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DISABILITY PENSION DUE TO COMMON MENTAL DISORDERS - SUBSEQUENT PSYCHIATRIC MORBIDITY AND SUICIDAL BEHAVIOUR

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Disability pension due to common mental disorders -
subsequent psychiatric morbidity and suicidal behaviour

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Dedicated to the Martyrs of Bangladesh, who did not fear to sacrifice their lives to protect our mother tongue 'Bangla' and gave birth to a country named after the mother tongue 'Bangladesh'

Abstract

Background: Mental diagnoses have become the most common disability pension (DP) diagnoses in OECD countries. Up to half of DP due to mental diagnoses are due to common mental disorders (CMDs). So far, research has mainly focused on risk factors of DP rather than on the future life situation of people with DP. Nevertheless, the latter types of studies suggest higher mortality, including suicide among DP recipients. Therefore, knowledge on morbidity and suicidal behaviour following DP is needed. Investigations of the associations between DP and adverse mental health outcomes should be multifaceted, considering socio-demographics, co-morbidity, existing regulations about DP benefit, medical factors, i.e., healthcare use and prescribed medication, etc. The thesis aimed to gain knowledge about the association of DP due to CMD with subsequent psychiatric morbidity and suicidal behaviour in the general population of Sweden. **Methods:** In study I and II all individuals who were on DP due to CMD throughout 2005 were included. Cox regression analyses calculating hazard ratios (HRs) were conducted for measuring the associations between socio-demographics, specialized healthcare use, medication, and measures of DP with suicidal behaviour during a 5-year follow-up. In study II, all analyses were stratified by sex and age. In study III, Generalized Estimating Equations (GEE) were applied to identify the trajectories of specialized healthcare use before and after granted DP during a 7-year period in cohorts with DP due to CMD, granted either in 2005-06 or in 2009-10. The latter cohort also comprised the study population for study IV. In study IV, a group-based trajectory method was used to identify different trajectory groups according to the amount of defined daily doses of prescribed antidepressants (AD) during 6 years of observation. Information on socio-demographics, DP, specialized healthcare use, medication, and death was derived from five nationwide registers. Data were linked at individual level by unique identification numbers. **Results:** In the disability pensioners, sex, age, education level, family situation, previous in- or specialized outpatient care due to mental diagnoses or suicide attempt, and medication were strongly associated with subsequent suicidal behaviour (HR range: 1.15-3.89) (study I). Among the DP measures, stress-related mental disorders as main DP diagnosis, compared to depressive disorders were associated with a lower risk for subsequent suicidal behaviour (HR range: 0.4-0.7). Among other measures, psychiatric comorbidity, and full-time DP were associated with a higher risk of subsequent suicidal behaviour (HR range: 1.3-3.3) compared to no comorbidity and part-time DP, respectively (study II). Moreover, healthcare use due to mental diagnoses increased until the year preceding DP and declined thereafter (study III). After the introduction of stricter DP granting criteria, people had higher levels of such healthcare preceding DP, nevertheless, still less than half of the individuals received specialized mental healthcare a year prior to granted DP. Analyses also showed a steeper decline in healthcare use due to mental diagnoses immediately following DP among individuals granted DP with stricter criteria (study III). Among the disability pensioners, five trajectory groups were identified according to the annual amount of prescribed ADs. The groups differed particularly regarding age, main DP diagnosis, and previous healthcare use. Moreover, many had a very low dose of AD before granted DP, and for most of them, there was hardly any decline in the AD trajectories following granted DP (study IV). **Conclusion:** Important aspects to consider for subsequent psychiatric morbidity and suicidal behaviour in individuals after granted DP due to CMD should include, socio-demographics, the main and secondary DP diagnoses, grade of DP, and diagnosis specific previous specialized healthcare use. The frequency of healthcare use was lower immediately following DP, but the amount of prescribed ADs did not alter for most of the disability pensioners in that period. Both DP granting and subsequent mental health appears to be associated with the DP granting regulations. Importantly, the low frequency of specialized mental healthcare use and amount of prescribed ADs during the pre-DP period may indicate a sub-optimal treatment before the premature labour market exit among individuals granted DP due to CMD.

Sammanfattning

Bakgrund: Psykiska diagnoser har blivit den vanligaste anledningen till att individer beviljas sjuk- och aktivitetsersättning (SA), tidigare förtidspension, i OECD-länder. Närmare hälften av alla personer som beviljats SA i psykiska diagnoser har diagnoser relaterade till depression, ångest- eller stressrelaterade syndrom. Hittills har forskningen framförallt fokuserat på riskfaktorer för att beviljas SA snarare än på den framtida livssituationen för personer med SA. De få studier som finns om framtida situation visar bl.a. på en högre mortalitet, inkluderande självmord, bland personer med SA. Mer kunskap behövs därför om risk för framtida morbiditet och suicidalt beteende bland personer som beviljats SA. Sådana studier behöver bl.a. ta hänsyn till sociodemografiska faktorer, samsjuklighet, regelverk, sjukvård och medicinering. Syftet med denna avhandling var att studera sambanden mellan att ha SA i depression, ångest- och stressrelaterade syndrom och framtida psykisk sjuklighet och suicidalt beteende i Sverige. **Metod:** Fyra delstudier gjordes, baserade på länkade individdata angående sociodemografiska faktorer, SA, specialiserad sjukvård, medicinering och död från fem olika rikstäckande register. I studie I och II inkluderades alla personer som bodde i Sverige under 2005 och som beviljats SA i depression, ångest- och stressrelaterade syndrom. Samband mellan sociodemografiska faktorer, specialiserad sjukvård, medicinering och suicidalt beteende under de följande fem åren beräknades med hjälp av Cox regressionsanalyser. I Studie II stratifierades de analyserna för kön och ålder. I studie III identifierades mönster av användning av specialiserad sjukvård under en 7-årsperiod före och efter beviljad SA i depression ångest- och stressrelaterade syndrom i två kohorter - de som fick SA antingen under 2005-06 eller under 2009-10 - med hjälp av Generalized Estimating Equations (GEE) (i juli 2008 infördes striktare regler för beviljande av SA). Den senare kohorten studerades även i studie IV beträffande mönster för användning av receptbelagda antidepressiva läkemedel under en 6-års period. **Resultat:** Bland personer med SA i depression, ångest- och stressrelaterade syndrom hade kön, ålder, utbildningsnivå, familjesituation, specialiserad sjukvård för psykiatriska diagnoser och medicinering samband med framtida suicidalt beteende (hazard ratios, HRs: 1.15–3.89, studie I). De som hade SA i stressrelaterade syndrom hade lägre risk för framtida suicidalt beteende jämfört med de med depression (HRs: 0.4–0.7). Psykisk samsjuklighet och SA på heltid hade samband med högre risk för framtida suicidalt beteende (HRs: 1.3–3.3) jämfört med ingen samsjuklighet och SA på deltid (studie II). Specialiserad öppen- eller slutenvård för psykiatriska diagnoser ökade före beviljandet av SA och minskade därefter (studie III). Efter att striktare regler introducerades för SA beviljades betydligt färre personer SA i depression, ångest- och stressrelaterade syndrom och en större andel av dem som beviljades SA i dessa diagnoser hade psykiatrisk specialistsjukvård innan beviljandet. Trots detta hade färre än hälften fått sådan psykiatrisk specialistvård under året före beviljandet av SA. Andelen med psykiatrisk specialistsjukvård efter beviljandet av SA minskade kraftigare efter att striktare regler för SA införts (studie III). Fem olika mönster för användning av antidepressiva läkemedel kunde identifieras bland personer med SA. Dessa grupper skiljde sig åt framförallt med avseende på ålder, SA diagnos samt tidigare specialistsjukvård. Dessutom hade många väldigt låga doser av antidepressiva läkemedel före beviljandet av SA och för de flesta personerna minskade inte sådan medicinering efter att ha fått SA (studie IV). **Slutsatser:** Faktorer som kan ha betydelse för framtida psykisk sjuklighet och suicidalt beteende bland personer med SA i depression, ångest- eller stressrelaterade syndrom är såväl sociodemografiska faktorer som typ av huvuddiagnos, omfattning av SA (hel- eller deltid) och tidigare typ av specialistvård. Nyttjandet av specialiserad sjukvård var lägre direkt efter beviljandet av SA däremot inte receptbelagd antidepressiv medicinering. Både beviljande av SA och framtida psykisk hälsa verkar ha samband med regler för SA. Det är viktigt att poängtera att den låga förekomsten av psykiatrisk specialistvård och låga dygnsdoser av antidepressiva medel före beviljandet av SA kan tyda på en mindre optimal behandling innan beviljandet av SA.

List of scientific papers

- I. Rahman S, Alexanderson K, Jokinen J, Mittendorfer-Rutz E.
Risk Factors for Suicidal Behaviour in Individuals on Disability Pension Due to Common Mental Disorders – A Nationwide Register-Based Prospective Cohort Study in Sweden. PLoS ONE 2014;9(5): e98497.
- II. Rahman S, Alexanderson K, Jokinen J, Mittendorfer-Rutz E.
Disability pension due to common mental disorders and subsequent suicidal behaviour; a population-based prospective cohort study. BMJ Open 2016;6:e010152.
- III. Rahman S, Mittendorfer-Rutz E, Alexanderson K, Jokinen J, Tinghög P.
Disability pension due to common mental disorders and healthcare use before and after policy changes; a national study. European Journal of Public Health. 2016 Nov 17. pii: ckw211. [Epub ahead of print]
- IV. Rahman S, Wiberg M, Alexanderson K, Jokinen J, Mittendorfer-Rutz E.
Trajectories of prescribed antidepressants in individuals before and after being granted disability pension due to common mental disorders- a nationwide register-based study. *Submitted*.

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List of abbreviations

AD	Antidepressant
AR	Autoregressive correlation
ATC	Anatomical Therapeutic Chemical
BIC	Bayesian Information Criterion
CI	Confidence interval
CMD	Common mental disorder
DDD	Defined daily dose
DP	Disability pension
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
GAZEL	French Gas and Electricity Company
GEE	Generalized Estimating Equations
HR	Hazard ratio
IB/SB	Incapacity benefit/sickness benefit
ICD	International Classification of Diseases
IMAS	Insurance Medicine All Sweden
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
MiDAS	Micro Data for Analysis of the Social Insurance
MSD	Musculo-skeletal diagnoses
OECD	Organisation for Economic Co-operation and Development
PIN	Personal Identity Number
QOL	Quality of life
RTW	Return to work
SA	Sickness absence
SAS	Statistical Analysis System
SCB	Statistics Sweden
SES	Socio-economic status
SIA	Social Insurance Agency
SPSS	Statistical Package for the Social Sciences
SRMD	Stress-related mental disorder
WHO	World Health Organisation
WHOCC	WHO Collaborating Centre for Drug Statistics Methodology

1 Introduction

A disease or injury may lead not only to limitation of function of an individual but also to one's work incapacity, and that individual might be entitled to sickness absence or disability pension benefit, here called work incapacity [1-3]. If such work incapacity was merely a socio-economic, biomedical, or political matter in the past, it is now perceived as a public health problem in many of the member states of the Organization for Economic Co-operation and Development (OECD) countries [2, 4-6].

Work incapacity can be influenced, among others, by psychological, social, administrative, or cultural aspects. Work incapacity, may lead to temporal (i.e., sickness absence) or permanent (i.e., disability pension) exclusion from the labour market. This thesis is focused on disability pension (DP). There are some other similar English terms, expressing more or less the permanent exit from the labour market due to work incapacity caused by disease or injury, of which the following are widely used: disability benefit [7], incapacity benefit [8], disability retirement [9], ill-health retirement [10, 11], permanent workplace disability [12], work disability pension [13], pension on medical ground, health-related early retirement [14] etc.

Despite the fact that the prevalence of DP across the OECD countries seems to be stable for the last few years, at around six percent, yet since early 2000s there is a remarkable increase in the incidence of mental DP diagnoses, especially in DP due to common mental disorders (CMDs), e.g., depression, anxiety, and stress-related mental disorders [3, 5, 6, 15-19]. In Sweden, these increases were especially high in young adults. From 1995 to 2015 the yearly incidence of DP in individuals below 30 years of age increased for more than four-fold, from 1931 to 8400 [3]. In Sweden, the incidence of DP due to mental diagnoses doubled in only ten years, from 25% to 51% from 2000 to 2010 [3]. This development implies high costs for society, possible shortage of labour, and for the people on DP possible different types of economic, social and health outcomes.

Despite the fact that knowledge on the positive and negative outcomes or "side effects" of being granted DP is of crucial clinical and public health interest, the scientific literature is surprisingly sparse. With regard to long-term outcomes among individuals on DP, the risk of all-cause and cause-specific premature death was found to be higher compared to in the general population, regardless of the DP diagnoses [20-22]. The scientific knowledge base regarding the association of DP with future morbidity and mortality due to mental diagnoses is even more limited. Being granted DP seems to involve a higher risk of suicide when comparing with the general population not on DP, also when adjusting for hospitalization due to mental diagnoses, socio-economic status, and parental risk factors such as parental suicidality, DP, and educational level [23-25]. Potential other mechanisms underlying the association of DP with subsequent psychiatric morbidity and suicidal behaviour (suicide attempt and suicide) may involve life dissatisfaction, unhealthy life styles (high alcohol and tobacco use), or co-morbid disorders, as these conditions seem to be related to DP [26-28] and may encompass high risk of mental disorders and suicidal behavior after DP.

There are also only few studies investigating if transition to DP has an effect on individuals' mental health status. Five recent Scandinavian studies suggest that self-reported symptoms of depression and anxiety as well as prescription of antidepressants (ADs) to increase before being granted DP, after which a decrease in these measurements was noted [29-33]. Some of the mentioned studies, however, suffer from different shortcomings, e.g., data have often been derived from selected segments of the work force or from selected regional areas. Furthermore, there is a lack of studies investigating if effect sizes in the associations with mental health outcomes vary with different subgroups of people granted DP, e.g., related to age, sex, DP diagnosis, as well as socio-economic status. Definition of subgroups in the analyses would help to improve the specification of potential risk groups regarding the future development of the underlying mental disorders as well as suicidal behaviour. Early detection of vulnerable individuals might thus be facilitated, and preventive, possibly tailor-made, interventions could be started earlier.

The prevalence and incidence of DP are very complex phenomena, affected by many aspects including changes in social insurance regulations [34]. Furthermore, particularly since the 1990s, several conditions that are potentially relevant for DP prevalence and incidence have changed. These factors include temporal changes in unemployment rates, increase in psychosocial work stress, reorganizations within the public and private sectors, and deteriorating mental well-being particularly among younger persons [35-37]. In order to acknowledge these temporal trends affecting incidence and prevalence rates and the profile of DP diagnoses, analyses using different cohorts were carried out in this thesis. A recent study showed that risk estimates for all-cause mortality were considerably lower in a cohort of individuals being granted DP due to mental disorders in 2005 compared to in 1995 [21]. These findings have to be interpreted in the light of strong increase in the incidence of DP due to mental diagnoses during that period.

1.1 Disability pension policy across OECD countries

Social security and insurance systems may differ substantially between countries resulting also in different regulations with regard to granting of DP in different countries [2, 5, 38]. In general, compensation for disability may be cause-based or disability based [38]. For cause-based, the coverage is only if the injury or disease is attributable to a specific cause, e.g. work related. It generally covers access to medical care and expenses related to accidents and occupational diseases directly related to the work place. Here, the definition of occupational disease may vary widely. Cause-based insurance can be private, e.g., as in the United States, or public, e.g., as in Canada and Australia. Disability-based systems tend to be more generous, cover both occupational diseases/injuries and other types of diseases and injuries, and can be temporal or permanent. Disability-based systems are practiced in many European countries such as, Sweden, the Netherlands, Denmark, etc. These differences have to be considered when comparing results from studies on DP from different countries [39].

DP policy models have been categorized in three main streams. The ‘Social-democratic’ policy model, the ‘Liberal’ policy model, and the ‘Corporatist’ policy model [6]. The social-democratic model can be divided into two sub-models. The first sub-model, currently in Denmark, Switzerland, and the Netherlands is less generous in terms of benefits and employment supports, but provides better work incentives and has very strong sickness absence (SA) monitoring and/or sick-pay eligibility control focus compared to the other two models. Germany belongs to the second sub-model, together with Finland, Sweden, and Norway, which is the most generous model in the OECD. It covers the whole population, has comparatively lower entry thresholds, reasonably high benefits, and good rehabilitation measures. However, this sub-model involves the strongest employer obligations of all the models [6].

The Liberal policy model also includes two sub-models. One, including Australia, New Zealand, and the United Kingdom, is very well organized and coordinated, resulting in good access. At the same time, it has very low compensation levels but with universal coverage. The other sub-model, covering Canada, the United States, Japan, and Korea, has the strictest eligibility criteria for a full disability compensation, including less flexible rehabilitation system, and the shortest sickness benefit payment duration, compared to all other models [6].

There are three sub-models within the Corporatist policy model. The first sub-model, including Austria, Belgium, and Hungary, contains well developed rehabilitation and employment programs with lower benefit levels, thus having a stronger employment orientation. In the second sub-model, including France, Greece, Luxembourg, and Poland, there are better sickness and disability benefits compared to the other countries in the Corporatist cluster; they also put a focus on temporary disability benefits, and more attention to sickness absence. The third and biggest subgroup, including the Czech Republic, Ireland, Italy, Portugal, the Slovak Republic, and Spain, does not have well-developed employment and rehabilitation policies. This leads towards a stronger compensation orientation, though the level of compensation is much lower than in the other subgroups of this cluster but with a longer sickness compensation payment duration [6].

Among the European countries, the rules for SA or DP also vary in terms of qualification criteria, benefit levels, duration, taxation of benefit, etc. For instance, in the Netherlands, one has to have a loss of work capacity to a minimum extent of 15% and requires being on sick-leave for at least two years before being granted DP, whereas, in Sweden, the extent of lost work capacity must be at least 25%. The benefit can reach up to 64% of the lost salary in Sweden or in Germany, while it can be 100% in France. In most of the countries, such benefits related to DP granting are fully taxable and paid up until the old-age retirement, whereas in Germany such benefits are exempted from tax [2].

1.2 The Swedish Social Insurance System

Sickness benefit covers all individuals aged above 16 years, who are living in Sweden and have a minimum level of annual income from work, unemployment, or from parental

benefit [3]. Sickness benefit is paid in case of reduced work capacity for at least 25% due to disease or injury. An individual can receive 25%, 50%, 75% or 100% sickness benefit based on reduced working capacity. An employee usually receives compensation from the employer during days 2-14 of a sick-leave spell, the first day is a qualifying day and from day 15 the compensation is paid by the Social Insurance Agency. Unemployed people and those on parental leave can be granted sickness benefit from the Social Insurance Agency from the second day of a sick-leave spell. Self-employed can have different numbers of qualifying days. Reimbursement by the employer is called 'sick pay' and by the Social Insurance Agency 'sickness benefit'. Usually the first seven days of a sick-leave spell can be self-certified, from day eight a medical certificate from a physician is also required. Around 80% of lost income, up to a certain level, can be paid by the Social Insurance Agency for 364 days within a period of 450 days. If the work capacity is still reduced, the individual can in some cases receive sickness benefits for longer periods, at the level of 75% of lost income - however, at 80% if the disease is classified as 'severe' [3].

All residents in Sweden aged 19-64 years, who due to disease or injury have a long-lasting or permanent reduction of their work capacity to an extent of at least 25%, can be granted temporary or permanent DP from the Social Insurance Agency [3]. In Sweden, DP can be granted for 25%, 50%, 75%, or 100% of reduction in work capacity in relation to ordinary working hours. Since 2003, individuals aged 19-29 years can be granted temporary DP for two main reasons, if their work capacity is reduced for at least one year, or due to the failure to complete compulsory or upper secondary school in due time [3]. DP amounts to 64% of lost income, up to a certain level. Those with no previous income receive a minimum specific amount.

The disability pension system in Sweden has a long history [40]. In Sweden, a law on compensation for accidents at work was enforced in 1901, a public social insurance with income-related sickness benefit and subsidized health started in 1955. During the same year occupational injury insurance was initiated [41]. From 1972 and onwards, the eligibility criteria for DP also included labour market issues. In 1991, the possibility for being granted DP for purely labour market reasons was removed [41]. However, up through 1996, employees aged over 60 years could still receive DP when their unemployment benefit expired [41].

