratio 3.2; 95% confidence interval 2.74–3.76). A multivariate statistical model revealed that men had a 28% lower probability ($p<0.001$) of participating in cardiac rehabilitation, and the odds of attending cardiac rehabilitation decreased with increasing age ($p<0.001$). Contributors to higher odds of cardiac rehabilitation participation were educational level >12 years (odds ratio 1.50; 95% confidence interval 1.32–1.71) and body mass index>25 (odds ratio 1.19; 95% confidence interval 1.05–1.36). Prior coronary artery bypass graft was associated with lower odds of cardiac rehabilitation participation (odds ratio 0.47; 95% confidence interval 0.32–0.70)

Conclusion: The estimated cardiac rehabilitation participation rate among patients undergoing first-time percutaneous coronary intervention is low in Norway. The typical participant is young, overweight, well-educated, and had an acute coronary event. These results varied by geographical region.

Keywords

Cardiac rehabilitation, secondary prevention, coronary heart disease, myocardial infarction, coronary artery disease

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Introduction

Improved survival coupled with an increasingly ageing population has led to a growing number of people living with cardiovascular disease (CVD) and a growing need for medical follow-up. Cardiac rehabilitation (CR) makes an important contribution to secondary prevention of cardiac events. The World Health Organization defines CR as 'The sum of activities required to influence favourably the underlying cause of the disease, as well as to ensure the best possible physical, mental and social conditions, so that they may, by their own efforts, preserve or resume when lost as normal a place as possible in the life of the community' (p. 5).[1]

According to international guidelines, CR should be a core component of the care received by patients with established coronary heart disease (CHD).[2,3] The elements of CR consist of lifestyle interventions, risk factor management, and psychosocial and vocational support.[4] The short-term goals for CR are to manage cardiac symptoms, improve functional capacity, limit psychological distress, and give vocational support to the patient. The long-term goal is to stabilise or slow the progression of arteriosclerosis, thereby reducing morbidity and mortality, and minimising the risk of future cardiac events.[5]

Despite scientific doubt, a recent meta-analysis showed that CR in patients with established CHD is associated with reductions in cardiovascular mortality and hospital admissions, and improved quality of life.[6] Despite the evidence of benefits, referral to and participation in CR programmes vary widely across Europe.[7,8] In Norway, availability of CR varies widely within geographical regions and across the country.[9,10] In addition, acute myocardial infarction (MI) patients require more information after discharge,[11] and experience discontinuity of care after percutaneous coronary intervention (PCI).[12] Furthermore, no national estimates exist on the proportion of patients participating in CR programmes.

The aims of this study were to determine the approximate proportion of Norwegian cardiovascular heart disease patients participating in CR programmes after PCI and to determine predictors of CR participation.

Methods

Design and settings

The present study uses an observational cohort design and is a substudy of the Norwegian Coronary Stent Trial (NorStent). NorStent is a nationwide, multicentre, randomised controlled trial conducted at all PCI centres in Norway. Its primary objective is to compare the effect of drug-eluting and bare-metal stents on long-term mortality and cardiovascular morbidity.[13] Clinical variables and patient-reported outcomes were collected at baseline and three years after the PCI procedure.

Study participants

Patients were included in NorStent from September 2008–February 2011. In addition to the ability to communicate in Norwegian and having a Norwegian personal identification number, patients were included if this was their first PCI due to either stable angina or acute coronary syndromes, were at least 18 years old, had a lesion in native coronary arteries or coronary-artery grafts, and provided informed written consent. The study had a pragmatic design, with few exclusion criteria.[13] A total of 9013 patients were included in NorStent, 54% of all Norwegian patients who underwent PCI during the study period. The response rate after three years was 82%.

Data collection

Clinical data were retrieved from the patients' electronic medical records by specially trained registered nurses. Self-reported patient outcomes were measured three years after the PCI procedure using validated questionnaires[14,15] as well as questions developed specifically for this study. Attendance in a CR programme was assessed by asking study participants the following questions representing two possible CR alternatives: (a) Have you participated in a shorter ambulatory CR programme lasting for hours or days? (b) Have you participated in a hospital- or centre-based in-patient CR programme lasting for one or more weeks? The response options were 'yes', 'no', or 'uncertain'. The variable was coded as CR participation if the patient answered 'yes' to one or both questions. 'Uncertain' and 'no' responses to both questions were coded as lack of CR participation. A study coordinating centre at the Institute of Clinical Medicine, the Arctic University of Norway, administered the follow-up data collection. Patients were sent reminders by phone and letter to complete and return their questionnaires.

Ethical issues

The study conforms to the principles outlined in the Declaration of Helsinki.[16] All patients gave written informed consent to participate in the study and were informed about the opportunity to withdraw consent at any time without giving a reason. Study participants received the same routine medical treatment regardless of whether they had not participated in the trial. The NorStent trial protocols were reviewed and approved by the National Committees for Research Ethics in Norway and by the Norwegian Social Science Data Services (NSD19480, PREKNORD40/2008), and the trial is registered at ClinicalTrial.gov (NCT00811772).

Statistical analysis and data management

Categorical data are presented as counts and percentages, and continuous data as means with standard deviations, or medians with interquartile ranges. All the data were

checked for outliers. Gender, living arrangement, educational level, smoking status, medical history, and clinical findings were similarly distributed among CR alternative one and two, allowing us to conduct pooled analyses of the two alternatives. Further, separate analyses for the two alternatives of CR showed no differences in predictors (results not published), justifying analysing both CR alternatives together. Differences at baseline were tested using Pearson chi-square or Fisher's Exact test for categorical variables. For continuous variables, we used independent Student's *t* test or Mann-Whitney U test.

Logistic regression analysis was used to identify predictors of CR participation. The multivariable model was built using independent variables that had a statistically significant ($p \leq 0.05$) univariable (unadjusted) association with CR participation (age, health authorities (HAs), living arrangement, educational level, smoking status, MI, coronary artery bypass graft (CABG), body mass index (BMI), and indication for PCI) in addition to existing evidence indicating an association (gender). All significant two-way interactions were tested in the full multivariate model, and only HA×age remained significant. A *p*-value equal to or below 0.05 was considered statistically significant.

Data management and all the statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corporation, Armonk, New York, USA).

Results

Patient characteristics

After three years of the study, 7068 patients responded to the survey, and 27.6% reported having participated in a CR programme (CR<1 week; 52%, CR≥1 week; 48%). Baseline characteristics of the cohort, according to CR participation, are presented in Table 1. Males comprised 75.3% of the group, and the mean age of all participants was 63.1 years. A total of 75.9% of participants lived with a partner, and 31.1% had more than 12 years of education. Daily smoking was reported by 34.4% of participants. A prior MI or a diagnosis of diabetes mellitus was reported by 9.4% and 11.3% of patients, respectively. An acute coronary syndrome was the indication for PCI among 69.8% of the patients (Table 1).

CR participants vs non-CR participants

Compared to non-CR participants, the typical CR participant was younger, had more than 12 years of education, was currently smoking, had less severe prior CHD, and to a larger extent had acute coronary syndrome as the indication for PCI (Table 1).

CR programme participation

CR participation rate differed among the four HAs in Norway: 20% reported CR participation in the North HA, 21% in the West HA, and 31% in each of the Central and the South-East HAs.

The multivariate logistic regression analysis revealed that men had a 28% less probability of participating in a CR programme compared to women, and the odds of attending CR decreased with increasing age ($p<0.001$), with higher attained level of education ($p<0.001$), and higher BMI ($p=0.009$) (Table 2). Patients hospitalised with an acute coronary syndrome had higher odds for attending CR than patients hospitalised with stable angina (odds ratio (OR) 3.21, 95% confidence interval (CI) 2.74–3.76). Having had a prior CABG decreased the odds for CR ($p<0.001$).

When stratified by HA, the regression model showed that chronological age was a predictor for non-participation in all HA regions, with decreasing odds of CR participation for those above 70 years of age of 0.54 in the Central HA, 0.31 in the South-East HA, 0.24 in the West HA, and 0.18 in the North HA (*p* for the interaction term=0.001) when controlling for the other significant factors. In the North and South-East HAs, women had a higher chance of participating in CR than men, but this difference was not significant (*p* interaction=0.16). In the North HA prior MI and in South-East HA prior CABG were significant contributors to a reduced CR participation rate.

Discussion

The present study indicates that 28% of patients who underwent first-time PCI in Norway during 2008–2011 participated in a CR programme. The typical participant in Norway was young, overweight, well-educated, and had suffered from an acute coronary event. These results differed somewhat depending on the geographical location of the patients.

CR participation rates vary among European countries,[7,17] and a participation rate of 28% revealed in the present study for Norwegian patients is consistent with previous results reported for patients being treated in other European countries.[18–20] In addition, our findings reveal that geographical differences within Norway exist for participation rate, which varied from 20–31% depending on the HA. These differences may be due to differences in systemic barriers across the different regions of Norway. The four regional HAs are financed separately, and differences in the economic support that CR programmes receive might affect the availability of these programmes in different regions. Differences in referral strategies across regions may also explain to some extent the differences in CR participation rate.[21] Furthermore, accessibility, excessively long travelling distances and transportation difficulties are factors proven to affect patient participation in CR programmes.[22]

Previous research has shown that women are less likely to participate in CR.[20] It has been suggested that factors, such as transportation, comorbidities and family responsibilities affect women disproportionately, which then serve as higher barriers for women to participation in CR programmes.[23] Surprisingly, when other factors are controlled

Table 1. Baseline characteristics of cardiac rehabilitation (CR) participants and non-participants.

