From the Division of Insurance Medicine
Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

ACTIVITY RESTRICTIONS, TREATMENT AND WORK DISABILITY AMONG PEOPLE WITH MULTIPLE SCLEROSIS

Fitsum Sebsibe Teni

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Activity restrictions, treatment and work disability among people with multiple sclerosis

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Fitsum Sebsibe Teni

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Principal Supervisor:
Associate Professor Emilie Friberg
Karolinska Institutet
Department of Clinical Neuroscience
Division of Insurance Medicine

Co-supervisor(s):
Doctor Alejandra Machado
Karolinska Institutet
Department of Clinical Neuroscience
Division of Insurance Medicine

Associate Professor Hanna Gyllensten
University of Gothenburg
Sahlgrenska Academy
Institute of Health and Care Sciences

Doctor Katharina Fink
Karolinska Institutet
Department of Clinical Neuroscience
Division of Neurology

Opponent:
Professor Emeritus Anne-Marie Landtblom
Uppsala University
Department of Medical Sciences
Neurology

Examination Board:
Associate Professor Theo Bodin
Karolinska Institutet
Institute of Environmental Medicine
Unit of Occupational Medicine

Associate Professor Constanze Leineweber
Stockholm University
Department of Psychology
Division of Epidemiology

Associate Professor Hanna Persson
University of Gothenburg
Department of Clinical Neuroscience

To Samri and Brook

Popular science summary of the thesis

Multiple sclerosis (MS) is a chronic disease that involves the brain and spinal cord, which mainly starts during working ages and occurs more commonly among women. MS presents with a diverse set of symptoms based on the part of the brain or spinal cord affected by the disease. These symptoms negatively influence day-to-day work and other aspects of the lives of people with MS (PwMS). The drugs provided to treat MS have shown rapid increase in the last 30 years with more new drugs coming into the market recently. Hence, the aim of the present thesis was to add to the current knowledge on the activity restrictions related to MS, how the treatment is used over time, and how it relates to work ability, sickness absence, and disability pension.

In conducting the studies, questionnaires were sent out to PwMS in a large survey to study the restrictions they experience due to MS in different aspects of their lives, and to assess how they perceive their ability to work. To determine the trends in the use of MS treatments over time and how they relate to sickness absence and disability pension, a combination of several large nationwide datasets were used. These data were processed using different statistical analysis methods.

The results of the studies showed that PwMS faced substantial levels of restrictions in their work and private life aspects often related to tiredness/fatigue. Considerable levels of restrictions were reported even among PwMS considered to have no disability associated with the disease. In the studies of the trends in the treatment with MS drugs, both showed four main approaches commonly used in neurology clinics. The level of participation in work, measured in terms of sickness absence and disability pension, showed that PwMS treated with MS drugs of lower effectiveness had relatively lower associated sickness absence and disability pension in the follow-up. This could be attributed to PwMS on drugs of lower effectiveness starting at relatively better health status in the follow-up. Similarly, PwMS on drugs of lower effectiveness reported their work ability to be higher than those on higher efficacy treatments, and higher than those not receiving treatment, which could also be related to the better health status the group treated with drugs of lower efficacy had. Across the studies, the important role of factors such as age, sex, education, severity of MS, and type of MS, among others, were shown.

Overall, this thesis highlighted the important restrictions PwMS face in their daily work and private lives by focusing on PwMS reporting on the impact of MS on them. The views of patients on their ability to work in relation to the type of treatment they are taking were also revealed. In terms of treatment, the thesis showed how MS treatments are used over long periods of time and their link with the levels of sickness absence and disability pension among PwMS.

Abstract

Background: Multiple sclerosis (MS) is a disease that commonly occurs among individuals of working age. Its symptoms are heterogeneous and affect people with MS (PwMS) considerably in different aspects of their lives. Disease-modifying therapies (DMTs) have helped a lot in the improvement of health and work productivity. However, studies on the impact of MS in different facets of life as well as the long-term DMT use trends in relation to corresponding changes in work disability measures such as sickness absence and/or disability pension (SADP) as well as work ability are lacking. So, the present thesis aimed at increasing knowledge on activity restrictions, trends in disease-modifying therapy use, and associated work disability among PwMS in Sweden.

Methods: In studies I and IV, data were collected in a cross-sectional survey among PwMS in Sweden in 2021. Among them, 4052 who responded to the questions on restrictions on the four domains of work, family, leisure activities, and contact with friends/acquaintances were included in the analysis. In study II, 1923 PwMS with MS onset during 2007-2010 were included in a longitudinal register-based study to assess the DMT use trajectories over 10 years and the associated trends in SADP days for over 11 years. A similar study was conducted in study III among 1395 PwMS with DMT start/decision time of 2014/2015 assessing DMT use trajectories for 5 years and the associated SADP days for 7 years (from two years before treatment start). In study IV, utilizing the same survey material as study I, a total of 4103 PwMS were included in the study of how DMT use and work ability are associated as well as the role of other factors. For the analyses, in study I, multinomial logistic regression analysis was performed to assess predictors of reporting restrictions in the work and private life domains. In study II and III, sequence analysis was used to describe the sequences of DMT use over the follow-up time and to identify clusters of DMT use. The factors associated with cluster belonging were assessed using multinomial regression analyses conducted in each study. In assessing the trends in SADP by cluster, generalized estimating equations (GEE) were used in study II while zero-inflated negative binomial regression analysis was conducted in study III. In study IV, linear regression analyses were conducted to assess the association between DMT use and work ability score (WAS) and the role of additional socio-demographic, clinical, and self-reported health variables.

Results: About two-thirds of the 4052 PwMS in study I reported some form of restriction in the work (64.3%), family (61.3%), leisure activities (68.9%), and contact with friends/acquaintances (59.7%) domains. Tiredness/fatigue was the most-limiting symptom in half (49.5%) of the PwMS. Neurologically normal PwMS (expanded disability status scale (EDSS) score of zero) still reported restrictions in the four life domains ranging from 39.6% (friends/acquaintances) to 45.7% (leisure activities). Overall, older PwMS, women, those with lower levels of education, people with progressive forms of MS, with invisible limiting symptoms and higher EDSS scores had higher odds of restrictions in the work and private life domains. In study II, four clusters of DMT use trajectories were identified: *long-term non-high-efficacy DMTs* (38.6%), *escalation to high-efficacy DMTs* (31.2%), *delayed start and escalation to high-efficacy DMTs* (15.4%), and *discontinued/ no DMT* (14.2%). Younger ages, higher EDSS scores, progressive MS, and higher frequency of DMT switch were generally associated with being in clusters other than *long-term-non-high-efficacy*. The trends in SADP showed fewer mean SADP days among PwMS in the *long-term non-high-efficacy DMT cluster* than in the others about 9 years after MS onset. The GEE models on SADP trends showed comparable findings to the descriptive statistics. Similarly, in study III among 1395 PwMS also four clusters of DMT use trajectories were identified. These include *long-term non-high-efficacy DMTs* (34.6%), *long-term high-efficacy DMTs* (41%), *escalation to high-efficacy DMTs* (15.8%), and *discontinued/no*

DMTs (8.5%) clusters. Progressive MS and higher EDSS scores were associated with the clusters other than the *long-term non-high-efficacy* one. Individuals in the *long-term high-efficacy DMTs* cluster had a higher likelihood of being on SADP. However, starting high-efficacy DMTs showed a larger decline in SADP days than other clusters. In study IV, among the 4103 PwMS, just over half reported *good* (37.0%) or *excellent* (16.3%) WAS. The association of DMT use and WAS showed that PwMS on non-high-efficacy DMTs had higher WAS than those on high-efficacy and those not on DMTs but explaining only 1.24% of the variation in WAS. Occupation, EDSS score, fatigue, and health-related quality of life (HRQoL) explained high proportions of the variance in WAS.

Conclusions: The thesis showed that PwMS experience substantial levels of restrictions to their work and private lives, which were often associated with symptoms such as fatigue. Restrictions were also experienced among PwMS considered neurologically normal. The thesis also described long-term trajectories of DMT use and associated SADP days in two studies with different cohorts, showing the recent trend toward initiation of high-efficacy DMTs becoming more common. Trends of SADP days across clusters were stable and lower in the *long-term non-high-efficacy DMTs* cluster. Higher work ability was noted among PwMS on non-high-efficacy DMTs despite very low explanatory power. The important roles of occupation, disability, fatigue, and HRQoL were also observed.

List of scientific papers

I. Teni FS, Machado A, Murley C, Fink K, Gyllensten H, Dervish J, Hillert J, Friberg E. Self-reported restrictions in different life domains and associated factors among people with multiple sclerosis in Sweden. *European Journal of Neurology* 2023; 30, 1843–1853.

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IV. Teni FS, Machado A, Dervish J, Fink K, Gyllensten H, Friberg E. Disease-modifying therapy use and work ability among people with multiple sclerosis in Sweden. *Manuscript submitted*.

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List of abbreviations

BMI	Body mass index
CI	Confidence interval
CIS	Clinically isolated syndrome
CNS	Central nervous system
DALYs	Disability-adjusted life years
DMF	Dimethyl fumarate
DMT	Disease-modifying therapy
DNA	Deoxyribonucleic acid
DP	Disability pension
EBV	Epstein-Barr Virus
EDSS	Expanded Disability Status Scale
GEE	Generalized estimating equations
HRQoL	Health-related quality of life
ICF	International Classification of Functioning, Disability and Health
IM	Intramuscular
IV	Intravenous
LISA	Longitudinal Integrated Database for Health Insurance and Labor Market Studies
MHC	Major histocompatibility complex
MiDAS	Micro-Data for Analysis of the Social Insurance System
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
OR	Odds ratio
PIN	Personal identification number
PPMS	Primary progressive multiple sclerosis
PwMS	People with multiple sclerosis
QoL	Quality of life
PAM	Partitioning around medoids
RRMS	Relapsing-remitting multiple sclerosis
SA	Sickness absence
SADP	Sickness absence and/or disability pension
SC	Subcutaneous
SCR	Swedish Cancer Register
SD	Standard deviation
SEK	Swedish Krona
SIA	The Social Insurance Agency of Sweden
SMSreg	The Swedish Multiple Sclerosis Registry
SPMS	Secondary progressive multiple sclerosis
US	United States
USD	US Dollar
WAI	Work ability index
WAS	Work ability score
WHO	World Health Organization
ZINB	Zero-inflated negative binomial regression

1 Introduction

Multiple sclerosis (MS) is commonly diagnosed at younger ages (20-40 years), which highly affects the prospect of career building and family formation leading to a substantial impact on work and other aspects of the life of people with MS (PwMS).[1,2] Gaining insight into the views of PwMS and the challenges they face could provide crucial information regarding unmet needs and other important aspects.

In addition, the treatment landscape of MS is a rapidly evolving area with different disease-modifying therapies (DMTs) becoming available in a relatively short time, particularly in the 2010s and early 2020s.[3] Hence, assessing DMT use trajectories provides useful information on how different DMTs are being used and their evolution over time. Furthermore, studies on work disability (sickness absence (SA) and/or disability pension (DP)) among PwMS and in the context of DMT use are limited. Studying how work disability evolves in relation to DMT use will provide important insights on the level of work disability across different groups of DMTs and the implications of DMTs on work disability over time.

In addressing the above issues, the present thesis tackled the questions of how the treatment of MS using DMTs evolves over long follow-up times and how the associated work disability evolves over time. Furthermore, the views of PwMS on the restrictions they face due to MS in their work and private lives as well as on their work ability were the focus of the present thesis.

In this Introduction section of the thesis, MS is described briefly in terms of its epidemiology, burden, risk factors, pathology, diagnosis and the disease course, its characterization in terms of age and sex as well as common comorbidities. The heterogeneous symptoms of MS and the associated restrictions PwMS experience as well as the common neurological disability measure in MS, Expanded Disability Status Scale (EDSS), are also introduced. Brief information is also provided on the treatments given to PwMS to prevent relapses and to slow disability progression as well as for acute exacerbations. The areas and studies in the fields of work ability and work disability (SA and/or DP (SADP)) among PwMS generally, and in the context of Sweden, are also presented briefly in the Introduction section.

1.1. Multiple sclerosis

MS is a chronic inflammatory disease of the central nervous system (CNS), which leads to damage to the myelin sheath and axonal loss in the brain and spinal cord.[4,5] It is the most prevalent disabling non-traumatic neurological disease among young and middle-aged adults in the ages 20-40 years old.[6,7] Overall, MS occurs more often among women than in men with an approximate 2-3 to 1 ratio.[7–11] The significant burden MS poses to PwMS and society at large; the demographic, as well as the different clinical features of MS are described in this subsection.

1.1.1. Epidemiology

Globally, an estimated 2.8 million people lived with MS as of 2020 at a prevalence of 35.9 per 100,000 population with the highest figures noted in Europe (142.8 per 100,000 population) and the Americas (117.5 per 100,000 population).[8] In Sweden, as of 2008, the estimate of nationwide prevalence of MS was 188.9 with higher prevalence reported at higher latitudes.[12]

1.1.2. Burden

The Global Burden of Disease Study 2016 estimated that nearly 19,000 deaths occurred globally due to MS in 2016 and a total of about 1.2 million disability-adjusted life years (DALYs) were attributed to the disease. Globally, the age-adjusted death rate due to MS decreased significantly by 11.5% from the estimate in 1990. However, the change in age-adjusted DALYs was not significant (-4.5%).[13] In the same study, the estimate for Sweden showed no significant (7.2% [95% confidence interval (CI): -37.9-31.7]) change in deaths from 1990 to 2016, while the age-adjusted rates of DALYs was estimated to have increased significantly (27.2% [95% CI: 5.4-40.3]).[13] A study in Sweden covering the period 1952 to 1992 showed that the nationwide mortality due to MS has increased from 1.0 to 2.1 per 100,000 inhabitants per year with an overall mean of 1.65 per 100,000 population during the 41 years.[14] In the period from 1990 to 2010 a higher overall mortality rate of 2.04 per 100,000 persons was reported.[15] However, a cohort study comparing trends of mortality in PwMS to those without, from 1968 to 2012, reported hazard ratios of 2.92 [95% CI: 2.86-2.99] and that improvements were noted overall as well as in cause-specific mortality over the period.[16]

In economic terms, the burden of MS covers several aspects, including medical and non-medical costs as well as productivity losses. Substantial costs have been reported in different studies, including a survey across 16 European countries where mean societal cost of MS in 2015 was estimated to range from 22,800 euros among PwMS with mild disease to 57,500 euros in those with severe MS.[17] In the United States (US), an estimate for 2019 showed a total cost of 85.4 billion US dollars (USD) where direct medical cost constituted the majority (63.3 billion USD) with the average annual excess medical cost per person being 65,612 USD.[18] Another estimate from Spain showed the annual cost of MS to be about 1.4 billion euros with an average cost of 30,050 euros per person.[19] Studies also showed that healthcare accounts for a larger proportion of the cost among PwMS with milder disease while productivity losses were reported as the major components in more severe MS.[17,19,20]

Several studies in Sweden also showed the substantial burden of MS in terms of cost of illness.[17,21–26] In one study, the average annual total societal cost of MS in 2015 was estimated to range from 244,000 Swedish Kronor (SEK) among PwMS with mild disease to 384,000 SEK among those with severe disease.[17] Over a 9-year follow-up, another study showed an excess healthcare cost of about five times and an excess of more than twice productivity losses than a reference population without MS.[25] The total cost of MS was shown to have a gradient with the level of severity/disability with higher costs in more severe forms of the disease[17,21] and with higher proportions of indirect costs in the more severe forms of the disease.[26] In addition, it has been shown that MS related costs start occurring even before diagnosis and continues to increase.[25] At an individual level, the negative impact MS has on the income of PwMS and the role of social transfers such as SA and DP in countering the loss of income has also been shown.[27]

1.1.3. Risk factors

The cause of MS is yet unknown. However, it occurs through a complex interaction of genetic and environmental factors.[2] A register-based study in Sweden showed a 15.4% and 1.7% crude risk of MS among monozygotic and dizygotic twins respectively, while indicating that familial risk might be relatively modest.[28] Overall, it has been shown that people of northern European ancestry have higher risks for MS in comparison to other ethnic groups residing in the same latitude.[2] So far, 236 genetic variants reported to increase MS susceptibility have been determined.[29] Among the major ones are the polymorphic genes (Human Leucocyte Antigens) coding for the major histocompatibility complex

(MHC) proteins, which play an important role in adaptive/acquired immune function through antigen presentation to T cells.[30–32]

In terms of environmental and lifestyle risk factors associated with MS, it is more prevalent in northern regions/hemisphere of the world, which has been explained in relation to relatively lower levels of exposure to the sun (ultraviolet radiation) and lower vitamin D levels.[33–35] Vitamin D has been reported to relate to MS both at environmental and genetic susceptibility levels.[35,36]

Epstein-Barr Virus (EBV) infection is another important environmental risk factor linked to MS with an odds ratio (OR) of 3.6.[2,34,35] It is a herpes virus acquired mostly in childhood and often asymptomatic. It is found in most people (around 90%), commonly in the memory B cells. Although no clear causal link is known, the EBV-MS link is commonly explained through molecular mimicry. This involves the antigen on EBV mimicking cell adhesion sites on oligodendrocytes (which forms the myelin sheath around axons) and astrocytes leading to generation of cross-reactive antibodies leading to immune reaction against them.[2,33–35]

Smoking, including passive smoking, has also been linked to increased risk of MS in a dose-response manner with a higher risk with increased level of smoking.[2,33,34] In contrast, studies in Sweden have shown that oral tobacco use (snuff) has a negative (protective) association (OR of 0.5) with the risk of MS in a dose-response manner.[34,35]

More recently, obesity has been identified as an important risk factor for MS especially in relation to the risk of high body mass index (BMI) at adolescence with an OR of about 2.[34,35] However, high BMI in adulthood was not found to be associated with increased risk of MS. Obesity has also been associated with pediatric onset MS.[33–35]

In addition to the above, several other factors have also been associated with the risk of MS, including shift work at young age. It has been shown that individuals engaged in shift work before the age of 20 had a higher risk of MS (ORs of about 1.5) compared to those who were 20 years and older.[37,38] Another lifestyle factor assessed in terms of risk for MS is alcohol intake. The literature shows mixed findings ranging from no associations[39–42] to findings which showed negative (protective) associations with MS.[43,44] Similarly, mixed findings ranging from no to protective (OR of around 0.7) associations have been reported on the risk of caffeine intake on developing MS.[39,45,46]

1.1.4. Pathology

The hallmark of MS pathology is the occurrence of lesions/plaques in multiple focal areas in the CNS with myelin loss.[47] The inflammatory process is considered to be triggered through activation of T cells reactive to antigens on the myelin sheath through antigen presentation by B cells.[48] Infiltration of CNS by lymphocytes from the periphery through weakening of the blood brain barrier is an important feature of the early stages of the disease.[47,48] Previously, T cells have been considered the main immune system cells involved in inflammatory demyelination and damage in the CNS. It is now recognized that B cells and other immune cells are involved in the disease process.[48] Overall, the main immune cells include macrophages and CD8+ T cells while CD4+ T cells, B cells and plasma cells are also involved.[47] Inflammation occurs in all the stages of the disease. However, its severity decreases with age and duration of the disease.[47,49] In the earlier stages of MS, neurons and axons are preserved but later in the disease phase their damage/loss will lead to disability and brain atrophy.[47]

1.1.5. Diagnosis

The diagnostic criteria for MS assess the dissemination of lesions in the CNS in space and time. According to the 2017 McDonald criteria,[50] two or more clinical attacks with objective clinical evidence of two or more lesions are necessary to diagnose relapsing-remitting MS (RRMS). When one of these two aspects of the criteria are lacking, additional data which demonstrate dissemination in space and/or time are required. In diagnosing primary progressive MS (PPMS), one year of disability progression (prospective or retrospective) independent of relapse and two of the following need to be fulfilled: 1) one or more MRI hyperintensity on a T2 sequence characteristic of MS in one of the areas periventricular, cortical or juxtacortical or infratentorial; 2) two or more T2 hyperintense lesions in the spinal cord; 3) presence of cerebrospinal fluid specific oligoclonal bands.[50]

The MS diagnosis criteria have been improved over the past years, which has helped to reduce the time to diagnosis.[51] Early diagnosis of MS is important as it has been shown that it helps to start treatment earlier preventing relapses and slowing disease progression. In situations where treatment is not available, earlier diagnosis helps determine lifestyle modifications to manage the disease.[52,53]

1.1.6. Disease courses

MS has different clinical courses/phenotypes/types and a first round of standardized definition has been provided in 1996,[54] and a revision in 2013,[55] which took the changes and improvements in the diagnostic approaches over time, such as imaging and biological aspects, into consideration.