At the turn of the century, 2000, the levels of SA and DP were very high in Sweden and several interventions were taken to reduce the levels. The 'halveringsmålet' the government stated in 2003 (halving the 'sick-leave rate' = 'sjuktalet' in five years) was one of those interventions [42, 43]. In 2003, the regulations related to DP were amended in relation to age, that is, young individuals aged 19-29 years could be granted temporary DP if the work capacity was reduced for at least one year in order to complete upper secondary education. However, individuals aged 30-64 years, with at least 25% reduced work capacity for one year were still eligible for temporary or permanent DP. Before, they could be granted DP from the age of 16 years. In the following years there was a dramatic decrease in both SA and DP

incidence [3]. In 2005, a new authority, the Social Insurance Agency, was established, including the 21 previous regional social insurance agencies as well as a national agency (Riksförsäkringsverket). One of the reasons for this new authority was to decrease regional differences in handling of decisions regarding SA and DP [44].

In 2008, the eligibility requirements for SA and DP were tightened. Now sickness benefit was limited to one year for most of the individuals and the maximum number of days of a sick-leave spell was set at 914 days. The so called ‘rehabilitation chain’ was introduced so that officers at the social insurance agency were to take actions earlier in the SA trajectory. For instance, specific assessments were to be conducted at 90 days, 180 days, and 364 days of a sick-leave spell. In case of DP grant, an individual had to have a diagnosed disease or injury that led to a permanent loss of work capacity of at least 25% of ordinary work hours with regards to the entire labour market, that is, the possibility of temporary DP was removed from the age of 30 years [3].

1.3 Incidence and prevalence of disability pension

In general, around six percent of the working-aged people across OECD countries are on DP [6]. In Sweden, in total 345 000 individuals were receiving temporary or permanent DP benefits at the end of 2015 [3]. This corresponds to a prevalence measure of six percent of the total working-age (19-64 years) population, thus, the same as the OECD average [3, 6]. Of those on DP, 58% were women. With regard to incidence measures: 8 400 and 13 000 individuals were granted temporary and permanent DP in 2015, respectively [3]. In the age groups 19-29 a slightly higher proportion of men than women were on DP. In other age groups, starting from age 35 years, the rate of women on DP was higher, and even much higher in the ages 40-64 (Figure 1).

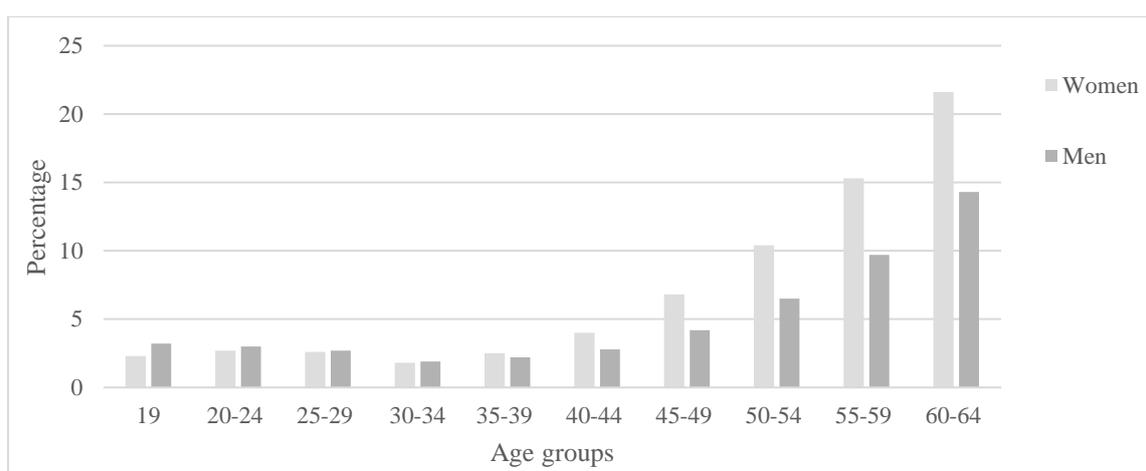


Figure 1. Prevalence of disability pension (DP) in December 2015 in Sweden, among individuals aged 19-64 years, stratified by sex and age group [3].

The proportion of individuals applying for or being granted DP due mental diagnoses is increasing across the OECD countries [6, 18]. Among those with such DPs, the most common diagnoses for such early exit from the labour market are the CMDs [3, 6, 15, 19]. On an average, one in every three new DP claims is due to a mental diagnosis, rising to as high as 40% in some countries and nearly 50% in Denmark [6]. The highest proportions are found among the 20-34 age groups, with around 70% of all claims [6]. In Finland, from 1992 to 2003, the proportions of prevalent DP due to mental diagnoses increased from 31% to 42%, and 33% of incident DP were due to mental diagnoses in 2003 [15, 45]. In Germany, there was nearly a three-fold increase in the proportion of mental diagnoses among those with incident DP, from 1986 to 2001 (from 11% to 28%, respectively). The rate of mental and behavioural disorders among new recipients of DP in Iceland, from 1991 to 2004, increased from 15% to 29% for women and 18% to 38% for men [46, 47]. In Sweden, since 2003 among the younger individuals aged 19-29 years and since 2007 among the older age group of 30-64 years, mental diagnoses form the dominant group among incident DP. In Sweden, mental diagnoses accounted for 86% of temporary DP in young women and 89% among young men granted in 2015, and corresponding figures for the older age group with permanent DP were 46% among women and 43% among men (Table 1) [3].

There is a higher incidence of DP claims due to mental diagnoses among women than among men, and there is a higher proportion of women on DP than men [3, 6, 18, 48].

Table 1. Proportions of incident DP among individuals living in Sweden, stratified by age and DP diagnoses [3].

Sex	Age in years	Year of DP grant	Main DP diagnosis	
			Mental %	Musculoskeletal %
Women	19-29	2003	66	12
		2015	86	02
	30-64	2003	29	44
		2015	46	29
Men	19-29	2003	69	05
		2015	89	01
	30-64	2003	26	36
		2015	43	17

In Sweden, since 1998, the prevalence of DP increased persistently until 2004 followed by a decline from 2005 until 2012 [3, 49]. The decline in the total prevalence of DP was due to the decrease in the incidence of permanent DP. After 2012, the prevalence rates have been relatively stable. However, since 2003, the number of individuals 19 to 29 years of age on DP has steadily increased (Figure 2).

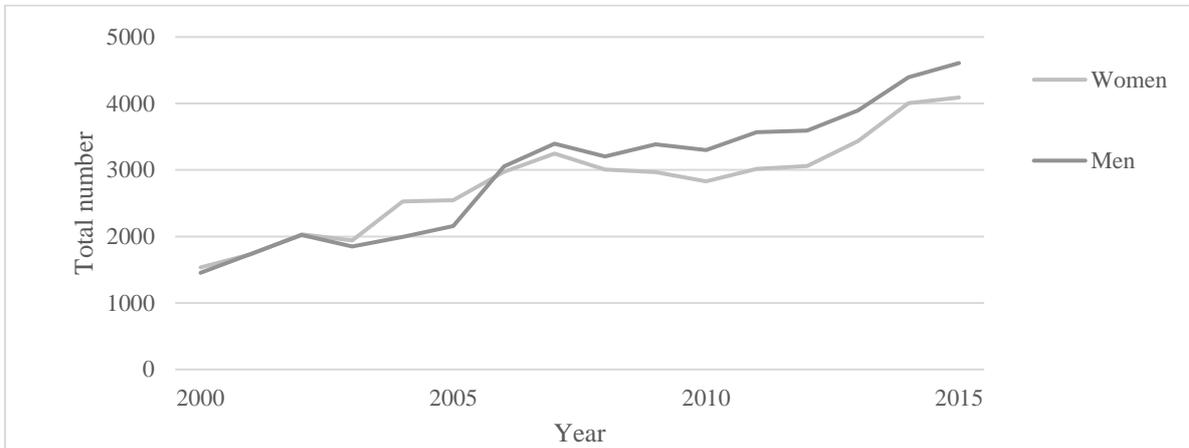


Figure 2. Incidence of disability pension (DP) among individuals aged 19-29 years during 2000 to 2015, in Sweden [3].

Among people aged above 29 years, the incidence of DP steadily declined during 2004–2011, and begun to rise somewhat in 2012. During 2015, around 11 700 individuals, aged 30-64 years were granted DP (Figure 3) [3].

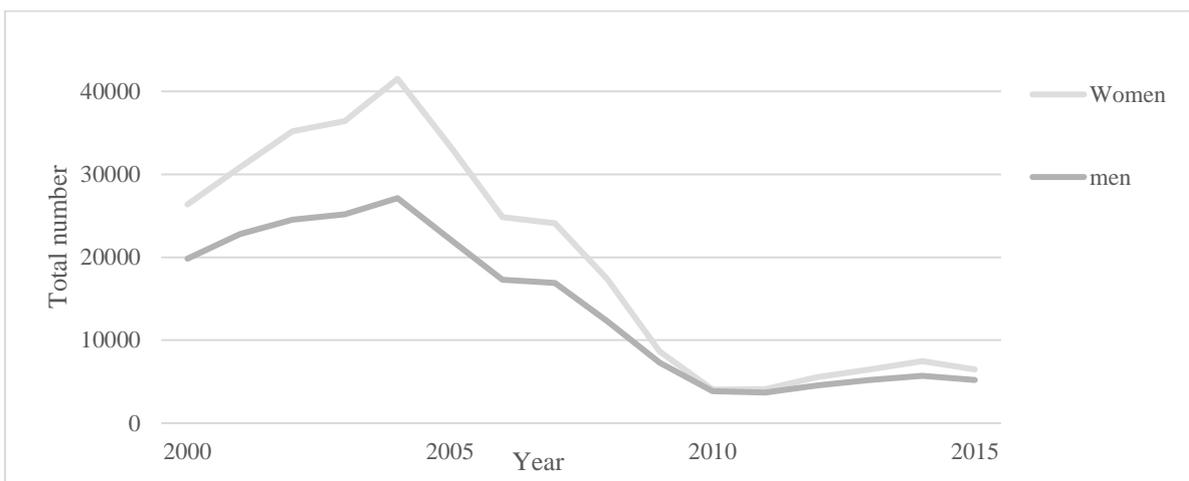


Figure 3. Incidence of disability pension (DP) among individuals aged 30-64 years from 2000 to 2015, in Sweden [3].

1.4 Socio-demographic factors and disability pension

The associations between different socio-demographic factors and DP are well recognized [23, 50-58]. The existing literature suggests a higher likelihood of women to be on DP compared to men [23, 55, 59]. On the other hand, contradictory findings have also been reported. For instance, Gjesdal et al. in 2002, found no sex difference in the risk of DP when controlling for income and employment status, despite that a sex difference was present in the crude analyses [60]. Family situation also seems to play a role in the risk of being granted DP [55, 57, 61]. To live alone has been found to be a risk factor for subsequent DP [62]. Although, Dahl et al., in a study based on a Norwegian cohort, in 2000 reported that divorced women had a lower risk of DP, whereas divorced men had a significantly higher risk of DP [63]. Additionally, research findings regarding having young children at home as a risk factor for future DP are inconsistent and have mainly focused on women [60, 62, 64].

Higher age has previously been reported to be associated with a higher risk of DP [60, 65-67]. Still, particularly due to mental disorders, the incidence of DP is high in younger adults [3, 6, 17]. A number of studies investigated the association between low socio-economic status and the risk of long-term SA or DP, and reported a higher risk for subsequent DP among individuals with low-socio economic status [6, 51, 66, 68-73].

Moreover, the role of type of living area as well as of regional area in granting of DP has been described by authors from different countries [53-55, 74-78]. In Norway, there seems to be a regional difference in granting of DP, both in all-cause and diagnosis-specific DP, with a higher frequency in the rural or semi-rural areas [54]. This association was influenced by job type, lower educational opportunities and poorer healthcare facilities. [54, 74, 76]. Similar findings regarding outpatient care due to depression were reported in Sweden by Mittendorfer-Rutz et al. [55]. Regional differences in the risk of DP granting in Finland has also been reported by Laaksonen et al., where the differences were affected by area-level deprivation, differences in the healthcare services, rehabilitation, and employment services [53, 79]. The risk of being granted DP may also vary with country of birth [55, 57, 61, 80-82]. Among other social factors, social isolation and low social participation have also been found to be associated with higher risk of DP [56].

In addition, health-related behaviour, such as smoking, alcohol use and physical activity have been reported to be associated with subsequent DP [9, 83-87]. Among other health determinants, obesity [88-90] and sleep disturbances [91-93] are also significant risk factors for premature exit from the labour market in the form of DP. Different work-related factors, e.g., heavy physical job type, poor working conditions, high job strain, shift work, effort-reward imbalance and low job control have been associated with future DP [94-101].

1.5 Medical factors and disability pension

Different medical factors, such as healthcare use, psychotherapies, or prescriptions of psychiatric medication before being granted DP may reflect the severity of an underlying mental disorder, due to which DP is granted, and might act as predictors for DP granting. On the other hand, mental health of individuals after being granted DP can be evaluated by the frequency of healthcare use, by assessing prescriptions of psychiatric medication, etc. during the post-DP period. In this PhD project, medical factors included in- and specialized outpatient care due to mental and somatic diagnoses (study I, II, III, and IV), inpatient care due to suicide attempt (study I and II) and prescribed dispensed antidepressants (study I and IV) or anxiolytics (study I).

Below is a brief description about healthcare use and prescription of ADs in individuals granted DP.

1.5.1 Disability pension and specialized healthcare use

In general, frequency and patterns of healthcare use might be related to the type of disease and may reflect its clinical severity. The more severe cases are usually treated by specialists either at specialized outpatient care or at inpatient care facilities. Therefore, it can be assumed that individuals, with a disease leading to work incapacity, are likely to have a high degree of severity of the disorder and are supposed to go through different and extensive healthcare and rehabilitation measures prior to applying for DP. Moreover, CMDs have a good prognosis with treatment and rehabilitation methods, which are relatively well accessible, and they are likely to worsen with inactivity [102-104]. Therefore, granting of DP, which in fact is enabling or even more promoting inactivity by exclusion from the labour market, would be less anticipated. Surprisingly, the majority of the DP applications throughout Europe today are due to mental diagnoses, and CMDs are the most common among them [2, 3, 6, 15]. Adequate healthcare measures before considering a DP claim are, therefore, crucial in order to prevent transition to DP. Existing scientific knowledge regarding this issue, though very scarce, indicate an inadequate treatment before the DP grant in terms of healthcare use, pharmacotherapy, and psychotherapy [105-107]. Similar findings were reported by Eisenberg et al. in 2007 when investigating help-seeking and access to mental healthcare in a university student population [108]. The scientific literature on the pattern of healthcare use among the DP individuals suggests an immediate decrease following DP, but still much higher compared to those retired not due to health reasons [109], or even lower compared to those with similar clinical features and not on DP or denied DP [110]. Beckman et al., reported in 2006, that socio-demographic factors like country of birth, family situation, education, etc. may also affect the granting of DP by affecting healthcare use patterns [61]. Suboptimal treatment of the disorder leading to DP may also depend on the living area due to access to healthcare by altering the help seeking behaviour or due to lack of skilled personnel causing longer waiting time, or due to lack of facilities, e.g., beds, at the healthcare center [53, 76, 111].

1.5.2 Disability pension and antidepressant use

Adequate pharmacological treatment during the pre-DP period may play a crucial role in terms of preventing DP due to mental disorders. Specifically, when impaired functioning is due to depression, adequate pharmacotherapy may reduce symptoms and improve productivity [112-114]. In Swiss studies, conducted in 2002 and 2004, on individuals claiming DP due to mental diagnoses, it was reported that only 20% and 37%, respectively, received adequate pharmacotherapy before applying for DP [115]. Similar findings were also reported from Finland and Norway [106, 107, 116]. Trajectory studies of AD prescriptions or purchases in individuals on DP due to mental disorders may contribute to depict the treatment situation in terms of dosages and trend. Laaksonen et al. [30], in 2012 reported an increase in purchases of psychiatric medication, measured by calculating defined daily doses (DDD), particularly in ADs during the pre-DP period, which was then decreased in the post-DP period. The DDD, as defined by ‘the WHO collaborating center for Drug Statistics Methodology’, is the tentative average maintenance daily dose for a medication, used as its main indication in adults [117]. However, looking at the amount of purchases one year before the DP grant, which was around 40 DDDs in a three months’ interval per individual, one could suspect a suboptimal treatment [30]. Similar findings regarding AD trajectories were reported by other Finnish researchers [31, 32].

In addition to the specialized healthcare factors, previous prescriptions of antidepressants and anxiolytics were also taken into account for study I. In study IV, trajectories of prescribed ADs were identified and studied during the pre- and post-DP periods.

1.6 Potential outcomes of being on disability pension

Most of the scientific research has so far focused on risk factors rather than potential outcomes of being on DP (Tables 2 and 3). Among the studies on different outcomes following granted DP, the majority have emphasized the higher risk of premature death among people on DP compared to in the general population [20-22, 24, 118-127]. Studies also suggest a higher suicide risk in people on DP compared to the general population [21, 24, 25, 120, 127, 128]. Previously, DP has also been shown to be a risk factor for suicide in a population-based longitudinal study in the Danish population [25]. Although, Hult et al. claimed that there is no association between DP per se and higher mortality, stating that it is rather the DP diagnosis that explains the higher mortality among people on DP [129].

There is an association between main DP diagnoses, particularly mental diagnoses and higher mortality, including due to suicide [21, 24, 120, 126, 130]. It can be assumed, that similar to the general population, this risk might be considerably higher when comorbid with other mental or somatic disorders [131-137]. Sick-leave duration of more than 90 days due to a mental diagnosis is reported to be associated with a higher risk for all-cause mortality and suicide [138]. Additionally, higher suicide risk immediately following granted DP [119, 121] may indicate a possible association between duration of DP and subsequent higher risk of premature death including suicide. DP grade, which can be seen as a reflection of the severity

of the DP diagnosis, has also been shown to be associated with subsequent suicidal behaviour [121, 139].

Long-term or permanent exclusion from the labour market due to DP may adversely influence health due to lack of positive effects from paid work, including social contacts with colleagues, prospects of career and income progression, a sense of purpose, or even daily routines and structures [140]. Additionally, DP or long-term SA itself may imply alterations of health behaviour (e.g., regarding alcohol and tobacco use, exercise, diet) or social isolation [141, 142].

In general, studies on trajectories of purchased ADs, show an increase in such purchase until the DP grant, especially during the DP granting year, and particularly in individuals granted DP due to mental diagnoses [30-32]. The trajectories would immediately decline following granted DP with a further stabilization in purchase of ADs [30-32]. Disability pension has also been shown to be a predictor of benzodiazepine use 20 years after granted DP in a study from Norway [143].

Overland et al., while studying health status of DP recipients before, during, and after DP grant, reported a ‘U-shaped’ trend of symptom level, including mental, somatic, pain distribution, sleep problems, etc. [33]. From ‘the 2000 Psychiatric Morbidity Survey’, carried out in the UK, Buxton et al., in 2005, reported a higher prevalence of CMD among men who were already on DP compared to their working peers, while such differences were not obvious in women [144]. In another UK study, conducted by Pattani et al. in 2004, surveying national health service employees, concluded that despite improvements in the quality of life (QOL) among DP recipients following a year after DP grant compared to the QOL at baseline, it was still significantly poorer compared to their working colleagues, and to those who had returned to work [145].

A survey by Ejlertsson et al., of individuals on DP due to Musculoskeletal diagnoses, was carried out in 1992 and 1994 in Kristianstad municipality, Sweden [146]. The aim of the study was to find predictors of positive health¹ among such DP recipients. The authors reported that the high age (55 or more years) and not being an immigrant, absence of fibromyalgia and other general pain disorders, no regular use of analgesics to be predictors of positive health, and recommended extend rehabilitation efforts, focusing on how to cope with chronic pain, especially for the individuals younger than 55 years. They also advised to intensify efforts to support immigrants to adjust to situations related to ill-health and

¹ Positive health was defined based on the two questions, ‘How would you describe your overall health status at present?’ (answers: good, neither/nor, poor) and ‘How would you describe your health status today in comparison with two years ago?’ (answers: better, unchanged, worse). If an individual answered good health in 1994 and for whom the health status had not deteriorated in the last two years then it would be considered as positive health. Similarly, negative health was defined a poor health status in 1994, and health status had not improved in last two years.

retirement and to strengthen activities of daily living in DP recipients to support an independent active life.