		Entire cohort (*n*=7068)		Participants (*n*=1949)		Non-participants (*n*=5119)		*p*-value
Socio-demographics								
Age (years) ±SD		63.1	±10.2	59.7	±9.6	64.4	±10.1	*<0.001*
Male gender, *n* (%)		5321	(75.3)	1473	(75.6)	3848	(75.2)	0.723
Living arrangement, *n* (%)	Spouse/partner	5132	(75.9)	1447	(78.6)	3685	(74.9)	0.005
Educational level attained, *n* (%)	≤12 years	4683	(68.9)	1162	(61.6)	3521	(71.7)	*<0.001*
	> 12 years	2112	(31.1)	725	(38.4)	1387	(28.3)	
Clinical characteristics								
Smoking status, *n* (%)	Never	1960	(30.3)	493	(28.7)	1527	(32.2)	*<0.001*
	Former	2282	(35.3)	527	(30.7)	1755	(37.0)	
	Current	2226	(34.4)	699	(40.7)	1467	(30.9)	
BMI (kg/m^2) mean±SD		27.1	±4	27.4	±4.1	26.9	±3.4	*<0.001*
Medical history, *n* (%)	Prior MI	664	(9.4)	120	(6.2)	544	(10.7)	<0.001
	Diabetes mellitus	801	(11.3)	201	(10.3)	600	(11.7)	0.097
	Prior CABG surgery	443	(6.3)	54	(2.8)	389	(7.6)	<0.001
	Prior stroke	260	(3.7)	50	(2.6)	210	(4.1)	0.002
	Prior lipid treatment	3872	(55.6)	972	(50.7)	2900	(57.5)	<0.001
	Prior HT treatment	3003	(42.8)	709	(36.7)	2294	(45.1)	<0.001
Troponin T before procedure (ng/l)	Median (IQR)	21	(204)	39.5	(301)	16	(168)	*<0.001*
Creatinine concentration (µmol)	Median (IQR)	76	(21)	74	(21)	77	(21)	*<0.001*
Left ventricle ejection fraction, *n* (%)	>40%	2619	(93.1)	538	(89.4)	2081	(94.1)	*<0.001*
	≤40%	194	(6.9)	65	(10.6)	130	(5.9)	
BP systolic, mean±SD		135.1	±23.8	132.1	±24	136.2	±23.6	*<0.001*
BP diastolic, mean±SD		76.8	±13	77.5	±13.4	76.5	±12.8	0.003
Angiographic and procedural characteristics and outcome								
Indication for PCI, *n* (%)	Stable angina	2124	(30.2)	297	(15.3)	1827	(35.9)	*<0.001*
	Unstable angina	875	(12.5)	206	(10.6)	669	(13.2)	
	NSTEMI	2183	(31.1)	665	(34.3)	1518	(29.8)	
	STEMI	1843	(26.2)	771	(39.8)	1072	(21.1)	
Multivessel disease, *n* (%)		2746	(38.9)	711	(36.5)	2035	(39.8)	0.012
Stent treatment, *n* (%)	Drug-eluting stents	3549	(50.2)	980	(50.3)	2569	(50.2)	0.942
	Bare-metal stents	3519	(49.8)	969	(49.7)	2550	(49.8)	
Medication at discharge, *n* (%)	Clopidogrel	7039	(99.7)	1938	(99.5)	5101	(99.8)	0.040
	Aspirin	7025	(99.5)	1942	(99.6)	5083	(99.4)	0.272
	Beta-blockers	5219	(74.4)	1544	(79.6)	3675	(72.5)	*<0.001*
	ACE inhibitors	1637	(23.3)	491	(25.3)	1146	(22.6)	0.016
	A-II blockers	1288	(18.4)	307	(15.8)	981	(19.3)	0.001
	Warfarin	92	(1.5)	27	(1.6)	65	(1.4)	0.748

A-II: angiotensin II; ACE: angiotensin-converting enzyme; BMI: body mass index; BP: blood pressure; CABG: coronary artery bypass graft; HT: hypertension; IQR: interquartile range; MI: myocardial infarction; NSTEMI: non ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-elevation myocardial infarction.

for in regression models, we observed in the present study that women were more likely to participate in a CR programme than men. One possible explanation for this apparent disparity with previous studies is that women tend to participate later in the disease trajectory than men,[24] and since the follow-up time in our study was relatively longer at three years, barriers to participating for women were eventually lowered. Furthermore, our adjusting for prior CHD might have excluded more men that previously had participated in a CR programme, effectively uncovering true participation rates for genders. Another explanation is that the women in our study may have been more aware of the importance of CR than men. Indeed, in the last decade, there has been an increasing focus internationally on women and cardiovascular health issues, especially with regard to strategies that promote guideline implementation in women. Such initiatives could have affected how the women in our study viewed CR, causing them to view it more positively and to recognise the importance of participating in it.

Table 2. Parameters of logistic regression model predicting cardiac rehabilitation participation (n=1949).

		Unadjusted			Adjusted		
		OR	95% CI	*p*-value	OR	95% CI	*p*-value
Male		1.02	0.91–1.15	0.723	0.72	0.62–0.83	*<0.001*
Age (years)	≤59	1		*<0.001*	1		*<0.001*
	60–69	0.57	0.51–0.64		0.64	0.56–0.73	
	≥70	0.30	0.26–0.35		0.31	0.26–0.37	
Living arrangement	Spouse/partner	1.24	1.08–1.42	0.002	1.06	0.91–1.25	0.442
Education level attained	>12 years	1.58	1.42–1.77	*<0.001*	1.50	1.32–1.72	*<0.001*
Smoking status	Never	1		*<0.001*	1		0.816
	Former	0.19	0.77–1.03		1.02	0.90–1.20	
	Current	1.36	1.19–1.56		0.97	0.83–1.14	
Prior MI/CABG	Yes	0.51	0.42–0.63	*<0.001*	0.71	0.55–0.91	0.007
BMI	>25	1.17	1.05–1.31	0.005	1.19	1.04–1.35	0.012
Indication for PCI	Acute	3.10	2.71–3.55	*<0.001*	3.23	2.76–3.79	*<0.001*
Health authorities	North	1		*<0.001*	1		*<0.001*
	Central	1.80	1.47–2.22		1.73	1.38–2.16	
	South-East	1.80	1.52–2.13		1.76	1.46–2.13	
	West	1.06	0.86–1.30		0.89	0.71–1.12	

BMI: body mass index; CABG: coronary artery bypass grafting; CI: confidence interval; MI: myocardial infarction; OR: odds ratio; PCI: percutaneous coronary intervention.

Results from the present study confirm previous results showing that CR participation rate declines with increasing age.[22] Several factors influence the low CR participation rate among the elderly: decreased odds of being referred, less likely to attend, comorbidities, poorer understanding of the benefit, inadequate transportation, and caregiver responsibilities at home.[25] Regarding the regional differences in participation, we observed that the elderly living in the northern and western parts of Norway participate in CR the least. This may be due to both lower availability of CR and longer travelling distances to locations offering a CR programme in these regions.

Previous research shows that current smoking increases the chance a patient will be referred to CR, but it does not predict CR participation.[26] After controlling for other factors, we confirmed these findings. The strong correlation between smoking and lower educational level can explain the lack of a significant association.[26] Having knowledge of how CR benefits one's cardiac health is another important factor affecting participation in a CR programme, and the present study confirmed that patients with a higher attained educational level are more likely to participate in CR.

The present study showed that patients who suffer from an acute coronary event are more likely to participate in CR. In Norway, the majority of patients who participate in CR are referred to CR by the physician when they are discharged from hospital. Patients who are hospitalised for MI are more likely to receive information about the benefits of participating in CR and more likely to be referred to CR than are elective PCI patients. Thus, because they receive more encouragement to participate, patients who suffer from an MI are more likely to participate in CR. Prior CR participation can explain why a patient with prior MI or CABG reports engaging in CR less often compared to those with newly diagnosed CHD.

Methodological issues

The main strength of this study is its large sample size, representing all HA regions in Norway, and its high response rate. Indeed, this study included more than 50% of all patients in Norway undergoing PCI during 2008–2011, and had a response rate of 82%.

The major limitation of the study was the use of a self-report assessment tool to determine CR participation. Since the follow-up time was relatively long at three years, there is a chance of recall bias with the self-report approach. However, research mitigating this possibility has shown that it is less common for a person to wrongly believe that they have participated in CR than to remember an event that did not occur.[27] In addition, assessment of CR participation by self-report has been validated in a previous study, showing nearly perfect agreement between self-report and site-verified CR participation.[28] Furthermore, we do not know the level of participation or the length and content of the different CR programmes. Finally, a limitation is lack of knowledge of referral rate that enables us to calculate adherence to CR.

