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BARRIERS IN SECONDARY CARDIOVASCULAR PREVENTION

CARDIAC REHABILITATION REFERRAL, NON-ADHERENCE TO MEDICATION, AND ADVERSE CLINICAL OUTCOMES AFTER ACUTE CORONARY SYNDROME IN DENMARK

BY
CHRISTINA BOESGAARD GRAVERSEN

DISSERTATION SUBMITTED 2021

AALBORG UNIVERSITY
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LIST OF PAPERS

This dissertation includes the following three papers:

Paper I: Graversen CB, Johansen MB, Eichhorst R, Johnsen SP, Riahi S, Holmberg T, Larsen ML. Influence of socioeconomic status on the referral process to cardiac rehabilitation following acute coronary syndrome: a cross-sectional study. *BMJ Open* 2020; **10**: e036088.

Paper II: Graversen CB, Valentin JB, Larsen ML, Riahi S, Holmberg T, Zinckernagel L, Johnsen SP. Perception of pharmacological treatment and subsequent non-adherence to medication in patients with ischemic heart disease: A population-based cohort study. *Under review at BMJ Open.*

Paper III: Graversen CB, Valentin JB, Holmberg T, Larsen ML, Riahi S, Johnsen SP. Non-persistence to medication as a mediator for the social inequality in risk of major adverse cardiovascular events in patients with incident acute coronary syndrome: A nationwide cohort study. *Under review at European Heart Journal – Quality of Care and Clinical Outcomes.*

ENGLISH SUMMARY

Acute coronary syndrome (ACS) is a leading cause of morbidity and mortality worldwide. Accordingly, the purposes of secondary cardiovascular prevention are to reduce risk of these adverse clinical outcomes and to improve patients' daily living with a chronic heart disease. However, inequality and different barriers in secondary cardiovascular prevention have repeatedly been reported. The overall aim of this dissertation was therefore to evaluate the existence of barriers in secondary prevention following ACS. A multifaced approach was applied using different data to evaluate the presence of barriers related to referral to cardiac rehabilitation (CR), adherence to medication, and risk of major adverse cardiovascular events (MACE). The individual aims of the three papers were: to assess the influence of socioeconomic status on the referral process to CR (**Paper I**); to evaluate how patients' perception of pharmacological treatment was associated with subsequent non-adherence to medication (**Paper II**), and to investigate the mediating role of non-persistence to medication on the association between socioeconomic factors and MACE (**Paper III**).

In **Paper I**, 69.5% of the eligible ACS patients were referred to CR. There was a skewed socioeconomic gradient in referral to CR, especially in the phase of being willing to participate in CR. For example, patients with medium (odds ratio (OR): OR: 1.35 (95% CI: 0.94-1.94)) and high level of income (OR: 1.55 (95% confidence interval (CI): 1.02-2.35)) had higher odds of being willing to participate, compared to low-income patients.

In **Paper II**, patients' perception of being adequately informed about their secondary pharmacological treatment influenced the risk of non-adherence to medication. For example, risk of non-implementation of antiplatelets was 1.67 (95% CI: 0.95-2.93) and non-persistence of antiplatelets was 1.89 (95% CI: 1.10-3.25) among patients reporting 'to a lesser level' compared to patients' reporting 'to a high level' of perception of pharmacological treatment at follow-up after 365 days.

In **Paper III**, a total of 16,958 (35.7%) patients with incident ACS experienced MACE during a median follow-up time of almost 3.5 years. Patients with higher levels of income and education had a significant decreased risk of MACE compared to patients with low income levels. Differences in non-persistence to medication mediated the inequality in risk of MACE between high- and low-income men by 12.6% (95% CI: 11.1%-14.1%).

In conclusion, the findings of this dissertation call for increased awareness of the role of patients' socioeconomic factors and perception about pharmacological treatment as barriers to secondary cardiovascular prevention and improved clinical outcomes following ACS.

DANSK RESUMÉ

Akut koronarsyndrom (AKS) er en hyppig årsag til sygdom og død verden over. Formålet med sekundær præventiv kardiologi er derfor at reducere risikoen for uønskede kliniske udfald og forbedre patienternes livskvalitet. Der er dog gentagne gange blevet rapporteret ulighed i og barrierer til brugen af den sekundære præventive behandling. Det overordnede formål med denne afhandling var at undersøge forekomsten af disse barrierer. Forskellige data blev brugt for at få en flersidig tilgang til at undersøge barrierer til henvisningsprocessen til hjerterehabilitering, adhærens til medicin samt risikoen for kardiovaskulær udfald, herunder død, hjerterelateret død samt genindlæggelse af kardiel årsag. Studierne havde følgende formål: at undersøge betydning af patienternes socioøkonomiske status for henvisningsprocessen til hjerterehabilitering (**studie I**); at evaluere hvordan patienternes opfattelse af deres medicinske behandling var associeret med risikoen for manglende adhærens til medicin (**studie II**) samt at undersøge hvorvidt associationen mellem socioøkonomiske faktorer og risiko for kardiovaskulært udfald var medieret af manglende adhærens til medicin (**studie III**).

I **studie I** blev 69,5 % af AKS patienterne henvist til hjerterehabilitering. Der var en social gradient i henvisningsprocessen, særligt vedrørende patienternes interesse for at deltage i hjerterehabilitering. Patienter med middelindkomst (odds ratio (OR): 1,35 (95 % konfidensinterval (KI): 0,94-1,94) og højindkomst (OR: 1,55 (95 % KI: 1,02-1,55) havde større sandsynlighed for at ville deltage i hjerterehabilitering, sammenlignet med lavindkomst patienter.

I **studie II** sås, at patienternes oplevelse af at være ordentligt informeret om deres farmakologiske behandling var associeret med adhærens til medicin. For eksempel havde patienter, som rapporterede, at de "i mindre grad" oplevede at være tilstrækkelig informeret om deres medicinske behandling, øget risiko for manglende implementering (hazard ratio (HR) 1,67, 95 % KI: 0,95-2,93)) samt fastholdelse af pladehæmmer-behandling (HR: 1,89 (95 % KI: 1,10-3,25) sammenlignet med patienter, der angiv "i høj grad" ved 365 dages opfølgning.

I **studie III** oplevede 16.958 (35,7 %) patienter et kardiovaskulært udfald i løbet af en gennemsnitlig opfølgningstid på ca. 3,5 år. Højere indkomst- og uddannelsesniveau mindskede risikoen for kardiovaskulært udfald signifikant sammenlignet med lavt indkomst- og uddannelsesniveau. Bedre fastholdelse af medicinsk behandling medierede den lavere risiko for MACE blandt højindkomst mænd med 12,6% (95 %: 11,1 % - 14,1 %), sammenlignet med lavindkomst mænd.

Samlet set antyder resultaterne i denne afhandling, at der skal sættes større fokus på patienternes socioøkonomiske faktorer samt deres oplevelse af tilstrækkelig information vedrørende deres farmakologiske behandling, hvis man skal mindske barriererne til optimal sekundær kardiovaskulær behandling og forbedre de kliniske udfald blandt patienter med AKS.

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Christina Boesgaard Graversen

July 2021

ABBREVIATIONS

ACE-inhibitor	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
ARB	Angiotensin-receptor blocker
CR	Cardiac rehabilitation
CCI	Charlson comorbidity index
DAG	Directed acyclic graph
DNPR	The Danish National Prescription Register
ESC	The European Society of Cardiology
HR	Hazard rate ratio
ICD	International classification of disease
ISCED	International standard classification of education
IHD	Ischemic heart disease
MACE	Major adverse cardiovascular event
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
PDC	Proportion of days covered
RR	Relative risk
SEF	Socioeconomic factors
SES	Socioeconomic status
STEMI	ST-elevation myocardial infarction
UAP	Unstable angina pectoris
WHO	World Health Organisation

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CHAPTER 1. INTRODUCTION

Cardiovascular diseases cause a substantial burden of morbidity and mortality globally [1]. In recent decades a decrease in the mortality of acute coronary syndrome (ACS) has precipitated patients living longer with the disease [2]; thus, attention should be put on secondary prevention in cardiovascular disease [3].

The overall aim of secondary prevention in cardiovascular disease is to reduce any risk of adverse clinical outcomes and improve patient's quality of life [4]. The vital elements of secondary cardiovascular prevention following ACS include pharmacological and non-pharmacological treatments starting at the hospital admission and continuous with life-long behavioural change. The benefits of secondary cardiovascular prevention are e.g. proved by reduction in cardiac-related readmission and mortality [5]. However, these improvements are not allocated equally among patients, and research repeatedly reports socioeconomic disparity in the utilisation of secondary cardiovascular prevention and in the risk of adverse clinical outcomes like mortality. This implies a continued struggle to handle barriers to the utilisation and life-long coherence of the intervention.

Consequently, this dissertation has an ambition to understand the occurrence of these barriers and provide suggestions of improvement. The dissertation comprises three papers based on different data to explore plausible reasons. First, the referral process to cardiac rehabilitation is examined in a regional setting using a cross-sectional study design. Next, patient-reported experiences are used in a cohort study with register-based follow-up to assess the association between perceived information on pharmacological treatment and subsequent non-adherence to medication at follow-ups after 180 and 365 days. Finally, a large-scale nationwide cohort study evaluates the mediating role of non-persistence to medication on the association between socioeconomic factors and risk of major adverse clinical outcomes.

CHAPTER 2. BACKGROUND

This dissertation concerns barriers to the utilisation of secondary cardiovascular prevention, including cardiac rehabilitation (CR) and pharmacological treatment, as well as the related risk of adverse clinical outcomes in patients with acute coronary syndrome (ACS). In the following, ACS is presented along with core components of secondary cardiovascular prevention including different barriers in its utilisation. The section ends with an overview of the social gradient in adverse clinical outcomes also present in countries with equalitarian healthcare structure.

ACUTE CORONARY SYNDROME AND THE NEED OF SECONDARY CARDIOVASCULAR PREVENTION

ACS is a subcategory of ischemic heart disease (IHD), which remains one of the leading causes of disability-adjusted life-years and death worldwide [1,6]. In 2018, approximately 165.000 people lived with IHD in Denmark and the prevalence is increasing [7]. The yearly incidence of IHD decreased from 20,937 cases in 2008 to 16,050 cases in 2018, as well as yearly IHD-related mortality that decreased from 5,946 cases in 2007 to 3,298 in 2018 [7].

ACS covers a group of diagnoses including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). Diagnosis of ACS is based on symptoms, electrocardiogram presentation and biochemical markers [8,9]. Development of IHD is complex and multifactorial. The predisposing risk factors revolve around the SCORE chart using age, sex, smoking status, systolic blood pressure and cholesterol level to calculate a 10-year risk of fatal cardiovascular disease [10–13]. Further selected risk factors and potential modifiers include family history/genetics [14,15], diabetes mellitus [16], physical inactivity [17], poor diet [18], socioeconomic factors (SEF) [19] and social deprivation or isolation [20,21].

The initial treatment of ACS depends on diagnosis and involves invasive management and acute pharmacological treatment [8,9]. It has been demonstrated that approximately 15% of patients with incident myocardial infarction die within the first year [22], but that this risk rapidly decreases in the years following diagnosis [23]. Accordingly, it is crucial to encourage patients to cohere to secondary pharmacological and non-pharmacological treatment to minimize risk of adverse clinical outcomes following ACS.

CARDAC REHABILITATION AND GUIDELINES

During the first 20th century, prolonged bed rest and physical inactivity were recommended after being diagnosed with myocardial infarction [24]. This approach was questioned in the 1950s and over the next decades, research found that implementation of physical exercise shortened patients' recovery time, hospitalisation and improved clinical outcome [24,25]. As evidence grew, CR underwent several modifications whereas lifestyle intervention and psychosocial support are acknowledged as important features together with the traditional pharmacological and surgical treatment [26]. Consequently, the World Health Organization (WHO) advocated that treatment should shift from the paradigm of the patient passively receiving medical treatment into a more educational approach in which patients were educated in and encouraged to actively take responsibility for own health and well-being [26]. In 1993, the WHO defined the goals of rehabilitation as: ''*to improve functional capacity, alleviate or lesson activity-related symptoms, reduce unwarranted invalidism, and enable the cardiac patient to return to a useful and personally satisfying role in society*' [27].

Guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association recommend CR to all patients with ACS (Class I, Level A) [4,8,9,28,29]. CR is a structured programme divided into three phases according to intervention and place of implementation [3,30]. Figure 1 presents the setting and content of CR in Denmark [31]. The content of phase II comprises an intervention lasting minimum 12 weeks, whereas phase III CR covers long-term support to maintain improved lifestyle and risk factors control [32]. Each phase contributes substantially to the aim of improving patients' health outcome following ACS, but it should be noted that most time takes place in the out-of-hospital settings. This dissertation revolves in different ways around all phases and tries to aim attention to occurrence of selected barriers.

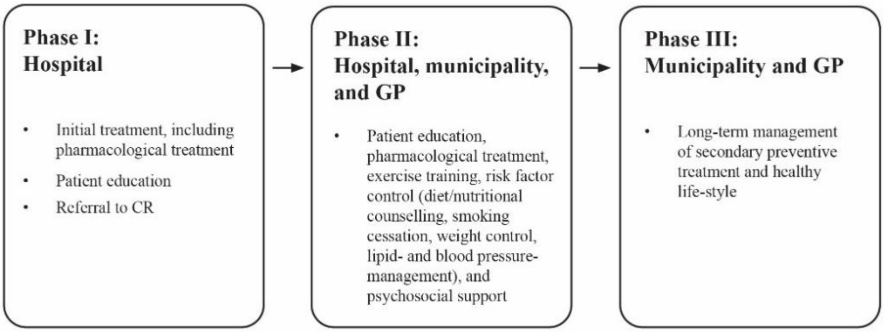


Figure 1. Cardiac rehabilitation phases, setting and content in a Danish context. Abbreviations: GP, general practitioner; CR, cardiac rehabilitation.

Several meta-analyses, including Cochrane reviews, show the clear benefits of CR [5,33–35]. The latest Cochrane review from 2016 found that CR reduced the risk of cardiovascular mortality by 26% (relative risk (RR): 0.74 (95% confidence interval(CI): 0.64-0.86) and hospital readmission by 18% (RR: 0.82 (95% CI: 0.70-0.96) [5]. Controversial, the study did not find significant reduction in overall mortality otherwise reported in an earlier Cochrane review from 2011 [36]; however it was hypothesised to be caused by inclusion of the RAMIT study from 2012 that showed no effect on mortality [37]. Interestingly, a recent study from the Netherlands found CR to reduce all-cause mortality by 32% in a population with an acute coronary event [38], which further advocates the benefit of CR on all-cause mortality.

Utilisation of CR has for a long time been unsatisfactory and European studies find the proportion of eligible patients being referred to range between 23-90%, of which 13-41% of the patients complete the programme [39–44]. However, it should be noted that definition of utilisation of CR is inconsistent, and some studies define it as minimum participation in some elements [40,44], whereas others define it as participation in minimum 50% of the entire programme [41–43]. In Denmark, the latest results on utilisation of municipality-based CR found that patients were persistent with the overall CR treatment but did not fulfil the desired indicators of e.g. physical exercise, smoking cessation or screening of anxiety and depression [45,46]. However, these problems also exist in in-hospital CR settings [47].

Abundant evidence reports that this poor utilisation is influenced by barriers at system- and personal-level, and factors associated include older age, female sex, long transportation time, ethnicity, comorbidities, social deprivation, psychosocial risk factors, beliefs about intervention, SEFs as well as physician attitude towards CR [42,48,57,49–56]. Although being identified to be associated with referral to CR [58], it remains uncertain how social inequality occurs in the referral process to CR and if it is dominated by system-level barriers, personal-level barriers, or a combination of both. Thus, there is a lack of studies addressing barriers in the referral process to CR.

PHARMACOLOGICAL TREATMENT AFTER ACS

The pharmacological component in secondary cardiovascular prevention after ACS is essential to obtain proper clinical outcome [59]. Table 1 presents the different types of medication, to whom they should be administered, duration and level of evidence.

Table 1. Secondary pharmacological therapy of ACS patients (inspired by [8,9,60]).

Type of medication	To whom?	Duration	Class, level
Acetylsalic acid	ACS	Long-term	I, A
$P2Y_{12}$-inhibitor	ACS	First year after ACS	I, A
Lipid-lowering (statins)	ACS	Long-term	I, A
B-blockers	ACS ÷ HF	2 years	*
	ACS + HF and/or LVEF ≤ 40% unless contraindicated	Long-term	I, A
	ACS without contraindications	Long-term	II, A
ACE-inhibitor/ARB	ACS and decompensated, or LVEF < 40%, or DM, hypertension, CKD, PAD, or at high risk of secondary event	Long-term	I, A

Abbreviations: ACS, acute coronary syndrome; HF, heart failure; LVEF, left ventricular ejection fraction; DM, diabetes mellitus; CKD, chronic kidney disease; PAD, peripheral artery disease; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers. *According to Danish national guidelines [41].