In another study among men on DP from Eskilstuna, Sweden, the authors reported higher healthcare use among men on DP aged between 30-54 years compared to men of similar age group (reference group) from the general population [109]. Over time, healthcare use declined among DPs and was constant in the reference group, however, it remained twice as high compared to the reference group. Below are tables 2 and 3 showing possible outcomes of being on DP.

Table 2. Studies on disability pension (DP) and mortality.

Author, year published, country	Study design; Type of data	Study period	Exposure	Outcome measures	Total study population	Covariates	Results
Qin et al. 2000 [147], Denmark	Retrospective case control, register	1980-1994	DP	Suicide	811 suicide cases, 79 871 controls	Family situation, socio-economic status (SES), type of living area, labor market participation incl. DP, psychiatric admission, alcohol/drug use	DP was associated with higher risk of suicide only in crude analysis
Quaade et al. 2002 [119], Denmark	Prospective cohort study, registers	1986-1996	DP and early retirement (latter is earned through long-term membership in unemployment benefit scheme)	All-cause mortality	Total Danish population born between 1926-1936	Age, sex, primary occupation (including old age pension, disability benefit, and early retirement benefit)	DP was associated with higher risk for mortality, the association was even stronger than with early retirement; risk was highest immediately after granted DP
Qin et al. 2003 [25], Denmark	Retrospective case control, register	1981-1997	DP	Suicide	21 169 suicide cases, 423 128 controls	Family situation, SES, type of living area, labor market participation incl. DP, ethnicity, psychiatric admission	DP was associated with higher risk of suicide in both men and women, also in multivariate models
Ahs et al. 2006 [127], Sweden	Prospective, questionnaire survey	1984–1989 and 1992–1997	Employment status	All-cause and cause-specific mortality	Unemployed 2067, retired/ temporal DP 2674, economically inactive for other reasons 1373, employed 38 293	Age, sex, education, family situation, country of birth, type of living area, longstanding illness, self-rated health, previous unemployment	Higher risk of mortality including suicide especially among those on temporary DP and only suicide among the unemployed

Author, year published, country	Study design; Type of data	Study period	Exposure	Outcome measures	Total study population	Covariates	Results
Wallman et al. 2006 [20], Sweden	Prospective cohort, registers	1971-2001	DP	All-cause and cause-specific mortality	6887 persons younger than 65 years at baseline (1683 (24.4%) were on or receiving DP at baseline)	Age, sex, diagnosis, family situation, education, smoking, drug use, hospital admission	Higher risk for mortality among DP; risk declines with age
Bambra C et al. 2006 [148], UK	Ecological study	2002	Sickness absence (SA) > 1 year (equivalent to DP in Sweden)	All-cause and cause-specific mortality and self-rated health	376 local government areas		Medically certified SA (>1 year) is associated with a higher risk of all-cause mortality
Karlsson N, 2007 [122], Sweden	Prospective cohort studies, register, records	1985-1996	DP diagnoses	All-cause and cause specific mortality	143 933 persons, 16-64 years old	Age, sex	All-cause DP was associated with higher mortality due to same and different diagnoses; no association with DP due to labour market reasons; high risk for suicide in both sexes due to mental diagnoses, and in men due to cardiovascular diagnoses
Karlsson et al. 2007 [121], Sweden	Prospective cohort study, records, registers	1985-1996	DP (full- and part-time, and due to labour market reasons)	All-cause mortality	245 704 persons, 16-64 years old	Age, sex	Higher risk of mortality with DP in both sexes and all age groups, particularly in the youngest; lower risk with part-time DP, and for labour market reasons
Gjesdal et al. 2008 [149], Norway	Prospective cohort study	1990-1996	DP all-cause and diagnosis specific	All-cause mortality	148 942 persons	Age, education, income	DP was associated with higher mortality with exception of men with musculoskeletal diagnoses (MSD), the

Author, year published, country	Study design; Type of data	Study period	Exposure	Outcome measures	Total study population	Covariates	Results
							effect was stronger in men when adjusted for income and education
Gjesdal et al. 2009 [124], Norway	Prospective cohort study. register	1994-2003	DP all-cause and diagnosis specific	All-cause mortality	2492 persons	Age, sex, income, DP diagnosis	DP was associated with higher mortality; men with mental diagnoses had higher risk for DP and mortality than men with MSD; higher risk of mortality among men of higher age and low income
Gjesdal et al. 2009 [22], Sweden, Norway	Prospective cohort. Registers	1990-1996	DP all-cause and diagnosis specific	All-cause mortality	71 293 women, 76 928 men from Norway, and 68 181 women and 7950 men from Sweden	Age, sex, DP diagnosis	Higher mortality, especially among male workers
Hult et al., 2010 [129], Sweden	Prospective cohort, registers	1971-1993	DP all-cause	All-cause mortality	24 369 male construction workers	Age at DP grant, DP grade	DP per se was not associated with higher mortality, rather illness explained it
Shaw et al., 2011 [118]	Retrospective cohort, registers	Census 1981, 1986, 1991, 1996, 2001 each with 3 years follow-up	Sickness benefit (SB) and Incapacity benefit (IB)	All-cause mortality	14 373, 20 307, 26 016, 39 090, 45 840, respectively	Age, sex	SB and IB was associated with higher mortality
Leinonen et al. 2013 [120], Finland	Prospective cohort, registers	1997-2007	DP due to mental diagnosis	All-cause and cause specific mortality	392 985 with no prior DP due to	Age, social class, living arrangement	Higher mortality among DPs due to depression and other mental diagnoses

Author, year published, country	Study design; Type of data	Study period	Exposure	Outcome measures	Total study population	Covariates	Results
					mental diagnoses at baseline		compared to non-DP; especially for unnatural and alcohol-related death
Björkenstam et al. 2014 [21], Sweden	Prospective cohort, registers	1996-2009	All-cause and diagnosis-specific DP	all-cause and cause-specific mortality	Cohort 1995: 5 006 523 (DP 37 945) Cohort 2000: 5 066 144 (DP 45 302) Cohort 2005: 5 072 599 (DP 58 146)	Age, sex, family situation, education, living area, country of birth, previous inpatient care	Higher mortality risk among people granted DP; higher suicide risk in DP due to MSD, neurological, mental diagnoses
Narusyte et al. 2014 [125], Sweden	Prospective twin cohort, registers	1996-2008	1 .SA 2. SA or DP	1. DP 2. Mortality	59 598 (twin individuals)	Age, sex, zygosity	1. Incident SA was associated with higher risk of subsequent DP 2. SA or DP were associated with higher mortality risk Very little influence from familial factors
Polvinen et al. 2015 [126], Finland	Prospective cohort, registers	1987-2007	All-cause and diagnosis-specific DP	Cause-specific mortality	58 937 men and 52 289 women	Age, sex, DP diagnosis, SES	Higher mortality among DPs compared to non-DPs; manual workers had a higher risk of mortality than upper non-manual employees

Table 3. Studies on disability pension (DP) and different outcomes.

Author, year published, country	Study design; Type of data	Study period	Exposure	Outcome measures	Total study population	Covariates	Results
Ejlertsson et al. 2002 [146], Sweden	Survey, prospective, questionnaires	1992-1994	DP due to MSD	Positive self-reported health	352 DPs	Household composition, healthcare and medication use, SES, psychosocial determinants, perception of life situation	Positive health was associated with older age, not being an immigrant, not having fibromyalgia, no regular use of analgesics, positive subjective health before the study period
Wallman et al. 2004 [109], Sweden	2 cohort studies, questionnaires, registers	1986-1999	DP	Diagnosis-specific healthcare use from 5 years before to 13 years after retirement	215 men (30-54 years) on DP, 620 referents from general population (same age) in Eskilstuna of Sweden	Education, smoking habits, employment and family situation	Men on DP had a higher risk for healthcare use at baseline and follow-up
Pattani et al. 2004 [145], UK	Prospective cohort study, survey questionnaires	1998-1999	DP	Return to work (RTW) under same or different employer, quality of life (QOL)	1317 employees with DP	SES, age, sex, type of employment, marital status, ethnicity	RTW improved QOL, but it was still lower in DPs compared to the general population, lower age and better QOL at baseline predicted RTW
Hartz et al. 2009 [143], Norway	Prospective cohort, health survey 1985-1989 and prescribed drug register 2004-2006	2004-2006	DP	Later prescription of Benzodiazepines	6645-men 6455-women	Age, gender, alcohol use and smoking, marital status, physical activity, use of analgesics, and somatic (cardiovascular morbidity) and mental health problems	About 20% of all men and 30% of all women reporting being on DP at the age of 40 years had started benzodiazepines 20 years later, a period covering most of their potential workforce period

Author, year published, country	Study design; Type of data	Study period	Exposure	Outcome measures	Total study population	Covariates	Results
Øverland et al. 2008 [33], Norway	Prospective cohort, HUSK survey and DP register	7 years before to the 7 years after granted DP (DP register January 1992 to December 2004)	DP	Health status	8598 men 9983 women	Depression, anxiety, somatic symptoms, pain distribution, sleep problems, physical diagnoses, blood pressure medication	For most measures, the level of health problems was equal 3–7 years before compared to 3–7 years after granted DP, the exceptions being an increase in prescribed medication and more sleep problems after granted DP
Oksanen et al. 2011 [32], Finland	Prospective cohort, registers	9 years	Retirement (including DP)	Use of ADs and diabetic medications	11 019	Sex, SES, geographic area (Southern, Middle, Northern Finland, based on the location of the workplace), and type of employer (town or hospital), long-term SA, chronic disease	<i>Statutory retirement:</i> decreased AD purchase during from 1 year before to 1 year after retirement (more decrease for high SES, history of long-term SA), increased for men in post-retirement. <i>DP due to mental diagnoses:</i> AD purchase increased in pre-retirement, peak in retirement year, decrease in post-retirement, more decrease in high SES. <i>DP due to somatic diagnoses:</i> AD purchase increased in pre-retirement but little decrease in transition or postretirement
Laaksonen et al. 2012 [30], Finland	Prospective cohort, registers	10 years of observation for incident old age pension (OAP) and DP granted		Trajectories of ADs, hypnotics and sedatives	DP (N=2549) OAP (N=4456),	Sex, retirement year, age at retirement and social class	Steep increase in purchases of psychiatric medication before DP, following decreased purchase of ADs after granted DP due to mental diagnoses

Author, year published, country	Study design; Type of data	Study period	Exposure	Outcome measures	Total study population	Covariates	Results
		during 2000-2008					
Leinonen et al. 2013 [31], Finland	Prospective cohort, registers	15 years of observation for incident OAP and DP granted during 1997-2007		Trajectories of ADs	DP (N=42 937) OAP (N=19 887) DP (N=2549) OAP (N=4456)	Sex, calendar year, age at retirement, social class, family situation	Increased purchase of ADs before DP, especially steep among those retiring as DP due to depression and other mental disorders, with a decline in similar purchases following DP grant

1.7 Conceptual framework

In all four studies of this PhD thesis, the focus was on the future life situation after being granted DP due to CMD regarding psychiatric morbidity and suicidal behaviour. Suicidal behaviour here refers to suicide attempt and suicide. Risk factors for suicidal behaviour following being granted DP were assessed in study I and II, and healthcare use frequencies and trajectories (study III) along with amounts of prescribed dispensed ADs (study IV) were considered before and after granting of DP. A conceptual framework for the four studies is presented in Table 4.

Table 4. Conceptual framework of the performed studies in this thesis according to a structure for categorizations of studies on sickness absence (SA) and disability pension (DP) [150]. Those relevant for this thesis are marked in **bold**.

What is studied	-Design -Studied -Data -Analyses	Scientific discipline	Perspective taken in research questions	Structural level of factors included in the analyses	Diagnoses
1. Factors that hinder or promote sickness absence/disability pension 2. Consequences of (being on) sickness absence/ disability pension 3. Factors that hinder or promote return to work 4. Sickness certification practice 5. Methods, theories	<u>Study design</u> -Cross sectional -Longitudinal -RCT, CT, etc. <u>Studied</u> General population Insured In paid work (general or special) Diagnosed On SA/DP Other <u>Type of data</u> Interview Questionnaire Register Medical files Insurance files Notes Documents Video Other <u>Type of analyses</u> -Qualitative -Quantitative	Economy Law Management Medicine Psychology Sociology Public health Epidemiology Philosophy Other	That of the: -Society -Insurance -Healthcare -Employer -Family -Patient	-National -Local -Worksite -Healthcare -Family -Individual	All together Mental Musculoskeletal Cancer Circulatory Infections Other

1.8 Common mental disorders

In 2014, the World Health Organisation (WHO) defined mental health as, “a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community” [151]. Mental disorders have been defined as “health conditions that are characterized by alterations in thinking, mood, or behavior (or some combination thereof) associated with distress and/or impaired functioning” [152]. The two concepts of ‘mental health’ and ‘mental disorders’ are not distinct, rather it is the presence of one or the other as a continuum which determines the human behaviour. Common mental disorders (CMD) are mental conditions that cause marked emotional distress and interfere with daily function, [153]. The most common mental disorders, therefore referred to as ‘Common mental disorders’, include depressive, anxiety, and stress-related mental disorders [153-160]. These disorders are labeled as CMD in this thesis. In general, CMDs are more prevalent among women, whereas men tend to have a higher prevalence of substance abuse disorders [155, 157, 160]. The onset of mental disorders often occurs already in childhood or adolescence, and anxiety disorders might have an earlier age of onset than depressive disorders [160, 161]. Risk factors for CMDs may include socio-economic status, comorbid mental or somatic disorders, ethnicity, family history of CMD, and family situation [160].

Common mental disorders share a number of common etiological factors, are often comorbid, and have similar treatment and rehabilitation measures [102, 153, 160, 162, 163]. The symptoms of such disorders can include not only loss of interest, fatigue, sleep complaints, poor concentration, and subsequent forgetfulness, but also indecisiveness and reduced attention, agitation and irritability, social withdrawal and somatic pain, which in turn may play a detrimental role in terms of work incapacity [160, 164]. Common mental disorders can strongly impact individuals’ quality of life by affecting social and occupational functioning [165-169], and thereby causing temporary or permanent exclusion from the labour market [11, 170-176], and may even lead to suicidal behaviour [131-135, 177-184]. Moreover, such disorders are likely to worsen with inactivity, e.g., exclusion from work, while adequate treatment and rehabilitation efforts are found to enhance a positive prognosis [102-104]. Nevertheless, CMDs have become one of the leading causes of DP claims and labour market marginalization in many European countries [2, 6, 15, 17, 18, 185]. Depressive disorders, for example, are a major contributor to the global burden of disease [186] and predicted to be the leading cause of loss of disability adjusted life years (DALYs) in high-income countries by 2030 [187].

1.8.1 Incidence and prevalence of common mental disorders

In general, CMD may affect up to 15-20% of the population at any given time [154, 155, 157, 158, 160]. In Western countries, the lifetime prevalence of any mental disorder is up to 25% in the general population, whereas the 12-month prevalence is around 10% [158]. Globally, more than 350 million people suffer from depression [186]. The lifetime prevalence of any depressive disorder is around 14%, which is similar to the lifetime prevalence of any anxiety

disorder [154, 158]. In 2013, Johansson et al. conducted a study to investigate the point prevalence of depression, generalized anxiety disorder, anxiety disorders in general, and comorbidity in a Swedish sample [162]. The study concluded that, about 17.2% of the Swedish general population experience clinically significant depression (10.8%) or anxiety (14.7%) that are likely to affect their daily lives [162]. It should be noted that symptoms of depression were measured by the 9-item Patient Health Questionnaire Depression Scale (PHQ-9) and anxiety was measured by the 7-item Generalized Anxiety Disorder Scale (GAD-7). The PHQ-9 has a total score between 0 and 27, each item is valued between 0 to 3 (0: Not at all; 1: Several days; 2: More than half of the days; 3: Nearly every day). Total scores of 0–4 indicate no depression, 5–9 mild depression, 10–14 moderate depression, 15–19 moderately severe depression and 20–27 severe depression [188]. GAD-7 has a maximum total score of 21; each of the 7 items can be scored between 0 and 3. While the cut-off of 10 is optimal for detecting GAD, a cut-off of 8 has been found to maximize sensitivity (77%) and specificity (82%) when detecting any anxiety disorder [189].

1.9 Suicide and suicide attempt

Suicide, as defined by WHO, is the act of deliberately taking one's own life [190]. It has become the second leading cause of death globally among 15-29 year olds and nearly one million people worldwide are estimated to end their lives by means of suicide every year [191]. The global annual age-standardized suicide rate was reported to be 11.4 per 100 000 inhabitants (15.0 for men and 8.0 for women) in 2012 [192].

In Western countries, men are more likely to die from suicide than women, whereas such differences might not be present in Asian countries [133, 193, 194]. Suicide rates increase with increasing age and are highest in individuals aged 70 years and older regardless of sex in almost all regions of the world [192]. Suicide rates may vary widely between regions and countries in Europe, such rates are generally higher in northern European countries than in southern European countries [133]. Former Soviet states, particularly Baltic countries, Russian Federation, Belarus and Ukraine, still have the highest suicide rates in Europe [192, 195]. In 2015, the overall suicide rate in Sweden was 11.6 per 100 000 inhabitants, 16.8 being attributed to men and 6.8 to women. The overall Swedish suicide figure was similar to the European-28 average suicide rate which was 11.7 in 2013 [194]. In Sweden, suicide rates were high particularly among those 25 years and older in the early 1980s (Figure 4) [196]. Since 1984, there has been a steady decrease in suicide rates in individuals aged 25 years and older, though the youngest group, including individuals 15-24 years, showed stable suicide trends without any notable decline (Figure 4) [196].

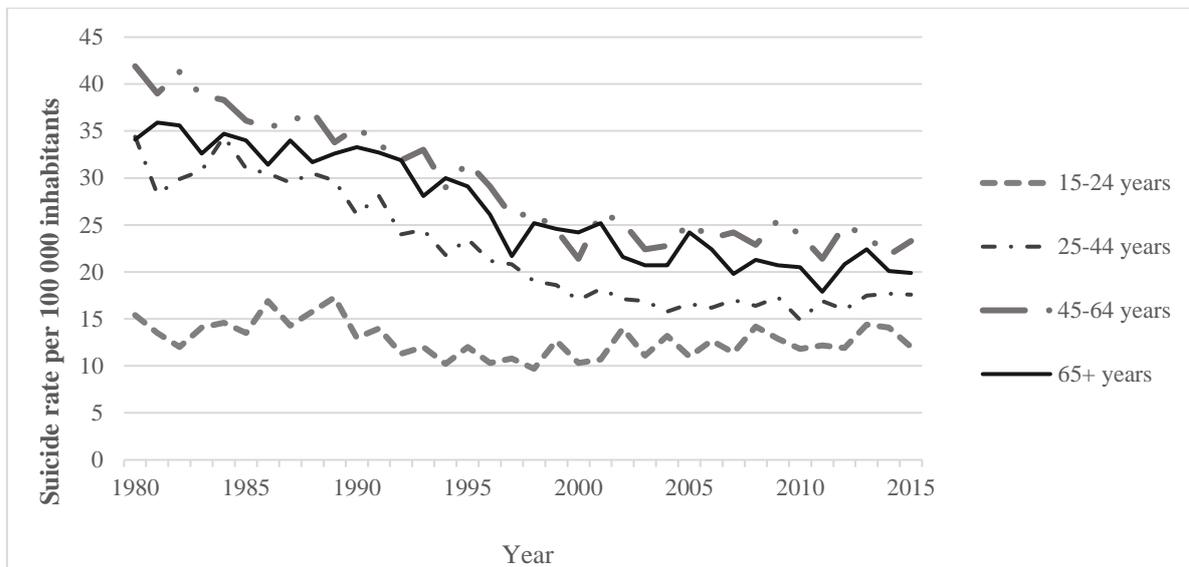


Figure 4. Suicide rates per 100 000 inhabitants in different age groups in Sweden, 1980-2015 [196].