Conclusions

The estimated CR participation rate in Norway is below 30%. The typical CR participant in Norway is young,

overweight, well-educated, and has suffered from an acute coronary event. This is consistent with previous research findings. Our findings also point out that CR participation varies geographically. This indicates that there is a need in Norway to establish uniform national standards and guidelines for CR. More research is needed to determine CR referral and adherence rates.

Implications for practice

- Despite the beneficial evidence, referral to, and participation in, cardiac rehabilitation programmes varies widely across Europe, and in Norway less than 30% of patients with established coronary heart disease participate in a cardiac rehabilitation programme.
- In contrast to previous research, the present study suggest that women, are more likely than men to participate in cardiac rehabilitation.
- Healthcare professionals play an important role in promoting secondary prevention to patients with established coronary heart disease, and further actions to increase cardiac rehabilitation participation are needed.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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II

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Cardiac rehabilitation and symptoms of anxiety and depression after percutaneous coronary intervention

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Abstract

Background: Anxiety and depression are related to coronary heart disease, and psychological support is recommended in cardiac rehabilitation.

Purpose: The aims of this study were: to compare the prevalence of anxiety and depression with respect to cardiac rehabilitation participation among patients who have been treated with percutaneous coronary intervention; to examine prevalence of anxiety and depression among percutaneous coronary intervention patients compared to the general population; and to identify predictors of symptomatic anxiety and depression among percutaneous coronary intervention patients.

Methods: We included 9013 patients undergoing first-time percutaneous coronary intervention. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale in a representative sample of 775 patients at baseline and after three years of follow-up, and in the entire cohort at three-year follow-up.

Results: Cardiac rehabilitation participants had more anxiety and depression than cardiac rehabilitation non-participants at baseline, and both groups had a more anxiety than the general population. The levels of anxiety and depression fell significantly during three years of follow-up, but the changes did not differ between cardiac rehabilitation participants and cardiac rehabilitation non-participants. Three years after percutaneous coronary intervention the prevalence of anxiety was 32% ($p < 0.001$), higher among cardiac rehabilitation participants compared to cardiac rehabilitation non-participants. Female gender and younger age were associated with anxiety, whereas older age, lower levels of education and cardiovascular morbidity were associated with depression.

Conclusion: The levels of anxiety and depression were prevalent among percutaneous coronary intervention patients and the levels were not affected by cardiac rehabilitation participation. Anxiety is prevalent among female and younger patients, whereas depression is related to older age and cardiovascular co-morbidity.

Keywords

Psychological factors, Hospital Anxiety and Depression Scale, Norwegian Coronary Stent Trial, coronary heart disease, secondary prevention

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Introduction

Psychological factors such as anxiety and depression are predictors of a worse prognosis in patients with coronary heart disease (CHD).[1,2] The association between CHD and psychological illness can be explained by several mechanisms. In the behavioural pathway, poor control of coronary risk factors due to an unhealthy lifestyle and poor medication adherence leads to a poorer prognosis. In the physiological pathway, autonomic dysfunction, endothelial dysfunction, and changes in platelet aggregation or inflammation

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processes increase the risk of myocardial ischaemia.[3,4] Tawakol et al. recently found an association between perceived stress, regional brain activity, and cardiovascular disease, and this association was possibly mediated by inflammatory mechanisms.[5]

The prevalence of anxiety among CHD patients is reported to be 16%, which is higher than the prevalence found in the general population.[6] Approximately 15–20% of patients with CHD meet the criteria for major depression, and even more are suggested to have clinically relevant depression.[2,7] Recently, the EUROASPIRE IV survey reported that 39% of women and 22% of men with CHD had symptoms of anxiety and depression at 1.4 years after the index event and the prevalence seem to differ between countries.[8] In the general population, the lifetime prevalence of major depressive disorder is reported to be between 4% and 10%.[9]

Exercise-based cardiac rehabilitation (CR) has been shown to reduce anxiety[10] and depression,[10,11] and psychological support is thus recommended as a component of CR.[12] However, the scientific evidence for this recommendation was recently challenged by a review that did not find any effect on total mortality, need for revascularization, or the risk of non-fatal myocardial infarction of adding psychological interventions to traditional CR.[13] However, cardiac mortality was reduced, and symptoms of anxiety, depression and stress were improved.[13]

The predictors of symptomatic anxiety and depression in CHD patients are reported to include female gender, low educational level and more sedentary lifestyle.[8] Anxiety was more prevalent in younger individuals. Depression increased with advancing age and was associated with current smoking, central obesity and diabetes.[8] Despite an increasing focus on psychocardiology in the past few decades, there is a need for more knowledge on the symptoms of anxiety and depression related to CR participation.

In the present study, we compared levels of anxiety and depression among patients who did and did not participate in a CR programme after percutaneous coronary intervention (PCI). Next, we compared levels of anxiety and depression in PCI patients with the levels in the general population. Finally, we assessed predictors of symptomatic anxiety and depression three years after PCI.

Methods

Setting and participants

This prospective observational study included patients undergoing first-time PCI in Norway. Patients were recruited from the Norwegian Coronary Stent Trial (NorStent).[14] NorStent was performed at all centres in Norway that perform PCI, covering a total population of more than five million inhabitants. NorStent was a randomised controlled trial comparing the long-term clinical effects of drug-eluting and bare-metal stents.[14] Patients were included from September 2008–February 2011, and the median follow-up time was five years. Patients at least 18 years old were included if they were able to communicate in Norwegian, had a Norwegian personal identification number, were receiving their first PCI due to either stable angina or an acute coronary syndrome, and provided informed written consent. The study used a pragmatic study design with few exclusion criteria.[14] A total of 9013 patients were included in NorStent, 72.5% of patients with protocol eligibility.

Data collection

Clinical data were retrieved at baseline (defined in this study as the time of the index PCI) from the patients' electronic medical records by specially trained registered nurses. Patient-reported symptoms of anxiety and depression were measured in a representative sample of 775 patients at baseline and after three years of follow-up, and in the in the entire cohort after three years of follow-up. After three years of follow-up, 7068 patients (82%) responded to the survey.

A study-coordinating centre at the Institute of Clinical Medicine, The Arctic University of Norway, collected the follow-up data. Patients were sent reminders by phone and letter to complete and return their questionnaires.

Symptoms of anxiety and depression

Patient-reported symptoms of anxiety and depression were measured using the Norwegian version of the Hospital Anxiety and Depression Scale (HADS).[15] The HADS consists of a seven-item subscale for anxiety (HADS-A) and a seven-item subscale for depression (HADS-D). All questions have a four-point response option, ranging from no points for no symptoms to three points for the maximum number of symptoms. The scores on each subscale range from 0 to 21 points. Lower scores reflect a lower symptom presence. The HADS has demonstrated good psychometric properties across various patient samples and settings.[16,17]

The Norwegian reference population

The Norwegian reference population comprised participants in the second wave of a large population-based general health survey, the 1995–1997 Nord-Trøndelag Health study (The HUNT 2 study). A total of 66,140 individuals participated in the study, and 71% of those invited were in the ≥20-year-old age group.[18] The present study compared the results of the HADS among PCI patients with the results from 54,867 subjects without previous

self-reported cardiovascular disease. In both the HUNT study and the present study, the HADS was assessed by self-report using mailed questionnaires.

Cardiac rehabilitation

Attendance in a CR programme during follow-up was assessed after three years of follow-up by asking study participants the following questions, which assessed two possible CR alternatives: (a) Have you participated in a shorter ambulatory CR programme lasting for hours or days? (b) Have you participated in a hospital- or centre-based in-patient CR programme lasting one or more weeks? The response options were 'yes', 'no', or 'uncertain'. The variable was coded as CR participation if the patient answered 'yes' to one or both questions. Responses of 'uncertain' and 'no' to both questions were coded as CR non-participation.

Ethical issues

The study conforms to the principles outlined in the Declaration of Helsinki.[19] All patients provided written informed consent to participate in the study and were informed about the opportunity to withdraw consent at any time without stating a reason. Study participants received the same routine medical treatment as non-participants. The NorStent trial protocols were reviewed and approved by the National Committees for Research Ethics in Norway and by the Norwegian Social Science Data Services (NSD19480, PREKNORD40/2008), and they are registered at ClinicalTrials.gov (NCT00811772).

Statistical analysis and data management

Categorical data are presented as counts and percentages, and continuous data are presented as means with standard deviations (SDs) or medians with interquartile ranges. All variables were checked for outliers. Differences in baseline characteristics were assessed using Pearson's chi-square or independent samples Student's t-test, as appropriate. A p-value ≤ 0.05 was considered statistically significant. Data management and all statistical analyses were performed using IBM SPSS Statistics for Windows, versions 23 and 24 (IBM Corporation, Armonk, New York).

Between-group comparisons in HADS scores were performed using the independent samples t-test, and within-group comparisons were performed using paired sample t-tests. Less than 2.5% of the items in the HADS had one or more missing responses. Simple mean imputation[20] was performed when the respondent had answered at least four of the seven items in each subscale. A cut-off score of eight on the subscales has been found to provide an optimal balance between sensitivity and specificity for identifying possible or probable cases of anxiety or depressive disorder,[16] with scores <8 representing no symptoms of anxiety or depression.[15] The internal consistency (Cronbach's alpha) was 0.86 for the HADS-A and 0.80 for the HADS-D at baseline and 0.88 for the HADS-A and 0.84 for the HADS-D at the three-year follow-up.

