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DISABILITY PENSION AMONG PATIENTS UNDERGOING CORONARY REVASCULARISATION

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Disability pension among patients undergoing coronary revascularisation

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"Give me a place to stand and I will move the earth"

(Archimedes)

Abstract

Background: Cardiovascular disease (CVD) is the main cause of death both in Sweden as well as globally, and represents a major public health problem also regarding impaired physical capacity and work disability. After musculoskeletal and mental diagnoses CVD is the third largest diagnostic group for disability pension (DP) in Sweden. Annually about 10 000 working-aged individuals undergo coronary revascularisation, i.e., coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). These are established and well-documented interventions, resulting in symptom reduction, improved physical capacity, and among some patient groups, lower mortality. Coronary revascularisation could, hence, prevent early labour market exit. However, scientific knowledge is scarce regarding DP among patients with coronary revascularisation. The aim was to study general and diagnosis-specific DP, and its association with all-cause and CVD mortality among working-aged women and men with a first coronary revascularisation in 1994-2006, accounting for socio-demographic and medical factors.

Methods: Nationwide, population-based, cross-sectional and prospective cohort register studies were conducted. All, 78 153 patients, 30-65 years of age at time of their first coronary revascularisation in 1994-2006 in Sweden, were identified using the SWEDEHEART register, with information on all such interventions as well as patient characteristics, indication, date and type of intervention, and diabetes. Information on socio-demographic and medical factors was linked at individual level from nationwide registers held by the Social Insurance Agency, the National Board of Health and Welfare, and the Statistics Sweden. Logistic regression analyses were performed to estimate the probability of being on DP at the time of a first intervention (study I) and Cox regression analyses were performed to estimate the risk of being granted DP (study II), or the risk of all-cause mortality (study III) or all-cause and CVD mortality (study IV) within five years following a first intervention.

Results: At the time of the coronary revascularisation, 24% were on DP; sixty two percent had been on DP for at least four years before intervention. The largest DP-diagnostic group was musculoskeletal diagnoses. The odds ratio for DP was higher among: CABG-patients, women, older individuals, lower level educated, foreign-born, individuals living in smaller communities and individuals with another indication for PCI than acute coronary syndrome or stable angina pectoris (study I). Within five years following the intervention, 32% had been granted DP. The hazard ratio for DP was higher among: CABG-patients, women, individuals with in-patient care for mental diagnoses (except for women, CABG), or musculoskeletal diagnoses in the five years before the intervention, with ≥180 sick-leave days in the year before the intervention, with diabetes at the intervention, and individuals with ≥1 re-intervention within the five following years (study II). Four percent died within five years following coronary revascularisation, most due to CVD. DP at the time of the intervention was associated with higher risks of mortality five years following intervention (study III). The mortality risk was higher among all the studied DP-diagnostic groups (CVD, musculoskeletal, and mental diagnoses) compared with no DP at the time of the intervention, and did not differ between the DP diagnoses (study IV).

Conclusions: A quarter of the patients already had DP at the time of CABG or PCI, a majority for at least 4 years before the intervention. In addition, the largest DP-diagnostic group was musculoskeletal diagnoses. One third was granted DP within a five-year follow-up. The mortality risk was higher both with all-cause and diagnosis-specific DP which could not be explained by the studied socio-demographic and medical factors. No differences in mortality were found between most of the studied DP-diagnostic groups; also musculoskeletal diagnoses were associated with higher five-year mortality. More detailed knowledge regarding these associations is needed.

Svensk sammanfattning

Bakgrund: Hjärt-kärlsjukdom är den vanligaste dödsorsaken, både i Sverige och globalt, och utgör ett stort folkhälsoproblem även gällande försämrad fysisk kapacitet och arbetsförmåga. Efter muskuloskeletala och mentala diagnoser utgör hjärt-kärlsjukdom den tredje största diagnosgruppen för sjukersättning (DP) i Sverige. Årligen genomgår cirka 10 000 hjärt-kärlsjuka individer under 65 års ålder en kranskärlsintervention av antingen koronar bypass-kirurgi (CABG) eller perkutan kranskärlsintervention (PCI). Dessa är etablerade interventioner som resulterat i minskade symptom, förbättrad fysisk kapacitet och, bland vissa patientgrupper, lägre dödlighet. Dessa två interventioner skulle därför kunna förebygga ett förtidigt utträde ur arbetslivet. Dock är den vetenskapliga kunskapen begränsad gällande både prevalens och incidens av DP bland patienter med kranskärlsintervention. *Syftet* var att studera generell respektive diagnos-specifik DP samt dess samband med dödlighet (generell och på grund av hjärt-kärlsjukdom) bland kvinnor och män i arbetsför ålder vid en första kranskärlsintervention 1994-2006, justerat för sociodemografiska och medicinska faktorer.

Metod: Populationsbaserade studier baserade på rikstäckande registerdata genomfördes; en tvärsnittsstudie och tre prospektiva kohortstudier. Sammanlagt genomgick 78 153 patienter under åren 1994-2006 en första kranskärlsintervention (CABG eller PCI) i Sverige när de var 30-65 år gamla. De identifierades genom SWEDEHEART-registret, där även information om patientkaraktäristika, indikation, datum och typ av intervention samt diabetes inhämtades. Länkad information om sociodemografiska och medicinska faktorer hämtades från Försäkringskassan, Socialstyrelsen och Statistiska centralbyrån. Logistiska regressionsanalyser genomfördes för att beräkna sannolikheten för DP vid interventionen (studie I). Cox regressionsanalyser genomfördes för att beräkna risk för framtida DP (studie II), generell dödlighet (studie III), samt generell och hjärt-kärl dödlighet (studie IV) inom fem år efter interventionen.

Resultat: Vid kranskärlsinterventionen hade 24 % DP. Sextiotvå procent av dem hade haft DP sedan minst fyra år före intervention. Den största DP-diagnosgruppen var muskuloskeletala diagnoser. Sannolikheten för DP vid interventionen var högre bland: CABG-patienter, kvinnor, äldre individer, de med lägre utbildningsnivå, utrikesfödda, boende i mindre samhällen, samt de med annan indikation för PCI än akut kranskärlssjukdom eller kärlkramp (studie I). Totalt beviljades 32 % av de som inte hade DP, detta inom fem år efter interventionen. Risken för sådan DP var högre bland: CABG-patienter, kvinnor, de med slutenvård för mentala (förutom kvinnor, CABG) och/eller muskuloskeletala diagnoser inom fem år före intervention, de med ≥180 sjukfrånvarodagar tolv månader före intervention, de med diabetes vid intervention, samt de med minst en re-intervention inom fem år (studie II). Fyra procent avled inom fem år efter interventionen, de flesta på grund av hjärt-kärl sjukdom. DP vid interventionen var associerad med högre risk för död inom fem år (studie III). Risken för förtida död var högre bland samtliga av de studerade DP-diagnosgrupperna (hjärta-kärl, muskuloskeletala, och mentala diagnoser) jämfört med de utan DP vid interventionen. Resultaten var likartade mellan de flesta av DP-diagnosgrupperna (studie IV).

Konklusion: En fjärdedel av de studerade patienterna hade redan DP vid sin första CABG eller PCI och majoriteten hade haft DP sedan minst fyra år före intervention. Muskuloskeletala diagnoser var den största DP-diagnosgruppen. En tredjedel beviljades DP inom fem år efter interventionen. De med DP vid interventionen hade högre risk att avlida inom fem år, jämfört med de utan DP. Denna risk var högre i samtliga av de studerade DP-diagnosgrupperna. Den högre risken kvarstod trots justering för de inkluderade sociodemografiska och medicinska faktorerna. Inga skillnader fanns mellan de flesta studerade DP-diagnosgrupperna; även muskuloskeletala diagnoser var associerade med högre risk för död inom fem år efter interventionen. Mer detaljerad kunskap om dessa samband behövs som underlag för preventiva insatser.

LIST OF SCIENTIFIC PAPERS

I. Zetterström K, Voss M, Alexanderson K, Ivert T, Pehrsson K, Hammar N, Vaez M. Prevalence of all-cause and diagnosis-specific disability pension at the time of first coronary revascularisation: A population-based Swedish cross-sectional study. PLoS ONE 2014:10(1): e0115540.

II. Zetterström K, Vaez M, Alexanderson K, Ivert T, Pehrsson K, Hammar N, Voss M. Disability pension after coronary revascularization: A prospective, nationwide, register-based Swedish cohort study.
European Journal of Preventive Cardiology, 2015, 22(3): 304-311.