Suicide attempt on the other hand, is as much as twenty times more frequent than suicide in the general population [192]. It is also amongst the most important risk factor for subsequent suicide [132, 133, 193, 197-200]. Suicide attempt can be defined as “a non-fatal, self-directed, potentially injurious behaviour with an intent to die as a result of the behavior” [201]. There exists a wide range of terms regarding ‘self-harm’, e.g. ‘deliberate self-harm’, ‘intentional self-harm’, ‘parasuicide’, ‘self-poisoning or self-injury’, ‘self-mutilation’, ‘self-directed violence’, etc. [200-202], each of which may differ with regard to intent or motivation to die and outcome of such behaviour. It might be difficult to determine the intent behind such behaviour.

In the ‘WHO/EURO Multicenter Study’, suicide attempt was defined as “an act with non-fatal outcome, in which an individual deliberately initiates a non-habitual behaviour that, without intervention from others, will cause self-harm, or deliberately ingests a substance in excess of the prescribed or generally recognized therapeutic dosage, and which is aimed at realizing changes which the subject desired via the actual or expected physical consequences” [202]. In this thesis, the term ‘suicide attempt’, similar to the definition of the WHO/EURO multicenter study has been used.

In contrast to suicide, suicide attempt is usually more frequent among women and younger individuals compared to men and older individuals, respectively [135, 192, 202-204]. Age-standardized suicide attempt rates are higher in the northern part of Europe than in the southern parts [202]. In Sweden, suicide attempt rates for individuals 25 years and older are more or less at the same level from 1987 to 2014 (Figure 5). However, there was a sharp increase in suicide attempt rates among individuals 15-24 years of age during 1997-2007, with a subsequent decline. Still, rates stayed at a higher level than in 1997 (Figure 5) [205]. In

2014, the age-standardized total suicide attempt rate (i.e. inpatient care due to suicide attempt) in Sweden was 102.7 (84.5 for men; 120.7 for women) [205].

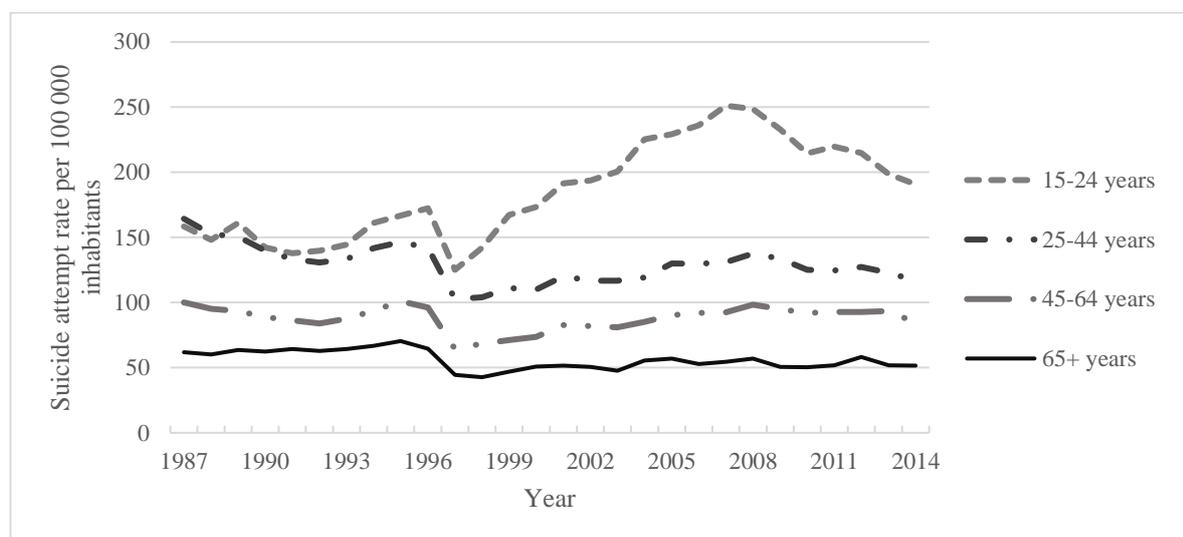


Figure 5. Suicide attempt rates per 100 000 inhabitants in different age groups in Sweden 1987-2014 [205].

The outcome of a suicidal behaviour, whether fatal or non-fatal, may largely depend on the method of such behaviour [133, 206]. Method, in turn, may depend on the availability, sex, and geographical location [207, 208]. Usually, in the high-income countries, men tend to use more violent methods, such as hanging or shooting, whereas women are more prone to use poisoning or jumping from high place [133, 192]. Globally, hanging accounts for about 50% of suicides in the high-income countries, and firearms for about 18%, however, in the WHO region of the Americas, firearms are used in almost 50% of the suicides. In other high-income countries firearms account for only around five percent of all suicides [192, 209].

Suicidal behaviour (i.e., suicide attempt and suicide) is a sensitive issue, or even illegal act in many countries. It is often under-reported and can be misclassified to some extent as an accident or another cause of death in the records even in countries with good statistics [133, 192, 210, 211]. The majority of the suicide attempts do not end up at a healthcare settings and only about one in every fourth suicide attempter receives treatment in specialized healthcare [200, 212].

In Sweden, in case of a suspected unnatural death, which is decided by the police, the Forensic Department carries out examination of the deceased, often with an autopsy, to determine the cause of death [213]. Since the 1990s, about 97% of all suicide cases have been autopsied by the Forensic Autopsy Department. The death certificate, which includes information regarding the cause of death, is then submitted to the National Board of Health and Welfare. Then, all diagnoses and injuries reported on the certificate are converted into

codes of the International Classification of Diseases (ICD-codes). The ICD is the standard diagnostic tool developed by WHO, used mainly in epidemiology and research, health management and clinical purposes. Applications include monitoring the incidence and prevalence of a disease, observing reimbursements and resource allocation trends, and keeping track of safety and quality guidelines. They also include the counting of deaths as well as diseases, injuries, symptoms, reasons for encounter, factors that influence health status, and external causes of disease [214]. Since 1969, when the 8th revision of ICD was introduced, it became possible to classify death as an undetermined intent [213]. Suicidal behaviour can be deliberate with a clear intent or determination to die and regarded as intentional self-harm. However, in many cases it is difficult to detect or understand the intent of such behaviour. As a result, suicidal behaviour is often underreported or reported as undetermined cause [211, 215]. It is an accepted practice to combine determined and undetermined intent in order to limit under-reporting of suicide attempt or suicide and to account for temporal and geographical differences in ascertainment methods [216-218]. This approach has also been used in this thesis.

1.9.1 Risk factors for suicide and suicide attempt

Previous suicide attempt is reported to be the strongest risk factor for subsequent suicide attempt and suicide [131-133, 219, 220]. Around 16% of the suicide attempters repeat attempt and two percent of the attempters die by suicide in the following year and over five percent die by suicide within nine years of an attempted suicide [220].

Female sex and younger age are risk factors for suicide attempt [135, 200, 202, 209, 221], whereas, male sex and older age are risk factors for suicide [133, 209, 222]. Suicidal behaviour has also been reported to be more frequent among people with lower level of education, with low socio-economic status, unemployed, unmarried or divorced [135, 178, 192, 200, 202]. Adverse childhood experience or adverse life events during adulthood, critical family situation, social isolation are reported to be associated with suicidal behaviour [217, 223-225]. Such behaviour may also have genetic predisposition [226, 227].

Mental disorders are main risk factors for suicide and suicide attempts [133, 193, 200, 209]. The majority of the suicide attempters suffer from anxiety disorder [134, 183, 200, 228], and depressive disorders have been found to be the strongest risk factors for any suicidal behaviour [103, 131, 132, 136, 229-231]. Depression with comorbid anxiety increases the risk for suicide [131, 133, 163, 232, 233]. Additionally, substance abuse disorders, specifically alcohol abuse has been shown to be a risk factor for suicidal behaviour [132, 135, 234-236]. Personality disorders, either independently or comorbid with other mental disorders, have also been reported to increase the risk of suicidal behaviour [177, 237, 238].

A wide range of somatic disorders, comorbid with depressive disorder, have been shown to be associated with suicidal behaviour, especially, cancer [239], multiple sclerosis [240], stroke [241], HIV/AIDS [242-244], chronic pain-related disorders [245], epilepsy [246, 247], injury [248] are associated with suicidal behaviour [132, 133, 178].

In this thesis, associations of different socio-demographics and medical factors with suicidal behaviour among individuals on DP due to CMD were tested. Socio-demographic factors included age, sex, education, country of birth, type of living area, and family situation, whereas in- and specialized outpatient care due to mental/somatic diagnoses, inpatient care due to suicide attempt and prescribed antidepressants or anxiolytics were tested as medical risk factors.

2 Aim

2.1 Overall aims

To gain knowledge about the association of DP due to CMD with subsequent psychiatric morbidity and suicidal behaviour in the general population of Sweden.

2.2 Specific aims

2.2.1 Study I

This study aimed to explore whether different socio-demographic factors, healthcare use, and medication were associated with suicidal behaviour (suicide and suicide attempt) in individuals on DP due to CMD.

2.2.2 Study II

This study aimed to examine 1) how different measures of DP (main diagnosis, secondary diagnosis, duration, and grade) were associated with subsequent suicidal behaviour (suicide attempt and suicide) in individuals on DP due to CMD and 2) possible differences in these associations with regard to sex and age.

2.2.3 Study III

The aims were to study 1) in- and specialized outpatient healthcare use among individuals granted incident DP due to CMD over a 7-year period (three years prior, the year during, and three years after being granted DP) and 2) whether these trajectories differed before and after the introduction of stricter DP granting criteria in Sweden in 2008.

2.2.4 Study IV

The aims of the study were 1) to identify and describe different types of trajectories of prescribed dispensed ADs among individuals receiving DP due to CMD during 2009-2010 over a 6-year period (three years prior, and three years after being granted DP), and 2) to characterize the trajectory groups with regard to socio-demographics and previous healthcare use.

3 Methods

The methods of the four studies are summarized in Table 5.

3.1 Design and study population

All four included studies were population-based, prospective in nature, and based on Swedish nationwide register data. The population included in this PhD project, was exclusively on DP (incident or prevalent) due to CMD, which comprised the following ICD-10 diagnostic codes: F32 (depressive episode), F33 (recurrent depressive disorder), F40 (phobic anxiety disorder), F41 (other anxiety disorder), F42 (obsessive-compulsive disorder), and F43 (reaction to severe stress, and adjustment disorder) [164].

Study I included all individuals aged 19-64 years, living in Sweden on 31 December 2004, on DP due to CMD throughout 2005 (N= 48 803). Individuals with a history of schizophrenic spectrum (ICD 10: F20-F29) or bipolar disorder (ICD 10: F31) as main diagnosis at specialized outpatient or inpatient care (n=1656) during 2001-05 and/or on old-age pension during 2005 (n=402) were excluded. The final cohort thus comprised 46 745 individuals. This cohort was followed up for five years (2006-10). The associations of different socio-demographics, previous healthcare use and medication with subsequent suicidal behavior (i.e., suicide attempt and suicide) were estimated.

In study II, the same cohort as in study I was used, however, it was somewhat altered as more information was added. Particularly, individuals, treated for schizophrenic spectrum or bipolar disorders as secondary diagnoses at specialized outpatient or inpatient care during 2001-05 (n=230) were also excluded. Thus, a cohort of 46 515 individuals was followed up for five years. The associations of different DP measures, namely main and secondary diagnoses, duration and grade of DP with subsequent suicidal behavior were assessed.

In study III, all individuals living in Sweden and aged 19-64 years with incident DP due to CMD before (wave 1, 2005-06, N=25 435) or after (wave 2, 2009-10, N=4722) the introduction of stricter DP granting criteria in 2008 were included. The individuals who emigrated or died during the 3 years after granted DP and/or for whom information regarding socio-demographics were missing, were excluded (wave 1=1137 (4.5%), and wave 2=666 (14.1%)), hence the final cohorts included 24 298 and 4056 individuals for wave 1 and wave 2, respectively. Socio-demographically adjusted healthcare use trajectories (in- and specialized outpatient care due to mental or somatic diagnoses) during the three years before, the year during, and the three years after DP were assessed.

In study IV, from 4722 individuals with incident DP due to CMD in 2009-10, 80 were excluded due to missing in amount of prescribed ADs in all six measured time points. Therefore, the study population included 4642 individuals. Trajectories of annual DDDs of ADs were analyzed over a 6-year period by a group-based trajectory method. Associations between socio-demographic and medical factors and different trajectories were estimated.

Table 5. Overview of the four studies.

	Study I	Study II	Study III	Study IV
Aim	To explore whether different socio-demographic factors, healthcare use, and medication are associated with suicidal behaviour (suicide and suicide attempt) in individuals on DP due to CMD	To examine (1) how different measures of DP (main and secondary diagnosis, duration and grade) were associated with subsequent suicidal behaviour (suicide attempt and suicide) in individuals on DP due to CMD and (2) possible differences in these associations with regard to sex and age	To study (1) in- and specialized outpatient healthcare use trajectories before, during and after being granted DP due to CMD and (2) whether these trajectories differed before and after the introduction of stricter DP granting criteria in Sweden in 2008	To (1) identify and describe different trajectories of ADs over a 6-year period (before, during and after DP) and (2) analyze the heterogeneity, if any, between the trajectories by socio-demographics and medical factors
Design	Prospective cohort study with baseline data on 31 December 2004 and follow-up until 31 December 2010	Prospective cohort study with baseline data on 31 December 2004 and follow-up until 31 December 2010	Cohort study with prospective and retrospective repeated measurements, baseline data on 31 December prior to DP granting year, observation for 7-years	Cohort study with prospective and retrospective repeated measurements, baseline data on 31 December prior to DP granting year (2008-09), observation for 6-years
Study population; n	46 745 (66.3% women; aged 19-64 at baseline)	46 515 (66.4% women; aged 19-64 at baseline)	24 298 (cohort 2005-06; 69% women, aged 19-64 at baseline); 4056 (cohort 2009-10; 63.5% women, aged 19-64 at baseline)	4642 (2009-10, 62.4% women, aged 19-64 at baseline)
Inclusion criteria	On 31 December 2004: alive, living in Sweden, aged 19-64, on DP due to CMD throughout 2005, not treated due to schizophrenic spectrum or bipolar disorder (as main diagnosis) at specialized healthcare during 2001-05, not on old age pension during 2005	On 31 December 2004: alive, living in Sweden, aged 19-64, on DP due to CMD throughout 2005, not treated due to schizophrenic spectrum or bipolar disorder (as main or secondary diagnosis) at specialized healthcare during 2001-05, not on old age pension during 2005	Incident DP due to CMD either during 2005-06 or 2009-10, who did not emigrate or die during the 3 years following DP and did not have missing in the socio-demographics	Incident DP due to CMD during 2009-10, not having missing regarding amount of prescribed ADs through observation period
Data sources	LISA ¹ , MiDAS ² , National Patient Register, Prescribed Drug Register, Cause of Death Register	LISA ¹ , MiDAS ² , National Patient Register, Cause of Death Register	LISA ¹ , MiDAS ² , National Patient Register, Cause of Death Register	LISA ¹ , MiDAS ² , National Patient Register, Prescribed Drug Register, Cause of Death Register
Outcome measures	Suicide attempt (n=1046, 2.2%) and suicide (n=210, 0.4%)	Suicide attempt (n=1036, 2.2%) and suicide (n=207, 0.5%)	Trajectories of in- and specialized outpatient healthcare use due to mental or somatic diagnoses	Trajectories of ADs
Factors included in the analyses	Sex, age, educational level, type of living area, country of birth, family situation, previous suicide attempt, previous in- and specialized outpatient mental and somatic healthcare use and previous and current (during the exposure year) prescribed antidepressants and anxiolytics	Sex, age, educational level, type of living area, country of birth, family situation, previous suicide attempt, previous in- and specialized outpatient mental and somatic healthcare use, main and secondary DP diagnoses, duration and grade of DP	Sex, age, educational level, type of living area, country of birth, family situation	Sex, age, educational level, type of living area, country of birth, family situation, main DP diagnosis, in- and specialized outpatient mental and somatic healthcare use
Statistical analyses	Descriptive, Chi ² -test, Cox proportional hazards regression models, Survival curves	Descriptive, Chi ² -test, Cox proportional hazards regression models	Descriptive, Chi ² -test, Generalized Estimating Equations with autoregressive correlations	Descriptive, Group-based trajectory modelling, Multinomial logistic regression, Chi ² -test

¹LISA: Longitudinal Integration Database for Health Insurance and Labour Market Studies;

²MiDAS: Micro Data for Analysis of the Social Insurance.

3.2 Data sources

All four studies of the thesis were of the Insurance Medicine All Sweden (IMAS) project, including de-identified data obtained from nationwide registers maintained by Statistics Sweden (SCB), the National Board of Health and Welfare, and the Social Insurance Agency (SIA). The ten-digit unique personal identity numbers (PIN) attributed to all inhabitants of Sweden were used to link information from the different registers [249].

3.2.1 Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA)

This register was initiated in 1990 and is updated annually since then by Statistics Sweden (SCB) [250]. LISA contains information on socio-demographics and social insurance measures of all individuals aging from 16 years and above and living in Sweden on 31 December of a given year. LISA, in all four studies, was used in order to obtain socio-demographic information at baseline, namely sex, age, educational level, country of birth, type of living area, family situation, date of emigration, and old-age pension.

3.2.2 Micro Data for Analysis of the Social Insurance (MiDAS)

The dataset ‘Micro Data for Analyses of Social Insurance (MiDAS)’ is maintained by the Social Insurance Agency (SIA). MiDAS contains detailed information on DP and SA benefits since 1994 [251]. Among others, information on main DP diagnoses (study I, II, III, and IV), secondary DP diagnoses (study II), start and end date of DP spell (study I, II, III & IV), extent of DP to determine grade as full-time or part-time and change of DP grade (study II) was used in the respective studies. MiDAS was used to define the study population in all four studies.

3.2.3 The National Patient Register

The National Patient Register, which is held by the National Board of Health and Welfare, contains data on inpatient care and specialized outpatient care [252]. This register was established in 1964, when data on inpatient care due to somatic disorders began to be collected in six Swedish counties. From 1973, data on inpatient care due to mental diagnoses was included in this register. In 2001, it became compulsory to report specialized outpatient care visits. The inpatient care register is of good quality and covers almost ninety nine percent of all hospital admissions, whereas about eighty percent of specialized outpatient care is recorded in the outpatient care register [252, 253]. All diagnoses for in- or specialized outpatient care were determined according to the ICD-10 [214]. In all four studies, this register was used to obtain data on mental and somatic in- and specialized outpatient care, and suicide attempt from inpatient care. In study I and II, information on schizophrenic spectrum and bipolar disorders from in- and specialized outpatient care was used to exclude individuals from the cohort. The National Patient Register does not include information from primary healthcare.

3.2.4 The Prescribed Drug Register

The Prescribed Drug Register, from the National Board of Health and Welfare, was established in July 2005 [254]. The register includes information for all prescribed and dispensed medication in Sweden [254]. The register contains information on date of prescription and dispensing of medication, generic and trade names, form of a prescribed medication (e.g., tablets, syrup, suspension, etc.), anatomical therapeutic chemical (ATC) codes, amount of dispensed medication per package, and DDDs per package [254, 255]. Information on antidepressants and anxiolytics obtained from this register was used in study I and IV.

3.2.5 The Cause of Death Register

This register is maintained by the National Board of Health and Welfare and was established in 1952 [256]. It records all deceased individuals, regardless of whether the death was inside Sweden or abroad and has about one percent of missing information of all deaths [213]. The causes of death are determined according to ICD-10 [213]. In study I and II, the Cause of Death Register was used to identify the outcome, suicide deaths; and to calculate person-time by censoring for death due to other causes than suicide. The date of death was used to exclude individuals during the follow-up in study III and to calculate DDDs during the death year and onward in IV.

3.3 Exposure, covariates and outcome measures

Socio-demographic factors, for all four studies, were measured at baseline, which is on 31 December of the year preceding DP grant. Specialized healthcare use, for study I and II, was considered before and during the exposure year and medication for study I was considered during the year of exposure. In study III, specialized healthcare use was measured at seven different time points, whereas in study IV, medication was measured at six different time point.