To adjust for the effect of non-random distribution of covariates, a propensity score (PS) method was used for comparisons of anxiety and depression after three years of follow-up among CR participants and non-participants.[21] In the present study, the PS was calculated for each patient using a logistic regression model to estimate the probability of participating in CR. The variables included in this model were age, gender, educational level, smoking status, body mass index (BMI), prior myocardial infarction (MI), diabetes mellitus, prior coronary artery bypass surgery, prior stroke, prior lipid-lowering treatment, prior hypertension treatment, creatinine concentration, left ventricle ejection fraction, health authority and indication for PCI. Once the PSs were estimated for each patient, matching was performed using a match tolerance level of 0.02. Covariate balance was checked as recommended for studies reporting PS analysis.[22]

The expected HADS-A and HADS-D scores in the general population were calculated using previously developed formulas based on the Norwegian general population, controlling for each participants age, gender, educational level and smoking habit.[23] Differences between the observed score in the study population scores and the expected scores in the general population were analysed using the one-sample t-test.

Logistic regression analysis was used to identify predictors of symptomatic anxiety and depression. The multivariable model was built using independent variables associated with anxiety and depression;[4] severity of CHD,[24] gender, age, living arrangement, educational level attained, smoking status, BMI, prior MI/coronary artery bypass grafting (CABG), prior stroke, prior diabetes mellitus, prior lipid-lowering treatment, prior hypertension treatment, left ventricular ejection fraction, PCI indication and CR. Two-way interactions between the independent variables and gender, age and CR were assessed in the full multivariable model.

Results

Baseline characteristics

After three years in the study, 7068 patients responded to the survey. Of these patients, a subgroup ($n = 941$) had also been invited to report symptoms of anxiety and depression at baseline, with a response rate of 82.4%

($n = 775$). The subgroup population was similar to the rest of the cohort for most of the clinical characteristics, except for PCI indication (see the Supplementary Material Appendix Table 1). Table 1 shows the baseline characteristics of the subgroup stratified by CR participation. Compared with the CR participants, the CR non-participants were older, had a lower level of education, were less likely to smoke, had a higher degree of comorbidity and were less likely to have acute MI as an indication for PCI. Twenty-seven per cent of patients had a HADS anxiety score ≥ 8, and 19% of patients had a HADS depression score ≥ 8 at the time of PCI.

CR and symptoms of anxiety and depression at baseline and after three years

Table 2 shows the scores for anxiety and depression according to participation in CR for the subgroup with HADS scores both at baseline and after three years. Compared to non-participants, CR participants had significantly higher anxiety and depression scores at both baseline and the three-year follow-up. Levels of anxiety and depression fell significantly ($p < 0.001$) in both groups during the follow-up, but the changes over time did not differ between those who did and did not participate in CR (Table 2).

Table 3 shows prevalence of anxiety and depression after three years of follow-up according to CR participation in a propensity-matched cohort representing 3402 patients with available HADS scores. The covariate balance is shown in Supplementary Material Appendix Table 2. After three years of follow-up, there was a 32% higher prevalence of anxiety ($p = 0.003$) among CR participants than non-participants, whereas prevalence of depression did not differ.

Table 1. Baseline characteristics according to cardiac rehabilitation participation.[a]

		All		Cardiac rehabilitation				
Characteristics		($n = 775$)		Yes ($n = 183$)		No ($n = 592$)		p-Value
Age	Years ± SD	64.0	±9.2	60.1	±8.1	65.3	±9.2	<0.001
Gender – *n* (%)	Male	583	(75.2)	142	(77.6)	441	(74.5)	0.396
Living arrangement – *n* (%)	Spouse/partner	591	(79.6)	139	(83.2)	452	(78.6)	0.191
Educational level attained – *n* (%)	≤12 years	495	(66.7)	105	(59.3)	390	(69.0)	0.017
	>12 years	247	(33.3)	72	(40.7)	175	(31.0)	
Smoking status – *n* (%)	Never	235	(31.3)	61	(34.7)	174	(30.3)	0.018
	Former	319	(42.5)	59	(33.5)	260	(45.3)	
	Current	196	(26.1)	56	(31.8)	104	(24.4)	
Body mass index (kg/m^2)	>25 kg/m^2	529	(68.3)	131	(71.6)	398	(67.2)	0.269
Medical history – *n* (%)	Prior myocardial infarction	76	(9.8)	14	(7.7)	62	(10.5)	0.259
	Diabetes mellitus	98	(12.7)	23	(12.6)	75	(12.7)	0.991
	Prior CABG surgery	58	(7.5)	7	(3.8)	51	(8.6)	0.031
	Prior stroke	27	(3.5)	2	(1.1)	25	(4.2)	0.044
	Prior lipid lowering treatment	459	(59.8)	93	(51.7)	366	(62.4)	0.011
	Prior HT treatment	321	(41.7)	66	(36.7)	255	(43.2)	0.119
Left ventricular ejection fraction – *n* (%)	>40%	282	(95.6)	60	(92.3)	222	(96.5)	0.144
	≤40%	13	(4.4)	8	(3.5)	5	(7.7)	
Indication for PCI – *n* (%)	Stable angina	330	(39.8)	39	(21.4)	268	(45.5)	<0.001
	Unstable angina	98	(12.6)	15	(8.2)	83	(14.1)	
	NSTEMI	218	(28.3)	68	(37.4)	150	(25.5)	
	STEMI	148	(19.2)	60	(33.0)	88	(14.9)	
HADS-anxiety score	≥8, *n* (%)	210	(27.1)	68	(37.2)	142	(24.0)	<0.001
HADS-depression score	≥8, *n* (%)	147	(19.0)	50	(27.3)	97	(16.4)	0.001

CABG: coronary artery bypass graft; HADS: Hospital Anxiety and Depression Scale; HT: hypertension; PCI: percutaneous coronary intervention; NSTEMI: non ST-elevation myocardial infarction; SD: standard deviation; STEMI: ST-elevation myocardial infarction.
Values are the mean (SD) or *n* (%).
[a]This analysis includes 775 patients who were examined using the Hospital Anxiety and Depression Scale at both baseline (i.e. the time of the index PCI) and the three-year follow-up.

Table 2. Changes in symptoms of anxiety and depression during follow-up according to cardiac rehabilitation participation.[a]

	Cardiac rehabilitation				
	Yes ($n = 183$)		No ($n = 592$)		
	Observed	Expected	Observed	Expected	p-Value[b]
HADS-anxiety score, mean ± SD					
Baseline	6.31 ± 4.33	3.50 ± 0.50[c]	5.04 ± 4.03	3.49 ± 0.46[c]	<0.001
3 Years	4.52 ± 4.14	3.40 ± 0.44[c]	3.52 ± 3.50	3.42 ± 0.45	0.001
Change	−1.79 ± 4.23[d]		−1.53 ± 3.47[†]		0.396
HADS-depression score, mean ± SD					
Baseline	4.69 ± 4.10	3.59 ± 0.42[c]	3.84 ± 3.45	3.84 ± 0.44	0.005
3 Years	3.78 ± 4.09	3.67 ± 0.41	3.08 ± 3.33	3.94 ± 0.46[c]	0.019
Change	−0.91 ± 4.05[d]		−0.76 ± 3.33[d]		0.607

HADS: Hospital Anxiety and Depression Scale; PCI: percutaneous coronary intervention; SD: standard deviation.
[a]This analysis includes 775 patients who were examined with the HADS at both baseline (i.e. the time of the index PCI) and the three-year follow-up.
[b]Values of p indicate differences between patients who did and did not undergo cardiac rehabilitation.
[c]$p \leq 0.001$. Values of p indicate differences between observed and expected HADS scores
[d]The change represent a significant reduction ($p < 0.001$) from baseline to three-year follow-up.

Table 3. Symptoms of anxiety and depression (Hospital Anxiety and Depression Scale (HADS) ≥ 8) in cardiac rehabilitation (CR) participants and CR non-participants at three years of follow-up.[a]

	CR participants ($n = 1699$)	CR non-participants ($n = 1697$)	OR (95% CI)	p-Value
HADS-anxiety score ≥ 8	320 (18.8%)	254 (15.0%)	1.32 (1.10–1.58)	0.003
HADS-depression score ≥ 8	239 (14.1%)	214 (12.6%)	1.14 (0.93–1.39)	0.207

CI: confidence interval; OR: odds ratio.
[a]This table shows the results for the propensity-matched cohort ($n = 3402$).

Symptoms of anxiety and depression in PCI patients compared to the reference population

Table 2 shows observed and expected scores for anxiety and depression in the subgroup of patients with HADS measurements at baseline and after three years of follow-up. At baseline, the patients had significantly higher levels of anxiety than the reference population (Table 2). After three years of follow-up, the level of anxiety continued to be higher than expected among CR participants, but not among CR non-participants. At baseline the depression levels were higher than expected among CR participants but not among CR non-participants (Table 2). After three years of follow-up, depression levels did not differ among CR participants compared to the expected levels, whereas CR non-participants had lower depression levels than expected.