III. Zetterström K, Voss M, Alexanderson K, Ivert T, Pehrsson K, Hammar N, Vaez M. Disability pension at the time of coronary revascularisation is associated with higher five-year mortality: A prospective, nationwide, register-based, Swedish cohort study. 2015 *Submitted.*

IV. Zetterström K, Voss M, Alexanderson K, Ivert T, Pehrsson K, Hammar N, Vaez M. Associations between diagnosis-specific disability pension at the time of coronary revascularisation and mortality; A Swedish nationwide, population-based prospective cohort study. 2015 *Submitted.*

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Study I

Study II

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List of abbreviations

ACS	Acute Coronary Syndrome
CABG	Coronary Artery Bypass Grafting
CI	Confidence interval
CHD	Coronary heart disease
CVD	Cardiovascular disease
DP	Disability pension
HR	Hazard ratio
ICD	International Classification of Disease
IHD	Ischemic Heart Disease
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
MiDAS	Micro Data for the Analysis of Social Insurance
MI	Myocardial infarction
OR	Odds ratio
PCI	Percutaneous Coronary Intervention
RIKS-HIA	The register of Information and Knowledge about Swedish Heart Intensive Care Admissions
SA	Sickness absence
SCAAR	The Swedish Coronary Angiography and Angioplasty Registry
SPSS	Statistical Package for the Social Sciences
SWEDEHEART	Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
WHO	World Health Organization

1 Introduction

This thesis concerns disability pension (DP) among patients, both women and men, in working ages, who had a first coronary revascularisation by either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) in Sweden between the years 1994-2003 (study II) or 1994-2006 (study I, III-IV). Each year many thousands of working aged patients (<65 years) undergo CABG or PCI in Sweden. These two interventions are well documented treatments for acute coronary syndrome (ACS) and angina pectoris [1-8]. Cardiovascular disease (CVD) is a major public health issue, worldwide as well as in Sweden [9]. CVD leads to impaired physical capacity, work disability, and mortality, and is the number one cause of death globally, for both women and men. In Sweden, CVD constitutes the third largest diagnostic groups for DP, after mental and musculoskeletal DP diagnoses [10, 11]. In 2003, the Swedish Council on Technology Assessment in Health Care (SBU) [12] concluded that research about sickness absence and DP is very limited and that more scientific knowledge is needed regarding DP both in general [11, 13] as well as for CVD [14]. There are only few studies about sickness absence or DP and CVD, including coronary interventions, especially considering the magnitude of the problem both for society, health care and individuals [14]. The few conducted studies are based on smaller samples, the data is seldom presented for both women and men, and some only include CABG-patients [14-18]. More comprehensive studies including larger populations are needed to investigate DP among patients, both women and men, with a first coronary revascularisation by type of intervention. Such studies should focus on risk indicators of early exit from the labour market and to further develop strategies for preventive measures among women and men with coronary revascularisation by CABG or PCI, in higher risk for DP.

1.1 Cardiovascular disease

Cardiovascular disease (CVD), including coronary heart disease (CHD) is a group of disorders involving the heart and the blood vessels. CVD is the main cause of death worldwide [19]. Globally, a total of 17.5 million individuals died in CVD during 2012; of these, 7.4 million died due to CHD. Also in Sweden, the study setting of this thesis, CVD constitutes the main cause of death [20]. In 2010, about 40% of all mortality among women and men were caused by CVD [21]. There are gender differences in CVD; women get the symptoms later in life, and are older at the onset of their diagnosis [22-24]. In 2010-2012 in Sweden, 67% of the women and 43% of the men were 75 years or older at the onset of their first myocardial infarction (MI) [25]. Moreover, women have smaller coronary arteries and more co-morbidity than men [2]. These facts might explain previous study findings of higher short-term mortality [26] and lower long-term mortality risk [26-29] among women compared to among men. During the last decades the number of deaths caused by CVD has declined [20] The number of MIs has, however, foremost decreased among older individuals. Among younger women (45-64 years) there have been no decreases in MIs since the 1990s.

There are several known risk factors for CVD. Age, gender, and family history are non-modifiable factors. However, many other established risk factors are modifiable and can thus

be controlled, treated, or modified. Examples of such risk factors are: hypertension, raised blood glucose level (diabetes mellitus), and hyperlipidaemia, as well as lifestyle factors as tobacco use, harmful use of alcohol, unhealthy diet, obesity, physical inactivity, etcetera (9). Socio-demographic factors, such as low socio-economic position e.g., regarding educational level, employment status, and financial situation, may also increase the risk of CVD (5, 30, 31).

1.1.1 Coronary revascularisation

Annually in Sweden, about 10 000 patients of working age (<65 years), with stable effort angina pectoris or acute coronary syndrome (ACS), i.e., ST-elevation myocardial infarction and non-ST elevation myocardial infarction, undergo coronary revascularisation by either CABG or PCI. A majority of these patients are men.

1.1.1.1 *Coronary artery bypass grafting (CABG)*

CABG is an invasive technique performed to bypass the obstructed coronary artery with a shunt of a vein or an artery to improve the blood supply oxygen to the ischemic myocardium. The chest has to be opened and grafts harvested from the leg. Usually CABG requires use of a heart- and lung machine.

1.1.1.2 *Percutaneous coronary intervention (PCI)*

PCI is a much less invasive procedure. It involves catheter dilation of the diseased coronary artery by an inflatable 'balloon' and the placing of a stent in the narrowed or blocked blood vessel, so that the blood can pass. The artery is reached, using fine instruments administrated through artery after puncture of an artery in the groin or more and more frequently at the wrist. Therefore, the recovery time after PCI is shorter than after the more invasive CABG why PCI nowadays often is a first-hand choice. The method is e.g., used among patients with uncomplicated coronary obstruction.

CABG and PCI are established and well documented treatments for these conditions (1, 2, 4-8). To a high degree these interventions result in relive of symptoms, improved physical capacity, and in some subgroups of patients, reduced mortality (6). Since the 1980's, the number of PCIs has increased continuously, and has, for some patient categories replaced CABG. This has led to a considerable shift of the population undergoing CABG to an increased proportion with multi-vessel and more severe coronary artery disease (14, 32). It is, however, more usual that patients have recurrence of symptoms, after PCI than after CABG and require repeated intervention.

1.1.2 Information on CABG and PCI

As CVD is a major public health issue, much health care concerns treatment of CVD patients. Different strategies to acquire more and better knowledge on effects of various treatments have been introduced over the last decades. Several nationwide registers regarding this patient group have been established by clinicians in Sweden. These registers are called 'quality registers' as the purpose is to contribute to improvement of health care quality (33).

1.1.2.1 SWEDEHEART

The patients included in this thesis were identified using the nationwide SWEDHEART register (3, 34). This comprehensive register includes data from three registers that were merged in December 2009, namely the Swedish Heart Surgery Register, SCAAR, and RIKS-HIA; described more in detail below. These registers cover all the 73 hospitals with heart intensive care in Sweden. Information about all CABG procedures is complete from 1992. The aim of the SWEDEHEART register is to provide a basis for studies that can lead to improvement of the quality of care of patients with CVD and to constitute a platform for scientific research on CVD. The long-term goal is to contribute to reduced morbidity and mortality among patients with cardiac disease and to improve cost-effectiveness in health care. The SWEDHEART register includes information about a large number of variables for each registered patient. The registration is performed both at the time of hospital care, at cardiac interventions, and for some patients at revisits at eight weeks and one year following the treatment. The reporting is conducted on-line through the SWEDEHEART's web-based program. Annual reports are published on-line. The SWEDEHEART register has also been utilised for evaluation of treatment strategies and has through scientifically international reports contributed to an improved cardiovascular health care worldwide, reducing complication rates and mortality (3, 34). Below some more information about the registers in SWEDHEART is given.

1. The Swedish Heart Surgery Register has, from the start in 1992, included information on all heart surgeries performed in Sweden. The register includes all patients who have had CABG with information on: date and type of intervention and indication as well as patients' age, sex, length, weight, and date of death. A risk profile of each patient can be identified using the Euro score based on 18 patient-related variables (34).

2. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) was established in 1998, and was in 2001 connected to the Uppsala Clinical Research Centre (UCR) (34).

3. The register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA), was established in 1995. It includes information on cardiac care before and following the cardiac interventions. All the included hospitals had coverage of 95% of the patients in 2001 and of 100% in 2008 (34).

1.2   Disability pension

Now as well as during the period studied (1994-2007) in this thesis, the public social insurance system (35), covering all residents in Sweden aged 19-65 years, involves the possibility to be granted disability pension (DP) benefits. DP can be granted individuals with a disease or an injury that has led to long-time or permanent reduction of work capacity in relation to the demands of ordinary work at the labour market (35). DP can be granted for full or part time of ordinary working hours. For individuals with no, or a low previous work income, the DP benefits amount to a minimum level. Those with a previous income could be granted benefit for at least 64% of lost income, up to a certain level. The Social Insurance

Agency officers decide if a claimant fulfils the criteria for being granted DP. That decision is based on medical assessments regarding the diagnoses, the limitations in function that the diagnoses have led to, and to what extent this impairs activity and work capacity. During the years studied it was possible to be granted temporary DP, for one or several years. Individuals with income from work or unemployment benefits were generally on sickness absence for at least 12 months before being granted DP (36).