3.3.1 Socio-demographic factors

The considered socio-demographic factors included in the studies were age, sex, level of education, country of birth, type of living area, and family situation. They were used as risk factors for study I. In studies II, III, and IV, socio-demographic characteristics were considered as covariates and all the analyses were controlled for such covariates. Besides controlling, they were also taken into account to determine significant sex (study I, II and IV) and age (study II) differences between the sub-groups. In study III, they were additionally used to identify the significant differences between the two cohorts that were granted DP before and after policy changes. In study IV, socio-demographics along with main DP diagnoses, were used to explain heterogeneity between the trajectory groups.

In study I, reference categories for the different socio-demographic risk factors for subsequent suicidal behaviour were chosen as those groups with lower risk (based on

previous findings) or groups covering the majority of individuals in the study population. Age was categorized in years as follows: 19-24, 25-34, 35-44, 45-54, and 55-64 (reference). In study II, age was categorized as 19-44 years and 45-64 years (reference). Level of education was calculated in years and classified as compulsory (0-9), high school (10-12) and university (13 or more) (reference) in all four studies.

Type of living area, which was determined by the population size of a given area of living, included big cities (e.g., Stockholm, Gothenberg and Malmo) (reference category), medium-sized cities (with more than 90 000 inhabitants within 30 kilometre distance from the center) and small cities/ villages area [257]. Family situation was constructed from two variables from the LISA dataset, containing information regarding civil status and children (age and if living at the same place as the parents). This variable was classified into ‘married/cohabiting without children living at home’, ‘married/cohabiting with children living at home’ (reference group), ‘single (living without partner/divorced/separated/widowed) without children living at home’, ‘single (living without partner/divorced/separated/widowed) with children living at home’ and ‘adolescents living with parents, 16-20 years old’. The last category, except for study IV, was merged with the category ‘single (living without partner/divorced/separated/widowed) without children living at home’ due to power issues. Country of birth was categorized into Sweden (reference in all studies), other Nordic countries, EU 25 without Nordic countries, and the rest of the world. The second and the third sub groups of country of birth were pooled together for statistical convenience in study III and IV.

Eventual missing values of covariates were coded as separate categories (study I and II).

3.3.2 Used measures of disability pension

Different DP measures, namely, main (study II and IV) and secondary (study II) DP diagnosis, duration and grade (study II) of DP were considered as risk factors. All information on DP diagnoses was based on the corresponding codes of ICD-10 [214]. Information on the main and secondary DP diagnoses, which was recorded on the basis of corresponding ICD codes, was obtained from MiDAS. Main diagnoses were categorized as, ‘depressive disorders’ (reference) including ‘depressive episode’ (F32) and ‘recurrent depressive disorder’ (F33); ‘anxiety disorders’ comprising ‘phobic anxiety disorder’ (F40); ‘other anxiety disorder’ (F41); ‘obsessive–compulsive disorder’ (F42); and ‘stress-related mental disorders’ including ‘reaction to severe stress, adjustment disorders, acute stress reaction and posttraumatic stress disorder’ (F43) [153, 174]. Secondary diagnoses (study II) were categorized as: ‘no secondary diagnosis’ (reference); ‘substance abuse disorders’ (F10–F19); ‘personality disorders’ (F60–F69); ‘other mental disorders’ (F00–F99 except F10–F19, F60–F69); ‘musculoskeletal disorders’ (M00–M99); and ‘other somatic disorders’ (all diagnoses except M00–M99 and F00–F99). Schizophrenic spectrum and bipolar disorders (i.e. individuals with these disorders were excluded in study I and II) were coded as follows: ICD-10 codes F20–F29 and F31.

DP duration was calculated by subtracting the start date of DP from the end date of exposure (31 December 2005) in gross days. Gross days of DP were considered as full days disregarding the extent, that is, duration of DP of an individual with a part-time DP for 365 days would be recorded as 365 days, similarly as of another individual on fulltime DP for 365 days. Thereafter, the days were converted into years and were categorized as ‘1 year’ (reference), ‘2–3 years’ or ‘ ≥ 4 years’. ‘DP grade in 2005’ was classified as ‘part-time’ (reference) and full-time. Full time was regarded as 100% and any other extent less than 100% was included in the part-time sub-group.

3.3.3 Suicide and suicide attempt

In this PhD project, suicidal behaviour included both suicide attempt and completed suicide. Suicide attempts were identified from the inpatient care register and suicides from the cause of death register according to the ICD-10 codes. In order to limit underreporting and to compensate for regional and temporal variation in ascertainment methods, intentional self-harm (ICD-10: X60-X84) and events of undetermined intent (ICD-10: Y10-Y34) were combined for the entire PhD project. Sensitivity analyses were carried out to ensure that the estimates for determined and undermined suicide were similar. Similar sensitivity analyses were also carried out with respect to suicide attempt also.

In study I and II, suicide attempt and suicide were considered as outcome measures and contributed in calculating person-time, also inpatient care due to previous suicide attempt was considered as a risk factor in study I and as a covariate in study II.

3.3.4 Healthcare and medication

In this PhD project, healthcare related factors included in- and specialized outpatient care due to mental or somatic diagnoses and inpatient care due to suicide attempt. In study I and II, in- or specialized outpatient care due to mental or somatic diagnoses, and inpatient care due to suicide attempt before or during the exposure year were taken into consideration. For study III, similar healthcare use (except for inpatient care due to suicide attempt) during pre- and post-DP period was analyzed to understand the trends of such healthcare-related factors. Study IV included in- and specialized outpatient care due mental or somatic diagnoses before granted DP.

Information on in- and specialized outpatient care due to mental or somatic diagnoses was regarded as risk factors for study I, covariates for study II and was additionally used to describe the differences between the identified AD trajectory groups in study IV. In study III, information on such healthcare use was measured annually for 7-years of observation, including the pre-DP, transition, and post-DP periods. Such information was retrieved from the National Patient register. Information on specialized healthcare use was measured as total number of individuals having had such care during the studied years (yes/no) in all four conducted studies. Regarding the main diagnoses of healthcare use, those who had code F00-

F99 (ICD-10) were categorized as mental and all others as somatic diagnoses. Inpatient care due to suicide attempt included the following ICD-10 codes: X60-84 and Y10-34.

In addition to the specialized healthcare factors, prescribed dispensed psychiatric medication, determined by respective ATC codes [255], particularly antidepressants (N06A) and anxiolytics (N06B) were used as risk factors in study I. In study IV, trajectories of prescribed ADs (N06A) were studied at six time points, during the pre- and post-DP period. In study I, all considered psychiatric medications were categorized as ‘yes’ and ‘no’ and was coded as ‘yes’ if the medication was prescribed at least once during the exposure year. Amount of ADs, for study IV, was calculated based on the prescribed amount of DDDs of the prescribed AD.

3.4 Statistical analyses

In this PhD project, the study cohort included individuals either on prevalent (study I and II) or with incident DP (study III and IV) due to CMD. In all four studies, descriptive statistics, including frequencies, percentages, means with standard deviations, and medians of covariates were calculated. In studies I, II, and IV, descriptive statistics were presented with sex stratification. Potential sex (studies I, II, and IV) and age (study II) differences in these factors were assessed by chi²-test. Differences between socio-demographics with regard to year of granted DP were tested in study III using the same method.

In order to analyse the associations of different socio-demographic and medical factors (including healthcare and medication) (study I), along with DP measures (study II) with subsequent suicidal behaviour (suicide attempt and suicide) in individuals with prevalent DP due to CMD throughout 2005, Cox proportional hazards regression models were applied with crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI). Proportional hazard assumptions were tested prior to the application of these models. The partial likelihood ratio test was used to test for possible interactions with sex (study I and II), and age (study II). The proportions of suicide attempts during follow-up were estimated by life tables and plotted in 1-survival curves for previous suicide attempt and medication, stratified by sex (study I).

In study I and II, individuals were followed up until the event (suicide attempt, death due to suicide), death (due to other reasons than suicide), emigration, or end of follow-up which ever came first. In both these studies, follow-up time started after the exposure year (2005), on 01-01-2006 and ended 31-12-2010. In addition to crude/univariate models, multivariate HRs were estimated where all the factors were mutually adjusted for in study I and II.

In study III, analyses were based on annual diagnosis-specific specialized healthcare use, namely in- and specialized outpatient care due to mental or somatic diagnoses, with a 7-year observation window for each individual with incident DP due to CMD granted either during 2005-2006 or 2009-2010. The year of DP granting was defined as time point ‘t0’ and the three years of observation for both before and after the t0 year comprised t-3 to t-1 and t+1 to t+3, respectively. Individuals, granted DP during 2005-2006 and 2009-2010, comprised wave

1 and wave 2, respectively. Initially, the between-wave differences in socio-demographics and annual prevalence of healthcare use were assessed by Chi² test. In order to adjust for between-wave variations with regard to socio-demographics, estimated annual prevalence rates of healthcare use with 95% CI were assessed during the three years before, the DP granting year, and the three years after DP. Hereby, repeated measure logistic regression analyses with a Generalized Estimating Equations (GEE) method and autoregressive (AR) correlation structure were used [258].

GEE is a repeated measure regression, which takes the interdependence between the repeated intra-individual measurements into account by assigning correlations between measurements in longitudinal studies. An autoregressive correlation (AR) structure assumes the correlation between time points to be greater the nearer the measurements are to each other. Therefore, we used AR based on the assumption that the correlation of healthcare use is stronger between time points that are closer to each other in time. Estimated annual prevalence and odds ratios (OR) with 95% CI of healthcare use at different time points (from t-3 to t+3) between the waves (wave 1 and 2) were compared. Significant between- and within-wave differences in the trend of healthcare use (in- and specialized outpatient care due to mental and somatic diagnoses) by introducing interaction terms between period (pre-DP: t -3 to t-1; transition: t -1 to t+1; and post-DP: t +1 to t+3) and wave (wave 1 and wave 2) in the model. The chosen statistical method provides a flexible approach to analyses of longitudinal data by accounting for correlations between outcomes across time within the same individual and allowing for specification of both time-varying effects and individual differences in variables. Moreover, GEE does not depend on the normal distribution of the data and can incorporate subjects in the models even if they have missing values on the dependent variable. All models were adjusted for sex, age, education, type of living area, country of birth, and family situation. Individuals with missing values in the socio-demographic factors were excluded from the GEE models. Sensitivity analyses indicated the comparability of results in the study populations with and without exclusion due to missing values.

In study IV, group-based trajectory modelling was used to estimate trajectories of ADs among individuals with incident DP due to CMD during 2009-2010, for each person at six time points (i.e. within a six-year window, starting from three years before and ending at three years after the date of being granted DP). For this purpose, annual purchases of ADs in DDDs were calculated for the six studied years, considering the date of granted DP; t₀. There were 194 annual purchases exceeding 1500 annual cumulative DDDs (around 4 DDDs per day). This was assessed as an unusually high dosage and therefore DDDs were truncated at a level of 1500. Such high amounts of ADs might have been due to special cases, i.e., need of large purchases before traveling abroad, or error in data. Group-based trajectory models estimate 1) changes in AD patterns over time in multiple subgroups within the cohort, 2) a regression model for each discrete group and 3) assess proportions of individuals in each group. Additionally, this flexible model allows for different polynomials of the outcome [259]. The Bayesian information criterion (BIC) was used to test the best-fitted model related to the number of groups between 2-8. While six and seven group models had better BIC

values compared to the five-group model, there were very few individuals in some of the groups. Therefore, the model with five groups was considered to be most appropriate. Probabilities for an individual to be assigned to a specific trajectory group were calculated. The highest estimated probability was used to decide each individual's group belonging.

Thereafter, the association of covariates in each AD trajectory group were estimated by chi²-test and multinomial logistic regression. Moreover, likelihood ratio tests were used to evaluate whether socio-demographic and medical factors (main DP diagnosis, in- and specialized outpatient care due to mental or somatic diagnoses) were associated with type of trajectory group in the full model. Additionally, Nagelkerke pseudo R² values were estimated to evaluate the strength of these associations. By consecutively excluding and re-including each factor from the full model, we calculated differences in R² for each factor in order to examine the contribution of a given factor to the full model. In case of death or emigration during the study period, due to differences in the exposure time, annual DDD was considered missing for the event year and onwards.

Analyses were performed using statistical software SPSS version 20.0 (study I), version 22.0 (study II, study III and study IV), and SAS for Windows version 9.4 (study IV) (SAS-based procedure "Traj" [260]).

4 Results

The results of the four studies are presented below.

4.1 Study I

In total in Sweden, there were 46 745 individuals on DP due to CMD during 2005. Out of these, 17 181 (36.8%) were on DP due to depressive episode, 11 022 (23.6%) had a diagnosis of reaction to severe stress and adjustment disorders, 9799 (21.0%) due to other anxiety disorders, 4950 (10.6%) due to a recurrent depressive disorder, 2783 (5.9%) received DP due to phobic anxiety disorder and 1010 (2.2%) because of an obsessive-compulsive disorder. The majority (66.3%) were women, 38.7% were aged 55-64 years, nearly half (47%) had been to high school, most lived in big or medium sized cities (74%), and 3 out of 4 were born in Sweden. Almost half of the study population (41.9%) was living without a partner and without children at home. Furthermore, in the five years preceding start of follow-up (2001-05), only 28% had had specialized outpatient care and 11% inpatient care due to mental diagnoses. Around 33% were hospitalized due to somatic diagnoses and three percent of the cohort had been treated for attempted suicide (2001-05). While approximately one third of the disability pensioners were prescribed only ADs during the exposure year (2005), 16% were prescribed and dispensed both antidepressants and anxiolytics.

In the cohort, 1046 (2.2%) individuals attempted and 210 (0.4%) committed suicide during the five-year follow-up (2006-10). Women were more likely than men to attempt suicide (women: 2.4%, men: 2.0%), while a higher proportion of men completed suicide (women: 0.3%, men: 0.7%). Mean follow-up time for suicide attempt and suicide was around 5 years (4.85 (standard deviation (SD) 0.70) and 4.91 (SD 0.52), respectively).

Table 6 shows, that female sex, younger age, low education, and living without partner and with or without children were associated with a higher risk for suicide attempt (range of HRs 1.15 to 2.11) compared to men, age over 55 years, high education, and living with a partner and children, respectively. Additionally, previous in- and specialized outpatient healthcare use due to mental diagnoses (range of HRs 1.30 to 2.88), previous inpatient care due to suicide attempt (HR 3.89; 95% CI: 3.29-4.60) compared to those without similar healthcare use was strongly associated with a higher risk for subsequent suicide attempt. Moreover, prescribed medication in 2005, especially antidepressants and anxiolytics in combination (HR 3.35; 95% CI: 2.83-3.98) was associated with subsequent suicide attempt compared to no medication.

Statistically significant interactions were observed between sex and inpatient care due to previous suicide attempt in 2001-05 ($p=0.009$) and prescribed medication ($p=0.004$) in 2005. Women with previous inpatient care for suicide attempt had a higher risk for subsequently attempting suicide (HR 4.43; 95% CI: 3.63- 5.41) compared to women without such care. The comparable HR for men was 2.75; 95% CI: 1.99-3.79. With regard to prescribed dispensed antidepressants and anxiolytics together, the HR for attempting suicide for women

was 3.96; 95% CI: 3.19-4.92 and for men 2.48; 95% CI: 1.86-3.31 compared to individuals with no such medication during the follow-up.

Multivariate HRs and 95% CI for suicide indicated that male sex and living without partner and without children was associated with a higher risk for suicide (range of HRs 1.68 to 2.14) compared to female sex and living with partner and children. Previous inpatient care due to mental diagnoses or suicide attempt as well as medication, namely anxiolytics alone or in combination with antidepressants, were still strongly associated with completed suicide (range of HRs 2.1 to 3.3) compared to individuals without such inpatient care or medication.

Table 6. Multivariate hazard ratios (HRs) with 95% confidence interval (CI) for suicide attempt and suicide (2006-10) among 46 745 women and men, aged 19-64 years and living in Sweden on 31 December 2004, on DP due to CMD throughout 2005.

Characteristics	Suicide attempt		Suicide	
	n (%)	HRs (95% CI)	n (%)	HRs (95% CI)
Sex				
Men	310 (2.0)	1	108 (0.7)	2.14 (1.61-2.85)
Women	736 (2.4)	1.15 (1.01-1.32)	102 (0.3)	1
Age (years) in 2005				
19-24	61 (7.2)	2.11 (1.55-2.89)	9 (1.1)	1.23 (0.59-2.60)
25-34	161 (4.8)	2.06 (1.64-2.59)	28 (0.8)	1.32 (0.82-2.14)
35-44	342 (3.5)	2.06 (1.69-2.52)	40 (0.4)	0.90 (0.58-1.39)
45-54	306 (2.1)	1.52 (1.25-1.85)	74 (0.5)	1.26 (0.88-1.81)
55-64	176 (1.0)	1	59 (0.3)	1
Educational level (years)				
Compulsory (0-9)	347 (2.9)	1.57 (1.29-1.91)	63 (0.5)	0.90 (0.62-1.32)
High school (10-12)	540 (2.5)	1.38 (1.15-1.65)	95 (0.4)	0.80 (0.57-1.12)
University (13 or >)	152 (1.2)	1	50 (0.4)	1
Unknown	7 (1.4)	0.86 (0.40-1.85)	2 (0.4)	0.80 (0.19-3.33)
Family situation				
Married/cohabit. with no children at home	88 (0.9)	0.73 (0.56-0.95)	29 (0.3)	1.23 (0.72-2.10)
Married/cohabit. with children at home	201 (1.9)	1	30 (0.3)	1
Single ¹ no children at home	558 (2.8)	1.23 (1.04-1.45)	125 (0.6)	1.68 (1.11-2.53)
Single ¹ with children at home	199 (3.1)	1.29 (1.06-1.57)	25 (0.4)	1.48 (0.86-2.54)
Diagnosis-specific specialized outpatient care in 2001-05 (ref. no diagnosis-specific outpatient care)				
Somatic diagnosis	872 (2.5)	1.12 (0.94-1.33)	164 (0.5)	0.95 (0.67-1.35)
Mental diagnosis	571 (4.4)	1.30 (1.14-1.48)	103 (0.8)	1.23 (0.91-1.66)
Diagnosis-specific inpatient care in 2001-05 (ref. no diagnosis-specific inpatient care)				
Somatic diagnosis	613 (3.9)	1.45 (1.26-1.67)	107 (0.7)	1.29 (0.94-1.76)
Mental diagnosis	507 (10)	2.88 (2.47-3.35)	90 (1.8)	2.71 (1.94-3.80)
Suicide attempt	314 (22.0)	3.89 (3.29-4.60)	46 (3.2)	3.00 (2.00-4.50)
Prescribed medication dispensed in 2005 (ref. no medication)				
Antidepressants only	299 (2.2)	1.82 (1.52-2.17)	47 (0.3)	1.32 (0.89-1.96)
Anxiolytics only	109 (3.2)	2.24 (1.77-2.82)	23 (0.7)	2.10 (1.28-3.44)
Both prescribed	423 (5.8)	3.35 (2.83-3.98)	86 (1.2)	3.30 (2.31-4.72)

¹single includes living without partner, divorced, separated or widowed

4.2 Study II

Of the 46 515 individuals on DP due to CMD during 2005, the majority (66.4%) were women and 70% were aged between 45-64 years. As main DP diagnosis, nearly half of the women (48.3%) and older individuals (51.5%) had depressive disorders, while 32% of men and 43% of the younger individuals had anxiety disorders. The two predominant main DP diagnoses for the entire cohort were 'depressive episode' (36.8%) and 'stress-related mental disorder' (23.6%). More than half of the cohort had a secondary DP diagnosis (56.9%). More men and older individuals had substance abuse disorders as a secondary diagnosis, while more women and younger individuals had comorbid personality disorders ($p < 0.001$). The majority of the individuals had full-time DP (75.6%). Part-time DP was more common among women (28%) than men (17.4%) and among older (26.7%) than younger individuals (19.2%) ($p < 0.001$). Regarding the covariates, nearly half (47%) of the study population had been to upper-secondary education, most lived in big or medium sized cities (74%), and 75% were born in Sweden. Almost half of them (42%) lived without a partner and without children.