One of the clinical courses of MS is clinically isolated syndrome, which is regarded as the first clinical presentation of MS characterized by inflammatory demyelination. However, it is generally not regarded as MS until the criteria of dissemination in time is fulfilled. It is, though, considered to be on the spectrum of an MS phenotype.[55,57] On the other hand, radiologically isolated syndrome describes a situation where imaging indicates inflammatory demyelination but no clinical signs or symptoms of MS. Such a case is not considered a definite MS. However, it could indicate a possible occurrence of MS with time and needs to be followed up although it is not yet defined as an MS phenotype (Figure 1).[55,57]

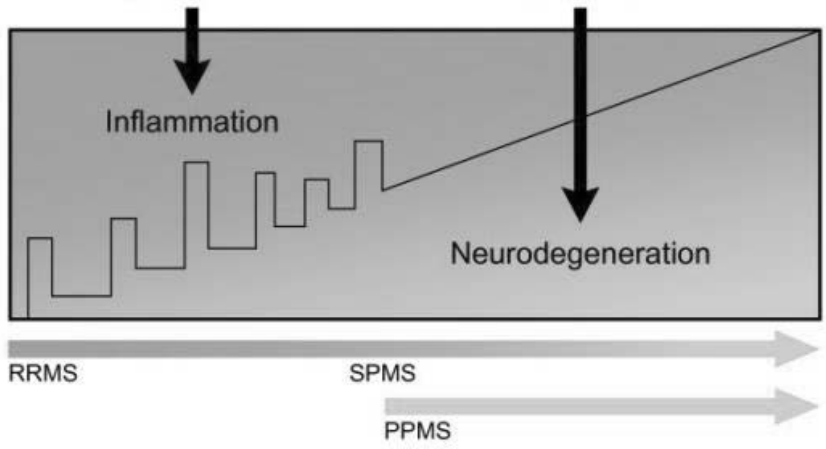

Figure 1: Multiple sclerosis disease courses. Adapted from "Recent developments in multiple sclerosis therapeutics" by Spain et al, 2009,[56] *BMC Medicine 7 (74)* p. 2. Copyright 2009 by Spain et al. Licensee BioMed Central, creative commons attribution license)

The most common disease course in MS is RRMS accounting for around 85% of PwMS. The main clinical features of RRMS are relapses, neurological symptoms, and remissions, which indicate periods of relative clinical stability without symptoms. On average, individuals with RRMS suffer from 1.5 relapses per year.[57] A relapse usually occurs for at least 24 hours.[58] In many of the PwMS experiencing relapses, gradual accumulation of disability occurs despite remission (Figure 1).[57]

The disease course secondary progressive MS (SPMS) results from RRMS converting into a progressive form over time (Figure 1). Following symptom relapses, disability will accumulate gradually leading to progressive course. This change is commonly diagnosed retrospectively as there are no clear criteria to identify the point of transition. The detection is considered to take up to 3 years from the beginning of the transition to its diagnosis.[55,57,59] About 80% of PwMS with RRMS go on to develop SPMS within 10 to 20 years of diagnosis.[47]

In a considerable proportion of PwMS (10-20%) the disease takes the PPMS disease course in which accumulation of disability begins without the occurrence of prior clinical relapses/ exacerbations (Figure 1).[55,57] Unlike RRMS, the sex ratio of PPMS is more even. The onset age of PPMS is also older (40 years) than in RRMS (around 30 years). The process of diagnosing PPMS is expected to be more rigorous in comparison to RRMS as making a confident diagnosis is more difficult. The clinical signs and symptoms of PPMS are also considered somewhat different from the RRMS, with higher occurrence of spinal cord symptoms mainly related to movement - spastic paraparesis (80-85%) and progressive cerebellar syndrome (including tremor and ataxia).[60]

1.1.7. Age and multiple sclerosis

MS commonly occurs among young adults with an average diagnosis age of 32 years as of 2020. It was found to be relatively consistent, ranging from 30 to 33 years in different regions of the world.[8,61] The age of MS onset has also been linked to genetic predisposition with earlier onset age among those with higher genetic risk.[62]

MS in the pediatric population, MS onset before the age of 18, has been described to account for about 3 to 5% of PwMS. In terms of sex distribution, girls to boys ratio of MS increases from around 1 to 1 early in childhood to 2 to 1 in adolescence.[63] In comparison to adult PwMS, the disease has some distinct features as pediatric PwMS accumulate significant disabilities at early ages reaching permanent disability or SPMS when they are about 10 years younger than PwMS with adult onset MS although they reach them in relatively longer time than adults.[64] In addition, in nearly all pediatric PwMS the disease course is RRMS (95-98%) and PPMS is a very rare disease course.[65–67] Relapse rate among pediatric PwMS was also found to be higher than among adults.[68]

Among PwMS, increasing age is associated with different changes in the disease course. These include an increased occurrence of comorbidities, changes from an inflammatory to a more neurodegenerative course of the disease due to immunosenescence - the weakening of the immune system associated with aging.[69–71] Besides these changes among PwMS with increasing age, the onset of MS in older ages – late onset MS (onset after 50 years of age) – which accounts for about 5% of MS cases, is another age-related aspect of MS in older ages. Among its main features are a progressive type of MS and higher proportions of motor disabilities.[72,73] Treatment options for older PwMS are also limited and tend to be of lower efficacy due to the increasingly neurodegenerative nature of the disease.[71,74]

1.1.8. Sex and multiple sclerosis

MS occurs more among women than in men with earlier onset and more relapses. However, the disease generally shows faster progression and worse outcomes among men.[75–77] The female to male ratio of occurrence of MS is higher in the relapsing form of the disease while it nears 1 to 1 in the PPMS.[77,78] The large female to male ratio also starts to disappear after age 50.[76] Shorter times to the occurrence of disability and greater rates of brain atrophy and lesions have also been reported among men.[79,80] In relapsing MS, differences in the occurrence of some symptoms between women and men have also been discussed, which include more sensory symptoms among women and more cerebellar and brainstem symptoms among men. For example, cognitive decline has been reported to occur more among men than in women.[81]

During pregnancy, the rate of MS relapse has been shown to decrease compared to pre-pregnancy levels. Relapse rate rebounds to higher than pre-pregnancy rates in the months postpartum, later becoming stabilized to pre-pregnancy levels.[82,83] The decrease in relapse during pregnancy was also shown by a recent study in Sweden across three groups of women with MS – those who stopped natalizumab or rituximab within 6 months of pregnancy and those who were not on treatment in the past 1 year. The study also showed that rebound phenomenon did not occur after pregnancy with relapse rate remaining at the same level as pre-pregnancy time.[58] The decrease in MS relapse rate during pregnancy has been described to be associated with the increase in the levels of the hormones estrogen, progesterone and prolactin due to their anti-inflammatory effect.[82] Overall pregnancy has not been shown to have a long-term effect on the course of MS.[84]

1.1.9. Comorbidities

A number of diseases co-occur with MS with common comorbidities being cardiovascular, other autoimmune, cancer and psychiatric diseases, among others. The most frequent ones are depression, anxiety, hypertension, hypercholesterolemia, and chronic lung diseases.[85] Of psychiatric comorbidities, anxiety and depression occur more among PwMS than in the general population.[85] Depression is the most prevalent psychiatric comorbidity with MS with a more than 50% lifetime risk with an average prevalence of about 1 in 4 (ranging from 5% to up to 59%) in PwMS.[86] Anxiety occurs in around a fifth to a third of PwMS.[86] Vascular comorbidities such as diabetes and hypertension have been described to be associated with increased disability progression.[87] Overall, higher occurrence of comorbidities has been shown to contribute to increased severity of MS.[88]

1.2. Symptoms and associated activity restrictions

The symptoms of MS presents with heterogeneous signs and symptoms, which involve different pathways, including sensory, motor, visual and brainstem.[89] The type of symptoms PwMS experience depend on the nerves affected. Among the symptoms of MS are fatigue, vision problems, muscle weakness, spasticity (muscle stiffness and spasm), problem of balance and coordination, numbness, tremor and slurred speech, problems of swallowing, thinking and memory problems and problems with bladder control.[90,91] The different symptoms of MS lead to different restrictions and challenges in day to day activities, work, and other aspects of life. These include physical challenges in performing routine activities and the impact of MS on emotional as well as social aspects of life of PwMS.[92–94] Symptoms of invisible/silent nature,[95] such as fatigue,[96,97] pain, depression and anxiety, have been shown to predict quality of life (QoL) among PwMS.[98,99]

Fatigue is one of the most common symptoms among PwMS and one of the most debilitating. A recent systematic review showed its prevalence ranged from 36.5% to 78.0%.[96] It has also been reported that fatigue is more prevalent in the progressive forms of MS.[97] Fatigue is a multidimensional symptom with physical, cognitive and psychosocial aspects.[100] Comparable prevalence of cognitive and motor fatigue in younger ages with higher prevalence of motor fatigue in older ages have also been reported.[101]

Fatigue could be described as primary or secondary dependent on the mechanism involved. Primary fatigue occurs as a result of the MS disease process in the CNS or due to the involvement of the immune system. Secondary fatigue results from other conditions or the accumulation of disease burden. Some of the conditions that are related to fatigue include sleep disorders, depression, MS type and disability status.[100,102]

Fatigue could have diverse impacts on work, family, and socioeconomic aspects of life.[103] A systematic review showed fatigue (presence and severity) was associated with poorer employment outcomes, SA as well as reduced capacity to work.[96]

In the treatment of fatigue in MS, different pharmacological and non-pharmacological approaches are employed. Among the pharmacological treatments are amantadine, pemolin and modafinil, although the evidence is generally weak and inconclusive.[104,105] The non-pharmacological treatments include physical (e.g. aerobic exercises), psychological (e.g. cognitive behavioral therapy) and a mix of the two approaches.[106]

Depression has also been described as one of the symptoms of MS.[107,108] It occurs commonly among PwMS as reported in several studies, which showed a prevalence ranging from 16% up to 50%.[109] These include a study in the US where 41.8% of PwMS had clinically significant depression with moderate to severe depression among 29.1% of them. In Canada, a twelve-month prevalence of major depression was found among 15.7% of PwMS about twice as high as among those without MS. The prevalence was much higher among PwMS 18 to 45 years old with about one in four having major depression.[110] In Sweden a register-based study reported that 8.5% of PwMS had at least one inpatient/outpatient visit due to depression. It has also been shown that disability worsening is faster among PwMS with depression.[111] The restrictions PwMS face associated with depression have been described in different studies, including unemployment and disability as well as presenteeism.[112,113] Depression was also shown to contribute to the negative impact of MS on work, family, domestic activities and social aspects of the lives of PwMS.[114]

Cognitive impairment is among the common symptoms among PwMS with studies reporting prevalence ranging from 43% to 70%.[115–118] It occurs across the course of MS but it is more common in the late stages and in the progressive forms of the disease.[116] Cognitive impairment in MS includes processing speed, visual learning and memory, which are more commonly affected, as well as attention, information processing efficiency and executive function.[115,119] Its impact on language and intelligence has been less clear with studies showing they are generally preserved although some impairments have also been reported.[119] Cognitive impairment has substantial impact on the day to day life of PwMS including work, driving as well as social interactions[120] with an overall impact on the QoL of PwMS.[119]

Spasticity is a disabling condition associated with MS, which occurs due to an involuntary stimulus, where the muscle contracts resulting in muscle spasm and immobility, fall, fatigue, pain as well as sleep problems.[121] Spasticity is also among the most common symptoms PwMS experience with a

prevalence ranging from 52.5% to 97% reported in different studies from Germany, the United Kingdom, north America and Spain.[122–126] More generally, mobility problems - with underlying neurologic problems such as spasticity, loss of motor function, imbalance and sensory loss - have been discussed as important challenges to PwMS, family members and healthcare providers.[127] Spasticity has been shown to affect the lives of PwMS in different ways including physically, psychologically and socially, which are also related to one another.[125,128,129]

Dysphagia, dysarthria and dysphonia are also disabling symptoms to PwMS. Dysphagia is difficulty to swallow, which occurs due to the effect of MS lesions in neurons that control swallowing.[130] Two systematic reviews and meta-analyses showed substantial levels of dysphagia with pooled prevalence of 36% and 43%.[131,132] On the other hand, a study in Sweden showed that speech difficulties were reported by at least one-third (based on register data) and four-fifths (based on survey data) of the PwMS respectively.[133] Substantial levels of speech difficulty have also been reported elsewhere, including the negative impact it has on QoL,[134,135] as well as participation restrictions in communication which include work, household activities and management and leisure activities.[136,137]

Visual problems in different forms, including optic neuritis, double vision and blurred vision, among others, occur commonly among PwMS.[138] In a study in the US among PwMS two-thirds reported some form of visual disability.[139] Among these, optic neuritis is an inflammatory condition where loss of vision develops over days/weeks. It commonly occurs early in MS as the first clinical presentation of the disease in around a fifth of PwMS. About half of PwMS are considered to get optic neuritis at some point in the disease course.[140] The negative impact of optic neuritis in terms of restricting PwMS employment and productivity has been shown in the higher levels of unemployment, lower in income from employment and higher levels of receiving social support in comparison to general population control groups.[141]

Bladder as well as sexual dysfunctions are important but often overlooked, underreported, under diagnosed and undertreated problems PwMS experience.[142–144] Studies have shown bladder dysfunction to be a common problem among PwMS, ranging from 35% to more than two-thirds,[142,143,145–147] with urinary urgency and frequency described as the more common ones.[145,147] The impact of bladder dysfunction on daily life and QoL has also been shown.[148] Similar to bladder dysfunction, a large proportion of PwMS also experience sexual dysfunction with some studies reporting up to 80%.[146,149–154] Severity of MS associated disability and depression have been indicated among the possible factors associated with sexual dysfunction.[150–153] The association of sexual dysfunction with lower health-related quality of life (HRQoL) among PwMS has also been highlighted.[155,156]

Sleep disturbance/disorder is among the common symptoms among PwMS, which impacts QoL to a substantial level.[157–161] However, problems with sleep among PwMS are often under-recognized and untreated.[159,162,163] A number of studies have reported the prevalence of sleep problems to be higher than in the general population.[159,162] Daytime sleepiness and insomnia are among the aspects of sleeping disorders reported commonly.[159,161] The negative impact of sleep disturbance on QoL has also been described.[164,165] The symptoms of insomnia such as fatigue, mood problems, and impairment in attention, concentration and memory are also associated to restricting activities during the daytime.[165]

1.2.1. Restrictions on family life and other aspects of social life

MS has a substantial impact on different aspects of private life including family, leisure activities and social interactions with friends/acquaintances. Studies showed that as the disease progresses PwMS commonly require increasing support from family members and close relatives mostly spouses. In addition, challenges with being able to go out, decreasing contact with relatives and increased risk of divorce have been discussed in relation to increasing disability.[166] The fear of losing self-sufficiency, negative impact of MS on the quality of relationships with family, including with partners, and limitations on daily activities at home have been highlighted.[167]

Studies have also indicated the impact MS has on family members caring for PwMS in different ways including financial, psychological and social aspects.[168] It has also been shown that family members of PwMS caregivers could have challenges in coping with the situation and be at risk of depression for which monitoring is recommended.[169] Overall, the impact of MS on different aspects of life including the QoL of PwMS and their caregivers has been demonstrated.[170]

1.2.2. Implications on health-related quality of life

The concept of QoL has been described as multidimensional where individuals provide their view of their life covering different facets such as physical, psychological, functional and social life.[171,172] The concept of HRQoL focuses on the health aspect of QoL while being a broad concept in itself with no agreed upon definition. Overall, multidimensionality and incorporation of both subjective as well as objective perspectives characterize the concept of HRQoL. The role of HRQoL has increased in recent decades to get the views of patients on their own health to complement information from clinical assessments.[173,174]

As a chronic disease with heterogeneous symptoms and limitations on day-to-day activities, MS has been associated with lower HRQoL in comparison to individuals without MS.[175] A multi-country study on the burden and cost of MS showed that HRQoL among PwMS was very much influenced by the level of disability (EDSS score) indicating severity as well as prevalent symptoms such as fatigue and cognitive difficulties influenced HRQoL.[176] The impact of MS on HRQoL and the importance of the mental aspect of HRQoL and identification of optimal instruments for assessment have also been discussed.[177] The burden of MS in different aspects, including QoL among individuals and family members who provide care and support to PwMS has also been shown in a number of studies.[178–181] The HRQoL implications of MS have also been reported by several studies in Sweden showing low HRQoL among PwMS and even lower at severe levels of disability.[21,22,182,183]

1.2.3. The Expanded Disability Status Scale measure in multiple sclerosis

Neurological impairment in MS is commonly measured using the EDSS.[184] This measurement is an expansion of an original measurement called Disability Status Scale, devised to measure disability in MS. The score ranges from 0 (*normal*) to 10 (*death due to MS*). In the EDSS, the Disability Status Scale has been expanded to increase sensitivity in measuring differences by adding midpoints (0.5) in the scores from 1 to 9. The EDSS score is determined based on the assessment of eight functional systems, which are different neurophysiologic structures, with dysfunction scored from 0 to 1, 5 or 6 with higher scores indicating more dysfunction. These systems are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, mental and other functional systems (Figure 2).[185–187]

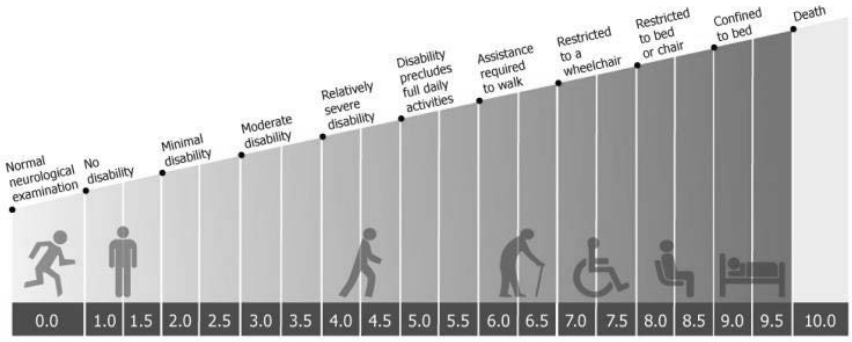

Figure 2: Illustration of the Expanded Disability Status Scale. Reprinted from "What Do Effective Treatments for Multiple Sclerosis Tell Us about the Molecular Mechanisms Involved in Pathogenesis?" by Buzzard et al, 2012[188], *International Journal of Molecular Sciences 13 (10), p. 12667* Copyright 2012 by Buzzard et al. Licensee MDPI, creative commons attribution license.

1.3. Treatment of multiple sclerosis

Treatments used in the management of MS are commonly aimed at preventing relapses and slowing the progression of the disease. In addition, MS treatments are provided to manage relapses as well as specific symptoms of MS.[189] Treatment of MS using DMTs and the management of acute exacerbations are described below.

1.3.1. Disease-modifying therapies

Treatments with DMTs are aimed at reducing relapses, decrease the accumulation of MRI lesions, and slowing down disability progression.[190] Different categories of DMTs are used in MS. The first DMT approved by the Food and Drug Administration in the US was interferon beta-1b in 1993.[191] In the following two to three decades, about 20 DMTs have been introduced to the therapeutic landscape of MS. Among these were injectables that include interferons and glatiramer acetate. Another group were oral DMTs: dimethyl fumarate (DMF), fingolimod and teriflunomide, among others. Currently, infusion therapies are the mainstay of MS treatment. They include anti-CD20 monoclonal antibodies such as rituximab, ofatumumab, and ocrelizumab. Other monoclonal antibodies like natalizumab and alemtuzumab have also been used in MS.[191,192] Almost all DMTs are used in treating RRMS with very few options to treat PPMS and SPMS (Table 1).[190,192]

In terms of efficacy, infusions such as alemtuzumab, ocrelizumab and natalizumab have shown higher efficacy than other DMTs with up to 70% reduction in annualized relapse rate in comparison to placebo. Oral DMTs fingolimod and DMF have shown to be the second efficacious group with relapse reduction rates ranging from 47%-54%.[192,193] Injectables and teriflunomide were of relatively lower efficacy (17%-37%).[192–196]

Many recent studies show early treatment with high-efficacy DMTs could be beneficial in preventing early accumulation of damage in contrast to an escalation approach. In the escalation approach, treatment starts with low- to moderate-efficacy DMTs and changing to high-efficacy DMTs if/when the disease shows clinical or radiological breakthroughs. In emerging evidence, through consideration of the relatively narrow window of opportunity to prevent/delay neurological damages, initiation with high-efficacy DMTs in the earlier phases of MS has become a recommended approach.