In Sweden, the general age for old-age pension is 65 years. Old-age pension can be taken later or earlier, e.g., from 61 years of age – individuals on early old-age pension cannot be granted DP even if they are not 65 years old.

1.2.1 Prevalence and incidence of disability pension

In this thesis the prevalence and incidence of DP as well as mortality among patients on DP, and not on DP at time of a first coronary revascularisation were studied. Prevalence data contributes with information on a specific number of individuals that (in this case) are on DP, at a specific given time point or period of time, and are therefore valuable for estimating the proportions of individuals receiving DP at a certain time point, in a certain population, in this case among patients with a first coronary revascularisation. Incidence data involves information of new cases, here, the rates of new individuals being granted DPs, per individual at risk in a given time period.

This thesis includes studies investigating either DP at the time of coronary revascularisation (in 1994-2006) or granted DP five years following the CABG or PCI (up through year 2007) among working-aged (30-64 years) women and men. During this period, the annual DP rate, among the general population, increased from about 8% in 1990 to about 10% in 2007 (36). At the end of the studied period (in 2007) a total of 524 827 women and men, aged 30-64 years were on DP in Sweden. Hence, in 2007 about 12.3% of all working-aged women and men had left the labour market early due to DP. Of those, the majority (60.4%) were women, and further, DP was more common in the highest age group (60-64 years).

The annual incidence of DP varied during the studied years (10, 37). In 2004 (with the so far highest incidence of DPs), a total of 68 551 individuals were granted DP. This number decreased to 41 003 in 2007 and to 13 144 in 2014. Moreover, there were gender differences also regarding incident DP: of all the new DPs granted in 2004, about 60.5% were granted to women, with a slightly decrease in gender differences during the following years (58.8% in 2007 and 56.7% in 2014).

1.2.2 Factors associated with disability pension

Several studies have investigated associations between socio-demographic factors and DP in general (36, 38-68). Among these, female gender (36, 38, 39, 41, 44, 45, 49, 51, 53, 54, 56, 58, 59, 64), higher age (38, 41, 47, 53, 55, 58, 64), lower educational level (41, 46-48, 55, 59, 66, 67), living in rural areas (60, 61), being unmarried (41, 44, 46-48, 50, 52, 59, 62), and being foreign-born (43, 49, 57, 68) were associated with higher DP rates.

Also long-term sick leave (17, 69) and inpatient care (36, 45, 70, 71) have been associated with higher general DP rates. However, it has not yet been established whether these factors also are important for DP among working-aged women and men with a first coronary revascularisation. Since many of these factors also have been associated with CVD (72), it would be reasonable to also study these in relation to DP among patients with CABG or PCI. Most previous studies concerns DP in general, that is, do not include the specific DP diagnoses among individuals with CVD diagnoses (41).

1.2.3   Coronary revascularisation and disability pension

In Sweden CVD constitutes the third largest diagnostic group for DP, after mental and musculoskeletal diagnoses (10, 14). However, there are hardly any studies on DP in relation to coronary revascularisation (14-18). These studies are based on smaller samples, including only CABG-patients, and the results of DP are not presented stratified by women and men; even if it is well known that DP in general is more common among women than among men (36, 38, 39, 44, 45, 49, 51, 53, 54, 56, 59) and that more men compared to women of working ages, undergo these interventions (22, 23). One study from Finland found that 25% of all the patients working one year after CABG and who were below 60 years of age at the 10-year follow-up, had DP (16). Another Finnish study found that 17% of post-operatively working patients were on DP before 60 years of age (15).

More comprehensive studies including larger populations could increase the scientific knowledge on DP among working-aged women and men with coronary revascularisation by CABG or PCI, and contribute to the development of strategies for preventive measures among specific subgroups of these patients. One way to conduct such studies is using nationwide registers.

1.2.4   Associations between disability pension and mortality

Previous studies on DP have found higher mortality rates among individuals with both all-cause and diagnosis-specific DP compared to those not on DP (73-79). This in spite of that most DP diagnoses (e.g. musculoskeletal and common mental disorders) seldom are causes of death.

Previous studies on associations between coronary revascularisation and mortality found that women have a higher short-term mortality risk (30 days) (26) but a lower long-term mortality risk (9 months up to 10 years) compared with men, following coronary revascularisation (26-29).

To the best of my knowledge, no studies have so far investigated associations between DP at the time of a first coronary revascularisation and the risk of mortality. Since both CVD and DP have been associated with higher mortality, it would be of interest both from a clinical, individual, and societal perspective to also investigate mortality among patients with CVD, treated with CABG and PCI and associations with DP. Such studies could constitute a knowledge base for health care regarding identification of the more vulnerable patient groups, in need of more individual-based rehabilitation following intervention.

1.3 Research approaches

Research on sickness absence and DP has been conducted from different scientific disciplines and different theories and models have been used (80, 81). This research is, for instance, performed within medical science, public health, sociology, psychology, or economics, and is often based in explanatory models (research models in organisational psychology, theories on absence culture, economic and rational selection theories, stress theories, explanatory models in medicine and for changes in levels of sickness absence, strain, attitudes, sickness insurance system, and labour market condition), elaborating the causes of sickness absence. However, it is not possible to synthesise knowledge from the different theoretical perspectives and disciplines, into a combined theory explaining the causes of sick leave. Nevertheless, together, all these different perspectives contribute with a broader knowledge base in the research field of sickness absence.

Studies on sickness absence (SA), including the long-term SA, that is, DP, can be categorised according to: what is studied, study design, type of data and analyses, scientific discipline, perspective taken in the research questions, structural level of factors included in the analyses, and diagnoses studied (Table 1) (82, 83). In table 1, the items involved in the studies of this thesis are marked in bold. That is, two of the studies concern risk factors for DP and two possible consequences, in terms of mortality, of DP. One is cross- sectional and the others are prospective cohort studies, all based on quantitative analyses of register data. The studies are conducted within the realm of medicine and public health using epidemiological methods. The research questions are posed from a health care perspective and all the factors included in the analyses are at the individual, patient level. All included patients had CVD. Also information about their mental and musculoskeletal DP diagnoses is included.

Table 1. A structure for categorisation of studies of sickness absence/disability pension (83). Aspects included in this thesis in bold letters.

What is studied	-Design -Data -Analyses	Scientific discipline	Perspective taken in research questions	Structural level of factors included in the analyses	Diagnoses
1. Risk factors for sickness absence or **disability pension** 2. Factors that hinder or promote return to work **3. Consequences of (being)** sickness absent**/(on) disability pension** 4. Sickness certification practice 5. Methods and theories	**Study design** **-Cross sectional** **-Longitudinal** -RCT, CT, etc. **Type of data** Interview Questionnaire **Register** Medical files Insurance files Notes Documents Video Other **Type of analyses** **-**Qualitative **-Quantitative**	Economy Law Management **Medicine/Public health/Epidemiology** Philosophy Political Science Psychology Sociology Others	That of the: -Society -Insurance **-Health care** -Worksite -Family -Patient	**-**National -Local -Worksite -Health care -Family **-Individual**	All together Cancer **CVD** Infections Injuries *Mental Musculoskeletal* Nervous system Pregnancy Skin Others

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2 Aims

The general aim of this doctoral thesis was to study general and diagnosis-specific DP, and its association with mortality (all-cause and in CVD) among working-aged women and men with a first coronary revascularisation in Sweden in 1994-2006, accounting for socio-demographic and medical factors.

The specific aims were as follows:

- To investigate the prevalence of all-cause and diagnosis-specific DP at the time of a first coronary revascularisation, accounting for socio-demographic and medical factors (study I).

- To investigate the incidence of DP within five years following a first coronary revascularisation, accounting for socio-demographic and medical factors (study II).

- To investigate the five-year all-cause mortality within five years following a first coronary revascularisation, among patients on DP and not on DP at the time of intervention, accounting for socio-demographic and medical factors (study III).

- To investigate the five-year all-cause and CVD mortality within five years following a first coronary revascularisation, among different DP-diagnostic groups (CVD, musculoskeletal, and mental diagnoses) at the time of intervention, accounting for socio-demographic and medical factors (study IV).

3 Methods

The primary study population in this thesis consisted of all patients in Sweden (N=78 153), 30-65 years of age when undergoing a first coronary revascularisation by either CABG (n=28 234), or PCI (n=49 919), during the years 1994-2006. All analyses were based on data from the following five nationwide registers: SWEDEHEART (3), the LISA database (Statistics Sweden), the MiDAS database (Swedish Social Insurance Agency), the National Patient Register, and the Cause of Death Register (both from the National Board of Health and Welfare). An overview of the four studies is presented in Table 2, regarding aim, design, study population, inclusion criteria, data sources, main outcomes, variables included in the studies, and statistical analyses.