In the cohort, 1036 (2.2%) individuals were treated in inpatient care due to suicide attempt and 207 (0.5%) committed suicide during the five-year follow-up (2006-10). Women were somewhat more likely than men to attempt suicide (women: 2.4%, men: 2.0%, $p < 0.01$) while a higher proportion of men completed suicide (women: 0.3%, men: 0.7%, $p < 0.001$). Mean follow-up time for suicide attempt and suicide was 4.85 (SD: 0.70) and 4.91 (SD: 0.52) years, respectively.

In the univariate analyses, anxiety disorders were associated with a higher risk for subsequent suicide attempt in both women and men (range of HRs 1.4 to 1.5) and suicide in the younger age group (HR 1.9; 95% CI: 1.1-3.3) compared to depressive disorders as main diagnoses. These associations became insignificant after controlling for socio-demographics in the multivariate models, except for suicide in individuals aged 19-44 years (HR 1.7; 95% CI: 1.0-3.0) (Table 7 and 8). In general, stress-related mental disorders (SRMD) as main DP diagnosis, compared to depressive disorders, were associated with a lower risk for future suicide attempt and suicide in both crude and multivariate adjusted models. There was a significant interaction between age and main diagnosis ($p = 0.017$) regarding suicide. Individuals aged 45-64 years with a main DP diagnosis of SRMD had a significantly lower risk for committing suicide during the follow-up compared to individuals with a depressive disorder as main DP diagnosis (HR 0.4; 95% CI: 0.2-0.6). This association was not observed in younger individuals.

In the univariate models, secondary DP diagnoses of mental origin were associated with a higher risk for subsequent suicide attempt in all subgroups (range of HRs 1.2 to 7.1). These associations remained significant (range of HRs 1.3 to 2.3) in the multivariate models, except for the group of other mental disorders as secondary diagnoses in men and in the older age group. Comorbid substance abuse and personality disorders increased the risk for suicide (range of HRs 1.9 to 9.6) in women and in both age groups in the crude analyses compared to

their counterparts without a secondary diagnosis. However, in the adjusted model, only substance abuse disorders predicted suicide among women and younger individuals (range of HRs 2.6 to 3.3). A statistically significant interaction between sex and secondary diagnoses ($p=0.029$) in relation to subsequent suicide was found. Women with substance abuse disorders as secondary DP diagnoses were at a higher risk for subsequent suicide compared to women without a secondary diagnosis. Such associations were not observed among men.

DP duration did not predict suicidal behaviour in the adjusted models. On the other hand, full-time DP in the univariate analyses was associated with a higher risk for suicidal behaviour in all sex and age subgroups (range of HRs 1.3 to 3.1) compared to individuals on part-time DP. After multivariate adjustment, these associations remained significant (range of HRs 1.4 to 1.7) for suicide attempt in women and both age groups, and for suicide among the older individuals. A statistically significant interaction was observed between sex and DP grade ($p=0.001$) in relation to subsequent suicide attempt. Women on full-time DP had a higher risk for future suicide attempt compared to women who were on part-time DP. No such association was found for men.

Table 7. Multivariate hazard ratios (HR) with 95% confidence interval (CI) for suicide attempt and suicide (in 2006-2010), in the 46 515 individuals, aged 19-64 years, living in Sweden on 31 December 2004, and on disability pension (DP) due to common mental disorders in 2005, stratified by sex.

Characteristics	Suicide attempt						Suicide					
	Women			Men			Women			Men		
	n	%	HR (95% CI)	n	%	HR (95% CI)	n	%	HR (95% CI)	n	%	HR (95% CI)
Main DP diagnosis												
Depressive disorders	355	34.3	1	139	13.4	1	53	25.6	1	50	24.2	1
Anxiety disorders	278	26.8	1.0 (0.9-1.2)	140	13.5	1.0 (0.8-1.2)	32	15.5	0.9 (0.6-1.4)	47	22.7	1.3 (0.8-2.0)
Stress-related mental disorders	99	9.6	0.8 (0.6-1.0)	25	2.4	0.6 (0.4-0.9)	17	8.2	0.9 (0.5-1.6)	8	3.9	0.4 (0.2-0.9)
Secondary DP diagnosis												
No secondary diagnosis	232	22.4	1	100	9.7	1	34	16.4	1	45	21.7	1
Substance abuse disorders	43	4.2	2.1 (1.5-2.9)	34	3.3	1.6 (1.0-2.4)	9	4.3	3.3 (1.5-7.1)	7	3.4	0.8 (0.3-1.7)
Personality disorders	83	8.0	1.4 (1.1-1.8)	39	3.8	1.4 (1.0-2.1)	12	5.8	1.8 (0.9-3.5)	9	4.4	0.9 (0.4-1.8)
Other mental disorders	253	24.4	1.3 (1.1-1.5)	95	9.2	1.2 (0.9-1.6)	27	13.0	1.1 (0.6-1.8)	29	14.0	0.9 (0.6-1.5)
Musculoskeletal disorders	56	5.4	1.1 (0.8-1.5)	10	1.0	0.7 (0.4-1.4)	<7	2.9	0.8 (0.3-2.0)	<7	2.4	0.7 (0.3-1.9)
Other somatic disorders	65	6.3	1.1 (0.9-1.5)	26	2.5	1.0 (0.7-1.6)	14	6.8	1.6 (0.9-3.0)	10	4.8	0.8 (0.4-1.7)
Number of years on DP in 2005												
1 year	100	13.7	1	42	13.8	1	13	12.7	1	14	13.3	1
2-3 years	308	42.1	0.9 (0.7-1.1)	137	45.1	1.0 (0.7-1.4)	46	45.1	1.0 (0.5-1.8)	51	48.6	1.0 (0.6-1.8)
≥4 years	324	44.3	1.0 (0.8-1.2)	125	41.1	0.9 (0.6-1.3)	43	42.2	1.0 (0.5-1.8)	40	38.1	0.7 (0.4-1.3)
DP grade												
Part-time	84	8.1	1	42	4.1	1	16	7.7	1	10	4.8	1
Full-time	648	62.8	1.7 (1.4-2.2)	262	25.4	0.9 (0.6-1.3)	86	41.6	1.5 (0.8-2.6)	95	45.9	1.7 (0.9-3.3)

Adjusted for: sex, educational level, family situation, country of birth, type of living area, previous suicide attempt, inpatient care due to mental diagnoses, specialized outpatient care due to mental diagnoses.

Table 8. Multivariate hazard ratios (HR) with 95% confidence interval (CI) for suicide attempt and suicide (2006-2010), in 46 515 individuals, aged 19-64 years and living in Sweden on 31 December 2004, and on disability pension (DP) due to common mental disorders in 2005, stratified by age.

Characteristics	Suicide attempt						Suicide					
	Age 19-44 years			Age 45-64 years			Age 19-44 years			Age 45-64 years		
	n	%	HR (95% CI)									
Main DP diagnosis												
Depressive disorders	217	21.0	1	277	26.7	1	20	9.7	1	83	43.0	1
Anxiety disorders	278	26.8	1.1 (0.9-1.3)	140	13.5	0.9 (0.8-1.2)	44	21.3	1.7 (1.0-3.0)	35	16.9	0.9 (0.6-1.3)
Stress-related mental disorders	62	6.0	0.8 (0.6-1.1)	62	6.0	0.7 (0.5-0.9)	12	5.8	1.7 (0.8-3.6)	13	6.3	0.4 (0.2-0.8)
Secondary DP diagnosis												
No secondary diagnosis	140	13.5	1	192	18.5	1	20	9.7	1	59	28.5	1
Substance abuse disorders	40	3.9	2.3 (1.6-3.3)	37	3.6	1.5 (1.1-2.2)	8	3.9	2.6 (1.1-6.1)	8	3.9	1.0 (0.5-2.3)
Personality disorders	85	8.2	1.5 (1.1-2.0)	37	3.6	1.6 (1.1-2.2)	13	6.3	1.7 (0.8-3.4)	8	3.9	1.1 (0.5-2.3)
Other mental disorders	233	22.5	1.5 (1.2-1.9)	115	11.1	1.0 (0.8-1.3)	30	14.5	1.3 (0.8-2.4)	27	13.0	0.8 (0.5-1.3)
Musculoskeletal disorders	23	2.2	1.1 (0.7-1.8)	43	4.2	0.9 (0.7-1.3)	<7	1.9	1.7 (0.6-4.9)	7	3.4	0.6 (0.3-1.3)
Other somatic disorders	36	3.5	1.2 (0.8-1.8)	55	5.3	1.1 (0.8-1.4)	<7	1.0	0.5 (0.1-2.1)	22	10.6	1.3 (0.8-2.2)
Number of years on DP in 2005												
1 year	95	17.1	1	47	9.8	1	7	9.2	1	20	15.3	1
2-3 years	254	45.6	0.8 (0.7-1.1)	191	39.9	1.0 (0.7-1.3)	39	51.3	1.8 (0.8-4.0)	58	44.3	0.7 (0.4-1.2)
≥4 years	208	37.3	0.9 (0.7-1.4)	241	50.3	1.0 (0.7-1.4)	30	39.5	1.7 (0.7-3.8)	53	40.5	0.6 (0.3-0.9)
DP grade												
Part-time	56	5.4	1	70	6.8	1	7	3.4	1	19	9.2	1
Full-time	501	48.6	1.4 (1.1-1.9)	409	39.6	1.5 (1.1-1.9)	69	33.3	1.3 (0.6-3.0)	112	54.1	1.7 (1.0-2.8)

Adjusted for: sex, educational level, family situation, country of birth, type of area of living, previous suicide attempt, inpatient care due to mental diagnoses, specialized outpatient care due to mental diagnoses

4.3 Study III

There were 24 298 and 4056 individuals granted DP due to CMD in 2005-2006 (wave 1) and 2009-2010 (wave 2), respectively. In both waves, more than two-thirds were women, whereas, the proportion of young individuals (19-29 years) was more than three times higher in wave 2 than in wave 1 (18.3% vs. 5.4%). The proportion of singles without children living at home was also higher in wave 2 (48.1%) compared to those in wave 1 (37.4%). Moreover, there were more individuals born outside the Nordic countries and EU 25 in wave 2 (18.0%) than in wave 1 (14.9%).

The proportion of individuals with mental healthcare use was generally significantly higher in wave 2 than in wave 1 (p-values <0.001). In the year preceding DP, 4.6% and 19.2% of individuals had had mental in- and specialized outpatient care, respectively, in wave 1, compared to 7.9% and 46.6% in wave 2. Stratified analyses for the similar time points showed that corresponding figures in younger individuals (19-29 years of age) were 11.8% and 38.4% in wave 1 and 14.3% and 65.1% in wave 2; and for the older individuals (30-64 years of age) 4.1% and 18.2% in wave 1 and 6.5% and 42.5% in wave 2.

Multivariate adjusted prevalence rates of inpatient healthcare use due to mental diagnoses were higher in the year preceding DP and lower thereafter in both waves (Figure 6). Compared to the year of granting DP (reference: OR=1), odds ratios (ORs) of inpatient care due to mental diagnoses in wave 1 increased from 0.8 to 1.2 (t-3 to t-1) and later decreased to 0.8 at t+3 (figure 7). There was a significant between-wave difference of these trajectories in the transition period, showing a steeper decline in wave 2 (p<0.05)².

Multivariate adjusted trajectories of specialized outpatient care due to mental diagnoses followed similar patterns as those of mental inpatient care, with exception of an increasing trend after being granted DP in wave 1 (Figure 6 and 7). There were significant between-wave differences in trajectories of specialized mental outpatient care at all three phases (pre-, transition, and post-DP) (p<0.05)³.

In accordance with mental healthcare use, specialized care due to somatic diagnoses was significantly more common in wave 2 than in wave 1 (p-values <0.001). In wave 1, annual prevalence rates corresponded to 9.1% and 40.3% of somatic in- and specialized outpatient care, respectively. The corresponding figures for wave 2 were 13.6% and 50.6%. There were no clear within-wave trends in somatic healthcare use observable in the pre-, transition, and post-DP periods. Still, slopes differed significantly in the transition period between waves due to a relatively stronger decline in wave 2 than in wave 1 (p<0.05)⁴.

² Please see supplementary table in the appendix

³ Please see supplementary table in the appendix

⁴ Please see supplementary table in the appendix

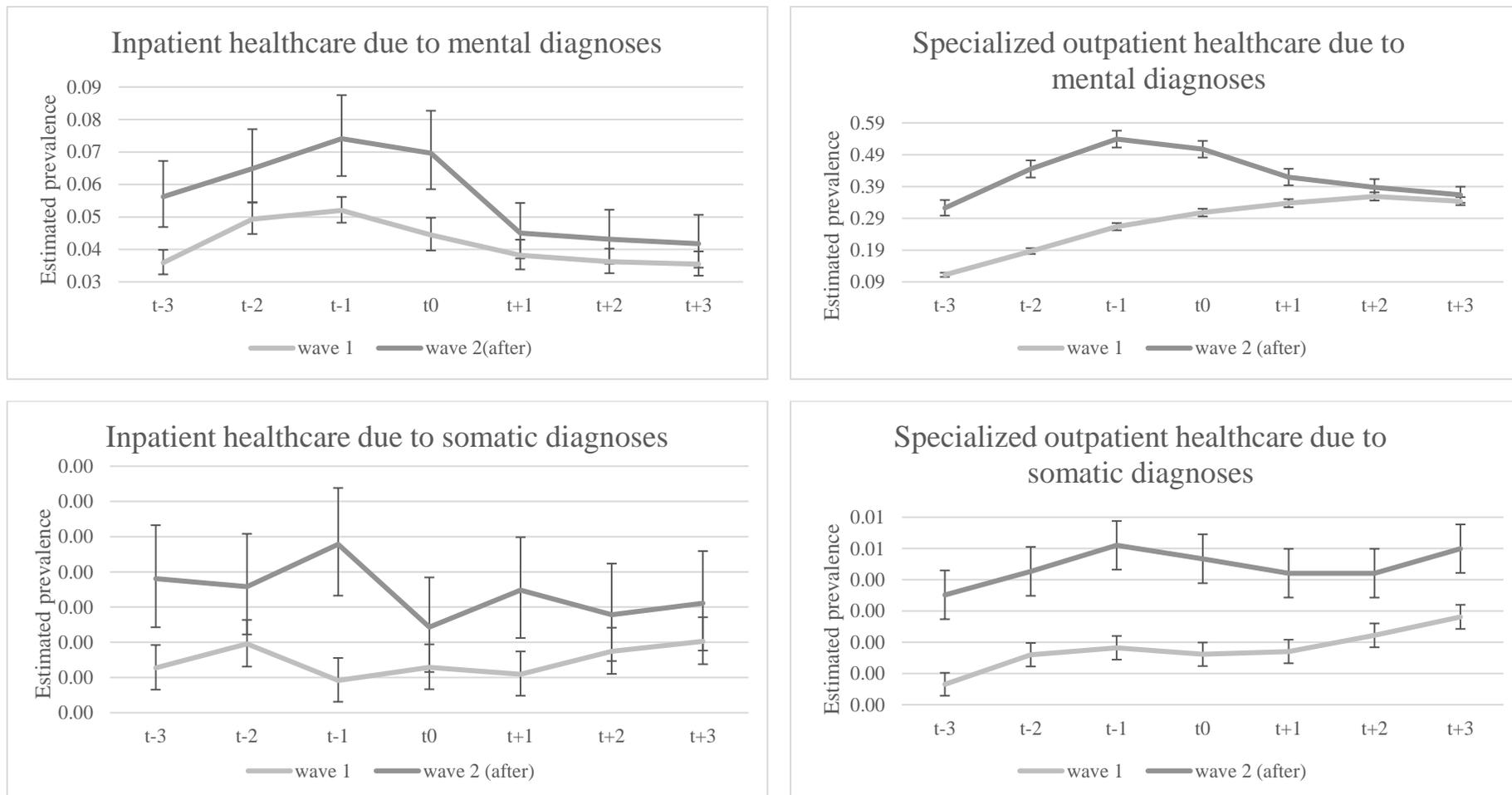


Figure 6. Estimated prevalence rates of diagnosis-specific specialized healthcare use adjusted for sex, age, education, type of living area, country of birth, and family situation, at different time points[#] before and after being granted disability pension (DP) due to common mental disorders in the two studied waves* (error bars indicate 95% confidence intervals).

* wave 1- DP granted during 2005-2006 (before); wave 2- DP granted during 2009-2010 (after the introduction of stricter DP rules)

[#] t-3: 3 years before DP, t-2: 2 years before DP, t-1: 1 years before DP, t-0: year of DP grant, t+1: 1 years after DP, t+2: 2 years after DP, t+3: 3 years after DP

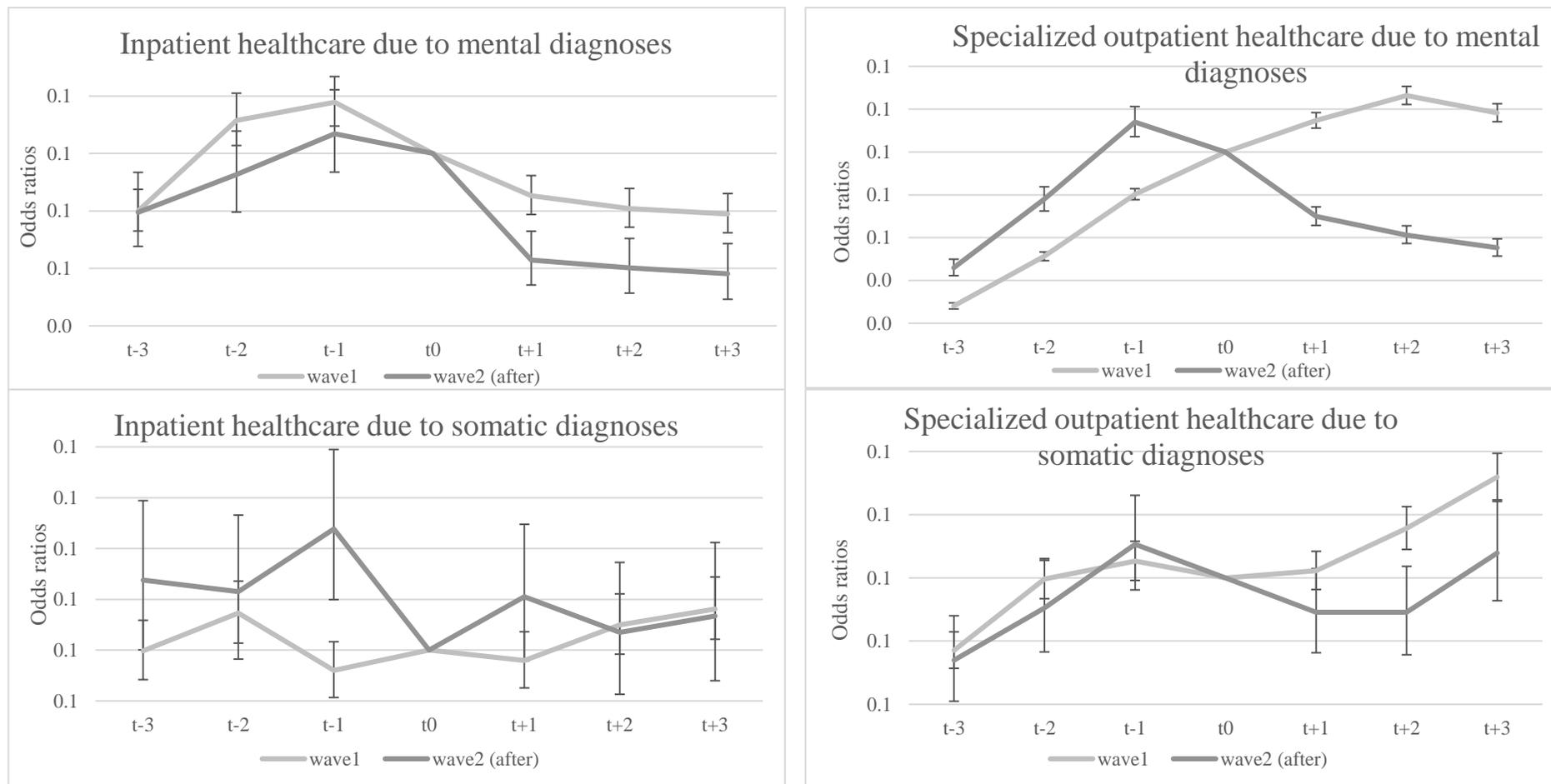


Figure 7. Odds ratios (OR) of healthcare use adjusted for sex, age, education, type of living area, country of birth, and family situation at different time points[#] compared to disability pension (DP) granting year (t0) before and after being granted DP in the two studied waves* (error bars indicate 95% confidence intervals).