In a separate analysis of the total cohort of 7068 patients the HADS-A score after three years of follow-up was significantly higher than that in the reference population (3.92 (SD: ±3.63) vs 3.44 (SD: ±0.45), $p < 0.001$), while the HADS-D score after three years of follow-up was significantly lower than in the reference population (3.42 (SD: ±3.44) vs 3.85 (SD: ±0.48), $p < 0.001$).

Predictors of symptomatic anxiety and depression

Multivariable-adjusted analyses showed that male gender and older age were associated with lower risk of anxiety, whereas CR participation was associated with higher risk of anxiety (Table 4). Higher levels of education and an acute coronary event as the indication for PCI were associated with lower risk of depression, whereas older age, former smoking, prior myocardial infarction, CABG and stroke were associated with higher risk of depression (Table 4).

Discussion

We found that 27% and 19% of patients undergoing PCI reported symptoms of anxiety and depression, respectively, with the highest levels found in the CR

Table 4. Predictors of anxiety and depression measured three years after percutaneous coronary intervention (PCI) ($n = 7068$).[a]

	Anxiety							Depression						
		Unadjusted			Adjusted[b]				Unadjusted			Adjusted[c]		
	n	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	*n*	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Male (female = reference)	7047	0.51	0.45–0.59	<0.001	0.45	0.35–0.58	<0.001	7053	0.74	0.64–0.86	<0.001	0.84	0.64–1.12	0.230
Age (years)	7047			<0.001			<0.001	7053			<0.001			0.016
≤59 (reference)		1.00	–			–			1.00	–		1.00	–	
60–69		0.51	0.44–0.60		0.55	0.41–0.73			0.77	0.65–0.91		0.94	0.68–1.28	
≥70		0.64	0.55–0.75		0.74	0.53–1.03			1.10	0.93–1.30		1.45	1.03–2.05	
Living arrangement (no = reference)														
Spouse/partner	6747	0.74	0.64–0.87	<0.001	0.87	0.65–1.16	0.349	6752	0.75	0.64–0.88	0.001	1.04	0.76–1.42	0.798
Education level attained (≤12 years = reference)														
>12 years	6777	0.8	0.69–0.93	0.003	0.92	0.70–1.19	0.514	6782	0.69	0.59–0.81	<0.001	0.71	0.53–0.95	0.020
Smoking status	6449			<0.001			0.058	6456			<0.001			0.012
Never (reference)		1.00	–		1.00	–			1.00	–		1.00	–	
Former		1.89	1.60–2.24		1.39	1.02–1.89			1.63	1.36–1.94		1.48	1.06–2.05	
Current		1.12	0.94–1.34		1.01	0.75–1.34			1.07	0.89–1.29		0.93	0.69–1.26	
Body mass index (≤25 kg/m^2 = reference)														
>25 kg/m^2	7047	0.95	0.83–1.09	0.481	1.18	0.91–1.54	0.216	7053	1.00	0.87–1.15	0.995	1.16	0.89–1.54	0.276
Medical history (no = reference)														
Prior MI/CABG	7017	1.05	0.87–1.27	0.632	1.29	0.93–1.81	0.132	7023	1.43	1.18–1.72	<0.001	1.40	1.01–1.94	0.045
Diabetes mellitus	7037	1.09	0.89–1.32	0.424	1.34	0.95–1.89	0.097	7043	1.47	1.21–1.78	<0.001	1.18	0.83–1.69	0.349
Prior stroke	7036	1.34	0.98–1.84	0.065	0.82	0.43–1.59	0.559	7042	1.87	1.39–2.53	<0.001	1.95	1.16–3.27	0.011
Prior hypertension treatment	6995	1.10	0.97–1.25	0.145	0.92	0.71–1.18	0.509	7001	1.36	1.19–1.56	<0.001	1.16	0.90–1.51	0.253
Prior lipid lowering treatment	6941	1.16	1.01–1.32	0.032	1.23	0.94–1.60	0.126	6947	1.23	1.07–1.41	0.004	1.15	0.87–1.52	0.335
Left ventricular ejection fraction (>40% = reference)														
≤40%	2801	0.93	0.61–1.42	0.750	0.70	0.41–1.22	0.211	2806	1.08	0.71–1.65	0.709	0.90	0.53–1.51	0.676
PCI indication (no = reference)														
Acute	7004	1.08	0.93–1.24	0.318	0.87	0.67–1.11	0.261	7010	0.91	0.79–1.06	0.213	0.73	0.56–0.95	0.018
CR participation (no = reference)	7047	1.40	1.22–1.61	<0.001	1.47	1.12–1.95	0.006	7053	1.09	0.93–1.26	0.287	1.28	0.94–1.75	0.114

CABG: coronary artery bypass graft; CI: confidence interval; CR: cardiac rehabilitation; HT: hypertension; IQR: inter quartile range; MI: myocardial infarction; NSTEMI: non ST-elevation myocardial infarction; OR: odds ratio; SD: standard deviation; STEMI: ST-elevation myocardial infarction.

[a]Anxiety (yes/no) was defined as a score ≥8 on the Hospital Anxiety and Depression Scale. Depression (yes/no) was defined as a score ≥8 on the Hospital Anxiety and Depression Scale.

[b]2409 and [c]2414; patients included in the multivariable-adjusted analyses.

participants. There were no differences in the change in symptoms of anxiety and depression between the CR participants and CR non-participants. After three years, both the CR participants and CR non-participants had a higher level of anxiety, but not depression, than the reference population. Female gender and young age are associated with anxiety, while older age, lower-education and previous cardiovascular morbidity are associated with depression.

The present study revealed a higher prevalence of symptomatic anxiety[6,23] and depression[8,23] at the index event than reported in previous studies in CHD patients from Nordic countries. This prevalence was consistent with the mean results in Europe[8] and lower than that reported in a PCI population.[25] After three years, both the CR participants and CR non-participants had a higher level of anxiety but lower level of depression than expected, indicating that symptoms of anxiety are a long-term concern after PCI, while the level of depression normalises.

Fear is the essence of anxiety and is often used as a motivator for people in need of reducing risky behaviours.[26] Fear increases the chance of one-time behaviours[26] and can explain why the present study shows that more anxious patients reported having participated in CR programmes. Variation in anxiety over a lifetime is normal; however, the present study revealed that CR participants reported a higher level of anxiety at three years of follow-up compared with the reference population. These findings indicate that some of the CR participants had a generalised anxiety disorder with more persistent symptoms.

It has previously been suggested that psychological screening and management of psychological disorder in CHD patients are well suited in the CR context.[27] However, the CR participation rate is generally reported to be low.[28] Depressed patients are also reported to be at a higher risk of not participating, as well as dropping out of CR.[29] This result is in contrast to our findings, which show that CR participants report higher depression scores than CR non-participants. Similar findings were reported in a retrospective study of 158,991 post-MI patients, in whom depression was strongly associated with CR attendance.[30] Overall, the present study suggests that the patients most in need, i.e. those with the highest level of symptoms of anxiety and depression, are identified and encouraged to participate in CR programmes in Norway.

The present study did not identify any changes in symptoms of anxiety and depression between the CR participants and CR non-participants. However, there were significant improvements over time in both groups. It has previously been suggested that the positive correlation between CR and improvement in anxiety and depression is related to the positive effect of exercising,[10,31] especially in women.[32] However, a Cochrane review reported only a small effect of exercise on the reduction of symptoms of depression compared to a control intervention when analysing studies of methodological robustness.[33] In Norway, however, there is no standard regarding the content of physical activity in CR programmes, which can vary from a single day of exercise for one hour to exercise training over several weeks. Consequently, this may be a possible reason for the lack of effect in the present study. In addition, the level of psychological intervention during CR in Norway is not standardised. However, this lack of standardization may be of less importance, as the effect of psychological interventions on anxiety and depression has a low level of evidence.[13] Overall, despite a reduction in the level of symptoms of anxiety and depression after three years, the present study did not identify a beneficial effect of CR participation.

CHD patients with symptoms of anxiety and depression are known to have a poorer cardiac health prognosis, which in turn makes it necessary to ensure that psychological treatments reach patients in need. The recommendation of systematic screening for anxiety and depression in CHD patients is disputed.[34,35] However, knowledge regarding the predictors of future symptomatic anxiety or depression can help to target the treatment. Regarding anxiety, the present study showed that women are at risk of reporting symptomatic anxiety. The gender difference corresponds to findings from the general population[36] and the EUROSPIRE IV study, which includes CHD patients.[8] Pogosova et al. also reported similar findings for age.[8] The present study suggests that less-educated older patients with cardiovascular diseases, a history of smoking and acute coronary syndrome are at risk of symptoms of depression. The EUROSPIRE IV study yielded similar results in terms of educational level and age. Overall, the present study suggests that healthcare providers should pay attention to younger patients and women to prevent long-term symptoms of anxiety and to older, comorbid and less-educated patients to prevent long-term symptoms of depression after PCI.