Table 2. Overview of the four studies, based on register data on all patients with coronary revascularisation 1994-2003, and 1994-2006 (N=78 153; 21% women)

	Study I	**Study II**	**Study III**	**Study IV**
Aim	Investigate prevalence of all-cause and diagnosis-specific DP at the time of a first coronary revascularisation, accounting for socio-demographic and medical factors.	Investigate incidence and risk factors for future DP following a first coronary revascularisation by CABG or PCI, among women and men in working ages, accounting for socio-demographic and medical factors.	Investigate all-cause, and diagnosis-specific mortality within the five years following a first coronary revascularisation among women and men on and not on DP at time of intervention, accounting for socio-demographic and medical factors.	Investigate associations between diagnosis-specific DP at time of coronary revascularisation and mortality (all-cause and in CVD) among women and men in working ages.
Design	Nationwide, population-based, cross-sectional study	Nationwide, population-based, prospective cohort study	Nationwide, population-based, prospective cohort study	Nationwide, population-based, prospective cohort study
Study population	N: 65 676 (20% women)	N: 34 643 (16% women)	N: 70 040 (20% women)	N: 61 525 (18% women)
Inclusion criteria	Having a first coronary revascularisation in Sweden, during 1994-2006, when aged: 30-63 years, and with no old-age pension at intervention..	Having a first coronary revascularisation in Sweden, during 1994-2003, when aged: 30-63 years, with no DP or old-age pension at time of intervention, alive 30 days after intervention, and with no re-intervention within 30 days.	Having a first coronary revascularisation in Sweden, during 1994-2006, when aged: 30-64 years, and alive 30 days after intervention.	Having a first coronary revascularisation in Sweden, during 1994-2006, and not on DP before 1994, when aged: 30-64 years, and alive 30 days after intervention.
Data sources	SWEDEHEART, LISA, MiDAS, the National Patient Register	SWEDEHEART, LISA, MiDAS, the National Patient Register, the Cause of Death Register	SWEDEHEART, LISA, MiDAS, the National Patient Register, the Cause of Death Register	SWEDEHEART, LISA, MiDAS, the National Patient Register, the Cause of Death Register
Main outcomes	DP at the time of a first CABG or PCI	DP within five years following a first CABG or PCI	All-cause mortality within five years following a first CABG or PCI	Mortality (all-cause and in CVD) within five years following a first CABG or PCI
Variables included in the studies	Type of intervention, gender, age, level of education, country of birth, living area, year of intervention, indication for intervention, diabetes mellitus at intervention, degree of DP, years on DP before intervention, DP diagnoses.	Type of intervention, gender, age, level of education, living area, marital status, country of birth, indication for intervention, year of intervention, re-intervention, diabetes mellitus at intervention, in-patient care within 5 years before intervention, sick-leave days in the 12 months before intervention.	Type of intervention, gender, DP at time of intervention, age, level of education, country of birth, living area, year of intervention, indication for intervention, diabetes mellitus, in-patient care within 5 years up to one day before intervention, re-intervention.	CVD, musculoskeletal, and mental DP diagnoses, type of intervention, gender, age, level of education, indication for intervention, diabetes mellitus at time of intervention, in-patient care within 5 years before intervention, and re-intervention within 5 years after intervention.
Statistical analyses	Descriptive statistics , logistic regression analyses	Descriptive statistics, Cox proportional hazard regression analyses	Descriptive statistics, Cox proportional hazard regression analyses	Descriptive statistics, Cox proportional hazard regression analyses

The project was approved by the Regional Ethical Review Board of Stockholm, Sweden (2006/661-31).

3.1 Study design and populations

In this doctoral thesis, four different studies were conducted: one cross-sectional (study I) and three prospective cohort studies (study II-IV). The first study had a cross-sectional design in order to investigate the prevalence of DP among patients, 30-63 years of age, at the time of their first coronary revascularisation (CABG or PCI) in 1994-2006 in Sweden. This since no previous studies had a specific aim to investigate DP among patients undergoing revascularisation by CABG or PCI. The three cohort studies investigated: granted DP within five years following a first coronary revascularisation (study II), all-cause mortality among DPs and non-DPs, within five years following the intervention (study III), and all-cause and CVD mortality, among DP-diagnostic groups and non-DPs, within five years following the intervention (study IV).

Study I was a population-based cross-sectional study that comprised 65 676 individuals in Sweden, who during 1994-2006, when aged 30-63 years, underwent a first CABG (n=22 959) or PCI (n=42 717) and were not on old-age pension.

Study II was a population-based prospective cohort study comprising all patients in Sweden (n=34 643) who during 1994-2003, when aged 30-63 years, had a first CABG (n=14 107) or PCI (n=20 536), were not on DP or old-age pension at the time of the intervention, and were alive and had no re-intervention in the 30 days after intervention.

Study III was a population-based prospective cohort study comprising all patients in Sweden (n=70 040) who during 1994-2006, when aged 30-64 years, had a first CABG (n=24 987) or PCI (n=45 053), and were alive within 30 days after intervention.

Study IV was a population-based prospective cohort study comprising all patients in Sweden (n=61 525) who during 1994-2006, when aged 30-64 years, had a first CABG (n=21 093) or PCI (n=40 432), were not on DP before 1994, and were alive within 30 days after intervention. The reason for only including DPs from 1994 was due to the non-available information on DP diagnoses through the MiDAS database before that year. Thus, 8515 individuals who were granted DP before 1994 were not included in this study.

3.2 Data

The study population was identified through the SWEDEHEART-register, held by the Uppsala Clinical Research Centre [8] that includes data on e.g., indication and date of intervention and whether one had diabetes mellitus at the time of the intervention. Additional data were obtained by linkage of four other nationwide registers using the unique 10-digital personal identification number assigned to all individuals registered as living in Sweden. The linkage was conducted by SCB and de-identified data were delivered to the research group. These four registers are described in detail below.

3.3 The Swedish Social Insurance Agency

3.3.1.1 The MiDAS database

The Swedish Social Insurance Agency has established a register for research regarding sickness absence and DP, the Micro Data for the Analysis of Social Insurance (MiDAS) database. This database includes information from 1994 regarding sickness absence and DP benefits paid by the agency regarding date and degree (full or part time) of sickness absence and DP as well as DP diagnoses (DP diagnoses obtained for 1994-2008). Most employees have sick pay from their employers during the first 14 days of a sick-leave spell, why information on the shorter sick-leave spells for employees are not included in this thesis (84).

3.4 The National Board of Health and Welfare

3.4.1.1 The Swedish National Patient Register

From the Swedish National Patient Register, also called the Hospital Discharge Register, data on main diagnoses and dates of in-patient care from 1964 through 2008 was obtained. This register was established in 1964. It has a complete coverage from 1987; more than 99% of all somatic and psychiatric hospital discharges are included. A validation by the National Board of Health and Welfare found that 85-95% of all included diagnoses in this register are valid (85). This register includes information on in-patient care (and visits to a physician within specialised outpatient care from 2001, not used in this thesis) due to CVD and other diseases (86). This is one of the few individual-based registers worldwide, covering in-patient healthcare for a whole population. The quality is controlled regularly. The main diagnosis is missing for about 1% of all occasions.

3.4.1.2 The Cause of Death Register

The Cause of Death Register includes data from 1961 for all deceased individuals, registered and living in Sweden at the time of their death, regardless if the death occurred within or outside the country. From this register, date of death (through 2007) and cause of death (through 2006) was obtained for the included patients. The missing information on cause of death has been about 1-2% during the last years (87).

3.5 Statistics Sweden

3.5.1.1 The LISA database

The longitudinal integration database for health insurance and labour market studies (LISA) database include annual data on socio-demographic, socio-economic factors and other data from 1990, for all individuals, ≥16 years of age, registered as living in Sweden in December each year (88). Of those, level of education, marital status, type of living area, country of birth, and emigration were obtained and used in the analyses. The included factors are summarised in Table 2 and further described in detail below.

3.6 Outcome factors

In study I and II, the main outcomes were all-cause DP (regardless of full- or part-time DP); in study I in terms of prevalent DP including DP diagnoses, and in study II in terms of future DP.

In study I, the main outcome was defined as being on DP at the time of a first coronary revascularisation by either CABG or PCI, during 1994-2006. All-cause DP was the outcome of the logistic regression analyses and diagnosis-specific DP the outcome of the descriptive analyses. The DP diagnoses were coded according to the World Health Organizations' (WHO's) International Classification of Diseases, version 10 (ICD 10) [89]. The DP diagnoses were classified into CVD (I00-I99), mental (F00-F99), musculoskeletal (M00-M99), other DP diagnoses, and missing DP diagnoses.

In study II, the main outcome was defined as being granted a first DP, regardless of DP diagnosis, within five years, or through 2007, following a first coronary revascularisation by CABG or PCI during 1994-2003.

In study III and IV, the main outcomes were all-cause mortality (study III-IV) and mortality in CVD (study IV).