* wave 1- DP granted during 2005-2006 (before); wave 2- DP granted during 2009-2010 (after the introduction of stricter DP rules)

[#] t-3: 3 years before DP, t-2: 2 years before DP, t-1: 1 years before DP, t-0: year of DP grant (reference, OR=1), t+1: 1 years after DP, t+2: 2 years after DP, t+3: 3 years after DP

4.4 Study IV

The study population for study IV included 4642 individuals, who were granted DP due to CMD in 2009-10 in Sweden. Two thirds of the cohort were women (62.4%) and 77.3% were born in Sweden. When granted DP, most of them were aged 45-64 years (57.8%), had proceeded to high school education (46.0%), lived in big cities (39.9%), and were single without any child living at home (45.3%). A higher proportion of the women (14.5%) than of the men (3.3%) were single with children living at home. Depressive disorders comprised the most common (46.3%) main DP diagnosis. A history of specialized outpatient healthcare use due to mental and somatic diagnoses was more common than such inpatient care (57.6%, 74.0% compared to 16.7%, 29.1%, respectively).

Figure 8 shows the estimated five groups of different trajectories of DDDs of ADs. The groups were labelled as, 'low constant', 'low increasing', 'middle constant', 'high constant', and 'high increasing'. Many of the individuals ('low constant' 33.5% of the cohort) had none or very low (less than 50) annual DDDs of ADs. Nearly six percent ('low increasing') had very low annual DDDs three years before DP granting, and showed a steep increase in annual DDDs of ADs up to 785 at two years following DP. The group 'middle constant' (33.7%) had annual DDDs in between 200-300 during the study period. The 'high constant' group included 20.8% of the cohort, and had 500-600 DDDs per year throughout the study period. In the groups 'middle constant' and 'high constant', there was a slight decline in DDDs of ADs following the DP. Six percent of the cohort increased from approximately 800 DDDs three years before DP granting and levelled off at around 1100 DDDs per year in the years after DP granting until the end of follow-up (high increasing).

All socio-demographic and medical factors, but sex and previous healthcare use due to somatic diagnoses, were significantly associated with different trajectory groups ($p < 0.05$) in the unadjusted analyses. In the full model, along with other variables, sex was significantly associated with the trajectory groups. The full model explained 17.2% of the variance between the groups (using Nagelkerke pseudo R^2). The highest estimated difference of five percent was observed for 'previous mental outpatient care' (diff. in $R^2 = 0.05$), otherwise the individual factors, other than age (diff. in $R^2 = 0.021$) and main DP diagnosis (diff. in $R^2 = 0.015$), merely effected the full model independently.

All the groups had a larger proportion of older individuals (>50%, 45-64 years), except for the 'low increasing', where younger individuals constituted the absolute majority (>60%, 19-44 years), and notably 41.3% of those in this group were in the 19-24 age range. This group also had fewer individuals (17.3%) who have been to university compared to the other groups, whereas the 'high increasing' group had the highest proportions of individuals having attended high school or university (53% and 29.6%, respectively). In the 'low increasing' group, 80% of the individuals were single and did not have any children living at home. Other socio-demographic factors were fairly equally distributed among all five groups.

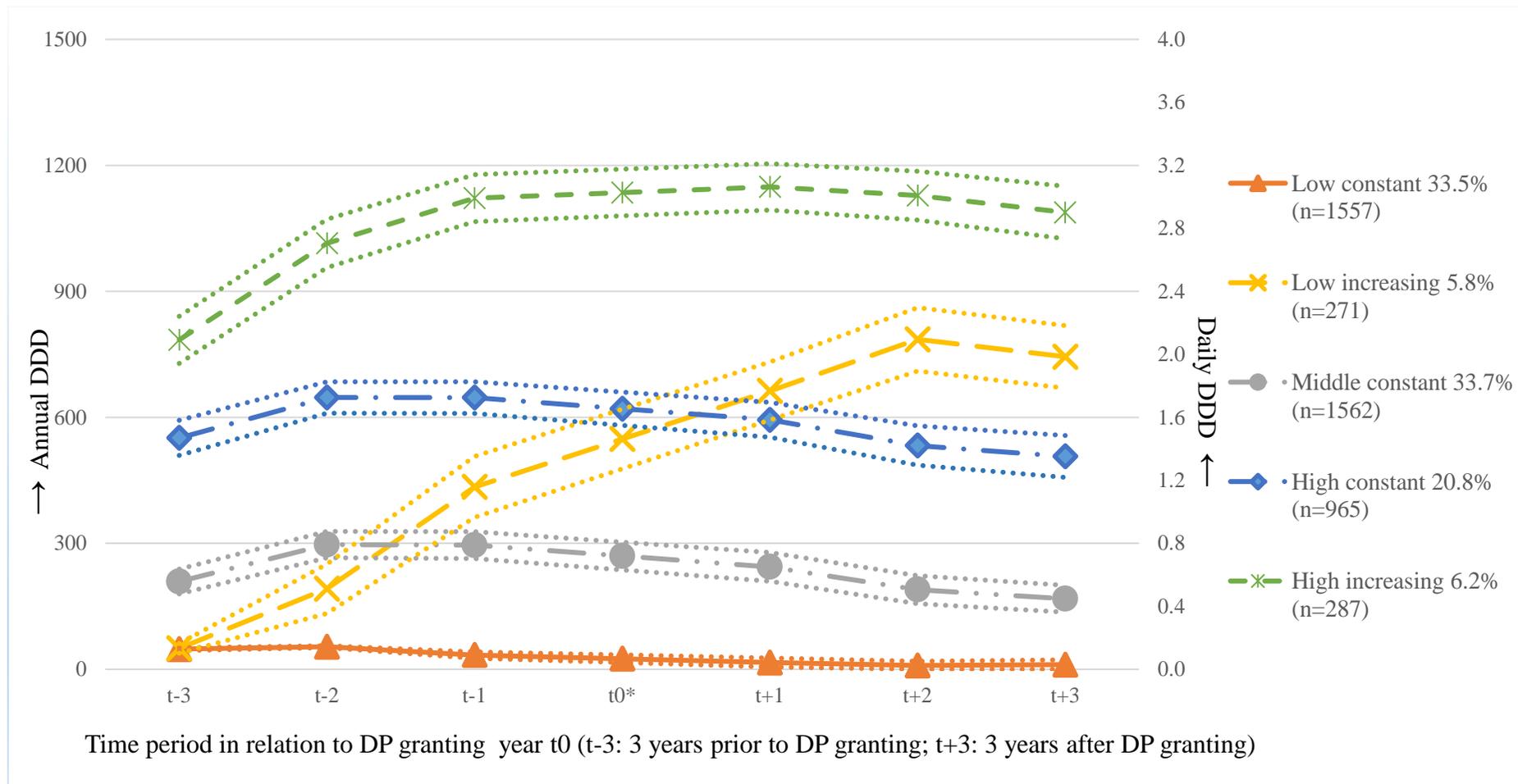


Figure 8. Trajectory groups of antidepressants according to annual defined daily doses (DDDs) and percentages of individuals with disability pension (DP) due to common mental disorders in 2009-2010 (N=4642) within each trajectory group. The dotted lines represent 95% confidence intervals.

* t0 was calculated as the average of t-1 and t+1 for the graphical presentation

Regarding the main DP diagnosis, the 'low increasing' group had equal proportions of depressive and anxiety disorders (43% each), whereas in all other trajectory groups, depressive disorders dominated (40-54%). The percentage of the individuals with 'stress-related mental disorders' as main DP diagnosis was largest in the 'low constant' (31.5%) and 'middle constant' (21%) groups. The proportions of the individuals from the 'high increasing' group who had had previous in- or specialized outpatient care due to mental diagnoses were approximately twice as high compared to the proportions of the 'low constant' group (24%, 79.4% and 9.1%, 40.5%, respectively).

5 Discussion

5.1 Main findings

In these nationwide prospective cohort studies of people on DP due to CMD, female sex, younger age, low educational level, living without a partner, previous specialized healthcare use due to mental or somatic diagnoses, previous suicide attempt, as well as previous prescribed psychiatric medication (both antidepressants and anxiolytics alone or combined) were associated with a higher risk of subsequent suicide attempt. While, male sex, living without partner and no children living at home, previous inpatient care due to mental diagnoses or suicide attempt along with concomitant prescription of antidepressants and anxiolytics were predictive of completed suicide.

Risk of suicidal behaviour was also found to be related to the type of DP diagnoses and DP grade. Stress-related mental disorders as the main DP diagnoses were associated with a lower risk of subsequent suicidal behaviour compared to depressive disorders as main DP diagnoses. Moreover, comorbid substance abuse disorders and personality disorders, as well as full-time DP were associated with a higher risk of suicide attempt and suicide during follow-up. Some sex and age differences in these associations emerged.

After (wave 2) implementation of stricter DP granting regulations in 2008 in Sweden, incidence of DP due to CMD was almost six times lower than in before (wave 1). On the other hand, proportions of individuals who had used specialized healthcare were higher in wave 2 than in wave 1 (in the year preceding DP, wave 2: inpatient care 7.9%; specialized outpatient care 46.6%; wave 1: inpatient care 4.6%; specialized outpatient care 19.2%). Moreover, it was found that in both waves inpatient mental healthcare use increased before granted DP, after which it decreased. With regard to trajectories after granted DP, there were differences between the two waves. While outpatient mental healthcare use declined in wave 2 (from 43.5% at DP granting year to 32.8% at two years following DP), it continued to increase in wave 1 (from 22.7% at DP granting year to 26.8% at two years following DP). Trajectories of specialized somatic healthcare use did not follow any obvious pattern.

According to the annual DDDs of ADs, five trajectory groups were identified over a 7-year period among all 4642 individuals granted DP due to CMD during 2009-2010. For the vast majority of individuals (89%), namely for low-, middle- and high constant groups, DDDs of ADs – though on different levels – varied only slightly before and after granting of a DP. In the low- and middle constant groups (67% of the cohort), about a third of the individuals, who more often had stress-related DP diagnoses and less healthcare due to mental diagnoses, received very low levels or no AD during the years around the time of DP grant. Two smaller groups (6% each) showed increases of DDDs up to granting of the DP, in one group DDDs levelled off afterwards and in the other group they kept increasing. Individuals in this latter group tended to be younger and were more likely to have an anxiety disorder as a DP diagnosis.

5.2 Discussion of results

5.2.1 Suicidal behaviour following disability pension

Increased mortality including suicide among disability pensioners, especially among those granted DP due to mental diagnoses has been shown previously [24, 120, 121, 127, 128, 138, 141]. In study I, the aim was to identify risk factors for suicidal behaviour in individuals with DP due to CMD. The study identified that women were at a higher risk for suicide attempt and men for suicide. These findings are in line with studies in the general population, providing well-established results on sex differences regarding suicidal behaviour [25, 221, 261, 262]. Moreover, younger age and low education were associated with a higher risk of suicide attempt, which is also in line with previous research [133, 199, 261, 263]. Results also suggest that living without a partner and without children increased the risk of suicidal behaviour in this cohort. Similar results from studies on the general population [261] and on disability pensioners [263] have been reported. In contrast, living with a partner but without children seemed to have a protective influence with regard to suicide attempt compared to those who are living with a partner and with children. These risk and protective indicators should be taken into consideration when monitoring mental health of disability pensioners due to CMD.

Previous and ongoing in- and specialized outpatient care due to mental diagnoses and previous suicide attempt turned out to be the strongest predictors for subsequent suicidal behaviour. This is in line with findings from previously conducted studies on suicidal behaviour in the general population [132, 133] and among psychiatric patients from in- and outpatient care [25, 198, 264]. Additionally, a statistically significant interaction between sex and inpatient care due to previous suicide attempt was observed. Women with previous inpatient care for suicide attempt had a higher risk for future suicide attempts compared to women without such care (HR 4.43; 95% CI: 3.63–5.41). In men, this association was found to be not as strong as in women (HR 2.75; 95% CI: 1.99–3.79). It should be noted that suicide attempts were found to be more common among women than men in several European countries, except for Finland [193, 202, 204], and suicide attempt is in itself a strong risk factor for subsequent suicide attempt in the general population or in individuals with depression [202, 265].

In this cohort, an association between inpatient care due to somatic diagnoses and future suicide attempt was observed. Previous research suggests that somatic disorders, for instance, cancer, stroke, epilepsy, multiple sclerosis, and different other neurological disorders are associated with an increased risk of suicidal behaviour [261, 266]. Such associations might be due to chronic pain or the terminal nature of the disease. This observed association was independent from the effect of mental disorders treated in in- or specialized outpatient care and prescribed psychiatric medication. Still, these measures might not entirely cover underlying mental disorders and residual confounding is likely.

Our results also suggest that disability pensioners with prescribed solitary anxiolytics, or in combination with antidepressants, had a higher risk of suicidal behavior than those without any such prescription. Moreover, statistically significant interactions were found between sex and prescribed psychiatric medication for subsequent risk of suicide attempt. ADs are recommended for treatment of depression and anxiety disorders [160, 267-270]. Additionally, anxiolytics, particularly benzodiazepines, can be prescribed for acute conditions or for individuals with predominant sleep disorders [160, 269, 270]. It is known that comorbid anxiety may worsen the prognosis and may pose an increased risk for suicidal behaviour in patients with depressive disorder [131, 182, 271, 272]. Additionally, an association of benzodiazepines with increased suicidal behaviour have previously been reported [273-275]. Future studies are warranted in order to understand the association of type, frequency, and dosage of prescribed anxiolytics and subsequent suicidal behaviour in disability pensioners due to CMD.

Study II have explored the risk of suicidal behaviour related to DP diagnoses, duration, and grade. Such risk, related to a main DP diagnosis of anxiety disorders did not differ from that of depressive disorders, while those with ‘stress-related mental disorders’ as main DP diagnoses had a lower risk for future suicidal behaviour. This is in line with a recent study on diagnosis-specific SA, suggesting higher risk estimates for subsequent suicide among people on SA due to depressive and anxiety disorders than due to stress-related mental disorders, after adjustment for socio-demographic factors and morbidity [130]. A potential reason for this is that the reported lower risk of suicidal behaviour can be interpreted as lower levels of morbidity in individuals receiving a stress-related diagnosis when work disabled compared to individuals receiving a depressive or anxiety disorder as main DP diagnosis [276].

There was a significant interaction with age and main DP diagnoses in relation to suicide. While there was a significantly lower risk for suicide in the older age group (45-64 years) with a main DP diagnosis of ‘stress-related mental disorders’ compared to ‘depressive disorders’, this association was not found in the younger individuals. On the other hand, ‘anxiety disorders’ as main diagnoses were associated with a higher risk of subsequent suicide in the individuals aged 19-44 years, compared to the similar age group with a main DP diagnosis as ‘depressive disorders’. One likely explanation of such findings includes age differences in the association of mental disorders with suicide risk [133, 231]. Anxiety disorders often have an early onset, and younger individuals may tend to have higher impulsivity, which might have contributed to suicidal behavior [277]. Moreover, early onset anxiety disorders leading to DP might be more difficult to treat and probably are associated with a high degree of comorbidity [278, 279]. Adequate treatment and suicide risk assessments might be of particular importance in young individuals with DP due to anxiety disorders in order to prevent suicidal behaviour [163, 233].

Furthermore, findings show that having a mental secondary DP diagnosis was associated with a higher risk of suicide attempt and suicide compared to not having a secondary diagnosis in individuals on DP due to CMD. This is in line with previous research regarding the general

population [133, 135] and individuals with a diagnosed mental disorder [131, 134, 136]. Substance abuse and personality disorders were the strongest predictors of subsequent suicide attempt. A high risk of suicidal behaviour among individuals with substance abuse disorders has previously been reported [132, 135, 236]. A significant interaction was observed between sex and substance abuse as secondary DP diagnosis in relation to subsequent suicide. Women with 'substance abuse disorders' as the secondary DP diagnosis were at a higher risk of subsequent suicide compared with women without a secondary diagnosis (HR 3.3; CI: 1.5 to 7.1). In contrast, a secondary DP diagnosis did not seem to be associated with an elevated risk of subsequent suicide in men. Substance abuse might be less prevalent and less frequently diagnosed in women compared to in men. Therefore, it can be hypothesized that women who are diagnosed with such a DP diagnosis form a selection of cases with particular medical severity, which in turn might be the reason for their higher suicide risk [132, 133, 236]. It is also possible that health consequences of substance abuse disorders might be worse in women compared to men [280]. Moreover, substance abuse disorders may aggravate an existing comorbid depression, which itself is a risk factor for suicidal behaviour [280-283]. Comorbid personality disorder was strongly associated with a higher risk of suicide attempt compared to those who did not have any secondary DP diagnosis. Current literature suggests that personality disorder, comorbid with depression or by itself, involves a higher risk of suicide attempt [177, 238]. Therefore, monitoring of individuals with such comorbidities is of particular importance in order to prevent suicidal behaviour.

Full-time DP was associated with a higher risk of suicidal behaviour compared to part-time DP. This has not been reported before in disability pensioners but is in line with a previous study reporting a higher risk of suicidal behaviour concerning full-time compared to part-time SA [263]. Full-time DP might here be associated with a higher severity of the underlying disorder. On the other hand, full-time DP might also be related to an alteration in health behaviour (regarding alcohol consumption, smoking, physical activity, diet, etc.) or to social isolation due to the loss of working colleagues [140-142]. More knowledge is warranted on the mechanisms behind these associations [141].

A statistically significant interaction was observed between sex and DP grade, women with full-time DP had a higher risk for subsequent suicide attempt than women with part-time DP (HR 1.7; CI: 1.4-2.2). Such higher risk was not found in men on fulltime DP compared to the men on part-time DP (HR 0.9; CI: 0.6 to 1.3). In Sweden, the proportion of women on part-time DP tends to be much higher compared to men [284]. It might be anticipated that if women are granted full-time DP then they might have a higher severity of the underlying mental disorder and, therefore, they might have a higher risk of subsequent suicide attempt [263].

5.2.2 Healthcare use trajectories

Considerable differences regarding incidence of DP before and after changes in the DP granting criteria in 2008 were found. Incidence of DP due to CMD was almost six times higher before the policy changes (incidence in 2005-06, wave 1) than after (incidence in

2009-10, wave 2). A similar decline in all-cause DP incidence, around the time of the introduction of stricter DP granting criteria in 2008 has previously been reported [3].

Our results show that trajectories of mental in- and specialized outpatient healthcare use followed a similar pattern in both waves in the pre-DP period, namely a steep increase up until the year prior to DP granting. This is in line with previous studies showing an increase in prescription of psychiatric medication, suicide attempts as well as in self-reported symptoms of depression and anxiety just before granted DP [30-33, 285]. The patterns of between-wave differences were consistent also when adjusted for socio-demographic factors such as sex, age, education, type of living area, country of birth, and family situation. Such increase in healthcare use might be related to a worsening medical condition just before DP granting, which in fact might have led to applying for DP. It could be also due to needing assessments from specialists when claiming DP.

The results also indicated that in general, use of specialized mental healthcare decreased after being granted DP due to CMD. This resembles findings from similar recent research on prescribed psychiatric medication, suicide attempts and reported symptoms of depression and anxiety [30, 31, 33, 285, 286]. The decline may be related to improvements in symptoms and/or relief from psychosocial work demands. It might also be that, improvements in symptoms occurred as individuals did not have to worry any longer if the physician will certify a prolongation of the sick-leave spell, or if the Social Insurance Agency will accept the sickness-benefit claim. With regard to trajectories after granted DP, there were differences between the two waves. While outpatient mental healthcare use declined in wave 2, it continued to increase in wave 1. Reasons for such dissimilarities might arise from differences in wave 1 and wave 2 with regard to rehabilitation processes before granted DP, the medical severity of individuals granted DP, and specificities in the regulations. In wave 1 it was still possible to be granted temporary DP when between 30 and 64 years of age. It is possible that DP did not have a strong influence on specialized mental outpatient care in individuals from wave 1 with temporary DP, possibly due to a lower medical severity of the underlying disorder compared to individuals granted DP in wave 2. Future research is warranted to elucidate this potential explanation.