Table 1. Summary information on individual disease-modifying therapies used in the treatment of multiple sclerosis

DMT	Indications	Mode of administration	Frequency	Mechanism of action	Common adverse reactions	Sources
Interferon beta-1a	RRMS, CIS, SPMS	Intramuscular (IM) / subcutaneous (SC)	IM: once weekly SC: 3 times per week	- Several different mechanisms - Increase production of anti-inflammatory agents and - Down-regulating inflammatory cytokines	Flu like symptoms, including chills, fever, myalgia	[197–199]
Interferon beta-1b	Relapsing forms of MS	SC	Every other day	- Mechanism not fully understood - Immunomodulatory effects (interference with T-cell activation, reduction of pro-inflammatory cytokines, down-regulation of antigen presentation and inhibiting T-cell penetration into CNS)	Injection site reaction, lymphopenia, flu like symptoms, among others	[198,200,201]
Peginterferon beta-1a	Relapsing forms of MS	SC	Once every two weeks	- Unknown	Injection site erythema, influenza like illness, headache, pyrexia and injection site pain, among others	[197,198,202]
Glatiramer acetate	RRMS, CIS	SC	Once a day or three days per week	- Not fully understood - Binds strongly to major histocompatibility molecules in competition with myelin peptides - Antagonism at T-cell receptor of myelin specific T cells - Inducing secretion of anti-inflammatory cytokines	Injection site reactions, vasodilation, rash, dyspnea and chest pain	[203–205]
Teriflunomide	Relapsing forms of MS	Oral	Once a day	- Not fully understood - Diminishing inflammatory response by inhibiting a mitochondrial enzyme involved in the synthesis of pyrimidines in proliferating T and B lymphocytes	Diarrhea, nausea, hair thinning	[206–208]
Dimethyl fumarate	Relapsing forms of MS	Oral	Once a day	- Immunomodulating - Anti-inflammatory - Anti-oxidative effects	Flushing, gastrointestinal events, diarrhea, nausea	[209,210]

Fingolimod	Relapsing forms of MS	Oral	Once a day	- Functions through sphingosine1P1 receptor and prevents the entry of auto aggressive T-cells	Headache, liver transaminase elevation, diarrhea, cough, influenza	211,212
Siponimod	RRMS, CIS, SPMS	Oral	Once daily	- It is a sphingosine1P1 receptor modulator and prevents the infiltration of CNS by lymphocytes from the periphery	Headache, hypertension, increase in transaminase	213,214
Ozanimod	RRMS, CIS, SPMS	Oral	Once daily	- It modulates Sphingosine1P1 and 5 receptors	Upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension	215,216
Cladribine	RRMS, SPMS	Oral	Once daily for 5 days each in month 1 and month 2. A similar treatment course after 1 year.	- Reduces cells of adaptive immune system such as B and T cells	Upper respiratory tract infection, headache and lymphopenia	217,218
Natalizumab	Relapsing forms of MS	Intravenous (IV) infusion	Once every four weeks	- Blocks leucocyte infiltration into the brain thereby reducing inflammation in the CNS	Headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression and pain, among others. Rare but serious adverse effect: progressive multifocal leukoencephalopathy has also occurred	219,220
Ocrelizumab	RRMS, CIS, SPMS PPMS in adults	IV infusion	300 mg two weeks apart followed by 600 mg every six months	- Not fully understood - Thought to bind to CD20 and reduce CD20+ cells in number and function through antibody-dependent cell cytotoxicity	Relapsing MS: upper respiratory tract infections and infusion reactions PPMS: upper respiratory tract infections, infusion reactions, skin infections and lower respiratory tract infections	221,222

Ofatumumab	RRMS, CIS, SPMS	SC	Week 0, 1, 2 and 4. Weekly after that	- Not fully understood - Binds to CD20 on B cells, at a site different from other anti-CD20 antibodies, leads to B and T cell depletion through B cell lysis and antibody-mediated cytotoxicity	Upper respiratory tract infections, headache, injection-related reactions	[223,224]
Alemtuzumab	Relapsing forms of MS	IV infusion	12 mg once daily for five days; after 12 months, 12 mg daily for 3 days.	- Depletes cells expressing CD52 receptor from the circulation (depletes circulating B and T cells)	Rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia and upper respiratory tract infections among others	[225,226]
Rituximab	Off-label for relapsing and progressive forms of MS	IV infusion	Commonly used at 500/1000 mg every 6 months sometimes after a higher dose treatment with 1000 mg given 1 month apart	- Depletes CD20 positive B cells through mechanisms that include antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, suppressing inflammatory disease activity	Infusion related reactions (fever, rash, chills, nausea, vomiting and others), allergic anaphylactic reactions, risk of infections	[227–230]

CIS: clinically isolated syndrome, **CNS**: central nervous system, **FDA**: Food and Drug Administration (USA), **IM**: intramuscular, **IV**: intravenous, **MS**: multiple sclerosis, **RRMS**: relapsing-remitting multiple sclerosis, **PPMS**: primary progressive multiple sclerosis, **SPMS**: secondary progressive multiple sclerosis

Early use of high-efficacy DMTs is aimed at both clinical and subclinical disease activities to prevent/delay long-term neuronal damage and brain atrophy.[231,232] In Sweden, recent studies showed the longer term clinical implications of the strategy of early initiation of high-efficacy DMTs in comparison to an escalation approach with relatively lower occurrence of disability among PwMS who started high-efficacy DMTs earlier.[233,234] The off-label use of rituximab in Sweden forms the main part of the early initiation of treatment with high-efficacy DMTs, growing substantially starting in the early 2010s accounting for over half of the DMTs according to different studies.[235,236]

In the use of DMTs in MS, de-escalation and discontinuation as treatment strategies are becoming important areas of discussion. The relatively lower effectiveness of DMTs among older PwMS and an increased risk of infections are among the rationales in the discussion of de-escalation and discontinuation of DMTs. However, much remains to be studied in relation to their outcomes, the approach to implement them and possible risks of disease worsening or recurrence.[237,238]

1.3.2. Treatment of acute exacerbations

A number of treatments are used in the management of acute exacerbation/relapse phases of MS. Of these, glucocorticoids, which include methylprednisolone, prednisone and dexamethasone, are the first line treatments. They are aimed at reducing the severity of relapses and shortening the duration. In cases where relapses are unresponsive to corticosteroids, other treatments such as plasmapheresis (plasma exchange) are used.[190,239] This involves a process of replacing the plasma of PwMS through filtration of the blood and replacing it with an albumin solution to retain volume. It is usually provided three to five times every other day and has been effective in the management of relapses.[240–242]

1.4. Work disability in multiple sclerosis

According to the International Labour Organization, work is defined as “any activity performed by persons of any sex and age to produce goods or provide services for use by others or own use”. On the other hand, employment has been defined as “any activity performed to produce goods and services for pay or profit”.[243] In addition, work has been defined in different ways over the years, including as an activity crucial to human survival, to satisfy needs in life and for professional fulfilment. It is also viewed as a contribution to society and the way individuals connect to their society.[244–246]

In relation to work, the concept of work ability and the instruments used to measure it as well as the models of work disability and research around it, in the context, of MS are presented in this subsection. The social insurance system in Sweden in relation to SADP is also introduced briefly.

1.4.1. Work ability, work ability index and work ability score

Work ability is defined to be the balance between the demands of work and individuals’ resources.[247] It has been described in different ways, which address a number of attributes, including health, competence (basic and occupational), occupational virtues as well as motivation.[248] The work ability concept and research around it dates back to the 1980s in Finland with the aim of preventing decline in work ability with ageing work force.[249] Besides objectively measured functional capacities, aspects such as education, experience, skill and motivation are important components in the context of work ability. Assessment of work ability is an approach that encompasses health, functional capacities and work demands. The instrument constructed to address the measurement of work ability in such a manner is the work ability index (WAI).[250]

The development of WAI involved a multidisciplinary group using the stress-strain concept.[251] The WAI instrument contains seven items, including aspects of health and work demands, which are summarized into a single score ranging from 7 to 49.[252,253] The validation of the instrument through studies over the years showed that decline/improvement in work ability is affected by different factors, including management, ergonomics and lifestyle ones. The findings led to important long lasting steps, including the promotion of work ability at work places and the promotion of the concept of work ability.[251] The use of WAI has increased internationally and it has been translated into many languages and validated in different settings.[251,252]

Work ability score (WAS) is the first item in the WAI instrument where respondents are asked to score their current overall work ability out of a maximum score of 10.[252,253] Many studies showed that the summary score of the complete WAI instrument and the WAS component are largely similar and that WAS can be used in place of WAI in circumstances where the full instrument may not be feasible to apply.[254–257]

Few studies have been conducted using WAI/WAS among PwMS. Among these, in a study from the Netherlands comparing workers with MS with that of the general population, lower work ability was observed among PwMS as measured using WAS.[258] Similarly, another study from Italy on work impairments among PwMS showed they had lower WAI than the control group.[259] In the Netherlands, fatigue was shown to be associated with worse levels of work ability measured through WAS.[260] Lower WAS, among PwMS, than healthy controls has also been reported by another study from the Netherlands.[261] In a study from France, WAI has been associated with early job loss among PwMS.[262]

1.4.2. Work disability

Work disability has been defined as the inability to participate in a gainful activity due to physical or mental health problems that could lead to death or is expected to last at least 1 year according to the Social Security Act in the US.[263] It has also been described as an inability to remain or return to work while a person is going through a course of an injury/illness or after that.[264]

Work disability has been suggested as a measure of physical, psychological and social functioning.[265] The broader multidimensional attributes of work disability have also been emphasized through its link to work environment, behavior and functional abilities indicating health problems or symptoms affect work ability differently depending on the context of the job.[266]

In explaining work disability, different conceptual models have been discussed over the years. The medical (biomedical) model focuses on the patient in explaining disability. So, disability is evaluated in terms of the level of impairment and clinical response to treatments provided to the patient. The socio-ecological model, proposed by Saad Nagi, puts more emphasis on the external environment in explaining disability.[264] Accordingly, the same medical issues could result in different types of disability and different medical problems could result in similar disability patterns dependent on external environmental factors.[264] These could be external physical demands as well as social environment. Another model of disability was the social model of disability that describes disability as being a result of the pattern of societal organization indicating that there are several barriers for a person to participate in the activities of the community. In this model social environment is considered as a reason for disability and the solution lies in the societal level of adjustment and aspects like attitude change in relation to disability.[264]

Among the disability models widely accepted currently is the biopsychosocial model which originated in the context of disability related to low back pain. The model discusses the multi-causal and multi-directional nature of illness and health using behavioral perspectives where pain is described to be modulated by mental, emotional and sensory mechanisms. So, health and illness are explained holistically through complex interactions of biological (e.g. genetic predispositions), behavioral (e.g. life style) and social factors (e.g. culture, social support).[264] A model with the biopsychosocial perspective is the International Classification of Functioning, Disability and Health (ICF) developed by the World Health Organization in 2001 with an origin in 1980 as International Classification of Impairments, Disability and Handicaps. In the ICF model, the social aspects *human activities* and *participation* are linked to the clinical concepts *body functions and structures*. In this model, functioning or a problem with it are related to the interaction between the health condition of an individual and contextual factors including personal and environmental factors (Figure 3).[264,267]

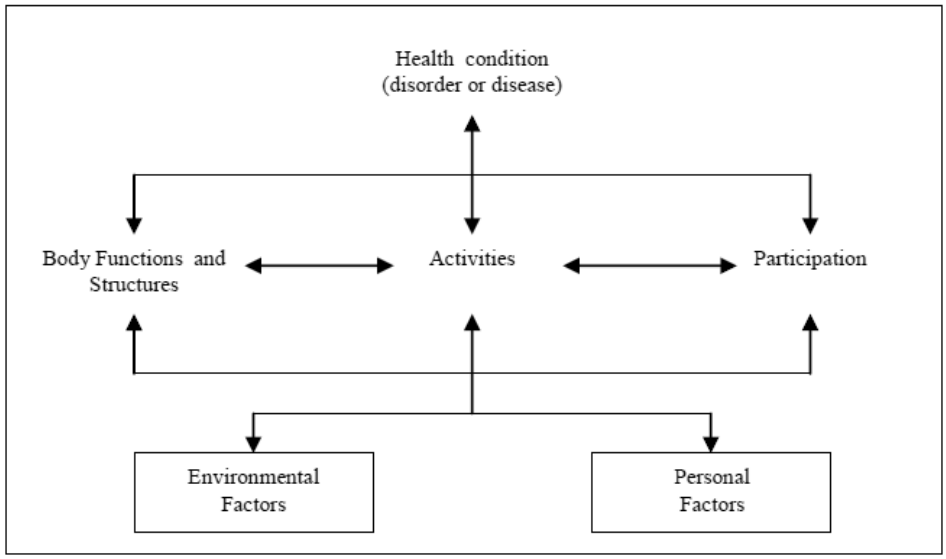

Figure 3: Illustration of the International classification of functioning, disability and health (ICF) model.
Reprinted from "International classification of functioning, disability and health" by World Health Organization (WHO), 2001[188], Geneva: WHO. Copyright 2001 by WHO. Reprinted with permission.

The healthcare focused view in the ICF model with emphasis on the individual functioning is described as a limitation, for overlooking the role of social actors outside the individual patient and healthcare provider, which are involved in the context of the disability. Another limitation raised in relation to the ICF model is that it does not explain the mechanism by which contextual factors affect disability and work.[264] Another biopsychosocial model in the context of musculoskeletal disorders at the work place is the *Institute of Medicine-National Research Council* model. The model focuses on *person-environment* interaction and the role of medical, biomechanical, work environment and psychosocial factors in musculoskeletal disorders and disability.[264]

A broader model that shifted attention to a system wide view of the issue of disability and its organized management and prevention is the *case management ecological model*. The model covers the full arena of social actors. The different social structures, including the personal, workplace, healthcare and the compensation systems are described in this model. The worker is at the center surrounded by the four structures that could influence the worker.[264,268]

1.4.3. Correlates of work ability and work disability

Different studies conducted among workers in various occupations reported the inverse association between age and WAI.[269,270] Relatively lower WAI has also been reported among women, divorced/widowed individuals and those who work part-time.[270] However, higher WAI among women and older workers has been reported in mainly younger cohorts.[271,272] Higher levels of work ability were also associated with higher education levels. At work place level, factors such as physical, chemical and psychosocial environment and gender segregation were described to influence SA. At national level, sickness insurance systems, general attitudes and level of unemployment have been discussed.[270]

A systematic review summarized general risk factors for SA which include many socio-demographic factors, including age, sex, socio-demographic factors as well as area of residence. These variables are considered important confounders in SA research.[273] Another systematic review also showed numerous factors at individual, workplace/community and national levels to be associated with SA. Among these were several socio-demographic factors, which include age, sex, socioeconomic status, family situation as well as lifestyle factors.[274]

In terms of the association of socio-demographic factors with SADP, a number of studies showed that age, sex and type of employment, among others, were significantly associated. In a large study (n=60,000) in Italy, SA has been associated with employment in big companies or in the public sector and the permanence of employment, among others. Among men, higher risk of SA was observed among those with lower education level and in manual work. In both women and men, permanent employees were at higher risk of SA.[275] In another large scale study among more than 74,000 individuals from the United Kingdom, Finland and France different lifestyle factors such as drinking, smoking, being overweight and lack of physical activity have been associated with SA due to various diagnoses such as musculoskeletal disease, depression and respiratory diseases, among others.[276] Long term SA was associated with low socioeconomic status by a study conducted in Japan.[277] In another study in Finland, the association of DP with low income and lower level of education has been shown in the context of mental disorders. Furthermore, white collar workers had higher risk of DP due to mental disorders than blue collar ones.[278]

In Sweden, different studies explored factors associated with SADP. In relation to SA, different factors such as the role of physical and psychosocial working conditions in the health and social care have been shown to be associated with the risk of SA.[279] Sex difference in SA has also been discussed in a large Swedish study, which showed higher levels of SA among women while the level of mortality was higher among men across the investigated diseases.[280]

Similarly, socio-demographic factors associated with DP have been shown in a number of studies, which include a study of twins where older individuals, women and unmarried individuals were shown to have higher risk of DP.[281] Similarly, a study among individuals with depression showed youngest (25 years) and older (45+ years) age groups, women, and individuals with lower education levels, among others, were associated with increased risk for DP.[282] The social gradient of being on SA has also been associated with physical working conditions.[283] Higher risk of DP has also been associated with SA among individuals with musculoskeletal disorders.[284]

1.4.4. Studies of work and work disability among people with multiple sclerosis

A recent meta-analysis of 33 studies showed that employment among PwMS ranged from 12 to 74% with an average of 44%.[285] The report of MS International Federation in 2016 showed that 61% were in employment in 2016 and 43% of PwMS who were not in employment became so within 3 years of diagnosis and the number increased to 70% within 10 years.[286] The negative impact of MS on the work life of PwMS has been shown in different studies.[287] A study in New Zealand showed that over 90% of PwMS had a previous history of work but 54% no longer worked, which happened early in the disease course leading to decreased income.[288] A mixed methods study from the United Kingdom showed that anxiety and depression among PwMS were associated with work instability similar to findings from a study in Argentina.[289,290] Neurological disability, fatigue and age were also associated with employment status among PwMS.[291] A study in France showed that about three quarters of the PwMS reported symptoms affecting occupational activity, including fatigue and motor disorders.[292] A review of 42 studies on determinants of work-related difficulties among PwMS, including unemployment, fewer working hours and exiting work showed that neurological disability (measured in EDSS), duration of MS, age as well as fatigue and walking problems were important determinants.[293]

In Sweden, several studies showed the impact of MS on the work life of PwMS. Of these, an eight-year longitudinal study of SADP among PwMS showed higher levels of SA and DP in comparison to a matched general population starting from four years before diagnosis and continuing after diagnosis.[294] In yet another study the excess SA and DP among PwMS was demonstrated with excess SA than the control group going back 15 years before diagnosis.[295] The relatively higher levels of SADP among PwMS has also been shown by another study where 61.7% of PwMS were on DP in comparison to 14.2% of the control group.[296]

Although studies on the impact of treatment of MS on work life and productivity are limited, some studies showed work/employment implications of DMTs. One such study of 874 PwMS from Australia showed that those on DMTs of higher efficacy such as natalizumab, alemtuzumab and fingolimod had two to three times higher likelihood of increased self-reported work amount, work attendance and productivity in comparison to those on injectables such as interferons.[297] A similar study among 630 PwMS in the US comparing ocrelizumab with injectables and oral DMTs showed higher odds of employment among ocrelizumab treated PwMS than the other groups despite worse EDSS score at treatment initiation.[298] The positive association of a good level of adherence with employment has also been highlighted in another study from the US. Paid employment was more common among veterans with MS adhering to their DMTs than non-adherent ones.[299]

The positive impact of increased adherence in decreasing lost work days and indirect work loss costs, among others, was shown in another study in the US.[300] A study in Sweden on the cost-of-illness trends among PwMS on different DMTs (interferons, glatiramer acetate and natalizumab) showed lower productivity loss (measured in SADP) among PwMS taking interferons. In addition, individuals on natalizumab sustained their work ability for longer period than glatiramer acetate with lower progression of DP.[301] The positive impact of DMTs of higher efficacy, particularly natalizumab, on work ability has also been highlighted in a number of studies in Sweden.[302–304]

1.4.5. Sickness absence and disability pension in Sweden

In the welfare state of Sweden, the social security system includes various forms of compensations and benefits to people with morbidity and several of them are administered by the national Social Insurance Agency (SIA), (*Försäkringskassan* in Swedish).[305]

One important component of the social insurance system is SA. The SA benefit is provided to insured individuals whose work capacity is reduced due to disease or injury. Sickness absence benefits can be granted for full-time or for part-time of ordinary work hours; for part-time, in relation to the level of incapacity, 25%, 50% or 75% of ordinary work hours. In the first seven days of a SA spell, self-certification is usually possible. After that, a medical certificate provided by the treating physician is needed. The certificate is to include the diagnosis/diagnoses that led to the reduction in function and how this hinders the patient in conducting his/her specific work tasks, and to what extent (25%, 50%, 75%, or 100%) and the possible duration of this work incapacity. Information from this certificate is used by the social insurance officer to assess whether the claimant fulfils the criteria for being granted SA benefits.[306–310] The rules and practices for such assessments have changed over time and between regions and officers. Since 2007, during the first 90 days of SA spell, an individual's work capacity is assessed in relation to their ordinary job. In the next 90 days, the ability to work is assessed in relation to any work available from the current employer. After 180 days, the work capacity is to be assessed in relation to work available in the overall job market, with some exceptions.[307–309]

The first day of a SA spell is a qualifying day (*karensdag* in Swedish), with no reimbursement. From the second to the 14th day, employers provide sick pay. The SIA provides SA benefits from day 15 and onwards for employed individuals. For unemployed individuals, the SIA pays SA benefits from day 2, and for self-employed individuals who have chosen more qualifying days, after these days have ended.[307]

The minimum income requirement for SA benefits is 24 percent of the price base amount in a specific year and the maximum income eligible for SA is 10 times the price base amount. The price base amount is calculated annually based on the development of the consumer price index. In the year 2023, the price base amount is 52,500 SEK.[307,311] Individuals are provided SA benefits to compensate around 80 percent of lost income, up to a certain level. From day 365, this in most cases is reduced to 75%. There is no time limit to the duration of a SA spell.[307]

Individuals aged from 19 to 64 years who are unable to work full time due to long-term disease or disability could be eligible for DP. Among individuals 19 to 29 years old, DP is provided in cases of disease or disability where the individual is not able to work now or in the future in the broader job market. Individuals aged 30 or older can be granted DP if their work incapacity due to morbidity is permanent. The payment of DP is on an income-based manner but with a guaranteed minimum amount for individuals who do not fulfil the minimum income requirement. The guaranteed compensation is aimed at providing basic economic protection regardless of the previous income of an individual. The DP compensation covers around 64% of lost income, up to a certain level.[308,312,313] It can, similar to SA, be granted for 25%, 50%, 75% or 100% of ordinary work hours.

2 Research aims

Overall aim

The overall aim of this thesis was to increase knowledge on activity restrictions, trends in disease-modifying therapy use and associated work disability among PwMS in Sweden.

Specific aims

Study I

- To describe the extent of restrictions in different life domains that PwMS experience in relation to their symptoms and level of disability

Study II

- To identify 1) trajectories of DMT use over 10 years among PwMS, 2) socio-demographic and clinical factors associated with the trajectories, and 3) to assess the association between identified trajectories and SADP days

Study III

- To describe the trajectories of DMT use in recent years (treatment start in 2014/2015) and their association with SADP among PwMS in Sweden

Study IV

- To assess the association between DMT use and work ability among PwMS and the role of other socio-demographic, clinical and self-reported variables

3 Materials and methods

The field of study, the study designs employed, the study populations, data sources, the variables included, the different analysis methods and ethical considerations are described in this section.

3.1. The thesis in the context of insurance medicine research

In addressing the above objectives, the present thesis investigated research areas in the field of insurance medicine. Accordingly, the thesis touches up on the following different components in the study of SADP in insurance medicine research as per the guide *structure for categorization of studies of SADP*.[314] The structure covers the specific and the broader scientific discipline, study designs, perspectives taken in the study, coverage level of the data and the diagnoses focused on in the study. The areas covered in the present thesis are indicated below in bold (Table 2).

Table 2: The focus areas of studies in the thesis in the area of insurance medicine according to the structure for the categorization of studies in sickness absence/disability pension by Alexanderson, 2021[314]

What is studied?	**-Study design -Type of data -Analyses**	**Scientific discipline**	**Perspective taken in the research questions**	**Studied**	**Structural level of the data/factors included in the analyses**	**Diagnoses** (of included and/or of sickness absence or disability pension diagnoses)
1. **Occurrence of sickness absence/disability pension** 2. **Factors that hinder or promote sickness absence/disability pension** 3. Factors that hinder or promote return to work 4. "Consequences"/ "side-effects" of (being on) sickness absence/disability pension 5. Sickness certification/assessment practices/processes 6. Methods, theories	**Study design** **-Cross-sectional** **-Longitudinal** -Randomized controlled trial, clinical trial, etc. **Type of data** Interview **Questionnaire** **Register** Medical files Insurance files *Certificates* *Documents* Observations Video Other **Type of analyses** -Qualitative **-Quantitative**	Economy (health economy) **Epidemiology** Law Management **Medicine** (**insurance medicine**, psychiatry, occupational health, social medicine, healthcare science, etc) Philosophy Psychology **Public health** Social work Sociology Other	That of the: -**Society** -Insurance -Healthcare -Employer -Colleagues -Family -Patient	-General population -Insured -In paid work (general or special jobs/ organizations) -**Diagnosed/ patients** -Sickness absent/ disability pensioned -Organizations -Professionals -Countries	-International -National -Regional -Municipality -Worksite -Healthcare -Family **-Individual**	**All together** Mental Musculoskeletal Cancer **Multiple Sclerosis** Hearing Cardiovascular diseases Infections Injuries Diabetes Head ache Others Multimorbidity

3.2. Study design and period

An overview of the methodological aspects of the studies is provided in Table 3. The four studies in the present thesis were all conducted among PwMS with records in the Swedish Multiple Sclerosis Registry (SMSreg). Studies I and IV were conducted based on data from a cross-sectional survey among PwMS conducted in Sweden from May 2021 to September 2021 (Table 3).