In study III, the outcome was defined as all-cause and cause-specific mortality, within five years or at the end of the follow-up, that is through 31 December 2006, following a first coronary revascularisation by CABG or by PCI. Those deceased within 30 days following intervention were excluded from the study. All-cause mortality was the outcome of the Cox regression analyses, and diagnosis-specific mortality the outcome of the descriptive analyses.

In study IV, the outcome was defined as all-cause mortality and mortality in CVD (ICD 10, I00-I99) within five years or through 31 December 2006, following a first coronary revascularisation by CABG or PCI. Those deceased within 30 days following intervention were excluded from the study.

3.6.1 Socio-demographic factors

In all four studies, several socio-demographic factors were included, as descriptive and/or independent variables. The following factors were obtained from the SWEDEHEART-register (age and gender) or from the LISA database (level of education, marital status, type of living area, country of birth, and emigration) and are further described below.

3.6.1.1 Age

Age at the time of intervention was categorised into four groups: 30-49 (reference group), 50-54, 55-59, and 60-63 years (study I-II), and 60-64 (study III-IV) and was used as an independent variable (study I-IV).

3.6.1.2 Gender

Most of the analyses were stratified by gender (study I-IV). Gender was further used as a descriptive variable (study I-IV) or an independent variable (study I-II).

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3.6.1.3 Level of education

The individuals' highest attained level of education at the time of the intervention was included as a descriptive variable or an independent variable (study I-IV). The original variable (SUN2000NIVA) obtained from the LISA database had seven categories; 1. Pre high-school level (<9 years), 2. Pre high-school level (9 years), 3. High school, 4. Post high-school level (<2 years), 5. Post high-school level (≥2 years), 6. Research education, and 7. Missing data. In study I, III and IV, these seven categories were merged into three: elementary school (≤9 years), high school (9-12 years), and college/university (>12 years), respectively. The last category, college/university, was further used as reference group in the regression analyses. However, in study II, "college" (referred to post high-school level) together with "high school" were included in the category medium level of education. The category "missing data" (<1%), was merged with "elementary school" in study I (0.7%, table 2, 4-5), study III (0.7%, table 4-5), and in study IV (0.9%, table 1-4).

3.6.1.4 Marital status

The factor marital status was included in study II, and involved seven different categories (unmarried, married, divorced, widow/widower, registered partner, divorced partner, widow/widower partner), which were dichotomised into: married and non-married (unmarried, divorced, widow/widower, divorced partner and widow/widower partner) and used as a descriptive or an independent variable.

3.6.1.5 Type of living area

The variable 'type of living area', included as a descriptive and an independent variable in study I-III, was created by using data on type of municipality in which the patients lived at the time of their first intervention. In the Statistics Sweden the definition "H-regions" (homogenous regions) were defined by how urban or rural the respective municipality was considered. The version of the following six H-regions was used [90]: (H1) Stockholm, Södertälje, (H2) Göteborg, Malmö, Lund, Trelleborg, (H3) larger cities (>90 000 inhabitants within 30 km from the city centre), (H4) middle-sized municipalities (27 000 to 90 000 inhabitants within 30 km from the city centre, and >300 000 inhabitants within 100 km from the same point), (H5) smaller municipalities (27 000 to 90 000 inhabitants within 30 km from the municipality centre, and <300 000 inhabitants within 100 km from the same point), and finally (H6) rural areas (<27 000 inhabitants within 30 km from the municipality centre). These categories were merged into three groups: larger cities (H1-H2) (reference group in regression the analyses), medium-sized cities (H3), and smaller communities (H4-H6), also called: larger, medium, smaller (study I), and large, medium, small (study III).

These H-regions, rather than geographical regions, were used due to the assumption that it might be easier to change employment due to health problems when living in a more urban area.

3.6.1.6 Country of birth

The information on country of birth (study I-III) was divided into ten categories: 00=Sweden, 01=the Nordic countries (except Sweden), 02= EU25 (except Denmark, Finland, and Sweden), 03= Europe (except EU25 and the Nordic countries), 04=Africa, 05=North America, 06=South America, 07=Asia, 08=Oceania, 09=Soviet Union, 11=Unknown). These were merged into five groups: "Sweden", "Other Nordic countries", "Other EU25", and "Other countries" (study II), and dichotomised into: "Sweden" (reference group), versus "Other" (study I and III). Country of birth was included both as a descriptive and an independent variable (study I-III).

3.6.1.7 Emigration and old-age pension

Date of emigration was obtained from the LISA database and used for censoring in the Cox regression analyses of study II-IV. Information on old-age pension was obtained from the Swedish Social Insurance Agency and LISA.

3.6.2 Medical factors

In all four studies, medical factors were included as descriptive and/or independent variables. Information on these factors was obtained from the SWEDEHEART-register (year of, and indication for the intervention, type of intervention, diabetes mellitus at the time of intervention, and re-intervention following the first intervention), the Swedish National Patient Register (main diagnoses of in-patient care), and the MiDAS-database (number of sick-leave days in the 12 months before the intervention, number of years on DP before the intervention, degree of DP).

3.6.2.1 Year of intervention

The year of the intervention was included both as a descriptive and an independent variable (study I-III) and was categorised as follows: 1994-1996, 1997-2000, 2001-2003, and 2004-2006 (study I), 1994-1996, 1997-2000, and 2001-2003 (study II), and 1994-1997, 1998-2001, and 2002-2006 (study III). The categorisation of years differed in study III due to the fact that information on cause of death was not available after 2006, thus, those who had an intervention in 2002 and forward were followed for less than five years, and therefore, they constituted an own category (year 2002-2006).

3.6.2.2 Indication for the intervention

Indication for the intervention was included as a descriptive and/or an independent variable (study I-IV) and was categorised according to ICD 10 into: acute coronary syndrome (ACS) classified according to electrocardiographic findings as non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction, stable angina pectoris, and other.

3.6.2.3　In-patient care in the five years before the intervention

Information on main diagnoses for in-patient care in the five years before the intervention was included as a descriptive and/or an independent variable (study II-IV) and categorised according to ICD 10 into: angina pectoris (I20), myocardial infarction (I21-I22), heart failure (I50), cerebrovascular disease (I60-I69), transient cerebral ischaemic attacks (G45), mental disorders (F00-F99), and musculoskeletal disorders (M00-M99). The five years were calculated in relation to the exact date of the intervention. In the regression analysis of study II, CVD (myocardial infarction, heart failure, cerebrovascular decease, and transient cerebral ischaemic attacks), and mental, as well as musculoskeletal disorders, were analysed separately. In study III-IV all the original diagnoses for in-patient care were dichotomised into: "yes" and "no" in-patient care.

3.6.2.4　Diabetes mellitus at the time of intervention

Diabetes mellitus at the time of intervention was included as a descriptive and/or an independent variable (study I-IV) and was categorised into "yes", "no", and "missing data". Information on whether one had diabetes mellitus was missing for 12% of the patients and was considered as a separate category in three of the studies (study I and III-IV) and included in the non-diabetes category in one of the studies (study II). The reason for the missing data is unclear. However, since information on diabetes mellitus was originally collected by the physicians asking if the patients had diabetes mellitus at the time of the intervention, a no-answer might not have been documented at that time point. This could be an explanation for why these were merged with the non-diabetes patients in study II.

3.6.2.5　Re-interventions (one or more) in the five years following the first intervention

Re-intervention at least once, either by CABG or PCI within the five years following the first intervention was included as a descriptive and/or an independent variable in study II-IV, and dichotomised into "yes" versus "no".

3.6.3　Sick leave and disability pension

3.6.3.1　Sick-leave days in the twelve months before the intervention

Information on number of sick-leave days with benefits from the Social Insurance Agency in the 12 months before the exact date of the intervention was included in (study II) and categorised into: 0, 1-89, 90-179, and 180-365 days. The group with 0 days with benefits from the Social Insurance Agency can include shorter sick-leave spells reimbursed by the employer. In the regression analyses, the two first groups were combined and used as reference group.

3.6.3.2 Years on DP before intervention

Years on DP before the exact date of the intervention were included (study I, III) and categorised into three groups: ≤3 years, 4-10 years, and 11-35 years.

3.6.3.3 Degree of DP

Degree of DP was included as a descriptive variable (study II). The original variable with six degrees of DP was dichotomised into: full-time DP: >50%, and part-time DP: ≤50%.

3.6.3.4 Diagnoses for DP

Information on the ICD 10 code of the main DP diagnoses was obtained from the MiDAS register. As this register was started up in 1994, information on diagnoses for DP granted before 1994 was not included in the register. However, duration and grade of DP could be obtained before 1994. DP diagnoses was categorised into the following four groups: CVD (ICD-10 code I00-I99), musculoskeletal (M00-M99), mental (F00-F99), and other/missing DP-diagnoses at the time of a first coronary revascularisation by CABG or PCI.

3.7   Statistical analyses

In all four studies, results from descriptive statistics were presented in frequencies and proportions. All the analyses were performed separately for women and men as well as for type of intervention (CABG, PCI).