The results showed that the annual prevalence of in- and specialized outpatient care use due to mental diagnoses was considerably higher among individuals granted DP in 2009-2010 (wave 2) than in 2005-2006 (wave 1), and the same was true for somatic healthcare use. Specifically, in terms of specialized outpatient healthcare use due to mental diagnoses prior to DP, a much higher proportion of individuals from wave 2 (27-47%) had used such healthcare before being granted DP than their peers from wave 1 (8-19%). Such differences in healthcare use may point to a worse medical condition of the individuals granted DP with the stricter criteria in 2009-2010 compared to those granted DP in 2005-2006.

Nevertheless, although a larger proportion had received specialized care before being granted DP in wave 2, still less than 50% had used such healthcare, meaning that the majority of the individuals did not receive specialized healthcare for mental diagnoses a year prior to DP due

to CMD. This finding is in line with findings from Norwegian and Finish studies [105, 106], indicating inadequate mental healthcare before granted DP. Adequate healthcare before DP might prevent a number of people from premature exclusion from the labour market. It is therefore important to provide suitable treatment and rehabilitation options for individuals with CMD in the pre-DP period, as these disorders are reported to be treatable and likely to relapse or worsen otherwise [103, 104].

Specialized healthcare use seems to decline in general immediately after granted DP, with further stabilization. However, if such frequency of specialized healthcare use during the post-DP period is optimal still remains a question, and requires adequate attention for further research. In a former study among men on DP from Sweden, Wallman et al. reported that, though the frequency of healthcare use decreased among DP men in the post-DP period compared to pre-DP, still it was higher compared to their peers who received old age pension (OAP) or who were still at work [109]. Similar pattern of trajectories in the post-DP period was also reported regarding amount of purchased psychiatric drugs [30-32], self-reported symptoms of depression and anxiety [33], or even regarding risk of suicide attempt in young adults [285]. Such a decline might have been due to a relief from work demands. Adequate healthcare should of course also be assured after the DP granting to prevent a poor prognosis.

Not only mental healthcare use, but also somatic healthcare use was considerably more prevalent among individuals in wave 2 compared to in wave 1. The trajectories of specialized somatic healthcare use were relatively stable throughout the study period. This is the first study investigating trajectories of specialized somatic healthcare use in relation to DP granting due to CMD. Study II shows that around 24% of individuals on DP due to CMD had somatic comorbidity. It is likely that these somatic comorbid disorders are of a chronic nature, requiring regular somatic healthcare use and might therefore be not directly affected by or related to the timing of DP granting. Additionally, to control for the possible discrepancies in access to healthcare between different regions of Sweden, we controlled for living area, which was categorized according to the size of the population.

5.2.3 Trajectories of prescribed antidepressants

The five identified trajectory groups were heterogeneous regarding levels of dispensed amounts of ADs. A third of the individuals in the study population, the 'low constant' group, either had very low or no annual DDDs of ADs during the six years of observation. This group of individuals had stress-related DP diagnoses more often and less healthcare use due to mental diagnoses. This might give an indication that these individuals have had a lower medical severity. They might also have received some other forms of treatment like psychotherapy instead of ADs. Information on psychotherapy was unfortunately not available in this study. Additionally, in acute situation or due to other comorbidity some might have received other forms of psychiatric drugs, i.e. anxiolytics or sedatives, there were around ten percent of such individuals in the study cohort. One should also consider the adherence to prescribed dispensed medication, since possibilities of not taking the prescribed dispensed medication cannot be excluded [287]. Still, this study focused on the indication and amount

of a prescribed dispensed medication rather than its efficacy. Therefore, non-adherence does not seem to be a considerable limitation of this study.

A relatively smaller group, 'low increasing', was similar to the 'low constant' group in terms of amount of ADs during the first two years of the observation period, but with a further steep increase thereafter up until two years following granted DP. Nearly half of the individuals in this group were aged 18-24 years and unlike the other trajectory groups, anxiety disorders contributed similarly as depressive disorders for granting of DP in this group. Depressive disorders were the most common DP diagnoses in all the trajectory groups. Such prevalence of anxiety disorders in this group might be due to the fact that many of them were young and anxiety disorders usually have an earlier onset [154, 288, 289].

Previous mental inpatient or specialized outpatient healthcare use was proportionate to the amount of ADs, i.e., the highest AD purchases were found in the 'high constant group' and the lowest in the 'low constant' group. A greater proportion of individuals from the 'low increasing' group was treated at in- or specialized outpatient care for both mental and somatic diagnoses than other groups. Based on these facts, it seems that individuals from the 'low increasing' group might have suffered from severe mental disorders several years before granted DP, and that the disorders worsened with time leading to DP.

One should also consider that individuals might still have received adequate dosages of AD and subsequently improved clinically, but not regarding their work capacity [166, 173, 290]. The findings show that most trajectory groups had relatively stable annual DDDs of ADs around the time when granted DP. This is in contrast to findings from a Finnish project, where prescription of ADs substantially increased before and decreased immediately after granted DP, especially among those with a mental DP diagnosis [30, 31]. These discrepancies in findings might arise from the differences in DP diagnoses, i.e. in our study the focus was on CMD, while most other previous studies included all mental disorders. Differences in the DP granting system between Sweden and Finland may also contribute in this regard.

Additionally, it should also be considered that this cohort is a very special one, as it is the immediate cohort following a policy change. Still, this study is internationally the first study considering groups of trajectories and not only one trajectory common for all individuals with DP. Therefore, this study highlights the importance of elucidating the heterogeneity in treatment patterns before and after granting of DP. One group differed considerably from the patterns of the other trajectory groups, i.e., the 'low increasing' group which showed a steep increase in DDDs of ADs since the beginning of the study period (t-3) up to DP granting and continued to increase after that.

The study findings also indicate heterogeneity regarding socio-demographics and medical factors between the trajectory groups. Among the socio-demographic variables, age had the strongest association with trajectory groups in the full model. There were also observable differences in educational level and family situation between the trajectory groups. For instance, unlike other groups, only a small proportion of individuals from the 'low constant' group had university education and the majority was single. Differences in educational level

or in the family situation in the ‘low increasing’ trajectory group might have been due to the younger age distribution in that group.

Overall, 20-60% of the individuals, depending on the trajectory group, did not receive any specialized mental healthcare during the three years prior to DP. This is not in accordance with the Swedish sick-leave guidelines [291], stating that all patients on SA due to depression for more than six months, should be referred to a specialist. This may indicate that these individuals might have not received optimal treatment during the pre-DP years, leading to further worsening of work capacity and later resulting in exclusion from the labour market by being granted DP [105-107].

5.3 Discussion of methods

Main strengths of the four studies are that they were all population-based, prospective in nature, including microdata of a very large number of factors either for each of the studied years or at an even more detailed level, derived from high quality Swedish nationwide registers [223, 253, 292-294]. Moreover, as we could include the whole working age population in Sweden, of the first two studies had enough power in relation to rare outcomes like suicide attempt or suicide. There were also no dropouts or loss to follow-up during the studies. Additionally, the studies were conducted with several years of follow-up, and the covariates were derived from different registers of different sources.

Below is a brief discussion on different methodical aspects including limitations of the studies.

Validity of diagnoses and coverage of information: In all four studies, cohorts were defined as all individuals on DP due to CMD. For the first two studies, the cohorts included prevalent DP cases and the latter two included incident DP cases for particular years. The ICD-10 codes, F32-33 and F40-43 were used to define CMD. The codes for underlying DP diagnoses were derived from the MiDAS register. The validity of the diagnoses of SA and DP is often discussed. A study from 1991, comparing sick-leave diagnoses with diagnoses from medical records, showed high validity of sick-leave diagnoses [294]. Moreover, DP diagnoses are set by the treating and certifying physician through thorough assessments of the patients’ disease, functioning, and work incapacity. As DP benefits are often paid for several years, granting of DP in most cases is preceded by long-term SA and is granted after a long process of medical evaluation and work capacity assessments [3]. Furthermore, the stigma around mental diagnoses [295, 296] lets us assume that a mental diagnosis is given as a main DP diagnosis only when the patient actually has a mental disorder and when the main reason of work incapacity cannot be contributed to a somatic diagnosis [297]. On the other hand, this implies that some people with CMD might not have been given CMD as the main DP diagnosis on the DP certificate. Thus, they would not be included in this study. This can also be seen as a strength, as our cohort of individuals with DP due to CMD is more strictly defined, or as a limitation as we do not know if the effect size would be bigger when including them.

The national patient register and the cause of death register have been used in all four studies. The first one has been validated by Ludvigsson et al., in 2011, which states that more than 99% of all somatic and mental hospital discharges are registered in the national inpatient register [253]. According to this study, the positive predictive value of the diagnoses that are registered in the national inpatient register is 85-95%. Nevertheless, since the start of this register, primary diagnoses are missing in around three percent of all mental healthcare [253]. A point to note is, that there are indications of regional differences with regard to the specialized outpatient care services reporting information on diagnoses and treatment to the National Board of Health and Welfare during the first years of reporting [298]. This might have led to an underestimation during the years before DP granting for the cohort with incident DP during 2005-2006 in study III. Still, there is no reason to anticipate that this considerably affected the trajectories reported in this study. The cause of death register has, according to the report from the National Board of Health and Welfare, only about one percent missing, indicating good quality [213]. Moreover, Allebeck et al. in 1991, concluded that the causes of death regarding injury related death in young age are recorded with high accuracy [211]. The quality of the Swedish drug register, which was used in study I and IV, has been found to be good by Wettermark et al., in 2007 [254, 299]. A limitation of using the drug registers is, that we have no information on whether the individual actually used the dispensed medication.

Internal and external validity: Selection bias, information bias and confounding are the main factors that can reduce the internal validity by introducing systematic or random errors [300].

Selection bias refers to the fact when a sample, which is selected from a population, does not represent the population, meaning that selection of the sample is not adequately randomized [300]. Fortunately, all four studies were population-based resulting in the fact that all individuals from all over Sweden who were eligible were included, and not a sample from the population. Therefore, the possibility of selection bias is minimal.

Information bias includes misclassification, which can occur in the case of exposure or outcome measurements [300]. If the misclassification of exposure differs with regard to the outcome measure, then there occurs differential misclassification; whereas if such misclassification is not related to the outcome (random misclassification) then it is regarded as non-differential misclassification. A common way to introduce a differential misclassification is via recall bias, which should not to be an issue here as all the studies are based on high quality nationwide Swedish registers. However, a question may arise regarding combining suicide attempt and suicide with determined and undetermined intent for study I and II where underreporting or misclassification may occur. In order to compensate for underreporting of suicidal behaviour in study I and II, determined and undetermined suicide attempt and suicide have been combined. Sensitivity analyses were carried out to ensure that the estimates for determined and undermined suicide were similar. Similar analyses were conducted with respect to suicide attempt.

A confounding factor is associated with the exposure and the outcome and must not be an intermediate step in the causal path between the exposure and the outcome [300].

Considering the confounders while calculating the estimates for the association between exposure and outcome shall lead to more accuracy. A wide range of potential confounders including socio-demographic and medical factors were taken into account in all four conducted studies. Socio-demographics included age, sex, education, type of living area, family situation and country of birth. Among the medical factors, in- and specialized outpatient care due to mental or somatic diagnoses, inpatient care due to suicide attempt, prescriptions of antidepressants and anxiolytics were considered. Still, residual confounding is not unlikely. I could use data only from the specialized outpatient care and inpatient care, but did not have the possibility of using data from primary care and data on health complaints not leading to any healthcare. This means that it was not possible to control for the visits to primary care and for health complaints without healthcare, thus missing a part of the picture of the morbidity. Likewise, information about the individuals treated elsewhere than in inpatient care due to suicide attempt, and the attempts that were managed outside the healthcare settings was not available. Additionally, data on health behaviour such as smoking, alcohol consumption or physical activity as potential confounders was not available [133, 301].

In study I, information of prescribed antidepressants and anxiolytics was included. In this study, individuals with prescription of antidepressants and/or anxiolytics were compared to individuals without any such prescription in relation to suicide attempt and suicide, so confounding by indication is likely. The individuals with and without prescriptions are inherently different, since those with prescriptions have an indication or reason for such prescription. Therefore, prescription may also indicate a higher current medical severity of the underlying CMD in these prevalent DP cases, which thus results in a higher risk for suicidal behaviour.

External validity is the extent to which results of a study can be generalized, from a sample to the general population, or from one population to another. All studies in this thesis included the whole working age population on DP due to CMD in Sweden, i.e., not a sample. Therefore, the question of external validity regarding general population in Sweden does not arise in this thesis. Additionally, results from these studies can be generalized to other countries, with similar healthcare and social insurance systems, e.g. other Nordic countries.

5.4 Conclusions

- In this thesis, the following factors were found to be associated with higher risk of suicidal behaviour following granting of DP due to CMD:
 - for suicide attempt: female sex, younger age, low education, living single, previous use of in- and specialized outpatient healthcare due to mental diagnoses and previous inpatient care due to suicide attempt.
 - for suicide: male sex and living single without children, previous inpatient care due to mental diagnoses or suicide attempt as well as medication, namely anxiolytics alone or in combination with antidepressants.Risk factors for suicidal behaviour among individuals on DP due to CMD seem to be similar to the known risk factors for suicidal behaviour in the general population.
- This thesis revealed that different measures of DP, i.e., depressive and anxiety disorders as main DP diagnosis, mental co-morbidity (particularly substance abuse and personality disorders), and fulltime extent of DP play a role when attempting to identify individuals with a higher risk of suicidal behaviour after being granted DP due to CMD.
- Young adults (19-44 years of age) on DP due to anxiety disorders were found to have a higher risk for subsequent suicide. Particular attention should therefore be given to this group.
- A remarkable decrease in the incidence of DP due to CMD was observed between the cohorts granted DP before and after the introduction of stricter DP granting regulations in 2008 in Sweden. Such difference might be related to the fact that a higher threshold of disease severity was set for DP granting after the changes in DP regulations.
- The low frequency of specialized mental healthcare use in the year before being granted DP due to CMD indicates the importance of treatment awareness during the pre-DP period to minimise possible suboptimal treatment.
- The identified five trajectory groups based on annual amounts of prescribed dispensed ADs among individuals granted DP due to CMD were heterogeneous regarding main DP diagnoses, age, and the severity of the mental diagnosis.
- The fact that more than one third of the individuals who were granted DP due to CMD in 2009-2010 were prescribed either very low dose or no ADs during the pre-DP period indicates a possibility of suboptimal pharmacological treatment before DP granting. Additionally, the marginal variation in the levels of prescribed dispensed ADs among the majority of the individuals between pre- and post-DP periods suggests that granting of DP does not affect the amount of prescribed ADs.

5.5 Further research

Research on DP is still very limited. Among the existing literature, the majority of studies have focused on risk factors for being granted DP rather than potential outcomes of being on DP. More research on the post-DP period including investigations of health and social outcomes is therefore warranted. Changes of DP granting regulations have been carried out in some European countries. Therefore, future research should also focus on if such regulatory changes are associated with future health and social outcomes of individuals on DP.

In this thesis, associations between different socio-demographics, medical factors, DP measured in different ways and suicidal behaviour after being granted DP were found. The studies carried out in this thesis project were the first of its kind, analysing health outcomes among individuals on DP due to CMD. It would therefore be important to conduct similar studies in order to find out if the findings can be replicated.

The follow-up period used here regarding suicidal behaviour was five years and observation periods for the healthcare use and AD trajectories comprised seven and six years, respectively. Future studies with longer follow-ups are required to ensure good statistical power in measuring associations with rare outcomes like suicidal behaviour.

The studies in this thesis could not include information on the severity of the DP diagnosis. Further research, including such information may help to be more precise with regard to the risk of suicidal behaviour subsequent to DP, and to better explain the trajectories of healthcare use and amount of prescribed dispensed ADs. Including information from primary healthcare use, for instance regarding comorbidity might also contribute in this regard.

In this thesis, prescriptions of antidepressants and anxiolytics were taken into account. Considering information on all types of treatment modalities for CMDs in future studies, e.g., information on other treatments such as psychotherapy, might help to understand if individuals on DP due to CMD receive optimal pharmacotherapy.

The cohorts used in the studies included individuals on DP due to CMD. Further studies considering and comparing more specific DP diagnostic groups, e.g., specific depressive and anxiety disorders would help to obtain more detailed knowledge and might have more clinical relevance.

The incidence of DP due to CMD was found to be four fold higher in 2005-2006 than in 2009-2010, between which, in 2008, a major reform in the DP regulations took place in Sweden. Further analyses including age-period-cohort analyses may shed light on possible differences in the incidence of DP granted during different years, specifically before and after changes in the DP granting regulations.

This thesis was based on register data. Future research could favorably include information regarding medication intake, self-rated health, multi-morbidity, social connectedness, work environment, life style factors such as smoking, alcohol consumption, physical activity, as

well as different types of treatment and rehabilitation measures, work adjustments, etc. Inclusion of these factors may supplement the register data and better explain the health-related and social aspects of being granted DP.

The studies included information on main and secondary DP diagnoses defined by ICD-10 diagnostic codes at a three-digit level. Access to such information at four- or five-digit level for all DP diagnoses would help in future studies to be more precise in defining the study population and subsequently detecting different effects.

Studies of this thesis identified risk factors of future suicidal behaviour in individuals with DP due to CMD. The intent to single out the effect of DP from the effect of the underlying medical disorder on potential outcomes of being on DP is challenging. In the future, research methods should be developed to disentangle the effect of DP per se from the effect of the underlying disorder on health-related and social consequences of being on DP.

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Appendix:

Supplementary table for paper III. Odds ratios (OR) of trends in healthcare use⁺ among individuals aged 19-64 years, living in Sweden, and granted disability pension (DP) in 2005-06 (n=24298) or in 2009-10 (n=4056) due to common mental disorders within the pre-, transition and post-DP period by type of healthcare and DP granting year*.

Outcome measures in relation to different DP granting periods	Pre-DP period (Year t-1 vs t-3 [^]) OR (95% CI)	Effect modification χ^2 (p-value) df [#] =1	DP transition period (Year t+1 vs t-1 [^]) OR (95% CI)	Effect modification χ^2 (p-value) df [#] =1	Post-DP period (Year t+3 vs t+1 [^]) OR (95% CI)	Effect modification χ^2 (p-value) df [#] =1
Inpatient healthcare use due to mental diagnoses						
wave 1	1.48 (1.35 - 1.61)	0.95 (0.33)	0.72 (0.67 - 0.79)	5.21 (0.02)	0.93 (0.85 - 1.01)	0.00 (0.99)
wave 2	1.35 (1.15 - 1.58)		0.59 (0.50 - 0.69)		0.92 (0.77 - 1.11)	
Specialized outpatient healthcare use due to mental diagnoses						
wave 1	2.88 (2.74 - 3.02)	6.26 (0.01)	1.44 (1.39 - 1.49)	434.29 (<0.01)	1.03 (1.00 - 1.07)	48.63 (<0.01)
wave 2	2.55 (2.35 - 2.76)		0.60 (0.56 - 0.65)		0.78 (0.73 - 0.84)	
Inpatient healthcare use due to somatic diagnoses						
wave 1	0.96 (0.91 - 1.02)	3.24 (0.07)	1.02 (0.96 - 1.08)	3.98 (0.05)	1.10 (1.04 - 1.17)	3.83 (0.05)
wave 2	1.09 (0.96 - 1.23)		0.89 (0.79 - 1.00)		0.97 (0.86 - 1.09)	
Specialized outpatient healthcare use due to somatic diagnoses						
wave 1	1.16 (1.12 - 1.20)	1.04 (0.31)	0.99 (0.95 - 1.02)	4.96 (0.03)	1.15 (1.11 - 1.18)	1.08 (0.30)
wave 2	1.21 (1.12 - 1.31)		0.90 (0.83 - 0.97)		1.10 (1.02 - 1.18)	

⁺Adjusted for sex, age, education, type of living area, country of birth, family situation; * wave 1- DP granted during 2005-06; wave 2- DP granted during 2009-10; # df- degree of freedom; ^ reference