Table 3: Overview of the methodological aspects of the four studies in the thesis

Item	**Study I:** Self-reported restrictions	**Study II:** DMT use and SADP	**Study III:** Recent DMT use and SADP	**Study IV:** DMT use and work ability
Study design	A cross-sectional survey among PwMS in Sweden	A longitudinal register-based study among PwMS in SMSreg	A longitudinal register-based study among PwMS in the SMSreg	A cross-sectional survey among PwMS in Sweden
Study period	A survey was conducted among PwMS from May to September 2021	PwMS with MS onset in 2007-2010 were followed for 10.5 years (at 6-month periods) on their DMT use trends and for 11.5 years (6-month periods from Y_{-1}) on their SADP days	PwMS with MS treatment start/decision in 2014-2015 were followed for 5 years from treatment start for their DMT use (at 3-month periods) and for 7 years on their SADP days (yearly from Y_{-2})	A survey was conducted among PwMS from May to September 2021
Inclusion criteria	All PwMS registered in SMSreg and aged from 20-51 years were invited to the survey	The study included PwMS in the SMSreg with MS onset during 2007-2010 and aged 18-55 at baseline (Y_{-1})	PwMS in the SMSreg with treatment start/decision in 2014/15 and aged 18-60 at treatment start/decision	All PwMS registered in SMSreg and aged from 20-51 years were invited to the survey
Exclusion criteria	No complete response on restrictions experienced in the four domains	Missing information on onset, diagnosis and treatment start dates as well as diagnosis date before onset, pediatric onset MS, PwMS younger than 18 and older than 55 years old, PwMS who died or emigrated	Diagnosis before onset, treatment before onset or diagnosis, younger than 18 or older than 60 years old at treatment start, pediatric onset MS, exited the MS register, emigrated or died	No complete answer on work ability score, missing data on DMT use, type of MS, fatigue, education and long-term disease
Study population	N=4052 PwMS	N=1923 PwMS	N=1395 PwMS	N=4103 PwMS

Data sources	Survey among PwMS, SMSreg and LISA	SMSreg, LISA, the Cause of Death Register, the Swedish Prescribed Drug Register, the Swedish Cancer Register and MiDAS	SMSreg, LISA, the Cause of Death Register, the Swedish Prescribed Drug Register, the Swedish Cancer Register and MiDAS	Survey among PwMS, SMSreg and LISA
Outcome measures	Restrictions PwMS experience in their work and private life domains (family, leisure and friends/acquaintances)	Trajectories of DMT use, SADP during the follow-up	Trends/trajectories of DMT use, SADP during the follow-up	Work ability score among PwMS using different DMT categories
Factors included in the analysis	Socio-demographic variables: age, sex, education, type of area of residence; clinical variables: type of MS, pediatric onset MS, type of the most limiting symptom, EDSS score	Age, sex, type of MS, comorbidity, EDSS score, number of DMT switch, MS onset year	Age, sex, type of MS, comorbidity, EDSS score, number of DMT switch, health-related quality of life, MS treatment start year	Socio-demographic variables: age, sex, education, occupation, type of area of residence; clinical variables: type of MS, pediatric onset MS, EDSS score, time from treatment start, fatigue T score, long-term disease/disability besides MS, health-related quality of life
Statistical analysis	Descriptive statistics, multinomial logistic regression and binary logistic regression	Descriptive statistics, chi-square tests, one-way analysis of variance, Kruskal Wallis test, sequence analysis, log-multinomial regression, generalized estimating equations	Descriptive statistics, chi-square tests, independent t tests, Mann-Whitney-U tests, one way analysis of variance, sequence analysis, multinomial logistic regression, zero-inflated negative binomial regression	Descriptive statistics, linear regression analysis

DMT: disease-modifying therapy; **EDSS**: expanded disability status scale; **LISA**: Longitudinal Integrated Database for Health Insurance and Labor Market Studies; **MiDAS**: Micro-Data for Analysis of the Social Insurance System; **MS**: multiple sclerosis; **SMSreg**: the Swedish Multiple Sclerosis Registry; **PwMS**: people with multiple sclerosis; **SADP**: sickness absence and/or disability pension

In studies II and III, a register-based longitudinal study design was used. In study II, PwMS with onset during the period 2007 to 2010 were followed for a total of 10.5 years from MS onset, to assess the trajectories of DMT use. In assessing the corresponding trends in SADP days, the PwMS were followed for a total of 11.5 years starting from the one year before MS onset. In Study III, PwMS with DMT start/decision during 2014/15 were followed for a total of five years. The SADP days across the different DMT use trends were assessed from two years prior to treatment start date up to five years after that (Figure 4).

Figure 4 illustrates the timelines of the four studies. The bounded dark lines show the time from which the cohorts included in studies II and III were selected based on MS onset and treatment start/decision times respectively. The horizontal hollow arrows indicate the timelines of follow-ups in the two studies, the upper ones (top of the bounded lines) for those with the earliest MS onset/treatment start date among the cohorts, while the lower ones represent the timelines for those with the latest MS onset/ treatment start dates (Figure 4).

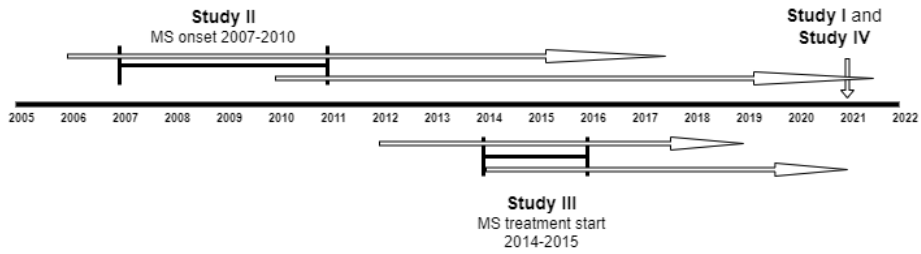

Figure 4: Timelines covered in the four studies

3.3. Study population

For studies I and IV, PwMS aged from 20-51 years old and registered in the SMSreg were invited to participate in a web-based survey on the work and life situation of PwMS in Sweden. From the total of 8458 PwMS, 4412 answered the survey with a response rate of around 52%. Overall, non-response analysis showed that relatively higher proportions younger, more men, with lower income and were born outside Sweden.

In study I, a final sample of 4052 PwMS who completed the questions on restrictions PwMS experience in all the four domains of life were included in the analysis. In study IV, PwMS with complete data on the questions of work ability (WAS), DMT use, type of MS, fatigue, education and long-term illness which came to be 4103 were included in the final analysis (Table 3).

In study II, from register records of 2373 PwMS with MS onset during 2007-2010, a study population of 1923 PwMS in the age range of 18 to 55 years at baseline were included in the final analysis. This was obtained after exclusion of missing information on onset, diagnosis and treatment start times, as well as diagnosis or treatment before onset or treatment before diagnosis, pediatric onset MS, emigration or death during the follow-up (Table 3). Following similar exclusions, in study III, from a total of 1741 PwMS with first treatment start/decision in 2014/15, a final study population of 1395 were included in the analysis. In terms of age groups, PwMS from 18 to 60, at treatment start/decision were included in the study.

3.4. Data sources

The data sources used in the present thesis range from the survey conducted among PwMS to the different nationwide registers described below.

3.4.1. The survey on the life and work situations of people with multiple sclerosis

The data used for studies I and IV were obtained from the survey conducted among PwMS in Sweden in 2021 with four rounds of reminders. The survey questionnaire contained a number of components that assessed the work and life situation of PwMS in Sweden from different aspects. These include work (impact of Covid-19 on work, work ability in terms of WAS, disclosure of MS diagnosis status and related aspects, job demands and control, potential adaptations for MS at the work place, the impact MS had on different work and education decisions), self-reported health (NeuroQoL short forms on fatigue, anxiety and depression; HRQoL through the EuroQol EQ-5D instrument), the restrictions PwMS experienced in relation to MS in the different domains of life, the presence of long-term illness or disability, the most limiting MS symptom, pregnancy, frequency of attendance and need of care from different healthcare professionals, the use of alternative medicine, support received in different formal and informal means, and possible positive experiences.

Questions in the survey formed the outcome variables for the two studies in the present thesis (I and IV). The questions for study I were about restrictions PwMS experienced in the different domains of life (work, family, leisure activities and contact with friends/acquaintances). For study IV, the survey question on WAS, which assesses the view of PwMS on their own current work ability, formed the outcome variable.

The data obtained from the survey for the two studies were linked to datasets from the SMSreg[315] (for clinical and demographic data) and the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) (for socio-demographic variables).[316]

3.4.2. Nationwide registers

In the different studies in the thesis, data from the six nationwide registers detailed below were used.

3.4.2.1. The Swedish Multiple Sclerosis Registry

Data of PwMS from the SMSreg is used in all the four studies. Data on clinical variables such as the age of MS onset, date of MS onset and diagnosis, type of MS, EDSS score and DMT use as well as HRQoL (for study III) were obtained from the SMSreg for the studies in the thesis. SMSreg is one of the about 100 nationwide clinical registers in Sweden (in Sweden often called *kvalitetsregister*).[317] It was founded in 2001 and became web-based in 2004. In terms of coverage, it encompasses all the neurology clinics in Sweden.[315] Currently, SMSreg holds records of around 19,000 active PwMS and has 84% coverage.[318] The registry was set up with the aim of assessing the long-term effects of DMTs. It contains information on demographic and numerous clinical variables covering diagnostic, disease course as well as DMT use aspects.[315] The validity of the SMSreg was also assessed in a recent study of records of more than 3000 PwMS.[319]

3.4.2.2. Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA)

The LISA register that is administered by Statistics Sweden compiles data on labor market, working life and life situations and demographics among the population in Sweden since 1990. The register includes individuals aged 16 years or older (15+ years since 2010). The register contains data on 500

variables about individuals. These include age, sex, area of residence, educational level, paid work, occupation, income, SA, DP, unemployment and migration.[316] In all the four studies in the thesis, data from LISA were used. These included age, sex, educational level, type of living area as well as family composition.

3.4.2.3. The Swedish Cause of Death Register

The Swedish Cause of Death Register contains an almost complete record of deaths in Sweden from 1952. It is used both for official statistics and for medical research. The register is administered by the National Board of Health and Welfare (*Socialstyrelsen* in Swedish). Data collected in the register include the date and cause of death using the International Classification of Diseases code, among others. Its high completeness and the wealth of data collected over a very long time are important advantages of the Cause of Death register.[320] In the present thesis, data from the Swedish Cause of Death Register on date of death was used in studies II and III to identify and exclude individuals who died during the follow-up periods.

3.4.2.4. The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register was established in 2005 and it is administered by the *Socialstyrelsen*. The register contains data on dispensed prescribed drugs to the whole population with individual patient identifiers that facilitates linkage of this information with other registers through Personal Identification Number (PIN). The data contained in the register include dispensed item (substance, brand name, formulation, and package), dispensed amount, dosage and expenditure, date of prescribing and date of dispensing, age, sex and PIN. This register doesn't include over-the-counter medications and drugs administered in hospitals.[321] Data on drugs, other than those for MS, were obtained from the Swedish Prescribed Drug Register in studies II and III. The data was used in determining the presence and number of comorbidities among the PwMS in the studies. Data on DMTs aimed at treating MS were obtained from the SMSreg.

3.4.2.5. The Swedish Cancer Register

Administered by the *Socialstyrelsen*, the Swedish Cancer Register (SCR) was established in 1958 and has coverage of the entire population. Around 60,000 cases of malignant cancer are registered annually. Newly detected cases of cancer are required to be reported to the register. The data held in the register covers patient data (sex, age, residence, PIN), medical data (includes details of the cancer and diagnosis information) and follow-up data (date and cause of death and date of migration).[322] A study in 2009 on the completeness of the SCR showed an overall high level of completeness considered comparable to other high quality registers in northern Europe.[323] In this thesis, data from SCR about the occurrence of cancer diagnoses were used in studies II and III as a complementary data in the assessment of comorbidity among PwMS.

3.4.2.6. Micro-Data for Analysis of the Social Insurance System

Micro-Data for Analysis of the Social Insurance System (MiDAS) is a register that is administered by the SIA. The register's objective is to avail administrative data for analysis in the area of social insurance with the aim of narrowing the gap between data and users.[307] Of the total of 47 benefits that the SIA administers, MiDAS contains data on seven of them.[324] These include data on SA, DP and family benefits. In studies II and III of this thesis, data on SA and/or DP (start and end date, grade (full- or part-time, and main diagnosis) were obtained from MiDAS to study trends in net SADP days across DMT use trajectories.

3.5. Outcome variables

The different outcome variables in the thesis include self-reported restrictions in study I, DMT use trajectories and associated SADP days in studies II and III, as well as work ability in study IV.

3.5.1. Self-reported restrictions

In study I, the outcome variable was the restriction PwMS experienced in relation to MS. This included restrictions in the domains of work, family, leisure activities and in contact with friends/ acquaintances. The question was stated as "*To what extent do you feel that MS restricts you in the following situations? Work situation; family situation; leisure activities; and contact with friends/acquaintances.*" Respondents provided a score from 1 *not at all* to 7 *very much*, which were later categorized as 1, *not at all*, 2-4: *moderate* and 5-7: *severe* restrictions. The restrictions experienced in the domains of life other than work were summarized into a *private life* domain with a resulting 6 categories: *not at all* for those with no restriction experienced in any of the three domains of private life; *no to moderate* when a respondent answers *no* or *moderate*; *moderate* when one answers *moderate* to all the three domains, *moderate* to *severe* when one experienced a mix of moderate and severe restrictions; *severe* when one answers severe in the three domains as well as *mixed* when one answers a mix of *no* and *severe* or *no, moderate* and *severe* restrictions.

3.5.2. Disease-modifying therapy use trajectories

In studies II and III, trajectories of DMT use were investigated and their association with SADP days was explored. In the first part of the analysis, the identified DMT use trajectories were outcome variables. These were identified through sequence analysis and clustering of the sequences. In study II, the trajectories of DMT use were assessed for a total of 10.5 years while in study III DMT use over a total of 5 years was assessed. On the other hand, different socio-demographic, clinical as well as HRQoL (in study III) variables were assessed in terms of their associations with the DMT use trajectories in the two studies. However, the DMT use trajectories were also assessed as factors for their association with SADP days during the follow-up in both studies.

3.5.2.1. Disease-modifying therapy (DMT) categorization and DMT use states

DMTs assessed in studies II-IV in this thesis were categorized as non-high-efficacy and high-efficacy DMTs. The categorization was based on review of the literature for studies, reviews and guidelines on the classification and efficacy/effectiveness of DMTs.[190,325–329] Accordingly, the DMTs alemtuzumab, daclizumab, hematopoietic stem cell transplantation, mitoxantrone, natalizumab, ocrelizumab, ofatumumab and rituximab were grouped as high-efficacy DMTs. The DMTs grouped in the non-high-efficacy group were cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferons (interferon beta-1a, interferon beta-1b, and peginterferon beta-1a), siponimod and teriflunomide. In the case of study II, sensitivity analyses were also conducted with a three-group categorization of DMTs as high-efficacy, modest-efficacy and low-efficacy DMTs. In the newer category of modest-efficacy DMTs cladribine, dimethyl fumarate, fingolimod and teriflunomide were grouped.

In studies II and III, DMT use was followed longitudinally from MS onset for 10.5 years in study II divided into a 6-month period each. In study III, DMT use was followed from DMT start/decision to 5 years later on a 3-month basis. In study IV on the other hand, it was measured as the latest DMT use status within the last two years based on the data from the linked SMSreg.

3.5.3. Sickness absence and/or disability pension days

In both studies II and III, net SADP days were outcome variables where their association with DMT use trajectories and how other demographic, clinical as well as self-reported variables associate with them. In study II, SADP was determined by calculating SADP days from one year before MS onset date to about 10.5 years after that over a total of 11.5 years of follow-up in each 6-month period. In study III, SADP was calculated from two years before DMT start/decision date to up to 5 years after that with a 1-year duration each. In both studies the SADP measure was constructed by calculating the number of SA or DP days within each of the 6-month/1-year follow-up and multiplying with the extent of SADP (25, 50, 75 or 100%) to get the net SADP days. In the case of study III, in an additional analysis, SADP due to MS diagnosis and SADP due to other diagnoses were assessed by categorizing the SADP days based on diagnosis.

3.5.4. Work ability

In study IV, work ability measured using WAS was the outcome variable. It forms the first question (stated as "*How is your current work ability in comparison to the best it has been?*") in the WAI instrument where respondents are asked to evaluate their overall work ability on a scale from 0 (*cannot work at all*) to 10 (*work ability at its best*).[253] The WAS was also presented categorized into *poor* (0-5), *moderate* (6-7), *good* (8-9) and *excellent* (10).[256]

3.6. Covariates

Across the four studies, the socio-demographic variables used in the analysis are described below. A number of specific variables were also created and used as covariates as well as outcome variables in the analyses. The data management involved in the process is described below.

3.6.1. Socio-demographic variables

Several socio-demographic variables were used in four studies, which include sex, age, educational level, the type of living area, country of birth, family composition and occupation.

In studies I and IV, age was measured from the time of response to the survey. In study II, age was measured at baseline (Y_{-1}) and in study III it was measured at treatment start. In studies I and IV, age was categorized as "*20-25*", "*26-35*", "*36-45*", and "*46-51*" years old. In study II, it was grouped as "*18-25*", "*26-35*", "*36-45*", "*46-55*" and "*56-65*" years old while a similar categorization was used in study III with an upper limit of 60 years old.

Educational levels were categorized into three groups based on years of education. The groups include "*elementary (0-9 years)*", "*high school (10-12 years)*" and "*university/college (>12 years)*" that were used in studies II and III. The first two groups were collapsed into "*up to high school*" and two groups of educational level were used in studies I and IV.

The type of living area was used in the four studies and was grouped into three categories. These include "*big cities*", "*medium-sized cities*" and "*rural areas*". The variable on the country of birth is used in studies II and III, and categorized as "*born in Sweden"* and "*outside Sweden"*.

The variable family composition was used in studies II and III and was categorized into four groups, "*married/cohabitant without children <18 years*", "*married/cohabitant with children <18 years*", "*Single without children*" and "*single with children*".

The variable occupation was used in studies I and IV based on an open-ended question on the occupation of respondents in the survey. The responses were categorized into the groups "*managerial*", "*office*", and "*manual*" occupations.

3.6.2. The most limiting symptom

In study I, the variable *the most limiting symptom* was created based on the question in the survey where PwMS were asked what they thought was the most limiting of the MS symptoms they experienced, as an open-ended question. On the basis of categorizations used in the American National MS Society,[330] on the MS clinical guidelines on symptom management for the United Kingdom,[331] and through discussion among authors, the most limiting symptoms PwMS experienced were categorized into 9 groups. These include 1) *no limiting symptom*; 2) *bladder, bowel or sexual dysfunction; 3) tiredness or fatigue*; 4) *mood problems/depression*; 5) *sensory and pain symptoms*; 6) *dysphonia, dysarthria, or dysphagia*; 7) *ambulation problems*; 8) *vision impairment* and 9) *others (such as medication-related symptoms, unspecified, and psychological implications of MS).* The nine groups were further categorized into three as 1) *no limiting symptom*, 2) *invisible symptoms* (groups 2 to 5 and 9) and 3) *visible symptoms* (groups 6 to 8).

3.6.3. Fatigue

Data on fatigue was collected in the survey that was the basis for studies I and IV. It was measured using the fatigue short-form questionnaire, which is a part of the Neuro-QoL, which comprises many different questionnaires to assess QoL in neurological disorders.[332] The fatigue short-form is made up of 8 questions, which address the following aspects on a 7-day recall period: *feeling exhausted*, *lack of energy*, *feeling fatigued*, *being too tired to do household chores*, *feeling too tired to leave the house*, *frustrations related to feeling too tired to do things*, *feeling tired and having to limit* social activities due to tiredness. The response options were *never*, *rarely*, *sometimes*, *often* and *always* scored from 1 to 5.[333]

The data collected on the fatigue short form was summarized out of a total score of 40 and this score was transformed into a fatigue T score using the Neuro-QoL scoring guide for fatigue with a reference clinical neurology (with Parkinson's Disease, MS, epilepsy, stroke or Amyotrophic Lateral Sclerosis) population, with a mean of 50 and standard deviation (SD) of 10. Fatigue T score ranges from a minimum of 29.5 to 74.1.[332,334] The fatigue T score constructed in this manner was used in study I and IV as a covariate.

3.6.4. Health-related quality of life

In the present thesis, HRQoL has been used as one of the covariates in studies III and IV. HRQoL was measured using the generic instrument of the EuroQol Group, the EQ-5D (the three-level response version), which contains two parts in the assessment of HRQoL. The first part questions on five dimensions: *mobility*, *self-care*, *usual activities*, *pain/discomfort* and *anxiety/depression*. The response options in the three-level questionnaire are *no problems*, *some/moderate problems*, and *severe/extreme problems*.[335] In both studies, the responses were summarized into a single value called the EQ-5D index using the Swedish experience-based EQ-5D-3L value set constructed through the time trade-off approach.[336] In study III, HRQoL in the two years (before or after) DMT start was measured based EQ-5D-3L data collected in the SMSreg. In study IV, the data on current HRQoL is collected in the survey among PwMS in 2021.