In study I, logistic regression analyses were performed to analyse the associations between socio-demographic and medical factors and the probability of prevalent DP (irrespective of full or part-time), among patients 30-63 years of age at the time of their first coronary revascularisation (CABG or PCI) in 1994-2006. Crude odds ratios (OR) with 95% confidence intervals (CI) were estimated and adjustments were made for age (model I), age, and level of education (model II), gender (model III), and age, level of education, country of birth, type of living area, year of intervention, indication for intervention, and diabetes mellitus at the time of the intervention (model IV).

Cox proportional hazard regression analyses were performed in study II-IV.

In study II, Crude and adjusted hazard ratios (HR) with 95% CI were estimated for granted DP within five years following a first coronary revascularisation, with regards to socio-demographic and medical factors as well as previous sick leave, among patients, 30-63 years of age at time of their first CABG or PCI in 1994-2003, with no DP or old-age pension at the intervention, and no re-intervention within 30 days following the intervention. All patients contributed with person time (days at risk) from the date of the first intervention until the date of being granted DP, starting old-age pension, emigration, death, or end of follow-up (December 2007).The HRs were adjusted for variables in the following models: age, level of education, country of birth, and year of intervention (model I), and age, level of education, country of birth, year of intervention, and sick-leave days in the 12 months before intervention (model II).

In study III, crude and adjusted HRs with 95% CI were estimated for all-cause mortality within five years following a first coronary revascularisation (1994-2006), among patients, alive 30 days following intervention, on all-cause DP compared with those not on DP at the time of intervention. The proportional hazard assumption was checked graphically and no indication of violation of this assumption was found. All patients contributed with person time (days at risk) from the date of the intervention (1994 through 31 November 2006) until the date of emigration, death or end of follow-up (December 2006). The HRs were adjusted for variables in the following models: age (model I), and age, level of education, country of birth, type of living area, year of intervention, indication for intervention, diabetes mellitus at time of intervention, in-patient care in the five years before intervention, and re-intervention within five years following intervention (model II).

In study IV, crude and adjusted HRs with 95% CI were estimated for mortality (all-cause and in CVD) within five years following a first coronary revascularisation, among patients, alive 30 days following intervention, on diagnosis-specific DP (CVD, musculoskeletal and mental diagnoses), granted from 1994, compared with those not on DP at time of intervention. All patients contributed with person time (days at risk) from the date of the first intervention (1994 through 31 November 2006) until the date of emigration, death or end of follow-up (December 2006). The HRs were adjusted for variables in the following models: age and level of education (model I) age, level of education, indication for intervention, diabetes mellitus at time of intervention, in-patient care in the five years before intervention, and re-intervention within five years following the intervention (model II, and III).

Data on diabetes mellitus were missing for 12% of all the included patients (study I-IV), and in study IV all who had been granted DP before 1994 were excluded (n=8515, 12%) due to the fact that data on DP-diagnoses was missing before that year.

All the statistical analyses were performed using IBM SPSS version 20 and 22.

4 Results

Below, general results from each study are presented; more detailed results are found in the studies in the appendix for respective study.

4.1 Study I

In total, 24% of the patients were on DP at the time of their first coronary revascularisation. Musculoskeletal diagnoses were the largest DP-diagnostic group. Among those on DP, 62% had had DP for at least four years before the intervention. The following groups had a higher adjusted probability of being on DP at the time of the intervention: women (OR: 2.40; 95% CI: 2.29-2.50), older individuals (50-63 years); especially 60-63-year old men with CABG (OR: 4.91; 95% CI: 4.27-5.66), lower level educated; especially men with PCI (OR: 2.96; 95% CI: 2.69-3.26), foreign-born; especially men with PCI (OR: 2.11; 95% CI: 1.96-2.27), and women with another indication for intervention than ACS or stable angina pectoris for PCI (OR: 1.72; 95% CI: 1.31-2.24).

4.2 Study II

Of all patients not on DP at the time of their first coronary revascularisation, 32% were granted DP within the five years following intervention. Women had higher HR for DP compared with men, also after adjustments for age and level of education respectively (education-adjusted HR 1.55; 95% CI: 1.48–1.62), and CABG-patients had higher HR for DP compared with PCI-patients, also after adjustments for age, and level of education respectively (education-adjusted HR 1.35; 95% CI: 1.30–1.40). The highest crude HR was found in patients with 180-365 sick-leave days in the 12 months before the intervention, especially among men with PCI (HR 6.25; 95% CI: 5.84-6.68).

4.3 Study III

Of all patients, 30-64 years of age at time of their first coronary revascularisation during 1994-2006, 4% died during the five year follow-up or through year 2006; most of them died due to CVD. Regardless of adjustments for socio-demographic and medical factors, women and men with DP at the time of CABG or PCI had higher HRs for mortality compared with those not on DP at the time of intervention (CABG: women HR 2.14; 95% CI 1.59-2.89, men HR 2.09; 95% CI: 1.84-2.38, PCI: women HR 2.25; 95% CI: 1.78-2.83, men HR 1.95; 95% CI: 1.72-2.21). Higher mortality risks were also found among most of the subpopulations on DP at time of intervention compared with those not on DP.

4.4 Study IV

Of all patients, 30-64 years of age at time of their first coronary revascularisation, excluding those granted DP before 1994, 14% were on DP at the time of their first coronary revascularisation. In total, 3.0% of all those patients died; 1.7% due to CVD. Of the patients on DP at the intervention, 5.9% died during the five-year follow-up or through year 2006. The HR for five-year mortality (all-cause or in CVD) more than doubled among women and men on DP due to CVD at time of CABG or PCI, compared with those not on DP at the time

of intervention. The included socio-demographic or medical factors (age, level of education, indication for intervention, diabetes mellitus at the time of intervention, in-patient care in the five years before intervention, and at least one re-intervention in the five years following intervention) could not explain the higher associations, except for CVD mortality among women on DP due to CVD at time of CABG.

All studied DP-diagnostic groups (CVD, musculoskeletal and mental diagnoses) were associated with higher five-year mortality (all-cause and in CVD), compared with those not on DP at intervention – with one exception: CVD mortality among those with mental DP diagnoses. However, when presenting gender-specific results, men with mental DP-diagnoses at time of PCI had higher HRs for CVD mortality compared with those not on DP. The HRs for mortality were particularly high among those with mental DP-diagnoses and all-cause mortality at time of intervention, especially women with PCI (HR 3.16; 95% CI: 1.46-6.82). The associations could not be explained by age, educational level, or medical factors. Moreover, no significant differences in estimated HRs were found between most of the DP-diagnostic groups (the CIs overlapped).

5 Discussion

This thesis covers all individuals of working-ages in Sweden who had a first coronary revascularisation of either CABG or PCI over a period of thirteen years (1994-2006). High quality data were linked from several nationwide registers and included in the analyses. The main results regarding the prevalence and incidence of DP and mortality are initially discussed separately for each study. In addition, the main results regarding the studied independent variables, and different aspects of the methods are discussed.

The associations between DP following a first coronary revascularisation and some of the possible contributing socio-demographic and medical factors, as well as sick leave in the year before intervention were investigated. However, other factors, not included in the analyses might contribute to the associations (91). One such possible factor is for instance employment status of the studied patients. Since previous studies have found higher probability of being granted DP among unemployed individuals (92, 93), this factor could be important to include in future studies on DP regarding this population.

5.1 Discussion of results

5.1.1 Study I

Of all investigated patients aged 30-63 years at the time of their first coronary revascularisation (1994-2006) by either CABG or PCI, about a quarter (24%) already had DP, usually for full time, at their first intervention. More than half of them had been on DP since at least four years before the intervention. Hence, many had been outside of the working life for many years before the intervention and maybe also before the indexed CVD-diagnosis. To what extent being on DP can be a risk factor or a risk indicator for future CVD is an issue that would be of interest to investigate further in order to get a knowledge base for possible preventive actions.

The proportion of DP in the study population, in 2004 (the year with the highest DP-rate in Sweden), was almost twice as high (22%) as the prevalence of DP in the general Swedish population, in the same ages, and in the same year (12%) (37). Further, DP was more than four times higher in the studied population as in the entire working population of OECD countries in 2007 (6%) and in 1990 (5%) (94) and in Sweden in 2007 (9%) (37). However, the studied population is different from the general population, in terms of age, gender distribution, and having CVD which might lead to loss of function, activity and work capacity. Moreover, during the studied years DP rates were much higher compared with DP rates of today (2010-2015). Therefore, it would be of interest to further investigate present DP prevalence among patients with a first coronary revascularisation.