Adherence to medication is crucial to obtain good clinical outcomes and involves the process when a patient chooses to follow the advice from a health practitioner. It may therefore be useful to look at adherence to medication using the ABC taxonomy and the EMERGE criteria that involves a three-phase structure of adherence to medication [61,62]:

1) Non-initiation: Does not initiate pharmacological treatment.
2) Non-implementation: Does not take the drugs as prescribed.
3) Non-persistence: Stop taking medication based on patient’s choice.

Non-implementation is in this dissertation evaluated by proportion of days covered (PDC) and is defined as time from initiation until eventual discontinuation and allow breaks in treatment; Non-persistence is in this dissertation evaluated by time-to-event analyses and is defined as time from initiation until break in treatment lasting > 90 days. All terms cover different elements and have been used without uniform terminology in the literature, which may explain the inconsistent findings regarding reasons for non-adherence. Moreover, the different settings of the studies in relation to structure of the welfare systems should be taken into consideration when interpreting study findings.

In patients with ACS, adherence to medication in clinical practice remains overall on an unsatisfactory level despite guidelines’ recommendations and the compelling evidence of pharmacological treatment on clinical outcomes [4,63,64]. Several factors are found to predispose such patterns, many of which also predispose to general development of ACS and poorer utilisation of CR. Despite inconsistency in results,

predisposing factors include, but are not limited to, age [65], sex [66], educational level [19], income [67] and comorbidity [68].
Communication and good patient-provider relationship may be ways to lower non-adherence to pharmacological treatment, as patients have reported insufficient information concerning their medication, for example regarding risk of adverse effects, frequency of dosing and duration of treatment [69]. The potential effect of good communication is further supported by a study that emphasises e.g. patient trust in their provider as well as making patients understanding the necessity of medication to be importation to obtain good adherence [70]. The ESC has also acknowledged the positive potential of communication as a strategy, most recently in an expert opinion paper on adherence to statins [71].

PATIENTS' PERCEPTION OF SECONDARY PHARMACOLOGICAL TREATMENT

In 2017, the ESC further included patient engagement as a strategic objective to raise attention to the benefits of involving patients in their condition and treatment, including the potential to increase adherence to treatment [72]. A tool may be patient-reported experience measures that are questionnaires investigating patients' perspectives of a given situation, e.g. a patient hospital journey or a specific treatment, and could be used as an indicator of the quality of care [73]. The importance of such involvement of patients has been demonstrated in different settings, i.e. a growing body of evidence finds that patients with negative beliefs about medications have higher risk of non-adherence to medication [74–76] – also in patients with IHD [77–79]. It is further reported that perception about CR is associated with lower self-reported adherence to medication at 6 months follow-up [80], and that patients report a continuous need of information regarding their secondary pharmacological treatment after suffering ACS [81]. Studies exploring patients' perceptions mainly use self-reported adherence measures, and none has used register-based adherence measures to evaluate how patients' perception about pharmacological treatment is associated with adherence to medication. This should be a priority to avoid the limitations of self-reported adherence measures, including risk of recall and social desirability bias causing adherence overestimation [82].

There is no consensus on how to measure quality of healthcare and to obtain patients' experiences of such. Consequently, multiple survey instruments can be used for the same purpose and the selection of a specific instrument should therefore be based on a mix of reliability and utility [83]. Nonetheless, patient-reported experiences have revealed a need for the healthcare workers to prioritise and actively work with disease and treatment engagement in patients with a chronic (cardiac) disease. A 'whole-system approach' using patient experiences and perceptions to lower the proportion of non-adherence to secondary treatment is advocated [84].

Text box 1. Social inequality in health from a Danish context [85].

In general	Low educational level increases risk of poverty
	Higher income-related inequality in the Danish society measured by the Gini coefficient
Health	Reverse probability of life expectancy and income as well as educational level
	Increased risk of overall mortality in people with lower education
IHD	Social gradient according to educational level in incident IHD and risk of 5-year mortality

Accordingly, a paradigm shift into shared-decision making and patient engagement may be the (natural) next step to improve clinical outcomes in cardiovascular patients [72]. This may help lower presence of the social gradient in cardiovascular health, for example unbeneficial risk profile, utilisation of secondary preventive treatments, and risk of adverse clinical outcome. This is important, also in a Danish setting, as presence of inequality in health and IHD recently was documented in a national report from 2020, of which select main results are presented in text box 1 [85].

SOCIAL INEQUALITY IN CR AND RISK OF ADVERSE CLINICAL OUTCOMES

The implementation of a comprehensive CR programme, specifically the exercise component, has found to improve quality of life and reduce risk of hospital readmissions and cardiovascular mortality [5]. Similar results could not be found when exclusively investigating the effect of the educational and psychosocial component in CR; however, the importance of the components' on patients' quality of life remain indisputable [34,86]. Further, a Danish study using the $\text{IMPACT}_{\text{sec}}$ model recently supported the positive effect of CR on clinical outcomes; in this, rates on mortality caused by coronary heart disease dropped by about 75% over a period of 16 years (1991-2007) [87]. Improved risk factors accounted for 2/3, and improved treatment (pharmacological and interventional during hospitalisation) accounted for 1/3 of this estimation [87]. However, the study also found that patients with lower personal income were less likely to benefit from improved treatment utilisation compared to those with the highest income (18.6% vs. 25.3%). Further, research has implied that patients with lowest educational level less likely improve cardiovascular risk factors and VO_2 peak following participation in CR [88]. This is problematic, as compelling evidence has reported patients' SEF to be associated with increased risk of secondary cardiovascular events and mortality [22,89–91]. For example, a large-scale Swedish cohort study reported that among survivors of incident ACS, patients with high income had 27% (hazard ratio: 0.73, 95% CI: 0.62-0.83) reduced risk of secondary coronary event at one-year follow-up compared with low-income patients [89]. Research further report that differences in received interventional treatment only have a minor effect on this association [92,93]. Thus, besides focusing on how to increase participation in CR among the socially deprived patients, future studies are encouraged to evaluate pathways of SEF on clinical outcome, e.g. the mediating role of non-adherence to medication on this association [89]. This has recently been investigated in relation to patients with heart failure [94]. Herein it was found that suboptimal pharmacological treatment mediated the income-related inequality in risk of mortality at the 1-year follow-up in single-living men [94]. Similar mediating role can reasonably be suspected among patients with ACS as inequality in risk of non-adherence to pharmacological treatment has been demonstrated, especially in regard to level of income [95,96]. Research further find women to be more non-adherent to medication compared to men [97,98].

It is noteworthy to highlight that it is not the lower socioeconomic status (SES) itself that is responsible for the more disadvantaged profile but the more dominating risk factors in these persons [99]. The mechanism binding SEF to poorer outcome is complex and has been suggested to be attributed to an unfortunate combination of biological, behavioural and social risk factors [100]. What is seldom included in research is the reflection on e.g. why do patients with low SES have higher risk factors – is it merely something they are born into or rather a result of life experiences and circumstances? Also, when looking at social inequality by dichotomising patients into high vs. low instead of a gradient (high – middle – low), there is a risk of displaying those with low SES and thereby putting them in a vulnerable situation [101]. Using SEF to evaluate social inequality, it is important to realise that a person with lower SES is not necessarily more vulnerable than a person with higher SES. Vulnerability may first occur, be maintained or worsened during the encounter with the health system due to insufficient capability among healthcare workers to acknowledge (and treat) them in a manner that they can relate to [102]. For example, social inequality occurs if the healthcare system fails to take care of patients with more complex needs related to their social status – or simply needs that are a bit more time-consuming. Thus, it is utterly important to address (socioeconomic) barriers in secondary preventive cardiology and go a step further to evaluate what can be done. This was also recently discussed by the ESC regarding adaption of CR in respect to patients' socioeconomic needs [103].

ROOM FOR IMPROVEMENT IN SECONDARY CARDIOVASCULAR PREVENTION

This background section reflects that secondary preventive cardiology still does not fulfil the guideline criteria of high utilisation of CR and adherence to medication, despite its indisputable effect on the decline in hospital readmissions and mortality after ACS. Furthermore, there is an increasing inequality in adverse clinical outcome following ACS. Barriers to secondary cardiovascular prevention are highly present and it is important to learn more about possible explanations of their occurrence. There is room for improvement also expressed in a recent update on cardiovascular disease in clinical practice by the ESC: '*It is essential to identify health system-related* *difficulties and weaknesses in the management and support of secondary cardiovascular prevention post-ACS discharge'* [104].

CHAPTER 3. AIMS AND HYPOTHESES

This dissertation concerns potential barriers in secondary prevention among patients with ACS in a Nordic welfare state. Different suggestions in order to improve the process from referral to CR to reasons why patients do not meet optimal adherence to medication and how these affect clinical outcomes will be presented throughout this dissertation. Below, Figure 2 presents the framework of this dissertation. It should be noted that **Paper II** included patients with IHD due to risk of insufficient power if we had chosen only to assess patients with ACS.

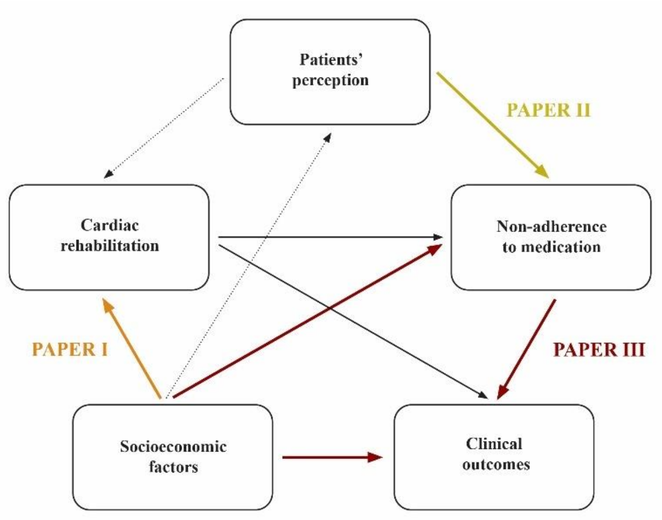


Figure 2. Framework of dissertation.
Lines: documented pathway, dotted lines: hypothesised pathway, coloured lines: investigated pathways in present dissertation.

Paper I. Socioeconomic barriers to CR referral
The aim was to investigate the hypothesis of SES being associated with referral to CR among patients with incident ACS. This was done by division of the referral process into three phases looking at information about CR, willingness to participation in CR, and assigned CR setting.

Paper II. Patients' perception and subsequent non-adherence to medication
The aim was to evaluate the hypothesis that lower perceptions of pharmacological treatment increased risk of non-adherence to medication in patients with incident IHD.

Paper III. SEF, clinical outcomes, and the mediating role of non-persistence to medication.
The aim was to explore the hypothesis that the social gradient in risk of major adverse cardiovascular events (MACE) is mediated by non-persistence to medication in patients with incident ACS.

CHAPTER 4. METHODS, MATERIALS AND SETTING

This section provides an overview of the different data sources and methods used in the three papers, as well as an overall presentation of the setting of the studies. Table 2 presents the most important conceptions of design, data sources and prerequisites in each study. For a more detailed description, please see **Papers I-III** in the Appendix section.

Table 2. Overview of aims, methods, and data sources used in the three papers of this dissertation.

	Paper I	**Paper II**	**Paper III**
Aim	To examine the association between SES and referral to CR after division into three phases	To investigate how perception of pharmacological treatment is associated with non-adherence to medication	To explore the mediating role of non-persistence to medication on the association between SEF and MACE
Design	Cross-sectional study	Survey study with register-based follow-up	Prospective cohort study with historical data
Level	System	Individual	Population
Data sources	Questionnaire, Danish national registers	Questionnaire-based survey, Danish national registers	Danish national registers
Study population	1,229 patients with ACS	829 patients with IHD	45,874 patients with ACS
Exposure	Income, education, occupation, civil status	Perception about pharmacological treatment	Income, education
Outcomes	Information about CR, willingness to participate in CR, assigned CR setting	Non-adherence to cardiovascular medication at follow-ups after 180- and 365 days.	Non-persistence to medication, MACE (all-cause death, cardiac death, cardiac readmission)
Covariates	Age, gender, ACS diagnosis, comorbidities	Age, sex, ethnicity, income, education, civil status, occupation, comorbidities, supportive relatives	Age, sex, ethnicity, civil status, somatic and psychiatric comorbidities, education/income when not defined as exposure
Statistical analyses	Multivariable logistic regression analysis	Multiple imputation, McDonald’s Omega, Poisson regression, Cox proportional hazards models	Multiple imputation, inverse probability treatment weight, discrete time survival analysis, cumulative incidence by Aalen-Johansen estimator, mediation analysis

All studies included register-based information.
Table 3 presents sources of exposure, outcome, and covariates in the three studies.

Table 3. Data sources used to define exposures, outcomes, and covariates.

	Data source	**Used in study**
Diagnosis	The Danish National Patient Register [105]	I, II, III
Income	The Income Statistics Register [106]	I, II, III
Education	The Population's Education Register [107]	I, II, III
Occupation	The Register-based Labour Force Statistics [108] Survey [109]	I, II II
Civil status	The Danish Civil Registration System [110]	I, II, III
Age	The Danish Civil Registration System [110]	I, II, III
Sex	The Danish Civil Registration System [110]	I, II, III
Ethnicity	The Danish Civil Registration System [110]	I, II, III
Somatic comorbidities	The Danish National Patient Register [105]	I, II, III
Psychiatric comorbidities	The Danish Psychiatric Central Research Register [111], The Danish National Prescription Register[112]	III
Referral to CR	Questionnaire	I
Perception of pharmacological treatment	Survey [109]	II
Supportive relatives	Survey [109]	II
Individual consultation in medication	Survey [109]	II
Non-adherence to medication	The Danish National Prescription Register [112]	II, III

SETTING

The overall aim of Danish health politics is equality in health and has been a focus area for different Danish government and ministries over the past decades [113–117]. Nonetheless, social inequality exists despite the equalitarian healthcare structure (Text box 1 [85]).

The Danish healthcare system is tax-financed and enables all 5.8 million Danish inhabitants to use treatments and consultations at public hospitals and general practitioners free of charge. This also includes CR.
Medication provided at public hospitals requires no co-payment by the patient, whereas medication bought on prescription at pharmacies often is sold with general reimbursement with some co-payment. The Danish society operates with different types of reimbursements, and the overall aim is to provide the highest public reimbursement to those patients with the highest expenditures on medication [118]. Accordingly, the personal level of reimbursement is calculated based on the prior year expenditures and ranges from 0-100%. This calculation is automatically done at the pharmacies [119]. Based on doctors' recommendations, patients can apply their municipality for extra reimbursement of their prescribed medication if they are unable to afford it themselves, according to Danish law [120].

The Danish CR programme was tested as an in-hospital intervention in the late 1990s and was followed by a more structured implementation in the early 2000s [113,121]. In 2007, a structural reform reduced the numbers of municipalities and counties (now called regions), which implemented that all public health services were to be managed by the regions. Thus, part of CR was placed in the municipalities and pledged to be structured according to local agreements, taking local resources into account in close collaboration with the treating hospital [122]. In 2018, the Danish Health Authority changed the legislation regarding the setting of phase II CR; going forward, CR should primarily be held in an out-hospital setting, limiting in-hospital CR to high-risk patients [123].

PAPER I

Objective: To investigate how a three-phase structure can provide new information regarding social inequality and barriers in the referral process to CR among patients with incident ACS.

Design: Cross-sectional study

Study population: Patients hospitalised with incident ACS (ICD-10: I200, I.21) and evaluated for eligibility of CR participation at Department of Cardiology, Aalborg University Hospital in the period 2011-2014. Exclusion criteria involved missing information regarding SES or acceptable reason for no referral to CR, including transfer to another hospital, unfinished treatment or death. Accordingly, the study population comprised 1,229 patients.

Data sources: Information on exposure (SES) and covariates was gathered from the Danish registers by linkage of the Central Personal Register number provided to all Danish residents. SES was estimated by: Educational level, which was categorised according to the International Standard Classification of Education (ISCED) definition and divided into three groups (low, medium, high); Personal income, which was assessed the year prior to hospitalisation and divided into tertiles (low, medium, high); Civil status, which was dichotomised (married/partnership, divorced/unmarried/widow); Occupation status obtained from the register the year prior to hospitalisation (employed, unemployed/out of workforce). Outcome was gathered by a questionnaire used as a referral tool to CR, and was divided into three phases: Information regarding CR (yes, no); Willingness to participate in CR (yes, no); Assigned CR setting (in-hospital or community centre). The selection of covariates was done a priori by literature review and depictured in a directed acyclic graph (DAG). Covariates included age, gender, type of ACS diagnosis, and comorbidities assessed by Charlson Comorbidity Index (CCI). Type of ACS diagnosis was included, as this influenced the type of CR setting which is described in detail below.

Statistical analyses: Patients with missing data on SES were excluded from the study under the assumption of not being missing at random and enabled complete case analyses. The descriptive analysis at baseline included summarisation by frequencies and percentage. The association of SES on referral to CR was estimated using crude and multivariable logistic regression adjusted for confounding variables and presented with odds ratio (OR) and 95% CI. Further, sensitivity analyses evaluated if results were altered after stratification by gender.

The questionnaire and local guidelines about CR referral in the study period

Outcome information was provided by the regional Rehab-North Register, which entailed patients that were assessed for referral to CR during hospitalisation at the

Department of Cardiology, Aalborg University Hospital between 01.01.2011-31.12.2014. The questionnaires used for assessment is further presented in a study published in 2017 [39]. Acceptable reasons for not informing patients about CR included forthcoming coronary artery bypass grafting, transfer to another hospital or death during hospitalisation. The questionnaire was originally introduced to the department in 2009. A run-in period from 2009-2010 secured proper implementation in the clinical routine before using the data in **Paper I**. CR nurses provided information about CR to patients, whereas medical doctors had the administrative and overall responsibility for the referral process to CR.

At the Department of Cardiology, Aalborg University Hospital, it was decided that assigned CR setting should be based upon hospital discharge diagnosis. Patients diagnosed with STEMI and complicated NSTEMI were to be referred to in-hospital CR, whereas patients with uncomplicated NSTEMI or UAP were to be referred to community-based CR. Exceptions could be made upon an individual assessment. The definition of NSTEMI as complicated or uncomplicated relied on a professional and an individual assessment but could be relevant if the patient had i.e. impaired left ventricular function, increased systolic blood pressure during hospitalisation that required close medical regulation, or other competing disease(s) that needed close regulation.

PAPER II

Objective: to investigate how patients' perception about pharmacological treatment was associated with risk of non-adherence to cardiovascular medication in a population of patients with incident IHD.

Design: Survey-based cohort study with register-based follow-up data.

Study population: The study population included patients diagnosed with IHD selected from a random population-based cohort of 5,000 patients included in a national survey [124]. The cohort was drawn from the National Patient Register (NPR) if having been diagnosed with either IHD (n = 2,116), atrial fibrillation (n = 1,695), heart failure (n = 642), or having underwent a heart valve surgery in 2013 (n = 547). Patients were eligible if ≥ 35 years of age and Danish residents at the time of sample establishment (1st October 2014).
It was identified that a total of 374 patients initially categorised as incident cases of IHD in fact were prevalent cases. This was most likely caused by a delayed update of the NPR after sample establishment as almost all prevalent cases were diagnosed during the autumn 2012. The affected patients were excluded, and the potential study population was downsized to include 1,742 patients with incident IHD. Of these, 829 patients fulfilled all inclusion criteria and were included in the study corresponding to a response proportion of 47.6%.

Data sources: The exposure variable 'perception about pharmacological treatment' was established using three items in the survey that covered subjects related to how well-informed they felt about their prescribed cardiovascular medication (Table 4). The study outcomes of non-adherence to medication (antiplatelets, statins, β-blockers or ACE-inhibitors/ARBs), were obtained using information from the Danish National Prescription register (DNPR). Non-adherence was categorised according to the ABC taxonomy and included non-initiation, non-implementation and non-persistence to medication [61]. Confounding variables were gathered from the Danish registers (age, sex, ethnicity, income, education, civil status, occupation, comorbidity) and the survey (supportive relatives), also illustrated in Table 3.

Processes in the questionnaire development and formation of the survey:
The development of the survey was carried out in several stages in the period between September 2013 and August 2014 by a study group from the National Institute of Public Health at the University of Southern Denmark. The development has been described in detail by Zinckernagel et al. in 2017 [109]. First, a literature review of 86 studies and a qualitative explorative investigation with a total of nineteen patients, four relatives and eight individual interviews with healthcare professionals were carried out. The aim was to investigate which elements the patients considered to be especially challenging during their journey through the healthcare system. Next, reference groups within fields of healthcare as well as experienced researchers

contributed to adjustment of the proposed questionnaire from the study group. The questionnaire was then pilot-tested on ten patients with cardiac disease, and seven themes were subsequently identified: information, communication, organisation, psychosocial aspects, rehabilitation/support, medication and involvement of relatives. Final adjustments were made before sending the questionnaire in paper alongside a covering letter and a pre-paid return envelope to the study cohort on 27th October 2014. Patients had until 14th December 2014 to answer the questionnaire. **Paper II** in this dissertation focuses on selected items regarding medication.

Statistical analyses: Item consistency was evaluated by McDonald's Omega, and item non-response was handled by multiple imputations under the assumption of data being missing at random [125]. The imputation model was run by ten rounds and included all variables used in the study. Non-initiation of medication was defined as not picking up prescribed medication in a follow-up period of 180 days after hospital discharge. Non-implementation was measured by proportion of days covered (PDC) and non-persistence was measured as risk of discontinuation using a 90-day grace period. Patients were followed 180 and 365 days after the time of first drug redemption. Poisson regression analysis evaluated the association between perception of pharmacological treatment and non-initiation and non-implementation of medication. Results were presented with RR and 95% CI. Cox proportional hazard regression evaluated the association between perception of pharmacological treatment and non-persistence during follow-up and presented as hazard rate ratios (HR) and 95% CI. All analyses were adjusted for confounding variables.
Sensitivity analyses were performed including stratification by sex, separate analyses of the used items and different grouping of medication.

Table 4. Survey items measuring patients' perception about pharmacological treatment [109].

Questions	**Reply options**	**Summarised item used in Paper II**
Item 1: Do you feel informed about why you get medication for your heart disease?	0: Yes, to a high level 1: Yes, to some level 2: To a lesser level 3: No, not at all 4: Do not know	0: To a high level 1: To some level 2: To a lesser level (including no, not at all; do not know)
Item 2: Do you feel informed about possible side effects of medications for your heart disease?	0: Yes, to a high level 1: Yes, to some level 2: To a lesser level 3: No, not at all 4: Do not know	
Item 3: Do you feel informed about how long you should take medication for your heart disease?	0: Yes, to a high level 1: Yes, to some level 2: To a lesser level 3: No, not at all 4: Do not know	

Modified from Graversen et al. (**Paper II**), Appendix II.

PAPER III

Objective: To evaluate the mediating role of non-persistence to medication on the association between SEF and subsequent adverse clinical outcomes.

Design: Nationwide prospective cohort study with historical data

Study population: A total of 45,874 patients diagnosed with incident ACS (ICD-10: I200, I21, I24) between 1st January 2010 and 31st December 2017. Patients were identified from the NPR. Patients had to be ≥ 18 years, discharged alive from hospital after incident ACS admission, without prior IHD diagnoses within the five years preceding hospital admission, without any emigration during the five years prior to admission, and redeem both statin and antiplatelet therapy within 180 days following hospital discharge.

Data sources: All information was gathered from the National Danish Registers using the unique Central Personal Register number. Exposure variables consisted of an average five-year equalised disposable family income divided into tertiles (high, medium, low) as well as the highest obtained educational level categorised by ISCED (high, medium, low). Possible confounding variables comprised age, ethnicity, civil status, somatic comorbidities (CCI) and psychiatric comorbidities. Further, income and educational level were used as confounding variables when not used as exposure. Patients were categorised as non-persistent if they had a break in redemption lasting no less than 365 days. The time of categorised non-persistence was calculated as 90 days expiration following an earlier redeemed prescription. Thus, non-persistence was a joined variable with rather demanding requirements and was investigated as a time-varying mediating variable. The primary outcome was MACE, which was categorised as a composite measure that included all-cause death, cardiac death (ICD-10 codes: I20-I25) or cardiac readmission (ICD-10: I11.0, I21-22, I42.0, I42.6, I42.8, I42.9, I46, I49, I50, I60-64). The secondary outcomes included non-persistent to medication, all-cause death, cardiac death, and cardiac readmission. Mediation analyses were furthermore undertaken on all clinical outcomes.

Statistical analyses: Two study populations were created to evaluate the effect of income and education as any missing exposure variables would not fulfil requirements of being missing at random and thus not eligible for multiple imputation. All missing confounding variables were handled by multiple imputation, and the model was run by 10 rounds and included baseline patient characteristics as well as relevant exposure and outcome measures.

All analyses were stratified according to sex and reported as unadjusted, adjusted for age and ethnicity (model 1) and additionally adjusted for civil status, income/education and somatic as well as psychiatric comorbidities (model 2).

The associations between SEF and non-persistence to medication or risk of adverse clinical outcomes were analysed by discrete survival time analyses using inverse probability treatment weighting and cubic splines with a 90-day interval and tied with 4 knots. Number of events, event rates as well as cumulative incidences of primary and secondary outcomes analysed using the Aalen-Johansen estimator in relation to both exposures were presented.

Finally, the mediating role of non-persistence to medication was tested by population average effect. The total effect that was obtained in the discrete time survival analysis was split into a direct and indirect effect. The mediated proportion (indirect effect) was calculated as the proportion between the total and direct effect, and its 95% CI was obtained after bootstrapping with 100 samples. It should be noted that the mediating variable had to lie within the pathway between exposure (here: income/education) and outcome (here: MACE) to undertake mediation analysis [126,127]. All results were presented by HR and 95% CI.

The robustness of the results was investigated by several supplementary analyses, including different grace periods, different time limits of initiation of medication, a categorisation of income that followed the national definition of poverty, and by analysing non-persistence to statins and antiplatelets as individual drug treatments.

CHAPTER 5. RESULTS

The overall objective of this dissertation was covered by the three papers. **Paper I** addressed the role of SES on the referral process to CR. **Paper II** evaluated how patients' perceived information of pharmacological treatment was associated with subsequent non-adherence to medication. Finally, **Paper III** investigated the mediating role of non-persistence to medication on the association between SEF and MACE.

This section provides a compiled presentation of the results in **Papers I-III** and follows the same structure: a summarised presentation of study participants and the main results, including tables and Figures. Please confer to **Papers I-III** in the appendices for a more detailed description.

PAPER I

This passage summarises the results of **Paper I** that investigated socioeconomic barriers in the referral process to CR after incident ACS in the Northern Region Denmark.

Summarised characteristics of study population

A total of 1,229 patients were included in the study population of which 32.7% had STEMI, 57.8% NSTEMI, and 9.4% UAP. Most patients were men (73.8%), aged ≥65 years (51.9%), cohabiting (64.5%), unemployed/out of workforce (61%) and 42% had upper-secondary or vocational school as their highest obtained educational level [128]. These characteristics differed slightly in respect to STEMI, NSTEMI or UAP diagnosis.

Number of patients referred to cardiac rehabilitation

As depicted in Figure 3, a large proportion of patients (91.4%) received information about CR, whereas only 2/3 of the entire study population were willing to participate in CR. Of these, a total of 349 (40.9%) patients were referred to a community-based CR setting, whereas a total of 505 (59.1%) patients were referred to an in-hospital CR setting [128].

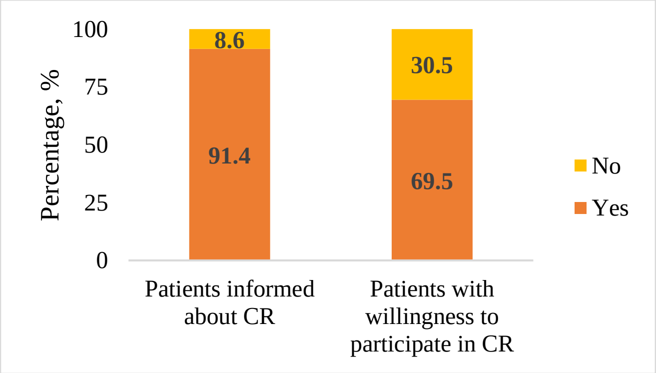


Figure 3. Proportion of patients in the referral process.
Abbreviation: CR, cardiac rehabilitation.
Modified from Graversen et al (**Paper I** [128]), Appendix I.

Association between SES and the referral process to cardiac rehabilitation

The following results were obtained in the adjusted analyses: the odds ratio of being informed was 1.40 (95% CI: 0.86-2.28) for medium level and 2.17 (95% CI: 1.01-4.64) for high level of income; being willing to participate in CR was odds 1.35 (95% CI: 0.94-1.94) for medium level and 1.55 (95% CI: 1.02-2.35) for high level of income; being assigned in-hospital CR was odds 1.14 (95% CI: 0.73-1.78) for medium level and 1.47 (95% CI: 0.91-2.36) for high level of income, compared to patients with a low level of income (figure 4). Similar tendencies, although weaker, were observed when estimating patients' educational level (Figure 4).

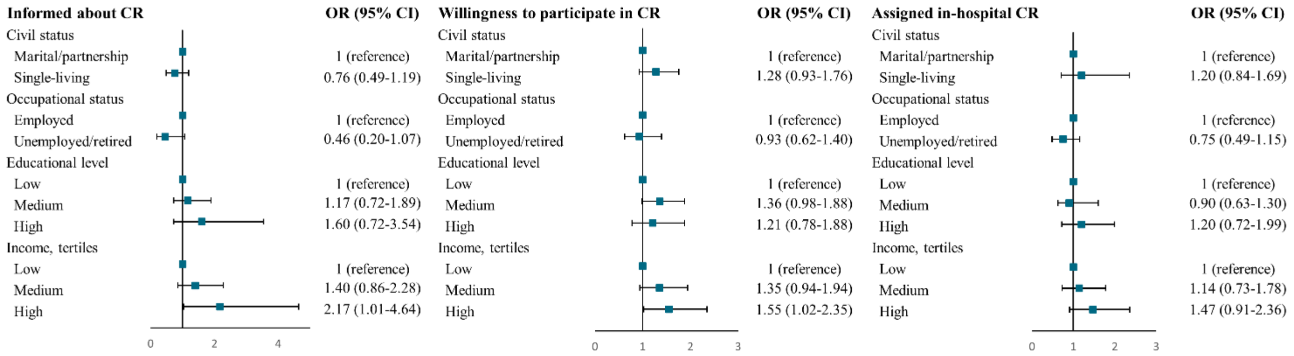


Figure 4. Association between SES and referral to cardiac rehabilitation.
Adjusted for age, gender, ACS diagnosis, CCI. Abbreviations: CR, cardiac rehabilitation; OR, odds ratio; CI, confidence interval.
Modified by Graversen et al (**Paper I**[128]), Appendix I.

PAPER II

This section presents select results of **Paper II** that investigates if patients' perceived adequate level of information of pharmacological treatment is associated with risk of non-adherence to antiplatelets, statins, ACE-inhibitors/ARBs and β-blockers following incident IHD.

Summarised characteristics of study population

In **Paper II**, a total of 829 participants answered the questionnaire, corresponding to 47.6% of the eligible study population. Most of the patients were men (67.2%), had a median age of 66.4 years, and were of ethnic Danish origin (92.8%). Only 25.5% of the participants reported 'To a high level' of perceived adequate information of pharmacological treatment, and these were to a greater extent younger, male, had a lower educational level, were cohabiting and disclosed received individual consultation regarding pharmacological treatment, compared to participants reporting 'To a lesser level' of adequate perceived level of information of pharmacological treatment.

Proportion of non-adherence to pharmacological treatment

As presented in Table 5, non-initiation ranged from 4.4% (β-blockers) to 13.2% (ACE inhibitors/ARBs). At 180 days of follow-up, measures regarding non-implementation and non-persistence of pharmacological treatment provided slightly divergent results in all pharmacological groups; however, results were more similar at 365 days of follow-up. Overall, the largest declines in non-implementation and non-persistence were observed within the first 180 days following initiation of treatment. The largest proportion was observed for ACE inhibitors/ARBs, and the smallest proportions were observed in antiplatelets and statins, respectively. The results are further available in **Paper II**, Appendix II.

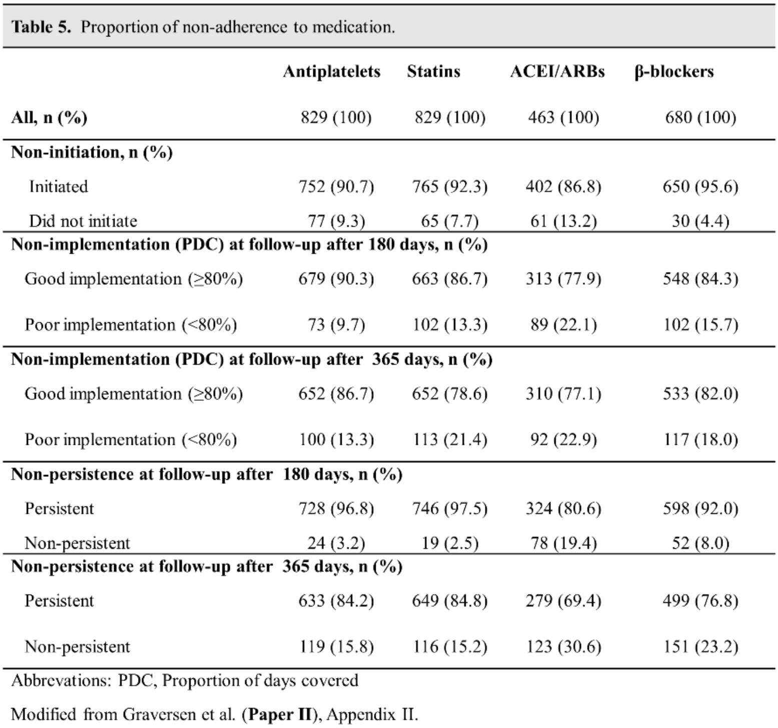


Table 5. Proportion of non-adherence to medication.

	Antiplatelets	Statins	ACEI/ARBs	β-blockers
All, n (%)	829 (100)	829 (100)	463 (100)	680 (100)
Non-initiation, n (%)				
Initiated	752 (90.7)	765 (92.3)	402 (86.8)	650 (95.6)
Did not initiate	77 (9.3)	65 (7.7)	61 (13.2)	30 (4.4)
Non-implementation (PDC) at follow-up after 180 days, n (%)				
Good implementation (≥80%)	679 (90.3)	663 (86.7)	313 (77.9)	548 (84.3)
Poor implementation (<80%)	73 (9.7)	102 (13.3)	89 (22.1)	102 (15.7)
Non-implementation (PDC) at follow-up after 365 days, n (%)				
Good implementation (≥80%)	652 (86.7)	652 (78.6)	310 (77.1)	533 (82.0)
Poor implementation (<80%)	100 (13.3)	113 (21.4)	92 (22.9)	117 (18.0)
Non-persistence at follow-up after 180 days, n (%)				
Persistent	728 (96.8)	746 (97.5)	324 (80.6)	598 (92.0)
Non-persistent	24 (3.2)	19 (2.5)	78 (19.4)	52 (8.0)
Non-persistence at follow-up after 365 days, n (%)				
Persistent	633 (84.2)	649 (84.8)	279 (69.4)	499 (76.8)
Non-persistent	119 (15.8)	116 (15.2)	123 (30.6)	151 (23.2)

Abbrevations: PDC, Proportion of days covered

Modified from Graversen et al. (**Paper II**), Appendix II.

Patients' perception of pharmacological treatment and non-adherence to medication

Overall, the multivariable regression analysis did not uniformly show a dose-dependent association between perception and risk of non-initiation (for results, please confer to **Paper II**, Appendix II).

Associations between perception of pharmacological treatment and risk of non-implementation and non-persistence were observed when comparing the three levels of perception of pharmacological treatment irrespectively of drug class; however, not all results were statistically significant. For example, among patients reporting 'To a lesser level', the hazard of non-implementation of antiplatelets was 1.67 (95% CI: 0.95-2.93), and the hazard of non-persistence of antiplatelets was 1.89 (95% CI: 1.10-3.25), compared to patients' reporting 'to a high level' of perception of pharmacological treatment at 365 days of follow-up (Figure 5). The results are further available in **Paper II**, Appendix II.

Summarised, patients that reported lower levels of perceived information of pharmacological treatment had increased risk of non-implementation and non-persistence to medication, although not all results were statistically significant. The sensitivity analyses confirmed the findings of these results. These, along with further results, are presented in Appendix II.

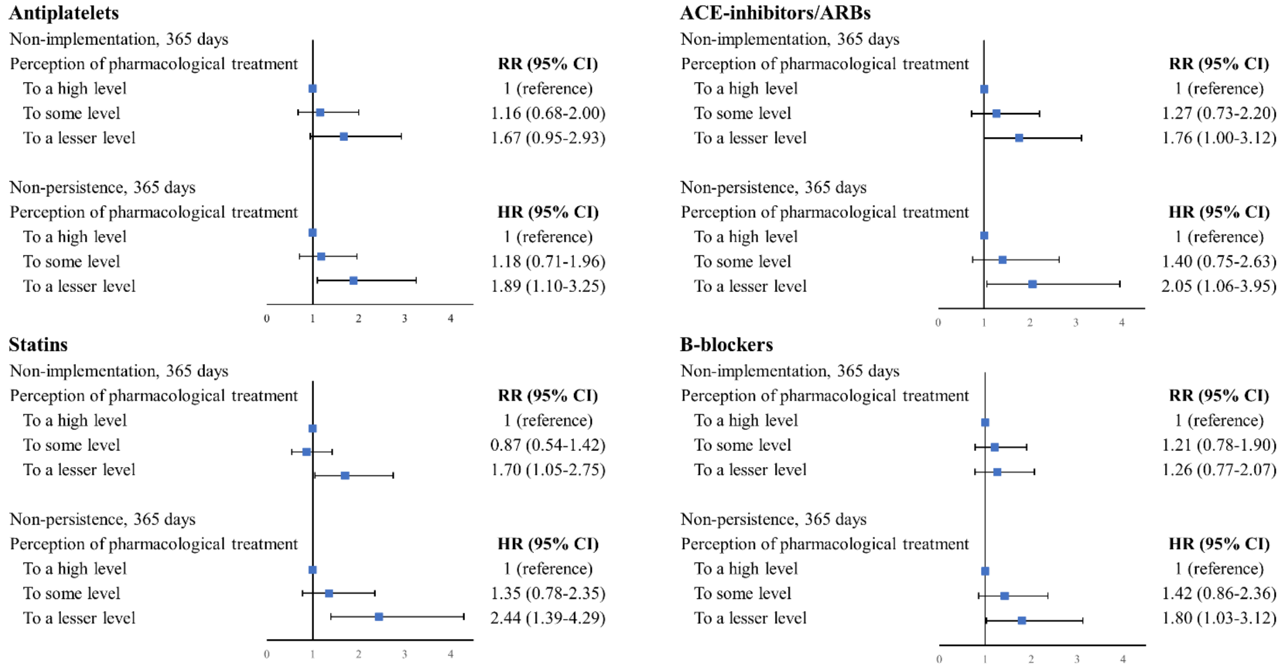


Figure 5. Non-implementation and non-persistence of medication.
Abbreviations: RR, relative risk; HR, hazard ratio; CI, confidence interval.
Modified from Graversen et al. (**Paper II**), Appendix II.

PAPER III

Below is a presentation of select results from **Paper III** that assess socioeconomic inequality in risk of adverse clinical outcomes and how this is mediated by non-persistence to antiplatelet and statin therapy in patients with incident ACS stratified by sex.

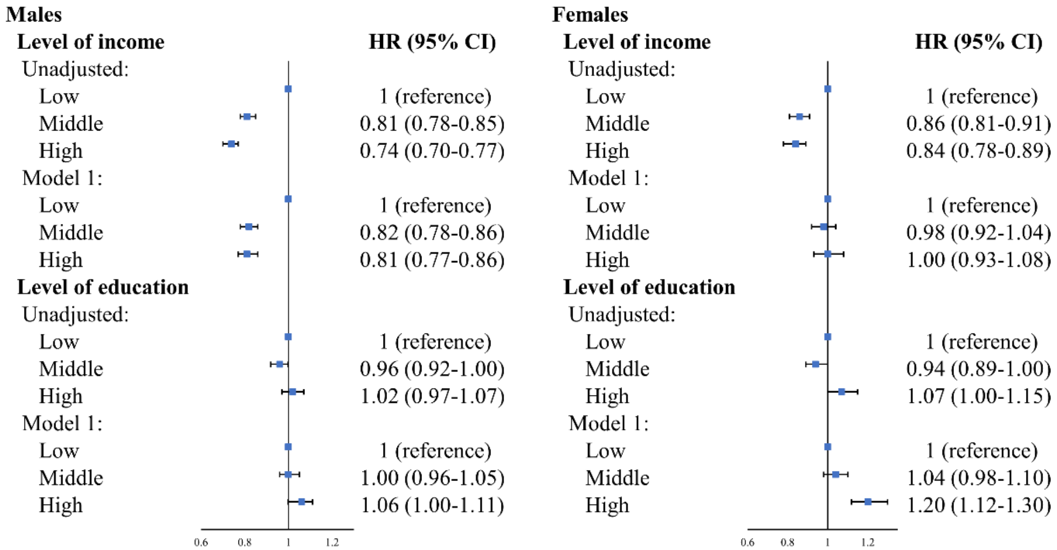
Summarised characteristics of study population

As presented in **Paper III** in Appendix III, a total of 45,874 patients with incident ACS were included in the entire cohort (mean age was 65.5 years and 67.7% were men). Of those, 45,781 patients were included in study population I (income as exposure) and 44,441 patients were included in study population II (education as exposure). Patients were followed for a median time of approximately 3.5 years.

SEFs and risk of non-persistence to medication

A total of 16,958 (37.0%) of the included study participants were categorised as non-persistent to medication during follow-up. In the adjusted analyses, higher levels of income significantly lowered the risk of non-persistence to medication among men, but not women; moreover, the patients' educational level was not associated with risk of non-persistence to medication in the unadjusted and adjusted analyses (Figure 6). Results are further available in **Paper III**, Appendix III.

In the analyses assessing non-persistence to statins and antiplatelets as disjointed measures, the level of non-persistence was approximately 24% for both drugs (results not shown, please cf. Appendix III).



Males	HR (95% CI)	**Females**	HR (95% CI)
Level of income		**Level of income**	
Unadjusted:		Unadjusted:	
Low	1 (reference)	Low	1 (reference)
Middle	0.81 (0.78-0.85)	Middle	0.86 (0.81-0.91)
High	0.74 (0.70-0.77)	High	0.84 (0.78-0.89)
Model 1:		Model 1:	
Low	1 (reference)	Low	1 (reference)
Middle	0.82 (0.78-0.86)	Middle	0.98 (0.92-1.04)
High	0.81 (0.77-0.86)	High	1.00 (0.93-1.08)
Level of education		**Level of education**	
Unadjusted:		Unadjusted:	
Low	1 (reference)	Low	1 (reference)
Middle	0.96 (0.92-1.00)	Middle	0.94 (0.89-1.00)
High	1.02 (0.97-1.07)	High	1.07 (1.00-1.15)
Model 1:		Model 1:	
Low	1 (reference)	Low	1 (reference)
Middle	1.00 (0.96-1.05)	Middle	1.04 (0.98-1.10)
High	1.06 (1.00-1.11)	High	1.20 (1.12-1.30)

Figure 6. Level of income and education and risk of non-persistence to medication stratified by sex. Model I: adjusted for age and ethnicity. Abbreviation: HR, hazard ratio; CI, confidence interval Modified from Graversen et al. (**paper III**), appendix III.

SEF and risk of MACE and the mediating role of non-persistence

A total of 16,365 (35.7%) patients experienced MACE during follow-up. In both unadjusted and adjusted analyses, a higher level of education and income significantly decreased the risk of MACE irrespectively of sex (Figure 7).

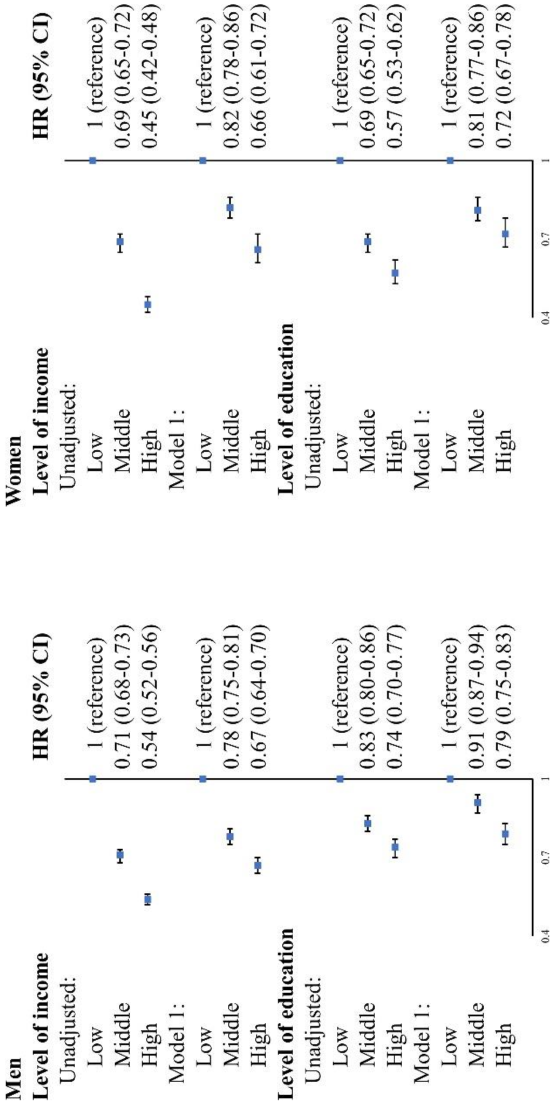


Figure 7. Level of income and education and risk of MACE stratified by sex.
Model I: adjusted for age and ethnicity. Abbreviation: HR, hazard ratio; CI, confidence interval.
Modified from Graversen et al. (**Paper III**), Appendix III.

Because of the above-mentioned results, the main requirement for conducting the mediation analysis (the mediator lies on the pathway from exposure to outcome) was only fulfilled when assessing the association between income and risk of MACE, and only in men. Compared with low-income men, the mediating proportion of non-persistence to medication was 17.5% (95% CI: 15.0%-20.1%) for middle-income men and 12.6% (95% CI: 11.1%-14.1%) for high-income men (figure 8). Results are further available in **Paper III**, Appendix III.

Accordingly, the lower levels of non-persistence to medication in men with higher levels of income could partly explain their lower risk of MACE. Further analyses investigated the mediating role of the disjointed measures of non-persistence to statins and antiplatelets and showed that statin therapy had a mediating proportion of approximately 16-18% and that antiplatelets had a mediating proportion of approximately 6-12% on the income-related gradient in risk of MACE among men (results not shown; please cf. **Paper III**, Appendix III).

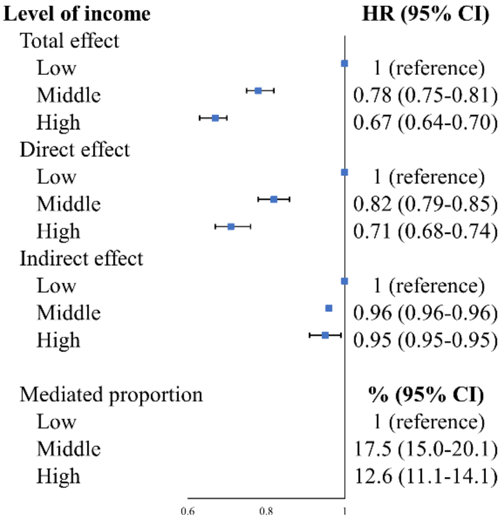


Figure 8. The mediating effect of non-persistence to medication on the income-related inequality in risk of MACE among men.
Abbreviation: HR, hazard ratio; CI, confidence interval.
Modified from Graversen et al. (**Paper III**), Appendix III.

CHAPTER 6. DISCUSSION

In the following section, the main findings of the dissertation are presented and discussed in relation to the existing literature. Thereupon, the methodological considerations of the three papers forming this dissertation are outlined.

MAIN FINDINGS

This dissertation aimed to explore barriers in secondary cardiovascular prevention. First, the impact of SES on the referral process to CR was investigated (**Paper I**). The results indicated a dose-response tendency showing that especially patients' level of income was inversely related CR referral, irrespectively of division into phases. Next, patients' perception of pharmacological treatment showed a dose-response relationship with non-adherence to medication during follow-ups 180- and 365 days after incident IHD diagnosis, thus providing a new aspect of barriers to medication (**Paper II).** Finally, significant associations between patients' income and education levels and risk of MACE were found in a study population with incident ACS during a median of about 3.5 years of follow-up (**Paper III**). Non-persistence to medication mediated the income-related inequality in risk of MACE by 12-17%, but only in men.

SOCIOECONOMIC BARRIERS IN REFERRAL TO CARDIAC REHABILITATION

As previously mentioned in this dissertation, studies have reported that one too small a proportion of patients are referred to CR, despite guideline recommendations and different position papers highlighting the importance [3,9,129]. To date, no previous studies have looked in detail on the importance of SES and the different phases in the referral process to CR. Interestingly, results from **Paper I** imply that not all eligible patients diagnosed with ACS are referred to CR and that there is social inequality in the referral process [128]. This knowledge may help identify at what phase to intervene in order to decrease the socioeconomic barriers and thereby gain a higher proportion of patients to be referred to CR.

Besides being less referred, patients with lower SES also have a higher risk of poor attendance and completion of CR [41,43,130]. Such have long been discussed, along with the identification of other predicting factors, including female sex and advanced age [3]. This emphasises the challenges of providing proper treatment to patients, irrespectively of their risk factors. Thus, there is room for improvement, also highlighted in the most recent guideline on management of patients presenting without persistent ST-segment elevation that called for attention to increase referral to CR [129]. To increase attendance and completion to CR among patients with lower SEF, it is necessary to increase referral in this patient group [129].

Social inequality in referral to CR has rather scarcely been illustrated in previous studies. In the two most recent EUROASPIRE surveys (IV and V) [43,57], patient characteristics were evaluated in relation to use of CR. In these separately conducted survey-based studies, approximately 8,000 patients were gathered from approximately 25 European countries with incident or recurrent coronary event or revascularisation. In the 2018 study, low educational level significantly lowered the chance of receiving advice of CR within three months following hospital discharge [43]. However, scarce information was provided regarding the distribution of patients according to their educational level, also after looking in the original EUROASPIRE IV study [131], but the findings were obtained from a population with a lower proportion of patients having a high educational attainment otherwise found in a high-income country such as Denmark. In the EUROASPIRE V study, more comprehensive material on sociodemographic information was available, but again, the distributions of educational level and self-perceived income illustrated the mixture of low-income and high-income countries participating in the survey. Regardless, lower educational level, and not income, was associated with increased risk of not being advised to CR both among men (OR: 1.75 (95% CI: 1.36-2.24) and women (OR:1.55 (95% CI: 1.04-2.32) [43]. Further, the 2018 EpiHeart cohort study including 853 patients demonstrated higher educational level (>4 years of schooling) and monthly household income (>€1,500) to be associated with referral to CR (OR: 1.72 (95% CI: 1.07-2.76) and OR: 2.79 (95% CI: 1.65-4.72)) [44]. However, the dichotomisation of patients' highest educational attainment may have hidden dose-response associations, and data was based on self-reported measure of referral to CR at the six-month follow-up.

A review study by Cortes also found that educational level and marital status influenced referral to CR [132]. However, the finding of educational level was based on unadjusted results from 1998-1999 [133]. In fact, the association was attenuated after multivariable adjustment; furthermore, the study included prevalent cases eligible for CR referral and information on referral and sociodemographic variables were all obtained from self-completed questionnaires [133].

Other and larger review studies report socioeconomic variables as barriers to CR referral, but not seldom the used references were based on prevalent cases or did not differentiate between referral and participation in CR [33,134,135].

None of above-mentioned studies investigated the phases of the referral process in relation to patients' SEF. However, barriers at both system and patient level have in other relation to CR been documented, including geographic factors, travel time and low self-efficacy among patients [41,136]. Accordingly, **Paper I** contributes with new information on challenges in referral to CR which may be target for interventions aiming at increasing the low proportion of patients being referred.

PERSPECTIVES OF PATIENT-REPORTED EXPERIENCES AS BARRIER TO SECONDARY PHARMACOLOGICAL TREATMENT

The results of **Paper II** implied that patients' perception of receiving adequate information of pharmacological treatment was associated with subsequent risk of non-adherence to cardiovascular medication. This association was found to be dose-dependent, although not all results were statistically significant after adjustment for confounding variables. Moreover, only 25.5% of the patients reported a high level of perception of medication, which illustrates inadequacy in informing patients properly in their pharmacological treatment. This finding would not have been recognised without including patient-reported experience measures, which emphasises the potential of using patient experiences to improve clinical practise.

When estimating risk of non-initiation in **Paper II**, the importance of patients' perception was not clear, especially in the ACE-Inhibitor/ARB and β-blocker drug groups. This finding implies that the decision of starting treatment is less influenced by an overall perception of medication.

Noteworthy, research suggest patients' perception to turn more negative during long-time treatment [137] and that patients, in general, have a continuous need of information regarding their medical treatment [81]. In **Paper II**, the effect of patients' experiences with medication did not alter much when comparing 180 and 365 days of follow-up. At these time points, the tendency was, with few exceptions, that lower levels of perceptions' increased risk of non-implementation and non-persistence to medication. Thus, the harmful effect of low perception was strengthened from the time after initiating pharmacological treatment. In clinical practice, this finding, along with the knowledge from other studies that patients' beliefs about medication change over time in a negative direction, underlines the importance of awareness towards patients' experience of taking medication when consulting patients during routine checks in the period following cardiac diagnosis.

It should be noted that the results from **Paper II** showed dose-dependent tendencies and were interpreted as clinically relevant despite not being statistically significant in a conventional manner. Accordingly, it is important to evaluate the tendency in results, as several issues may impact if a significant level is reached, e.g. size of study population. Finally, the exposure variable consisted of only three items and most likely did not sufficiently reflect all issues regarding patients' perspective on their information of pharmacological treatment. Further, a few items had almost 10% missing, and interpretation of these findings must be done with careful consideration as we cannot be certain if some underlining causes could explain this pattern.

The used exposure measure covered a patient journey from incident hospital admission to the outpatient setting and could thus not be used to identify single inadequacies in this period. Nonetheless, the results illustrated the potential of gathering information from patients to improve secondary cardiovascular preventive treatment. This is also consolidated by research finding a discrepancy in patients' and clinicians' perceptions of provided inpatient care and patient knowledge; accordingly, most patients reported never being informed about possible adverse effects to their newly prescribed medication, while only a minor proportion of physicians reported to never inform about this [138]. Further, studies have investigated the association between patients' beliefs about medication in relation to self-reported adherence measures in patients with IHD. In the study by LaPointe et al., which was a follow-up survey on 973 patients diagnosed with ACS, the researchers reported that patients' perceived necessity of their medication lowered the risk of non-adherence to β-blockers (OR: 0.94, 95% CI:0.91-0.98), ACE-inhibitor/ARBs (OR: 0.94, 95% CI:0.90-0.98) and lipid-lowering medication (OR: 0.96, 95% CI:0.92-1.00) at three months follow-up [77]. Moreover, perceived concern was found to be associated with higher risk of non-adherence to β-blockers (OR: 1.08, 95% CI:1.04-1.13), ACE-inhibitor/ARBs (OR: 1.07, 95% CI:1.02-1.11) and lipid-lowering medication (OR: 1.09, 95% CI:1.05-1.14). In the study by Byrne et al., patients' beliefs about medication predicted risk of non-adherence to medication and accounted for 7% of the variance of adherence to medication among the included (prevalent) patients [78]. However, both studies used prevalent cases, and this may cause a mix of patient characteristics, but the finding consolidates that clinicians should prioritise informing patients thoroughly when prescribing medication to avoid misunderstanding and unnecessary concerns.

In **Paper II**, three items were used to explore patients' perception of pharmacological treatment, which is in contrast to other studies using validated scales [77–79]. The summarised item showed sufficient internal consistency (estimated by McDonald's Omega) and was therefore used in the analyses. The observed associations were not influenced by this simple measure of exposure and the results consolidated earlier observation, as these were gathered using register-based adherence measures. Last, the timespan that inevitably happens when using patient-reported experience measures may help patients differentiate between trivial frustrations and more important flaws [139], despite researchers' reservation due to risk of poor recall introduction [140]. Consequently, combining the results of **Paper II** with the existing literature may imply patient-reported experience measures to be beneficial to help understand shortcomings in secondary cardiovascular preventive treatment and identify areas of improvement in quality of care.

SOCIAL GRADIENT IN RISK OF ADVERSE CLINICAL OUTCOMES AND THE MEDIATING ROLE OF NON-PERSISTENCE TO MEDICATION

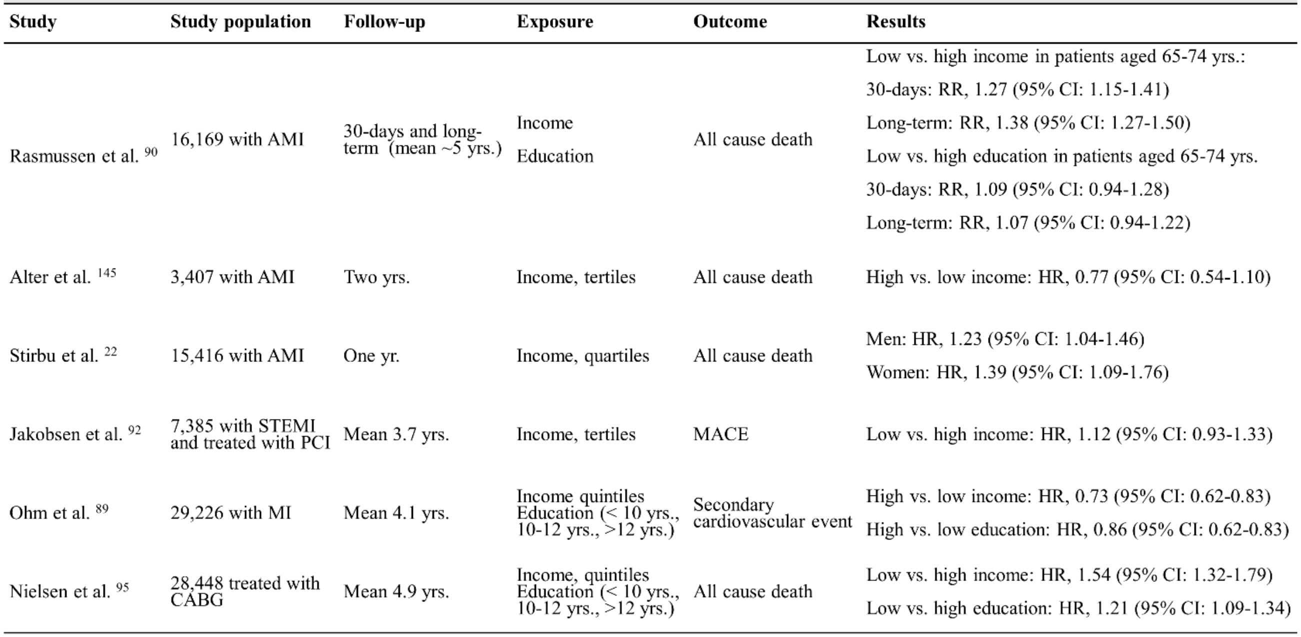
In **Paper III**, patients' income and educational levels were associated with risk of MACE and all secondary clinical endpoints. However, only the level of income had an association with risk of non-persistence to medication and solely in men.
This income-related inequality is worrying, as recent studies have reaffirmed that low adherence to medication increases the risk of mortality in patients with cardiovascular disease despite the introduction of interventional treatment [141,142].

The results of **Paper III** further embrace the problem that the overall finding of general improvement of cardiovascular mortality has predominantly been among the more affluent groups of patients. This social paradox in egalitarian welfare states has earlier been introduced as 'the Nordic paradox' [143]. An example of this could be the absolute reduction in mortality, but an increased relative mortality according to SEF implicating that the reduced mortality largely was observed in people with higher compared with lower educational level [144]. Three plausible reasons may cause low SEF to increase patients' risk of mortality: First, the material inequality has increased over the years and a considerable amount of people now live in relative poverty, which increases their risk of unhealthy behaviour and comorbidities. Second, improvement of the educational system has reduced the amount of people with a lower educational level, thus making them a more vulnerable group. Third, better educated patients have higher health literacy, thus making them able to benefit the most from the healthcare system and are more socioeconomically advantaged, allowing them to make necessary lifestyle changes [143].

Below is a condensed presentation of research that demonstrates inequality in adverse clinical outcomes, also in settings with equalitarian healthcare structures (Table 6). In 2006, a Danish cohort study reported an inverse association when comparing the highest and lowest income level on risk of mortality at 30day follow-up (RR: 1.27 (95% CI: 1.15-1.41)) and long-term follow-up (RR: 1.38 (95% CI: 1.27-1.50)) [90]. Educational level showed a similar tendency, although not being statistical significance after adjustment, and the association was hypothesised to be mediated by income. Almost similar associations have been demonstrated by studies from Canada (2006) [145], the Netherlands in 2012 [22], Denmark in 2012 [92] and Sweden in 2018 [89] and 2020 [95]. It should be mentioned that although the Canadian study reported an inverse association between income and 2-year mortality, this association was greatly attenuated after adjustment for age, past cardiovascular events, and current vascular risk factors and thus suggesting that risk factors substantially attributed to the observed association [145].
In summary, all studies report patients' income level to be significant and inversely associated with risk of adverse clinical event, and some also find lower educational levels to increase risk of adverse clinical event. The results of **Paper III** agree with

the findings of both income and educational levels to be associated with risk of adverse clinical event and irrespectively of sex.

Table 6. Overview of cohort studies evaluating inequality in risk of adverse clinical outcomes following coronary heart disease.



Study	Study population	Follow-up	Exposure	Outcome	Results
Rasmussen et al. [90]	16,169 with AMI	30-days and long-term (mean ~5 yrs.)	Income	All cause death	Low vs. high income in patients aged 65-74 yrs.: 30-days: RR, 1.27 (95% CI: 1.15-1.41) Long-term: RR, 1.38 (95% CI: 1.27-1.50)
			Education		Low vs. high education in patients aged 65-74 yrs. 30-days: RR, 1.09 (95% CI: 0.94-1.28) Long-term: RR, 1.07 (95% CI: 0.94-1.22)
Alter et al. [145]	3,407 with AMI	Two yrs.	Income, tertiles	All cause death	High vs. low income: HR, 0.77 (95% CI: 0.54-1.10)
Stirbu et al. [22]	15,416 with AMI	One yr.	Income, quartiles	All cause death	Men: HR, 1.23 (95% CI: 1.04-1.46) Women: HR, 1.39 (95% CI: 1.09-1.76)
Jakobsen et al. [92]	7,385 with STEMI and treated with PCI	Mean 3.7 yrs.	Income, tertiles	MACE	Low vs. high income: HR, 1.12 (95% CI: 0.93-1.33)
Ohm et al. [89]	29,226 with MI	Mean 4.1 yrs.	Income quintiles Education (< 10 yrs., 10-12 yrs., >12 yrs.)	Secondary cardiovascular event	High vs. low income: HR, 0.73 (95% CI: 0.62-0.83) High vs. low education: HR, 0.86 (95% CI: 0.62-0.83)
Nielsen et al. [95]	28,448 treated with CABG	Mean 4.9 yrs.	Income, quintiles Education (< 10 yrs., 10-12 yrs., >12 yrs.)	All cause death	Low vs. high income: HR, 1.54 (95% CI: 1.32-1.79) Low vs. high education: HR, 1.21 (95% CI: 1.09-1.34)

Abbreviations: AMI, acute myocardial infarction; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; yr.(s), year(s); MACE, major adverse cardiac event; RR, relative risk; HR: hazard rate ratio; CI, confidence interval.

The two above-mentioned Swedish studies further investigated how non-adherence to medication influenced the association between SEF and adverse clinical outcome by including the variable as a confounding variable in their regression analyses [89,95]. Both found non-adherence to attenuate the results; however, non-adherence more likely mediates this association and the use of the variable as a confounder may obscure the association and introduce overadjustment [126]. To our knowledge, the mediating effect of non-persistence to medication in relation to SEF and risk of MACE has not been investigated before.

A total of 37.0% of the patients were categorised as non-persistent to medication in **Paper III**. There was an income-related gradient in risk of non-persistence in men, but not women. However, women had a higher event rate of non-persistence, compared to men, which suggested that non-persistence in women was related to other factors than income and educational level in **Paper III**. The mediation analysis could thus only be performed in relation to income-level and risk of MACE in men.
Interestingly, the proportions of non-persistence to antiplatelet and statin therapy using disjoined measures were approximately 24%. Thus, many patients continued being persistent to one of the included drugs as the level of non-persistence to medication using the joined measure was 37%. We therefore performed mediation analyses with separate measures of persistence in relation to statin and antiplatelet therapy. Non-persistence to statin therapy had a higher mediating role (16-18%) compared with non-persistence to antiplatelet therapy (6-12%).
The finding of a clinical important mediating role in relation to income among men should be interpreted in the context of the study setting in **Paper III**. Thus, we hypothesise that non-persistence to medication would have a larger mediating role in study populations/settings with higher proportions of non-adherence to medication, especially observed in middle and low-income countries [63,64].
A recent Danish study reported similar mediating effect of pharmacological treatment on risk of mortality in patients with incident heart failure. The Danish study investigated the cohort with stratification on cohabiting status in addition to sex-stratified analyses and found that single-living low-income men would decrease their risk of one-year mortality by 1.0% (95% CI: -1.4;-0.5%) if they had the same probability of drug initiation as higher-income patients [94].

Social inequality in the risk of adverse clinical outcomes is still not fully understood and other mediating causes need to be explored. For example, smoking, high blood pressure, body mass index and physical inactivity have been reported to mediate the association between educational level and risk of incident cardiac disease [146,147]. Therefore, these mediating factors could potentially also mediate the social gradient in risk of adverse clinical outcomes – especially in populations with high level of persistence to medication.

Combining the results from this dissertation with existing literature implies that barriers to secondary preventive treatment may emerge at different stages and may be characterised by predisposing factors or factors occurring during the patient-journey from hospitalisation to daily living with a cardiac disease. These may range from the referral process (**Paper I**), to knowledge based on patients' experiences regarding adequate information of pharmacological treatment (**Paper II**), and to an understanding of non-persistence to medication as mediator of the association between SEF and risk of MACE (**Paper III**). Thus, this dissertation supports continued awareness regarding socioeconomic barriers to secondary preventive therapy and goes a step further to understand reasons to the paradox of social inequality in a society with equalitarian healthcare.

METHODOLOGICAL CONSIDERATIONS

Below, a brief sample of considerations is provided when using socioeconomic measures in research and is followed by a presentation of the different methodological considerations that should be considered when interpreting the results of the three papers included in the present dissertation.

In observational studies, issues relating to selection, information and confounding are threats to the internal validity whereas the external validity refers to the generalisability; that is, can the obtained results be applied to other populations besides the target population [126]?

Definition of socioeconomic factors and its implications in research

There is no clear definition of socioeconomic measures and which to include in research and it is generally recommended that the research question should facilitate the decision on how to define and classify socioeconomic measures. Further, definitions such as SES, SEF and socioeconomic position shift interchangeably although they conceptionally may cover slightly different areas [148]. Nonetheless, all definitions comprise categories of social group, education, income, occupation and to a lesser distinct civil status, and it is recommended to use several indicators simultaneously and try to avoid combining them into one indicator [148,149]. The indicators capture different conceptions and are interpreted in the context of the research. The interpretation of the indicators included in this dissertation is inspired by the work of Solar et al.[149] and Galobardes et al. [150]. Thus, income is thought to capture material resources and living standards; education captures the receptiveness of health care information; occupation is closely related to income and captures social network and autonomy; and civil status captures social support [149,150]. All four socioeconomic indicators were used in **Paper I** as they were hypothesised to have an individual influence on the outcome (referral to CR). Conversely, only level of income and education were included as exposure variables in **Paper III** due to an a priori hypothesis of having a stronger association with the outcome (MACE) opposed to civil status and occupation. The latter two were instead hypothesised as possible confounding or intermediate variables. Further, considerations regarding if it would be most beneficial to introduce adjustment of other socioeconomic variables or keep each variable unadjusted and thereby risk introduction of collinearity ought to be evaluated. There is no simple answer, and two different approaches have accordingly been used in this dissertation. In **Paper I**, no adjustment for other socioeconomic variables was made as each variable was hypothesised to have an independent association with referral to CR. In **Paper III,** two adjustment methods were implemented and included one with and one without adjustment of other socioeconomic variables and baseline comorbidity. The obtained results were only attenuated to a minor degree, and it was decided to use the findings from the model with the least confounding variable as the preferred multivariate model. Every choice is debatable, which advocates research methods to be transparent and publicly displayed, e.g. by DAGs.

Selection issues

Selection issues may arise if there is a difference in the estimated effect provided from a study population compared to what is observed if all information was available [151]. Such issues may occur if there is a substantial difference in the relationship between exposure and outcome among the study participants and non-participants or if any substantial loss-to-follow is differentiated between the exposure groups [126]. Problems relating to selection could arise in all three papers, although they are assessed to be at a minimal level.

In **Paper I**, the study population was rather small and gathered after admission at one hospital. More representative and conclusive findings would be expected when using larger study populations with more organisational and geographical variations. Patients excluded from the final study population in **Paper I** had lower SES than the included study population; however, any risk of bias introduction was limited, as a large proportion of these patients were categorised to receive CR elsewhere, i.e. after being transferred to another department or hospital.

Paper II used information obtained from a national survey with data collection done 10-22 months after hospital discharge in 2013 [124]. As one-year mortality after incident myocardial infarction is approximately 15% [22], this delay most likely resulted in deaths among patients admitted with incident IHD in 2013. It remains uncertain if these patients represented people being less adherent to medication or if their death was caused by a severe level of the disease; nonetheless, selection issues would only occur if the deceased patients had a different association between perception of pharmacological treatment and non-adherence to medication, which is considered to be less likely.

Almost 50% of the invited patients answered the questionnaire, bringing the response proportion at a moderate level. Non-respondents were in general at a slightly higher risk of not initiating and not being adherent to medication. Thus, respondents may more likely be healthier adherers and this could underestimate the proportion of patients being categorised as non-adherent in the study population. The implication of non-respondents on the estimated association between perception of pharmacological treatment and subsequent non-adherence to medication is difficult to quantitate;

however, it is recognised that patients with limited health literacy are older and lower educated [152], which also was observed in the population used in **Paper II**. It is therefore theoretically possible that perceived pharmacological treatment would have been reported higher or lower among non-respondents due to lower health literacy and expectation of provided healthcare. Nonetheless, non-response would only cause selection issues if non-responders had a different association between exposure and outcome compared to responders. In short, it cannot be ruled out that the proportion of non-responders may have affected the size of the estimates in **Paper II**.

Selection issues could also occur in **Papers II** and **III** when restricting the study population on initiation of pharmacological treatment as this opened an otherwise blocked path $(Exposure \rightarrow Intermediate \leftarrow Unobserved \rightarrow Outcome)$ [153]. In other words, the estimate of exposure and outcome were conditioned on initiation of pharmacological treatment and thereby enabling a combination of forces to influence both initiation and occurrence of outcome. Such issue could pose a problem for generalisability to the target population and it was therefore important to evaluate if this happened [126]. Consequently, sensitivity analyses were undertaken in both papers that evaluated different time limits of initiation. Further, a sensitivity analysis was performed in **Paper III** that categorised those not initiating both drugs as being primary non-adherent instead of having this as an exclusion criterion before study entry. All analyses supported the main results.

The outcome measures were provided from the national registers in **Papers II** and **III** which, aside from a few patients emigrating during the study period, enabled an essentially complete follow-up on outcome measures. The Cox proportional hazard regression model used as the time-to-event analysis enabled us to include time-to-censuring, which occurred if a patient emigrated or did not experience an event (time-to-non-event); moreover, this regression method enabled concomitant control of confounding variables [154]. In **Paper III,** discrete survival time analyses were used to obtain population-based average effect presented by HR and 95% CI. Results could have been presented by ordinary Cox regression models; however, as non-persistence to medication was a time-varying mediator, this model was the best fitted when estimating the role of non-persistence on outcome in the subsequent mediation analysis.

Information issues

Information issues may arise in cohort studies when the measurements of the included variables are not reliable. When addressing categorical variables, these errors are often labelled ‘misclassification’ and may be either differential or non-differential depending on their relation to the exposure, outcome or both [126].

Study population

The study populations in **Papers I** and **III** were identified as patients being diagnosed with ACS. In **Paper I**, the study population was identified using a questionnaire that was not created for scientific purposes; accordingly, there was a small risk of not including all patients diagnosed with ACS in the study period if fulfilled questionnaires were not stored correctly in the secretary office and thus not found during the gathering of data material. This loss was accounted as unsystematic and was therefore not considered to pose a problem for the introduction of information issues. All diagnoses were afterwards validated using the NPR, and in the event of any discrepancy, the register-based diagnosis was preferred. **Paper III** identified the patients directly in the NPR. Similar for both papers, the identifications were based on registrations not created for scientific purpose and could pose a problem if there was an inaccurate registration of diagnosis. However, the ACS diagnosis in the NPR is very accurate with a positive predictive value of for myocardial infarction ≥ 90% and between 80-90% for incident UAP, and it is unlikely to be associated with the exposure [155]. In **Paper II**, the study population was gathered from a national survey after originally identifying patients with IHD from the NPR. A total of 160 patients stated that they were not diagnosed with heart disease in 2013. This misclassification of patients most likely occurred due to the NPR being updated after the study population had been drawn or that they were diagnosed with IHD or another heart between 2008-20012. Accordingly, they were not diagnosed in 2013 and therefore did not participate in the survey. Furthermore, 374 patients initial categorised as incident cases of IHD were later classified as being prevalent cases due to an update in NPR and were therefore excluded from the study population. The observed misclassification of patients was non-differential as it was not related to neither exposure nor outcomes.

Misclassification on exposure

Information on socioeconomic exposure variables in **Papers I** and **III** were obtained from national registers and all exposures had high validity [106–108,110]. However, the use of register-based socioeconomic variables does not eliminate the risk of not capturing the full extent of the indicators.

Further, missing information on exposure variables caused exclusion of the study as these did not fulfill requirements of being missing at random and could therefore not be multiple imputed. This led to complete cases analysis in **Paper I**. Further, it only downsized the study populations in **Papers I** and **III** to a lesser extent.

The exposure variable in **Paper II** was provided from a national survey estimating patient reported perception of pharmacological treatment in relation to their IHD. The used items in the survey both assessed perceptions of pharmacological treatment provided at the present time of the questionnaire as well as in the time span starting at hospital diagnosis. Accordingly, any change in perception was hypothesised to be minimal and if poor recall occurred, this would most likely result in non-differential misclassification instead of systematic bias as any misclassification would be independent of the exposure.

When constructing a survey, it is always important to estimate if the items capture what was intended. The vast development of the survey based on patient interviews and pilot testing strengthened the content validity but other approaches in survey

development such as using theoretical frameworks might have improved the data quality. For example, the aim of the survey was not to undertake **Paper II** and it would have strengthened the exposure variable if the questionnaire items regarding perception of medication had been developed on scientific theory and not merely empirically founded. If the former has been done, the exposure variable evaluating patients' perception could most likely have been more accurate.
The three items used in **Paper II** were pooled into one and the McDonald's Omega concluded a moderate internal consistency of this new measure.
Last, any risk of bias was limited by measuring patient experience rather than satisfaction as this may be overrated due to gratitude [83].

Misclassification on outcomes

In **Paper I**, the outcome variable was gathered from the questionnaire. As data was gathered by a physical registration, there may be a risk of incorrect registration either when the clinician fulfilled the questionnaire or at time of data entry in the Rehab-North Register. However, 200 questionnaires were re-evaluated and there was no sign of any systematic flaw in the data handling from paper to electronic database. If any presence of misclassification, this would be suspected to be randomly distributed between the socioeconomic variables and classified as non-differential thereby leading bias towards the null [126].

In **Papers II** and **III**, the outcomes were obtained from the National Danish registers. The DNPR provided information on the outcome variables in **Papers II** and **III**, which eliminated risk of recall bias when assessing non-adherence to medication. The register provided information on reimbursed prescription but not if these were taken as intended or there were any reasons for discontinuation. However, all these issues were considered non-differential misclassification as they did not depend on the exposure. Further, the methodologically restricted classification of non-implementation and non-persistence to medication using two different methods to obtain valid outcome measures implied similar tendencies of an association with perception of pharmacological treatment (**Paper II)**. Accordingly, misclassification of non-adherence to medication was not considered to pose a problem.
Outcome measures in **Paper III** further comprised all-cause death, cardiac death and cardiac-related readmission that was obtained from the NPR. The overall PPV for cardiovascular diagnoses in the NPR is 88%, which provides high validity to the acute cardiac readmission [155]; however, the deviating PPV in the different cardiac diagnoses might represent a risk of misclassification, but this would be non-differential as it was not associated with the exposure of educational or income level. Risk of misclassification of all-cause death did not pose a problem [156]; however, the quality of reporting cardiac-related cause of death depends on physicians' notion, and no study has yet validated this measure.

Confounding

Observational studies are susceptible to confounding, which may bias the estimate of the association between exposure and outcome if left unhandled [126]. When selecting which confounding variable to adjust for, it is important to avoid overadjustment as this most likely affects precision and increases net bias [157]. Common to all three papers, the selection of possible confounding variables to be controlled for were identified a priori by literature review and depictured using DAGs, which enabled minimal sufficient adjustment, although a few possible confounding variables (e.g. smoking) could not be adjusted for. Further, selected confounding variables were grouped according to recognised categories, e.g. CCI.

In **Paper I**, the variable measuring comorbidity only covered diagnoses the year prior to ACS diagnosis, which increased risk of residual confounding. Results were further attenuated after adjustment, and it cannot be ruled out that unaccounted confounding occurred. It could be argued that type of ACS diagnosis should not have been included as confounder, as its association with SES could be debated. Nonetheless, no major attenuation of the results was found after omitting the variable as confounder in a sensitivity analysis (results not shown).

The presence of unmeasured confounding was suspected to be limited in **Papers II** and **III** due to vast access to covariates enabling minimal sufficient adjustment; further possible unmeasured reasons to non-adherence were displayed graphically in DAGs and did not reflect any open biasing path in both papers.
In register-based studies, it is not possible to evaluate patients' reasons to non-adherence to medication and there might be some unknown factors explaining why some patients were non-persistent with their treatment. Furthermore, there was a risk of misclassification of the mediating variable, non-persistence to medication, in **Paper III**, as its definition was based on assumptions. This could generate the role of non-persistence to medication to be greater than observed, as any misclassification in confounders/mediators affect results from adjusted analyses to be more like those obtained in unadjusted analyses.

Regarding risk of effect modification, there was an a priori hypothesis of effect modification by education and income in **Paper II**, but this was not supported in the analysis. This was most likely explained by the overrepresentation of patients with high education and income level among respondents compared to non-respondents (results not shown). The inverse probability of treatment weights performed in **Paper III** balanced all baseline covariates and provided population average effect thus limiting risk of effect modification in the regression analyses. The two different multivariate models showed similar results. Therefore, the model with the least confounding variable was preferred to lower risk of unnecessary adjustment. Also, the interrelationship among socioeconomic variables can be difficult to evaluate as they cover life-long latent socioeconomic factors including reduced health literacy and prevalence of risk factors [158].

Study design

Paper I was a cross-sectional study and the research question aimed to explore how SES was associated with referral to CR but did not intend to follow up on the patients, although doing so would have been highly relevant for further research. Accordingly, this study design was appropriate for the present study.

Paper II was designed as a nationwide population-based cohort study. If repeated to avoid the study limitations in **Paper II**, it would be preferred to consecutively collect data during hospitalisation and during check-ups with their general practitioners. Thus, it could be interesting to perform a longitudinal study to evaluate if perceptions about pharmacological treatment changed over time or investigate if an observed association between lower SEF and non-adherence to medication was mediated by differences in perception of pharmacological treatment.

Paper III was designed as a prospective cohort study with historical data. The results were robust due to the sensitive study design that handled the time-varying mediator using inverse-probability-of-treatment weights and provided population average effect measures. If repeated, it would be interesting to evaluate other potential mediators, e.g. smoking, or use study populations that have higher proportion of patients being non-persistence to medication.

External validity

This dissertation revolves around adult patients diagnosed with ACS, and the findings may accordingly be restricted to such a patient population being above 18 years of age. The Danish legislation of the referral process to CR has changed since the acquisition of patients in the period 2011 to 2014, which may have had an impact on the external generalisability of the results examining the setting of CR. Oppositely, the results regarding phase 1 (information) and phase 2 (willingness to participation) are considered generalisable to present clinical practice. With that said, the results found that patients were not always referred to the intended CR setting irrespectively of their ACS diagnosis, and this is most likely still the case, although most CR now is performed in the municipalities.

Further, the combination of a Danish healthcare system being tax-financed and reimbursement of pharmacological treatment with some co-payment for the patients should in theory lower barriers to utilisation caused by poor personal finances. This structure may influence the generalisability to countries with other healthcare structure; nonetheless, findings of barriers to secondary cardiovascular prevention and clinical outcomes have been reported in all different types of healthcare settings [19,22,50,96,130,159,160].

Altogether, these notations support the external validity and the findings of this dissertation to be of relevance in other countries, irrespectively of healthcare structure.

CHAPTER 7. CONCLUSIONS AND IMPLICATIONS

The results from this dissertation evaluating barriers in secondary cardiovascular prevention showed that:

- The proportion of eligible patients referred to CR following incident ACS was 69.5%, which implies a potential for improvement.
- Level of income, and to a lesser degree education, was associated with higher risk of not being referred to CR and this may especially be relevant in the phase of willingness to participate in CR.
- Only one fourth of patients reported perception of pharmacological treatment ‘To a high level’.
- Patients’ perception of pharmacological treatment has an inverse dose-dependent association with risk of non-adherence to medication, although all results did not reach statistical significance.
- During a median 3.5 years of follow-up, approximately 37% of patients were non-persistent to the combined measure of statin or antiplatelet treatment and almost one-third experienced MACE.
- Patients with a higher level of income had lower risk of non-persistence to mediation; furthermore, level of education was not associated with this outcome measure.
- Higher level of income and education significantly lowered risk of MACE and all secondary clinical endpoints. Non-persistence to medication mediated the income-related inequality in risk of MACE by 12-18%, but only in men.

Summarised, the results from **Papers I-III** found (socioeconomic) barriers to secondary cardiovascular prevention that influenced referral to CR, non-adherence to medication and risk of adverse clinical outcomes. This underlines the need to investigate why social inequality occurs and how to decrease the risk of putting patients with low SES in a vulnerable situation. Further, the socioeconomic paradox in a society with equalitarian healthcare reflects important issues for utilisation of secondary preventive treatment following ACS, and it is indisputable that actions are needed to overcome the observed inequality of health. Hopefully, this dissertation contributes to increased awareness about (socioeconomic) barriers in secondary cardiovascular prevention that can be used to inform healthcare practitioners and policy makers to understand and act upon the importance of treating the patient and not merely treating the disease.

Based on these findings, reflections on implications for public health, clinical practice, and further research will be presented in the following section.

Implication for public health and clinical practice

As presented in the background section, numerous clinical guidelines concerning CR have been developed. However, sometimes, shortcomings in the format of clinical guidelines causes barriers to their implementation [161]. Regarding social inequality in heart disease, the ESC guideline paper mentions patients' SES as a risk modifier potentially relevant for assessing total CVD risk and thus should be ranked equally important as the risk factors included in the SCORE chart [4]. Same guideline mentions that low SES is a barrier for optimal adherence to medication and change in unhealthy lifestyle. However, SES is not mentioned in the 28 'to do and not to do' messages despite the abundant knowledge regarding risk of CVD, lower utilisation of CR and non-adherence to medication. Furthermore, socioeconomic barriers are only barely addressed in the two most recently updated ESC guidelines on patients with and without ST-segment elevation; the first in relation to non-adherence to medication [9], the latter do not mention it, and the section about secondary cardiovascular prevention is referred to the supplementary materials [8].

In the guidelines on CR provided by the Danish Society of Cardiology, SEF is also presented as potential barriers to CR without any further elaboration [32]. Accordingly, SEF as a barrier is only presented without suggestions on how to be endorsed by action. However, there is room for improvement, and results from this dissertation call for increased attention to the (socioeconomic) barrier in secondary cardiovascular prevention in clinical guidelines as they were found at the system level (**Paper I**), individual level (**Paper II**), and the population level (**Paper III**).

In this dissertation, the system-level barriers reflected inequality in the referral process to CR, and this could possibly be endorsed by improving patients' willingness to participation. A previously study found that low willingness largely was explained by lack of interest in the intervention [39] and one possibility could thus be to make CR more manageable – maybe by facilitating home-based CR? Another possibility could be to provide a socially differentiated CR programme, as suggested by The Danish Heart Foundation in corporation with the Danish Regions in 2019 [162]. For example, implementation of social differentiated CR has previously shown good results in a Danish setting as they obtained a referral proportion of 86% of eligible patients to CR [163]. Although this intervention increased CR utilisation [163], no difference in recurrent events and mortality were reported at the ten-year follow-up [164,165]. These negative findings of long-term follow-ups after differentiated CR may be caused by persistent barriers related to unhealthy behaviour, or other unknown factors and should thus be acted upon. Further, it is necessary to improve referral and uptake of CR among patients with lower SEF as this intervention is considered cost-effective and has the possibility to reduce risk of adverse clinical outcomes [166,167].

Paper II showed that patients' perception of adequate information of their secondary pharmacological treatment was associated with subsequent risk of non-adherence to medication. This individual-level barrier is important to address and is urged to be implemented at routine check-ups at the GPs as they primarily are responsible for phase III CR. Further, long-term checking with unbeneficial risk factors may also lower the increased risk of MACE found in **Paper III** among patients with lower SEFs. Higher levels of income, but not education, were also associated with a decreased risk of non-persistence to medication in **Paper III.** This is a problem at the population level, and a reduction in co-payment would hopefully alter this difficulty, as research reports that patients with lower income are sensitive to changes in user charges [168]; however, this would most likely be more prominent in countries without reimbursements. The level of education could be interpreted as a latent measure of health literacy, which in a recent meta-analysis was reported to be associated with higher levels of adherence to medication [169]. Combined with the finding that a higher level of education significantly decreases risk of MACE, this suggests that the healthcare setting needs to emphasise patients' different personal prerequisites to obtain good clinical outcomes. One way could be to (financially) strengthen both the primary and secondary healthcare sectors to allocate more resources to treat patients with lower SES as they often have several comorbidities and thus are more time-consuming.

Overall, the finding of barriers in secondary cardiovascular prevention in this dissertation illustrates the importance of easing proper persistence to pharmacological treatment and facilitating interventions that decrease the risk of MACE, irrespectively of patients' socioeconomic position. This could be done by introducing interventions with both short-term and long-term effects (e.g. life course approaches [170]). The results from this dissertation provide contributions to the existing literature and may serve as inspiration to interventions with short-term effects: accordingly, one way could be to facilitate attention to the CR referral process, especially regarding patients' willingness to participate in CR as found in **Paper I**, or to increase awareness to patients' perceived level of adequate information of their secondary pharmacological treatment, as this was associated with risk of non-adherence to medication in **Paper II**. These methods could very well contribute towards decreasing the social gradient in risk of MACE as observed in **Paper III**, and possibly facilitate a better persistence to medication.

Implication for further research

Future research needs to delve deeper into potential causes of barriers in secondary cardiovascular prevention and to produce substantial evidence that may enable and provide suggestions to handle social inequality at an organisational level.

It is acknowledged in daily clinical practice that proper treatment involves high quality communication with the patients and that lack of this can increase patients' vulnerability [102]. However, many clinicians experience not having enough time, which adversely affects the more socially deprived patients and thus puts them in a vulnerable situation[102,168]. Accordingly, future research should focus on how to improve the organisation and how to take the patients' needs into consideration when offering secondary cardiovascular prevention. This may encompass the referral process in which results from this dissertation found potential for improvement (**Paper I**) and risk of non-persistence to medication and MACE (**Paper III)**.

In **Paper II**, the findings of only 25.5% reporting a high level of perception of pharmacological treatment also leaves room for improvement. Larger-scale studies are warranted to explore if this is dependent on SEF and if patient-reported experience measures are a mediator of the association between income and non-adherence to medication.

This dissertation investigated how non-persistence to medication mediated the association between SEF and MACE (**Paper III**). It would furthermore be interesting to investigate this in a cohort restricted to patients receiving coronary intervention. Future direction of research could also comprise investigation of other mediating variables, which include smoking, hypertension and BMI as all of these have been categorised as mediators linked to incident CHD [146].

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APPENDICES

APPENDIX A. PAPER I

APPENDIX B. PAPER II

APPENDIX C. PAPER III

APPENDIX A. PAPER I

BMJ Open

Influence of socioeconomic status on the referral process to cardiac rehabilitation following acute coronary syndrome: a cross-sectional study

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ABSTRACT

Objective To evaluate the association between socioeconomic status (SES) and referral to cardiac rehabilitation (CR) after incident acute coronary syndrome (ACS) by dividing the referral process into three phases: (1) informed about CR, (2) willingness to participate in CR, (3) and assigned CR setting.

Design Cross-sectional study.

Setting Department of Cardiology at a Danish University Hospital from 1 January 2011 to 31 December 2014.

Participants A total of 1229 patients assessed for CR during hospitalisation with ACS were prospectively registered in the Rehab-North Register from 2011 to 2014. SES was assessed using data from national registers, concerning: personal income, occupational status, educational level and civil status. Patients were excluded if one of the following criteria was fulfilled: (1) missing data on SES, or (2) acceptable reason for not informing patients about CR (treatment with coronary artery bypass grafting, transfer to another hospital, still under treatment or death).

Main outcome measures Outcomes were defined by dividing the referral process into three phases: (1) informed about CR, (2) willingness to participate, and (3) assigned CR setting (in-hospital/community centre) after ACS.

Results A total of 854 (69.5 %) patients were referred to CR. After adjustment for age, gender, ACS diagnosis (ST-elevated myocardial infarction, non-ST-elevated myocardial infarction, unstable angina pectoris) and comorbidity, high income had the strongest association of referral to CR in all three phases (informed about CR: OR 2.17, 95% CI 1.01 to 4.64; willingness to participate in CR: OR 1.55, 95% CI 1.02 to 2.35; assigned in-hospital CR: OR 1.47, 95% CI 0.91 to 2.36). Educational level showed similar tendencies, however not statistically significant. The results did not vary according to gender.

Conclusion This is the first study to investigate the referral process to CR using a three-phase structure. It suggests income and education to influence all phases in the referral process to CR after ACS.

Strengths and limitations of this study

- This is the first study to investigate the referral process to cardiac rehabilitation (CR) using a three-phase structure (informed about CR, willingness to participate in CR and assigned CR setting) which provides better knowledge in understanding why social inequality persists in referral to CR.
- Socioeconomic variables were provided by highly validated Danish register data using the unique 10-digit civil registration number that is given to all Danish citizens.
- Multivariable logistic regression analyses were used to minimise potential confounding.
- Data were not gathered for specific scientific purposes and it cannot be ruled out that not all patients admitted with acute coronary syndrome were identified. However, such loss was considered unsystematic and unintended and should not pose a problem for bias introduction.

INTRODUCTION

Low socioeconomic status (SES) is associated with higher risk of developing ischaemic heart disease (IHD) and poorer subsequent outcome, including higher risk of recurrent cardiovascular events and cardiac-related mortality.[1–5] Cardiac rehabilitation (CR) is an important step to reduce disease outcomes and is an integral part of IHD care as it aims to improve quality of life as well as patients' physical, psychological and social functioning.[4]

CR comprises exercise therapy, psychological consulting, treatment-targeted therapy and lifestyle-changing modules (dietary modification and smoking cessation).[4] The programme is a coordinated effort made by cardiologists, nurses, physiotherapists, dietitians and, eventually, occupational therapists. If needed, psychologists, social workers or priests may be included as well.[4]

The efficacy of CR in reducing cardiovascular mortality and risk of hospital readmissions is well documented.[6–8] It therefore seems irrational that international research in general continues to find CR 'referral' or 'participation and completion' rates to be unsatisfactory.[9–13]

Different socioeconomic characteristics (income, educational level, occupational status, civil status) are shown to be associated with CR underutilisation.[14] Low income and educational level have irrespectively of type of healthcare system repeatedly been associated with limited participation and completion rate.[11 15] It is consequently of major importance to eliminate the socioeconomic differences in CR if the inequality in IHD burden is to be reduced.

Obstacles in referral and participation to CR among patients with lower SES may be due to system-level and personal barriers.[16] System-level barriers cover physician recommendations, the interaction with the healthcare team and misconceptions about CR. Personal barriers include perception about IHD and CR, and belief about the ability to control IHD.[16] However, vulnerable elements in the referral process prone to socioeconomic inequality among patients with acute coronary syndrome (ACS) remain unexplored. By dividing the referral process into three phases, it is possible to evaluate if such inequality is the result of selection of patients at the system level (the process of informing patients about CR and the setting of CR that patients are referred to) rather than the person level (patients' own willingness to participate in CR). To our knowledge, no study has analysed the entire referral process using such three-phase structure while controlling for confounders in a population of patients surviving ACS. Therefore, the objective of this study was to investigate how SES is associated with the patients' chances of (1) being informed about CR, (2) willingness to participate, and (3) assigned CR setting (in-hospital or community centre). Phase 3 was determined by regional guidelines: patients suffering ST-elevated myocardial infarction (STEMI) or complicated non-STEMI (NSTEMI) were offered in-hospital CR whereas patients with uncomplicated NSTEMI and unstable angina pectoris (UAP) were offered CR in a community centre.

METHODS

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cross-sectional studies.[17]

Study design

This population-based study used data from the Rehab-North Register. Its content has previously been described.[18] In short, the Rehab-North Register holds data on all patients hospitalised at the Department of Cardiology, Aalborg University Hospital, from 1 January 2011 to 31 December 2014 with a diagnosis of ACS. All were assessed for eligibility to CR using a questionnaire.[18]

In Denmark, CR fully or partially takes place in-hospital or at community centres. In-hospital CR is reserved for high-risk patients and is structured with a more complex intervention. The Danish Public Health System is tax paid, enabling CR to be free of charge for the patient.

Patient and public involvement

No patients were involved in the design, or conduct, or reporting, or dissemination plans of our research.

Study population

The study population was identified in the Rehab-North Register as patients diagnosed with ACS (International Classification of Diseases 10th Revision: I20.0, I21). The registered diagnosis was verified by linking data from the Rehab-North Register with the Danish National Patient Register (NPR) and the Danish Register of Causes of Death.[19] If any discrepancy arose, the diagnosis registered in the NPR was selected. Patients were excluded if one of the following criteria was fulfilled: (1) missing data on SES, and (2) acceptable reason for not informing patients about CR, including treatment with coronary artery bypass grafting, transfer to another hospital, still under treatment or death. Patients who underwent coronary artery bypass grafting were informed about CR at the thoracic surgery department performing the operation. Patients who were 'transferred to another hospital' received information about CR at other cardiology departments. We were not able to receive confirmation regarding referral to CR in this patient group.

The study population and referral design using three phases is illustrated in figure 1.

Socioeconomic status

Different indicators of SES (personal income, occupational status, educational level and civil status) were chosen due to a priori knowledge about their proposed mechanisms associated to the outcome variable. Ascertainment of socioeconomic variables from national registers was done by linkage of a unique personal number given to all Danish residents.

The Income Statistics Register provided information regarding both disposable personal income (low, medium, high) calculated for the calendar year before disease onset, and occupational status (employed, unemployed/out of workforce) set for the calendar year before disease onset.[20] A person's highest obtained educational level (low, medium, high) was based on the International Standard Classification of Education[21] from the Student's Register,[22] and civil status (married/partnership, divorced/unmarried/widow) from the Civil Registration System (CRS).[23]

Outcomes

Outcomes were defined by dividing the referral process into three phases: (1) informed about CR, (2) willingness to participate, and (3) assigned CR setting (in-hospital/community centre) after ACS.

All outcome information gathering was done during the patients' hospitalisation and included in the questionnaires that founded the Rehab-North Register.

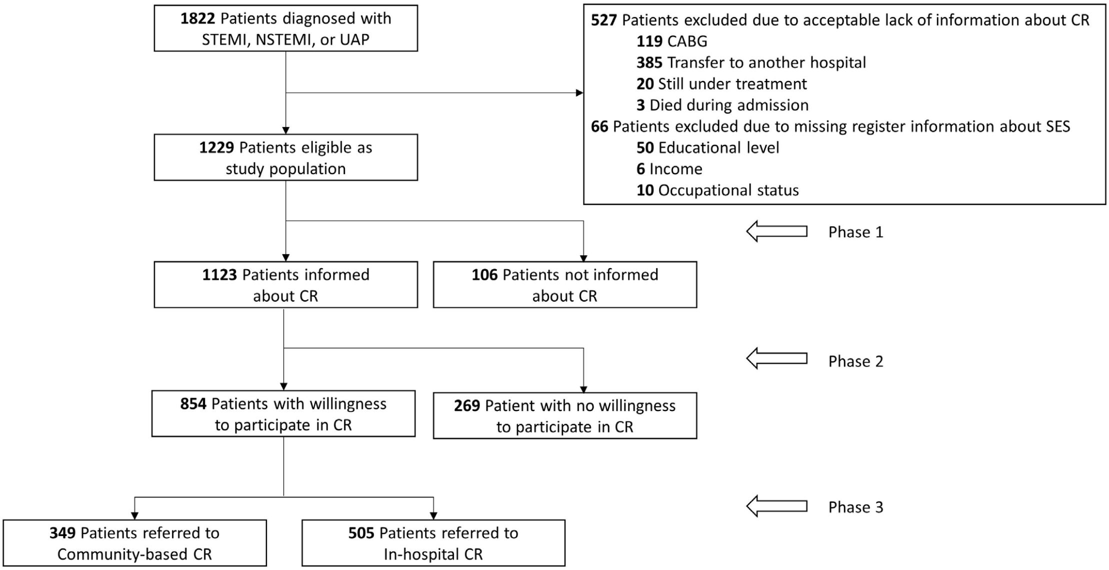

Figure 1 Flow chart of the referral process to cardiac rehabilitation. CABG, coronary artery bypass grafting; CR, cardiac rehabilitation; NSTEMI, non-STEMI; SES, socioeconomic status; STEMI, ST-elevated myocardial infarction; UAP, unstable angina pectoris.

Covariates

The selection of covariates to be included in the multivariable analyses was done based on directed acyclic graph (not shown). Age was registered at time of diagnosis and categorised into three groups: <65 years, 65–74 years and ≥75 years. Information regarding age and gender was gathered from the CRS.[23] Comorbidity diagnoses were defined by the Charlson Comorbidity Index (CCI), but only diagnoses from the year 2011 until hospitalisation were accessible. Comorbidity diagnoses was drawn from the NPR.[24] In general, patients with NSTEMI and UAP are less likely referred to CR compared with patients with STEMI.[25] Therefore, to get an accurate estimate of the impacts of patients' SES on CR referral, ACS diagnosis (STEMI, NSTEMI, UAP) was included as a covariate.[25]

Statistical analysis

Baseline characteristics of study population were summarised by frequencies and percentages. The association between socioeconomic variables and being informed about CR, willingness to participate and assigned CR setting was assessed by crude (model 1) and multivariable logistic regression adjusted for confounders (age, gender, ACS diagnosis, CCI) (model 2). Results were presented in OR with 95% CI. Potential effect modification by gender was assessed by stratification and likelihood ratio tests as studies have found females to experience lower rates of referral to CR compared with males.[10 26] Statistical analyses were performed using Stata software (V.15.1; StataCorp, College Station, TX).

RESULTS

Of the original cohort of 1822 patients diagnosed with ACS, only patients with no missing socioeconomic variables, and no acceptable reasons for not being informed about CR were included in the study (figure 1). This resulted in a study population comprising 1229 patients (73.8% male). The patients' baseline characteristics, stratified by diagnosis, are presented in table 1. Patients with STEMI were relatively younger and still an available workforce with higher income. In the study population, 1123 (91.4%) patients were informed about CR of which 854 (76.0%) subsequently agreed to participate in the programme. Of those, 349 (40.9%) patients were referred to CR in a community centre and 505 (59.1%) patients were referred to in-hospital CR (figure 1).

Phase 1: SES and being informed about CR

Higher income and educational level had positive crude associations with being informed about CR whereas being unemployed/out of workforce or single living had a negative association (table 2). These associations were greatly reduced after adjustment for age, gender, ACS diagnosis and CCI. The adjusted regression analysis found high income to be associated with being informed about CR (OR 2.17, 95% CI 1.01 to 4.64). High educational level was also associated with being informed about CR although the association did not reach statistical significance (OR 1.60, 95% CI 0.72 to 3.54).

Phase 2: SES and willingness to participate in CR

High income, high educational level and being single living (divorced/unmarried/widow) were all associated

Table 1 Characteristics of study population stratified by diagnosis

Characteristics	Full population n=1229	STEMI n=402	NSTEMI n=711	UAP n=116
Male (n, %)	907 (73.8)	322 (80.1)	503 (70.7)	82 (70.7)
Age group (years)				
<65	591 (48.1)	227 (56.5)	308 (43.3)	56 (48.3)
65–74	371 (30.2)	116 (28.9)	215 (30.2)	40 (34.5)
≥75	267 (21.7)	59 (14.7)	188 (26.4)	20 (17.2)
Civil status (n, %)				
Married/partnership	793 (64.5)	253 (62.9)	449 (63.2)	91 (78.4)
Divorced/unmarried/widow	436 (35.5)	149 (37.1)	262 (36.8)	25 (21.6)
Occupational status (n, %)				
Employed	479 (39.0)	195 (48.5)	240 (33.8)	44 (37.9)
Unemployed/out of workforce	750 (61.0)	207 (51.5)	471 (66.2)	72 (62.1)
Educational level (n, %)				
Low	516 (42.0)	144 (35.8)	322 (45.3)	50 (43.1)
Medium	539 (43.9)	201 (50.0)	293 (41.2)	45 (38.8)
High	174 (14.2)	57 (14.2)	96 (13.5)	21 (18.1)
Income, tertile (n, %)				
Low	405 (33.0)	113 (28.1)	251 (35.3)	41 (35.3)
Medium	406 (33.0)	124 (30.8)	247 (34.7)	35 (30.2)
High	418 (34.0)	165 (41.0)	213 (30.0)	40 (34.5)
Charlson Comorbidity Index				
Low (0 point)	1088 (88.5)	358 (89.1)	630 (88.6)	100 (86.2)
Moderate/high (>0 point)	141 (11.5)	44 (10.9)	81 (11.4)	16 (13.8)

NSTEMI, non-STEMI; STEMI, ST-elevated myocardial infarction; UAP, unstable angina pectoris.

with a higher likelihood of willingness to participate in CR in the crude analyses (table 3). Being unemployed/retired was negatively associated with being willing to participate in CR. After adjustment, high income level had the highest OR (OR 1.55, 95% CI 1.02 to 2.35) in relation to willingness to participate. A similar pattern was observed for high educational level although the association was not statistically significant (OR 1.21, 95% CI 0.78 to 1.88). Likewise, being single living was also associated with willingness to participate in CR, although the estimates did not reach statistical significance (OR 1.28, 95% CI 0.93 to 1.76).

Phase 3: SES and assigned CR setting

Table 4 shows the association of SES on being assigned to in-hospital CR compared with CR in a community centre. High income was significantly associated with assignment to in-hospital CR (OR 2.10, 95% CI 1.49 to 2.97) but the association was attenuated after adjustment for confounders (income: adjusted OR 1.47, 95% CI 0.91 to 2.36).

Supplementary analyses

The analyses were stratified by gender in a supplementary analysis. The results were not substantially different from the main analysis (not shown).

The baseline characteristics of patients being excluded from the study population were obtained (online supplementary table S1). After multivariable logistic regression, patients being excluded from the study population have significantly lower SES compared with the patients being included (online supplementary table S2).

DISCUSSION

In this study, the referral process to CR was assessed using a three-phase structure: (1) informed about CR, (2) willingness to participate in CR, and (3) assigned CR setting. After adjustment, high income was the only variable that is statistically significantly associated with referral to CR in phases 1 and 2, and insignificantly associated with phase 3 of the referral process. High educational level had a similar pattern, but the association did not reach statistical significance.

Overall, 69.5% of the patients were referred to CR, which is in accordance with earlier findings (22%–81.5%).[9 10 25 26] Notably, in one study strikingly 86% was referred to CR after usage of a social differentiated intervention programme.[27] However, it would be difficult to

Table 2 Logistic regression model for being informed about cardiac rehabilitation, n=1229

	Full study population n (%)	Informed about CR n (%)	Unadjusted		Multivariable adjusted*	
			OR	95% CI	OR	95% CI
Observations	1229 (100)	1123 (91.4)				
Civil status						
Married/partnership	793 (64.5)	735 (59.8)	1 (ref)		1 (ref)	
Divorced/unmarried/widow	436 (35.5)	388 (31.6)	0.64	0.43 to 0.95	0.76	0.49 to 1.19
Occupational status						
Employed	479 (39.0)	469 (38.2)	1 (ref)		1 (ref)	
Unemployed/out of workforce	750 (61.0)	654 (53.2)	0.15	0.07 to 0.28	0.46	0.20 to 1.07
Educational level						
Low	516 (42.0)	452 (36.8)	1 (ref)		1 (ref)	
Medium	539 (43.9)	505 (41.1)	2.10	1.36 to 3.25	1.17	0.72 to 1.89
High	174 (14.2)	166 (13.5)	2.94	1.38 to 6.26	1.60	0.72 to 3.54
Income, tertiles						
Low	405 (33.0)	342 (27.8)	1 (ref)		1 (ref)	
Medium	406 (33.0)	374 (30.4)	2.15	1.37 to 3.38	1.40	0.86 to 2.28
High	418 (34.0)	407 (33.1)	6.82	3.54 to 13.14	2.17	1.01 to 4.64

*Adjusted for age, gender, acute coronary syndrome (ACS) diagnosis and Charlson Comorbidity Index.
CR, cardiac rehabilitation.

Table 3 Logistic regression model for willingness to participate in cardiac rehabilitation, n=1123

	Full study population n (%)	Willingness to participate in CR n (%)	Unadjusted		Multivariable adjusted*	
			OR	95% CI	OR	95% CI
Observations	1229 (100)	854 (76.0)				
Civil status						
Married/partnership	793 (64.5)	546 (48.6)	1 (ref)		1 (ref)	
Divorced/unmarried/widow	436 (35.5)	308 (27.4)	1.33	0.99 to 1.79	1.28	0.93 to 1.76
Occupational status						
Employed	479 (39.0)	388 (34.6)	1 (ref)		1 (ref)	
Unemployed/out of workforce	750 (61.0)	466 (41.5)	0.52	0.39 to 0.69	0.93	0.62 to 1.40
Educational level						
Low	516 (42.0)	322 (28.7)	1 (ref)		1 (ref)	
Medium	539 (43.9)	405 (36.1)	1.64	1.21 to 2.20	1.36	0.98 to 1.88
High	174 (14.2)	127 (11.3)	1.31	0.87 to 1.99	1.21	0.78 to 1.88
Income, tertiles						
Low	405 (33.0)	229 (20.4)	1 (ref)		1 (ref)	
Medium	406 (33.0)	288 (25.6)	1.65	1.19 to 2.30	1.35	0.94 to 1.94
High	418 (34.0)	337 (30.0)	2.38	1.69 to 3.34	1.55	1.02 to 2.35

*Adjusted for age, gender, acute coronary syndrome (ACS) diagnosis and Charlson Comorbidity Index.
CR, cardiac rehabilitation.

reproduce such a result in an observational study without this specific purpose.

The finding of patients' income and educational level to be associated with all three phases of the referral process to CR may be explained by 'the Nordic Paradox' observed in the Nordic European countries.[28 29] These countries, covering Denmark, Norway, Sweden and Finland, are 'welfare states' with equal access to healthcare which theoretically ought to diminish the importance of patients' level of income and education regarding access to healthcare services. However, this is not the case as inequality (eg, in mortality) persists.[29] Although income inequality is

Table 4 Logistic regression model for assigned cardiac rehabilitation setting, n=854

	Full study population n (%)	Assigned CR setting n (%)	Unadjusted		Multivariable adjusted*	
			OR	95% CI	OR	95% CI
Observations	1229 (100)	505 (59.1)				
Civil status						
Married/partnership	793 (64.5)	317 (37.1)	1 (ref)		1 (ref)	
Divorced/unmarried/widow	436 (35.5)	188 (22.0)	1.13	0.85 to 1.51	1.20	0.84 to 1.69
Occupational status						
Employed	479 (39.0)	268 (31.4)	1 (ref)		1 (ref)	
Unemployed/out of workforce	750 (61.0)	237 (27.8)	0.46	0.35 to 0.61	0.75	0.49 to 1.15
Educational level						
Low	516 (42.0)	177 (20.7)	1 (ref)		1 (ref)	
Medium	539 (43.9)	248 (29.0)	1.29	0.96 to 1.74	0.90	0.63 to 1.30
High	174 (14.2)	80 (9.4)	1.39	0.91 to 2.13	1.20	0.72 to 1.99
Income, tertiles						
Low	405 (33.0)	115 (13.5)	1 (ref)		1 (ref)	
Medium	406 (33.0)	161 (18.9)	1.26	0.89 to 1.78	1.14	0.73 to 1.78
High	418 (34.0)	229 (26.8)	2.10	1.49 to 2.97	1.47	0.91 to 2.36

*Adjusted for age, gender, acute coronary syndrome (ACS) diagnosis and Charlson Comorbidity Index.
CR, cardiac rehabilitation.

smaller in the Nordic countries, this still covers inequality in wealth, housing condition and material living conditions, and is used together with educational level to assess latent socioeconomic factors (health literacy, greater burden of behavioural and biological risk factors, and reduced access to quality care and medication).[30] Thus, our finding may imply such latent socioeconomic factors to be important in the referral process to CR.

We found single living to be potentially associated with the willingness to participate in CR. If such an association is reproducible in later studies, then attention should focus on these patients without a partner, who less often receive referral to CR, which has been attributed to lack of social support.[31]

International studies find younger age, male gender, living with a partner, high educational level and high gross income to be predictors of CR referral.[10 25 31] This inequality in CR referral causes concern as participation helps patients implement needed behavioural changes, which reduces cardiac-related deaths.[6] Patients with low SES often have biological, behavioural and psychosocial disadvantages that may accelerate risk of cardiovascular diseases. Therefore, the need of referral, attendance and completion of CR should be prioritised in this patient group.[1 2]

By splitting the referral process into three phases, new insights regarding importance of taking patients' SES into consideration when referring them to CR were gained. Our results show the importance of being aware of system-level barriers present in the referral process. Moreover, identifying those patients who need more motivation before being willing to enter a CR programme is highly important. In that way, patients are well informed about CR and able to make a well-considered decision regarding participation.

Definition of SES is a conceptual challenge often solved by use of personal/family income, educational level, civil status and/or occupation. There is no consensus on which parameters to use as indicators of SES. It has been argued to use single variables as proxy measurements for SES despite different causal pathways. However, others find it problematic only to estimate SES by one parameter, as this may increase the risk of residual confounding by unmeasured socioeconomic circumstances.[1 32] Moreover, the effect of socioeconomic variables seems rather outcome related and is suggested not to be used interchangeably without thorough consideration.[33] As our central interest was to investigate the impact of SES on the referral process to CR, and therefore use SES as exposure variable, we a priori hypothesised the different variables all to be linked to our outcome measures. The risk of such an approach was the introduction of collinearity. However, research finds educational level, occupation and income to measure different phenomena, to have different causal mechanisms and, in part, to be explained by other socioeconomic parameters.[33 34] Since literature finds income, educational level, occupational status and civil status to be important determinants for referral, participation and completion of CR, it seemed most appropriate to include all variables in order to answer our research questions. The consequence of this approach was that we cannot get a single estimate that illustrates the effect of SES.

Some caution must be taken when interpreting the results of our study. First, data were not gathered for specific scientific purposes and it cannot be ruled out that some patients admitted with ACS were not included in the Rehab-North Register. However, such loss was considered unsystematic and unintended and should not pose a problem for bias introduction. Moreover, the non-response analysis found excluded patients to have lower SES compared with the included study population. As exclusion was due to clinical implications (patients were to receive CR referral elsewhere), this should not pose a problem for participation bias introduction in our study population.

Second, use of register data minimised risk of information bias, due to nationwide good algorithms for correct diagnosis coding. Despite linkage to other registers, risk of residual or unmeasured confounding may be present.[35] Third, there may be a risk of residual or unaccounted confounding, if data on confounding variables were not classified with adequate precision. The CCI variable may be inaccurate which is caused by the limited time frame for inclusion of comorbidities. This increases the risk of unaccounted confounding and should be taken into consideration when interpreting the results.

Participation and completion rates of in-hospital CR and CR in community centres remained unexplored as our study only focused on the referral process to CR.

CONCLUSION

High income and educational level were associated with a larger chance of being informed about CR, willingness to participate in CR and assigned in-hospital CR in patients with ACS.

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ONLINE SUPPLEMENTARY MATERIAL

Table S1: Baseline Characteristics of excluded patients

	Excluded
Characteristics	n = 593
Male (n, %)	423
Age Group (years)	
< 65	242
65-74	171
≥ 75	180
Civil status (n, %)	
Married/Partnership	378
Divorced/Unmarried/Widow	>210
Missing	<5
Occupational status (n, %)	
Employed	158
Unemployed/out of workforce	417
Missing	18
Educational level (n, %)	
Low	256
Medium	200
High	52
Missing	72
Income, tertile (n, %)	
Low	245
Medium	197
High	>145
Missing	<5
Charlson Comorbidity Index	
Low (0 points)	421
Moderate/High (>0 points)	75
Missing	97

Table S2: Logistic regression model for those excluded compared with those included in the study population, n = 1822

		Unadjusted		Multivariable adjusted*	
	n, (%)	OR	95% CI	OR	95% CI
Observations	593 (32.5)				
Civil status					
Married/Partnership	378 (20.7)	1 (ref.)		1 (ref.)	
Divorced/Unmarried/Widow	>210 (>11.5)	1.02	0.83-1.25	0.85	0.67-1.07
Missing	<5 (<1)				
Occupational status					
Employed	158 (8.7)	1 (ref.)		1 (ref.)	
Unemployed/Retired	417 (22.9)	1.69	1.36-2.09	1.54	1.14-2.08
Missing	18 (1.0)				
Educational level					
Low	256 (14.1)	1 (ref.)		1 (ref.)	
Medium	200 (10.1)	0.77	0.61-0.96	0.77	0.61-0.97
High	49 (2.7)	0.59	0.42-0.84	0.60	0.41-0.87
Missing	72 (4.0)				
Income, tertiles					
Low	245 (13.4)	1 (ref.)		1 (ref.)	
Medium	197 (10.8)	0.71	0.56-0.90	0.77	0.59-1.01
High	>145 (>7.9)	0.46	0.36-0.59	0.55	0.40-0.75
Missing	<5 (<0.3)				

* Adjusted for age, gender, ACS diagnosis, Charlson Comorbidity Index. OR: odds ratio; CI: confidence interval

APPENDIX B. PAPER II

Paper II has not been accepted for publication and is not included in this dissertation. Please contact me for further details.

APPENDIX C. PAPER III

Paper III has not been accepted for publication and is not included in this dissertation. Please contact me for further details.

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