3.6.5. Comorbidity assessment (Rx-Risk comorbidity index)

Data on comorbidity among PwMS was employed in studies II and III of the thesis using records on drugs dispensed to PwMS using the Swedish Prescribed Drug Register and complementary data on cancer diagnosis from SCR. The approach used to determine comorbidity was the modified Rx-Risk comorbidity index. It uses the list of prescription drugs dispensed to individuals to map comorbidities linked to the drugs. Rx-Risk comorbidity index has 46 categories of comorbidities.[337] Rx-Risk comorbidity index has been compared with other comorbidity measures and employed in studies among PwMS as well.[337–339] In the two studies, additional data on cancer diagnosis were used in the Rx-Risk comorbidity index calculation.

3.6.6. Expanded Disability Status Scale score data

In all the four studies, EDSS score has been employed as an important covariate in relation to outcome variables in each of them. In studies I and IV, the latest EDSS score in the last/previous three years was identified from the linked SMSreg data. In study II, the earliest EDSS score from the time of MS onset was used based on EDSS data in the SMSreg. In study III, EDSS score closest to the time of DMT start/decision was used in the analysis. Across the studies, EDSS scores were grouped into 0-2.5, 3-5.5 and 6-9.5 increasing in level of disability.

3.7. Data analysis

Several data analysis methods were employed in the different studies ranging from descriptive statistics to sequence analysis.

3.7.1. Descriptive statistics

In all the four studies, descriptive statistics were performed. In study I, the socio-demographic and clinical variables, restrictions PwMS experienced in the four domains of life and the most limiting symptoms were presented descriptively through tables and figures providing proportions and means. In studies II and III, socio-demographic and clinical characteristics of PwMS were presented using proportions and means. In addition, the distribution of study cohorts (MS onset during 2007 to 2010 in study II and DMT start during 2014 to 2015 in study III) by MS onset/treatment start years across socio-demographic and clinical variables were analyzed through chi-square, one-way analysis of variance, independent t-test, and Mann-Whitney U test. Furthermore, using the same analyses, the distribution of socio-demographic and clinical variables across DMT use trajectories were also assessed. In study IV, the distribution of socio-demographic characteristics across DMT use categories, WAS across DMT use categories and WAS across DMT use categories at different levels of disability were presented using proportions and means.

3.7.2. Multinomial logistic regression analysis

In studies I and III, multinomial logistic regression analyses were performed to assess the association of different predictors with the outcome measures in the studies. In study I, it was used in assessing the association of socio-demographic and clinical variables with self-reported restrictions in the work, family, leisure activities and contact with friends/acquaintances domains. In study III, on the other hand, multinomial logistic regression was used to assess the association of demographic, clinical and HRQoL variables with DMT use trajectories (clusters). Multinomial logistic regression analysis is an extension of the binary logistic regression when the outcome variable has more than two categories, which requires the outcome variable to be nominal (unordered).[340]

In some additional analyses, binary logistic regression analyses have been used in study I where the restrictions reported among PwMS were categorized into two (yes/no).

3.7.3. Log-multinomial regression analysis

In study II, the association of socio-demographic and clinical variables with DMT use trajectories (clusters) was assessed. The results of this analysis are expressed in terms of risk estimate - relative risk ratio. Similar to multinomial logistic regression analyses, log-multinomial regression analyses are used for nominal outcome variables with more than two categories.[341]

3.7.4. Linear regression analysis

In study IV, linear regression analysis was used to assess the association of DMT use with work ability as well as the association of different socio-demographic, clinical and self-reported health variables with work ability. In these analyses, the amount of variation in WAS explained by each of these variables was determined using R squared statistic. Adjusted models were also constructed sequentially starting from DMT use by adding socio-demographic, clinical and self-reported health variables.

3.7.5. Sequence analysis

In studies II and III, sequence analysis was used in identifying trends in DMT use over long-term follow-up of 10.5 and 5 years respectively. Sequence analysis is an approach employed in studies of longitudinal trends of categorical states. It has its origins in the study of DNA sequences and has been used in the social sciences studies for about four decades, particularly, in life course research with highly increasing interest and use in recent times. In sequence analysis, visual depiction of the sequence, timing and duration of the categorical states provides comprehensive and readable information on the trends of the DMT states.[342]

In both studies (II and III), the sequence analysis followed three main steps. In the first step, the sequence objects/states were prepared. In the case of study II, DMT use states were prepared for each 6-month period from MS onset until 10.5 years later. The states include *Before treatment*, *high-efficacy*, *non-high-efficacy* and *no DMTs*. In the case of study III, a similar approach was followed in preparing the sequence object. Specifically, the DMT states were *high-efficacy*, *non-high-efficacy* and *no DMT*. These states were constructed for each 3-month period over the 5-year follow-up from treatment start/decision.

In the second step of the process, the sequences of DMT use across all PwMS were assessed on how similar they are using dissimilarity analysis. Among the most common approaches in the dissimilarity analysis is optimal matching. It originated in the field of biology in the study of DNA sequences and later used in social sciences research of career trajectories and life course studies. In the assessment of dissimilarity through optimal matching the 'cost' associated with insertion, deletion or replacement of a state in one sequence to become the same as another is evaluated. This will provide information on the closeness/similarity of the compared sequences.[343–345] In both studies (II and III), the optimal matching approach was used in determining the level of similarity/dissimilarity across DMT use sequences.

In the third step of the sequence analysis, based on information from the previous two steps on the sequences and their dissimilarity, the overall trends/trajectories in DMT use over the follow-up times in both studies were clustered into four groups in each of the studies. The methods employed in

clustering the different sequences involved a combination of hierarchical clustering and partitioning around medoids (PAM) approaches.[345,346]

In the hierarchical clustering, the grouping begins from individual sequences being paired with other similar sequences and sequentially two closely related groups get combined into one reducing the number of groups.[346] In the case of PAM, clustering begins from specific starting points the number of which are determined beforehand (e.g. to get 4, 5 or 6 clusters). On the basis of the starting points (called medoids), sequences with the lowest distance from the medoids are identified. In the second step, a process of 'swapping' follows where the medoids are replaced with each of the other observations to check for the best possible (weighted distance globally and from the closest medoids) clustering. The process stops when improvement is no longer possible.[346] In studies II and III, the hierarchical approach was used to identify starting points, which were inputs for the clustering process via the PAM method.

The final number of clusters chosen in both studies were determined through the quality assessment approaches, which assess whether the observations in each cluster remain coherent and the distances in the clusters are reproducible. One such quality assessment method is Average Silhouette's Width that is used commonly and provides cutoff values to categorize the structural quality of clusters. These include: *0.71-1.00*: *strong structure*; *0.51-0.70*: *reasonable structure identified*; *0.26-0.50*: *the structure is weak and could be artificial* and <=*0.25*: *no structure*.[346]

On the basis of the clustering approaches and quality assessment of the resulting ones, statistically as well as their clinical plausibility, four clusters were identified in both studies.

3.7.6. Generalized estimating equations

In study II, the association between DMT use clusters and SADP were assessed using generalized estimating equations (GEE) with a negative binomial distribution. The model was adjusted for several demographic and clinical variables in a stepwise manner. The GEE model was used considering the skewed distribution of the SADP data and to account for within subject correlation over the follow-up time. The GEE addresses these issues as it can handle data with repeated measures, which are likely to be correlated. It is described as an extension of generalized linear models for clustered or repeated outcome variables.[347,348]

3.7.7. Zero-inflated negative binomial regression

In study III, the association between DMT use clusters and SADP were assessed using zero-inflated negative binomial (ZINB) model. It allows modeling of data with a large proportion of zeros as was the case in study III and has two component models one of which is the binary logistic regression model, which assesses the odds of an event occurring/not occurring (e.g. SADP days vs. no SADP days). The second component is the negative binomial regression where the count of the event (e.g. the number of SADP days) is modeled.[349]

Most of the analyses in the four studies were performed using R versions 4.1.1 and 4.1.2 (R foundation for statistical computing, Vienna, Austria). In studies II and III, the Rx-Risk comorbidity index variable was created using analysis conducted in SAS software version 9.4 (SAS Institute Inc, Cary NC, USA). The log-multinomial regression analysis in study II was performed using Stata Software version 17.0 (Stata Corp, College Station, Texas 77845, USA).

3.8. Ethical considerations

In the context of the present thesis, a number of ethical issues warrant consideration, which include privacy of individuals in the studies. An important issue is the balance between the risk of breach of privacy and the benefit from conducting the studies, which could contribute towards improving the care provided to PwMS. In ensuring that privacy and anonymity of individuals in the studies were protected, pseudonymized data was employed in addition to ensuring its security with access only to authorized individuals. These measures contribute to substantially decrease the risk of violation of privacy. Regarding the benefits, the present thesis contributes by adding to the knowledge in the area of restrictions PwMS experience, the treatment provided to them and the associated work ability and work disability. This will provide considerable benefit in the care provided to patients and in understanding the implications of the disease and its treatment in the work and other aspects of the lives of PwMS, for possible further studies and planning interventions.

Two of the studies in the present thesis (I and IV) were conducted based on pseudonymized data from a survey among PwMS linked to individual level data from two nationwide registers (SMSreg and LISA). The project was approved by the Swedish Ethical Review Authority (Dnr 2020-04996) and respondents provided informed consent by answering the questionnaire. The survey was conducted by Statistics Sweden that was also responsible for data linkage. The researchers received only anonymized data. Studies II and III were conducted using pseudonymized individual level data from the SMSreg linked with data from five other nationwide registers. The project was approved by the Regional Ethics Review Board in Stockholm (Ethics approval numbers: Dnr/ref no. 2007/762-31; 2009/23-32; 2009/1917-32; 2010/466-32; 2011/806-32; 2011/1710-32; 2014/236-32; and 2016/1553-32) and the Swedish Ethical Review Authority (Dnr 2021-06441-02). As data were obtained from pseudonymized register data, consent from participants was not applicable.[350]

The linkage of the microdata from the registers was conducted by Statistics Sweden, which keeps the linkage key. No data in PIN, names, addresses, etc. were delivered to the researchers. Furthermore, results are only presented at group level in order, to ensure that individual data will not be traced back, cells in tables with very few individuals (n<5) were combined into bigger groups.

In the nationwide clinical register SMSreg, unlike the other nationwide registers participants have the possibility to opt out of the registry and to have their data deleted according to the Patient Data Act (SFS2008:355).[351] Patients are to receive this information when they join the registry.

4. Results

The socio-demographic characteristics of the PwMS and findings of the individual studies are summarized in this section.

4.1. Socio-demographic and clinical characteristics of people with multiple sclerosis

In the four studies included in the present thesis, women accounted for a majority of the PwMS ranging from 69 to 71% across the studies, with a sex ratio of women to men ranging between 2 and 2.5. The mean age among PwMS ranged from about 34 years old in study II to 40 years in the studies (I and IV), based on the survey in 2021 (Table 4).

Table 4: Demographic and clinical characteristics of people with multiple sclerosis across the four studies

Variable	**Study I** Self-reported restrictions (n=4052) %	**Study II** DMT use and SADP (n=1923) %	**Study III** Recent DMT use and SADP (n=1395) %	**Study IV** DMT use and work ability (n=4103) %
Sex				
Women	71.4	70.4	69.2	71.1
Men	28.6	29.6	30.8	28.9
Age in years (mean (SD))	40.4 (7.2)	34.2 (9.4)	38.9 (10.6)	40.3 (7.2)
Education				
Up to high school	37.4	60.1	56.6	38.6
University/ college	62.1	39.9	43.1	61.4
Type of MS				
RRMS	92.8	82.0	85.6	93.3
PPMS	1.6	6.6	5.7	1.6
SPMS	4.5	9.1	8.0	5.1
Missing	1.1	2.4	0.6	0.0
EDSS score				
0-2.5	66.0	73.2	66.9	65.6
3-5.5	11.1	18.7	16.6	12.0
6-9.5	3.1	2.8	3.7	3.5
Missing	19.8	5.3	12.8	18.9

DMT: disease-modifying therapy; **EDSS:** expanded disability status scale**; MS**: multiple sclerosis; **PPMS**: primary progressive multiple sclerosis; **RRMS**: relapsing remitting multiple sclerosis; **SADP**: sickness absence and/or disability pension; **SD**: standard deviation; **SPMS**: secondary progressive multiple sclerosis

While the majority of PwMS in studies I and IV had university/college education, they accounted for about two-fifths to less than half in the studies of DMT use trajectories and their association with SADP (studies II and III) (Table 4).

Among the clinical characteristics, in all the four studies the RRMS type of MS accounted for the large majority of the PwMS ranging from 82 to 93% of the total PwMS in each study. Progressive forms of MS accounted for the remaining with higher proportions of PwMS with SPMS. The EDSS score shows that most of the PwMS had mild levels of disability ranging from 66 to 73% across the studies (Table 4).

4.2. Self-reported restrictions across domains of life (study I)

Findings of study I cover the restrictions PwMS experienced in the different life domains overall and at different levels of disability. In addition, findings on the factors associated with reporting restrictions in the work and private domains of life are presented.

4.2.1. Self-reported restrictions and the most limiting symptoms

Among the total 4052 PwMS, the majority reported some level of restriction (*moderate* or *severe*) in the work (64.3%), family (61.3%), leisure activities (68.9%) and contact with friends/acquaintances (59.7%) domains of their lives. Severe restriction accounted for a substantial amount in all the domains (work: 35.7%, family: 38.7%, leisure activities: 31.1% and contacts with friends/ acquaintances: 40.3%), with nearly a third to two-fifths of the PwMS experiencing them (Figure 1 and Table S1 in study I).

Among the symptoms which were considered the most limiting by PwMS, tiredness/fatigue took a lion's share of the proportion with half (49.5%) of the PwMS identifying it as the most limiting. Tiredness/fatigue and other symptoms of generally invisible nature were reported by a majority of the PwMS as the most limiting. Among the relatively more visible symptoms, problems of mobility accounted for the highest proportion (14.3%). A considerable proportion (12.8%) of the PwMS also reported not experiencing any limiting symptoms (Table 5, figure 2 in study I).

Table 5: The most limiting symptoms people with multiple sclerosis experienced

Type of the most limiting symptom	The most limiting symptom	n	%
Invisible	Tiredness/fatigue	2006	49.5
	Sensory/pain	279	6.9
	Mood problems/depression	112	2.8
	Bladder/bowel/sexual dysfunction	92	2.3
	Others*	43	1.1
Visible	Ambulation problems	579	14.3
	Vision	110	2.7
	Dysarthria/dysphonia/dysphagia	8	0.2
No limiting symptom		517	12.8
Missing		306	7.6
Total		4052	100.0

*medication-related symptom, unspecified, psychological implications of MS symptoms

Fatigue was also assessed through NeuroQoL's Fatigue short form and its pattern in relation to self-reported restrictions showed a gradient with more frequent fatigue symptoms reported among PwMS with more severe restrictions due to MS. Overall, PwMS reported experiencing problems in some frequency (*rarely* to *always*) across the fatigue short-form items in all the four domains - work, family, leisure activities and contact with friends/acquaintances. The reporting frequency of different fatigue symptoms by severity of restrictions (*no*, *moderate* and *severe*) were comparable across the four domains. Among PwMS reporting no restrictions, the lowest proportion reported experiencing fatigue related issues of having to limit social activity, frustration due to feeling tired and being too tired to leave the house. This finding was shown in a comparable manner across the four domains (Figure 5).

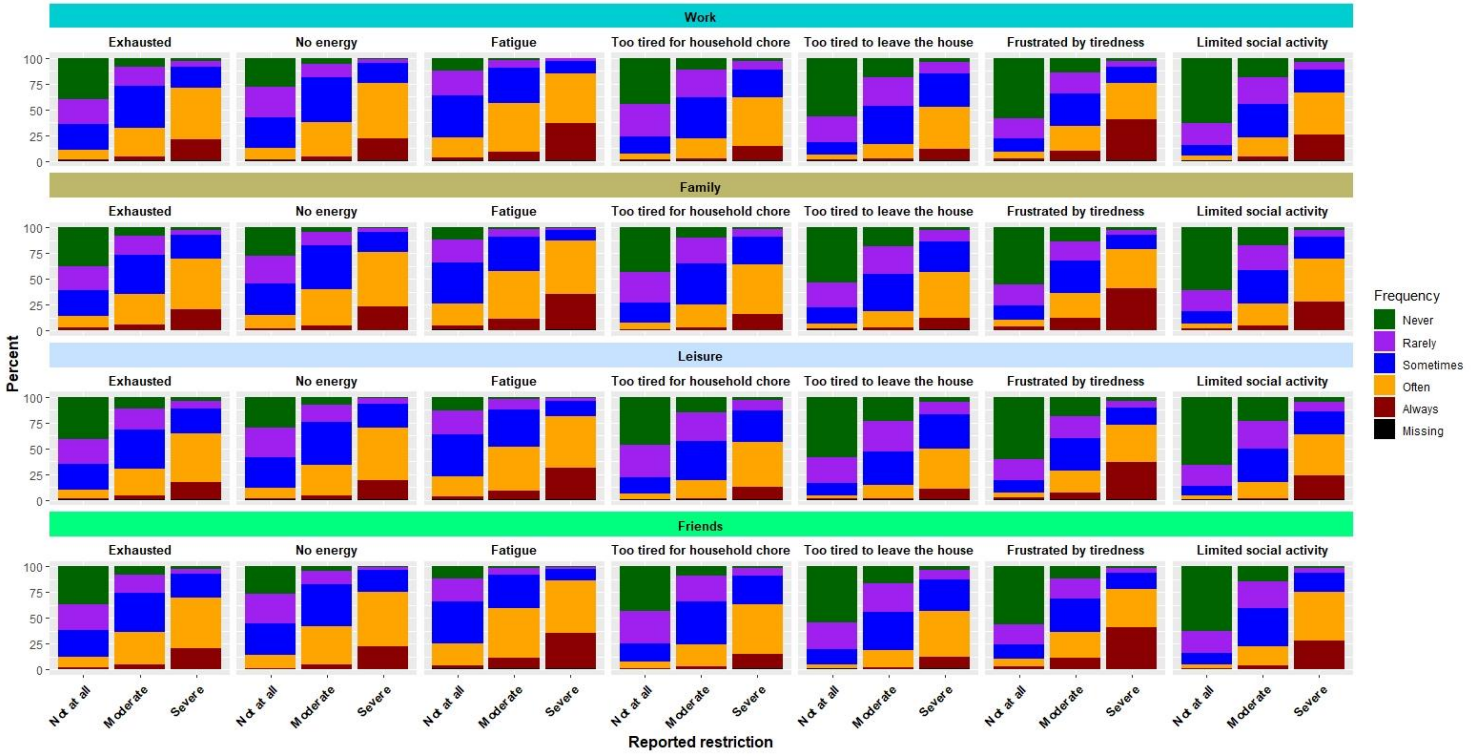

Figure 5: Problems reported on the NeuroQoL Fatigue short form item by severity of self-reported restrictions among people with multiple sclerosis

4.2.2. Self-reported restriction among people with multiple sclerosis with Expanded Disability Status Scale score of zero

The proportion of severity of restrictions reported by PwMS also showed a gradient across disability (EDSS score) levels with more restrictions reported among PwMS with more severe levels of disability (Figure S3 in study I).

Of the total 4052 PwMS, 929 (22.9%) had an EDSS score of zero indicating there was no neurological disability. The reporting of restrictions among this group showed a similar pattern but of lower proportions than PwMS in the mildest disability category (EDSS score=0-2.5). However, considerable proportions of restrictions were still noted among PwMS with EDSS scores of zero. While PwMS in the range of 55.5% (leisure activities) to 60.6% (friends/acquaintances) reported no restrictions, considerable proportions also reported severe restrictions ranging from 7.9% in the family domain to 11.5% in the leisure activities domain (Figure 4 in study I).

4.2.3. Factors associated with self-reported restrictions in work and private life

Regarding possible factors associated with reporting restrictions in the work domain, findings of the adjusted multinomial logistic regression analyses showed that progressive forms of MS, reporting invisible most limiting symptoms and higher EDSS scores were strong predictors of restrictions in the work domain at *moderate* or *severe* level. Lower education, rural residence and older ages were also associated with increased odds of self-reported restrictions. The odds of reporting restrictions were, however, lower among men and PwMS with no limiting symptoms (Figure 6, Table 3 in study I).

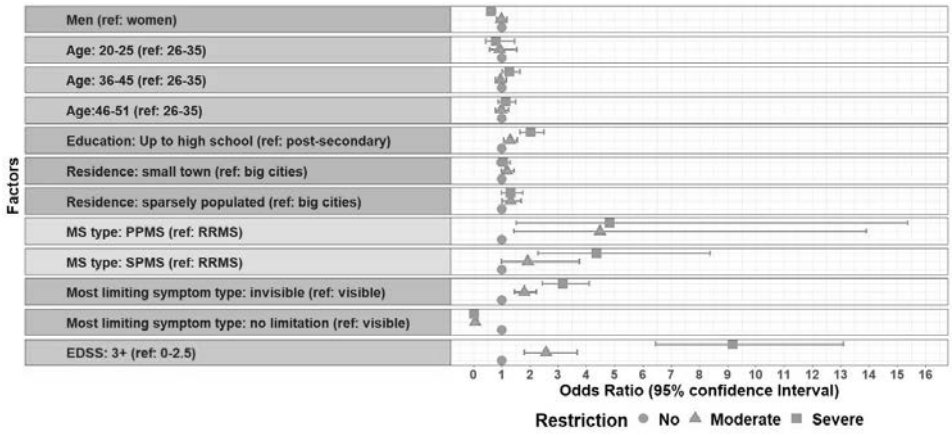

Figure 6: Predictors of self-reported restrictions among people with multiple sclerosis in the work domain

Similar analyses in the private life domain (the combination of family, leisure activities and contact with friends/acquaintances) showed that similar predictors as in the work domain were associated with reporting restrictions in the private life domain. Accordingly, older age, lower education, progressive forms of MS, higher EDSS scores and invisible limiting symptoms predicted higher odds of reporting restrictions. On the other hand, younger PwMS, men, and those with no limiting symptoms had lower odds of reporting restrictions in the private life domain.