5.1.2 Study II

Of all studied patients aged 30-63 years, with no DP at the time of their first CABG or PCI (1994-2003), almost a third (32.4%) of the women and men were granted DP within the five-year follow-up. Among all the studied patients with a revascularisation in 2003, the five-year

incidence for DP (3.2%), was more than twice as high as among the general population in the same ages, at the same year (1.4%) (37). There is no simple way to explain early exit from the labour market among some individuals, when others return to work or to other activities. The results of prevalent and incident DP, as well as mortality among patients on DP at the time of coronary revascularisation cannot be explained by one single factor, thus the explanations rest on a multifactorial ground. More knowledge is warranted on factors that can prevent exclusion form the labour market in this group. To gain further knowledge regarding the impact of medical factors on future DP in this patient group, further attention on specific DP diagnoses at the time of coronary revascularisation was implicated and further investigated in study IV.

5.1.3   Study III

Of all studied patients aged 30-64 years at the time of their first coronary revascularisation (1994-2006), and who were alive one month after the intervention, 4% died (in all-cause mortality) within the five-year follow-up (or through 31 December 2006). In accordance with previous studies (73-79) and regardless of adjustments, the five-year mortality was more than twice as high among both women and men on DP at the time of CABG or PCI compared with no DP; also in most of the subpopulations. This result was not explained by the included socio-demographic or medical factors.

However, there might be several other explanations for this association (79); a possible explanation could be the underlying disease or other morbidity than the main indication for intervention. However, since most of the mortality rates remained high when adjusting for medical factors such as in-patient care in the five years before, and re-intervention in the five years after the intervention, as well as diabetes mellitus at the time of intervention, this is less likely. Nevertheless, data were only available on main diagnosis for in-patient care, therefore, other co-morbidity as, for example, the second diagnosis for in-patient care might shed additional information on these results.

This study did not include DP diagnosis in the regression analyses; however, when including these as independent variables in study IV (almost the same population as in study III), all the three DP-diagnostic groups (CVD, musculoskeletal, and mental diagnoses), also the non-lethal, were associated with a higher five-year mortality risk compared with no DP at the time of the intervention.

Also, other factors than the disease itself could have contributed to the higher mortality rate among DPs, for example: the unfavourable risk factor profile found in previous studies among DPs (lower educational level, high alcohol intake, smoking, and not being in a relationship) (79). Moreover, the DP could be a negative health factor on top of the underlying disease (95). DP in itself might imply risk factors that are associated with the higher mortality risk among these patients. The loss of the work-related social network could imply loss of the own identity and position in the society.

5.1.4 Study IV

Of the studied women and men aged 30-64 years who were alive 30 days after their first coronary revascularisation in 1994-2006 and who were not granted DP before 2004, 3.0% died; 1.7% due to CVD. Among the patients on DP at the time of the intervention 5.9% died within the five-year follow-up or through 2006.

All except for mental DP-diagnoses were associated with higher five-year mortality (all-cause and in CVD) compared with those not on DP at the time of the intervention – However the gender-specific results showed higher mortality risks also among most of the mental DP-diagnostic groups. The higher mortality risks remained regardless of adjustments for age, educational level, and medical factors. Also those with non-lethal DP diagnoses, i.e., musculoskeletal diagnoses, had a higher mortality risk. This finding is in line with previous studies on DP in the general population (73-79). For example, Björkenstam et al. (73) found that also those with non-fatal DP diagnoses still had higher mortality risk, and that previous in-patient care did not explain this association. Future investigation both regarding other possible medical explanatory factors such as co-morbidity, severity of disease, and more detailed information on causes of death, as well as factors at other structural levels for example: work site and family factors, could further clarify these associations. These factors are especially important to regard among patients with DP due to musculoskeletal and mental diagnoses at the time of a coronary revascularisation, since previous studies have found associations between these disorders and higher risk of CVD (96), between depression and higher mortality among patients with MI (97), and between depression before CABG and a higher risk of death, heart failure, MI and stroke (98). Furthermore, accelerated cardiovascular morbidity and mortality occur in patients with Rheumatoid arthritis who have a high prevalence of coronary plaque (99).

5.1.5 Factors associated with DP and five-year mortality

5.1.5.1 Type of intervention

Data in all four studies in this thesis were stratified by type of intervention, that is, by CABG or PCI. This was done since patients with CABG often have more severe coronary heart disease than PCI patients (5-7, 36), and they might therefore have a higher DP and mortality risk. This was also confirmed by the results in this thesis (study I-II); DP was more common among patients who had had a first CABG than among those with a PCI. As the choice of intervention shifted over the studied years so that PCIs became more common, also year of intervention was included in the analyses.

5.1.5.2 Age

Among both genders with CABG or PCI, regardless of adjustments, and in accordance with previous studies on DP (38, 41, 43, 47, 51, 53, 55, 57, 58, 64, 67, 68, 88, 100-104) older patients, over 50 years of age, had both higher prevalence and higher five-year incidence of DP compared with younger patients (30-49 years) (study I-II); the probability of being on DP at the time of intervention was more than fourfold higher among the oldest men (60-63 years). However,

this was only slightly above the DP rates of men in the general Swedish population in the same age group (30% versus 27% respectively) (37). The finding of higher DP rates among older individuals may be explained by an increasing morbidity with age. The result of incident DP was not adjusted for medical factors. However, when taking medical factors (year of intervention, indication for intervention and diabetes mellitus) into account the associations between all age groups and prevalent DP increased; this remains unexplained. Another explanation of the higher DP rates among older patients could be the high employment rate among older individuals in Sweden, and that a higher rate of those in the older group had a lower level of education. Lower educational level often implies jobs with higher DP risks, less possibilities to find alternative jobs if one is not capable of handle the demands of the present jobs, and might also imply less coping strategies (64, 105).

Younger patients (30-49 years) (study III-IV) on DP at the time of the intervention had a markedly higher five-year mortality (more than a fourfold higher), compared with younger patients not on DP. After adjustments for socio-demographic factors (age, level of education, country of birth, or type of living area) and medical factors (year of intervention, indication for intervention, diabetes at the time of intervention, in-patient care in the five years before intervention, and ≥1 re-intervention), the HR for mortality remained high. The exception to that were women on DP at the time of CABG, for whom these factors explained the whole association. The finding of higher mortality among younger DP recipients is in accordance with another study on general DP (79). Apparently, DP or factors associated with DP at the time of intervention seem to highly influence the five-year mortality among younger patients. However, this finding needs further research.

5.1.5.3 Gender

In line with several previous studies on DP, in general and regarding musculoskeletal and mental diagnoses, (36, 38, 39, 41, 44, 45, 49, 51, 53, 54, 56, 58, 59, 64, 80, 106) women had both higher prevalent and incident DP compared with men. Women in both the intervention groups (CABG, PCI) had higher DP rates, also when adjusting for age and educational level. There are several theories about this (80, 107). Probable explanations or contributing factors for this could be women's higher age when being diagnosed with CVD (24), and that women have smaller coronary arteries and more co-morbidity than men (2). Other explanations are women's higher sick-leave rate (108), different demands at work, and possible gender bias in health care (80, 107, 109).

5.1.5.4 Level of education

In the analyses of this thesis, irrespective of type of intervention and gender, lower level of education (≤12 years) was found to be associated with a higher prevalent and incident DP compared with having higher level of education (>12 years). Individuals with at the most elementary education had up to tripled odds for being on DP at the time of intervention, and were up to two times more likely to be granted DP in the five years following the intervention. These findings are in accordance with previous studies (41, 46-48, 55, 59, 66, 67) and

also in line with findings of higher educational level as a protective factor for DP in general (51, 110).

5.1.5.5 Country of birth

The patients with coronary revascularisation, who were born outside Sweden, had both higher prevalent and incident DP (study I-II) compared with the patients born in Sweden. Men born outside of Sweden had a particularly higher probability of being on DP, both at time of CABG or PCI compared with the men born in Sweden. These results remained when adjusting for the included socio-demographic and medical factors (study I). These findings are in line with previous studies on DP in general (43, 57, 68, 100).

5.1.5.6 Sick-leave days in the twelve months before the intervention

Patients, both women and men, with more than 180 sick-leave days in the 12 months before the CABG or the PCI had the highest risk estimates for DP granted in the following five years, compared with those who had less than 90 sick-leave days before the interventions. Men with more than 180 sick-leave days before PCI had a six-fold higher risk of DP in the five years following the intervention. This result is in accordance with previous studies (17, 69). As DP, in most cases, is granted to individuals with a history of long-term sickness absence, this result was to some extent expected. Nevertheless, most people who are sickness absent, even for >180 days, are not granted DP. However, in this group, about 20% of those sickness absent for >180 days in the year before intervention were not granted DP.

5.1.5.7 In-patient care in the five years before the intervention

A higher risk for five-year incidence of DP following a first coronary revascularisation was found among patients with previous in-patient care for mental and/or musculoskeletal disorders. The higher risk remained when adjusting for socio-demographic factors and previous sick-leave (age, level of education, country of birth, year of intervention, and sick-leave days in the 12 months before intervention). This is in line with previous study findings on DP among other studied individuals than those with coronary revascularisation (36, 45, 54, 71). Furthermore, both women and men on DP at the time of CABG or PCI who had had in-patient care in the five years before the intervention had higher risk of five-year mortality compared with those not on DP at the time of the intervention. These results remained when adjusting for the included socio-demographic and medical factors (age, level of education, country of birth, type of living area, year of intervention, indication for intervention, diabetes mellitus at the time of intervention, and re-intervention). This indicates that the history of morbidity before coronary revascularisation is important for prevalence of DP at the time of intervention as well as for mortality following the intervention.