Methodological issues

One limitation of the present study is the inability to control for factors, such as previously diagnosed anxiety and depression disorders and treatment with antidepressants. Furthermore, not knowing the content and level of CR, especially physical activity and psychological support, may have influenced our findings. However, the major strengths of the study are the large representative sample, the prospective design, the high response rate and long-term follow-up, as well as the use of a standardised and validated instrument. In

contrast to diagnostic interviews and other self-reported instruments, the HADS systematically excludes somatic symptoms that can be mistaken as heart disease.[15] Furthermore, the PS matching method allows for the control of several possible confounding factors when analysing the effect of CR on symptoms of anxiety and depression.

Conclusions

In conclusion, the present study suggests that every fourth or fifth patient will report symptoms of anxiety or depression at the index event. However, three years after PCI, fewer patients reported symptoms of anxiety or depression and the level of depression was lower than expected in these patients compared to the reference population. Furthermore, the present study suggests that patients participating in a CR programme are those with the highest level of symptoms of anxiety and depression. Despite the decreased level of anxiety and depression after three years, the present study did not identify a beneficial effect of CR participation. Finally, the present study reports several patient characteristics that are related to future risk of long-term symptoms of anxiety and depression after PCI.

Author contribution

SJSO, HS, KHB and TAH contributed to the conception or design of the work. SJSO, HS, TW, KHB and TAH contributed to the acquisition, analysis or interpretation of data for the work. SJSO drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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III

Employment status three years after percutaneous coronary intervention and predictors for being employed. A nationwide prospective cohort study.

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Abstract

Background: Vocational support is recommended for patients in cardiac rehabilitation (CR), as returning to work is important in patients' social readjusting after an acute coronary event. Information is lacking whether CR leads to higher long-term employment after percutaneous coronary intervention (PCI).

Aims: The aims of this study were to determine employment status three years after percutaneous coronary intervention, to compare employment status between CR participants and CR non-participants and to assess predictors for employment.

Methods: We included first-time PCI patients from the NorStent trial, who were of working age (<63 years; n=2488) at a three-year follow-up. Employment status and CR participation were assessed using a self-report questionnaire. Propensity score method was used in comparing employment status of CR participants and CR non-participants.

Results: Seventy per cent of participants who were <60 years of age at the index event were employed at follow-up and CR participation had no effect on employment status. Being male, living with a partner, and attaining higher levels of education were associated with a higher chance of being employed, while being older, prior cardiovascular morbidity, and smoking status were associated with lower chance of being employed at follow-up.

Conclusion: Because a significant number of working-age coronary heart disease patients are unemployed three years after coronary revascularization, updated incentives should be implemented to promote vocational support. Such programmes should focus on females, patients lacking higher education and patients who are living alone, as they are more likely to remain unemployed.

Introduction

Cardiac rehabilitation (CR) is a recommended aftercare for patients with established coronary heart disease (CHD).[1, 2] Return to work was one of the main outcomes in the early eras of CR and vocational support is still an important aspect of contemporary CR. Additionally, risk-factor management, exercise training, nutritional counselling, and psychosocial support are integral parts of CR.[3, 4] Systematic reviews indicate that CR may reduce cardiac mortality, hospital admissions, symptoms of anxiety and depression, and increase the quality of life, although there is no strong evidence of these benefits.[5-7] Recently, a Cochrane review that examined interventions to support return to work for people with CHD concluded, with a low-certainty of evidence, that comprehensive CR may promote return to work within the first six months following CHD. There were little to no evidence that CR promote return to work between six months and up to one year after a CHD event, and no evidence that CR promote return to work after one year of follow up.[8] Despite that return to work plays an important part in social readjustment after an acute coronary event, and has important implications for both the individual and the society, the knowledge on long-term effect of CR on employment status is scarce.[8] In addition, knowledge on predictors of employment are of importance to decrease the risk of reintegration failure after an acute coronary syndrome.[9]

In the present study, we determined employment status three years after percutaneous coronary intervention (PCI). Next, we compared differences between CR participants and CR non-participants in employment status three years after PCI. Finally, we assessed predictors for being employed three years after PCI.

Methods

Setting and participants

The present study uses a prospective observational study design among patients that underwent first time PCI and were participating in the Norwegian Coronary Stent Trial (NorStent).[10] NorStent was an all-comer study with broad inclusion criteria and few exclusion criteria which was performed at all centres in Norway that perform PCI, thus covering the total Norwegian population of more than 5 million inhabitants. NorStent was a randomized controlled trial comparing long-term health effects of drug-eluting and bare-metal stents.[10] Participants were included from September 2008 to February 2011 with five years follow-up. Eligible participants were men and women who presented with stable angina or an acute coronary syndrome, had a lesion in native coronary arteries or coronary-artery grafts amenable for PCI, had a Norwegian national identification number and were able to communicate in Norwegian, and provided informed consent. A total of 9,013 participants were included in NorStent. After three years of follow-up, 7,068 patients (82%) responded to a postal survey which included questions on employment status. Baseline characteristics have been reported previously.[11] To avoid patients that became unemployed due to retirement, we excluded patients from analysis who were 60 years and older at the index event. A total of 2,488 patients with complete employment status data three years after PCI were accepted for inclusion in the present study.

Data collection

Clinical- and demographic data were retrieved from the patients' electronic medical records at the index event by specially trained registered nurses. Patient outcomes, including CR participation, were measured three years after the PCI procedure using validated questionnaires as well as questions developed specifically for this study. A study coordinating

centre at the Institute of Clinical Medicine, the Arctic University of Norway, administrated the collection of follow-up data. Patients were sent reminders by phone and postal letter to complete and return their questionnaires.

Cardiac rehabilitation

Attendance in a CR programme during the period from the index event and to 36 months, was assessed by asking study participants the following questions: (1) Have you participated in a shorter ambulatory CR programme lasting for hours or days? (2) Have you participated in a hospital- or centre-based in-patient CR programme lasting for one or more weeks? The response options were 'yes', 'no', or 'uncertain'.CR attendance was coded as "yes" if the patient answered 'yes' to one or both questions, and "no" if the patient answered 'uncertain' or 'no' to both questions.

Employment status

Employment status 36 months after the index event were ascertained by asking the study participants if they were currently employed full-time or part-time, unemployed, retired on disability pension, or on sick leave full-time or part-time, or if they were homemakers. Employment status was categorised as 'employed', 'unemployed' or 'retired'. Being employed was classified as employed full-time or part-time. Being unemployed was classified as unemployed or sick-leave full-time or part-time. Being retired was participants that reported to receive full-time or disability pension. The combinations part-time employed / part-time sick-leave or retired / part-time sick leave, were categorized as unemployed (<33 patients).

Ethical issues

The study conformed to the principles outlined in the Declaration of Helsinki.[12] All participants gave written informed consent to participate in the study and were informed about the opportunity to withdraw the consent at any time without giving a reason or prejudice regarding further treatment. Study participants received routine medical treatment after PCI. The NorStent trial protocols were reviewed and approved by the National Committees for Research Ethics in Norway and by the Norwegian Social Science Data Services (NSD19480, PREKNORD40/2008), and is registered in ClinicalTrial.gov (NCT00811772).

Statistical analysis

Categorical data are presented as counts and percentages, and continuous data as means with standard deviations. To adjust for the effect of non-random distribution of covariates on CR, a propensity score method was used for comparisons of employment status after 3 years of follow-up among CR participants and non-participants.[13] In the present study, the propensity score was calculated for each patient in the total cohort of 2,488 patients using a logistic regression model to estimate the probability of participating in CR. The variables included in this model were age, gender, educational level, smoking status, body mass index (BMI), prior myocardial infarction (MI) or coronary artery bypass graft, diabetes mellitus, prior lipid-lowering treatment, prior hypertension treatment, regional health authority and indication for PCI. Once the propensity scores were estimated for each patient, matching was performed using a match tolerance level of 0.02. This leaves us with 708 patients in each group (CR yes vs. CR no). Covariate balance was checked as recommended for studies reporting propensity score analyses[14] Between-group comparisons in employment status were performed using conditional logistic regression.

Logistic regression analysis was used to identify predictors of being employed three years after PCI. Possible predictors were independent variables known to be associated with severity of CHD[1] and geographical region; gender, age, living arrangement, educational level attained, smoking status, BMI, prior MI or coronary artery bypass grafting, prior stroke, prior diabetes mellitus, prior lipid-lowering treatment, prior hypertension treatment, left ventricular ejection fraction, PCI indication, CR, and regional health authority. Unadjusted and multivariable adjusted odds ratios (OR) of employment status were estimated with 95% confidence intervals (CI). The multivariable model included all independent variables. Due to missing values on some of the independent variables, the unadjusted odds ratios were calculated both with all available observations included and restricted to completed case analyses (n=2038). Two-way interactions between the independent variables and gender and age were assessed in the full multivariable model. A p-value of <0.05 was considered statistically significant. Data were organized in IBM SPSS data files, and statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corporation, Armonk, New York).

Results

Baseline characteristics

Of the 9,013 patients who were enrolled in the NorStent trial, 2,488 were of working age (<63 years) three years following PCI. Males compromise 83.2% of the group, and the mean age was 52 years. The majority of the participants lived with a partner, 36.5% had more than 12 years of education and approximately half of the participants were current smokers. Prior lipid-lowering treatment and prior hypertension treatment were reported by 51.1% and 34.0% of the participants, respectively. An acute coronary syndrome was the indication for PCI among 63.7% of the participants (Table 1).