The analysis of potential predictors of self-reported restriction in work life in the subsection of PwMS with no neurological disability (EDSS score=0) showed that there were no statistically significant differences by age and sex. Among PwMS with lower education and with invisible limiting

symptoms, the odds of restrictions were higher than in their respective references. Among PwMS with no limiting symptom, it was less likely to report restrictions than PwMS with visible limiting symptoms (Figure 7 and Table S7 in study I).

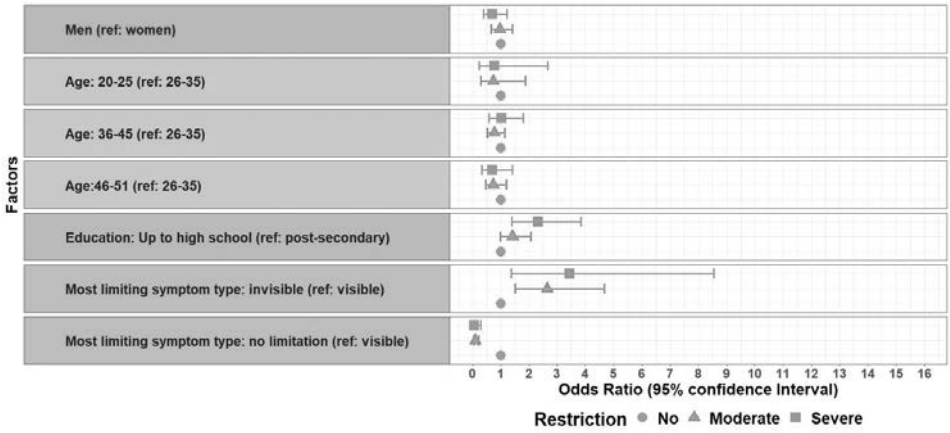

Figure 7: Predictors of self-reported restrictions among people with multiple sclerosis with expanded disability status scale score of zero, in the work domain

A similar analysis in the private life domain, conducted using binary logistic regression, showed comparable findings to the work domain. Higher odds of restrictions were observed among PwMS with lower education and those with invisible limiting symptoms, while lower odds were shown among those with no limiting symptoms than those with visible symptoms (Table S8 in study I).

4.3. Disease-modifying therapy use and work disability (studies II and III)

The findings on the DMT use trends and the associated SADP days assessed in studies II and III are presented below.

4.3.1. Disease-modifying therapy use trajectories

In studies II and III, trends in DMT use over long-term follow-ups were conducted using sequence analysis. Besides the high-efficacy, non-high-efficacy and no DMT states in both studies the state '*before treatment*' was also used in study II as the follow-up in that study started from the time of MS onset. The follow-up of the sequences covered 10.5 and 5 years in studies II and III respectively. In study II, the DMT states were followed on a six-month basis and in study III the DMT states were followed on a 3-month basis over the follow-up duration. The sequence analysis showed that a total of 916 unique sequences were found over the 10.5 years. In study III, 233 unique sequences were found over the 5-year follow-up (Table 6).

In both studies, four clusters were chosen in the sequence analyses based on cluster quality statistics and clinical plausibility. The individual clusters common to the two studies were *long-term non-high-efficacy DMTs* (hereafter *long-term non-high-efficacy*), *escalation to high-efficacy DMTs* (hereafter *escalation*) and *discontinued/no DMTs* (hereafter *discontinuation*) (Table 5). The clusters unique to each study were *delayed start and escalation to high-efficacy DMTs* (hereafter *delayed start*) in study II and *long-term high-efficacy DMTs* (hereafter *long-term high-efficacy*) in study III.

In study II, PwMS in the *long-term non-high-efficacy* cluster accounted for the highest proportion (39.2%) followed by those who escalated to high-efficacy DMTs accounting for nearly a third (31.2%) of the PwMS. On the other hand, in study III, PwMS in the *long-term high-efficacy* cluster accounted for the largest proportion with over two-fifths (41.0%) of the total. This was followed by the *long-term non-high-efficacy* cluster covering over a third (34.6%) of the PwMS. The *discontinuation* cluster accounted for 14.2% in study II and 8.5% in study III.

In terms of the duration in each of the DMT use states, in study II an average PwMS spent 4.5 out of the 10.5 years on the non-high-efficacy DMTs and 2.8 years on high-efficacy DMTs. On the other hand, in study III, half (2.5 years) of the total five years of follow-up were spent on high-efficacy DMTs followed by 2.1 years on non-high-efficacy DMTs (Table 6).

Table 6: Disease-modifying therapy use states and clusters of disease-modifying therapy use trajectories in studies II and III

Variable	Study II DMT use and SADP	Study III Recent trends in DMT use and SADP
DMT use states	Before treatment, high-efficacy DMTs, non-high-efficacy DMTs, no DMTs	High-efficacy DMTs, non-high-efficacy DMTs, No DMTs
Duration of follow-up	10.5 years from MS onset	5 years from DMT start/decision
Time periods	6 months	3 months
Number of sequences	916 unique sequences	233 unique sequences
Number of clusters	4	4
Clusters (%)	▪ Long-term non-high efficacy DMTs (39.2%) ▪ Escalation to high-efficacy DMTs (31.2%) ▪ Delayed start and escalation to high-efficacy DMTs (15.4%) ▪ Discontinued/no DMTs (14.2%)	▪ Long-term non-high-efficacy DMTs (34.6%) ▪ Long-term high-efficacy DMTs (41.0%) ▪ Escalation to high-efficacy DMTs (15.8%) ▪ Discontinued/no DMTs (8.5%)
Mean duration in each DMT use state	▪ Before treatment (1.8 years) ▪ High-efficacy DMTs (2.8 years) ▪ Non-high-efficacy DMTs (4.5 years) ▪ No DMT (1.4 years)	▪ High-efficacy DMT (2.5 years) ▪ Non-high-efficacy DMTs (2.1 years) ▪ No DMT (0.5 years)

DMT: disease-modifying therapy; **SADP**: sickness absence and/or disability pension;

The four clusters identified in the two studies are shown below as distribution plots, indicating the DMT use trajectories over the follow-up years. The plots provide the general/aggregated patterns of DMT use trajectories identified in each study (Figure 8, Figure 9).

The features of the four clusters identified in study II are shown in the distribution plot showing that the majority of the areas in each cluster covered by the characteristic DMT use state or transition from one to another (Figure 8). The same is shown in the distribution plot of the clusters in study III with the main features depicted in the overall distribution of the DMT use states in each cluster (Figure 9).

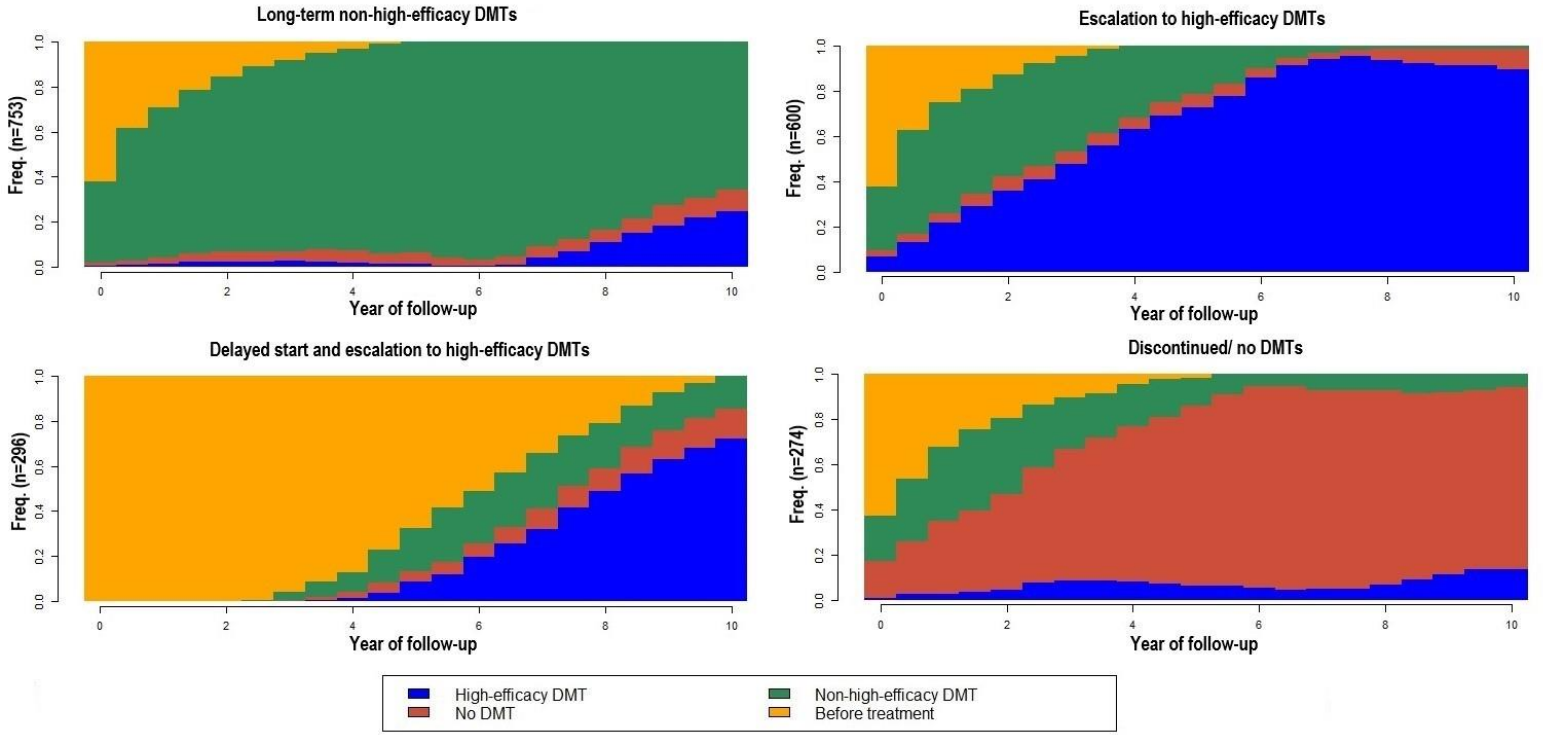

Figure 8: Sequence distribution plot of clusters of disease-modifying therapy use trajectories among PwMS in study II

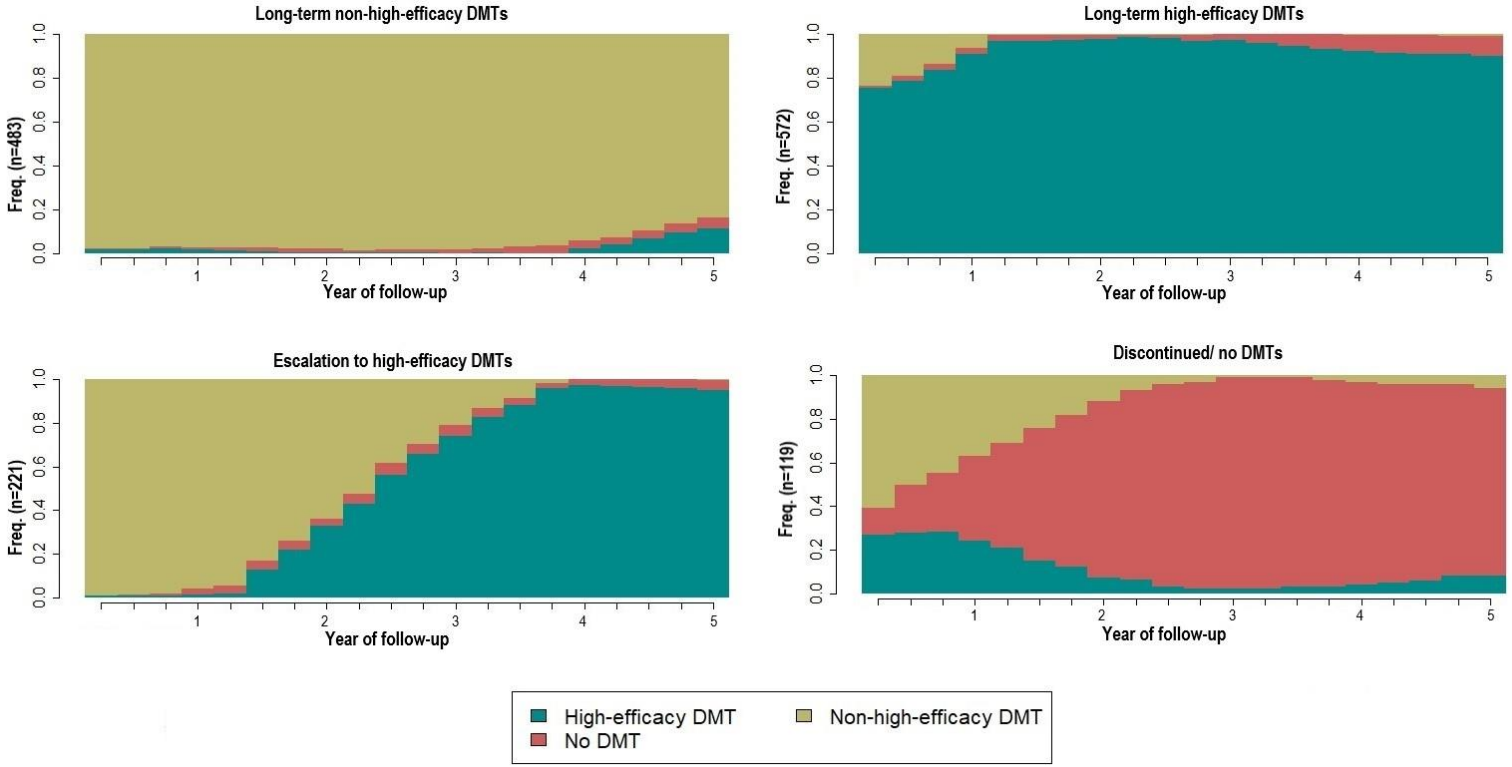

Figure 9: Sequence distribution plot of clusters of disease-modifying therapy use trajectories among PwMS in study III

4.3.2. Factors associated with clusters of disease-modifying therapy use trajectories

In terms of the factors associated with belonging to a specific cluster of DMT use trajectories, in both study II and study III, age, type of MS, EDSS score and frequency of DMT switches were significantly associated. In contrast, sex was not associated with belonging to a specific cluster in either study (Figure 10, Figure 11). In study II, in particular, while younger age (18-25 years) was associated to higher relative risk of being in the *escalation* cluster, the reverse was true in older ages (36+ years) (Figure 10).

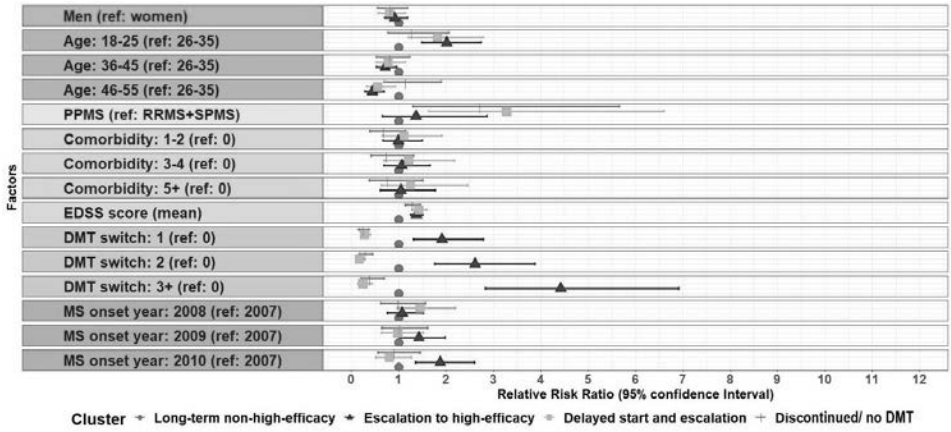

Figure 10: Log-multinomial regression analysis on factors associated with clusters of disease-modifying therapy use

Higher risk of belonging to the *delayed start* and *discontinuation* clusters was shown among individual with PPMS. On the other hand, higher EDSS score predicted increased risk of being in the other three clusters than in the *long-term non-high-efficacy* one. Frequency of DMT switch was associated with increased risk of being in the *escalation* cluster while at lower risk of being in the *delayed start* and *discontinuation* clusters. The year of MS onset was also associated with cluster belonging, MS onset in 2009 and 2010 having a higher risk of being in the *escalation* cluster (Figure 10).

In study III, higher odds of younger PwMS belonging to the *long-term high-efficacy* cluster and the reverse among older PwMS was also shown. Similarly, higher odds of belonging to clusters other than *long-term non-high-efficacy* were observed among PwMS with progressive type MS and higher EDSS scores. Frequency of DMT switch was associated with higher odds of being in the *escalation* cluster and lower odds of being in the *long-term high-efficacy* cluster. Lower HRQoL was associated with being in the *long-term high-efficacy* cluster (Figure 11).

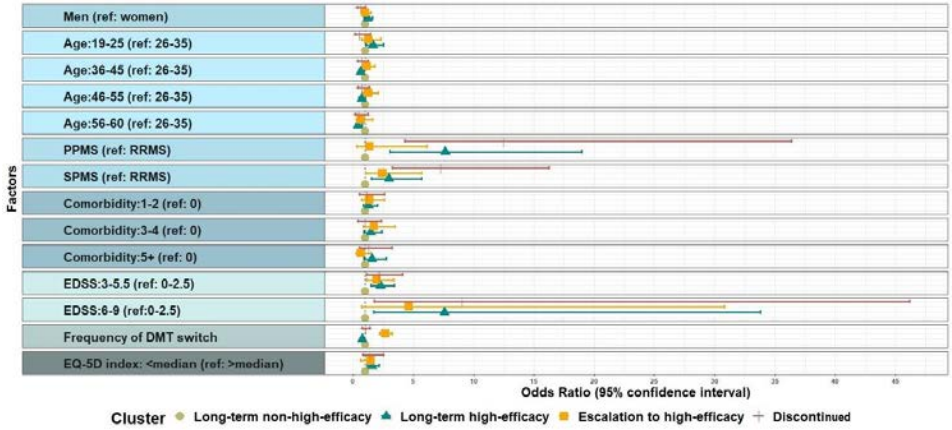

Figure 11: Multinomial logistic regression analysis on factors associated with clusters of disease-modifying therapy use

4.3.3. Work disability across disease-modifying therapy use clusters

In both studies, relatively lower SADP days were observed among PwMS on *long-term non-high-efficacy DMTs* in comparison to *long-term high-efficacy/escalation* and *discontinuation* clusters (Figure 2 in study II and Figure 2 in study III). In study II, in particular towards the end of the 11.5 years of follow-up, PwMS in the *long-term non-high-efficacy* cluster showed lower SADP days than the other clusters. In the final GEE model (adjusted for socio-demographic and clinical characteristics), a similarly lower adjusted mean SADP days were observed among PwMS in the long-term *non-high-efficacy* cluster compared to those in the *escalation* and *discontinuation* clusters (Figure 2 in study II). The figure below shows the changes in the SADP days estimated through GEE at different steps of adjustment by demographic and clinical variables (Figure 12).

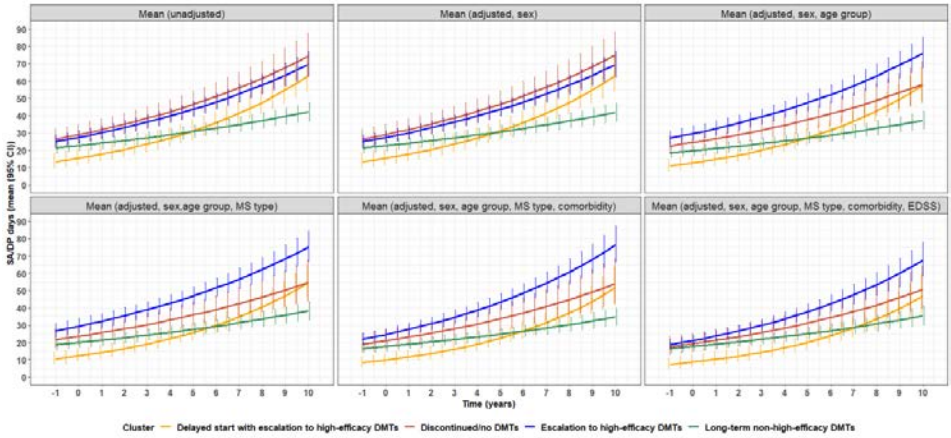

Figure 12: Generalized estimating equations models adjusted mean sickness absence and/or disability pension days at different stages of adjustment.

Overall, the GEE adjusted mean SADP days showed relatively higher values among PwMS in the *escalation* and *discontinuation* clusters over the follow-up, in the unadjusted model. The stepwise adjustments showed the SADP days in the *discontinuation* cluster decreased leaving SADP among

PwMS in the *escalation* cluster with the highest SADP days towards the latter half of the follow-up (Figure 12). In study III, similar to study II, the mean SADP days showed lower values among PwMS in the *long-term non-high-efficacy* cluster. On the other hand, PwMS in the *long-term high-efficacy* and *discontinuation* clusters had relatively higher mean SADP days over the follow-up. Looking at the two years before DMT start/decision, an increase in SADP was observed among PwMS in all the four clusters with a steepest slope among PwMS who would later initiate high-efficacy DMTs. Following the treatment start time, the same group of PwMS showed the largest decrease in mean SADP days in the second (Y_1) and third (Y_2) years of follow-up (Figure 2 in study III).

The findings of ZINB in the adjusted binary logistic regression component (for demographic, clinical and HRQoL variables) were comparable to the descriptive findings that higher odds of being on SADP were observed among PwMS in the *long-term high-efficacy* and *escalation* clusters in several of the follow-up years (Figure 3 in study III). In the adjusted negative binomial component of ZINB, more SADP days were noted among PwMS in the *escalation* cluster in two of the follow-up years, while the others remain comparable in the duration of SADP days (Figure 4 in study III).

4.3.4. Work disability across disease-modifying therapy use clusters by diagnosis

In study III, trends in SADP days across the four clusters over the seven follow-up years were further assessed by determining SADP days due to MS and those due to other diagnoses. Among the subgroup of PwMS with SADP due to MS, the SADP days were lower in the years before the start of treatment but increased in the time since treatment start. The overall trends in SADP days, however, were largely similar to the main analysis. Accordingly, PwMS in the *long-term non-high-efficacy* cluster had lower SADP days particularly in the time since treatment start, while SADP days comparable across clusters were found in the years prior to treatment start (Figure 13).

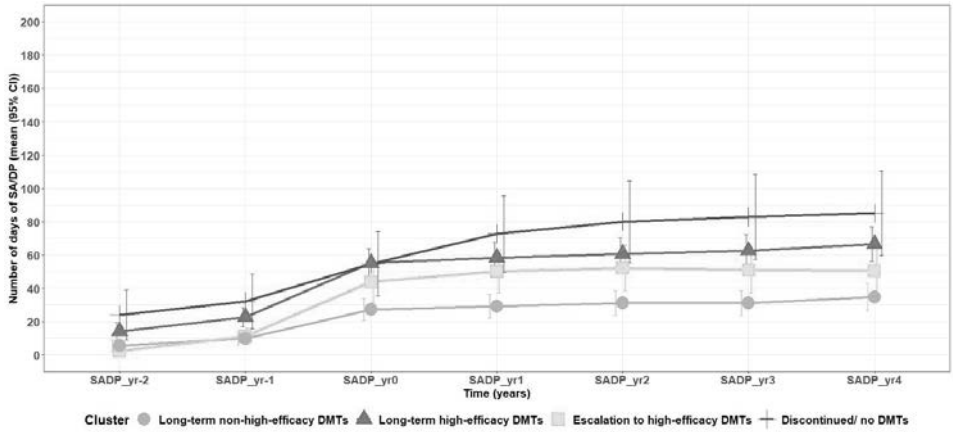

Figure 13: Trends of mean sickness absence and/or disability pension days per year among PwMS due to multiple sclerosis diagnosis (n=633) [SADP: sickness absence and/or disability pension]

The SADP days attributed to diagnoses other than MS showed some increase in all the four clusters until the time of treatment start. Following treatment start, the mean number of SADP days decreased considerably in the second (Y_1) and third (Y_2) years in all the four clusters. This was followed by a stable trend in the remaining follow-up years. The trend across the four clusters reflects largely the main analysis. However, the difference across the clusters was observed to be much lower with no clear differences in SADP days (Figure 14). When comparing the mean number of SADP days in the MS-specific and non-MS diagnoses, the latter started at higher mean SADP days (ranging from about

20 to 40 days) than the MS-specific SADP (ranging between 0 and just over 20 days). However, in the overall follow-up, SADP days due to MS reached higher mean SADP days (up to 80 days towards follow-up end) than SADP days due to other diagnoses (up to just over 60 days around treatment start) (Figure 13, Figure 14).

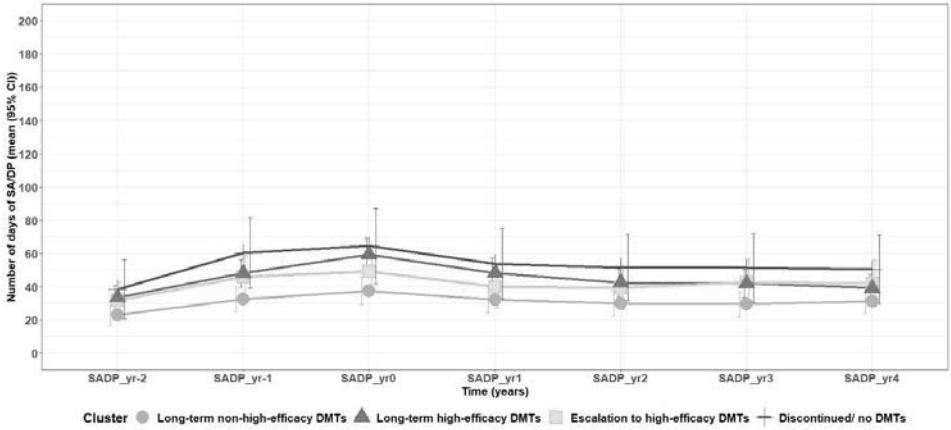

Figure 14: Trends of mean sickness absence and/or disability pension days per year among PwMS due to other diagnoses (n=764) [SADP: sickness absence and/or disability pension]

4.4. Disease-modifying therapy use and work ability (study IV)

The findings of the study on the association between DMT use and work ability, including the different determinants of work ability, is presented below.

4.4.1. Disease-modifying therapy use and work ability score

Overall, the distribution of DMT use within the last two years showed that more than two-thirds (67.6%) of the total 4103 PwMS in the study were on high-efficacy DMTs and more than a quarter (28.4%) were taking non-high-efficacy DMTs. The PwMS not taking DMTs accounted for 3.9% of the total.

In the categorized form, 16.3% of the PwMS reported *excellent* (WAS=10) levels of WAS while more than a third (37.0%) reported *good* (WAS=8-9) level of WAS. *Moderate* (WAS=6 to 7) and *poor* (WAS=0 to 5) levels of WAS were reported by 22.8 (WAS=8 to 9) and 24.0% of the PwMS respectively (Figure 1 in study IV).

The mean overall WAS was 6.92 (SD=2.8) [median=8.0]. The mean WAS was the highest (7.40) among PwMS on non-high-efficacy DMTs while those on high-efficacy DMTs had a mean of 6.74 and PwMS not taking DMTs had a WAS of 6.45. Median WAS, however, was the same (8.0) across DMT use categories.

Looking at WAS in relation to the individual DMT, the findings showed that it was comparable across PwMS on individual DMTs. Specifically, WAS among PwMS taking dimethyl fumarate and interferons, both non-high-efficacy DMTs, had a higher mean WAS than PwMS not taking DMTs and those on rituximab, a high-efficacy DMT (Figure 15).

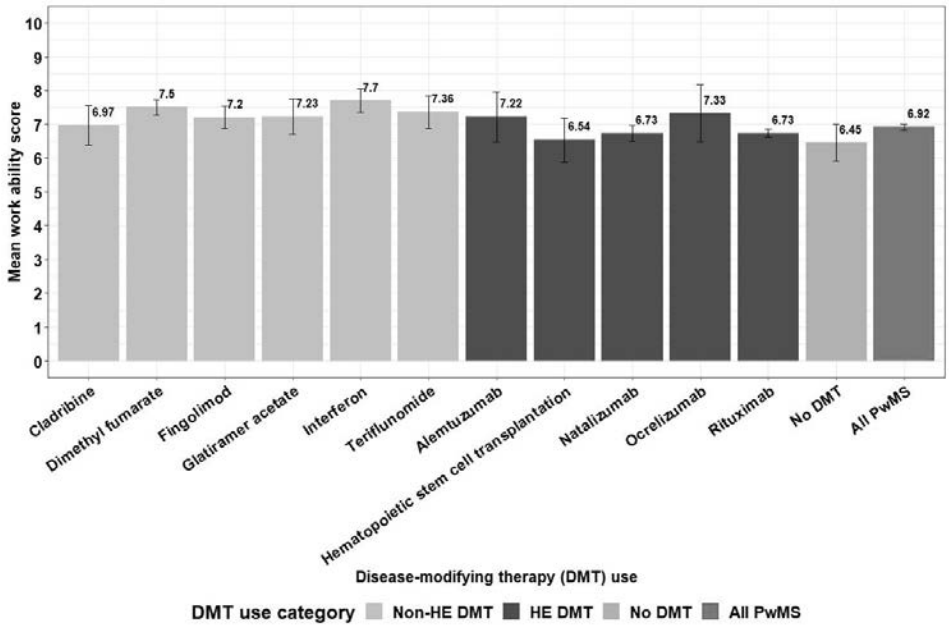

Figure 15: Disease-modifying therapy use (individual drugs) and work ability score among people with multiple sclerosis

4.4.2. Factors associated with work ability score

In terms of the association of DMT use with work ability, in the unadjusted model, PwMS on non-high-efficacy DMTs had higher WAS than PwMS on high-efficacy DMTs and no DMTs. However, only around 1% of the variation in WAS was explained by DMT use. Demographic (sex, age, education, occupation), clinical (pediatric onset MS status, type of MS, EDSS score, time from MS treatment start, long-term disease or disability) and self-reported health (fatigue T score, HRQoL in the form of EQ-5D) variables showed significant associations with WAS in univariable models. Among them, HRQoL (31.59%), fatigue (28.31%), EDSS (22.66%) and occupation (22.59%) explained the highest amount of variation in WAS. In contrast, sex, age, living area and the time since treatment start each explained less than 1% of the variability in WAS (Table 2 in study IV).

After adjustment by demographic, clinical and self-reported health variables, WAS remained higher among PwMS on non-high-efficacy DMTs than in those on high-efficacy DMTs. Among socio-demographic factors, younger age, higher education and managerial job were associated with higher WAS while older age (in comparison to 26-35 years old) and having no occupation was associated with lower WAS. Among clinical variables, EDSS score remained significant and higher scores were associated with lower WAS. In addition, long-term disease was also associated with lower WAS. The self-reported health variables fatigue and HRQoL were also strongly associated with WAS with lower scores at more severe fatigue levels and higher scores with higher HRQoL (Figure 16).

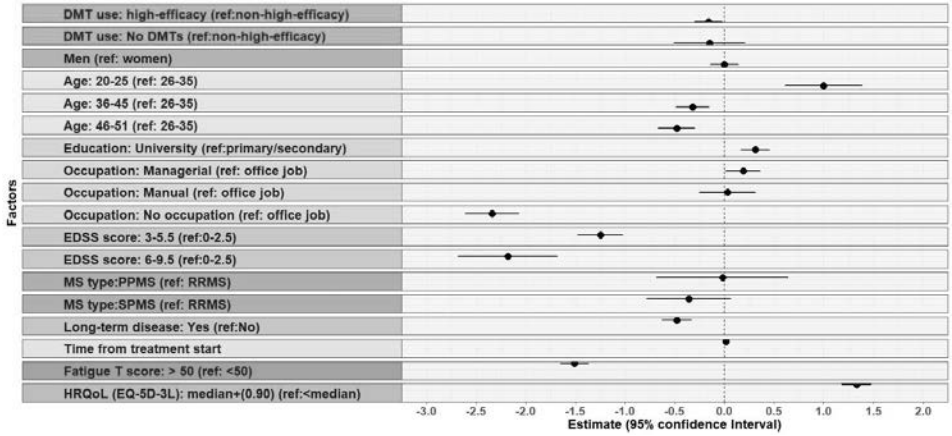

Figure 16: Linear regression analysis the association of disease-modifying therapy use and work ability on factors associated with clusters of disease-modifying therapy use

5. Discussion

The present thesis, in the four studies, explored the restrictions PwMS experienced in their work and private lives due to MS as well as their views on their ability to work in the context of DMT use and other demographic, clinical and self-reported health factors. Furthermore, MS treatment strategies over long periods of time and the corresponding trends in SADP days were also studied.

5.1. Main findings of the studies

Findings of the four studies in the thesis showed that substantial proportions of PwMS experienced restrictions in their work and private lives (study I). Moreover, four clusters of DMT use (in each of study II and study III) were observed over long-term follow-ups with relatively lower SADP trends among those who were in the *long-term non-high-efficacy* cluster. Furthermore, PwMS who were on treatment with non-high-efficacy DMTs showed higher levels of work ability with occupation, disability and HRQoL among the most important factors associated with it (study IV).

In study I, PwMS indicated their experience of restrictions, which affected them in different life domains: their work, family, leisure activities, and contacts with friends/acquaintances. Out of 4052 PwMS, around two-thirds experienced restrictions of *moderate* to *severe* levels in the four domains of life. A substantial proportion of the PwMS also reported severe restrictions in the range of nearly one-third (31.1%) in the leisure activities domain to two-fifths (40.3%) in the contacts with friends/acquaintances domain of life. Among the symptoms PwMS found to be the most limiting, fatigue was the most common, being reported by half of the PwMS in the study. Furthermore, the study showed the presence of restrictions experienced by PwMS despite there being no neurological disability (EDSS score of zero). This was shown by the over two-fifths of the PwMS with EDSS score of zero reporting some form of restrictions across the four domains and around one-tenth reporting even severe restrictions. The factors associated with reporting restrictions in the work and private life domains showed that progressive forms of MS, invisible limiting symptoms and higher EDSS scores, were strongly associated with self-reported restrictions.

The long-term DMT use trajectories among PwMS and the associated trends in SADP days were investigated in studies II and III using cohorts from different times. In each study, through sequence analysis, four clusters of DMT use trajectories were chosen as representing the DMT use over time. Three of the four clusters in each study similar trajectories (study II vs. study III); *long-term non-high-efficacy* (39.2% vs. 34.6%)*; escalation* (31.2% vs. 15.8%) and *discontinuation* (14.2% vs. 8.5%). While the *delayed start cluster* (15.4%) formed the fourth one in study II*, long-term high-efficacy* was identified in study III (41.0%). The findings on factors significantly associated with belonging to one of the clusters, in each of the studies, revealed similar variables such as age, type of MS, EDSS score, and frequency of DMT switches.

Across DMT use trajectories, in both studies, lower mean SADP days were found among PwMS in the *long-term non-high-efficacy* cluster than in the *long-term high-efficacy*/*escalation* or *discontinuation* clusters, for the majority of the follow-up. In study II, towards the end of the follow-up, SADP days among PwMS in the *long-term non-high-efficacy* cluster was lower than in the other clusters according to the GEE model when adjusted for different factors. In study III, relatively higher mean SADP days in the *long-term high-efficacy* and *discontinuation* clusters were shown than in the *long-term non-high-efficacy* cluster over the follow-up. However, the decrease in SADP since

treatment start time was the largest among PwMS in the *long-term-high-efficacy* cluster. Descriptive findings were also reflected in the outcomes of ZINB regression analysis.

In study IV, the association of DMT use and work ability was assessed and it showed that the majority (67.6%) of the PwMS were on high-efficacy DMTs. Over half of the PwMS reported excellent (16.3%) or good (37.0%) levels of WAS. The mean overall WAS among the PwMS was 6.92, with the highest WAS (7.4) among PwMS on non-high-efficacy DMTs and 6.74 and 6.45 among those on high-efficacy and those not on DMTs, respectively. Unadjusted linear regression analysis results also showed higher WAS among PwMS on non-high-efficacy DMTs. However, DMT use explained very little of the variation in WAS with less than 1%. Although almost all the demographic, clinical and self-reported health variables tested in univariable models showed statistically significant association with WAS, HRQoL (31.59%), fatigue (28.31%) and EDSS score (22.66%) explained the largest variation in WAS. After adjustment by the demographic, clinical and self-reported health variables, PwMS on non-high-efficacy DMTs remained with higher WAS than those on high-efficacy DMTs. Age, education, occupation, EDSS score, long-term disease, fatigue and HRQoL were significantly associated with WAS.

5.2. Discussion of the findings in the context of the literature

Here, the findings in each of the studies are discussed in in comparison with other studies in the literature.

5.2.1. Self-reported restrictions and associated factors

The negative implications of MS on the work and private lives of PwMS was shown in study II with around two-thirds of individuals experiencing restrictions in the different domains. Similar findings on such implications of MS on work have been reported in the literature from different perspectives. In a narrative review, work terminations, voluntarily or involuntarily, as well as reduced work participation have been discussed as important challenges to employment among PwMS.[287] The impact of MS on productivity, in the form of absenteeism and presenteeism, has also been discussed in different studies, indicating the increasing impact with more severity.[352–354]

The majority of PwMS also experienced restrictions in private life domains, including family life, leisure activities and contact with friends/acquaintances. In terms of the impact of MS on family life, previous studies from Belgium and Sweden have also shown the restrictions related to participating in activities at home.[93,355] Furthermore, the negative impacts of MS on relationships/family have also been described.[92,166] A related systematic review showed there were some negative psychological impacts among children of parents with MS and increased responsibility and reduced social relationships among adolescents with parents with MS.[356] The cited studies also described the important negative implications of MS on leisure activities such as outdoor activities, including walking and gardening as well as interactions with friends and other social contacts, which include social events.[92,93,355]

In the work and private life domains, the odds of reporting severe restrictions were significantly different between women and men with higher odds of reporting restrictions among women. This result is somewhat unexpected because of the higher occurrence of PPMS and the general faster disease progression among men.[76,357] One possible explanation could be difference between women and men in self-reporting of health in general.[358,359]

The variables which were strongly associated with restrictions in the work as well as private life domains included invisible limiting symptoms, EDSS score and the type of MS. Similarly, variables such as fatigue, EDSS score and progressive MS have been associated with work difficulties in the literature.[293] Similar to the findings in the present thesis, invisible symptoms such as fatigue and depression have been shown to lead to more health distress in comparison to visible ones among PwMS.[98] In another study, PwMS stressed the impact of invisible symptoms, such as fatigue, cognitive problems and pain, on their health unlike physicians who assumed visible ones such as ambulation were more impactful on the QoL of PwMS.[360]

Among the invisible symptoms, fatigue has been shown as the commonest in the present thesis, which is the case in several other studies as well.[292,361,362] In these studies, it has been shown that it affects the work life and productivity of PwMS.[292,361,362] Similar to study I, several studies have shown that fatigue was associated with various negative outcomes due to MS. These include employment status[94]; work difficulties (in relation to ability, productivity and activity)[259,293]; and limitations on daily activities in terms of personal, professional and social lives.[92] A systematic review of factors related to work difficulties among PwMS also showed that fatigue was a consistently common symptom across different studies. It has also been shown to have implications on occupation, increased likelihood losing a job, reducing working hours as well as changing work activities.[363]

The type of MS, namely progressive forms, were associated with increased odds of reporting restrictions. This has been shown in other studies as well where progressive forms of MS were associated with increased likelihood of job difficulties,[259] and higher levels of unemployment in comparison to those with RRMS.[293] A similar study on employment in MS also showed that progressive forms of MS were more likely among unemployed PwMS.[364] Among PwMS with progressive forms of the disease, the continuous neurodegenerative effect and the limited treatment options could contribute to the larger impact on ability to work among PwMS.

The association of disability levels with restrictions reported by PwMS showed that at higher EDSS scores the odds of self-reported restrictions were higher and even higher in more severe levels of disability. The important association of EDSS score with problems in the work and private life domains has also been discussed in different studies. These include studies reporting on the association of higher EDSS scores with increased job difficulties.[259] The association of higher EDSS scores with work difficulties, described as unemployment, reduced working hours or cessation of job, was reported to be strong in a literature review on MS related work problems.[293] In another literature review, disability level in terms of EDSS score has been shown to be consistently associated with different forms of outcomes in several studies.[363] Among these is the association of higher disability levels with unemployment and incapability to work.[363–366] The findings in the present thesis as well as the compared literature show the consistent predictive ability of EDSS score on different outcomes related to work and private life.

Although EDSS score is a strong predictor of several outcome measures in the context of MS, including restrictions individuals experienced as shown in the present thesis, it has some limitations too. These include its focus on gait, limitations in measuring cognition and problem of inter-rater variability, among others.[367] The difference in the views of patients on physical disability in comparison to physicians has also been discussed, where PwMS put relatively less weight on it. In addition, physical disability measures like EDSS were not correlated with overall HRQoL measures indicating a limitation in measuring aspects important to PwMS.[368] In the present thesis, the findings among PwMS with EDSS score of zero (neurologically normal) showed that there were still

substantial proportions of restrictions reported among PwMS. This, as indicated above, could relate to the fact that EDSS score may not fully capture possible implications the disease might have on PwMS in their work and private life. This can be emphasized in the fact that around 10% of the PwMS among the neurologically normal PwMS still reported severe restrictions in each of the four domains of life. In a study conducted among PwMS considered neurologically normal with EDSS score of zero, in comparison to healthy controls they showed sub-threshold deficits in balance and upper extremity coordination.[369] The above findings and comparisons indicate the need for incorporating patient-reported measures to get a more complete picture of how MS affects the lives of individuals in different aspects. There have been discussions of patient-reported versions of EDSS to improve on the time-consuming nature of measurement through the EDSS and to be able to do it outside clinic settings as well.[370]

5.2.2. Disease-modifying therapy use and work disability

In studies II and III, sequence analysis revealed the long-term trajectories of DMT use. While the follow-up started from the onset of MS in study II, treatment start/decision time was the starting point in study III. The two approaches allowed a broad picture of the trends and timing of treatment with DMTs. The studies also covered three-month and six-month periods of DMT use to capture varying levels of details of DMT use changes. The sequence analyses in the two studies resulted in different numbers of unique sequences with 916 in study II and 233 in study III. The more than twice time length of follow-up in study II, the four DMT use states (including '*before treatment*') vs. three in study III, as well as the larger study population in study II may have contributed to the larger number of unique sequences reported in study II. A similar study from France on DMT usage among 4474 PwMS, over a six-year follow-up period, reported 2481 unique sequences, which could relate to its large sample size, higher number of states (n=5), and 1-month state periods, which could have contributed to observing much larger number of unique sequences.[371]

In both of the studies, four clusters of DMT use trajectories were chosen, three of which were comparable across the two studies. These include the *long-term non-high-efficacy*, *escalation*, and *discontinuation* clusters. The clusters *delayed start* in study II and *long-term high-efficacy* in study III were the fourth clusters in the respective studies. The largest proportion of PwMS in study II were in the *long-term non-high-efficacy* (39.2%) cluster while long-*term high-efficacy* (41.0%) cluster was the largest in study III. This could partly show the changes in the treatment strategy over time with increased initiation of high-efficacy DMTs in comparison to earlier cohorts (study II). The *escalation* clusters in study II and study III also show the increasing shift from initiating non-high-efficacy to high-efficacy DMTs over time with the proportion of PwMS in the *escalation* cluster decreased from about a third in study II to about 16% in study III. However, besides the general treatment shift to initiation of high-efficacy DMTs, the shorter follow-up time in study III (5 years) may have also contributed to relatively lower proportions PwMS in the *escalation* cluster. The trend in the *discontinuation* cluster also showed lower proportion (half of that in study II) of PwMS in study III, which could also be related to the shorter follow-up in study III and increasing options of effective DMTs for MS.

Comparing the present findings on DMT usage with the French study, there were three similar clusters of DMT use with both of the studies in the present thesis. The French study also determined four clusters of DMT use over the follow-up among PwMS who initiated some form of DMTs in 2010. The *first line DMTs* cluster in the French study relates generally to the *long-term non-high-efficacy* cluster in both studies in the present thesis. The cluster *not treated* in the French study compares with

the *discontinuation* clusters in the two present studies. The cluster *second line DMTs,* which contained PwMS treated briefly with first line DMTs and switched to second line DMTs, was comparable to the *escalation* clusters in the two studies in the thesis. Despite the similarities with the findings from the French study, some differences were also evident. The DMTs categorized into second line groups were somewhat different from the present thesis in number and type. While fingolimod is grouped as a non-high-efficacy DMT in studies II and III, it was a second line DMT in the French study. In addition, many DMTs grouped as high-efficacy DMTs in the present thesis were not in use/in the categorizations in the cited study. This could be associated with the availability and type of DMTs used in the context of different health systems.[371] In relation to this, while it was not part of the *off-label use* cluster in the French study, rituximab has seen highly increased usage since the early 2010s in Sweden becoming common in MS treatment.[236]

Of the different demographic, clinical and HRQoL variables assessed to determine their association with membership to one of the four clusters in the two studies in the thesis, age showed significant associations. While younger PwMS were more likely to belong to the *escalation* and *delayed start* (study II) as well as *long-term high-efficacy* (study III) clusters, older PwMS were less likely to be in those clusters. The findings in the two studies are comparable to the French study where PwMS in the *not treated* cluster were older than those in the first line DMTs cluster. Also similar to the present thesis, PwMS in the *second line DMTs* were younger than those in the *first line DMTs* cluster.[371] In line with the above findings, it is shown in the literature that the effectiveness of DMTs, including high-efficacy ones, decreases with age and the risk of adverse effects related to high-efficacy DMTs increases.[372,373] It is discussed also that MS becomes progressive in older ages for which treatment options are currently limited.[374]

In the two studies, overall, progressive forms of MS were associated with belonging to the clusters other than *long-term non-high-efficacy*. These associations point to the approaches attempted at treating progressive MS by initiating high-efficacy DMTs, switching from non-high-efficacy to high-efficacy DMTs and in cases the treatments are not working, discontinuing, which also points to the limited options in the treatment of progressive MS disease courses.[375] Recently, the options such as ocrelizumab for PPMS and siponimod and cladribine for SPMS have become available.[375–377] The limited understanding of progressive MS is said to have contributed to the relatively few options of DMTs in its treatment.[378] In the French study the use of off-label drugs in the treatment of MS were indicated to be likely for the progressive forms of MS, which is comparable to some extent to the present thesis in that they represent the limited treatment options.[371]

Higher levels of disability (higher EDSS scores) have also been associated with belonging to the three clusters other than the *long-term non-high-efficacy* cluster in both studies. The higher likelihood of initiation of high-efficacy DMTs among PwMS with more severe disability, in study III, goes in line with the increasing shift toward early initiation of high-efficacy DMTs.[233,234,236] The higher likelihood of belonging to the *escalation* cluster also relates to the increasing shift to treatment with high-efficacy DMTs and their increasing availability.[192] Escalation to higher efficacy DMTs preceded by higher EDSS scores has also been shown by a study in Italy.[377] In the French study, a pattern similar to the present thesis was reported with higher odds of belonging to clusters *not treated* and *off-label use* compared to being in the *first line DMTs* cluster at higher disability levels. However, being in the *second line DMTs* cluster did not show significant difference by levels of disability.[371]

In the assessment of SADP days across the different DMT use clusters in both studies II and III, lower SADP days were noted among PwMS in the *long-term non-high-efficacy* clusters. The lower and

generally stable trends of SADP in these clusters over the follow-up could reflect milder disease as well as effective and tolerable use of DMTs among the PwMS. Accordingly, in both studies, significant proportions of PwMS in the *long-term non-high-efficacy* cluster were described as healthier with lower levels of disability, and in study III in particular, at higher HRQoL. A study in Denmark showed that among PwMS with clinically stable disease, the risk of losing income and being on DP was low.[379]

In studies II and III, relatively higher SADP days were observed in the clusters *escalation*/*long-term high-efficacy* and *discontinuation*. In the case of the *escalation* cluster, the higher and increasing SADP days over the follow-up in both studies could be attributed to worsening of the disease, which may have necessitated escalation to high-efficacy DMTs. Similarly, the high number of SADP days in the *discontinuation* clusters in both studies could also be reflective of worsening of the disease leading to discontinuation of DMTs. Overall, the baseline health status in these clusters were relatively worse than those in the *long-term non-high-efficacy* cluster with higher disability levels. This could also explain the relatively higher SADP days in the clusters. In line with this, previous studies showed the higher cost and SADP among PwMS at higher levels of disability.[22,380]

The SADP days across the clusters were also adjusted for several demographic and clinical variables using the regression model GEE in study II, which showed that SADP days among PwMS in the *long-term non-high-efficacy* cluster remained lower than in the *escalation* and *discontinuation* clusters towards the second half of the follow-up. This showed that the lower SADP days in the *long-term non-high-efficacy* cluster remained, with possible effective and tolerable treatment experienced among a substantial section of the PwMS who also had largely better baseline health status. The SADP results in study III adjusted for demographic, clinical and HRQoL variables through the ZINB model showed comparable findings to study II expressed in the odds of occurrence of SADP, which were higher among PwMS in the *long-term high-efficacy* and *escalation* clusters, while differences in the number of SADP days were relatively less evident.

In study III, additional analysis focusing on the assessment of whether the diagnosis for SADP was MS or others showed that SADP due to MS diagnosis were lower in the years prior to treatment start with increasing trend after, while the trends across clusters being comparable to the main analysis. A comparable trend of MS specific SADP days were shown in a previous study in Sweden.[294] In contrast to MS-specific SADP, SADP days due to other diagnoses were higher prior to treatment start but decreased in the time after that. The different trends in SADP by diagnosis could potentially relate to the attribution of possibly MS symptoms to other diagnoses when they occurred before establishing an MS diagnosis.

5.2.3. Disease-modifying therapy use and work ability

In the assessment of the association between DMT use and work ability, a mean WAS of 6.9 and a median of 8 was reported out of the maximum (10). To the best of the literature search performed, there are no studies which assessed the association between DMT use and WAS. However, the overall WAS in the present thesis was comparable with findings in studies from the Netherlands, where WAS was measured as part of studies among PwMS on self-reported occupational functioning (median=8.0) and capability set for work (mean=7.1, median=8.0).[258,260] The median WAS in the present thesis was slightly higher than another study in the Netherlands (median WAS=7) where disability level was somewhat higher (EDSS 2 vs. 1.5 in the present thesis). The mean WAS among PwMS in the present thesis was lower than the general population in Sweden (mean WAS=8.25) in a study of the validity

of WAI and its individual items in the general population.[381] Similarly, in another study on work impairments among PwMS, workers with MS showed lower WAI than among controls.[259]

Across DMT use categories, PwMS on non-high-efficacy DMTs reported higher mean WAS (7.40) than those on high-efficacy DMTs (6.74) and those not taking DMTs (6.45). The higher WAS in the non-high-efficacy DMTs group compared to the high-efficacy DMTs was statistically significant both in the unadjusted and adjusted linear regression models controlled for demographic, clinical and self-reported health variables. Despite the significant association with WAS, DMT use explained very little of the variation in the WAS of PwMS (R squared =1.24%). The relatively higher WAS among PwMS taking non-high-efficacy DMTs could relate to milder forms of MS. This was shown by the better disability profile in terms of EDSS score in the high-efficacy and no DMT use categories. So, the severity of MS which may have led to the choice of specific level of efficacy of DMT was also reflected in the WAS the PwMS reported. In studies II and III, similar findings were noted where PwMS in the *long-term non-high-efficacy* cluster had lower SADP days compared to other trajectories of DMT use, also partly attributed to milder forms of MS leading to the use of non-high-efficacy DMTs. In order to make direct comparisons on the impact of DMTs on WAS, studies comparing DMTs/groups head-to-head and with reference groups would provide clearer information. A study from Australia on the impact on employment of three groups of DMTs, indicated larger improvement in work attendance and productivity among PwMS on high-efficacy DMTs.[297] Another study from Sweden also showed the impact of DMTs, together with adjusted work environment, in the improvement of work ability among PwMS.[304]

Although almost all the variables in the analysis showed statistically significant associations with WAS, the amount of variation explained were different. Sex and age among other variables each explained very little of the variation in WAS (<1%). However, though not specifically on an MS population, a study on the association of chronic health conditions and work ability among workers in the Netherlands showed that sex was associated with WAS as an adjustment variable.[382] This, however, was not the case in other studies from Germany, which did not find significant difference in WAS by sex among workers and cancer survivors.[254,383]

Age also explained very little of WAS in the present thesis, which could partly be related to the relatively young group of PwMS in study IV, ranging from mainly young to middle age PwMS. More generally, age has been described to have a fairly linear association with work ability.[251] Findings from a Swedish study also associated older age with decreased ability to work using a different measure of work ability (Work Ability Questionnaire-Multiple Sclerosis).[304]

Occupation was among the variables that explained a large proportion of the variation in WAS. In the final adjusted model, PwMS with managerial job had higher WAS than those with no occupation. The long-term impact of MS and the possible difficulty to readapt after long absence from work could be attributed to the lower WAS among PwMS with no occupation. In line with this, unemployed PwMS had been shown to have more comorbidity and higher levels of disability.[384] These variables were associated with WAS in the present thesis and such clinical variables have previously been shown to affect occupational status.[289,385]

The EDSS score was one of the important variables associated with WAS in the present thesis, explaining substantial level of variation in WAS. EDSS score has been associated with adverse work outcomes in a number of studies where work difficulties were higher at higher disability levels.[259,293,354,386] However, the study from the Netherlands showed EDSS was not associated with WAS, which could possibly be related to their focus on RRMS, the inclusion of employed PwMS, exclusion

based on comorbidity and/or the relatively lower sample size (n=173).[260] The present thesis also showed a gradient in WAS by EDSS score with lower WAS at higher disability levels.

The self-reported health variables, fatigue and HRQoL (EQ-5D index), explained the largest proportions of variation in WAS in the univariable linear regression analyses. Similar findings were reported in the study from the Netherlands.[260] The strong association of HRQoL with WAS could indicate that individuals' views of their own health influences how they rate their work ability and at the same time their work ability could inform their views of own health. A similar strong association between self-reported health and WAS was reported by a study in Sweden of whiplash associated disorders.[387] The areas the EQ-5D instrument covers such as mobility, pain and anxiety/depression, among others, indicate possible impact on work ability.[335]

Fatigue is a very common and impactful symptom among PwMS, as also shown in study I. The association of the impact of fatigue with problems of unemployment, reduced working hours as well as higher number of SADP days has been described in the literature.[96,384,388] The fact that fatigue explained a large proportion of the variation in WAS could be due to its coverage of important aspects related to work ability such as its implication on both physical and cognitive functioning.[389]

5.3. Methodological considerations

In terms the methodological aspects, the four studies in the thesis were conducted based on microdata linked across several national registers as well as a large survey among PwMS. The use of survey data for studies I and IV provided a vital aspect to the thesis by including the perspectives and experiences of PwMS regarding the restrictions they face on a daily basis, in their work and private lives, as well as how they perceive their ability to work. As demonstrated in some of the findings in the two studies, self-reported data of PwMS added crucial perspective/information to the register-based data. This is among the important strengths of the present thesis.

Several data sources, the six nationwide register datasets, were linked across to provide comprehensive data addressing different aspects: demographic, socioeconomic, clinical and social insurance data, among others, for studies II and III. This demonstrates the richness of the data in covering a broad range of variables, when considering different potential factors in relation to the outcome variables. These high-quality nationwide datasets contribute to the validity of the studies in the thesis.

The longitudinal design, employed in two of the studies in this thesis, also highlights the importance of showing long-term trajectories in DMT use and SADP days contributing to the literature with rich data ranging from 5 to 11.5 years across the studies. In addition to the longitudinal design, the length of follow-up in studies II and III demonstrate crucial advantages of the present thesis with more than ten and seven years of follow-ups. Such long follow-ups helped provide clearer information on DMT use strategies as well as SADP trends.

Another strength in the present thesis concerns the use of sequence analysis in two of the studies to show the trends in DMT use over the above mentioned long-term follow-ups. Sequence analysis provided the advantage of presenting the trajectories of DMT use in a visually illustrative manner. The transitions in DMT use states (e.g. from a non-high-efficacy to a high-efficacy DMT or from a non-high-efficacy DMT to no DMT) are generally visible which gives an opportunity to see changes over time in the overall sample and in each DMT use trajectory after clustering. Overall, the possibility of

observing sequences of DMT use over time using sequence analysis adds an important advantage in gaining insight on treatment strategies as shown in the present thesis.

The above discussed strengths contribute to higher internal validity of the studies in the thesis, which concerns the accuracy of the measurements made in a specific study population. This depends on how much random error and biases are handled or controlled. Another aspect of validity, external validity concerns the generalizability of the findings to the broader population outside the study context.[390] The issues of biases such as selection, information and confounding are discussed below in the context of the studies in the present thesis.

Selection bias could result from any error that affects the selection of participants or from possible factors determining study participation. Selection bias leads to differences in the association between exposure and outcome variables between participants and non-participants.[391] In the present thesis, the studies included were conducted based on data from different national registers with high coverage rates. This aspect contributes to minimize selection bias in the studies. In the present thesis, the selection of the study participants started from the SMSreg records, which is known to have a high coverage rate (84%). However, there still remain important issues of selection bias in this thesis. In studies I and IV, the data used came from a survey among PwMS in Sweden with a response rate of about 52%. Although this could be among the relatively higher response rates, the profile of non-respondents showed that relatively younger, more men, with relatively lower income and born outside Sweden.

Information bias occurs as a result of a systematic distortion in the collection of data on exposures or outcomes. The most common type of such a bias is misclassification bias where assignment of exposure/outcome is performed wrongly. Misclassification could be differential (nonrandom) or non-differential (random). Differential misclassification occurs when exposure or outcome is assigned differentially in the comparison groups (e.g. cases vs. controls) resulting in under or overestimation of associations in the compared groups. In the case of non-differential misclassification, the assignment of exposure/outcome is the same for the comparison groups, which might lead to the comparison groups seeming similar in terms of the measured exposure/outcome.[391] In the present thesis, the use of high-quality data from the several national registers indicates lower risk of information bias. However, there still could be some important issues of information bias across the studies in the thesis. One concerns the data on EDSS which, in all of the studies, was used from the SMSreg and had substantial levels of missing data. This presented some challenge in data analysis which could potentially constitute information bias. However, a previous validation study of the SMSreg showed that the missing data was found to be missing at random with comparable mean.[319]

Another aspect of the issue of EDSS data was the timing of measurement and their use to establish baseline data. In the present studies, to minimize exclusion of large records due to lack of EDSS data at specific time points, earliest measurements (studies II and III) or latest measurements during specified durations (studies I and IV) were taken, which could have uneven timing of EDSS data collection. A similar issue of timing of DMT use in study IV has been observed. In addition, issues with the timing of data collection and missing observations of HRQoL data were also observed in study III.

Confounding occurs when the effect of an exposure on an outcome is mixed with other risk factors for the outcome. This means it happens when these other factors are distributed differently in exposed and non-exposed groups.[392] The opportunity in the studies in the present thesis to use a broad range of

variables from the linked data provides an advantage to assess and control for confounding. However, in studies II, III, and IV, confounding by indication (indication bias) could be noted when comparing DMT use categories such as non-high-efficacy and high-efficacy DMTs in terms SADP (studies II and III) and work ability (study IV). Confounding by indication refers to the situation of a clinical indication being a confounder in the association between a treatment and an outcome variable. The lower SADP days/higher work ability among PwMS on non-high-efficacy DMTs than those on high-efficacy DMTs could possibly be attributed to the severity of the disease, which could determine whether to provide high or non-high-efficacy DMTs as a treatment. Hence, the distribution of severity across the DMT groups could be a confounder in the association between DMT use and the outcomes of SADP or WAS.

External validity refers to the extent of the possibility of applying the findings of a study to other populations than it was conducted on.[393] Considering the datasets were obtained from registers with very high coverage of the population in Sweden, the external validity of the studies in the present thesis is considerably high. However, some potential limits to the generalizability of results in the present thesis include the age limits put on the study populations, most of which focus on working age PwMS. Hence, generalizability to other populations such as pediatric or older MS populations may be limited to a certain extent. Furthermore, the data on SADP from the present thesis is based on the social insurance system and the overall context of the labor market in Sweden. So, the findings may not be fully generalizable to other systems as differences in the labor market and coverage of benefits might be different across different settings.

6. Conclusions

Overall, the present thesis provided useful insights on the activity restrictions PwMS experience in different domains of life, the trajectories of DMTs use over the long-term and their association with SADP days, as well as how DMT use categories and work ability were associated among PwMS.

A majority of the PwMS in study I reported restrictions in their work and private life domains. Substantial levels of restrictions were also reported among PwMS with no neurological disability (EDSS score of zero). Several socio-demographic and clinical factors were associated with reporting restrictions in the work and private life domains, including invisible limiting symptoms such as tiredness/fatigue.

In study II, the long-term trajectories of DMT use were assessed for over 10 years using sequence analysis with four clusters of DMT use trajectories identified. These were *long-term non-high-efficacy*, *escalation*, *delayed start* and *discontinuation* clusters. Age, type of MS and disability level were important factors associated with belonging to the clusters. The trends in SADP days across the clusters showed that PwMS in the *long-term non-high-efficacy* DMTs cluster had lower SADP days than those in the *escalation* and *discontinuation* clusters towards the end of the follow-up.

In the subsequent study, study III, four clusters of DMT use trajectories were identified. These were *long-term non-high-efficacy*, *long-term high-efficacy*, *escalation*, and *discontinuation* clusters. This revealed that initiation of long-term high-efficacy DMTs have become more common. The trends in SADP days showed that PwMS in the *long-term non-high-efficacy* cluster had lower SADP days. On the other hand, those who initiated long-term high-efficacy DMTs showed the largest improvement in SADP days since treatment start.

Finally, the association of DMT use and work ability showed that PwMS on non-high-efficacy DMTs had higher WAS compared to high-efficacy DMTs although it explained very little of work ability. Other variables such as occupation, EDSS score, fatigue and HRQoL were the most important factors associated with work ability.

7. Future research

In the present thesis, the four studies addressed important aspects, including the views of PwMS on their health and work ability. However, further research addressing the different limitations encountered in the four studies are needed.

One important area for future studies in terms of self-reported restrictions among PwMS concerns conducting studies that delve further into the nature of restrictions PwMS face in the different domains of life. This could include the specific restrictions PwMS experience in each domain, for example, whether PwMS face restriction in their work situation in relation to reduced productivity or absenteeism or other aspects. Such information, in each domain will help identify potential areas of focus for intervention.

Studies where EDSS score measurement could be made in a complete manner at consistent time points could be very useful. For example, at baseline, or at specific follow-up times. This will facilitate comparisons that are uniform in terms of time of measurement. In relation to the content of the EDSS, studies looking further into improved measures, which broaden the current physically-focused feature of the EDSS to a more complete measure which could address other relevant aspects such as fatigue.

Studies on DMT use at individual DMTs level such as the commonly used rituximab and the association with how the corresponding SADP evolves could provide useful insight. As the present thesis focused on the categorized levels of DMTs in assessing treatment strategies over time, closer looks on individuals DMTs could be more informative. Rituximab could be an important such DMT to study considering its wide use in the treatment of MS. So, further information on its use and association with SADP over long-term follow-up would provide useful information on its impact on clinical outcomes as well as work disability.

Studies where different DMT use strategies such as initiating high-efficacy DMTs vs. starting with non-high-efficacy DMTs and escalating to high-efficacy ones are compared in terms of work disability and work ability, in a head-to-head manner, could provide useful insight by avoiding indication bias (confounding by indication). Such a bias in the context of the present thesis related to the severity of MS that could determine treatment choice. Hence, this mixes up with the comparison of work ability among PwMS in different DMT use groups as baseline severity of MS also plays a role in the work ability reported by PwMS. Such a bias could also be mitigated by designing a study where PwMS in different DMT groups could be made comparable, to identify the imoact of DMTs. In addition, a longitudinal design could help reduce the bias encountered in cross-sectional studies.

Studies on the topics addressed in the present thesis with a focus on PwMS with progressive forms of MS in larger samples could provide further useful information considering their peculiar clinical courses. In the present thesis, findings in the different studies showed progressive forms of MS showed important significant associations with outcome variables despite relatively lower proportions of PwMS with these forms of MS in the studies. Hence, studies focused particularly on progressive MS by drawing larger sample sizes and investigating the questions of the DMT use trends and associated work disability as well as self-reported restrictions and work ability could provide useful information with more power, to add to the literature and for potential interventions.

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