5.2 Methodological considerations

In this thesis one cross-sectional and three prospective cohort studies, based on register data have been conducted. Below, some methodological aspects of these studies are discussed.

5.2.1 Strengths

Main strengths of this thesis are the large study population, that all, not a sample were included, the wide set of included data, the high quality of most of the included factors, the long follow-up time, and that there were no losses to follow-up.

The included studies are the first nationwide, population-based studies investigating DP and mortality among DPs among both women and men in working-ages at the time of their first coronary revascularisation including both CABG and PCI, within a time period of up to 13 years. Further strengths are the population-based and prospective study designs, the high quality data linked together from several nationwide registers, including extensive information on medical and socio-demographic factors (85).

5.2.2 Limitations

A limitation in this thesis is that not all data on medical factors were complete, e.g., regarding diabetes mellitus (information was missing for 12% of the patients). However, since there is a strong association between diabetes mellitus and CVD, and these two diagnoses generally share the same risk factors (111); it was, nevertheless, important to include this medical factor in the studies. Missing data was regarded as an own category, both in the analyses and in the descriptive statistics (study I, III-IV). The data on diabetes mellitus, obtained from SWEDEHEART, was reported by the physicians who asked the patients about this diagnosis prior to the intervention. The reason for missing data on this is unclear. One explanation could be that physicians did not register those without diabetes at the time of the intervention. For some of the patients, information on diabetes mellitus could be obtained from the Patient Register.

Having had more than 180 sick-leave days in the year before the intervention was associated with a particularly high five-year risk of DP following the intervention. During the late 1990s and the early 2000 there was no limit to the duration of a sick-leave spell in Sweden, why some might have been on sick-leave for many years. In other countries they might have been granted DP earlier in the work disability trajectory. This means that some of the results, regarding prevalence of DP, incidence of DP, and mortality following DP might be underestimated. One way to handle this in future studies could be to define long-term sick-leave spells, e.g., those lasting for more than two years, as also being on DP (112).

Additional limitation is the shorter follow-up time among patients with the intervention in 2003 (study II), and 2002-2006 (study III-IV). This since DP data only were available through 2007 (study II) and mortality data through 2006 (study III-IV). Due to this limitation, the risk of DP (study II) and mortality (study III-IV) might have been underestimated.

When the analyses of study III and IV were stratified for many factors, the size of some subpopulations became small and generated rather wide confidence intervals. Mostly, wide CIs were found among women in these subpopulations, as the numbers of women were low.

Most studies on DP do not have access to information on DP diagnosis. In this thesis such information could be included, which is a strength. However, data on DP diagnoses was not available before 1994. Hence, this data was treated as a no-information category in study I. In study IV, individuals granted DP before 1994 were excluded. Many of the excluded individuals were in higher ages at the time of the intervention. Since higher age is a risk indicator for DP (113), the exclusion of these individuals might have contributed to an underestimation of the mortality risk among the DPs.

Even if excluding those with no information on DP diagnoses before 1994 (study IV), information on DP diagnoses was still missing for 15% of those on DP. These could have been in one of the three included DP-diagnostic groups. Hence, the HRs of the three groups could have been underestimated.

The validity of DP diagnoses is sometimes questioned; however, it has not yet been studied. To the best of my knowledge, only one study investigated the validity of sick-leave diagnoses compared with diagnoses in medical files. That study found that the validity was good (114). External validity concerns to what extend the results of a study can be generalised to the general population (115). The studies included in this thesis are all population-based and have relatively high statistical power. The patients included in the four studies were all aged 30-64 years of age, at the time of their first coronary revascularisation. Hence, the results might not be generalizable to other age groups. Moreover, it may be possible that changes of the public social insurance system with somewhat altered rules, as well as changes in the extent to which the Social Insurance officers adhere to the regulations, means that caution should be taken in generalising the results to other time periods than those studied. Furthermore, this thesis involves interventions conducted over a long time period, from 1994-2006. Since CABG and PCI have improved and changed over time, caution should also be taken when generalizing results to present time.

5.3   In summary
- About one quarter of working-aged patients who had a first coronary revascularisation sometime during 1994-2006 were already on DP at the time of intervention.
- The most common DP diagnoses among them were musculoskeletal diagnoses. More than half of those on DP at the time of intervention had been so for at least four years.
- Female gender, older age, lower educational level, and being born outside Sweden were associated with a higher prevalence of DP at the time of the first coronary revascularisation. The studied socio-demographic and medical factors could not explain these associations.

- A third of all the working-aged patients who had their first coronary revascularisation sometime during 1994-2003, were granted DP within five years following the intervention.
- Women, CABG-patients, long-term sick leave in the year before the intervention, in-patient care for mental or musculoskeletal disorders in the five years before the intervention, diabetes mellitus at the time of intervention, and having at least one re-intervention within five following years, were associated with higher risk of DP within five years following intervention.
- Four percent of all working-aged patients who had their first coronary revascularisation in 1994-2006, died within five years following the intervention; most of them due to CVD.
- DP at the time of intervention was associated with higher risk of five-year mortality, compared with no DP, overall as well as in most of the studied sub-populations. The studied socio-demographic and medical factors could not explain these associations.
- All studied DP-diagnostic groups (CVD, musculoskeletal, and mental diagnoses) were associated with higher risk of five-year mortality, compared to those not on DP at the intervention; also DP diagnoses that in themselves rarely are causes of death e.g., musculoskeletal diagnoses. These associations did not differ between DP-diagnostic groups, except for "all" with CVD or musculoskeletal DP diagnoses at PCI, and all-cause mortality.

5.4   Future research

The prevalence and incidence of DP among patients with a first coronary revascularisation seemed to be higher than among those in the general population, indicated by the national DP statistics. The prevalence and incidence of DP was high in Sweden during the years studied of this thesis. Further, the interventions (CABG and PCI) have been improved over the past decades (14). Therefore, to get a picture of the DP situation among patients with a coronary revascularisation of today, it would be fruitful to also study DP in present time.

More than half of the patients had been on DP for at least 4 and up to 35 years before the intervention. Although the indication for the intervention was CVD; more were on DP due to musculoskeletal DP diagnoses, in general as well as in most of the studied subgroups. This implies that many had been outside the labour market for many years before the intervention. Maybe musculoskeletal disorders, that were so severe that they lead to DP, could be associated with the CVD in itself. Another possibility is that being on DP in itself is either a risk factor or a risk indicator for CVD. This indicates that the patients' medical history, beyond CVD, is of importance for those undergoing coronary revascularisation, hence future studies could focus on co-morbidity among patients who had had long-term DP before their first CABG or PCI.

Women were associated with both higher prevalent and incident DP in the studied population, regardless of age or level of education. This could be due to that women have

smaller coronary arteries than men and that the intervention procedures are still not optimal for women. Also, women's higher sick-leave rate, other work arenas and demands, and possible other gender bias in health care could contribute to the higher DP rates in women. These gender differences show the importance of conducting gender-specific studies on DP in this patient group, in order to gain knowledge on possible mechanisms in both women and men.

Many socio-demographic factors were associated with DP in relation to coronary revascularisation at the time of intervention. Of these, several have also been associated with DP in the general population.

So far, only few studies have investigated the association between DP and mortality. In this thesis, the risk of both all-cause and cause-specific (CVD, musculoskeletal and mental diagnoses) five-year mortality was higher among patients on DP, compared with those not on DP at the time of intervention, also among most of the included subpopulations. These risks remained regardless of adjustments for socio-demographic and medical factors. Therefore, in future studies it would be justified to also include other factors such as employment status before intervention, severity of disease at the time of intervention, as well as other multi- or co-morbidity factors, in order to be able to more in detail explain these associations.

The scientific knowledge on the consequences of being on DP is limited. However, this thesis found a higher five-year mortality risk among patients in all studied DP-diagnostic groups (CVD, musculoskeletal and mental diagnoses) compared with those not on DP at the time of coronary revascularisation. Hence, the risk was also higher among DP diagnoses considered as non-lethal. This is in line with previous studies on DP in general and the risk of mortality. Furthermore, the all-cause mortality-risk was markedly higher among mental DP diagnoses, than among no DP at the time of intervention; over three times higher among women with PCI. This in spite of adjustments for age, level of education and medical factors (indication for intervention, diabetes mellitus at the time of intervention, in-patient care in the five years before intervention, and re-intervention in the five years following intervention). To further explain these associations, future studies may regard other medical factors, for example: history of other co-morbidity, such as, the second DP diagnosis, or the second diagnosis for in-patient care before intervention.

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