Employment status and Cardiac rehabilitation

After three years follow-up, the majority of the participants were employed, while 11.2% were unemployed and 18.6% were retired (Table 1). A total of 38.3% of the patients reported to have participated in a CR programme at some point during the period from baseline to 36 months (Table 1).

Table 2 shows employment status according to participation in CR in a propensity-matched cohort representing 1416 patients. The covariate balance is shown in Supplementary Material Appendix Table 1. In the propensity-matched cohort, employment status of participants who were in a CR programme did not differ from those who were not in a CR programme (p=0.580).

Predictors of being employed three years after PCI

The multivariable-adjusted analyses showed that male participants, participants living with a partner, and participants with a higher level of education had a significantly higher chance of being employed three years after PCI (Table 3). In addition, participants living in western part

of Norway had a greater chance of being employed compared to participants in the northern part of Norway (Table 3). Higher age, former smoking, prior myocardial infarction or coronary artery bypass grafting, and prior hypertension treatment were associated with lower chance of being employed (Table 3).

Discussion

In the present study we assessed participant employment status three years after PCI and whether CR participation and other demographic and clinical factors predict employment status. We found that 70% of participants 62 years and younger reported to be employed three years after PCI. A total of 38% of the participants reported to have participated in a CR programme. There were no differences in long-term employment status between CR participants and CR non-participants. Male gender, living with a partner and higher levels of education are associated with higher chance of being employed, while older age, previous cardiovascular morbidity, prior hypertension treatment and smoking status are associated with lower chance of being employed three years after PCI.

Differences between prior studies and the present study population, severity of the coronary disease, state of employment at inclusion and follow-up time make it difficult to compare our findings on employment status with previous studies. The present study showed that 70% of patients 62 years and younger reported to be employed three years after PCI. This percentage is only slightly lower than that for the general population in Norway aged 25 to 66 years old, 79% of which were employed during 2018.[15] In previous international studies of employed patients, 86-93% of the patients were found to have returned to work one year after acute MI.[16-19] However, detachment is present, in a Danish nationwide register-based study almost a quarter of MI patients reported to quit working one year after they successfully returned to work.[17] This demonstrates the importance of long-term follow-up when measuring return-to-work rates after cardiovascular revascularization. A population based Danish study including 21,926 patients, showed that five years after the first-time hospitalization for acute coronary syndrome, 88% were still a part of the workforce where 65% were in work, 19% were unemployed and 16% were on sick-leave.[20]

When it comes to retirement at an early age, a nationwide cohort study from Sweden found that approximately one-third of patients were granted disability pension within five years after CABG or PCI.[21] In the present study, about 19% of patients 62 years and younger, reported to be retired three years after PCI demonstrating that approximately twice as many patients suffering from CHD leaves the workforce in an early age compared to the general population.[15] A history of long-term sickness absence prior to revascularization is a strong predictor for long-term sickness absence following PCI, followed by disability pension.[21, 22] In addition, disability pension at the time of coronary revascularization is associated with higher five-year mortality.[23] Taken together, these findings indicate that employment status is an important component of secondary prevention after a first-time PCI. The aim of CR is to improve later working capacity in younger patients and to prevent premature death.

Information about the effects of CR on return to work is scarce, and of the relevant studies, findings are inconsistent. The present study reveals, as shown previously in the same population,[11] that patients in working age in a higher degree participate in a CR programme compared to older patients. This is consistent with previous findings.[24, 25] Notably, CR participation can contribute to a delayed return to work.[26] Our propensity-matched comparison of patient employment status three years after PCI showed that employment status of those participating in CR did not significantly differ from those who did not participate in CR. However, since the employment status of our participants before the index event was unknown, we could not confidently determine whether changes in employment status could be related to CR participation or not. Moreover, at the time of our study, no national or international standard on return to work in CR programmes existed.[27] Thus, we were unable to determine the level of vocational support during CR. Nevertheless, the present

study is an important contribution as todays' knowledge on the long-term effect of CR on employment status is scarce, of old age and inconclusive.[8]

A recently published guideline on reintegration strategies to promote optimal return to work in acute coronary syndrome patients recommend early identification of patients at risk of poor vocational outcome.[9] Knowing the predictors of future employment status can help to facilitate vocational reintegration for patients in need. The present study found that being male, living with a partner, and higher levels of educational attainment were associated with a greater chance of being employed three years after PCI. This is consistent with previous findings showing a beneficial association between educational level[16-18, 20] and living with a partner[16, 20] with return to work. Regarding gender differences, what we observed was consistent with the majority of previous findings, suggesting that women have lower rates of returning to work and longer sickness absences than men.[17, 20, 22] Dreyer et al. and Cauter et al, however, did not find gender differences in their study after adjustment for other characteristics.[16, 26]

The present study suggests that the chance of being employed decreases with age and previous cardiovascular morbidity. One possible explanation is that in Norway, disability pension could be granted to people with long-term work incapacity. In an early age, retraining for patients with blue collar work is an opportunity, but a less relevant option for patients that are to be granted old-age pension in near future. In addition, having a manual job has previously been associated with delayed return to work[26]. Patients reported to live in the Northern part of Norway have a higher chance of being unemployed in the present study. Fewer opportunities for retraining or changing type of job in the rural areas of Norway can be one explanation for these findings. Previous cardiovascular morbidity and current smoking

were associated with lower chance of being employed three years after PCI, corresponding to prior research findings.[19] Overall, healthcare providers should pay attention to factors that are associated with unemployment in patients undergoing PCI to prevent future poor vocational outcome.

Methodological issues

The present study had many strengths, such as a large representative sample with, inclusion of only patients who were of working age, a prospective study design, long-term follow-up, and high response rate. Despite these strengths, there were some limitations. Firstly, we had no data on the participants' employment status at the index event, the participants' job satisfaction, and whether the participants had worked in white- or blue-collar jobs. Those kinds of data could have had an impact on their employment status at the 36-month follow-up. Secondly, as this was a prospective observational study, it could be susceptible to bias. To reduce bias, however, and control for several possible confounding factors when analysing the effect of CR on employment status, we performed propensity score matching.

Conclusions

Despite improvements in the prognosis for CHD patients, the present study suggests that a significant number of working-age patients remain unemployed three years after their first coronary revascularization. These individuals' employment status was not aided by CR participation. Focusing more vocational support on PCI patients who are older, lacking higher education and patients who are living alone may improve return to work, probability of successful societal reintegration, and perhaps quality of life.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

SJSO, HS, KHB, and TAH contributed to the conception or design of the work. SJSO, HS, TW, KHB, and TAH contributed to the acquisition, analysis, or interpretation of data for the work reported here. SJSO drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of this work, ensuring integrity and accuracy.

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Table 1. Baseline characteristics of participants at index event and employment status at 3 years of follow-up

Characteristic	(n=2488)
Age (years ± SD)	52 ± 5.5
Male gender, n (%)	2071 (83.2)
Living with a spouse/partner, n (%)	1953 (84.4)
Educational level ≤12 years, n (%)	1511 (63.5)
Current smoker, n (%)	1137 (48.9)
Body mass index (kg/m^2)	
>25 kg/m^2	1782 (71.6)
Medical history, n (%)	
Prior myocardial infarction	125 (5.0)
Diabetes mellitus	242 (9.8)
Prior CABG surgery	51 (2.0)
Prior stroke	42 (1.7)
Prior lipid-lowering treatment	1256 (51.1)
Prior HT treatment	840 (34.0)
Left ventricular ejection fraction, n (%)	
>40%	897 (94.7)
Indication for PCI, n (%)	
Stable angina	586 (23.7)
Acute coronary syndrome	1889 (76.3)
3-year follow-up	
Employment status, n (%)	
Unemployed	278 (11.2)
Employed	1747 (70.2)
Retired	463 (18.6)
CR participation	
Yes	953 (38.3)

Values are means (SD) or n (%).

SD: standard deviation; CR: cardiac rehabilitation; CABG: coronary artery bypass graft; HT: hypertension; PCI: percutaneous coronary intervention.

Table 2. Differences in employment status between CR participants and CR non-participants three years after percutaneous coronary intervention[a]

	CR participants (n=708)	CR non-participants (n=708)	*p*-value[b]
Unemployed	85 (10.2)	77 (10.9)	0.580
Employed	499 (70.5)	494 (69.8)	—
Retired	124 (17.5)	137 (19.4)	—

Values are n (%).

[a]Table shows results for the propensity-matched cohort (n=1416).

[b] Between-group comparisons in employment status were performed using conditional logistic regression

CR: cardiac rehabilitation.

