PhD dissertation

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Life after Heart Disease

Patient-reported health measures and prognosis following PCI treatment

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This thesis is based on the following papers:

Study I:

Biering K, Nielsen TT, Rasmussen K, Niemann T, Hjollund NH (2012) Predictors of return to work after Percutaneous Coronary Intervention: The value of self-reported health compared to clinical measures. PLoS ONE 7(11): e49268. doi:10.1371/journal.pone.0049268

Study II:

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[submitted]

Study III:

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[submitted]

Study IV:

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Study V:

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Preface

My path into this project was based on a range of coincidences that took place during the summer of 2008, where Niels Henrik Hjøllund introduced me to the idea of using patient-reported outcomes and to the initial data collection in “Life after heart disease”. Unaware of the learning process ahead of me, I jumped into the intersection of clinical epidemiology and patient-reported outcomes. The work has been challenging in all aspects and the process of learning research skills has been a lifetime experience.

Many people have contributed to this project with support and inspiration.

First of all I would like to thank all the patients who have contributed with numerous answering of questionnaires, and The Danish Heart Association and The Danish Working Environment Research Fund for financial support.

I wish to express my gratitude to my supervisors, especially Niels Henrik Hjøllund, who had handed over his precious data to me, has encouraged me throughout the process and at all times, believed in my ability to find my own ways in the project. Unfortunately Torsten Toftegaard Nielsen, who has taken great part in the initial design of the study and in the beginning of the PhD, passed away all too soon. Hans Erik Bøtker agreed on taking up the work of supervision and has been a great help in advices related to cardiology.

Very special thanks goes to Morten Frydenberg for his enthusiastic help and engagement in the papers on repeated measurements, and missing data in particular, and for plenty of discussions related to science as well as life in general.

Also Thomas Lund, Kurt Rasmussen and Troels Niemann deserve my warmest appreciation for their comments on the manuscripts and great interest in the project.

A warm thanks to the entire staff at Department of Occupational Medicine, Herning, who, with their very different backgrounds, have always shown great interest in both my work and my well-being, most importantly to my “room-mates” Louise Pape Larsen and Stine Yde Nielsen for sharing ups and downs, and the entire PhD unit for creating an always supportive and humorous environment. Thanks to Gritt Bennedsen for help with layout and communication and to Inge-Lillian Klauber for help with accounting.

Finally I thank my husband Christian for endless practical and emotional support during the PhD process and especially for encouragement in the final sprint, and to my children Johanne and Tobias for just being there and reminding me what life is all about.

Karin Biering
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Abbreviations

AMI: Acute myocardial infarction
ACS: Acute coronary syndrome
BMI: Body mass index
CABG: Coronary artery bypass graft
CI: Confidence interval
CPR: Danish Civil Registration System
DNPR: Danish National Patient Registry
DREAM: Danish Register for Evaluation of Marginalisation
HR: Hazard ratio
ICD: International classification of disease
ICF: International classification of functioning, disability and health
LVEF: Left ventricular ejection fraction
MAR: Missing at random
MCAR: Missing completely at random
MCS: Mental component summary
MI: Multiple imputation
MID: Minimal important difference
MNAR: Missing not at random
OR: Odds ratio
PCI: Percutaneous coronary intervention
PCS: Physical component summary
ROC: Receiver operator characteristics
RR: Relative risk
RTW: Return to work
SAQ: Seattle Angina Questionnaire
SF12: Short Form 12-item survey
TPG: Transfer Payment Group
WDHR: West Denmark Heart Registry
WHO: World Health Organisation

Contents

1. Introduction

Coronary heart disease

Coronary heart disease is a major cause of morbidity and mortality in most parts of the world and is associated with significant physical, emotional and social consequences [1]. World-wide, coronary heart disease is the leading cause of death, and in Denmark, cardiovascular disease accounts for approximately 30% of all deaths [2,3]. In Denmark the prevalence of coronary heart disease was just under 150,000 in 2009 and the incidence was nearly 17,000 new cases in a population of 3.2 million persons over 35 years [4]. Since the 1960s, mortality has decreased, primarily among men, but also among women, and mortality is related to comorbidity, low educational level and socioeconomic status [2,5]. Coronary heart disease is a slow-developing process from arteriosclerosis that may begin already in adolescence. Arteriosclerosis may result in angina pectoris or myocardial infarction, both symptoms of coronary heart disease [6].

Treatment of coronary heart disease may consist of primary prevention, such as reduction of risk factors with medication and lifestyle changes, medical treatment with thrombolysis and invasive treatments with percutaneous coronary intervention (PCI) or by coronary artery bypass grafting (CABG) [6]. Well-known risk factors for arteriosclerosis are hypertension, hypercholesterolemia, diabetes, physical inactivity, smoking and overweight. While hypertension and hypercholesterolemia are reduced by medication and the numbers of smokers has decreased, problems related to physical inactivity such as diabetes and overweight are expanding in most parts of the world [7].

Percutaneous coronary intervention

In 1977, the first PCI was conducted in Switzerland by Andreas Grüntzig [8]. The idea was to treat a stenosis in a coronary artery, a disease that previously would need treatment with thrombolysis or the much more invasive operation: CABG. Since then, the procedure has become widely used. In the first procedures, the affected vessel was dilated by inserting a tiny balloon that was inflated to the desired diameter. Nine years later, the dilatation was supplemented with the insert of a metal stent that could retain the dilated vessel open. Another 14 years later, the drug-eluting stent was developed, which reduced restenosis considerably [8].

Today, PCI is a commonly used procedure and many patients who would previously have been treated with CABG are now treated with PCI and with secondary medical prevention. The number of PCI procedures is today much higher than CABG operations [2]. In Denmark, approximately 9000 patients are treated annually with PCI, of which 2500 are under 65 years [2].

Prognosis following coronary heart disease

Due to improvements in treatments, mortality has declined, resulting in more people living with heart disease as a chronic condition [9]. Mortality has declined in Denmark, even though patients treated with PCI are increasingly older [2,10].
Male and female patients share the same prognosis in terms of mortality after adjusting for age, as women are older at their first admission for coronary heart disease. In patients who suffer from high comorbidity, relative mortality is double compared to patients with no comorbidity [5].

The prognosis of coronary heart disease in terms of mortality and readmissions is well described in the literature, but prognosis regarding well-being and impairments in everyday life is important as well. As survival of coronary heart disease have improved during the last decades, assessment of health-related quality of life measures has become increasingly important to complement the traditional outcomes like readmissions and mortality [1]. This raises a need for studies assessing patient-reported health measures and recovery among patients with coronary heart disease.

Adverse events

Restenosis may occur following PCI in some patients. Previously, revascularisation was necessary in up to half of the patients treated with PCI without stenting, in 10-30% of bare metal stentings and is now below 10% for drug eluting stents. The risk of restenosis is increased among patients with diabetes mellitus, and some patients may be genetically predisposed to restenosis [11]. Due to the general arteriosclerosis, patients may also need treatment for occlusions in other arteries than the original target vessel. Choussat et al. investigated long-term clinical outcomes and found that shortly after the PCI, in-stent restenosis was the dominant reason for readmissions, while the long-term prognosis was related to the progression of coronary atherosclerosis in non-stented sites [12]. The same risk factors associated with primary coronary heart disease are related to both recurrent myocardial infarction and fatal coronary heart disease during follow-up [13].

Recovery and rehabilitation

For patients who suffer from coronary heart disease, whether this relates to an acute episode of myocardial infarction or to treatment of more chronic symptoms, recovery to the state of health desired by the patient and return to everyday life is crucial.

The World Health Organisation (WHO) defines health as "the state of complete physical, mental and social well-being" [14]. Complimentary to the International Classification of Diseases (ICD), WHO has introduced an International Classification of Functioning, Disability and Health (ICF), which is the cornerstone in rehabilitation. ICF focuses not only on medical or biological dysfunctions, but also places emphasis on the impact of disability in each patient [15]. Patients with coronary heart disease are placing new demands on cardiac health care services, and cardiac rehabilitation has been suggested as a solution [16]. The American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation have developed guidelines for cardiac rehabilitation that aim to improve health-related quality of life and promote a healthier lifestyle along with reduction of disability and cardiovascular disease risk[17].

Current guidelines in Denmark recommend comprehensive, individually tailored cardiac rehabilitation in three phases: I) in-hospital; II) outpatient; and III) community-based services. Cardiac rehabilitation is not fully implemented in hospitals and municipalities, and not all patients are willing to participate in cardiac rehabilitation [18]. A large Danish register-based cohort study found that the attendance rate in cardiac rehabilitation was 72.5%, but in this study, only patients aged 30-69 were selected. Non-attendees have a higher mortality risk, were older, had lower socioeconomic status, had atypical symptoms and were more often living alone [19].

Return to work

For patients of working age, reintegration into the workforce is an important outcome of high interests for patients, the clinicians and the society. A Danish register-based study on labour market participation among patients with coronary heart disease showed that they left the workforce faster compared to persons without coronary heart disease [20]. A large population-based study from Sweden (N=22,985) examined long-term sickness absence (>90 days) in PCI patients. They found that 36% of the PCI patients had long-term sickness absence. Women had increased risk of long-term sickness absence. For both genders, an acute indication for the PCI was associated with long-term sickness absence, while being unemployed or self-employed was inversely associated. Among men, a history of previous sickness absence and having manual work was associated with long-term sickness absence, while in women a history of hospitalisation for cardiovascular disease were associated with long-term sickness absence[21]. High age, female gender, low education, low socioeconomic status, low confidence in own ability to work, myocardial infarction prior to PCI, low LVEF, angina and depression have been suggested related to difficulties in return to work [22-27].

How return to work has been measured and defined in previous studies is subject to large variations. This compromises comparisons between studies. Return to work (RTW) following temporary work disability is often measured as a dichotomous outcome measured at a specified point in time preceding a specific event, e.g. onset of disability or a specific intervention. However, RTW may also be a time-to-event measure because the workers' RTW status can be measured continuously throughout the follow-up period [28,29]. Employees may furthermore experience one or several recurrences of absence and only gradually recover from their injury or illness [30-32]. The commonly used dichotomisation of the outcome into "returned yes/no" at a certain follow-up point ignores any information regarding when the person returned to work and information about subsequent recurrences. A recent study examined the measurement properties of three previously defined RTW outcomes using data on employees sick-listed due to soft tissue injuries in the back, upper or lower extremities, or low back pain, from two studies from two countries (Canada and The Netherlands, respectively). They found that differently defined outcomes yielded similar results in prediction, but seemed to differ when compared to functional status [33]. In different countries, the possibilities of obtaining RTW measures are different, depending on the possibilities of following all patients in registers compared to asking patients to report return to work themselves.

Patient-reported health measures in coronary heart disease

Already 10 years ago, Rumsfeld argued in an editorial in Circulation, that clinicians should measure the health status of their patients with the use of standardised surveys and use this information in clinical practice [34].
Patient-reported health measures are important throughout patient care. Initially, patient-reported health measures provide information about the patient's baseline health-related quality of life. On subsequent occasions, patient-reported health measures help evaluate dis-

ease progression or regression [35]. Lohr et al. emphasise the ethical perspective of the use of patient-reported health measures in clinical practice. They state that patient-reported health measures may reinforce ideas of patient autonomy and improve communication and decision-making between clinician and patient [36]. Use of patient-reported health measures in clinical practice has become increasingly more frequent during the last decade [37]. There is agreement that patient-reported health measures provide clinicians with valuable information, but some clinicians find patient-reported health measures time-consuming and difficult to handle in the clinical setting [34,36,38,39].

A wide range of both disease-specific and generic measures has previously been used in studies of patients with coronary heath disease [1,40]. Dempster et al. recommend a combination of disease-specific and generic measures [41].

Patient-reported health measures in relation to adverse events and mortality

A substantial proportion of patients treated with PCI experience readmissions in the years following the initial procedure. A systematic review of the literature on health status as a risk factor for adverse prognosis in coronary artery disease in terms of hospitalisations and mortality summarised that poor physical health was associated with adverse events, primarily readmissions but also mortality. However, most of the studies in the review were conducted in mixed populations of patients with coronary artery disease, treated with various procedures, e.g. coronary artery bypass grafts [40]. More recent studies not included in the review are presented in Table 1. One single study focused on PCI treated patients and demonstrated that poor health-related quality of life, measured with the disease-specific MacNew questionnaire that measures physical, mental and social functioning, was related to early events (<6 months) but not to later events [42]. The review also concluded that results based on generic measures were comparable to disease-specific measures in coronary artery disease.
More recent studies on PCI patients confirmed the review’s conclusions [43-46]. Denollet et al. found that also mental factors such as reduced positive affect and depression/anxiety were associated with cardiac events and death [45]. Schenkeveld et al. examined the eight separate domains of SF36, and found both mental and physical domains related to mortality, but with the strongest associations with the physical domains [43]. Lenzen et al. studied associations between self-rated health (using EQ5D) and 1-year mortality, and found a strong association, especially related to self-care and low rating of health status [47]. A similar study also using EQ5D found that primarily the dimensions mobility, self-care and low rating of health status were associated with the combined endpoint death and myocardial infarction [46].

The previous studies were in general large (N<500) and most with register-based information on adverse events, but most studies have been selective, either as part of randomised controlled trials or with large proportions of invited patients who did not participate and were thus excluded from analyses. The problem of studies carried out in secondary analyses of data collected for other primary purposes is also raised by Kuper et al. in their systematic review of psychosocial factors in the aetiology and prognosis of coronary heart disease [48].

Table 1: Overview of studies on associations between patient-reported health and adverse event*

First author	Ref.#	Year	N	Measure	Outcome	Design	Population
Denollet	[45]	2007	874	HADS	Cardiac events and mortality	Cohort	PCI patients**
Pedersen	[46]	2011	870	EQ5D	Myocardial infarction and mortality	Cohort	PCI patients
Schenkeveld	[43]	2010	872	SF36	Mortality	Cohort	PCI patients**
Thombs	[44]	2008	800	SF-12	Mortality	Cohort	Acute coronary syndrome

*Not included in the review by Mommersteeg et al. 2009 [40]
** Patient are from the same cohort

Course of patient-reported health measures in coronary heart disease

Previous studies of self-reported health after CHD have measured self-reported health either once after the PCI [44,49,50], or at two time points [43,51-54], but also repetitive follow-up measurements occur with up to six measurement points over a follow-up time of up to 3 years [54-57]; (Table 2). The largest study with multiple measurements included 1149 patients followed over 3 years with seven measurement points [58]. Most studies reported an increase in the first 6 months after which a stable level was reached. These findings applied to physical, mental and social domains. Most studies have reported group means only, while a few studies also analysed intra-individual changes [49,50]. None of the identified previous studies included non-respondents and patients lost to follow-up in the analysis, posing a threat to the external validity. Moreover, findings in previous studies are often based on selected populations, such as patients included in randomised controlled trials.

Table 2: Overview of studies accessing course of self-reported health using SF12/SF36

First author	Ref.#	Year	N	Measurements	Follow-up (months)	Design	Focus of study	Indication of PCI
Cohen	[55]	2011	903	Before+3	12 m	RCT	PCI/CABG	Elective
Hawkes	[49]	2006	24	Before +1	6 m	Cohort	Changes in SF36	Elective
Mortensen	[51]	2007	684	2	12 m	RCT/Cohort	Gender differences	Acute
Pedersen	[52]	2006	692	2	12 m	Cohort	Gender differences	Mixed
Rubenach	[56]	2001	65	Before*+4	3 m	Cohort	Validation of SF12	Acute
Schenkeveld	[43]	2009	697	2	12 m	Cohort	Mortality	Mixed
Skodova	[50]	2009	37	Before+1	12-24 m	Cohort	Psychosocial differences	Elective
Tofighi	[53]	2012	25	2	varying	RCT	PCI/CABG	Elective
Van Domburg	[57]	2010	1043	Before+3	36 m	RCT	PCI/CABG	Elective
Weintraub	[58]	2008	1149	Before+6	36 m	RCT	RCT PCI/Medicine	Elective
Wong	[54]	2006	65	Before+2	3 m	Cohort	Effect of PCI	Elective

*Before-measurement by recall.

Missing data and attrition in longitudinal studies

Missing data pose challenges for both reliability and the validity of estimates in studies in a range of research disciplines. Studies using patient-reported health measures are strongly depending on patients participating in the planned study period to provide the acquired data material. In studies using patient-reported health measures, missing data may arise in several situations. The respondent may overlook an item or a page in a questionnaire by accident or intentionally, leave an item blank if the respondent apprehends it as irrelevant or even offending [59]. In the data handling process, items may not be recorded or a paper form may simply be lost in the mail. Also initial non-participation and attrition (loss of participants who initially were in the study, during follow-up) is a well-known problem in epidemiology and implies problems in longitudinal studies.

Initial non-participation in a study may pose a challenge to both the internal and the external validity, as non-participants often differ from the source population with respect to disease severity and comorbidity as well as other covariates, e.g. gender, age and education [60]. This may result in selection bias as these factors are almost certainly related to both exposures and outcomes in the studies [61].

Attrition occurs in most clinical trials and observational studies if they involve more than one measurement point. Especially in clinical epidemiology, changes in disease severity or symptoms may influence patient participation [60]. During follow-up, the participants may be unwilling or too ill to continue participation, they may move and fail to report their new address, or they may even die, although the latter may not be regarded as attrition (see below)[62]. The opposite mechanism may operate if the patient considers himself to be marginal with respect to the aim of the study (e.g. too few symptoms or symptoms primarily related to comorbidity). The reasons why participants drop out are, however, usually unknown and consequently evaluation of the role, and even the direction, of bias may be speculative. Patients may find participation tedious and time consuming, and even co-morbidity or life events may play a role unknown to the researchers. Despite of widespread occurrence of this problem, attrition is rarely reported [63].

Both initial non-participation and attrition may introduce selection bias in a longitudinal study if persons who do not participate or leave the study differ from those who participate in the complete study course and if the reason for leaving the study is related to the exposure and the outcome of interest [61].

Specific analytical problems arise when patients die during follow-up. In this case it is not considered as a missing data problem, because patient-reported health measures are irrelevant when patients are dead. In most studies, patients who die during follow-up are simply excluded completely from the analyses, but results from these studies are often too optimistic[64]. In other approaches the ‘worst’ value is assigned to the health variable in patients who die during follow-up [65-67] or an indicator of been alive at the next point of measurement is introduced [68].

The problem with missing data is accentuated by the fact that most statistical methods (e.g. regression models) will include only cases for which complete observations of all covariates and responses are available – a complete case analysis. Traditionally, follow-up studies are analysed by complete case analysis, leaving the potential bias due to missing data, non-response and attrition unknown, however, this problem is often addressed in the discussion section.

Terminology of missing data

If the risk that data are missing is identical for the data that in fact are collected and the data that are not collected, then the data are missing completely at random (MCAR). In the case of MCAR, analyses of complete cases will introduce no bias, but will decrease the sample size and hence the precision of the estimates. However, if the risk of missing data is related to variables (observed or unobserved), i.e. if the data are not MCAR, then analyses based only on complete cases may cause bias. Now suppose that given all that is observed about a person, the risk that missing a specific observation independent of the actual value of that observation (e.g. the risk of data is missing is independent of the values of the unobserved variables given the observed variables) then the data are missing at random (MAR). The keystone in the missing data theory is that if data are MAR, then it is theoretically possible to make valid and efficient inference based on the collected data (but not by a complete case analysis). Finally, the data are said to be missing not at random (MNAR) if they are neither MCAR nor MAR [69].

Multiple imputation

In recent decades, different approaches have been developed to deal with missing data. One of the increasingly used methods is multiple imputation (MI). The idea behind imputation methods is that if it is known how the data should be analysed, if there were no missing data (“the-planned-analysis”) and the missing data could be filled in (imputed) then this imputed data set could be analysed. In MI several (*m)* imputed data sets are created, in which missing observations are replaced with random values from a statistical models based on distributions in the observed dataset and underlying assumptions on the nature of the missing data [70,71].

After this, each of the imputed data sets is analysed by the-planned-analysis to obtain *m* sets of estimates and corresponding standard errors. The final estimates are found as the average of the *m* sets of estimates and the standard errors by applying a simple formula called Rubin’s rule [69]. The keystone in the missing data theory is that if data are MAR and the models used in the imputation are chosen appropriately, then MI will give a valid inference [69-71]. As it is theoretically impossible to verify the assumption of MAR, the MI analysis should be accompanied by sensitivity analyses, which are analyses that illustrate how realistic departures from MAR would affect the results.

Synthesis

Prognosis following coronary heart disease consists of a variety of issues. Traditionally, ‘hard’ outcomes such as adverse events and death are given much attention, while measures that relate to the patient’s well being, recovery and reintegration into working life are rare. However, measuring ‘soft’ outcomes such as return to work and self-reported health is challenging. This thesis sets out to meet these epidemiological challenges and to use patient-reported health measures, also in interaction with traditional measures, using the cohort “Life after Heart Disease”.

2. Aim of the thesis

The overall aim of this thesis was to examine the possibilities available in the use of patient-reported health measures in determining prognosis following PCI. The aim was to use patient-reported health measures both as explanatory variables in relation to other prognostic measures as well as response variables describing prognosis itself.
The aims gave rise to a need for methodological studies on definitions of return to work and on missing data in longitudinal studies using patient-reported health measures.

Each of the studies had the following specific aims:

Study I:

The aim was to describe the frequency and time trends of RTW for the PCI-treated patients in an unselected working age population, and to identify predictors of RTW. Secondly, we aimed to describe the value of using a simple and easily obtained patient-reported measures in risk stratification for RTW.

Study II:

The aim was to describe a concrete application of MI in a follow-up study with numerous measurement points obtained from external data from national registers. The study focused on the challenges of missing data in longitudinal studies, the assumptions and methods behind a MI model and the use of sensitivity analysis of these results.

Study III:

The aim was to describe and analyse the long-term course of self-reported health after PCI in a large well-defined cohort with multiple measurement points.

Study IV:

The aim was to investigate the relationship between mental and physical self-reported health shortly after the procedure and adverse events in terms of cardiac readmissions, new cardiac events and all cause mortality in a complete population based cohort of PCI patients.

Study V:

The aim was to compare different measures of RTW within a 12-month period of follow-up using a well-defined population of patients treated with Percutaneous Coronary Intervention (PCI) and weekly national administrative data on social transfer payments.

3. Material

Population

Central Denmark Region is one of five administrative units in Denmark with 700,000 inhabitants between 25 and 67 years and includes both rural areas and the second largest city in Denmark, Aarhus [72]. All patients, whether referred acutely or electively to PCI, are treated in one single unit at Aarhus University Hospital, Skejby. We enrolled all PCI treated patients below 67 years of age from February 2006 to March 2008. In this period, in total 3966 persons were treated with PCI, including those older than 67 years.

Recruitment

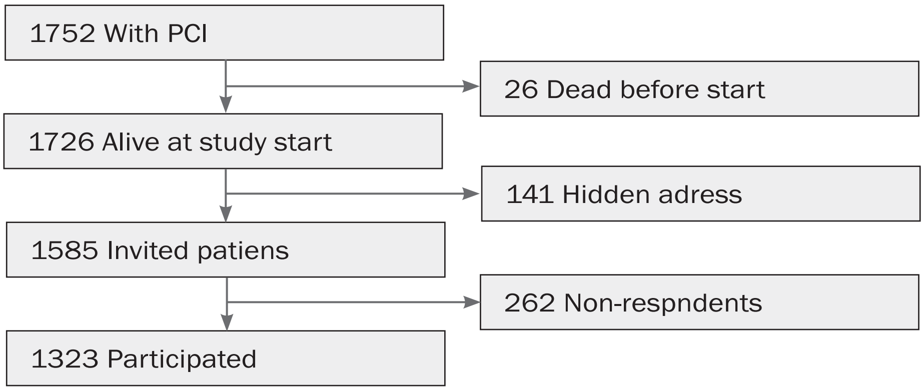
Patients (n=1752) were recruited from the hospital's administrative system of patients. Information on addresses and vital status were collected from the Danish Civil Registration System (CPR) prior to approaching each patient, and 167 patients were not contacted either because they died within the first four weeks (n=26) or because they had hidden address (n=141).

Data collection in "Life after Heart Disease"

Enrolment

One month after the PCI, the remaining 1585 patients were mailed a questionnaire including questions on self-reported health (SF-12). They were also asked to accept further participation in the long-term follow-up survey.

Figure 1: Flowchart

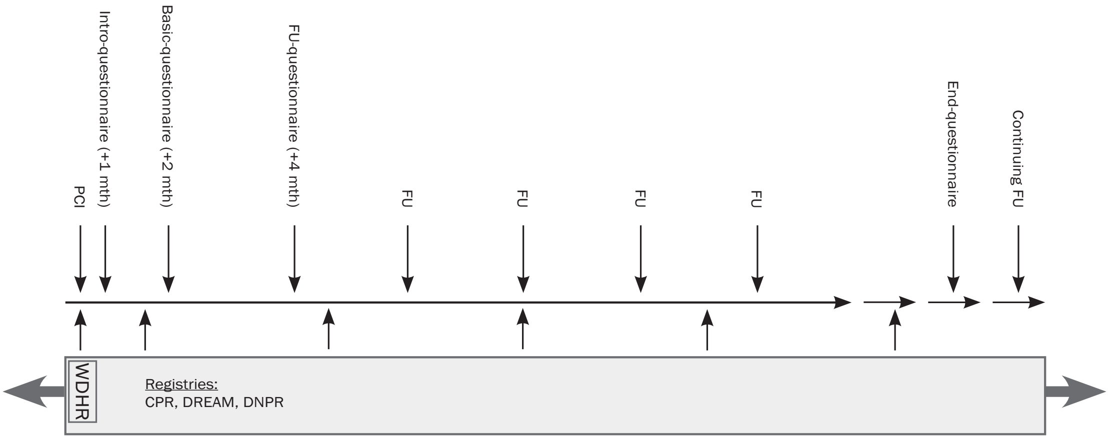


* Response-patterns during follow-up is described in detail in Table 4

Questionnaires

Three months after the PCI, the patients were mailed a longer questionnaire covering a range of topics including demographics, education, lifestyle, work, cardiac symptoms (SAQ) [73] and self-reported health (SF-12) [74]. After the collection of the basic variables, every patient was mailed a questionnaire every 4th month. These follow-up questionnaires contained the same scales as in the questionnaire at 3 months except from demographic information. After 2.5 years of follow-up the patients, received a final questionnaire with the same content as the follow-up questionnaires together with questions about "meaning" [75] and about lifestyle changes seen in a retrospective perspective. The complete data collection procedure is illustrated schematically in Figure 2. This thesis presents analyses related to self-reported health only.

Figure 2: Overview of data collection



Reminders:
If the patients failed to respond to a questionnaire within two weeks, a letter reminded them, and this procedure was repeated with a second reminder after two additional weeks.

Use of internet-based questionnaires
Patients were asked from the baseline questionnaire and onwards if they would prefer to answer the questionnaires on the internet, and this was initially chosen by 21%, rising to 40%. They were mailed an access code and the address of the webpage containing the questionnaire, and in connection with the first web questionnaire, their email addresses were obtained. These were used in the succeeding contacts to the patients. If patients did not reply after receiving an email, they were reminded at first with an additional email and then with a letter and a paper questionnaire. This mixed mode would prevent loss to follow-up if patients changed email addresses or changed habits in the use of a computer. This explains why the percentages of internet answers changed because the patients could change their method of answering during follow-up. Each paper questionnaire ended with a question about preferred channel of response, and during follow-up, patients kept changing methods. The main advantage of using internet-based questionnaires was the reduction of costs and the more complete answering of the questionnaires, as patients were reminded if they skipped an item on the internet. However, using internet-based questionnaires only would have reduced the response rate, as even though many patients had access to the internet, they preferred answering a traditional pen-and–paper questionnaire. Previous studies have shown no difference in the answers derived from internet/mixed mode questionnaires compared to pen-and-paper questionnaires [76,77].

Other data sources

Supplementary to the questionnaires, we had access to a variety of established register-based data. In Denmark accurate and unambiguous linkage of a registries and clinical databases at the individual level is possible due to a unique ID called the Danish Personal Identification Number assigned to each Danish citizen at birth and to residents on immigration [78]. Table 3 provides an overview of the registers used in the studies.

Table 3: Overview of the use of registries

Registry	Period used in study	Unit of observation	Utilized content
The Danish Civil Registration System (CPR)	2006-2011	Person	Unique ID, gender, date of birth, death and emigration
Western Denmark Heart Registry (WDHR)	2006-2008	Person/treatment	Unique ID, date of PCI, LVEF, indication, diabetes, smoking status, BMI.
The Danish Register for Evaluation of Marginalization (DREAM)	2005-2011	Person/week	Unique ID, transfer payment group, union membership.
The Danish National Patient Registry (DNPR	1977-2011	Person/hospital contact	Unique ID, date of contact, main diagnoses of contacts

West Denmark Heart Registry (WDHR)

The West Denmark Heart Registry includes data on patients who have been subjected to coronar angiography, PCI, cardiac valve and CABG [79]. The cardiologic interventionist enters clinical data during and after the PCI from a computer next to the intervention room. The clinical data from the WDHR are complete with respect to individuals, although not all variables were recorded for each patient [79]. We obtained clinical data related to the procedure, including indication for the PCI, left ventricular ejection fraction (LVEF), diabetes, smoking status, and body mass index (BMI).

Danish Register for Evaluation of Marginalisation (DREAM)

The Danish Register for Evaluation of Marginalisation includes information on all public transfer payments administered by Danish ministries and municipalities for Danish citizens since 1991 on a weekly basis [80]. At present DREAM contains 97 codes of different types of transfer income. We used DREAM to define the return to work outcomes and transfer payments groups at different time points.

The Danish Civil Registration System (CPR)

The Danish Civil Registration System is an administrative registry that keeps track of vital status, marital status and addresses of all Danish Citizens and is updated daily. The register provided us with address and vital status, prior to mailing each questionnaire. Gender and the date and year of birth could be derived from the Danish Personal Identification Number and during follow-up, and the exact date of death could be obtained for those who died during follow-up [78].

The Danish National Patient Registry (DNPR)

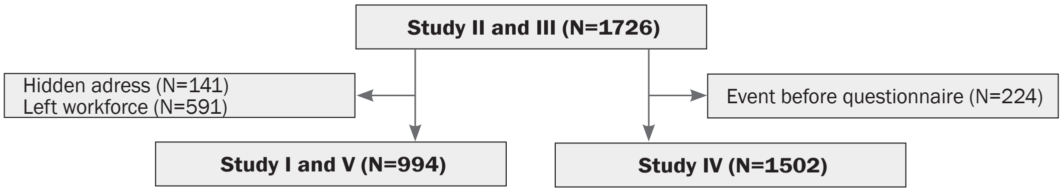
The Danish National Patient Registry includes information on all hospital admissions (from 1977), emergency room visits and outpatient visits (from 1995) in both private and public hospitals in Denmark. Both a primary diagnosis and several secondary diagnoses can be registered along with information on procedures and treatments. Up to 1993, the International Classification of Diseases version 8 (ICD-8) was used, and thereafter ICD-10 is used. Data are entered locally as part of the economic reimbursement system between the hospitals and the regions. The availability of the data can be delayed for several months due to several checks of the data [81]. We used DNPR to obtain comorbidity and adverse events. Data was complete until 1 January 2011.

4. Methods

Study population and design

All studies included in this thesis are based on the cohort “Life after Heart Disease”. Each of the studies used the complete cohort or a subsample, depending on the specific aim. Only patients who had not left the workforce permanently in the week before PCI (n=994) were included in the RTW studies (Studies I and V) and only patients who had not experienced a cardiac readmission before the first questionnaire (n=1502) were included in the study on adverse events (Study IV). In Study I, we provided information on transfer income groups for all invited patients (n=1585).
An overview of the samples used in each study is provided in Figure 3.

Figure 3: Overview of samples



An overview of each study’s topic, sample, data sources, independent and dependent variables and data analyses is provided in Table 4.

Table 4: Overview of study designs

	Paper I	Paper II and IV	Paper III	Paper V
Topic	Self-reported health and return-to-work	Course of self-reported health	Return-to-work definitions	Self-reported health and adverse events
Design	Cohort study	Cohort study	Cohort study	Cohort study
Inclusion criteria	Alive at 4 weeks following PCI, received first questinnaire,(+not left the workforce the week before PCI)	Alive at 4 weeks following PCI	Alive at 4 weeks following PCI, received first questinnaire,not left the workforce the week before PCI	Alive at 4 weeks following PCI, no cardiac readmissions before first questionnaire
Sample size	1585/994	1726	994	1205
Data sources	First questionnaire, CPR, WDHR, DREAM	All questionnaires, CPR, WDHR, DREAM, DNPR	First questionnaire, CPR, WDHR, DREAM	First questionnaire, CPR, WDHR, DREAM, DNPR
Independent variables (exposure)	Age, gender, LVEF, indication of PCI, SF12 (MCS, PCS and general health)	Age, gender, LVEF, indication of PCI, educational level	Age, gender, LVEF, indication of PCI	SF12 (MCS and PCS)
Dependent variables (outcome)	Transfer payment group and RTW	SF12 (MCS and PCS)	RTW (several definitions)	Cardiac readmission and death
Data analysis	Proportions, Pseudovalues in generalized linear model, Logistic regression incl. ROC	Mixed models of repeated measurement data, Logistic regression	Proportions, agreement and Cohen's Kappa, Logistic regression	Cox regression
Multiple imputation	Only among respondents	Full dataset	No	Full dataset

For explanation of abbreviations, see inside frontcover

Timing

In Studies II and III, we established eight fixed measure points during follow-up (1, 3, 6, 12, 18, 24, 30 and 36 months after PCI). The measure points were established to reflect the most precise timing of the answer to the questionnaire based on an algorithm that used the actual date of the answer compared to the date of the PCI procedure rather than the number of the questionnaire.

Key variables

Outcomes

Return to work

We used the DREAM database to obtain weekly transfer payment group (TPG), before the PCI and during follow-up. From the transfer payment group, we obtained the outcomes related to return to work.

DREAM codes were grouped in six transfer payment groups:

1. Self-supporting
2. Labour market–related benefits
3. Health-related benefits
4. Early retirement
5. Normal retirement
6. Dead/emigrated

If there was no transfer income registered for a specific week, the person was considered self-supporting. Self-supporting also includes persons who received state education fund grants, maternity leave pay, and different leave-of-absence schemes. Health-related benefits included persons receiving social assistance because of problems other than unemployment, sickness benefit, vocational rehabilitation benefit, in flex job (jobs created for persons with limited work capacity), or unemployed from flex job. Early retirement meant persons over 60 years who have retired voluntarily or patients who were on anticipatory pension scheme or in light job (jobs created for persons on anticipatory pension). These definitions were previously used in a validation study [80]. Persons receiving social assistance ranged from those unemployed without labour market insurance and no other problems than unemployment to people with severe social and psychological problems. Hence, those who were registered at job centres were allocated to the group with labour market–related benefit, while the others were allocated to the group with health-related benefits. In Studies II and III, the DREAM codes were reduced to 5, as the group of self-supporting and labour market–related benefits was combined to one group.

We used the transfer payment groups to define the RTW outcomes for both Study I and Study V.

In Study I, we defined RTW as four consecutive weeks of self-support or on labour market-related benefits. When using RTW in a time-to-event analysis, the time was defined at the first week of the four. The week of the PCI was defined as “health-related benefits” in all patients. In Study V, we defined RTW in several different ways for comparison:

- Dichotomous at six and 12 months.
  Proportions returned to work at six and 12 months after PCI were defined by looking at the specific week for each patient. Patients who had permanently left the workforce before the time point were excluded.

- Time to first period of four weeks of RTW (as in Study I)
  Time to first period of four consecutive weeks of RTW within 12 months after the PCI was registered. The measure was further dichotomized in events/non-events for use in comparisons.

- Time to first registration of one week of RTW
  Time to first RTW within 12 months after the PCI and this measure was further dichotomized in events/non-events for use in comparisons.
  This outcome was only used for comparison with the four weeks RTW above.

- Time to first period of four weeks of RTW with no relapses.
  Time to first period of four consecutive weeks of RTW within 12 months after the PCI, excluding patients who experienced a new sick listing during the first year after first return to work. The measure was further dichotomized in events/non-events for use in comparisons.

- “Work Participation Score” within 12 months following RTW, defined as a fraction with numbers of RTW weeks in the numerator and numbers of weeks receiving social transfer payments + numbers of RTW weeks in the denominator. The “Work Participation Score” was dichotomized at three points (25%, 50% and 75% percentiles) to enable for comparison with the other measures.

Adverse events

In Study IV, we defined three different adverse events: 1: Cardiac readmissions, 2: Cardiac events and 3: Death.

We identified all admissions for the cohort in The Danish National Patient Registry. The exact timing of answering the first questionnaire for each patient was obtained to determine if an event had occurred before answering the questionnaire. Patients experiencing any cardiac readmission before answering of the first questionnaire (or, for the initial non-respondents, during the first four weeks) were excluded. Time in the study was then defined from the date

of PCI, with delayed entry at the answering of the first questionnaire. Cardiac admissions were registered by the primary diagnosis in all hospital admissions and the time to each admission obtained. 'Cardiac events' were defined as ICD10 codes DI20.0 DI21, DI23 and DI24, while 'cardiac readmissions' also included ICD10 codes DI20.1, DI20.8, DI20.9 and DI25 along with the cardiac event codes.
For the adverse outcome 'cardiac events', we used two different variants of including information on death;
1: by censoring at the date of death
2: by including death in the outcome of adverse cardiac events
For the adverse outcome 'death', we obtained the exact day of death until follow-up ended the 1. January 2011

The use of SF12

We used SF12 both as an outcome in Study III and as an exposure in Studies I and IV.
For the outcome of Study III, we used the two component summaries from SF12 in their continuous form. In Study I we used both the two component summaries and the single item “General Health”. The summaries were used in both their continuous form and dichotomised. In Study IV, we used the component summaries divided into percentiles and dichotomised. SF12 (and the longer version SF36) has been widely used in a range of studies of patients with coronary heart disease. The summaries were originally developed in a US population, with a mean score of 50 and a standard deviation of 10 as the a reference [82].

De Smedt et al. found SF12 valid and reliable in a large population of European coronary heart disease patients [83] and Dempster et al. found SF-12 to be preferable to SF-36 in ischaemic heart disease patients [84]. Since SF-12 is shorter than SF-36, it minimises the respondent burden, but may not distinguish between different domains in patients following myocardial infarction [56]. In the original manual of SF-36, Ware et al. suggested that differences larger than 5 points were clinically and socially relevant and comparable to a moderate effect size in Cohen’s rule of thumb [82].

Exposure variables and covariates

Demographic variables

Age and gender were derived from the Danish Personal Identification Number. In some analyses, age was recorded in age groups (-44, 45-54, 55-59, 60-67), in others age was dichotomised at the median (55 years), due to power considerations.

The patient’s educational level was derived from self-report in the questionnaire at 3 months. School education and professional education was grouped as low, intermediate or high according to the International Standard Classification of Education [85]. If patients did not report their educational level, we used information from DREAM on the patient's membership of a trade union to obtain their educational level (possible in 512 patients out of 682 missing)

The transfer payment group during the week before each answering of a questionnaire was obtained and used in the MI.

Clinical variables

The indication for the PCI was derived from the WDHR, whereas the variable primary indication was recorded with acute myocardial infarction as acute and all other indications as elective.

Left ventricular ejection fraction (LVEF) was obtained from the WDHR as well. LVEF was measured before the PCI, unless this was not possible in an acute situation. In this case, LVEF was measured immediately after the procedure. In 130 patients, an observation of LVEF was missing. LVEF was in some analyses categorised into <30%, 30-44%, 45-59% and 60%+.

Body Mass Index originated primarily from the WDHR, but in 76 patients observations were missing. We supplemented from patients self-report on their height and weight in 34 out of 76 missing BMI values. BMI categorised according to WHO classifications (– 24.9 kg/m2, 25-29.9 kg/m2 and 30+ kg/m2) [86].
Smoking status was categorised into "never smokers", "previous smokers" and "current smokers" in the WDHR. In 70 patients, smoking status was missing in the WDHR, whereas 48 could be established according to patients self-report in the questionnaires.

Prevalent comorbidity was calculated as a Charlson Index [87] using data from The Danish National Patient Registry on the basis of the primary diagnoses. The Charlson Index excluded hospital admissions in the 7 days preceding the PCI to avoid the actual procedure being part of the index. In the analyses, Charlson Index was further categorised into 0, 1-2 and more than 3 points.

In Study IV, we used incident comorbidity consisting of two different variables. First, we defined an indicator variable with information on early non-cardiac admissions in the period from the PCI to answering of the first questionnaire. Admissions during the first week preceding the PCI were not defined as new admissions, but considered related to the PCI. Secondly, we identified admissions during follow-up that were not new cardiac admissions.

Other self-reported variables

Leisure time physical activity was accessed with a single question *"If you should describe your* *physical activity during the past year, including transportation to/from work, in which of the following groups would you consider yourself to belong?"* - with the following answer categories:

1. Almost physically inactive or slightly active for less than two hours per week
2. Light physical activity between two and four hours per week (walking, biking, gardening)
3. Light physical activity for more than four hours per week, or heavy physically active between two and four hours per week (fast walking or biking overtaking others, heavy gardening, working out and getting short of breath):
4. Vigorous physical activity more than four hours weekly or heavy training on a regular basis and competing on weekly basis.

In some analyses, we dichotomised physical activity between categories 2 and 3.

We used two dimensions from Seattle Angina Questionnaire (SAQ) SAQ, namely the Angina Frequency dimension and the Angina Stability dimension in the MI in Studies II and III [73].

Statistical analyses

Time to event analyses

In Study I and Study IV, we used time to event analysis. In Study I, the proportional hazard assumption for Cox regression was not met as the hazard ratio changed over time for the variables gender and indication for PCI. Instead, the pseudo-value regression approach was used to examine the cumulative risk ratio at two time points (12 weeks and one year after PCI, respectively). In the pseudo-value approach, a new set of observations (the pseudo-values) are generated and used in a generalised linear model [88]. This model has the additional advantage that it can take competing risks into account. In supplementary analyses, we defined death and early retirement (voluntarily or health-related) as competing risk factors to the event of interest (RTW), while keeping normal retirement and emigration as censoring variables.

In Study IV, the proportional hazard assumption was fulfilled, and thus Cox regression was the method of choice. We defined time in the study from the date of PCI to first admission of interest, but since we used questionnaire data obtained at least 4 weeks after the PCI, reverse causation could occur if admissions during the period from PCI to answering of first questionnaire were defined as events. Consequently, we excluded patients that experienced a cardiac

readmission before the questionnaire, and defined the questionnaire date as delayed entry.
In Study I, we made an additional analysis that excluded patients that experienced the outcome return to work before answering the questionnaire. Only patients ‘at risk’ of an event were included, so that in Study I, patients who had left the work force permanently prior to the PCI were excluded.

Logistic regression

We used logistic regression in Studies I, III and V. In Study I, we used post-estimation of the C-statistics (area under ROC curve)[89].

Mixed models

In the analyses of the repeated measurements, we used mixed models [90]. A mixed model allows both random effects (i.e. variation within and between subjects and measurement errors) and fixed effects (i.e. gender, age, etc.). We analysed the data with and without the assumption of interaction of time (months).

Multiple imputation

In Study I, we used MI only among the respondents based on available SF-12 items, age, gender and transfer payment group the week before PCI, but only as a supplementary analysis and therefore not reported.
In Studies II, III and IV, we based the MI on data from the questionnaires as well as on register-based information and took the individual time course into account. We imputed all types of missing data, whether it was a single observation or a whole series due to initial non-participation or drop out. However, data not available because a person died were not considered missing data (Studies II and III). In order to impute the missing values, we specified stochastic models for each variable in which values were missing. The model should resemble how the variable was related to the other variables and support the MAR assumption. The models are presented in Appendix 1, Paper II, and Appendix 1, Paper IV.

Sensitivity analyses

As the assumption behind MI is that data are MAR, we modified the dataset generated from MI in order to examine the consequences of departures from this assumption. We hypothesised that patients in whom data were missing had poorer health than the imputation model could reveal under the MAR assumption. We then repeated the analyses, using the modified datasets, to examine whether estimated data were sensitive to such scenarios. Details of the scenarios are presented in Papers II, III and IV.

5. Summary of results

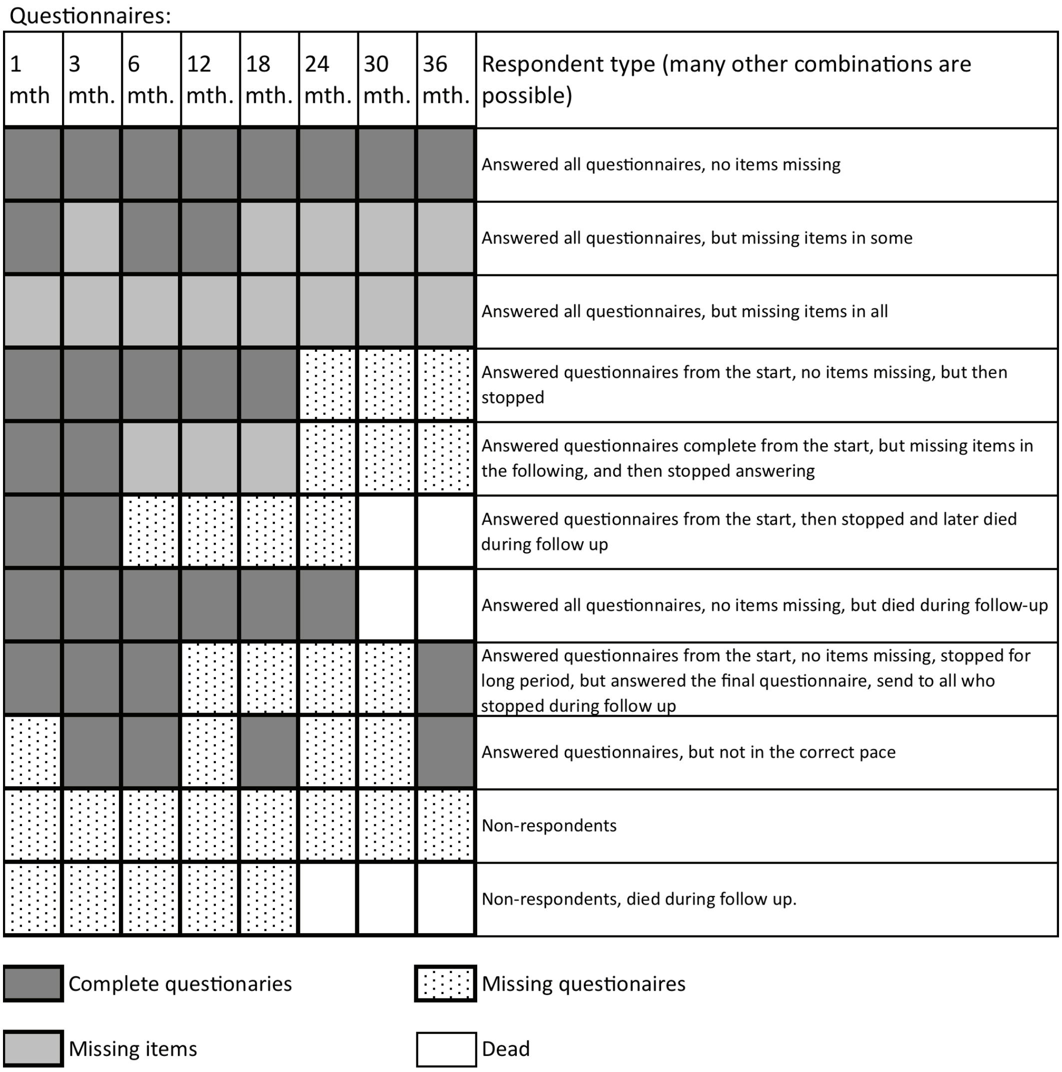
A summary of the main findings from the studies is given here. Additional results and a more detailed presentation are available in the appended papers.

Descriptive results

Participation and missing data

During the data collection, some patients skipped single items, some returned a scheduled questionnaire later than requested, some stopped answering the questionnaires and some died during follow-up. This resulted in several kinds of missing data on item, scale score, and questionnaire levels, along with attrition and initial non-participation. Figure 4 describes different patterns of response in an exemplified overview. All together 46 different response patterns were present in the cohort on the questionnaire level, not taking missing items into account.

Figure 4: Exemplified overview of some respondent types



Questionnaires:

1 mth	3 mth.	6 mth.	12 mth.	18 mth.	24 mth.	30 mth.	36 mth.	Respondent type (many other combinations are possible)
■	■	■	■	■	■	■	■	Answered all questionnaires, no items missing
■	▒	■	■	▒	▒	▒	▒	Answered all questionnaires, but missing items in some
▒	▒	▒	▒	▒	▒	▒	▒	Answered all questionnaires, but missing items in all
■	■	■	■	■	░	░	░	Answered questionnaires from the start, no items missing, but then stopped
■	■	▒	▒	▒	░	░	░	Answered questionnaires complete from the start, but missing items in the following, and then stopped answering
■	■	░	░	░	░	□	□	Answered questionnaires from the start, then stopped and later died during follow up
■	■	■	■	■	■	□	□	Answered all questionnaires, no items missing, but died during follow-up
■	■	■	░	░	░	░	■	Answered questionnaires from the start, no items missing, stopped for long period, but answered the final questionnaire, send to all who stopped during follow up
░	■	■	░	■	░	░	■	Answered questionnaires, but not in the correct pace
░	░	░	░	░	░	░	░	Non-respondents
░	░	░	░	░	□	□	□	Non-respondents, died during follow up.

■ Complete questionaries

░ Missing questionaires

▒ Missing items

□ Dead

The course of the data collection is presented in Table 5. The cohort included 1323 respondents who provided 7872 questionnaires covering the eight measure points. The 36-month participation was ~50% of the original cohort and ~36% attrition of the initial respondents. Seventy-four patients died during the 3 years of follow-up.

Whole-course respondents were defined as patients who responded to all questionnaires (n=761). Respondents who dropped out were defined as people who stopped answering during follow-up, including those who answered only the first questionnaire (n=470). Among the dropouts, 42 patients died during follow-up. Returnees were patients who completed parts of the study, but not in the scheduled pace, resulting in intermitting missing questionnaires (n=92). This group included the dropouts that were approached again at the end of the study. Non-respondents were defined as patients who initially did not return any questionnaires at all (n=403). The non-respondents also included the 141 patients who were never invited to take part of the study because they had hidden addresses. In the group of non-respondents, 32 patients died during follow-up. These response types can also be identified in Figure 4, where the upper three rows are patients who completed the whole study, the following four rows are examples of patient who stopped during follow-up, then two rows with returnees and the two bottom rows with non-responders.

A patient's response-category could change over time, e.g. at the beginning of the study a patient could be classified as a non-respondent, but return the initial questionnaire later than requested, and then be classified as a returnee. After that, the same patient could stop answering further questionnaires and thus be classified as a dropout. The categorisations into the three groups are made after the data collection had been completed.

Table 5: Response patterns and attrition (N=1726)

	1 mth.	3 mth.	6 mth.	12 mth.	18 mth.	24 mth.	30 mth.	36 mth.
Overall mortality		5	5	9	15	14	14	12
Alive in current round	1726*	1721	1716	1707	1692	1678	1664	1652
From previous round	-	1323	1112	1057	1012	980	954	892
- Attrition #	262	211	55	45	32	26	62	39
= Available for next round	1323	1112	1057	1012	980	954	892	
- Intermittent missing questionnaire**	29	8	31	53	64	73	53	-
= Returned questionnaires	1294	1104	1026	959	916	881	839	853**
Responserate according to previous round	-	83,4%	92,2%	90,7%	90,5%	89,9%	87,9%	95,6%
SF-12 PCS/MCS								
Complete	1144	979	945	899	858	827	783	780**
Incomplete	150	125	81	60	58	54	56	73
Seattle Angina Questionnaire (frequency dimension)								
Complete	-	1046	1007	888	798	728	682	731**
Incomplete	-	58	19	71	118	153	157	122
Seattle Angina Questionnaire (stability dimension)								
Complete	-	1056	1015	891	805	738	690	736**
Incomplete	-	48	11	68	111	143	149	117

* 141 patients had hidden addresses and were not sent questionnaires.

\# Dead and non-respondents after 2 reminders

** Intermittent missing questionnaire in first round occurred when the first questionnaire was delayed from the patient to the second time point 3 months after PCI. The following intermittent missing occurred because all patients who stopped answering during follow-up without any known reason was mailed a final questionnaire. This resulted in an increase in returned questionnaires in the final round.

Table 6 describes the baseline characteristics including missing data distributed according to whole-course respondents, dropouts, returnees, and non-respondents. Tendencies in differences between the response types are presented in the following.

Patients who were non-respondents differed from the respondents who completed the whole study course by being more often women, younger and more often treated for an acute PCI, suffered from more comorbidity and had unhealthier lifestyle in terms of smoking habits and high BMI. They had more often left the workforce (except from normal retirement, which was most common among respondents)
The patients who dropped out differed from the patients who completed the whole study course in the same aspects as those seen in the non-respondents and respondents. In addition, they were less physically active.

The returnees were similar to the patients who completed the whole study course, except that they were in general younger and thus more often treated acutely, they were more often current smokers and slightly overweight. They were slightly more educated, perhaps because of their younger age.
The non-respondents had a higher mortality than the patients who dropped out.

The patients who died during follow-up differed from those who were lost to follow-up for other reasons, as they were older and had a lower LVEF. They also suffered from more comorbidity. Many of those who died had left the workforce permanently already from the beginning of the study (data not shown).

In conclusion, there were many differences between respondents and non-respondents, between whole-course respondents and respondents who dropped out as well as between patients who died during follow-up compared to those who dropped out for other reasons. Based on these findings, results based on complete cases would most likely be biased, as the outcome self-reported health was strongly prone to be related to most of the variables about which non-respondents, patients who dropped out and dead patients differed from the whole course respondents. Note that the above description is related to the complete cohort. Differences between respondents and non-respondents in relation to Study IV are described in Paper IV, Table 2.

Table 6: Characteristics of response types

	All	Respondents			Non-respondents
		Whole study course	With dropout	Returnees	
Total	1726 (100.0%)	761 (100.0%)	470 (100.0%)	92 (100.0%)	403 (100.0%)
Gender					
Male	1360 (78.8%)	612 (80.4%)	364 (77.4%)	76 (82.6%)	308 (76.4%)
Female	366 (21.2%)	149 (19.6%)	106 (22.6%)	16 (17.4%)	95 (23.6%)
Age					
-44	168 (9.7%)	28 (3.7%)	53 (11.3%)	12 (13.0%)	75 (18.6%)
45-54	476 (27.6%)	183 (24.0%)	139 (29.6%)	38 (41.3%)	116 (28.8%)
55-59	393 (22.8%)	176 (23.1%)	115 (24.5%)	24 (26.1%)	78 (19.4%)
60-67	689 (39.9%)	374 (49.1%)	163 (34.7%)	18 (19.6%)	134 (33.3%)
Indication					
Acute	557 (32.3%)	233 (30.6%)	157 (33.4%)	32 (34.8%)	135 (33.5%)
Elective	1169 (67.7%)	528 (69.4%)	313 (66.6%)	60 (65.2%)	268 (66.5%)
Comobidity					
Charlson Index 0	1010 (58.5%)	476 (62.5%)	259 (55.1%)	54 (58.7%)	221 (54.8%)
Charlson Index 1	393 (22.8%)	169 (22.2%)	106 (22.6%)	26 (28.3%)	92 (22.8%)
Charlson Index 2+	323 (18.7%)	116 (15.2%)	105 (22.3%)	12 (13.0%)	90 (22.3%)
Transfer payment group (week before PCI)					
Working/unemployed	692 (40.1%)	308 (40.5%)	188 (40.0%)	44 (47.8%)	153 (38.0%)
Health-related benefits	400 (23.2%)	152 (20.0%)	109 (23.2%)	32 (34.8%)	107 (26.6%)
Early retirement	448 (26.0%)	187 (24.6%)	136 (28.9%)	10 (10.9%)	115 (28.5%)
Normal retirement	186 (10.8%)	114 (15.0%)	37 (7.9%)	6 (6.5%)	29 (7.2%)
Left ventricular ejection fraction					
-34	89 (5.2%)	30 (3.9%)	17 (3.6%)	1 (1.1%)	41 (10.2%)
35-54	612 (35.5%)	242 (31.8%)	197 (41.9%)	35 (38.0%)	138 (34.2%)
55+	895 (51.9%)	429 (56.4%)	226 (48.1%)	47 (51.1%)	193 (47.9%)
Missing	130 (7.5%)	60 (7.9%)	30 (6.4%)	9 (9.8%)	31 (7.7%)
Smoking					
Never	330 (19.1%)	186 (24.4%)	67 (14.3%)	16 (17.4%)	61 (15.1%)
Current	763 (44.2%)	272 (35.7%)	228 (48.5%)	40 (43.5%)	223 (55.3%)
Previous	597 (34.6%)	302 (39.7%)	164 (34.9%)	36 (39.1%)	95 (23.6%)
Missing	36 (2.1%)	1 (0.1%)	11 (2.3%)	0 (0.0%)	24 (6.0%)
Body mass index					
-24.9	485 (28.1%)	230 (30.2%)	126 (26.8%)	22 (23.9%)	107 (26.6%)
25-29.9	774 (44.8%)	357 (46.9%)	207 (44.0%)	51 (55.4%)	159 (39.5%)
30+	425 (24.6%)	173 (22.7%)	121 (25.7%)	19 (20.7%)	112 (27.8%)
Missing	42 (2.4%)	1 (0.1%)	16 (3.4%)	0 (0.0%)	25 (6.2%)
Physical activity					
<2 hours/week	96 (5.6%)	52 (6.8%)	39 (8.3%)	5 (5.4%)	-
2-4 hours/week	402 (23.3%)	277 (36.4%)	91 (19.4%)	34 (37.0%)	-
>4 hours/week	480 (27.8%)	352 (46.3%)	85 (18.1%)	43 (46.7%)	-
>4 hours/week, heavy	82 (4.8%)	61 (8.0%)	14 (3.0%)	7 (7.6%)	-
Missing	666 (38.6%)	19 (2.5%)	241 (51.3%)	3 (3.3%)	403 (100.0%)
Education level					
Low	253 (14.7%)	152 (20.0%)	66 (14.0%)	9 (9.8%)	26 (6.5%)
Intermediate	742 (43.0%)	278 (36.5%)	205 (43.6%)	41 (44.6%)	218 (54.1%)
High	561 (32.5%)	304 (39.9%)	139 (29.6%)	41 (44.6%)	77 (19.1%)
Missing	170 (9.8%)	27 (3.5%)	60 (12.8%)	1 (1.1%)	82 (20.3%)

Baseline characteristics

Table 7 presents the baseline characteristic of the complete cohort. For similar tables in the studies with smaller sample sizes, please refer to the corresponding tables in Studies I, IV and V. Almost 80% of the patients were men, and 32% were treated acutely. The baseline characteristics were much the same for men and women, except that women were less often overweight or obese. Patients treated acutely were younger, with a higher LVEF, more often smokers and suffered less often from comorbidity compared to patients with other indications (Table 7).

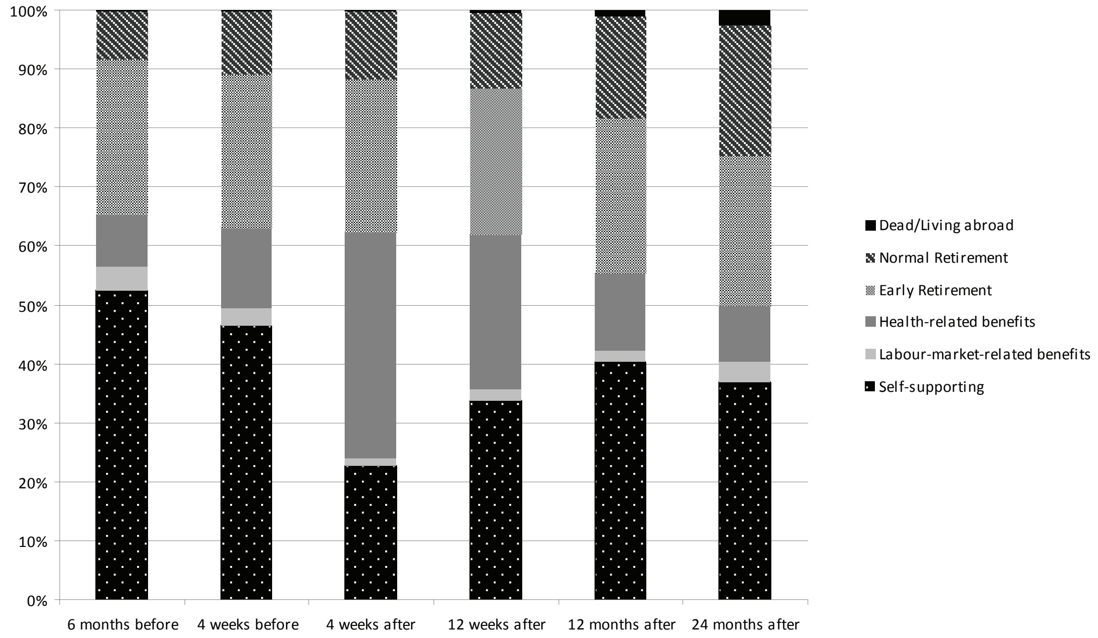
Table 7: Patient characteristics at PCI

	All patients	Gender		Indication	
	N (%)	Male N (%)	Female N (%)	Acute N (%)	Other N (%)
Total	1726 (100)	1360 (100)	366 (100)	557 (100)	1169 (100)
Gender					
Male	1360 (79)	1360 (100)		446 (80)	914 (78)
Female	366 (21)		366 (100)	111 (20)	255 (22)
Indication					
Acute	557 (32)	446 (33)	111 (30)	557 (100)	
Elective	1169 (68)	914 (67)	255 (70)		1169 (100)
Age					
-44 years	168 (10)	117 (9)	51 (14)	82 (15)	86 (7)
45-54 years	476 (28)	388 (29)	88 (24)	162 (29)	314 (27)
55-59 years	393 (23)	318 (23)	75 (20)	120 (22)	273 (23)
60-67 years	689 (40)	537 (39)	152 (42)	193 (35)	496 (42)
LVEF					
-34 %	89 (5)	69 (5)	20 (5)	35 (6)	54 (5)
35-54 %	612 (35)	505 (37)	107 (29)	283 (51)	329 (28)
55+ %	895 (52)	688 (51)	207 (57)	185 (33)	710 (61)
Missing	130 (8)	98 (7)	32 (9)	54 (10)	76 (7)
Educational level					
Low (<11 y)	253 (15)	186 (14)	67 (18)	79 (14)	174 (15)
Intermediate (11-14 y)	742 (43)	606 (45)	136 (37)	237 (43)	505 (43)
High (15+ y)	561 (33)	459 (34)	102 (28)	197 (35)	364 (31)
Missing	170 (10)	109 (8)	61 (17)	44 (8)	126 (11)
Comorbidity					
Charlson Index 0	1010 (59)	802 (59)	208 (57)	410 (74)	600 (51)
Charlson Index 1	393 (23)	312 (23)	81 (22)	80 (14)	313 (27)
Charlson Index 2+	323 (19)	246 (18)	77 (21)	67 (12)	256 (22)
Transfer payment group (week before PCI)					
Working/unemployed	692 (40)	592 (44)	100 (27)	316 (57)	376 (32)
Health-related benefits	400 (23)	311 (23)	89 (24)	63 (11)	337 (29)
Early retirement	448 (26)	320 (24)	128 (35)	127 (23)	321 (27)
Normal retirement	186 (11)	137 (10)	49 (13)	51 (9)	135 (12)
Smoking					
Never	330 (19)	262 (19)	68 (19)	84 (15)	246 (21)
Current	763 (44)	583 (43)	180 (49)	337 (61)	426 (36)
Previous	597 (35)	490 (36)	107 (29)	124 (22)	473 (40)
Missing	36 (2)	25 (2)	11 (3)	12 (2)	24 (2)
BMI					
-24.9 kg/m2	485 (28)	328 (24)	157 (43)	166 (30)	319 (27)
25-29.9 kg/m2	774 (45)	666 (49)	108 (30)	261 (47)	513 (44)
30+ kg/m2	425 (25)	332 (24)	93 (25)	109 (20)	316 (27)
Missing	42 (2)	34 (3)	8 (2)	21 (4)	21 (2)
Physical activity (at 3 mths)					
<2 h/wks	96 (6)	69 (5)	27 (7)	20 (4)	76 (7)
2-4 h/wks	402 (23)	293 (22)	109 (30)	125 (22)	277 (24)
>4 h/wks, light	480 (28)	406 (30)	74 (20)	157 (28)	323 (28)
>4 h/wks, heavy	82 (5)	77 (6)	5 (1)	21 (4)	61 (5)
Missing	666 (39)	515 (38)	151 (41)	234 (42)	432 (37)

Workforce participation

Roughly half of the patients were self-supporting prior to PCI. Four weeks after the PCI, 23% were self-supporting, and this figure increased to 34% after three months and to 40% at one year. Already six months before the PCI, 9% received health-related benefits, and this increased to 14% four weeks before the PCI. Four weeks after the PCI, 39% received health-related benefits, which after 12 weeks had decreased to 26% and at one year only 13% received health-related benefits. The proportion of early retirement was roughly constant at all measurement times, whereas normal retirement increased due to increasing age.
Restricting the population to those working the week before the PCI (n=593), 68% were back to work 12 weeks after PCI and 77% after 1 year (data not shown). Among those receiving health-related benefits in the week before the PCI (n=362), 36 % and 47% returned to work after 12 weeks and one year, respectively (data not shown).

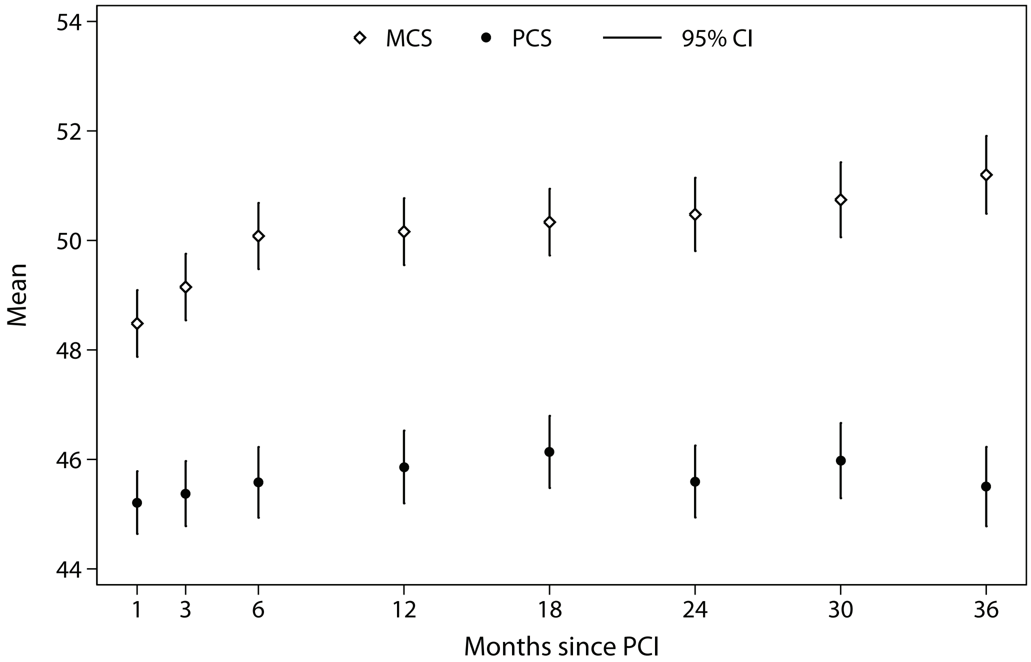
Figure 5: Income sources for patients before and after PCI



Course of self-reported health over three years follow-up post-PCI

Mental health improved slightly during follow-up, with an increase of 0.74 [0.50; 0.98] points pr. year, with most of the improvements in the first six months after PCI (Figure 7). The physical health did not improve; the estimated increase per year was 0.09 [-0.14; 0.32]. The means presented in Figure 7 are also available in Table 3, Paper III, first column, along with estimates for increase per year, level if assumed constant since PCI and tests for constant level since PCI.

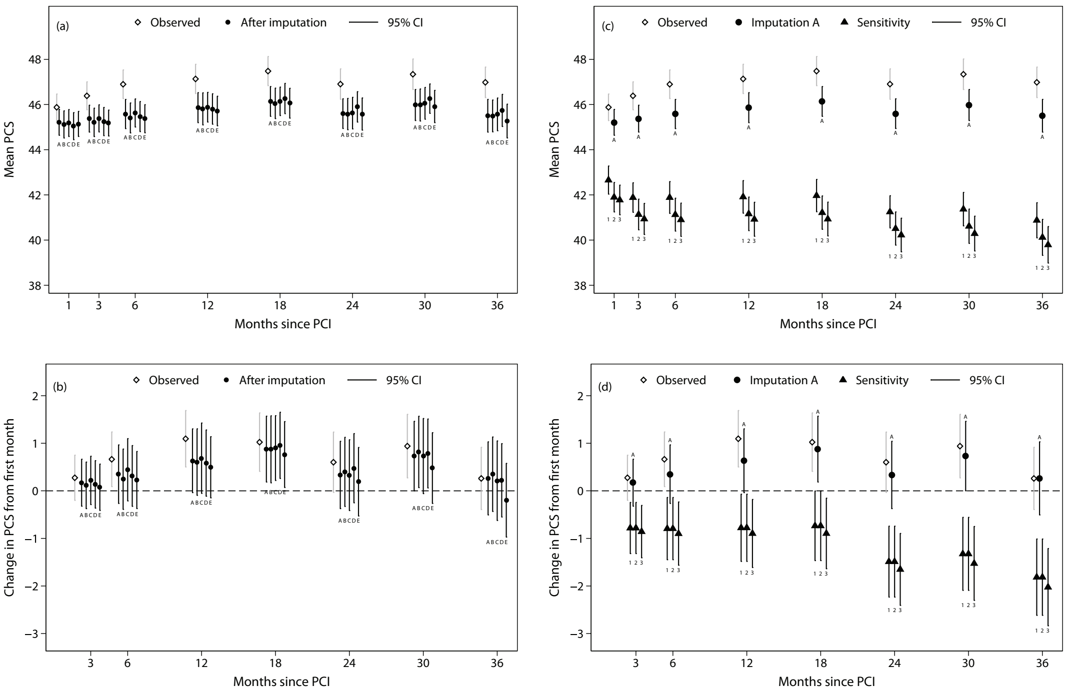
Figure 6: Course of MCS and PCS from SF-12 following PCI



Multiple Imputation (PCS)

To describe the impact of the different variants of MI the original data, and how the scenarios of sensitivity analyses influenced the mean scores and the changes from first measurement, results based on the physical component score are presented (Figure 6), whereas in Paper II, results related to the mental component score are presented. MI decreases both the mean scores and the changes over time. On applying sensitivity analysis, the mean scores and the changes over time decreased even more, especially towards the end of the study, at which time proportions of missing data increased.

Figure 7: Mean scores and mean changes in PCS with observed data, variations of multiple imputation approaches related to death (a and b), and sensitivity analyses (c and d)



Adverse Events

In Study IV, 224 patients were excluded prior to the analyses because they experienced a cardiac readmission before answering the questionnaire. Of the remaining 1502 patients, 526 patients experienced a cardiac readmission during follow-up, of which 148 patients had a new cardiac event and 529 patients were admitted in hospital for non-cardiac diagnoses. Eighty-three patients died during follow-up, of which 11 also had experienced a cardiac event on the same day. .

Analytic results

Prognostic factors of return to work

The single item, 'general health' four weeks after the procedure was strongly associated with RTW at both 12 weeks and after one year with a strong exposure-response effect (Table 8). Also the two component summaries were strongly related to RTW. Mental health was nearly as important as physical health. Low LVEF was also a risk factor in both the short and the long term. LVEF did not modify the effect of general health, because the estimates were stable within the strata of LVEF (data not shown).

In unadjusted analyses, young age was associated with low RTW shortly after the intervention, but this was not significant in adjusted analyses, and the effect diminished after one year (Table 8). Female gender was associated with low RTW especially shortly after the procedure, but also in the long term. Patients treated because of an acute indication had more difficulties in RTW shortly after the procedure compared to electively treated patients, but this difference diminished after one year. Gender and indication did not modify the effect of the other variables on RTW.

Table 8: Risk Ratio (RR) of Return to Work 12 weeks and one year after PCI according to demographics, clinical information and self-reported health. Low RR indicates difficulties.

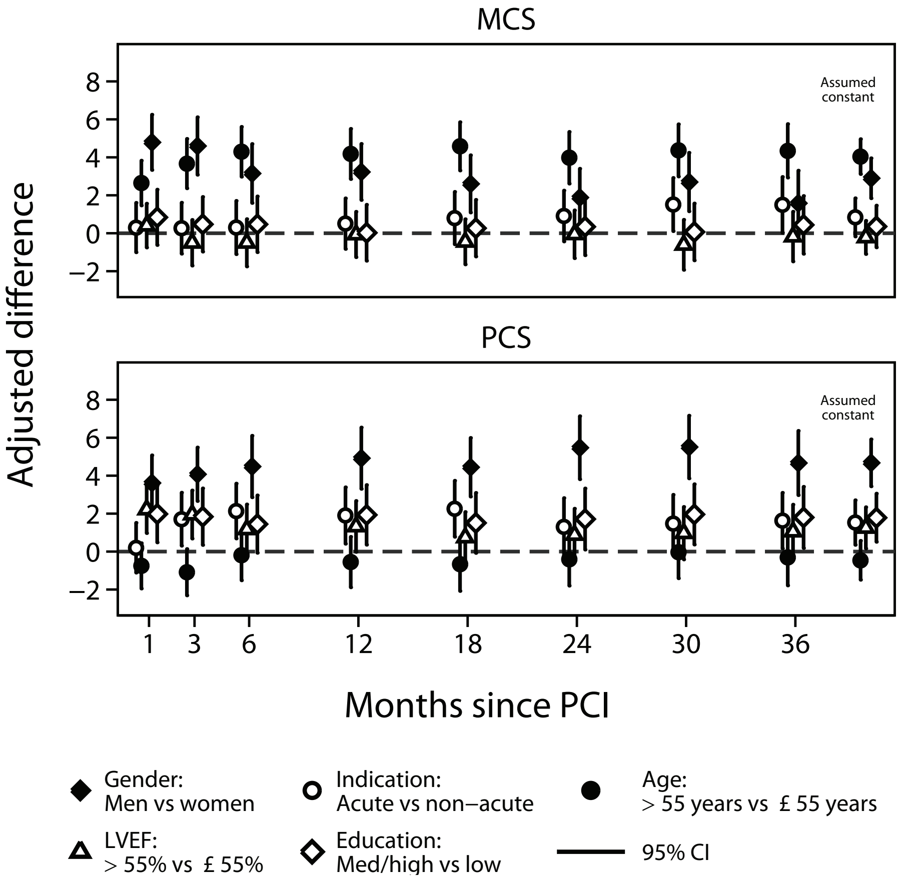
		12 weeks after PCI		One year after PCI	
		Crude RR	Adjusted RR*	Crude RR	Adjusted RR*
Age	-44	0.69[0.54;0.87]	0.86[0.68;1.08]	0.94[0.83;1.06]	1.03[0.92;1.15]
	45-54	0.94[0.82;1.08]	1.01[0.89;1.15]	0.97[0.89;1.05]	1.03[0.95;1.10]
	55-59	0.94[0.81;1.09]	1.00[0.87;1.14]	1.00[0.92;1.09]	1.05[0.98:1.14]
	60-67	Ref.	Ref.	Ref.	Ref.
Sex	Female	0.66[0.54;0.80]	0.72[0.58;0.90]	0.77[0.68;0.87]	0.85[0.75;0.96]
	Male	Ref.	Ref.	Ref.	Ref.
Indication	Acute MI	0.75[0.65;0.85]	0.78[0.68;0.89]	0.97[0.91;1.04]	1.00[0.94;1.07]
	Other	Ref.	Ref.	Ref.	Ref.
LVEF	-34	0.50[0.32;0.78]	0.66[0.40;1.09]	0.64[0.48;0.84]	0.71[0.53;0.95]
	35-54	0.80[0.71;0.90]	0.89[0.80;0.99]	0.90[0.84;0.88]	0.90[0.85;0.96]
	55+	Ref.	Ref.	Ref.	Ref.
SF12 GH	Poor	0.12[0.03;050]	0.14[0.04;0.58]	0.34[0.18;0.62]	0.38[0.21;0.70]
	Fair	0.45[0.34;0.60]	0.50[0.37;0.66]	0.50[0.43;0.63]	0.55[0.44;0.67]
	Good	0.66[0.56;0.77]	0.71[0.60;1.62]	0.82[0.77;0.88]	0.84[0.79;0.90]
	Very good	0.92[0.80;1.06]	0.93[0.80;1.08]	0.96[0.91;1.01]	0.95[0.90;1.00]
	Excellent	Ref.	Ref.	Ref.	Ref.
SF12 MCS	-49	0.63[0.56;0.72]	0.68[0.60;0.78]	0.79[0.74;0.86]	0.82[0.76;0.88]
	50+	Ref.	Ref.	Ref.	Ref.
SF12 PCS	-49	0.58[0.52;0.66]	0.62[0.55;0.70]	0.73[0.68;0.78]	0.76[0.71;0.82]
	50+	Ref.	Ref.	Ref.	Ref.

* Age, sex, indication and LVEF were mutually adjusted and adjusted for SF12GH

*SF12 GH, SF12 MCS and SF12 PCS were adjusted for age, sex, indication and LVEF.

Assessing the differences between the five factors in focus, the adjusted analysis of MCS showed that women reported their mental health to be lower than did men (Figure 8, upper part). The gender differences in mental health were not stable over time; they were largest in the first part, but diminished over time (p=0.01). There were no differences in mental health between patients treated acutely compared to other indications. Younger patients (<55 years) reported their mental health to be lower than did older patients. No difference between patients with low versus high LVEF was identified. Patients with low educational level reported their mental health to be at the same levels, as did patients with intermediate or high education.

Figure 8: Adjusted differences in MCS and PCS between the five factors in focus: indication, age, left ventricular ejection fraction, gender and educational level at 8 points of time following PCI



In the adjusted analyses of physical health, women reported their health to be lower than did men (Figure 8, lower part). Patients treated acutely reported their physical health to be higher than did electively treated patients (however not significant at all time points), except at the first measurement 4 weeks after the PCI. The differences in physical health between acute indication and elective indications were not stable over time (p=0.01). Contrary to the analyses of mental health, no difference between older and younger patients' rating of their physical health was identified. High LVEF had a minor positive influence at the beginning of the study, but this diminished over time. Patients with low educational level reported their physical health to be worse than did patients with intermediate or high education. All estimates related to Figure 8 are available from Table 3, Paper III.

Prognostic factors of adverse events

The time to event analysis (Table 9) showed that poor self-reported health was associated with cardiac readmissions, cardiac events and all cause mortality. The association was strongest between PCS and the outcomes, compared to MCS. Both measures showed significant exposure-response relationships, again stronger for PCS compared to MCS. The association between self-reported health and all cause mortality was stronger than with cardiac events and readmissions. Adjustment for possible confounders changed the estimates only slightly, in general towards a reduction of the estimates.

Table 9: Association between self-reported mental and physical health (SF-12) with four different adverse events in PCI patients

	Cardiac event		Cardiac event incl. death		Cardiac readmission		Death	
	Crude HR	Adjusted* HR	Crude HR	Adjusted* HR	Crude HR	Adjusted* HR	Crude HR	Adjusted** HR
Mental Component Summary								
<42	1.5[0.8;2,6]	1.3[0.7;2.4]	1.9[1.2;3.0]	1.7[1.0;2.8]	1.5[1.2;2.1]	1.5[1.1;2.0]	3.1[1.2;7.8]	2.9[1.1;7.5]
42-49.9	1.6[0.9;2.7]	1.5[0.8;2.5]	1.8[1.1;2.9]	1.8[1.1;2.8]	1.4[1.0;1.8]	1.3[1.0;1.8]	2.2[0.9;5.8]	2.5[0.9;6.6]
50-56.9	1.3[0.7;2.3]	1.3[0.7;2.2]	1.4[0.9;2.3]	1.4[0.8;2.3]	1.2[0.9;1.5]	1.1[0.8;1.5]	1.7[0.7;4.4]	1.7[0.7;4.5]
57+	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Test for trend:	p=0.34	p=0.53	p=0.029	p=0.10	p=0.007	p=0.022	p=0.017	p=0.039
Under 50	1.3[0.9;2.0]	1.2[0.8;1.9]	1.5[1.1;2.2]	1.5[1.0;2.1]	1.3[1.1;1.7]	1.3[1.1;1.6]	2.0[1.1;3.7]	2.0[1.1;3.8]
Physical Component Summary								
<38	2.1[1.3;3.6]	2.1[1.2;3.7]	3.1[2.0;4.9]	2.6[1.6;4.3]	2.0[1.6;2.7]	2.1[1.6;2.9]	7.6[2.7;21.5]	5.0[1.7;14.6]
38-45.9	1.5[0.8;2.6]	1.4[0.8;2.6]	2.0[1.2;3.2]	1.7[1.0;2.9]	1.3[1.0;1.7]	1.3[1.0;1.8]	4.4[1.5;12.5]	3.4[1.1;9.8]
46-52.9	1.3[0.7;2.3]	1.3[0.7;2.3]	1.5[0.9;2.6]	1.5[0.9;2.5]	1.2[0.9;1.6]	1.2[0.9;1.6]	2.9[1.0;8.5]	2.4[0.8;7.0]
53+	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
Test for trend:	p=0.004	p=0.01	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p=0.005
Under 46	1.6[1.1;2.3]	1.5[1.0;2.3]	2.0[1.5;2.8]	1.8[1.2;2.5]	1.5[1.2;1.9]	1.5[1.2;1.9]	3.2[1.7;6.0]	2.5[1.3:4.7]

* Adjusted for age, gender, comorbidity, indication of PCI, LVEF, educational level and lifestyle (smoking, physical activity and BMI)
** Adjusted for age, gender, comorbidity, indication of PCI, LVEF and hospital admissions during follow-up.

6. Discussion

Findings

In the following, the key findings for each study are discussed separately in light of other studies. A generalized section with discussion of methodological considerations across the studies will follow after the separate discussions of each study's results.

Study I:

A large proportion of the PCI patients (n=591) had left the workforce permanently already before the PCI. Among the patients working before the PCI, nearly 80% returned to work during the first year. This compares well with previous studies [22,23,25,26,91-96]. Risk factors related to delay in RTW in the short (12 weeks) and the long (one year) term were female gender, low LVEF, poor reporting of health (both mental and physical) and in the short time: acute indication for the PCI.

Age [22-24] and gender [23] have previously been found related to RTW in mixed populations of heart patients. However, another study found neither gender nor age related to RTW [25]. Nielsen et al. found that gender modified the effect of low LVEF on RTW [27]. Studies of mortality in heart disease have found that gender differences diminish after adjustment for age [5], but our results did not reproduce this with regard to the outcome, RTW, where large gender differences were identified. Gender differences in sickness absence are well known [97,98] and are suggested to come from both direct and indirect gender effects, such as differences in daily life and social position[99]. Both myocardial infarction prior to the PCI [26] and low LVEF [27] have previously been identified as risk factors.

The patients' self-reported health one month after the procedure was strongly related to RTW in both the short and long term compared to other variables, including LVEF. Mental health was nearly as important as physical health. The results were robust to stratifications with regard to gender and indication as well as restrictions with regard to patients who experienced RTW before the questionnaire.

In additional analyses, death and early retirement (voluntarily or health-related) were considered as competing risk factors to the event of interest (RTW), while normal retirement and emigration were kept as censoring variables. This did not change the estimates.

Self-reported health has previously been found related to prognosis in terms of readmissions and mortality after cardiovascular disease [34,100,101]. A large Dutch study of 1-year mortality after angiographic procedures found that problems with self-care and low self-reported health were the most powerful predictors among 22 clinical variables and reported that addition of self-reported health increased the model c-statistics from 0.78 to 0.81 [47]. In Study I, an addition of the single-item general health from SF12 to the clinical information increased the model c-statistics from 0.66 to 0.73 for RTW at 12 weeks and from 0.66 to 0.75 at one year. Adding the complete SF12 score increased the c-statistics even more.

In both the analysis of risk factors and predictors, the mental health component score were nearly as important as the physical component score. A recent review indicated that not only poor physical health, but also poor mental health was associated with adverse prognosis (mortality and rehospitalisation) in heart disease [40], and anxiety and depression have previously been found associated with RTW after heart disease [23,102].

Other countries may have different social systems and regulations, which may influence generalisability to other populations. Due to the financial crisis, absenteeism due to sick leave may have decreased, leading to so-called presenteeism, where people are working even though they are not feeling well [103]. This phenomenon may have influenced the patterns of RTW in the cohort, and should be considered when comparing the results to other populations.

Study II:

The study illustrated that MI supplemented with sensitivity analyses is a feasible method to deal with bias due to missing data, attrition and dropout in longitudinal studies. Previous studies have used available SF12 items in imputations in cross-sectional settings, but only among respondents and with limited use of auxiliary information [104,105]. Only few previous studies have used MI to deal with missing SF-12 (or SF-36) data in a cohort with repeated follow-ups. In patients with heart disease, Weintraub et al. used MI to impute intermittent missing scores in the Seattle Angina Questionnaire and SF-36 in a study with repeated measurements, following the same time pattern as our study. Their imputation strategy was to impute intermitting missing data only, and not missing data due to non-response or patients who dropped out [58]. One small study that used weighing to adjust for sampling bias was identified [56].

Imputation has previously been used in longitudinal studies. In a recent review Enders et al. suggested using MI methods instead of complete case analysis and that the choice of MI method should depend on context and assumptions behind the mechanisms of missing data[106]. Fielding et al. compared different single imputation methods with MI methods and found that MI was superior to single imputation in quality of life data [107]. In a longitudinal simulation study, Twisk compared different imputation approaches including MI. They recommended MI or longitudinal single imputation that led to similar different point estimates; however, MI had more valid variability [108]. We were not able to identify studies that used MI in a longitudinal design that took into account that deaths occurred during follow-up. Most studies used MI only in patients who took part in the complete study course. Other studies have used the strategy to replace dead persons' HRQOL scores with zero [65,66]. Dufouil et al. recommended that informative dropout due to death should be treated differently, possibly with an indicator of death in the model, that in this case used inverse probability weighting to deal with missing data [109]. The very similar results after the different approaches of treating death may be due to the low number of incident deaths in the follow-up period. In similar situations with few incident deaths during follow-up, it seems safe to use the simplest applicable method, imputing all missing data and recoding all values after death as missing and avoiding an indicator of being dead at the next measure point. However, in other populations with higher mortality-rates, the different approaches should be applied to evaluate the importance of the method of choice. If the number of dead patients is large, an indicator of death is desirable. How to handle death when using the strategy of the previous and the following measurements in the equations is still unknown and needs to be studied further in settings with higher mortality than in the present study.

Study III:

In a geographically well-defined population of patients treated with PCI, mental health improved during follow-up, with the largest improvements during the first half-year following PCI. Physical health did not improve. The pronounced gender differences in mental health diminished over time, while the gender differences in physical health rating were stable. Patients under 55 year were affected with regard to their mental health, but not their physical health, compared to the older patients.

Most previous longitudinal studies that report the course of mean scores of self-reported health in heart patients; find improvements in the first three to six months, after which a steady level is reached. However, the improvements in the component summaries are in general small, as in our current study. In general, improvements in the physical health were larger than in the mental health in previous studies [55-58]. This is in contrast to our findings, where improvements were only present in mental health. Whether this is related to the selection of study participants in previous studies is unknown, but in our study this pattern was present even in the observed data before MI (Figure 3, Study II), except that a small increase in physical health was present in the observed data (Figure 3, Appendix 2, Study II). It may also relate to the fact that no measurement at baseline (before the PCI) was available, as in several other studies. A measurement before the PCI could only have been obtained from patients treated electively, unless measured retrospectively by recall, and would have required different logistics in inclusion of patients.

Gender differences in self-reported health are well known from other studies [51,52,110]. Mortensen et al. found that women had lower scores in both MCS and PCS after both one month and 12 months, and they had a larger increase in scores over time [51]. This compares well with our findings in regard to MCS, but in our study the gender difference in PCS was stable over the follow-up period. Pedersen et al. found that women reported their health to be lower in all eight subscales of SF36, six and 12 month after PCI, but they did not find any interaction with gender over time [52]. This was in contrast to our findings, possibly because of the longer follow-up time and the multiple measure points in our study. Gender differences in prognosis in terms of mortality have been reported to disappear when adjusted for age and comorbidity [5,110,111] but these adjustments (along with adjustment for educational level, LVEF and indication) could not explain the differences in this study. The gender differences in MCS found in our study were larger than the in the general Danish population, aged 55-64, where the difference is ~1, equivalent to 0.1 standard deviation [112]. Especially at the beginning of the study, the MCS for women was lower than for men, but towards the end of the study the difference came closer to the gender difference in the general population. The gender difference in the PCS was larger than in the general Danish population, aged 55-64, where the difference is ~2.5, equivalent to 0.25 standard deviation [112] even after adjustment for possible confounding factors such as age, indication, LVEF, educational level and comorbidity.

No studies reporting self-reported health in relation to age were identified. In the general population, physical health decreases with age, while mental health is more constant [112]. Why younger patients in our study reported their mental health to be worse than did older patients is unknown, and these results need to be confirmed in future studies.

Previous studies have found differences related to socio-economic status in health related quality of life following PCI [113,114]. In the present study, these findings were only reproduced in the PCS, possibly due to different definitions of socio-economic status or other methodological differences. We a priori hypothesised that disease severity measured with LVEF and the indication for the procedure was associated with the self-reported health. This was not the case in respect to mental health, but only to physical health, and the differences were small.

Study IV:

This study demonstrates that poor self-reported health shortly after the PCI was associated with adverse outcomes during up to 5-years follow-up. The strongest association was found between self-rated health and death, but also associations between self-rated health and cardiac readmissions and cardiac events during follow-up were present, even with an exposure-response relationship. Physical health revealed the strongest associations, but also mental health was associated with adverse events.

Our findings are in line with previous studies that found that patient's self-reported health is associated with adverse outcomes in terms of readmissions and death [40,42-46]. As recent studies suggest, not only physical but also mental health plays an important role [42,43,45], and this was in line with our results.

We found that all outcome measures were associated with patient-reported health, but the mechanism behind these associations may either be related to disease symptoms, severity and progression [115] or related to the patient's health in general [116]. If patient-reported health is related to the disease, we would expect larger risk estimates in relation to cardiac events compared to cardiac readmissions, but this was not the case. If patient-reported health is related to the patients health in general, we would expect that the results were confounded by lifestyle and comorbidity, but adjustment for these factors did not change the association found. However, comorbidity measured with Charlson Index does not take diseases into account that are treated in general practice or that are not included in the range of diagnosis in the index, but still may have influenced the patients rating of their health. The mechanisms behind early and late events may different, but we were not able to identify differences between early and late events as found in the study by Pedersen et al. [42].

The broad outcome definition including all cardiac readmissions may reflect not only severe adverse events but also a high degree of self-care. Patients may be conscious about any symptoms related to the heart, lowering their iatrotropic threshold in general. This may lead to readmissions due to suspected angina pectoris and hence a higher possibility of examination and a diagnosis of restenosis. This behaviour may be closely related to patient reported physical and mental health. If patients are anxious about experiencing a new cardiac event, they may also tend to rate their health worse than less anxious patients, leaving other well-known risk factors of less importance. The more narrow definition of cardiac events may on the other hand exclude episodes of angina, which may lead to repeat vascularisation but, if untreated, may result in a myocardial infarction.
Large differences between participants and non-participants were observed in the cohort, and consequently MI was conducted preceding the analyses. Previous studies dealing with this possible selection bias in studies examining the association between self-reported health and adverse events could not be identified.

Study V:

Among those working before the PCI, 70% were back to work 6 months after the PCI and 76% after1 year, as assessed by cross-sectional measures and excluding those who left the workforce during follow-up. When using a time to event measure, 77% returned to work during follow-up, but only 60% returned to work without recurrent sick leave periods during the following year. The proportion of patients, who returned to work, ignoring recurrent sick leave periods, compares well with previous findings [22,23,25,26,91-96]. Moderate to near perfect agreement was found when comparing the measures, with the lowest agreement between the time-to-event measure without relapses compared to the other measures. The cut-off at 75% of the Work Participation Score did not agree well with the other measures, as it did not allow for a long period of sickness absence.

To our knowledge, only one other study has attempted a similar analytical approach [33], despite the fact that previous studies have yielded different results regarding RTW status depending on the RTW measure used [117] and the need for common measures and definitions have been suggested as a main tool to advancing the field of RTW research [28]. The overall finding of good to excellent agreement between the tested RTW measures is in line with the findings by Steenstra and colleagues [33]. However, the two studies can only be compared with regard to the findings of predictive abilities of common factors, as Steenstra and colleagues did not analyse the association between the different outcomes used in their study. The results from the present study suggest that the effect of certain variables varies according to recovery time (for example PCI indication and LVEF), whereas others remain stable throughout the RTW process. This illustrates the time dependency of certain predictor variables, which should be considered when choosing a RTW measure.

Previous sick leave episodes are strongly related to new sick leave episodes [118]. Taking such relapses into account seems inevitable if the study aim is related to prognosis and if it is possible to collect these data. The suggestion of using the Work Participation Score is easy to apply and obtain in longitudinal register data. It could possibly be recorded by self-report from the patient or the employer. Unfortunately, the Work Participation Score did not follow a normal distribution, as many patients were in the low end due to the fact that many patients did not work at all during the year, and there were patients in the high end because some patients went back to work immediately. Other advanced statistical approaches, such as multi-state models of transitions between transfer payments groups [119] frailty models [120]or other techniques taking recurrent events into account [121] could possibly take the vulnerability due to recurrent events into consideration.

Methodological considerations

Selection bias

Selection bias may result from procedures when selecting the study population and from factors influencing participation in studies [61]. The study population was considered unselected as it was based on all PCI patients in the working age from a specific region in Denmark, but a priori we were worried about selection bias due to non-response and attrition in the study. After the first round of questionnaires, the response rate was high compared to similar studies, and a large proportion of patients answered the repeated questionnaires though out the study. We set out to examine whether initial non-respondents and patients who left the study during follow-up differed from those who participated through the complete study course. As reported in Table 6, considerable differences were identified, indicating that our cohort could be prone to selection bias, as these differences probably are related to self-reported health.

Our general approach of method to deal with missing data was multiple imputation. In Study I, MI on missing items was conducted among respondents only, the possible selection bias due to non-response was not considered. Instead of using MI in the complete cohort, all non-respondents were placed in the group with lowest self-reported health in an extreme sensitivity analysis and the analyses repeated. This did not change the associations found, but was probably not correct. At that time, it was the best solution, but retrospectively an approach similar to the one used in Study IV would have been preferable.

In Studies III and IV, MI was used in the complete cohort in combination with different scenarios for sensitivity analyses. This implies that if the assumption of MAR was correct, the results were closer to not being prone to selection bias, but since the MAR assumptions could not be validated, sensitivity analyses were used to challenge these assumptions. The scenarios used, however, changed the mean scores and changes in scores over time, as illustrated in Figure 6. The estimates from Study III and Study IV were either unchanged or changed only slightly after applying the scenarios of sensitivity analysis. The confidence with the assumption of MAR relies on the ability to establish realistic scenarios, and this ability cannot be validated, but only be discussed for each individual research question.

The literature does not provide a guideline regarding how to develop these scenarios, and this topic could benefit from more studies and discussions. Norman et al. reviewed studies using health-related quality of life measures and identified the minimally important difference (MID) [122]. They concluded that MID is usually close to half a standard deviation, so this could be a suggestion as to the size of the deviations. Defining the scenarios a priori as part of the protocol is one way to ensure that the planned scenarios are applied, but initially when writing the

protocol, it was not the plan to use MI or sensitivity analyses.
Excluding patients (Study IV) with cardiac readmissions occurring in the weeks from the PCI to first questionnaire may have introduced bias and lowered the generalisability, as this may have involved patients with the most severe disease. On the other hand, keeping them in the dataset could cause a reverse causation. Excluding patients who had left the workforce prior to the PCI (Study I) may also have introduced a "healthy worker" bias [61], but these patients were per se not at risk of the event of interest (RTW).

Information bias

Information bias occurs when there is systematic error in the information collected from or about study participants. This may be a consequence of measurement errors, i.e. if the exposure, confounders or the outcome is subject to misclassification. Misclassification may be differential and vary between groups or be non-differential and be the same in all study groups. Differential misclassification may lead to systematic error of unknown size and direction, while non-differential misclassification is most likely to bias associations towards null [61]. In this study, misclassification may originate from self-reported information as well as information obtained from registers. In the following, possible sources of information bias are presented along with elaborations on whether they are non-differential or differential.

In registers, the data quality depends largely on the purpose of the register, the data collection method and the coverage.

No information bias was expected in the Danish Civil Registration System (CPR) because this is the cornerstone in the Danish Registries including valid information on date of birth and death. In a very few cases where patients had moved to a different address and the CPR had not yet been informed were questionnaires returned to us without reaching the patient. This placed the patients temporary in the dropout group, but some returned when the correct address was recorded.
This did not affect the linkage to the other registers, as the unique ID was unchanged.

In generel, misclassifications in The Danish National Patient Registry (DNPR) primarily relate to historical changes in coding of content, timing of registration and coverage [81,123]. The historical changes are primary related to outpatients, psychiatry and to differences in codes. The use of historical data in this study relates to the Charlson Index that uses primarily somatic diagnoses from inpatients. Timing and delay in registration did not directly influence our study. In Study IV, follow-up stopped at 1st Jan 2011, owing to data delay and with a longer follow-up time, more person years and events could have been added to the study, but this has no relation to information bias. From 2003, it has been mandatory to report all hospital contacts in Denmark, not only with regard to the public, but also to the private hospitals. This implies that the DNPR, in principle, has provided full coverage during the follow-up and during this period, only ICD-10 codes have been used. Joensen et al. specifically investigated the predictive value of acute coronary syndrome (ACS) diagnoses, including unstable angina pectoris, myocardial infarction, and cardiac arrest, in the Danish National Patient Registry by reviewing medical records. They found that the overall predictive value of ACS diagnoses was 65.5[63.1–67.9]%, but was better when the diagnosis had been made during hospital admission 80.1[77.7-82.3]% and for myocardial infarction separately 81.9[79.5-84.2]%. Consequently, they recommended restriction of analyses to patients diagnosed during hospital admission [124]. When defining the adverse event outcomes, only diagnoses related to hospital admissions were used, and not diagnoses from outpatient clinics or emergency rooms, without a subsequent transfer to a hospital ward.

Both the outcomes 'cardiac readmission' and 'cardiac events' in Study IV and Charlson index used as covariate in Studies II, III and IV may be misclassified, but probably unrelated to the exposures, and consequently non-differential.

The Danish Register for Evaluation of Marginalization (DREAM) is based on administrative data on transfer income and, as such, not designed for research. However, it has previously been validated in the context of sick leave, comparing workplace-registered data to DREAM [125] and in a study where self-reported information on transfer incomes was compared to transfer payment groups [80]. Both studies found high validity, but a few issues may be challenging when studying RTW. Only one transfer payment code is available for each week placed in hierarchical order, with more severe transfer incomes overwriting the less severe. If no transfer income is registered, the person is self-supporting, and, according to the definition of RTW, not sick listed. However, the patient may be living on their spouse's income or as a rentier, but not necessarily ready to work. In Denmark this is rather uncommon because only 2% of the population between 40 and 67 years are without personal income [126].

Another problem is related to the registration of sick leave; only sick leave of duration longer than 2 or 3 weeks (depending on regulations at the specific point of time) is registered and only if the employer remembers to claim for reimbursement for the employee. In Denmark, it is possible to gradually return to work through a part-time sick leave period, with partial reimbursement of wages. Unfortunately, due to technical issues, it is not possible to identify the point in time when a person goes from fulltime sick leave to part-time because the time with fulltime sick leave is overwritten by the part-time code, even though this could be defined as RTW. The definition of transfer-payment groups may cause misclassification in the following situation: if a person receiving labour market–related benefits, for example unemployment benefits, is not ready to work due to health problems, but fails to report this. However, as this group is small and as receivers of labour market–related benefits are requested to confirm their readiness to work on a weekly basis, this is considered a minor problem. These misclassifications in DREAM are most likely non-differential, but the problems related to fulltime and part-time sick leave may influence the proportions of patients who returned to work at specific points in time. Another problem relates to relapses with new period of sick leave, as described in Study V, because short-term sick leave is not registered, and thus not included in the study.

The clinical data from the Western Denmark Heart Registry (WDHR) are complete with respect to individuals and only a few values are missing. The data quality is secured by mandatory procedures, automatic validation rules and systematic validation procedures. The physicians enter data at the time of the procedure; so late complications may be incompletely registered, and must therefore be obtained from medical records or from the DNPR [79].

In WDHR there were missing values for LVEF, BMI and smoking. LVEF was measured before PCI only, except for the acute situations in which LVEF was measured immediately after the procedure. Usually changes in LVEF occur some days after the PCI [127]. The change may influence the patients reporting of their health, but only the baseline LVEF were available in the register. Even though BMI and smoking is derived from register data, the origin is often based on self-report to the clinician. Patients may underestimate their weight to some extent that is still realistic or they may claim to be non-smokers or have stopped smoking, due to the stigma of smoking and overweight in general and the well-known association between lifestyle and coronary heart disease in particular. Classification of this underreporting as non-differential is dubious, as patients' knowledge of their lifestyle is most likely also related to their reporting of their health. The misclassification is probably minor compared to the collected data being completely self-reported. We supplemented missing data on smoking and BMI from the WDHR with self-reported data from the questionnaire at three months. This implies that changes in weight or in smoking habits in the three months preceding PCI may have occurred, and these are no longer baseline data, but these misclassifications are most likely non-differential.

The questionnaires gave several possibilities for information bias. The primary measures were the two component summaries from SF12. The wording in SF-12 is retrospective: *"In the preceding four weeks…"*. This implies that the timing of each answer to a questionnaire may be related to health at any time point during the preceding four weeks or to the patient's perception of their current health on the day of answering. For the first questionnaire given four weeks after the PCI, this may have consequences if some patients primarily refer to the days immediately after the PCI, while others refer to their current health. In addition, patients may have experienced a new hospital admission or have returned to work during the first four weeks, and consequently the event of interest having occurred before answering the questionnaire. To address this problem in time to event analyses, patients who experienced the event of interest before answering the questionnaire were excluded. In Study I, this was an additional analysis, but in Study IV these patients were excluded in all analyses, and delayed entry at the time of the questionnaire was used. Retrospectively, the latter approach seems most attractive. In Studies II and III the advantages of this mechanism could be used, as the TPG status in the week preceding the answers was included in the imputation model, thus letting possible changes in TGP status influence the SF12 component summaries. Whether the choice of the week preceding the answer is the best choice or not remains unanswered; other time points or perhaps changes in TGP over time could be other relevant choices.

Confounding and effect modification

The most commonly used definition of a confounder is that it must be associated with both the exposure and the outcome in a study, without being an intermediate factor on the pathway between exposure and outcome. There are several methods to account for confounders in observational studies. In these studies, stratification and adjustment were used in the multivariable regression analyses. In all studies, the confounders were selected a priori, and considered possible confounders regardless of their statistical impact on the results. Effect modification is defined as a situation where the effect of an exposure on an outcome depends on the presence of another condition [61]. A priori we expected that there would be differences in the associations of interest between men and women and between patients treated with an acute indication compared to elective indications. All analyses were stratified with regard to gender and indication before using them as confounders in the analyses to examine whether gender or indication could modify the effect of the exposure and the outcome. Another possible effect modifier was time in the analyses of the repetitive measurements in Study III. In some of the analyses, there was evidence for an effect modification of time, and all estimates for each time point were reported separately. In the time to event analysis, time can be considered as an effect modifier if there was no proportional hazard. In Study I, proportional hazards could not be confirmed, and consequently the pseudo-value method was chosen, with report of relative risk at two time points. In order to examine whether the hypothesis of non-proportionality could be rejected, we examined whether log hazard ratios could change over time by allowing them to depend linearly on time in Study IV. This was not the case, allowing us to use traditional Cox regression in these analyses.

Prediction versus prognosis

In many studies, the words prediction and prognosis are used synonymously, and confusion regarding the differences between a predictor, a risk factor and a prognostic factor is common. The study designs when addressing prediction and prognosis are very similar, but the aims and the analytic strategies differ. In prediction studies, the aim is to predict a certain outcome with high precision using a number of available variables, not necessarily causally related to the outcome, while studies of risk factors aim to study whether one or more factors would affect prognosis, adjusted for relevant confounders (causal inference). A prediction model is usually developed in one cohort and validated in another cohort, or alternatively in two random parts of a cohort and needs examination of performance (discrimination, calibration and reclassification). Siontis et al. reviewed established prediction models for cardiovascular disease. They found that information on prognostic performance was rarely extending the reporting of the area under the receiver operating characteristic curve[128]. A similar shortcoming was made in Study I where areas under the ROC curve were compared, but without examining performance. The two studies examining factors related to prognosis (Studies I and IV) both belong to the type of studies that examines risk factors, as we did not aim to develop a prediction model, but rather to determine prognostic factors.

Generalisability

Because of the design of this cohort (including all patients in the working age from a specific region in Denmark) and the efforts to eliminate bias due to differential participation and attrition, this study has high generalisability. However, this is only true in countries where the patients treated with PCI are comparable to the patients in this study.

7. Conclusion

This thesis has confirmed that there is a close relation between patients' early rating of their health and prognosis in terms of return to work as well as in terms of adverse events such as cardiac readmissions, cardiac events and death. We found not only physical health, but also mental health related to these adverse outcomes.
Improvements in health during recovery were related to mental health and not physical health, and these findings were in contrast to previous findings and need confirmation in future research.

In most analyses, we found gender differences, suggesting that even though women share the same prognosis as men regarding survival when adjusting for age, there are still pronounced gender differences in prognosis in relation to wellbeing and recovery.
There are methodological challenges related to defining return to work. Our study suggests that definitions should depend on the context and the research question.

Missing data, non-response and attrition are well-known sources of bias because studies that rely on participation from patients are prone to possible selection bias due to initial non-participation and dropout in longitudinal studies. Previously, this has been a subject of discussion regarding the results of numerous studies, where presumption of the impact in each study could be speculative. Multiple imputation provides a possible solution to these problems, and, supplemented with sensitivity analysis, it qualifies the estimations so that they become closer to unbiased results. The population-based registers in Denmark provide excellent opportunities for the use of auxiliary data in multiple imputation.

8. Perspectives and future research

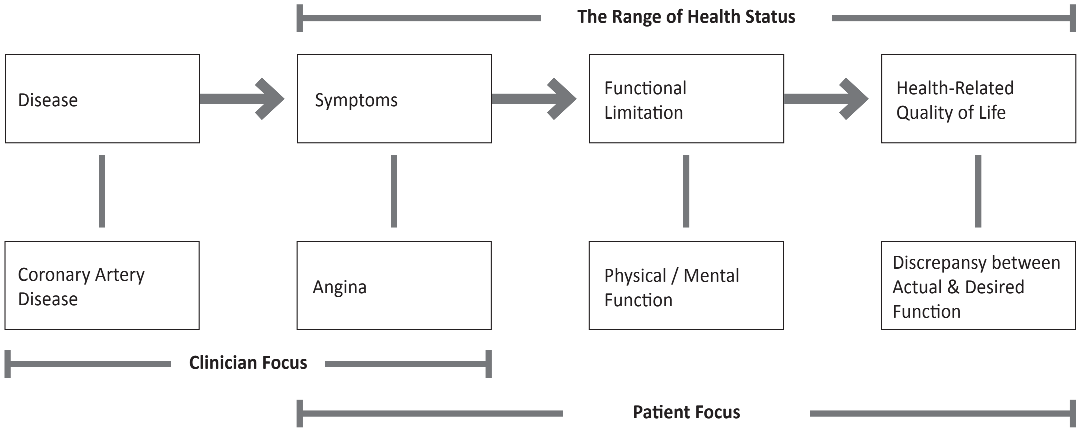
In our present cohort, only a limited part of the data material was analysed in connection with this thesis. The remaining data represent a treasure box that can provide material for the investigation of a range of research questions.

The findings on mental health in our studies, in combination with other recent studies, may indicate that further research in the intersection between mental health and coronary heart disease is needed. External factors such as participation in cardiac rehabilitation or medication compliance could influence the individual course of health and should be taken into account in future studies.

The next step could be analyses of the course of anxiety and depression. Analyses should include register-based information on medical use.

How patient-reported health measures could be used in clinical practice is a challenging question. When the focus of the clinician and the focus of the patient only overlap slightly, the clinicians' interest in patient-reported health measures is limited (Figure 9). On the other hand, clinicians and patients share interest in the patient's prognosis, and this is where patient's knowledge adds important information to more traditional measures.

Figure 9: The range of health status: Symptoms, function and quality of life



Adapted, with permission, from Rumsfeld JS (Circulation. 2002;106:5-7).

The figure above is closely connected to the thoughts behind WHO's International Classification of Functioning (ICF) and thus to the definition of health as "the state of complete physical, mental and social well-being [14]. The ICF framework covers domains from body structure and functioning, domains on activity and domains on participation, and this framework relates closely to Figure 1, where the clinicians' focus relates primarily to the domains related to body structure and functioning, while the patients' interests also include domains of activity and participation. Future studies on prognosis in patients with chronic disease could benefit from including patient-reported health measures, and thus cover a broader perspective on rehabilitation and recovery.

9. English summary

Improvements in treatment of coronary heart disease have resulted in decreased mortality and more patients living with a chronic heart condition. In order to describe prognosis exhaustively, patient-reported health measures on prognosis in terms of well-being and ability to work are crucial supplements to traditional outcome measures such as readmissions and mortality.

A population-based cohort of 1726 patients under 67 years of age, treated with Percutaneous Coronary Intervention (PCI) was followed with repetitive questionnaires over 3 years. In addition to the questionnaires, data from The Danish Civil Registration System, The Danish National Patient Registry, West Denmark Heart Registry and The Danish Register for Evaluation of Marginalisation (DREAM) were used.

The aim was to analyse self-reported health as a prognostic factor for return to work, heart-related readmissions and mortality. Another aim was to describe the course of self-reported health during the first three years of follow-up, along with an analysis of differences regarding gender, age, left ventricular ejection fraction, educational level and indication for the PCI.
The dissertation includes two method-papers: one paper on definitions of return to work and one paper on multiple imputation in longitudinal studies.

Paper I: Predictors of return to work after Percutaneous Coronary Intervention: The value of self-reported health compared to clinical measures

Ability to work is an important outcome in rehabilitation following PCI. We described patterns of RTW and analysed risk factors of non-RTW using time to event analysis. We also estimated ROC areas with and without self-reported health. Many patients have left the workforce even before their PCI. Among those working before their PCI, the majority return to work (RTW), but female gender, low self-reported health and a low left ventricular ejection fraction (LVEF) were risk factors for non-RTW. The patient's self-reported health four weeks after the procedure was a stronger prognostic factor for RTW than LVEF.

Paper II: Using multiple imputation to deal with missing data and attrition in longitudinal studies with repeated measures of patient-reported outcomes

Ignoring missing data may cause bias of unknown size and direction in longitudinal studies with repeated measurements. Usually this is ignored, but with MI and use of additional data it is possible to address these problems. We demonstrated how to use MI in studies with repeated measurements, including different approaches to the handling of death and scenarios of sensitivity analysis. MI is a useful and accessible tool to deal with the challenges of missing data, including attrition and non-response, and it use should be considered in longitudinal studies.

Paper III: Self-reported health following percutaneous coronary intervention. Results from a cohort followed for 3 years with multiple measurements

The course of self-reported health following PCI is an important supplement to clinical endpoints such as mortality and adverse event, but previously described only in small and selective populations. After multiple imputation, we described the course of mental and physical health.

The analysis of eight repeated measures over 3 years revealed that improvements were present regarding mental health, but not physical health shortly after the procedure. We found demographic differences in health, rather than disease-related differences.

Paper IV: Patient-reported health status as a risk factor for adverse events following percutaneous coronary intervention (working title)

Clinical factors are found related to adverse events, but self-reported health may be important in risk stratification following PCI. We analysed self-reported health as risk factors in a time-to-event analysis, adjusted for a range of possible confounders. The patients self-reported health four weeks after the procedure was strongly related to new cardiac events, cardiac readmissions, and mortality, even after adjustment for prevalent and incident comorbidity, events occurring before answering the questionnaire, LVEF, age and gender.

Paper V: Methods in Measuring Return to Work: A Comparison of Measures of Return to Work Following Treatment of Coronary Heart Disease

In the literature, consensus is lacking regarding the definition of RTW, resulting in incomparable studies. We compared different definitions derived from the same data with Cohen's kappa and compared estimates from different risk factors in models using different outcomes. Different measures revealed some differences in proportion of patients who returned to work. However, high agreement between different RTW definitions was found. Choice of return to work definitions should depend on study purpose; simple cross-sectional methods are sufficient in prediction of RTW and analysis of risk factors, while methods capturing relapses are recommended when sustainability, prognosis and vulnerability are in focus.

10. Dansk resumé

Forbedringer i behandlingen af iskæmisk hjertesygdom har resulteret i nedsat dødelighed og dermed i at flere patienter i dag lever med en kronisk hjertesygdom. For fyldestgørende at kunne beskrive prognosen, kan patient-rapporterede oplysninger tages i anvendelse. Prognosen i form af selvvurderet helbred og evnen til at vende tilbage til arbejdet er vigtige determinanter og kan supplere de mere traditionelle prognosemål såsom genindlæggelser og dødelighed.

En populationsbaseret kohorte på 1726 patienter under 67 år, behandlet med perkutan koronar intervention (PCI) blev fulgt med gentagne spørgeskemaer over 3 år. Udover spørgeskemaerne anvendtes data fra Det Centrale Personregister (CPR), Landspatientregistret, Vestdansk Hjertedatabase samt det Danske Register for Evaluering af Marginalisering (DREAM).
Formålet var at analysere selvvurderet helbred som en prognostisk faktor for tilbagevenden til arbejde, for hjerterelaterede genindlæggelser og for dødelighed. Et andet formål var at beskrive forløbet af selvvurderet helbred i løbet af de første 3 års opfølgning, sammen med analyser af betydningen af køn, alder, venstre ventrikel uddrivningsfraktion (LVEF), uddannelsesniveau og indikation for PCI for forløbet af selvvurderet helbred.

Afhandlingen indeholder, udover resultatartiklerne, to metodeartikler; én artikel om definitioner af tilbagevenden til arbejde og én artikel om multiple imputation i longitudinelle studier.

Artikel I: Predictors of return to work after Percutaneous Coronary Intervention: The value of self-reported health compared to clinical measures

Evnen til at vende tilbage til arbejdet er et vigtigt resultat i rehabiliteringen efter PCI. Vi beskrev mønstre af RTW og analyserede risikofaktorer for ikke-RTW ved hjælp af time-to-event analyse. Vi estimerede også arealet under ROC–kurver fra modeller med og uden selvrapporteret helbred. Mange patienter havde forladt arbejdsstyrken allerede før deres PCI. Blandt dem, der arbejdede op til deres PCI, vendte de fleste tilbage i arbejde igen, men kvindeligt køn, lavt selvvurderet helbred og lav venstre ventrikels uddrivningsfraktion (LVEF) var associeret med problemer med RTW. Patientens selvvurderede helbred fire uger efter PCI var en stærkere prognostisk faktor for RTW end LVEF.

Artikel II: Using multiple imputation to deal with missing data and attrition in longitudinal studies with repeated measures of patient-reported outcomes guide

Missing data kan forårsage bias af ukendt størrelse og retning i forløbsundersøgelser med gentagne målinger. Normalt ignoreres dette, men med multiple imputation og anvendelse af supplerende data er det muligt at imødekomme disse problemer. Vi udarbejdede et praktisk eksempel om brugen af multipel imputation i studier med gentagne målinger, herunder forskellige tilgange til håndtering af dødsfald og scenarier for sensitivitetsanalyser. Multipel imputation er et nyttigt og tilgængeligt værktøj til at håndtere problemer med missing data, herunder bortfald af deltagere og non-respondenter og bør derfor overvejes i longitudinelle undersøgelser.

Artikel III: Self-reported health following percutaneous coronary intervention. Results from a cohort followed for 3 years with multiple measurements

Forløbet af selvrapporteret helbred efter PCI er et vigtigt supplement til kliniske prognosemål, såsom genindlæggelser og dødelighed, men er tidligere kun beskrevet i mindre og selektive studier. Efter multipel imputation beskrev vi forløbet af mental og fysisk helbred. Analyse af 8 gentagne målinger over 3 år viste, at forbedringer primært vedrørte mentalt helbred og primært fandt sted i de første 6 måneder, mens det fysiske helbred var uændret. Vi fandt at forskelle i helbred var relateret til demografi frem for til sygdomsrelaterede faktorer.

Artikel IV: Patient-reported health status as a risk factor for adverse events following percutaneous coronary intervention (arbejdstitel)

Kliniske faktorer er tidligere fundet relateret til kardielle genindlæggelser og død efter PCI, men selvrapporteret helbred kan ligeledes være vigtig i risikostratificering efter PCI. Vi analyserede sammenhængen mellem selvvurderet helbred og kardielle tilbagefald og genindlæggelser samt død i en time-to-event analyse, justeret for en række mulige confoundere. Patientens selvvurderede helbred fire uger efter PCI var associeret til nye kardielle tilbagefald, genindlæggelser og dødelighed, selv efter justering for prævalent og incident komorbiditet, LVEF, alder og køn.

Artikel V: Methods in Measuring Return to Work: A Comparison of

Measures of Return to Work Following Treatment of Coronary Heart Disease

I litteraturen er der mangel på konsensus i definitionen af RTW, hvilket resulterer i usammenlignelige undersøgelser. Vi sammenlignede forskellige definitioner lavet ud fra det samme datasæt med Cohens kappa og sammenlignede estimater fra velkendte risikofaktorer i modeller med de forskellige definitioner.
Forskellige definitioner afslørede forskelle i andelen af patienter som var tilbage i arbejde. Der var dog stor overensstemmelse mellem definitionerne, målt med Cohens kappa. Valg af RTW definition bør afhænge af undersøgelsens formål, simple tværsnitsmål er tilstrækkelige ved undersøgelse af risikofaktorer for RTW, mens metoder der tager højde for tilbagefald anbefales når prognose og sårbarhed er i fokus.

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