Table 3. Odds ratios for being employed three years after percutaneous coronary intervention[a]

Unemployed[b] (reference) vs. employed	Unadjusted			Adjusted		
	OR	95% CI	P-value	OR	95% CI	*p*-value
Male (female = reference)	1.94	1.53 - 2.50	<0.001	1.93	1.50 - 2.50	<0.001
Age (years)						
<50 (reference)	1		<0.001	1		<0.001
50-55	0.62	0.48 - 0.81		0.66	0.50 - 0.87	
56-59	0.39	0.30 - 0.51		0.43	0.33 - 0.57	
Living arrangement (no = reference)						
Spouse/partner	1.48	1.15 – 1.91	0.002	1.40	1.07 - 1.82	0.014
Education level attained (≤12 years = reference)						
>12 years	2.17	1.76 - 2.70	<0.001	1.93	1.54 - 2.42	<0.001
Health Authorities						
North (reference)	1		<0.001	1		0.003
Central	1.10	0.78 - 1.53		1.07	0.75 - 1.53	
South/East	1.22	0.93 - 1.59		1.27	0.96 - 1.68	
West	2.07	1.47 - 2.90		1.89	1.32 - 2.71	
Smoking status						
Never (reference)	1		0.001	1		0.010
Former	0.65	0.51 - 0.83		0.71	0.55 - 0.93	
Current	0.81	0.62 - 1.06		0.98	0.74 - 1.31	
Body mass index (≤25 kg/m2 = reference)						
>25 kg/m2	1.00	0.81 - 1.23	0.997	1.00	0.80 - 1.26	0.997
Medical history (no = reference)						
Prior MI / CABG	0.49	0.34 - 0.71	<0.001	0.55	0.37 - 0.81	0.002
Diabetes mellitus	0.73	0.53 - 0.96	0.047	0.85	0.61 - 1.20	0.359
Prior stroke	0.48	0.24 - 0.96	0.038	0.65	0.31 - 1.35	0.244
Prior hypertension treatment	0.63	0.52 - 0.76	<0.001	0.69	0.55 - 0.86	0.001
Prior lipid-lowering treatment	0.71	0.59 - 0.86	<0.001	0.95	0.76 - 1.18	0.624
PCI indication (Stable AP = reference)						
Acute Coronary Syndrome	1.10	0.89 - 1.37	0.391	1.02	0.79 - 1.30	0.903
CR participation (no = reference)	1.02	0.83 - 1.24	0.877	1.01	0.82 - 1.25	0.940

[a] Due to missing in some of the independent variables, this analysis was restricted to completed case analyses of patients aged 59 years and younger at index event (n=2038).
[b] "Unemployed" was defined as patients who were unemployed or retired.

AP: Angina pectoris; CABG: coronary artery bypass graft; CI, confidence interval; CR: cardiac rehabilitation; HT: hypertension; MI: myocardial infarction; OR: odds ratio; PCI: percutaneous coronary intervention.

Supplementary Appendix Table 1. Baseline characteristics of the propensity-matched cohort (n=1416)

	Matched cohort		Standardised differences
	CR participants (n=708)	CR non-participants (n=708)	
Age, Years ± SD	52.3±5.3	52.1 ±5.6	0.037
Male, n (%)	572 (80.8)	567 (80.1)	0.018
Living arrangement, n (%)			
Spouse/partner	592 (83.6)	587 (82.9)	0.019
Educational level attained, n (%)			
≤12 years	442 (62.4)	444 (62.7)	-0.006
>12 years	222 (37.6)	264 (37.3)	0.006
Smoking status, n (%)			
Never	171 (24.2)	172 (24.3)	-0.002
Former	181 (25.6)	172 (24.3)	0.030
Current	356 (50.3)	364 (51.4)	-0.022
BMI (kg/m^2), mean ±SD	26.7 ±6.9	27.2 ±5.7	-0.079
Medical history, n (%)			
Diabetes mellitus	69 (9.7)	75 (10.6)	-0.030
Prior MI / CABG surgery	35 (4.9)	33 (4.7)	0.009
Prior lipid lowering treatment	346 (48.9)	345 (48.7)	0.004
Prior HT treatment	228 (32.2)	237 (33.5)	-0.028
Indication for PCI, n (%)			
Stable angina	106 (15.0)	114 (16.1)	-0.030
Unstable angina	74 (10.5)	78 (11.0)	-0.116
NSTEMI	245 (34.6)	249 (35.2)	-0.013
STEMI	283 (40.0)	267 (37.7)	0.047
Health authority, n (%)			
North	96 (13.6)	127 (17.8)	-0.116

Central	105 (14.8)	101 (14.3)	0.014
South/East	395 (55.8)	328 (46.3)	0.191
West	112 (15.8)	152 (21.5)	-0.047

SD: standard deviation; BMI: body mass index; CR: cardiac rehabilitation; MI: myocardial infarction; CABG: coronary artery bypass graft; HT: hypertension; PCI: percutaneous coronary intervention; NSTEMI: non ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

Supplementary material

(Paper II) Supplementary Appendix Table 1. Baseline characteristics of the entire cohort (n=7068) stratified by subgroups.

Characteristics		Subgroup (n=775)		Others (n=6293)		P-value
Age	Years ±SD	64	±9.2	63	±10.3	0.004
Gender– n (%)	Male	583	(75.2)	4738	(75.3)	0.965
Living arrangement – n (%)	Spouse/partner	591	(79.6)	4767	(79.2)	0.774
Educational level attained – n (%)	≤12 years	495	(66.7)	4188	(69.2)	0.179
	> 12 years	247	(33.3)	1865	(30.8)	
Smoking status – n (%)	Never	235	(31.3)	1725	(30.2)	<0.001
	Former	319	(42.5)	1963	(34.3)	
	Current	196	(26.1)	2030	(35.5)	
BMI (kg/m^2)	Mean ±SD / >25kg/m2	529	(68.3)	4121	(65.5)	0.127
Medical history – n (%)	Prior MI	76	(9.8)	588	(9.4)	0.696
	Diabetes mellitus	98	(12.7)	703	(11.2)	0.230
	Prior CABG surgery	58	(7.5)	385	(6.1)	0.136
	Prior stroke	27	(3.5)	233	(3.7)	0.840
	Prior lipid lowering treatment	459	(59.8)	3413	(55.1)	0.14
	Prior HT treatment	321	(41.7)	2682	(42.9)	0.512
Creatinine concentration (µmol)	Mean (IQR)	78.7	±17.6	78.8	±25.1	0.893
Left ventricle ejection fraction – n (%)	>40%	282	(95.6)	2337	(92.8)	0.088
	≤40%	13	(4.4)	181	(7.2)	
Indication for PCI – n (%)	Stable angina	3307	(39.8)	1817	(29.1)	<0.001
	Unstable angina	98	(12.6)	777	(12.4)	
	NSTEMI	218	(28.3)	1965	(31.4)	
	STEMI	148	(19.2)	1695	(27.1)	
Cardiac rehabilitation	Yes	183	(23.6)	1766	(28.1)	0.009

SD: standard deviation; BMI: body mass index; MI: myocardial infarction; CABG: coronary artery bypass graft; HT: hypertension; IQR: inter quartile range; PCI: percutaneous coronary intervention; NSTEMI: non ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction

(Paper II) Supplementary Appendix Table 2. Baseline characteristics of the propensity matched cohort (n=3402)

		Matched cohort		Standardised difference
		Participants (n=1701)	Non-participants (n=1701)	
Age	Years ±SD	60.3 ±9.4	60.0 ±10.1	0.031
Gender– n (%)	Male	1281 (75.3)	1276 (75.0)	0.007
Living arrangement – n (%)	Spouse/partner	1272 (78.5)	1227 (75.0)	0.083
Educational level attained – n (%)	≤12 years	1066 (62.7)	1140 (67.0)	-0.090
	>12 years	635 (37.3)	561 (33.0)	0.009
Smoking status – n (%)	Never	446 (29.1)	444 (29.1)	0
	Former	481 (31.4)	460 (30.2)	0.026
	Current	604 (39.5)	620 (40.7)	-0.025
BMI (kg/m^2)	Mean ±SD	26.4 ±6.5	26.7 (5.5)	-0.050
Medical history – n (%)	Prior MI	110 (6.5)	123 (7.2)	-0.151
	Diabetes mellitus	179 (10.5)	186 (10.9)	-0.013
	Prior CABG surgery	51 (3.0)	51 (3.0)	0
	Prior stroke	48 (2.8)	52 (3.1)	-0.066

	Prior lipid lowering treatment	841 (49.4)	864 (50.8)	-0.028
	Prior HT treatment	623 (36.6)	639 (37.6)	-0.021
Creatinine concentration (μmol)	Mean ±SD	76.6 ±23.1	76.6 ±21.4	0
Left ventricular ejection fraction – n (%)	>40%	495 (90.5)	503 (91.3)	-0.028
	≤40%	52 (9.5)	48 (8.7)	0.282
Indication for PCI – n (%)	Stable angina	270 (15.9)	306 (18.0)	-0.056
	Unstable angina	186 (10.9)	210 (12.3)	-0.044
	NSTEMI	589 (34.6)	577 (33.9)	0.015
	STEMI	656 (38.6)	608 (35.7)	0.060
Health authority – n (%)	North	195 (11.5)	301 (17.7)	-0.176
	Central	280 (16.5)	272 (16.0)	0.014
	South/East	1000 (58.8)	950 (55.8)	0.061
	West	226 (13.3)	178 (10.5)	0.087

SD: standard deviation; BMI: body mass index; MI: myocardial infarction; CABG: coronary artery bypass graft; HT: hypertension; PCI: percutaneous coronary intervention; NSTEMI: non ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction