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WORK DISABILITY, ECONOMIC SITUATION, AND SOCIETAL COSTS OF MULTIPLE SCLEROSIS IN SWEDEN

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Karolinska Institutet

Stockholm 2022

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Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-487-0
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Work disability, economic situation, and societal costs of multiple sclerosis in Sweden
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at Atrium, Karolinska Institutet, Nobels väg 12B, Stockholm, on the 6th May 2022.

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To my Nan and Poppa

ABSTRACT

Background: Multiple sclerosis (MS) affects many aspects of life and often leads to a reduction in an individual's work capacity. This reduction, referred to as work disability, may lead to the use of social protections to replace lost earnings upon being absent and societal costs from the lost production. This thesis aimed to investigate the working life and economic situation of individuals in the early stages of their MS as well as the societal costs of MS.

Methods: Four cohort studies using Swedish register data of working-aged individuals were conducted. Work disability was operationalised as net days with sickness absence (SA) and/or disability pension (DP). In **Study I**, the heterogeneity of disposable income (DI) trajectories from 7 years before to 4 years after the diagnosis year (2008-9) of 1528 people with MS (PwMS) was explored with group-based trajectory modelling. The trajectory members were characterised through use of chi^2-tests and multinomial logistic regressions. In **Study II**, common patterns of working life among 2652 PwMS diagnosed in 2008-11 were identified with sequence analysis. Sequences from 1 year before and 5 years after the diagnosis year were constructed and the members of the sequence types were characterised with multinomial logistic regressions and dependent t-tests. In **Study III** and **IV**, productivity losses were calculated with the human capital approach from the days with work disability. Healthcare costs included the costs of specialised out- and inpatient healthcare as well as dispensed drugs. Excess costs of MS were estimated by comparing the all-cause costs of PwMS with the costs of matched references with independent t-tests. **Study III** quantified the annual excess costs of 1988 PwMS and 7981 matched references without MS from 4 years before to 4 years after the diagnosis year (2010-12). Generalised estimation equation (GEE) models tested the interaction of MS and time. In **Study IV**, the excess costs from resource use in 2018 with bootstrapped 95% CIs were estimated for 2806 PwMS in Stockholm and 28,060 matched references without MS. Primary healthcare and disease modifying therapies were also costed, with analyses stratified by time since diagnosis.

Results: Seven DI trajectories were identified in **Study I**: Four increasing with different gradients (39.0% of individuals), two constantly low (50.7%), and one decreasing (10.3%). Older age profiles and higher proportions of men were observed in the increasing trajectories and higher proportions with work disability and without university education in the decreasing and constantly low trajectories. In **Study II**, six types of working life sequences were identified: Stable High Activity (48.4% of the sequences), three types with mixed activity and varying SA/DP regarding the number of days per year and timing (32.6%), Stable High SA/DP (14.5%), and Other (4.5%). Stable High Activity had the highest odds for university education. All sequence types, except Stable High SA/DP, had higher DI in the final study year than the first. In **Study III**, excess costs of MS were observed already before MS diagnosis. Mean annual excess costs of MS of 2285 SEK (95% CI: 613-3956) per person for healthcare costs and 16,310 SEK (95% CI: 8980-23,640) for productivity losses were observed four years before diagnosis. The excess costs of MS increased thereafter and were reflected in the MS and time interaction estimates. In **Study IV**, the mean annual excess healthcare costs of MS were 77,383 SEK (95% CI: 73,299-81,950) per person with MS. Primary healthcare accounted for 9% and disease modifying therapies for 48% of the excess healthcare costs. The mean annual excess productivity losses of MS were 138,121 SEK (95%

CI: 149,224-146,985) per person with MS, mostly due to DP (79%). The resource use behind the excess costs of MS differed by time since diagnosis.

Conclusions: The findings describe the economic situation of PwMS and quantify the excess societal costs of early MS. Most PwMS were in work and had increasing or stable DI in the study periods close to MS diagnosis. However, work disability was often and increasingly a part of PwMS' working life and was associated with decreasing DI trajectories or relatively low levels of DI as well as unstable working life sequences. Excess costs of MS for lost production and healthcare use were incurred already before MS diagnosis and increased thereafter. The progression of the excess costs of MS reflected different patterns of resource use with time from MS diagnosis. The increasing excess costs of MS from productivity losses began in the early stages of MS and may reflect unmet needs of PwMS regarding morbidity and work capacity which early intervention may ameliorate.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Min forskning handlar om arbetsliv och inkomster bland personer med multipel skleros (MS) samt de samhälleliga kostnaderna för sjukvård och sjukfrånvaro som uppstår till följd av MS. MS är en kronisk och ofta progressiv neurologisk sjukdom. Personer med MS kan behöva vara sjukfrånvarande med sjukpenning eller sjuk- eller aktivitetsersättning (tidigare förtidspension) om de inte kan arbeta på grund av sin MS.

Jag har studerat olika aspekter av sjukfrånvaro i Sverige bland personer som nyligen fått en MS-diagnos i fyra registerbaserade studier. I studie I observerade jag utvecklingen av disponibel inkomst under åren kring diagnosen. I studie II beskrev jag arbetslivsmönstren och deras ekonomiska konsekvenser under åren efter diagnosen. Arbetsdeltagande är inte bara viktigt för personer med MS utan också i förlängningen för samhället i stort. Därför kvantifierade jag det hypotetiska produktionsbortfallet för samhället med hjälp av antalet sjukfrånvarodagar i Studie III och IV. I dessa två studier undersökte jag de extra kostnaderna som MS medförde vilket betyder en kvantifiering av hur mycket större produktivitetsförlusterna och sjukvårdskostnaderna för samhället är på grund av MS.

Resultaten av denna avhandling visar på vikten av icke-klinisk forskning om tidig MS. Under de första åren efter MS-diagnosen fortsatte de flesta att arbeta och hade en stabil eller ökande disponibel inkomst. Sjukfrånvaro var dock ofta, och över tid en allt större del av deras arbetsliv, vilket illustreras av platta eller minskande utveckling av disponibla inkomster. De extra kostnaderna som MS medförde för förlorad produktion och ökad sjukvårdskonsumtion var synliga redan före MS-diagnosen och ökade över tid. Dessa extra kostnader tidigt i sjukdomsförloppet indikerar att personer med MS kan vara behjälpta av tidiga insatser och stöd.

POPULAR SCIENCE SUMMARY OF THE THESIS

Synopsis of the thesis

I research the working life and income of people with multiple sclerosis (MS) as well as the societal costs of MS from healthcare use and days off work. MS is a chronic and often progressive neurological disease. People with MS may require sickness absence (SA) or disability pension (DP) benefits if they are unable to work because of their MS. Receiving SA or DP benefits is referred to as having work disability. In this thesis, I studied aspects of work disability among people in Sweden around the time of their MS diagnosis in four register-based studies. In Study I, I observed different trajectories of disposable income in the years around diagnosis. In Study II, I described the working-life patterns and their financial implications in the years following diagnosis with MS. Being able to work is not only important for people with MS but also for society. I quantified the hypothetical loss of production to society using the number of days off work with work disability in Studies III and IV. In these two studies, I examined the excess costs of MS. These are a quantification of how much larger the productivity losses and healthcare costs to society are because of MS. The findings of this thesis highlight the importance of non-clinical outcomes in early MS. Importantly, in the first years after MS diagnosis, most individuals stayed in work and had stable or increasing disposable income. However, work disability was often and increasingly a part of their working life and was associated with static or decreasing disposable income trajectories. Excess costs of MS for lost production and increased healthcare use occurred before the MS diagnosis and increased with time. These early excess costs of MS indicate that early intervention and support may help people with MS.

Work disability, economic situation, and societal costs of multiple sclerosis in Sweden

Multiple sclerosis (MS) is a neurological disease that can affect many parts of everyday life. Living with a chronic disease can have far reaching consequences not only for the individual, but for their families, employers, healthcare systems, and society too. The wide-ranging symptoms of MS can pose challenges with daily activities, including work. Although work can have wider meaning than simply generating money, this thesis focuses on socioeconomic outcomes of MS. Being unable to work because of a disease can be referred to as work disability. Work disability is an important consequence of MS because the chronic and uncertain disease largely affects individuals of working ages. Therefore, MS has previously been associated with reduced earnings and changes in employment. Sickness absence (SA) and disability pension (DP) are the two social insurances in Sweden that compensate lost earnings in situations of temporary and permanent or long-term work disability. In this thesis, work disability was defined using information on days with SA and DP benefits. When an individual has work disability, this can mean a loss of earnings, but also a loss to society from the reduced productivity of the individual. The costs of lost productivity alongside the costs for healthcare use provide information on the socioeconomic burden of MS from society's perspective. This thesis combines the scientific disciplines of insurance medicine and health economics to gain further insight on the socioeconomic burden of MS.

The four studies comprising this thesis examined different aspects of the socioeconomic burden of MS using Swedish register data. The aspects studied included both work disability and incomes among the people with MS as well as the costs to society from work disability and healthcare use. Study I and II investigated the annual incomes and working life of

individuals with MS. In Studies III and IV, a societal perspective to work disability was applied. In these cost-of-illness studies, the socioeconomic burden of MS was quantified in monetary terms as the excess costs to society because of MS.

In **Study I**, annual mean disposable income (DI), earnings, and days with work disability of all working-aged people diagnosed with MS in 2008-9 were analysed from 7 years before to 4 years after their MS diagnosis year. DI is the after-tax sum of income from earnings, transfer payments such as SA and DP benefits, and capital gains. The people with MS had rather smooth and increasing trends for DI over the study. However, the year of MS diagnosis was noticeable in the dynamic trends for earnings and work disability. Seven distinct DI trajectories were identified among this group of people with MS using a method called group-based trajectory modelling. With this method, I identified subgroups or "trajectory groups" that had different patterns of DI: Two groups with consistently low and flat trajectories (50.7% of individuals); four groups with increasing trajectories (39.0%); and one decreasing trajectory (10.3%). The members of the trajectory groups had different sociodemographic and work disability profiles. The increasing trajectories had higher proportions of older-aged men. The consistently low-flat and decreasing trajectories had smaller proportions with university education and larger proportions of individuals with work disability in the diagnosis year. For many people with MS, there was stable and even increasing annual DI. DI can represent the total monetary resources available to the individuals and suggested that the social insurances were largely compensating for lost earnings. However, around 10% of people with MS were observed to have a decline in monetary resources in the years around MS diagnosis.

In **Study II**, working lives of all working-aged individuals with an MS diagnosis in 2008-11 were investigated. Sequences describing the working life of people with MS in terms of being in activity (e.g., working or studying) or with work disability were constructed from 1 year before to 5 years after the diagnosis year. I found 633 unique patterns of working life. A third of the studied individuals were in activity throughout their sequence. At lower levels of work disability, one was equally as likely to return to activity as to progress to a higher level of work disability in the next year. Being in activity became less frequent with time. There were more transitions later in the sequences, suggesting more changes and increasing diversity in working-life patterns. I identified six different types of working-life sequences from the individual sequences using cluster analysis. The types differed by the levels, timing, and patterns of activity and work disability within the sequences. All sequence types had higher DI in the final study year than the first, except for sequences with full-time SA/DP throughout. This study adds to Study I, by showing that most people in the years directly following their MS diagnosis have increasing monetary resources.

In **Study III**, I studied the excess costs of MS to society from 4 years before to 4 years after the year of MS diagnosis. For each year, healthcare use (inpatient healthcare, specialised outpatient healthcare and prescribed drugs dispensed at pharmacies) and days of lost productivity due to work disability were counted and then their costs were estimated. Excess costs of MS were calculated as the difference in the costs between all working-aged individuals diagnosed with MS in 2010-12 and those of a group of individuals without MS. I found that there were excess costs of MS already before diagnosis. The magnitude of the excess costs of MS from productivity losses was larger than from healthcare use. With time, the annual excess costs of MS became larger, with a steep increase around MS diagnosis for

both healthcare and productivity losses. People with MS had annual costs for healthcare that were five-times higher than people without MS, when summarising all study years, and two-times higher costs from lost production. The excess costs of MS before diagnosis could suggest unmet needs of people with MS with their morbidity and work situation. Earlier diagnosis and starting treatment quicker may reduce or delay future costs of MS.

People with MS also have healthcare costs for primary healthcare and disease modifying therapies. These costs were included in **Study IV** in addition to those in Study III. I calculated costs from resource use in 2018 for all working-aged residents in Stockholm with MS and a group of Stockholm residents without MS. When quantified into monetary terms, there was an annual mean excess cost of 77,383 SEK per person with MS, in addition to the usual healthcare costs. The largest part (48%) of these costs came from disease modifying therapies and primary healthcare accounted for 9%. Excess costs of MS for primary healthcare were largely from visits to healthcare professionals other than doctors. There was a mean annual excess productivity loss of 138,121 SEK per person with MS, mainly from DP (79%). The excess productivity losses of MS became larger with time from MS diagnosis. The excess costs of MS from healthcare were similar but the type of healthcare use differed by time since MS diagnosis. People newly diagnosed with MS had excess healthcare costs of MS mostly from disease modifying therapies whereas inpatient and primary healthcare drove the excess healthcare costs among people with a longer time since their MS diagnosis.

The findings of this thesis highlight the importance of socioeconomic outcomes of MS for both the individual and society around MS diagnosis. There is an important time window in the early stages of MS for appropriate treatment to help people with MS and potentially prevent or postpone future costs to society from disease worsening and progression. This thesis described the working life and economic situation of people with MS as well as the progression of excess costs of MS to society within this window. Most people with early MS stay in activity and have stable or increasing annual DI. However, this thesis found that work disability is often and increasingly a part of the diverse working lives of people with MS. Work disability was associated with static or decreasing DI. Excess costs of MS for lost production owing to work disability and healthcare use are incurred already before MS diagnosis. The pattern and sizes of the cost categories change with time. The increasing excess costs of MS to society at early stages of MS from productivity losses reflect the challenges people with MS may face with their work and morbidity.

LIST OF SCIENTIFIC STUDIES

I. **Murley C**, Yang F, Gyllensten H, Alexanderson K, Friberg E. Disposable income trajectories of working-aged individuals with diagnosed multiple sclerosis. *Acta Neurologica Scandinavica*. 2018; 138(6): 490-499.

II. **Murley C**, Tinghög P, Karampampa K, Hillert J, Alexanderson K, Friberg E. Types of working-life sequences among people recently diagnosed with multiple sclerosis in Sweden: A nationwide register-based cohort study. *BMJ Open*. 2020; 10(12): e039228.

III. **Murley C**, Tinghög P, Alexanderson K, Hillert J, Friberg E, Karampampa K. Cost-of-illness progression before and after diagnosis of multiple sclerosis: A nationwide register-based cohort study in Sweden of people newly diagnosed with multiple sclerosis and a population-based matched reference group. *Pharmacoeconomics*. 2021; 39(7): 835-851.

IV. **Murley C**, Tinghög P, Teni FS, Machado A, Alexanderson K, Hillert J, Karampampa K, Friberg E. Excess costs of multiple sclerosis: A register-based study in Sweden. *Submitted manuscript.*

RELATED SCIENTIFIC STUDIES

Karampampa K, Gyllensten H, **Murley C**, Alexanderson K, Kavaliunas A, Olsson T, Manouchehrinia A, Hillert J, Friberg E. Early vs. late treatment initiation in multiple sclerosis and its impact on cost of illness: A register-based prospective cohort study in Sweden. *Mult Scler J Exp Transl Clin*. 2022. [Accepted].

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Murley C, Mogard O, Wiberg M, Alexanderson K, Karampampa K, Friberg E, Tinghög P. Trajectories of disposable income among people of working ages diagnosed with multiple sclerosis: a nationwide register-based study in Sweden 7 years before to 4 years after diagnosis with a population-based reference group. *BMJ Open*. 2018; 8(5): e020392.

CONTENTS

LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical Classification System
CDR	Cause of Death Register
CI	Confidence interval
CNS	Central nervous system
COI	Cost of illness
DI	Disposable income
Diff R^2	Difference in Nagelkerke-R^2 values
DMT	Disease modifying therapy
DP	Disability pension
DRG	Diagnosis-related group
EDSS	Expanded Disability Status Scale
EUR	Euro
GEE	Generalised estimating equation
ICD	International Statistical Classification of Diseases and Related Health Problems
IRR	Incidence rate ratio
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
MiDAS	Micro Data for Analysis of the Social Insurance
MS	Multiple sclerosis
NPR	National Patient Register
OOP	Out of pocket
OR	Odds ratio
PPMS	Primary-progressive multiple sclerosis
PwMS	People with multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SA	Sickness absence
SCR	Swedish Cancer Register
SDMT	Symbol Digit Modalities Test
SEK	Swedish Krona
SMSreg	Swedish MS Registry
SPDR	Swedish Prescribed Drug Register
SPMS	Secondary-progressive multiple sclerosis
VAL	Region Stockholm's healthcare database

1 INTRODUCTION

Multiple sclerosis (MS) is the most common non-traumatic neurological disease among young adults.[1] The disease has the potential to affect an individual's working life due to the chronic and unpredictable relapsing nature of MS, as well as the progressive accumulation of disability. Both of which are magnified due to the onset of the disease commonly in one's working life. Work disability describes the situation of reduced work capacity due to disease. The fundamental principle underpinning social protection schemes in societies is that all individuals at some stage in their lifetime may require support. Having work disability as an example of one such situation among working-aged individuals. Work is not only of importance to the individual, but also contributes to society through the economy. Accordingly, MS can impact individuals, countries' healthcare and social security budgets as well as a loss to the economy.[2] The socioeconomic burden of MS encapsulates the wide array of these consequences. The objective of this thesis is to gain further knowledge of the socioeconomic burden of MS in Sweden during the window of opportunity of early MS. Two aspects of the socioeconomic burden of MS are investigated in relation to work disability among PwMS: Firstly, working life and the economic situation among individuals with newly diagnosed MS are described; and secondly a societal perspective is used to quantify the excess societal costs of MS. The updated diagnostic criteria, reduced diagnostic delays, and early initiation of the new therapeutic options to attenuate disability and potentially maintain work capacity emphasise a window for intervention as soon as possible and necessitate updated knowledge.

1.1 MULTIPLE SCLEROSIS (MS)

Multiple sclerosis is a chronic and often progressive disease in which the immune system mistakenly attacks and damages the protective myelin sheath surrounding nerve cells in the brain, spinal cord and optic nerves, collectively termed the central nervous system (CNS).[1,3-5] People with MS (PwMS) develop multiple areas with lesions, areas of damage or scaring (sclerosis), within the CNS causing communication problems between the CNS and the rest of the body. The variability in the locations of the lesions and extent of nerve damage leads to a high level of diversity in the manifestation and symptoms of MS among PwMS but also for an individual over time.[3,5] The chronic disease usually presents at a stage of life when one is building families and careers.[6] Consequently, MS has a substantial socioeconomic burden on the individual, their families, employer, and society.[6-10]

In recent years, PwMS are being diagnosed earlier due to changes in the diagnostic criteria, increased access to technology and diagnostic methods, better knowledge, and access to earlier and appropriate treatments.[11,12] There is a growing array of disease modifying therapies (DMTs) which provide opportunities to reduce disease activity and delay disability accrual.[12] Hence, there is a need to revaluate the socioeconomic burden of MS especially among newly diagnosed PwMS in light of these encouraging advances and the resultant improvements in functional capabilities for many PwMS.

1.1.1 MS epidemiology

Worldwide, an estimated 2.8 million people are living with MS. It is most often diagnosed among relatively young adults.[6] Multiple sclerosis affects more women than men; about

two-thirds of PwMS are women.[6,13] The global prevalence of MS is 35.9 per 100,000[6] and has risen over time, likely due to earlier diagnosis, improved diagnosis, and longer survival.[6] People with MS survive roughly 6-10 years less than expected relative to the general population, with a 2-3 times higher risk of mortality.[14-17] Both PwMS and the general population have experienced improvements in survival, and the excess mortality of MS relative to the general population seems unchanged.[14-16] The all-age estimates of incidence and prevalence in Sweden are 10.2 and 189 per 100,000,[13,18] and are among the highest estimates in the world.[6] The annual incidence of MS diagnosis in Sweden peaks at 30-33 years of age.[13] The prevalence of MS is slightly higher among the working-age population of Sweden (16–64 years) at 258.3 per 100,000.[19]

1.1.2 MS diagnosis and clinical course

An MS diagnosis is given only after the exclusion of other more likely explanations for the clinical symptoms.[20] Diagnoses are made with the integration of clinical, imaging, and laboratory findings[21] as there is no single clinical feature or diagnostic test for MS. Since 2001, diagnosis is made according to the McDonald criteria.[20] Important characteristics of MS leading to a diagnosis include establishing dissemination of lesions within the CNS in time (development or appearance of new lesions in the CNS over time) and space (lesions in distinct locations in the CNS).[20] The McDonald criteria,[20] and the subsequent revisions,[22-24] increasingly make the use of increased knowledge and technological advances, such as the combination of imaging, laboratory results, and neurologist examinations, to make an earlier diagnosis after clinical onset.[12,22-24] Currently, a diagnosis requires at least one clinical episode consistent with CNS demyelination in addition to either clinical, imaging, or laboratory evidence of CNS lesions in space and time.[24]

The clinical course of MS is complex.[25] The clinical onset of MS (first symptoms) usually occurs between the ages of 20 and 50 years, with the diagnosis made increasingly closer in time to the clinical onset.[6,24] The existence of a prodromal phase of MS, of an even earlier set of varying signs or symptoms prior to the clinical onset of MS, has increasing evidence.[26,27] After making the MS diagnosis, common clinical patterns of the disease activity and disability accumulation have been classified into three types of MS: relapsing remitting MS (RRMS); primary progressive MS (PPMS); and secondary progressive MS (SPMS).[28] Already in early MS there is demyelination, axonal damage, and accelerated brain atrophy.[1,3,4] Most (85-90%) PwMS initially have RRMS, characterised by alternating between periods of inflammation within the CNS causing transient neurological symptoms and disability called relapses, and periods of remission.[3,29] The disease severity and symptoms can therefore change over time both substantially and unpredictably. Recovery, full or partial, of the symptoms usually occurs over weeks to months.[11] With time, recovery from each relapse is incomplete and persistent symptoms accumulate, the individual's neurological reserve depletes, and the disease often becomes more progressive.[1,3,30] The majority of people with RRMS convert to SPMS with time, however 10-20% of PwMS have progressive MS from diagnosis (PPMS).[3,25,29,30] Individuals with SPMS may continue to have inflammatory relapses, but the course is mainly characterised with continuous progression of disability from the accumulation of neurologic deficits independent of relapses.[31] The median time to conversion from RRMS diagnosis to SPMS in Sweden is observed to be 19.9 years.[32] The clinical course definitions are not without debate, with these types also conceptualised as

occurring along a continuum, rather than distinct.[12] Accordingly, SPMS can be thought of as relapse-onset MS with sufficient time elapsed to observe the progressive course.[12,25,33] With this reasoning, individuals with PPMS are only recognised after they have reached progressive phases and the initial relapsing phase was not noticed clinically, perhaps due to being mild or brief in duration.[25]

1.1.3 MS symptoms, disability, and disease management

There is a wide range of cognitive, mental, and physical symptoms experienced by PwMS depending on the amount of nerve damage and which nerves that are affected.[1,34] Such symptoms can affect PwMS' functioning. Some PwMS may eventually lose the ability to walk independently, while others may experience a mild disease with long periods of remission without new symptoms. Invisible symptoms, those that affect the individual but may not be noticed by others, such as fatigue, pain, and sleep disturbances, are prevalent even at mild disability levels.[1,34] The most commonly reported symptoms when first contacting healthcare prior to an eventual MS diagnosis are sensory (40% reported), motor (39%), visual (30%), and fatigue (30%).[35]

The wide range of symptoms creates challenges to fully capture the spectrum of functional ability, MS disease activity, and disability in a reliable, valid, and comprehensive way.[34,36] Disability, or severity, is most often measured in terms of physical impairment and mobility by the Kurtzke's Expanded Disability Status Scale (EDSS).[37] The scores range from 0 to 10, with 0.5 step intervals representative of increasing physical disability (0.0 indicating no impairment/normal neurological functioning, 6.0 loss of independent gait function and 10.0 death). The Symbol Digit Modalities Test (SDMT) can be used to assess cognitive domains by quantifying cognitive processing speed.[38,39] Recently, socioeconomic outcomes, such as earnings or receipt of sickness absence (SA) or disability pension (DP) benefits when recorded in population-based registers, have been proposed as an alternative measure for clinical worsening and a proxy for MS disability.[40,41] These socioeconomic outcomes reflect the overarching functional abilities and disease worsening over time and encompass a wider spectrum of symptoms of MS than specific domains measured at irregular points in time.[40,41]

Multiple sclerosis and related complications as well as comorbidities and their respective treatments collectively contribute to the overall health status of PwMS.[42,43] The recommended overarching treatment goal for MS is to reduce the disease activity and maximise neurological reserve to preserve cognitive and physical functioning.[1] This involves both early DMT initiation, specific symptom treatment, and lifestyle changes.[1,21,44-46] The National Board of Health and Welfare (Swedish: Socialstyrelsen) recommend that PwMS have healthcare visits with a physician with MS experience at least once a year to manage MS symptoms and provide opportunities for DMTs.[21] Furthermore, access to a multidisciplinary team including various medical specialities (e.g., nurses, physiotherapists, and other rehabilitation services) is recommended to manage symptoms and improve and maintain functional capacities of PwMS through a range of specialised knowledge and perspectives.[21] However, access to such multidisciplinary teams varies across Sweden.[21] In addition to healthcare visits, the self-care and management of MS also requires time of the individual, taken at the expense of activities such as work and family.

Mental and somatic comorbidities are common among PwMS and may also explain some of the observed heterogeneity among PwMS.[42,43,47-50] Comorbidity may result in seeking additional healthcare for treatment,[43,51,52] increase the risk for socioeconomic consequences,[47,53-56] and may also alter the MS clinical course.[50,57,58] Likewise MS and its treatments can affect the diagnosis, risk and severity of comorbidities.[42] However, the relationship between MS and a comorbid disease is complex to determine as there are several ways diseases can co-occur.[42,48] One disease can lead to another and it is unclear as to which disease comes first or the contribution of MS to the co-occurring disease, or alternatively the disease may be a part of MS itself, as it can also be difficult to disentangle symptoms of MS from comorbidities.[42,48] Common risk factors can also lead to increased co-occurrence of a disease.[42,48] People with MS may also be more likely to be diagnosed with an additional disease because of their increased use of healthcare to manage their MS.[42] Lastly, the diseases may be unrelated.[42,48]

There has been a large expansion in the therapeutic options for MS in recent years, although there is not currently a cure for MS.[44] Treatment with MS DMTs can alter the disease course by reducing disease activity and the frequency of relapses especially among people with RRMS to slow disability accumulation and transition to the progressive MS phases.[59] The avoidance of delays within healthcare in initiating DMTs has been recommended since 2015 by the Swedish Medical Products Agency (Swedish: Läkemedelsverket).[46] Two DMTs were first available in 1993, with increasing options since 2006 and over 10 to date.[59,60] People with MS in Sweden have an increasing number of treatment options with different levels of efficacy and a range of administration methods, with newer oral or infusible therapies complementing the older injectables. The common treatment strategy in Sweden today is not only to initiate early, but to begin with highly efficacious DMTs, rather than to escalate treatment efficacy with signs of disease activity.[61,62] The most frequently used DMT in Sweden is rituximab, used off-label increasingly over the past decade, including for first line initiation.[62-64] Such changes have likely resulted in differences in healthcare utilisation patterns among PwMS due to changes in disease activity and routine visits for treatment.[65,66] Despite the relatively recent availability of DMTs, studies already indicate that early compared to late initiation is more likely to lead to better clinical outcomes, including reduced relapse risk, reduced disease worsening, and slower conversion to SPMS.[11,44,62,67-71] Therefore, there is an early key window for intervention and prevention. Improved socioeconomic outcomes have also been observed among early DMT initiators, such as reduced work productivity impairment, reduced risk of DP, and higher earnings.[40,53] The savings from these improved clinical and socioeconomic outcomes may partially offset the costs of DMTs.[66,72,73]

Accordingly, updated estimates of the societal costs of MS of both the potential changes in productivity and healthcare consumption are needed for planning as well as future economic evaluations. This thesis includes recent cohorts of PwMS of working ages in early stages of their MS. Early MS in this thesis refers to the years proximate to MS diagnosis. Although onset and symptoms may occur prior to a formal diagnosis, this is when one is aware of their MS. This group of relatively young adults potentially have many years of work ahead of them. However, there are three levels of uncertainty they may encounter which can also affect their working life: Day-to-day changes in symptoms; month-to-years regarding relapses and residual disability; and how MS disability may accumulate in the long-term.[74]

1.2 WORK AND WORK DISABILITY

Work and work disability are related.[75] The four studies comprising this thesis all consider aspects of the socioeconomic burden of MS in relation to work disability. In Study I and II, the working life and economic situation of newly diagnosed PwMS were studied and then in Study III and IV, the excess costs of MS from a societal perspective including the productivity losses from days with work disability were quantified.

1.2.1 Work

Work participation, or simply work, involves time and the application of physical or mental effort, skills, knowledge, or other personal resources.[76] Work is broader than one's paid job, and can include activities such as unpaid volunteer work, education, training, and family responsibilities such as caring.[76] Work is one major life domain among adults.[77] The literature supports the notion that work is generally beneficial for the health and well-being of individuals, dependent upon the quality or decency of the job and the social context.[76,78] Work is therefore a social determinant of health.[76,78] While the conditions of work can carry risks which may lead to poorer health outcomes, decent work and employment can have positive effects on health.[78] Paid work can provide economic resources and work can confer other benefits including personal development, structure to the day, and social connections.[74,78] Everyone creates their own meaning attached to their work, shaped by the social context they live in.[79] The importance of work for society and the individual is exemplified by the United Nations' Sustainable Development Goal 8, which aims to "Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all".[80] Accordingly, maintaining work and facilitating return-to-work in situations of work loss are desirable goals to maintain or improve wellbeing.[74,76,78]

Work is a central dimension of life for many and most value work and find it fulfilling, including people with medical conditions. Women in Sweden rate paid work as one of the most important aspects of life in the two years following a breast cancer diagnosis.[81] Paid work was also positively perceived among a group of employees with chronic health conditions in Sweden as it was reported to promote health, social cohesion as well as a sense of purpose, and reduce the impact of the chronic health condition on their quality of life.[82] There was a strong motivation to work among the participants and to find solutions to enable the continuation of a sustainable working life despite the challenges encountered owing to their chronic health condition.[82] There is no reason to believe that PwMS differ, provided there is a sustainable balance of work and private life. Quality of life among PwMS has also been observed to be positively associated with employment.[83,84]

However, there can be a health selection into and out of the labour force. One's level of health may make one more or less likely to seek or obtain work, influence their work performance (quality of work), and determine whether or not they are absent or leave work temporarily or permanently (quantity of work).[76,85,86] Five themes influencing the continuation of working life identified among employed people with a chronic health condition in Sweden were adaptation, lifestyle, motivation, confidence in one's own abilities, and support from others.[82] Problems with paid work participation, including due to a health condition, can result in substantial socioeconomic consequences from the high public

expenditure, hindered economic growth from the reduced productivity, and have implications for the individual's economic situation.[85]

1.2.2 Work disability

The literature contains diverse conceptualisations of work disability, without a shared single definition or language.[75,87-89] Work disability in this thesis refers to "The result of a (medical) condition that causes a worker to miss at least one day of work and includes time off work as well as any ongoing work limitations."[88] This definition is consistent with the World Health Organisation's International Classification of Functioning, Disability and Health "ICF"[77] and designed to be used alongside researching the process of return-to-work with a work disabling condition.[88] Medical conditions resulting in work disability can be both acute or chronic and the resulting work disability can also vary in duration. However, not all individuals with a disease experience work disability.[90] Rather, there must be a gap between the individual's functioning due to either mental or physical impairment and the demands of the environment or social context around the worker.[89]

Work disability is better thought of as a continuum than a dichotomy.[89] The notion of work incapacity due to a medical condition is broad, ranging from a total incapacity to work (e.g., absence from work) to a partial incapacity to work (e.g., part-time absences from work, able to fulfil certain tasks at work, or perform them at a lower speed). Accordingly, work disability can represent a productivity loss due to a medical condition from the reduced work output not only through absences from work ("absenteeism") but also through the individual's return-to-work or continuation of work but without full work capacity ("presenteeism").[75,88,91,92] The latter is less frequently measured, despite the importance among workers with chronic diseases who utilise remaining work capacity.[92]

Work disability is a complex phenomenon resulting from the interaction of multiple dimensions or arenas, including a medical condition, that overlap and influence each other at different structural levels.[75,87,93] One prominent model that maps out relevant factors and systems influencing work disability and the possibility of return-to-work is the Arenas of Work Disability Model.[93] This model encompasses not only the individual and healthcare system but also systems related to the workplace and wider social systems, including laws and regulations for compensation.[93] These determinants of work disability are visualised as surrounding the individual with a medical condition.[93] This understanding of work disability implies that individuals even with the same disease and comparable functional limitations will not always have the same level or pattern of work disability when considering their unique work demands and the wider determinants of work disability operating at different structural levels.[89,92] In particular, the individual and workplace context in which the impairment occurs are often considered key factors that mediate the complex and multidimensional relationship of morbidity and work disability.[89]

These wider determinants of work disability operate at different structural levels in society and highlight the shift from a purely biomedical understanding to a broader biopsychosocial model of work disability.[87] Work status was previously viewed as being entirely dependent upon the nature and severity of the medical condition and resultant impairments with the consequence that the ability to return-to-work was viewed as directly related to the trajectory of clinical recovery.[87-89,94] However, the situation is often much more complex and dynamic,

with varying patterns and symptom resolution occurring loosely associated with patterns of work disability, owing to the influence of environment and wider context.[75,88,94] A biopsychosocial understanding of work disability transfers the responsibility of outcomes from solely healthcare to be shared with a wider range of stakeholders and widens the potential barriers and facilitators to stay at work or return-to-work after an absence.[93] Generally, the common factors associated with work disability assessed in the literature fall within the categories of disease, job-related, and sociodemographic characteristics.[92] Therefore, medical and non-medical interventions may prevent the occurrence of work disability and interdisciplinary approaches are required.[92,94]

Work disability is operationalised in all four studies as absences from activity such as paid work, identified through net days with sickness absence (SA) and disability pension (DP) benefits. These two benefits combined (SA/DP) are therefore used synonymously with work disability. Sickness absence represents temporary work disability, whereas permanent or long-term work disability is captured with DP. Accordingly, aspects of lost working days or absences due to work disability (absenteeism) are studied. Although, the importance of reduced work capacity while at work (presenteeism) is acknowledged for both the individual's working life and productivity losses. The Swedish setting is summarised below as a key determinant of work disability, including the regulations for SA and DP benefits.

1.3 THE SWEDISH SETTING

The Swedish welfare state is a social determinant of health and this wider context that PwMS live in can affect both their health outcomes and mediate the consequences of living with MS, including work disability, economic situation, and the societal costs of MS.[95-97]

There are extensive social protections available in Sweden. Social protections provide a safety net to residents throughout the life-course. While they are present in most countries, they vary in respect of who is covered, the extent of protection, and the types of supports.[96] Social protection is defined in this thesis as referring to all benefits (transfer payments or services) with the purpose of reducing the economic consequences to individuals and their households from defined risks (e.g., loss of earnings in situations of work disability) or meeting specially defined needs (e.g., healthcare services).[98] The economic support through public transfer payments alongside service provision contribute to high expenditure in Sweden and the other Nordic countries.[99,100] In 2019, 27.7% of the gross domestic product was spent on social protections in Sweden.[98] International comparisons are challenging because of different taxation regulations where some countries, like Sweden, tax certain benefits. Furthermore, a benefit can either be paid directly or provided through a tax deduction. Social protections relevant to this thesis include the universal healthcare system and the transfer payments of SA and DP benefits from the Social Insurance Agency (Swedish: Försäkringskassan).

1.3.1 Healthcare system

The Health and Medical Service Act 2017 provides for universal healthcare coverage for all residents in Sweden and enshrines the goal for good health and equal care for all.[101] The Act also specifies that persons with greater needs should be prioritised commensurate with their greater needs. To meet these goals, healthcare is organised through the three tiers of Swedish administration, national (state), regional (county), and local (municipality), each with distinct

responsibilities.[101-104] The national level, through various agencies, administers transfer payments as well as wider oversight, monitoring, and recommendations. The county councils are responsible for financing and providing specialised healthcare services (in- and out-patient) and most primary healthcare services to their respective inhabitants. Healthcare providers can be either public (directly provided by the county council) or private (with an agreement for financing with the county council). The primary healthcare centre is often the entry point for non-acute health problems.[105] Primary healthcare centres typically have a range of healthcare professionals including physicians, nurses, midwives, social workers, physiotherapists, and psychologists. Specialised healthcare takes place at both outpatient clinics and hospitals, often after a referral from primary healthcare. At the local level, municipalities are responsible for social services, home help, and nursing homes.

Healthcare in Sweden is predominantly publicly financed through taxation.[103,104] In 2019, 85% of expenditure was publicly financed by local taxes and national statutory grants.[106] Accordingly, financing is largely sourced from progressive taxation and not via an individuals' risk profile.[107] There is cost-sharing with the patients, for example, visit fees and copayments for prescribed drugs.[102] The cost-sharing has two important features: an out-of-pocket (OOP) copayment and a maximum cap.[105,108] Patient OOP copayments (also referred to as user charges or fees in the literature), are the patient's financial contribution to healthcare services or reimbursable medicines at the time of use that are not covered by the respective county (third party payer).[109,110] Patient OOP copayments raise revenue to contain costs and are an instrument to reduce moral hazard, the situation describing the potential inappropriate overuse of resources when services are funded by a third party.[109] However, OOP copayments may also risk posing as a barrier to individuals accessing appropriate healthcare.[107] Although, the design of the OOP copayments can minimise this risk. In Sweden, a fixed copayment is charged when utilising healthcare services, and if the total OOP expenditure reaches the specified cap within a 12-month period, then the copayment immediately becomes zero for the remainder of the period.[108] The general principles are the same across Sweden, while the specific details are determined by each county.[105,108] The Swedish Dental and Pharmaceutical Benefits Agency (Swedish: Tandvårds- och läkemedelsförmånsverket) determines the drugs subsidised and included in the high-cost threshold scheme.[111] There are incremental reductions in the proportion of the cost an individual pays for the included prescribed drugs with a maximum cost of 2350 Swedish Krona (SEK) (in 2020) within a 12-month period.[111] In 2015, OOP copayments financed approximately 24% of the costs for drugs within the scheme.[99] This financing system with capped OOP copayments, provides a level of financial protection to individuals against catastrophic healthcare costs.

1.3.2 Labour market

The Swedish labour market is characterised by a high employment participation rate among older people and among women; a generally high level of work participation owing to active labour market policies; a high level of unionisation and collective bargaining; unemployment compensation systems; and relatively low wage inequality.[112]

The comprehensive social protections are supported by the high labour force participation rates (82.9% for all 15-64 years in 2019).[113] This reflects the high participation among women and also among older ages.[113] The labour force participation rate of women 15-64

years was 81.1% compared with the Organisation for Economic Cooperation and Development, OECD, average of 65.0% in 2019.[113] Nonetheless, the labour force participation rate among men in Sweden remains higher (84.6%).[113] Furthermore, part-time work is more common among women than men.[99] Labour force participation declines with age for both women and men. However, this decline with age is to a lesser degree in Sweden than in other countries.[114] The Swedish labour market is also characterised as gender segregated with different proportions of men and women across occupations.[115]

Sweden has a relatively compact income distribution with a relatively low level of income inequality.[116] However, like other countries, a pay gap exists in Sweden, with women earning approximately 12% less than men in 2019.[117] This unadjusted indicator reflects differences in the average characteristics of workers as well as differences in pay for the same characteristics.[117] The pay gap is generally smaller among younger individuals entering the labour market and tends to widen with age.

1.3.3 Transfer payments from social insurances

The most substantial transfer payments available in situations of work disability are the SA and DP benefits provided by the Social Insurance Agency.[118] Another relevant situation among working-aged individuals with transfer payments is unemployment.

1.3.3.1 Sickness absence (SA)

In the years this thesis covered, all people living in Sweden aged 16 and above were eligible for SA benefits if they received a minimum annual income from paid work, parental-leave benefits, or unemployment compensation and had reduced work capacity due to disease or injury.[119] Work capacity was required to be reduced by at least 25% of the usual working hours to be eligible for SA benefits. The assessment of work capacity reduction leads to the grade of compensation and absence (25, 50, 75, or 100% of ordinary working hours).[119]

Assessments of work capacity are based on the individual's unique conditions regarding both morbidity and work situation.[119,120] For employees, work capacity is assessed in relation to the individual's regular work for the first 90 days of a SA spell. Since the introduction of the "Rehabilitation Chain" in 2008, work capacity after day 90 is assessed against any work with the same employer and then after 180 days of an SA spell, work capacity is assessed in relation to all jobs within the Swedish labour market.[119,121] The work capacity of self-employed individuals is also assessed against the whole labour market after 180 days. The work capacity of unemployed individuals is always conducted in relation to the entire labour market. A physician's certificate is required from day eight of a SA spell, produced after assessing the patient's medical condition and work capacity. Both the healthcare system and the Social Insurance Agency work together in the process of assessing whether an individual fulfils the criteria for SA (or DP) benefits, but they hold different roles. The healthcare system is responsible for documenting the diagnosis as well as assessing an individual's specific functional limitations in medical terms and their work capacity in relation to the diagnosis and their work. The Social Insurance Agency decides if an individual fulfils the criteria for obtaining SA (or DP) benefits, based on the information provided by the physician and others.

Differences in work capacity occur both between PwMS, and over time for the same individual.[120] Heterogeneity in how the wide range of MS symptoms and disability can affect an individual's function and work capacity is highlighted in the sickness certification guidelines from the National Board of Health and Welfare.[120] Reductions in work capacity arising from acute relapses requires different solutions to that from more progressive elements of MS, cognitive difficulties, or fatigue. In situations of mild to moderate MS relapses that affect the individual's work capacity, the guidelines recommend up to two weeks with 100% SA.[120] Longer spells and part-time SA are instead recommended for individuals with progressive types of MS, with the grade increasing as functional limitations increase.[120]

The employer is mandated to pay the first 13 days of a SA spell of an employee, after the first qualifying day of the absence which is forfeited without compensation. From day 15, after the statutory employer payments, SA benefits (Swedish: sjukpenning) are covered by the Social Insurance Agency. If an employee's SA spell is less than 14 days, the loss of earnings is not reimbursed by the Social Insurance Agency and the SA spell is not registered. In situations of repeated SA spells within a short interval or for some chronic diseases, the responsibility of the employer to pay can be waived. Self-employed individuals have varying numbers of qualifying days (1, 7, 14, 30, 60, or 90 days) before the Social Insurance Agency pays. The more qualifying days a self-employed person chooses to have, the lower their insurance contributions are. SA benefits are paid by the Social Insurance Agency from the second day of a SA spell to individuals registered as unemployed and actively seeking employment or who otherwise have parental leave benefits.[119,121]

The minimum income required for SA benefits is set to 24% of the price base amount (Swedish: prisbasbelopp, an annual prospectively set amount used for indexation), equating to 10,632 SEK in 2016.[122] The level of compensation paid is based on the sickness benefit-basing income, grade of reduced work capacity, reimbursement level, and ceiling for income reimbursed.[119] Sickness absence benefits are based on prior and expected earnings like several other transfer payments such as parental leave benefits. These transfer payments are based on the sickness benefit-basing income (Swedish: sjukpenninggrundande inkomst), which is currently set to 97% of an individual's annual earnings. Benefits typically correspond to 80% of this amount but are capped for high income earners at 7.5 times the price base amount. As an example, in 2016 with a price base amount of 44,300 SEK, this amounted to a total of 706 SEK per day for SA.[122,123] Most employees also have an additional insurance, providing an extra 10%, so that 90% of lost earnings are covered, up to the ceiling.

A SA spell within this thesis is defined according to the Social Insurance Agency as a period of connected payments for SA, preventative SA (Swedish: Förebyggande sjukpenning), rehabilitation (Swedish: Rehabiliteringspenning), or occupational injury benefits (Swedish: Arbetsskadesjukpenning).[121]

1.3.3.2 Disability pension (DP)

All residents in Sweden aged 19-64 are eligible for DP benefits if assessed as having long-term or permanently reduced work capacity due to disease or injury.[119] Permanent DP (Swedish: sjukersättning) can be granted to residents in Sweden aged 30-64 if work capacity is permanently reduced by at least 25%. Temporary DP (Swedish: aktivitetsersättning) can be

granted to individuals aged 19-29 years with reduced activity level for periods of one to three years. Up to 64% of lost earnings are compensated by DP benefits. Unlike SA benefits, there are no previous income requirements, with a set amount paid in such circumstances. Among people in paid work, DP is often preceded with SA during the process of evaluation to determine the long-term or permanent nature of the reduced work capacity.

In Sweden, DP can be granted for part-time as well as for full-time (25, 50, 75, or 100%) in relation to work capacity. Accordingly, the Swedish social insurance system allows for part-time DP alongside part-time work. This flexibility is quite unique and seems to support PwMS in Sweden to manage symptoms, such as fatigue, and to stay in paid work to higher extent than PwMS in other countries.[124] As this is not the case in most other countries, special attention when operationalising SA and DP is needed because people in Sweden can simultaneously be on part-time SA and DP, for example, an individual with 25% DP due to MS could also have SA if the remaining work capacity is reduced when sustaining an injury. Throughout this thesis, gross days of SA and DP were transformed into net days to handle part-time absences, e.g., two gross days of 50% equals one net day. The combination of SA and DP as work disability handles the potential simultaneous grants of SA and part-time DP benefits and that those with full-time DP benefits are not eligible for SA benefits.

1.3.3.3 Unemployment compensation

Unemployment compensation is provided to individuals up to the age of 65 who are registered with the Swedish Public Employment Service (Swedish: Arbetsförmedlingen) as unemployed and actively seeking and immediately available for employment.[125] There is both an optional earnings-related insurance of up to 80% of lost earnings and a basic public insurance (Swedish: Arbetslöshetskassa).

Unemployment compensation is a less common source of income among PwMS in Sweden than among the general population but indicates that the individual is assumed to have work capacity and is available for paid work despite not being currently self-sufficient.[126]

Periods with these transfer payments (SA, DP, unemployment compensation, as well as parental leave benefits) can occur within one's working life. These transfer payments with replacement rates based on prior earnings are designed to maintain the possibility of a similar standard of living.[127] They are negatively correlated with one another, where the grant of one benefit reduces the possible compensation from others.

1.4 SOCIOECONOMIC BURDEN OF MS

This section contains a summary of the scientific literature regarding the following aspects of the socioeconomic burden of MS: The working life of PwMS, their economic situation, and the costs of MS. The focus throughout was on findings from Sweden, although findings of studies from other countries are also cited where relevant.

1.4.1 Working life of people with MS

Having MS can affect one's working life. Pfleger et al. operationalised the term 'working life' to broadly cover the complex situation of PwMS, including aspects of employment, receiving early pension or temporary unemployment compensation, and overall income level.[128] More generally, working life has been defined as the life course transitions,

alongside health outcomes or transitions (e.g. MS diagnosis), and labour market experiences or transitions.[129] The impact of MS on working life occurs early; differences in comparison to people without MS have been observed up to eight years prior to an MS diagnosis in a Danish study assessing employment rates,[10] and up to 15 years prior to an MS diagnosis in a Swedish study regarding SA.[130] Such changes in working life may have implications for the economic situation of PwMS. Working life is dynamic with transitions in and out of work,[131] however, MS research has largely focused upon PwMS ending their working lives rather than re-entering paid work.[132]

Working life is a heterogeneous field of research with a wide spectrum of measures,[91,133] with the measurement, methods, and instruments varying widely.[91] The literature reviewed regarding the working life of PwMS focused on narrower aspects of work among PwMS, namely, aspects related to paid participation in work and employment activity.[88] Earnings, SA and DP benefits, and disposable income (DI) all provide information of PwMS' working life and economic situation. Yet, each type of income provides different information and implications. Recently, two systematic reviews have attempted to summarise the socioeconomic consequences of MS in comparison to references without MS[134] as well as among PwMS by physical disability and cognitive function.[133] The older studies may not be fully generalisable to PwMS today. This is because they observed the working life, including work disability outcomes, among cohorts diagnosed with different criteria and before the availability of high-efficacy DMTs, so were either not treated with DMTs at all, treated with other DMTs, or started high-efficacy DMTs later.

1.4.1.1 Employment and earnings among people with MS

Most studies find PwMS have lower employment rates compared with references without MS, often with a difference between 15-30%.[134] Employment of PwMS steadily decreases with time.[10,53,126,134-136] Sweden has a comparatively high proportion of working-aged PwMS in paid work compared with other European countries.[137] Employment or participation in paid work can be inferred from register data if having earnings >0 SEK. In Sweden, 76% of PwMS were observed to have earnings, participating in paid work to some degree four years after their MS diagnosis.[138] However, a higher proportion of PwMS in comparison to references are not in paid work, and this proportion increases with time from MS diagnosis.[53,126,135] Situations unrelated to MS-morbidity can also result in zero earnings, including being on parental leave or studying. Similar observations have been made in Denmark, with an employment rate of PwMS around half of that of age and sex matched references in the eight years before and after MS diagnosis.[10]

People with MS often work part-time or with reduced hours.[124,132-134,139-141] The majority (77%) of PwMS in Sweden in paid work self-reported working part-time in the European burden of illness study.[124] Part-time work in Sweden is possible alongside the social insurances for partial reductions in work disability, limiting binary conceptualisations of being in paid work.

Earnings (income from paid work) constitute a primary source of income and economic security in early MS.[9,126,134] Although, the proportion of income from earnings decreases with time[126] as there is a negative association between having MS and earnings.[134] Earnings provides information on the labour market attachment, ability to generate income, and may

also reflect the gradual effects of MS.[126,135] Swedish register-based studies show that both the levels of and proportions with earnings decrease in comparison with references already prior to MS diagnosis and that the gap increases thereafter.[9,126,135,138] An increasing number of studies, from Sweden and abroad, demonstrate a negative association between MS and earnings, in comparison with references[9,10,126,134,135,138] and among PwMS by clinical characteristics.[41,128,133,135,139,142-144] People with MS have been estimated to have 85% of matched references' earnings in the MS diagnosis year and 73% five years later.[135] Landfeldt et al. observed that the earnings among PwMS diagnosed 2002-2011 did not change over the follow-up after MS diagnosis of up to eleven years (p=0.213), suggesting stagnation in earnings, while the matched references' earnings increased over these years.[9] Similarly, a steady increase in earnings and even interquartile range has been observed among matched references ten years prior to five years after inclusion, but for the PwMS, there was first a period of increasing earnings but then a decreasing trend in the years just before MS diagnosis, and static levels post-diagnosis.[135] Recently, clinically stable MS has been observed to be associated with a lower risk for loss of annual earnings (i.e., zero earnings) among Danish PwMS on DMTs.[144]

1.4.1.2 Work disability among people with MS and income from sickness absence and disability pension benefits

Sickness absence and DP benefits are also important sources of income for PwMS in situations of work disability.[126] Overall, in comparison with the general population, PwMS in Sweden have more SA and/or DP and accordingly more work disability.[54,55,126,130,135,145-148] This is similar in other Nordic countries.[10,128] There are many different measures of SA/DP in the literature reflecting different contents of the phenomenon (e.g., SA, DP or SA/DP; part- or full-time; and whether measure proportions on, annual sums from the transfer payments, or net days).[149,150] Having MS is associated with SA/DP.[10,54,55,126,128,130,134,135,145-148,151] People with MS have been observed to have more SA/DP than references, in terms of more months/days,[55,147,148] higher sums from the transfer payments,[126,138] and proportions with SA/DP.[128,130,135,145,146] Estimates of PwMS diagnosed in 2001 and after suggest that within a decade of their diagnosis, nearly eight of ten PwMS will be partially or fully absent from work with SA/DP.[130]

The levels of and patterns of work disability change along the MS clinical course.[55,130,147] People with MS have higher SA/DP compared with references already before MS diagnosis.[55,130,147] Significant differences in the proportions of PwMS and references with SA were observed up to 15 years before MS diagnosis and three years for DP.[130] The differences in SA/DP between PwMS and references increase significantly at diagnosis and continue thereafter,[130,135,138,147] implying increasing work disability with time. The proportions of PwMS with at least one spell of part- or full-time SA or DP were larger among the PwMS than among the references both in the MS diagnosis year and five years later.[135] Therefore, suggesting that work capacity is affected early in the disease trajectory and indicating that MS can prematurely end working lives.

The levels of SA among PwMS fluctuate, with a peak around MS diagnosis.[55,130,138,142,147,152] In the diagnosis year, 46.7% of PwMS have been observed to have at least one full-time SA spell >14 days and 10.0% a part-time spell.[135] These proportions decrease with time from MS diagnosis.[135] Conversely, DP among PwMS increases with time.[126,130,138,142,147,152] Both part-

and full-time DP are observed in early MS; 21.0% and 25.1% of PwMS versus 2.9% and 7.9% among references had part- and full-time DP in the fifth year after MS diagnosis.[135] The risk of future DP to indicate permanent exit from the labour market due to work disability is widely used, comparing PwMS with references as well as between subgroups of PwMS.[53-55,128,130,144,151-154] A Danish study estimated the probability of remaining without early pension was 70% for PwMS and 97% for their matched references five years after MS onset, and 22% and 86% 20 years from MS onset.[128] However, such analyses miss more gradual changes in working life.

Not all PwMS have SA/DP,[55,147,155] especially early in the disease course. In the four years before and after MS diagnosis in 2009-2012, 79.0–47.8% of PwMS in Sweden were without SA/DP in a given year and the corresponding numbers among references were 81.5-84.0%.[55] Furthermore, the excess of SA/DP among PwMS has been observed to not all be due to MS, even after being diagnosed with MS.[55,156] It is possible MS is a side diagnosis or that the recorded diagnosis is related to MS. Accordingly, there is diversity in the diagnoses underlying the work disability of PwMS as well as in the ways in which MS can affect work.

1.4.1.3 Characteristics associated with working-life outcomes among people with MS

Many of the characteristics associated with earnings are also associated with SA/DP but with the opposite relationship. However, it is somewhat an oversimplification to reduce them to binary alternatives given the different concepts and information that they capture.

1.4.1.3.1 Clinical characteristics

Clinical characteristics,[133] such as physical disability,[41,124,137,144,146,152,157,158] cognitive function,[143,159,160] disease activity,[144,161] time since diagnosis,[148] MS type,[142,154,158,162] DMT use,[40,53,140,163,164] and comorbidity[47,54-56,151] are associated with working life (e.g., employment, earnings, or work disability) among PwMS.

Physical disability affects the work life of PwMS considerably. Employment and consequent earnings are highly and consistently correlated with the EDSS.[41,124,137,144] The proportion of working-aged PwMS in Europe self-reporting employment in the European burden of disease study declined from 81.9% among PwMS at EDSS step 0 to 8.2% at EDSS step 9.[137] Similarly, a gradual decrease in the proportion of PwMS in Sweden with earnings greater than zero from 91.7% at EDSS step 0 to 4.0% at EDSS step 9 has been observed.[41] An increasing EDSS score is also positively associated with increases of SA/DP.[41,144,146,152] By EDSS step 4, PwMS in Sweden in 2010 had more income from transfer payments (including SA and DP benefits) than from earnings, with DP benefits on average accounting for 75% of the total income among PwMS with EDSS scores 7-9.5.[41]

The invisible symptoms of MS, such as fatigue, also impact working life, including in early MS.[1,124,133,143,157-160,165-168] Among PwMS in paid work in Europe, aspects not captured by the EDSS were self-reported to be underlying reduced work productivity, for example, fatigue (70% of participants), cognitive difficulties (34%), and pain (21%).[137] Cognitive difficulties seem to influence work capacity independently of the EDSS, and have been associated with less earnings and more SA/DP.[133,143,159-161]

The type of MS also is important for the heterogeneity among PwMS and is reflected in the sickness certification guidelines (See 1.3.3.1).[120] People with RRMS have roughly twice as

high earnings as those with progressive MS types.[142,162] MS type has also been somewhat associated with SA/DP;[142,154] people with RRMS have been observed to have lower proportions on SA and DP over time in comparison with progressive MS types[142] or lower income from social transfers.[162] However, MS type was no longer significant regarding proportions on SA/DP after statistical adjustment for EDSS scores in one study.[142]

The literature directly testing associations of DMTs and working life indicates that there are more favourable outcomes among PwMS treated with high-efficacy DMTs,[140,163,164] achieving disease stability,[144] and initiating treatment early.[40,53] Disease modifying therapies, especially DMTs initiated early, are associated with less SA[169] and lower risks for DP.[53,144]

Comorbidity, particularly mental disorders, are associated with higher risks for DP among PwMS.[54,151]

1.4.1.3.2 Sociodemographic characteristics

Sociodemographic characteristics are also important explanatory factors of the heterogeneity in working life of PwMS. Age,[126,130,147,153,158] sex,[9,10,41,126,130,145,146,152] level of education,[9,53,126,130,135,146,147,158,170] and type of occupation[135,144,148] have been observed to pattern working life among PwMS, often following similar trends to those observed within the general population in Sweden.[170-172] Other potential protective sociodemographic factors include living in densely populated areas,[41,126,145] married/cohabitating,[9,41,130] and having been born in Sweden.[41]

Age is an important factor for both working life outcomes and MS.[173] People with MS generally have lower annual earnings than their reference peers. With increasing age, the earnings of PwMS were observed in a Swedish cross-sectional study to be more dissimilar to their reference peers.[126] People with MS' earnings were observed to peak a decade younger than references, at ages 35-44 years.[126] Sickness absence and DP days per year generally increase with age[171] and at each age, PwMS have higher levels than references.[126,130,147,153]

General trends regarding sex and earnings or SA/DP are largely also observed among PwMS. Men with MS have higher annual income than women with MS[9,10,41,126] including earnings.[9,41,126] Among PwMS in Sweden, besides high EDSS scores, being a woman was observed to have the largest negative association with earnings, an average annual difference of -89,000 SEK compared to men in 2010.[41] Similarly, more women with MS are observed to be on SA/DP than men with MS, and this reflects trends within the general population in Sweden.[130,145,146,152,170-172] In 2019, 63% of the recipients of SA benefits during the year were women however, the average daily amount of the benefits was 6% higher for men due to differences in prior earnings.[171] Although the choice of measure of SA has been observed among privately employed white-collar employees in Sweden to affect the magnitude of the observed sex differences.[174] The literature is therefore mixed, there are also indications that men with MS may be more at risk to have SA/DP or zero earnings than expected from background risks.[9,145]

Educational level influences PwMS' earnings[9,126,135] and SA/DP.[53,130,146,147,170] A hierarchical pattern is observed, where higher levels of education are associated with relatively higher levels of earnings.[135] People with MS with university/college level education have been observed to have annual earnings more alike their reference peers than those with at most

elementary school education,[126,135] with one register-based study finding that PwMS with university/college education had 78% of reference peers' earnings five years after their MS diagnosis, whereas those with at most elementary school had 53%.[135] The gradient in risk for SA/DP among PwMS by education level reflects general trends in Sweden.[53,146,147,170] Higher educational level is associated with less SA/DP, especially around the time of MS diagnosis, with PwMS with lower educational levels having larger differences in SA/DP compared with references.[135,147] Somewhat similar proportions of PwMS with SA have been observed five years after MS diagnosis across educational levels, but with part-time DP more frequent among PwMS with university education and full-time DP among PwMS without university level education.[135]

There are also differences by type of occupation. A gradient has been observed among PwMS in the level of mean earnings between managers, office workers, and manual labourers.[135] People with MS with more qualified occupations have been observed to be most alike their reference peers.[135] Conversely, PwMS in manual work had the largest relative difference in earnings, 67% lower earnings compared to their reference counterparts five years post-diagnosis (office workers 78%), however, the largest absolute difference in earnings was observed among managers (SEK -113,000), corresponding to 70% of the mean earnings of the managers in the reference group.[135] Higher SA/DP have been observed among PwMS in Sweden than references in all occupational groups.[148] Among PwMS, managers had the lowest annual SA/DP days while administration and construction sectors had the highest numbers of SA/DP days.[148] People with MS working as managers have previously been observed to have lower proportions of SA than PwMS in other occupations, as well as manager or office work occupations having higher proportions of PwMS with part-time rather than full-time DP five years after diagnosis.[135]

1.4.2 Economic situation of people with MS

An individual's economic situation can be comprehensively described using DI.[175] Disposable income includes the after tax sum of earnings, transfer payments received, such as SA or DP benefits or unemployment compensation, as well as other types of income or deductions, including capital, business activities, student loans, or housing allowances.[176,177] Hence DI accurately describes an individual's economic situation in the Swedish context, where social protections can mediate the potential impact of MS on economic situation, by combining all declared income sources.[126,175] Disposable income can refer to the individual's personal income or household income.[176] This thesis used individualised (or equivalent) household DI (hereafter referred to as DI), with the sum of all incomes within a household transformed by equivalisation weights to adjust for the household size.[176] This measure assumes that the economic resources within the household were shared and enables a thorough estimation of economic resources available, irrespective of the income source.[95,175]

Despite an increasing number of studies on PwMS receiving SA and DP benefits or about earnings, less is known about how MS impacts DI development. There are two studies considering annual DI among PwMS in Sweden with comparison groups without MS.[9,138] Collectively, they show that despite many PwMS experiencing reductions in earnings, on average, PwMS still have a relatively unaffected economic situation in terms of mean DI in the years directly before and after MS diagnosis.[9,138] Statistically significant differences in the levels of mean annual DI were observed only after nine years between PwMS and

references.[9] Consistently, we previously observed parallel development of annual DI between PwMS and references in the seven years prior to the MS diagnosis year and also for the four years after.[138] Furthermore, a cross-sectional study looking at six income sources (including SA and DP benefits) suggested that PwMS were compensated by the redistributing social protections for changes in earnings.[126] These interpretations are consistent with the Danish findings of mean differences in annual gross income between PwMS, with onset between 1980-1989, and matched references without MS observed to manifest about 10 years after MS onset.[128] By 20 years from MS onset, the mean annual gross income among PwMS was 70% of that among the references.[128] A subgroup analysis considering only those in paid work indicated that PwMS maintained similar levels of gross income to the references without MS.[128] Therefore, the authors attributed the difference in gross income to the early retirement benefits, compensated as a proportion of previous earnings, which increasingly became the largest income source.[128] Despite the differences in the Danish and Swedish settings and cohort/income definitions, it is likely that PwMS in Sweden may also experience reduced DI with longer follow-up.[9,128,147]

These studies indicate that for PwMS collectively, the redistributing social protections seem to balance reductions in earnings from changes in work capacity in the years immediately following MS diagnosis. However, future decreases in DI may be experienced by PwMS as the disease progresses and increasing proportions of PwMS are no longer participating in paid work. Furthermore, SA spells >14 days have been associated with weaker DI growth two to six years after the spell among the working-age population in Sweden, especially after longer SA spells.[175] Increasing variation in mean annual DI among PwMS was observed with time from MS diagnosis.[9,138] The widening confidence intervals (CIs) observed could be partially due to the smaller numbers included, but also the increasing heterogeneity among PwMS with time. These studies considered PwMS overall, and did not consider heterogeneity other than by sex-stratification.[9] Heterogeneity in the economic situation among PwMS has been somewhat considered in Sweden, often in cross-sectional studies in terms of combined income from six sources, and proportions of each component (earnings, DP, SA, disability allowance, unemployment compensation, and social assistance), and in Denmark regarding sex,[9,126,142] disability,[41] cognitive function,[143] and MS type.[142,162] However, the impact of MS on longitudinal economic situation remains largely unknown regarding subgroups of PwMS.

While the economic consequences of premature loss of employment among PwMS may be buffered by the social protections, the work loss results in wider costs to society through the reduction in size of the labour market and potential productivity that is lost.

1.4.3 Cost of illness

The socioeconomic burden of MS can also be considered as monetary values representing the cost of illness (COI) from a societal perspective. Cost-of-illness studies identify important cost components of morbidity, magnitudes of costs in a given setting and point in time, and potential variations in the costs.[178] The findings can map the stakeholders and provide insights to what extent these different stakeholders bear the costs, be it society, the healthcare sector, patients, or their employers.[178] The resource use underlying the cost components can indicate unmet needs and consequently where intervention is required and potential cost savings could occur. The findings may also encourage policy debate, inform planning of healthcare services, evaluation of policy options, and prioritisation of prevention research.[179]

Outcomes or effects need to be included alongside the costs to provide direct guidance in terms of resource allocation.[180,181]

There are three steps to estimating the costs associated with a disease.[180]

First, all relevant resources used or consumed as a consequence of the disease of interest should be identified.[180] Costs can be divided into different categories. The COI of MS is most often described by the costs of healthcare resources consumed (healthcare costs) and production losses resulting from work disability (productivity losses).[8,178,180] In addition to healthcare costs (e.g., healthcare visits, drugs), there are also non-medical direct costs which stem directly from the disease, for example, transportation, informal care, investments, and personal assistance costs. Healthcare and non-healthcare cost components with direct payments because of the disease may be summarised as "direct costs".[178] Then there are the wider costs that are not paid directly but nonetheless arise from lost resources due to the disease, sometimes referred to as "indirect costs". The most studied within this category are the costs associated with production losses,[182,183] the output loss due to reduced labour input.[86] Productivity losses are therefore a quantification of the socioeconomic burden of work disability into monetary values. They can be incurred by both absences from work due to disease (absenteeism, covering temporary absences to permanent exit from the labour force) and reduced productivity while at work due to disease (presenteeism).[178,183] The third category of costs, intangible costs, are seldom included. They represent the non-monetary effects of the disease, such as pain and discomfort.[92,178]

The resource items relevant to include depends on the perspective of the analysis. The chosen perspective underlies both the design and interpretation of results. The two predominant perspectives are the healthcare and societal perspectives. The healthcare perspective includes only the costs borne by the healthcare system or payer. In contrast, the wider societal perspective should comprise all costs incurred for the treatment and wider morbidity of the disease, regardless of who bears the cost (e.g., patients, families, employers, healthcare sector, other sectors).[180,184] This is the broadest perspective and is always relevant; otherwise key costs may be ignored, which would lead to incomplete assessments and eventual inefficient resource allocations.[180,185] In practice, the costs included may be a limited selection of the relevant costs. The guidelines for economic evaluation when applying for reimbursement issued by the Swedish Dental and Pharmaceutical Benefits Agency state that a scenario with a societal perspective should be included.[184] It is particularly pertinent to look beyond healthcare costs as MS is a chronic and often progressively disabling disease that affects many life domains.[186]

Second, the quantities for each identified type of resource used or consumed as a consequence of the disease should be counted as physical units, for example, the number of hospital admissions, physician visits, or days off work due to work disability.[180] Such data can be obtained from registers, patient charts, or self-reported via questionnaires.

The third step involves collating unit costs as a value of the physical unit for each type of resource.[180] Resources should be valued at their opportunity cost, the value of benefits forgone because of not using these resources for the next best alternative.[180] There are a range of approaches to estimate the opportunity cost, with differing levels of precision.[180] The precision of healthcare costs ranges from microcosting of each individual component of resource use within the visit to an average cost per visit, for example, a per diem cost of a

hospitalisation.[180] National price lists or market prices are often used for healthcare resources, although these may be an approximation and may not truly convey the opportunity cost due to distortions in the market from monopolies and state policies. Other valuation approaches are needed for resources not sold on the marketplace, such as lost production or informal care by family members. The majority of MS COI studies use the human capital approach to value productivity losses[187] and this is the preferred approach in Sweden.[184] With this approach, the cost of employment (mean gross salary plus employer's social security contributions) is the value of the lost production and this value is applied across the total period of absence.[180,183] An alternative method is the friction cost approach, which limits the costs related to an absence to the time required to hire and train a replacement worker.[183,188] Thus, these two alternatives differ in the duration of economic consequences costed in situations of work disability related absences. Ultimately, the valuation method and value chosen is dependent upon the analysis objective, perspective, and audience.

1.4.3.1 Costs of MS

The costs of MS are substantial. The estimated annual total cost per person with MS in Europe is 40,303 Euro (EUR) (2015 values) from a societal perspective, with higher costs (44,589 EUR) in Northern Europe.[189] Context matters and differences render MS COI studies hard to compare across countries due to different cost components, methods, and general differences in the setting.[7,8,181] There are variations between countries in the healthcare organisation which may produce different patterns of consumption and prices for use, as well as differences in the regulations and attitudes towards the use of social insurances.[190] Even within the same country, comparisons can be hampered due to heterogeneity in methods used.[7] Nonetheless, there are two series of multinational MS COI studies with harmonised patient-reported resource use. The first series, the European burden of illness study, was first published by Kobelt et al. 2000-2006 and then updated with a questionnaire sent to PwMS in 16 European countries in 2015,[137,191,192] including Sweden.[124,193] There is also a series published from 2012 as part of the Treatment Experience, Burden and Unmet Needs "TRIBUNE" project.[194] The cost estimates presented below mostly relate to Sweden with broader trends or cost ratios (rather than absolute cost estimates) also reported from systematic reviews. Cost ratios or relative costs have been suggested to be more robust as they reduce some of the heterogeneity and dependence on context that estimates of the magnitude of costs involve.[7] The estimates presented below are in the currency and values (if differing to the year in which the resources were consumed) presented in the respective studies.

Sweden has a relatively high level of MS COI research output.[8] The previous Swedish studies have estimated prevalent costs.[124,156,193,195-202] Prevalence-based COI studies estimate the total costs incurred within a given time-period, usually a year, whereas the more data-intensive incidence-based approach involves calculating the lifetime costs of the newly diagnosed PwMS and attributes these lifetime costs to the year of diagnosis.[178] While the prevalence costing approach is the most common among MS COI studies,[8] the inclusion of PwMS may be based on their MS diagnosis year,[156,196,200,203] or more often prevalent cohorts including PwMS at all stages.[124,193,195,198,199,202] Currently, there is a trend to focus on more recently diagnosed PwMS, to capture the resource use and costs incurred in early MS.[156,196,200,203]

Estimates of costs can be conducted with a "top-down" or "bottom-up" approach.[178,180] Bottom-up costing involves identifying and quantifying the resource use among individuals, and then multiplying these counts by unit costs to estimate the total COI as described above, while the top-down approach allocates a proportion of the total expenditure from aggregated published data on consumption and costs to the specific disease category.[178,180] The bottom-up approach permits a more comprehensive inventory of the resources used as well as the resulting costs. Bottom-up costing of patient-reported resource use from prevalent MS cohorts are the most common methods in the international MS literature, although many Swedish studies utilise the rich individual-level register data.[8] Swedish MS COI studies, except for one older study in 1994,[201] have used bottom-up methods, with the individual-level resource use informed by either patient questionnaires,[124,193,199,202] chart review,[202] or register data.[156,195-198,200,203]

Costs may refer to the costs of all resource use among PwMS.[156,195-198,200] This approach to costing is common when the aim is to compare costs among PwMS. With time from diagnosis, a greater proportion of the costs among PwMS tend to have an International Statistical Classification of Diseases and Related Health Problems (ICD) code for MS.[156] However, comorbidities are common among PwMS, with the causal pathways difficult to disentangle.[42,48] Side diagnoses are also possible in register data alongside the main diagnosis, so one cannot imply that the healthcare use or SA/DP with another diagnosis was not due to MS. Moreover, some PwMS may have an ongoing SA spell or DP with a different diagnosis than MS, and only the first diagnosis is recorded. Accordingly, not all the identified costs among PwMS will be incurred because of their MS.

There are three approaches to attribute costs to a specific disease, such as MS.[204] First, one can attribute 100% of the cost to the main diagnosis listed. This approach is most common in the literature, whether by an ICD code for MS as the main diagnosis or by asking the patients in questionnaires about their resource use due to MS. This can lead to underestimations of the costs and is only recommended when the underlying cause is straightforward to determine.[204] MS-specific costs of PwMS have often been considered, indicated either by the main diagnosis registered for the resource use[156,197,200] or as reported by patients.[124,193,199,202] The second alternative, weighted attribution, involves attributing a portion of the cost, often depending on the diagnosis position in the list of diagnoses and relevance of any comorbidities.[204] This is not common in the MS literature. Last, an incremental analysis of the costs in comparison with the costs of a cohort without the disease can establish the excess costs associated with the diagnosis from the mean difference in all-cause costs.[198,204] This excess cost method is recommended when there are comorbidities that influence the resource use or for costing chronic diseases.[204] Accordingly, with a disease like MS, it is difficult to separate the costs due to having MS from the costs among PwMS without reference groups.

Using register data, annual healthcare costs of 986 million SEK and productivity losses of 2963 million SEK were calculated for the all-cause resource use in 2010 of all 14,077 identified PwMS of working ages in Sweden.[197] Productivity losses, indicated by net days with SA or DP benefits, comprised 75% of the costs. For the healthcare costs, 38% was for resource use with MS recorded as the main diagnosis,[197] representing a lower bound estimate of the healthcare costs of MS. The diagnosis chapters for diseases of the nervous system and of the genitourinary system had the highest healthcare resource use. The proportion of the

estimated productivity losses with MS recorded as the main diagnosis was higher at 67%.[197] Diseases of the nervous system, mental disorders, and musculoskeletal disorders were the largest contributing diagnoses to PwMS' productivity loss estimates.

Costs of MS are more often presented in the literature per person. PwMS have higher total costs than their respective peers without MS. One register-based study in Sweden has included population-based matched references to indicate the excess costs of MS, with the annual average differences in total costs ranging between 225,923 and 243,751 SEK per year among prevalent MS cohorts in 2006, 2009, and 2012 and their respective reference peers (in 2012 values).[198] Among the 2012 cohort, the cost for all-cause healthcare (inpatient and specialised outpatient healthcare and prescribed drugs dispensed in pharmacies as well as the MS DMTs rituximab and natalizumab) among the PwMS was 97,575 SEK, with an excess cost of MS of 84,643 SEK (95% CI: 82,717-86,568). Similarly, the cost of foregone production due to SA and DP among PwMS was 182,658 SEK, with an excess cost of MS for productivity losses of 141,280 (95% CI: 137,601-144,960). The largest contributors to the excess costs were drug costs and DP. However, this study requires updating with information on DMT use throughout the year as well as primary healthcare.

A relapse is associated with additional costs,[7,124,194,205] estimated to be an excess quarterly cost of 36,900 SEK (2015 values) in Sweden.[124] However, relapses were infrequently reported in this study with high proportions of PwMS included with higher ages, higher EDSS scores, and progressive MS types. Relapse costs have been found to be particularly high among PwMS with shorter disease durations and lower EDSS scores.[205] Relapse costs are largely incurred from inpatient stays, day admissions, informal care, and work disability resulting in absences as well as reduced productivity at work.[181,205]

In a small study of PwMS in Stockholm Region, primary healthcare accounted for most (65%) outpatient healthcare services,[206] however, as of yet, register-based COI studies in Sweden have not included the costs of primary healthcare. When primary healthcare has been included, for example, from questionnaire data, the physician consultations in all outpatient settings (specialised outpatient and primary healthcare) are often combined.[124,202] This makes comparisons to nationwide register-based COI studies challenging, where only physician visits in specialised outpatient settings are included. However, 9.1% of PwMS in Sweden reported a visit with a general practitioner in the preceding three months in the European burden of illness study, and higher proportions with MS nurses (23.5%) and physical therapists (21.4%),[124] thus indicating high use of primary healthcare services among PwMS.

Direct non-medical costs also require other data sources than the nationwide Swedish registers. Studies indicate that these wider costs may dwarf healthcare costs, especially among PwMS with higher EDSS scores.[7,8,124,202,207] A systematic review regarding neurologic diseases summarised that PwMS have on average 9.2-249 hours of informal care per person per month.[207] Swedish findings also highlight the use of informal care as well as costs for community and social services concentrates among PwMS with severe disability.[124,202] Informal care supported 17.4% of the PwMS with mild disability with this increasing to 61.5% among PwMS with severe disability.[124]

The intangible costs of MS are infrequently included. In Sweden, an annual estimate of 325 million EUR was estimated for all PwMS in 1998,[199] or a mean cost of 11,400 EUR per

person with MS per year was estimated in 2005,[193] using the willingness-to-pay threshold of 50,000 EUR as the cost per quality-adjusted life year lost.[193,199]

The literature often focuses on differences in costs among PwMS. The heterogeneity of costs within the PwMS in Sweden has been explored in terms of disability,[124,193,195,199] year of MS diagnosis,[156] relapses,[124,193] spasticity,[202] DMTs,[203] comorbidities,[196] and by MS type.[200] The costs are skewed among PwMS; 25% of PwMS accounted for half of the total COI.[197] The total COI tends to rise with disability level.[7,8,124,181,195] In Sweden, a seven-fold increase in total costs from EDSS scores 0-1 to 8-9 has been observed.[193] Across COI studies, the ratios of total COI between different EDSS levels are relatively stable, at 1:2:3 for the categories of mild, moderate and severe disability.[8] Further support of this progression in costs was found in a recent review of COI reviews, where compared to mild disability, total costs for moderate disability were 1.4–2.3-fold higher and 1.8–2.9-fold higher for severe disability.[7] Accordingly, costs are often reported by EDSS group rather than for PwMS overall. In the last two decades, drug costs, including DMTs, have become a key cost driver among PwMS.[7,8,181,198] Costs outside the healthcare sector like informal care and productivity losses drive the costs among PwMS with more severe disability.[7,8,181]

The costs of early MS are of interest too.[168,208] Despite productivity losses concentrating among PwMS with more severe disability, both presenteeism and absenteeism aspects of work disability are already observed in early MS.[156,168,196,208] With time from MS diagnosis, productivity losses are increasingly comprised of DP costs, representing societal costs for long-term work disability as the SA-related costs decrease.[156,203] There are also considerable healthcare costs in early MS, which could be associated with the MS diagnosis and management. The progression of the costs of early MS have been previously observed in Denmark, before and after MS diagnosis, and in Sweden, after MS diagnosis.[10,156,196,200,203] Jennum et al. observed PwMS of all ages diagnosed in 1998-2006 in Denmark up to eight years before and after MS diagnosis in comparision with age and sex matched references, with differences in healthcare as well as social transfers observed already eight years prior to MS diagnosis resulting in excess costs of MS.[10] The all-cause costs among working-aged PwMS diagnosed in 2006-2009 in Sweden were explored to identify four subgroups of PwMS with similar COI-progression in the five years following MS diagnosis: “high direct and indirect costs” (32.1% of the cohort), “low direct and indirect costs” (19.9%), “high direct, but low indirect costs” (31.8%), and “low direct, but high indirect costs” (16.1%).[156] Accordingly, relatively high healthcare costs do not always correspond with high productivity losses and vice versa. Furthermore, the cost trajectories were dynamic, the relatively high-cost trajectories first increased then decreased over the study period, while the lower cost trajectories increased later in the study period at lower levels. These studies all suggest that the costs around MS diagnosis may be substantial and are dynamic.

2 RESEARCH AIMS

2.1 OVERALL AIM

The overall aim of this PhD thesis was to gain deeper knowledge of the socioeconomic burden of MS, especially among people newly diagnosed and of working ages. Work disability was a key aspect of the aim that covered both the economic situation and working life among the individuals themselves as well as the costs of MS from a societal perspective.

2.2 SPECIFIC AIMS

Four empirical studies were conducted with narrower scopes and aims to contribute with knowledge towards aspects of the wide overall aim.

2.2.1 Study I: Economic situation and work disability

Study I had the aim to investigate the heterogeneity in the annual levels and development of DI both before and after MS diagnosis by identifying distinct DI trajectories within a cohort of working-aged individuals. A secondary aim was to describe the associations of socio-demographic characteristics with the identified DI trajectories.

2.2.2 Study II: Working life, work disability, and economic situation

Study II had the aim to investigate working-life sequences among newly diagnosed PwMS of working ages. There were three sub aims: First to explore the sequences of annual states among PwMS; secondly to identify types of working-life sequences from the individuals' sequences; and finally, to investigate characteristics associated with and the economic implications of the identified types of working-life sequences.

2.2.3 Study III: Progression of the costs of MS before and after diagnosis

Study III had the aim to explore the progression of annual healthcare costs and productivity losses before and after MS diagnosis in Sweden among PwMS of working ages with comparison to the costs of a population-based, matched reference group.

2.2.4 Study IV: Costs of MS in Stockholm

Study IV had the aim to estimate the annual costs of MS including primary healthcare, among all PwMS in Stockholm County with comparison to the healthcare costs and productivity losses of population-based, matched references. A secondary aim was to investigate the annual costs of MS by time since MS diagnosis.

3 MATERIALS AND METHODS

This thesis comprises four exploratory population-based cohort studies. The data used and a summary of the methods are outlined below, then the specific methods of each study are described in turn, and lastly ethical considerations of the thesis are presented.

3.1 DATA SOURCES

All four studies utilised pseudonymised data from the larger Insurance Medicine All Sweden "IMAS" project at the Division of Insurance Medicine, Karolinska Institutet, which is part of the Relations, Work and Health across the life-course - A Research Data "REWHARD" infrastructure.[209] Within the project, different aspects of SA and DP are studied using a dataset following seven population-based cohorts of individuals aged 16-64 years and registered as alive and living in Sweden on 31 December of 1984, 1989, 1994, 1999, 2004, 2009, or 2014, respectively. This was the source population for all four studies. Linkage of the pseudonymised register data was conducted at an individual level by Statistics Sweden (Swedish: Statistiska centralbyrån) who hold the code key of the unique personal identity numbers assigned to all residents in Sweden.[210]

The eight registers used in this thesis were:

- **National Patient Register (NPR)**

The National Patient Register (NPR) (Swedish: Patientregistret) is maintained by the National Board of Health and Welfare and contains information of inpatient and specialised outpatient healthcare visits throughout Sweden.[211-213] It is mandatory for all in- and specialised outpatient visits with physicians to be reported, with nationwide coverage of inpatient admissions since 1987 and of specialised outpatient visits since 2001.[211,212,214]

The NPR contains information regarding the dates, main and side diagnoses according to the Swedish version of the ICD, and a diagnosis-related group (DRG) code for each visit. The NPR has high and increasing coverage as well as high validity,[214] with 99% of all inpatient discharges recorded.[212] Despite the overall quality of the NPR, in some cases disease-specific registers may be more optimal as the NPR does not contain disease-specific clinical information or whether the diagnosis was pre-existing or newly established at the recorded visit.[212]

- **Swedish MS Registry (SMSreg)**

The Swedish MS Registry (SMSreg) (Swedish: MS-registret) is the MS-specific part of NEUROreg, maintained by Region Stockholm.[215] It is a nationwide clinical register used for pharmacological surveillance and for enhancing the quality of MS care, forming part of the National Quality Registry system.[60,216,217] It is voluntary for neurologists and their patients to include information into the SMSreg. Coverage of the register is increasing with time, in 2019 all neurology clinics reported information for an estimated 80.1% of all PwMS in Sweden.[218] For the included PwMS diagnosed by a neurologist, the register contains high quality and comprehensive clinical information,[216] including diagnosis and clinical onset dates as well as detailed information on DMTs, with information predating the register's establishment in 2001.

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

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) (Swedish: Longitudinell integrationsdatabas för Sjukförsäkrings- och Arbetsmarknadsstudier) was established in 1990 and is maintained by Statistics Sweden.[123,219] The register has annual information for all individuals living in Sweden on the 31 December of the respective year regarding demographics, education, incomes, and social insurance benefits, with data provided from other authorities to supplement the information held by Statistics Sweden.[123,219]

- **Swedish Prescribed Drug Register (SPDR)**

The Swedish Prescribed Drug Register (SPDR) (Swedish: Läkemedelsregistret), held by the National Board of Health and Welfare, was established in July 2005.[220,221] The SPDR contains information (dispensing dates, Anatomical Therapeutic Chemical Classification System (ATC) codes, quantities, and costs) for all prescribed drugs dispensed at community pharmacies in Sweden. This register does not contain information of drugs purchased over the counter or controlled drugs procured for administration within healthcare.[221,222]

- **Cause of Death Register (CDR)**

The Cause of Death Register (CDR) (Swedish: Dödsorsaksregistret), established in 1952, is administered by the National Board of Health and Welfare.[223,224] The CDR contains information on dates for all registered deaths of residents.

- **Swedish Cancer Register (SCR)**

Established in 1958 and maintained by the National Board of Health and Welfare, the Swedish Cancer Register (SCR) (Swedish: Cancerregistret) has compulsory reporting by healthcare providers of all newly detected cancer cases.[225,226]

- **Micro Data for Analysis of the Social insurance (MiDAS)**

The Micro Data for Analysis of the Social insurance (MiDAS) (Swedish: MikroData för Analys av Socialförsäkringen) is a database administered by the Swedish Social Insurance Agency containing detailed information on the SA and DP benefits paid by the agency.[121] The information includes the start and end dates, extent (full- or part-time), and the diagnoses coded with ICD codes for each SA spell and DP. The MiDAS contains data from 1994, with information on SA diagnoses from 2005. Data on SA-spells ≤14 days were not included from MiDAS to avoid introducing bias regarding employment status.

- **Region Stockholm's healthcare database (VAL)**

The healthcare database (VAL) (Swedish: Vårdanalysdatabasen), is an administrative healthcare register administered by Region Stockholm since 1993.[227,228] The VAL contains information of all visits to both public and private healthcare providers with contractual agreements with Region Stockholm. Since 2003, VAL has also included information on primary healthcare contacts, including the date, diagnosis (main and secondary) by ICD code, type of visit, and healthcare professional contacted.[228] The latter means that, unlike the NPR which relates only to healthcare with physicians, the VAL also includes information about contacts with other types of healthcare professionals. The data in the VAL is of high validity

and accuracy with approximately 85% of primary healthcare contacts having a recorded diagnosis.[227]

3.2 THE FOUR STUDIES INCLUDED IN THIS THESIS

All four studies investigated the socioeconomic burden among working-aged PwMS. The definition and process of identifying PwMS from the register data developed across the studies and is summarised in Table 1. Study I-III all included newly diagnosed PwMS from the NPR; however, the NPR does not contain information regarding when the diagnosis was established. Therefore, these criteria strengthened assumptions that it was a newly established diagnosis (Study I-III) and that the MS ICD code identified a person with MS (Study II and III). Study IV differs in that PwMS were identified from the SMSreg and included all prevalent diagnoses.

Table 1: Summary of the definitions of having a diagnosis with MS within the four studies.

	Study I	**Study II**	**Study III**	**Study IV**
Target population	Working-aged people with newly diagnosed MS in 2008-2009 in Sweden	Working-aged people with newly diagnosed MS in 2008-2011 in Sweden	Working-aged people with newly diagnosed MS in 2010-2012 in Sweden	Working-aged people with prevalent MS in 2018 in Stockholm
Age at MS diagnosis	24-58	20-55	23-59	18-63
MS	MS ICD code in the NPR	MS ICD code in the NPR	MS ICD code in the NPR	Inclusion in the SMSreg with a diagnosis before 31 December 2017 with recorded onset of MS when ≥18 years
Newly diagnosed MS	First ever MS code recorded - 3 consecutive years of residence prior to first MS ICD code	First ever MS code recorded - 2 consecutive years of residence prior to first MS ICD code AND - No prior diagnosis in the SMSreg >365 days prior to the NPR date	First ever MS code recorded - 5 consecutive years of residence prior to first MS ICD code AND - No prior diagnosis in the SMSreg >365 days prior to the NPR date	Not applicable: Prevalent cohort, stratified by years since MS diagnosis
Verified MS diagnosis		- At least 1 additional MS ICD code in the NPR OR - Inclusion in the SMSreg	- At least 1 additional MS ICD code in the NPR OR - Inclusion in the SMSreg	Inclusion in the SMSreg

Abbreviations: ICD: International Statistical Classification of Diseases and Related Health Problems; MS: Multiple sclerosis; NPR: National Patient Register; SMSreg: Swedish Multiple Sclerosis Registry.

There is no fixed age for old-age retirement in Sweden, with a right to work until one is 68.[229] Therefore, throughout the thesis, age limits were set so that follow-up would not surpass an upper age limit, set as the customary age of 65,[114] or fall below 19 years of age, when one is eligible for DP. However, it is acknowledged that some individuals start old-age pension earlier while others continue to work after 65.

Work disability was operationalised throughout with information on net days with SA and DP (See 1.3.3 for details on SA and DP benefits). Several measures of the complex

phenomena work disability were used:[149,150] Annual net days of SA, DP, and SA/DP; proportions on SA, DP, and SA/DP; and the annual sums from SA and DP benefits were incorporated within the DI measure. Information was sourced from LISA in Study I and II and from MiDAS in Study III and IV. All-cause SA/DP was used in this thesis, like much of the literature which does not differentiate on SA/DP diagnoses.

All analyses were performed using Statistical Analysis System (SAS) v.9.4 except for the sequence analysis conducted in R v.3.5.2 (TraMineR[230] and WeightedCluster[231]) and the costing data management with STATA v.15. For all statistical analyses, a *p*-value <0.05 was considered statistically significant.

An overview of the materials and methods of the four exploratory studies is contained in Table 2 and a detailed description of the methods in each respective study follows.

Table 2: Summary of the four included studies.

	Study I	**Study II**	**Study III**	**Study IV**
Design	Longitudinal cohort study.	Longitudinal cohort study.	Longitudinal cohort study with a reference group.	Cohort study with a single year of observation with a reference group.
Study period	12 study years (Y_{-7} to Y_{+4}) (2001-2013) relative to MS diagnosis year (Y_0).	7 study years (Y_{-1} to Y_{+5}) (2007-2016) relative to MS diagnosis year (Y_0).	9 study years (Y_{-4} to Y_{+4}) (2006 to 2016) relative to MS diagnosis year (Y_0).	1 year (2018).
Study population	1528 newly diagnosed PwMS (69% women).	2595 newly diagnosed PwMS (70% women).	1988 newly diagnosed PwMS and 7981 matched references without MS (1:4 with exact matching) (69% women).	2806 prevalent PwMS and 28,060 matched references without MS (1:10 with propensity score matching) (70% women).
Inclusion and exclusion criteria	First ever MS diagnosis in 2008-2009; working-aged (25-59 years, Y_0); lived in Sweden for the 3 years before Y_0; and living in Sweden in Y_0.	First ever MS diagnosis in 2008-2011; working-aged (20-55 years, Y_{-1}); lived in Sweden for the 2 years before Y_0; at least 1 additional MS code; and living in Sweden Y_{-1}-Y_{+5}.	PwMS: First ever MS diagnosis in 2010-2012; working-aged (23-59 years, Y_{-1}); lived in Sweden for the 5 years before Y_0; living in Sweden in Y_0; and at least 1 additional MS code. References: No MS; lived in Sweden for the 5 years before Y_0; and living in Sweden in Y_0. All: Living in Sweden Y_{-4}-Y_{+4}.	Working-aged (19-64 years, Y_{-1}) Stockholm residents in 2018. PwMS: MS identified as a diagnosis in the SMSreg in 2017 or before; and MS onset when aged ≥18. References: no MS, other demyelinating disorders, or MS DMTs.
Data type and source	Register data: NPR, LISA, and CDR.	Register data: NPR, LISA, CDR, SCR, SPDR, and SMSreg.	Register data: NPR, LISA, CDR, SPDR, SCR, SMSreg, and MiDAS. Unit costs.	Register data: NPR, LISA, SMSreg, CDR, VAL, SPDR, and MiDAS. Unit costs.
Outcome measure	Annual DI, earnings, and net days of SA/DP.	Clusters of sequences of 7 annual states representing the types of working-life sequences. Annual earnings, income from activity and DI.	Annual COI: healthcare costs (inpatient and specialised outpatient healthcare, and prescribed drugs) and productivity losses (net days with SA/DP).	Annual COI: healthcare costs (as in Study III as well as primary healthcare and MS DMTs) and productivity losses.
Statistical analyses	Descriptive, two-proportion z-tests, dependent t-tests, group-based trajectory models, multinomial logistic regressions, chi^2 tests, and likelihood ratio chi^2 tests.	Descriptive, chi^2 tests, sequence analysis, multinomial logistic regressions, and dependent t-tests.	Descriptive, chi^2 tests, independent t-tests, and repeated measure Poisson regressions with GEEs and an autoregressive correlation structure.	Propensity score calculated with a logistic regression model. Descriptive, chi^2 tests, and independent t-tests with bootstrapped 95% CIs.
Factors included in the analyses	Annual outcomes stratified by sex and age. Multinomial logistic regressions of the trajectory group membership (sex, age, educational level, birth country, type of living area, family composition, and work disability).	Sex, age, and cohort year.	MS, cohort year, and matching variables (sex, age, educational level, type of living area, and birth country) with and without an interaction term MS*study year. Other models: educational level, type of work, family composition, and comorbidity.	Sex, age, birth country, degree of urbanisation of the municipality of residence, educational level, and family composition included in the logistic regression to calculate the propensity score. Costs stratified by time since MS diagnosis.

Abbreviations: CDR: Cause of Death Register; CI: Confidence interval; DI: Disposable income; DMT: Disease modifying therapy; DP: Disability pension; GEE: Generalised estimating equation; LISA; Longitudinal Integration Database for Health Insurance and Labour Market Studies; MiDAS: Micro Data for Analysis of Social Insurances; MS: Multiple sclerosis; NPR: National Patient Register; PwMS: People with multiple sclerosis; SA: Sickness absence; SCR: Swedish Cancer Register, SMSreg: Swedish Multiple Sclerosis Registry; SPDR: Swedish Prescribed Drug Register; VAL: Region Stockholm's healthcare database.

3.2.1 Study I: Economic situation and work disability

In Study I, titled *Disposable income trajectories of working-aged individuals with diagnosed multiple sclerosis*,[232] the heterogeneity of economic situation among newly diagnosed PwMS was investigated.

3.2.1.1 Design and study population

Study I was an explorative longitudinal population-based cohort study of 1528 PwMS of working ages diagnosed with MS in 2008-2009. The study period spanned a maximum of 12 years with annual information, from Y_{-7} (2001 or 2002) to Y_{+4} (2012 or 2013). A relative time scale to Y_0, representing 31 December of the diagnosis year, was constructed to form a single cohort (n=1528 at Y_0). Register data (NPR, LISA, and CDR) were available up until 31 December 2013. A longer pre-diagnosis period was incorporated to capture early changes to one's economic situation, between the onset of symptoms and a diagnosis of MS.

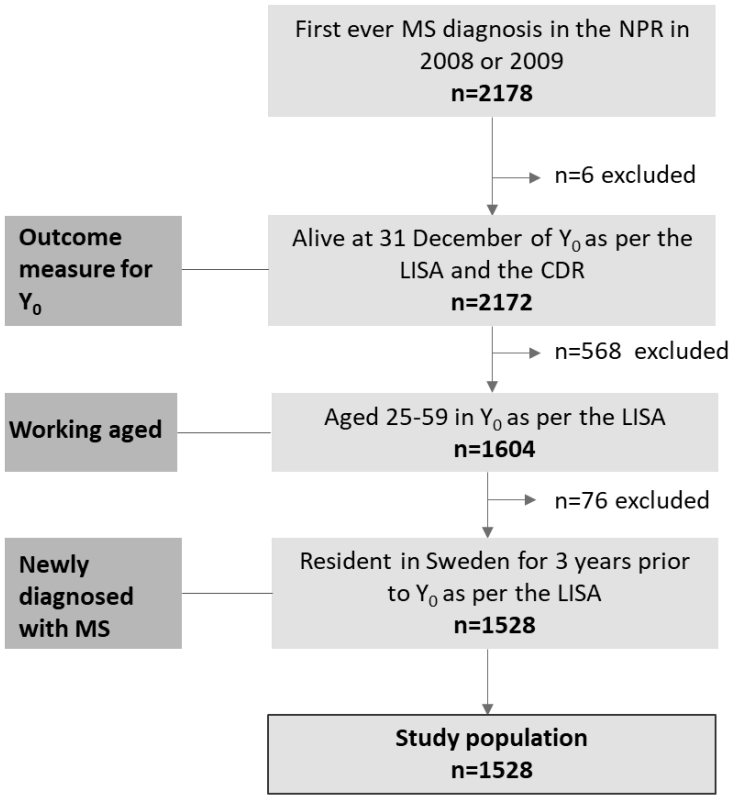

Figure 1: Study population flow chart for Study I.

Notes: Y_0 refers to the year of MS diagnosis (2008-2009).

Abbreviations: CDR: Cause of Death Register; LISA: Longitudinal Integration Database for Health Insurance and Labour Market Studies; MS: Multiple sclerosis; NPR: National Patient Register.

Newly diagnosed MS was defined in Study I as the first ever recorded MS ICD code (G35, with no prior code recorded for G35 or 340) as a main or secondary diagnosis for inpatient or specialised outpatient healthcare in the NPR. The study population was formed by identifying all individuals with a first ever recorded MS diagnosis in the NPR in the years of interest (2008 or 2009, n= 2178) (Figure 1). Individuals were then included if alive 31 December Y_0, aged 25-59 in Y_0, and having three years of residence in Sweden prior to the

MS diagnosis (in total, n=650 excluded). The final study population comprised of 1528 individuals in Y_0 (2008 cohort n= 768, 2009 cohort n=760).

The cohort was followed from Y_{-7} (n=1491), or year of immigration (n=37), until Y_{+4} (n=1502), year of death (n=17), or year of emigration (n=9), whichever occurred first. Emigration within this thesis was assumed after two consecutive years without LISA records and set as occurring the 31 December of the first year with missing records. A single year missing was sufficient if missing in the last year of available data. In total, 98% of the included individuals had outcomes observed in Y_{+4}.

3.2.1.2 Outcomes

Annual outcome measures were sourced from the LISA and analysed for the 12-year study period. The main study outcome to investigate individual's economic situation was DI. In addition, earnings from paid work as an active income source and a measure of work disability were included as secondary outcomes as two significant components of DI among PwMS.[126] Incomes were inflated by Statistic Sweden's Harmonised Consumer Price Index[233] and presented as 2016 monetary values in SEK.

3.2.1.2.1 Disposable income (DI)

The main outcome measure was the annual level of individualised household DI over 12 years. Disposable income is the combined total sum of incomes received within the household, adjusted for the household size by a total household consumption weight (See 1.4.2).[176] This continuous measure per person (consumption unit) was constructed by Statistics Sweden. The consumption weights facilitate the comparison of living standards of households with different compositions by dividing (equivalising) household income. The weights implicitly assume that the economic resources are shared within the household. This DI measure reflects informal arrangements to adapt to MS, such as spousal support. The statistical definition of a family may differ from the actual household composition, with the largest difference between two unmarried adults living together without common children, which are classified as single in the register data.[176]

A modification of the DI calculation in 2004 allowed for capital deficits to be included as negative values, if exceeding the capital gains.[176] Therefore, all negative DI values were set to zero, the previous floor value (<0.5% of entries).

3.2.1.2.2 Earnings

Earnings comprised the annual gross income from paid work (salaries/wages) and income from other active business activities, excluding deficits (hereafter referred to as earnings).[176] Any SA among employees paid by the employer could not be disentangled from the total and was included as earnings.[176]

3.2.1.2.3 Work disability

The annual number of net days with SA or DP benefits paid for any diagnosis recorded in the LISA were combined as work disability.[176] Net days were calculated combining part-time days (25-75%) to full days (100%) of absence. In all four studies, net days are used rather than gross days to consider the possibility of work disability giving rise to part-time absences

(different grades of reduced work capacity) and different durations of time. The total net days of SA and DP were combined and capped at the number of possible days in the respective year. This is because an individual with 50% DP for MS could, for example, have simultaneous SA due to an injury up to 100% of their usual working hours.

3.2.1.3 Covariates

Sociodemographic characteristics were included to describe the individuals following particular DI trajectories. The mean outcomes over time were also stratified by age and sex. The following sociodemographic characteristics from the LISA were included with information from Y_0:

- Sex (women/men);
- Age was calculated from year of birth and categorised (25-34; 35-44; 45-54; and 55-59 years);
- Educational level (university/college education, yes/no) was dichotomised from the highest level of education (elementary school, high school, or university/college) with passed courses or completed.[176] Data on education is available for 98% of individuals aged 25-64 years in LISA, with those with missing data mainly born outside Sweden.[123] Individuals with missing data were categorised as having elementary school level education throughout the thesis. There is an estimated accuracy of the highest level of education of 85%.[123] This variable refers to initiation of education at the respective level, for example, completion of a semester at university and the registration of a passing grade of these course points would equate to university/college level education. Accordingly, the estimates for university/college education could be slightly higher than estimates based on an awarded degree or diploma;
- Type of living area was based on the population density of the municipality of residence and calculated by Statistics Sweden (large cities, Stockholm, Gothenburg, and Malmö; medium-sized towns, those with >90,000 inhabitants within 30km; and rural areas, small towns and rural areas);[234]
- Country of birth was dichotomised as a binary variable (Sweden, yes/no) throughout the thesis, with missing categorised as born outside of Sweden; and
- Family household composition was included as two binary variables throughout the thesis regarding being married/cohabiting (yes/no) and living with at least one child (yes/no). Cohabitants are identified only if living with children in common, otherwise they coded as single within the LISA database.[123,176] Family composition was included as working life is best understood in broader context including partnership and family formation.[235]

Two measures of work disability in Y_0 were constructed with information from the LISA:

- The annual number of net days with SA/DP benefits (0; <90; 90-180; and >180); and
- Disability pension benefits at any point within the year (yes/no).

3.2.1.4 Statistical analyses

Before merging the two diagnosis year cohorts into a single cohort of 1528 PwMS, differences in the sociodemographic and work disability characteristics were compared with two-proportion z-tests. Only the proportions with work disability >180 days in Y_0 differed.

Then the distributions of the outcomes were investigated. Incomes in LISA are reported as hundreds of SEK, all incomes (in all studies) were converted to SEK to conform with usual units of the currency. After setting all negative DI values to zero, the incomes were capped and top-coded at the 99% level for the study (DI =549,650 SEK and earnings = 753,812 SEK).[236] Disposable income and earnings were observed to have an approximately normal distribution with slight right-skewness after trimming extreme outliers to the 99% level. This reduced the potential influence of a few extreme values and produced a more normal distribution than logarithmic transformation due to the presence of zeros.

Next, the means of annual DI, earnings, and work disability, in total and stratified by sex and age-group were calculated. The mean differences in annual DI between the diagnosis year (Y_0) and end of follow-up (Y_{+4}) with 95% CIs were estimated in this sufficiently large cohort with dependent t-tests.[237]

Group-based trajectory modelling was then used to identify trajectories of mean annual DI among the PwMS from Y_{-7} to Y_{+4} (SAS procedure Proc Traj[238]). Trajectories were investigated to move beyond annual estimates to trends that reflect the dynamic nature of income. Through this method, subgroups of individuals who followed distinct trends of DI were identified (trajectory groups), and a regression model was estimated for each subgroup to approximate the heterogeneity among PwMS.[238,239] This method allowed for investigation into the unobserved diversity of DI trends rather than summarising all with a single trend or relying solely on observed grouping variables.[238] Accordingly, this method provided an understanding of the different patterns of DI existing within the MS population over time. In situations of death or emigration after Y_0 (or immigration before Y_0), the outcome was considered as missing for that year and all remaining (or prior).

Regression models for two to eight trajectory groups were tested with an underlying censored normal distribution[238] and linear, quadratic, or cubic functions. The number of trajectories in the final model was determined based on interpretability, a Bayesian Information Criterion "BIC" value closer to zero to identify the best fitted model,[240] and an average group belonging probability ≥0.7 from the individual model-fit estimates of a multinomial logit function.[238,241] A quadratic model with seven trajectories was determined as the best fitting model to illustrate the variations in DI development around the years of MS diagnosis. The estimated Bayesian Information Criterion values suggested little additional benefit after fitting for seven groups and the mean belonging probabilities for the seven identified trajectory groups ranged 0.89-0.97, indicating a good model fit.[238,239,241] Spaghetti plots of annual DI were constructed for the seven trajectory groups to visually inspect the plausibility of group assignments and variability of the individual trajectories within each trajectory group.[239] Group One had the smallest membership (1.3%) but was included as improved model fit and was consistent with skewed income within a population. This group's trajectory was artificially levelled off by the 99% cap.

After ascertaining the optimal number of trajectory groups to describe economic situation around MS diagnosis, the individuals were assigned to the group to which they had greatest probability of belonging to. The associations of sociodemographic characteristics and trajectory group membership were then investigated. Pearson's chi^2 tests compared the trajectory groups regarding sociodemographic composition. Likelihood chi^2 tests assessed whether the sociodemographic covariates were associated with all trajectory groups in the full

model including all covariates. Lastly, differences in Nagelkerke-R^2 (Diff R^2) evaluated the strength of these associations. Diff R^2 were calculated by comparing the Nagelkerke-R^2 value from a multinomial logistic regression model where the examined covariate was included with that from a model with the covariate excluded. The Diff R^2 values were interpreted as the increased variance explained by adding the covariate to the model.[155]

3.2.2 Study II: Working life, work disability, and economic situation

In Study II, titled *Types of working-life sequences among people recently diagnosed with multiple sclerosis in Sweden: a nationwide register-based cohort study*,[242] the typical patterns of working life among newly diagnosed PwMS were described and the economic implications of these identified working-life patterns were investigated.

3.2.2.1 Design and study population

Study II was an exploratory longitudinal cohort study with a population-based cohort of 2595 PwMS of working ages diagnosed with MS in 2008-2011. There was a relative time scale to the year of MS diagnosis (Y_0) with annual observation for seven years to identify sequences of working life from one year prior (Y_{-1}, 2007-2010) to five years after (Y_{+5}, 2013-2016) Y_0. Register data (NPR, LISA, CDR, SCR, SPDR, and SMSreg) were available up until 31 December 2016.

Newly diagnosed with MS was again defined by identifying the first ever registered MS code in the NPR as a main or secondary diagnosis in the years of interest (2008-2011) (n=4314) (Figure 2). Working-aged was defined as 20-55 in Y_{-1} (n=3142). Several exclusions were then applied to confirm the individuals were newly diagnosed with MS and to verify the MS diagnosis (in total, n=490 excluded). This resulted in 2652 PwMS (2008 cohort: n=650; 2009 cohort: n=668; 2010 cohort: n=623; and 2011 cohort: n=711). Individuals were censored after MS diagnosis from the year of emigration (n=27) or death (n=30) if occurring before the end of Y_{+5}. In total, 2595 (97.9%) PwMS had complete follow-up and were included in the analyses.

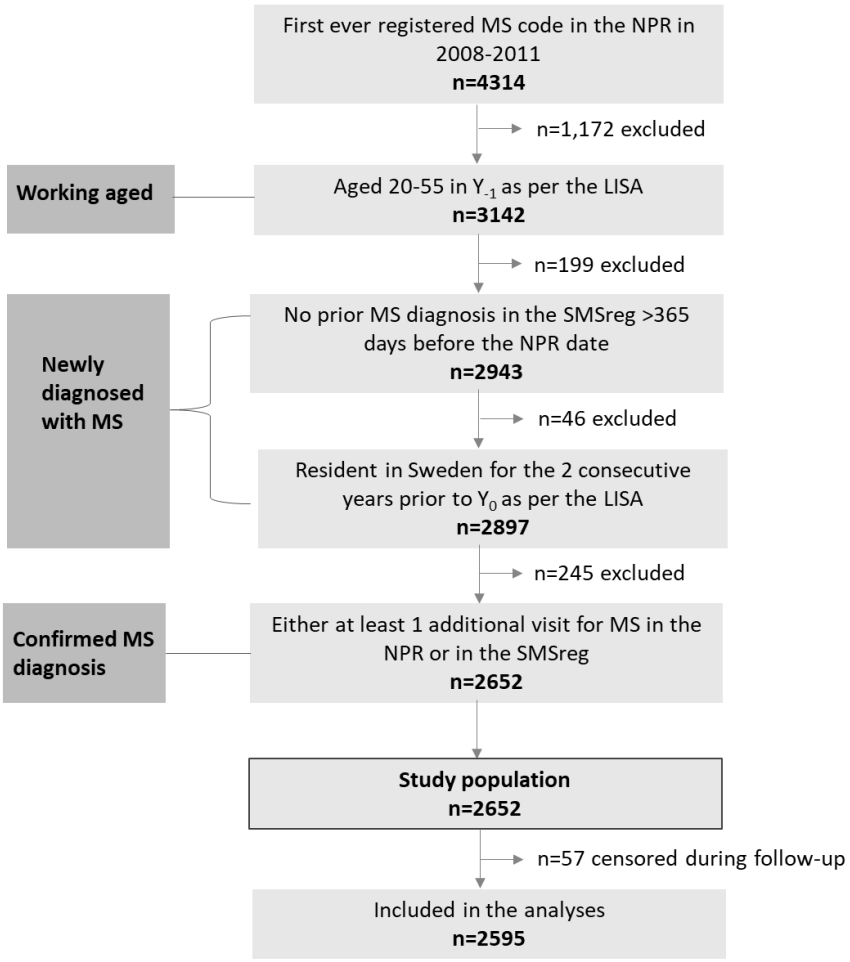

Figure 2: Study population flow chart for Study II.

Notes: Y_0 refers to the year of MS diagnosis (2008-2011).

Abbreviations: LISA: Longitudinal Integration Database for Health Insurance and Labour Market Studies; MS: Multiple sclerosis; NPR: National Patient Register; SMSreg: Swedish Multiple Sclerosis Registry.

3.2.2.2 Outcomes

3.2.2.2.1 Working-life sequences

The term 'working life' has previously been operationalised within MS research to broadly capture the complex situation among PwMS, including not only paid work, but also transitions to and from unemployment or work disability,[128] as well as both health outcomes or transitions (e.g. MS diagnosis) and labour market experiences and transitions.[129] This broad conceptualisation facilitates the focus on maintaining activity as well as transitions to and from activity, rather than on a specific single consequence. Working life is often framed by a school to work transition at the beginning and then a work to old-age retirement transition at the end.[129] Based on the study cohort's age, most individuals were likely followed somewhere in between these two events. The length of the sequences was limited to include newly diagnosed PwMS recently in time.

The individual-level sequences of working life were constructed from annual states with information from the LISA. Everyone was assigned seven working life states, one to summarise each of the study years. The annual states were defined to focus on how PwMS remain in activity, including with different levels of support from social protections if

experiencing work disability. Given that there may be overlaps between the states, the states were ranked to set a discrete state for each position within an individual's sequence. In order of assignment, the possible states were *Censor, SA/DP, Mixed: SA/DP 180+ days, Mixed: SA/DP 30-180 days, Activity,* and *Other*.

A *Censor* state was assigned to individuals who had died or emigrated in that year and all remaining study years. Individuals with a *Censor* state at any point in their sequence were subsequently excluded from the analyses.[243] Accordingly, all other states require individuals to be alive and registered as living in Sweden 31 December of the relevant year.

Three states were constructed to represent a year in which one experienced work disability but with a different extent of work disability in terms of grade and duration. Work disability was again operationalised by combining the net days of SA and DP recorded in the LISA. The net days with SA and DP benefits paid by the Social Insurance Agency were again combined and capped at the maximum possible days in the year. The *SA/DP* state was defined as ≥364 net days of work disability in the calendar year. This state represents a high grade of reduced work capacity for the entire year. Two states with mixed activity and some extent of work disability were constructed based on the number of net days of SA/DP during the year to illustrate more nuanced reductions in work capacity. *Mixed: SA/DP 180+ days* described a year predominately with work disability alongside some activity and *Mixed: SA/DP 30-180 days* for a year mostly in activity but with some work disability.

The *Activity* state was defined as having combined income from earnings, student allowances, compensated parental leave, or the active unemployment compensation above 24% of the annually adjusted price base amount.[122] The lowest possible annual income from activity to be assigned this state ranged between 9925-11,125 SEK. The four sources of income were included with the assumption that the recipient was usually active and had work capacity, irrespective of whether the income was derived from economic activity. The assumption of having work capacity is premised on these individuals' eligibility for SA and that individuals with these time limited benefits would rather apply for SA benefits in situations of work disability to preserve their possible days with the other benefits/allowances.[126] Earnings was the predominant (86-93%) income source in each year. Accordingly, the *Activity* state captured more than simply no work disability, but also that these individuals would be eligible for SA/DP and are usually active. Given the inclusion of student allowances, activity refers to broader functioning of usual activities and capacity to do these activities, consistent with the International Classification of Functioning, Disability and Health "ICF" definition of activity as executing a task or an action.[77]

Finally, the *Other* state constituted individuals who were alive and registered as living in Sweden but did not meet the definitions for the above states, for example, individuals who were homemakers or unemployed but ineligible for unemployment compensation.

3.2.2.2.2 Economic implications of the working-life sequences

Three measures of annual income were included from the LISA as continuous outcomes for the first and final study year (Y_{-1} and Y_{+5}). All incomes are presented in 2015 SEK values with adjustment for inflation.[233]

- Earnings were included with extreme values top coded at the 99% level for this study (759,001 SEK) to reduce right skewness.[236]
- Income from activity (combined income from: earnings, student allowances, compensated parental leave, and unemployment compensation) was constructed from the composite incomes and top coded at the 99% level for the study (764,656 SEK).
- Disposable income was also included with all negative values were set to 0 (<0.8% of entries) and top coded at the 99% level (683,681 SEK).

3.2.2.3 Covariates

All sociodemographic characteristics were measured on 31 December Y_{-1}, informed by the LISA. These included:

- Sex (women/men);
- Age at diagnosis (groups, 20-24, 25-34, 35-44, 45-55);
- Country of birth (Sweden, yes/no);
- Educational level (university/college education, yes/no);
- Type of living area (large cities, medium-sized towns, rural areas);
- Family composition: married/cohabiting (yes/no) and living with children (yes/no);
- Geographic area of residence within Sweden (North, South, East), based on Eurostat's Nomenclature of Territorial Units for classification of the municipality of residence to classify Sweden into three geographic areas;[244] and
- Type of work (manager, office work, manual labour, unclassified work, not in paid work) was constructed based on the degree of physical demands by combining information regarding employment status and occupation.[135] In this thesis, individuals employed by the armed services were placed within unclassified work due to small numbers (n= 3 in Study II). Employment status described whether an individual was working (employed or self-employed) or not.[123,176] Occupation referred to the occupation which comprised the largest income source for the individual.[176]

Comorbidity in Y_0 was operationalised with a modified unweighted Rx-Risk Comorbidity Index constructed from pharmacy information.[245,246] Comorbidity was included because in general, PwMS have more comorbidity than the general population in Sweden in terms of more disease categories and receiving additional chronic diagnoses at an earlier age.[49] Internationally, PwMS with numerous comorbidities have been observed to be more likely unemployed, suggesting that comorbidity poses a further challenge and can disrupt working life.[47,56] Psychiatric comorbidities in particular have been observed among Swedish PwMS as associated with a higher risk for DP.[54]

The Rx-Risk Comorbidity Index, originally called the Chronic Disease Score, mapped the ATC codes from a single dispensing in the SPDR of a drug to a condition or clinical group representing a comorbidity group.[245,247] Given most cancer treatments are administered within healthcare and not captured in the SPDR data, if individuals had a cancer detected in Y_0 and were in the SCR (yes), they were included in the cancer comorbidity group (n=18). Furthermore, MS DMTs dispensed in pharmacies were excluded from the index and instead measured separately as MS drugs (yes/no) (ATC codes: L03AB07; L03AB08; L03AX13; L04AA23; and L04AA27 for Study II). Comorbidity was then classified as 0, 1-2, 3-4, ≥5 comorbidity groups.

Specific conditions of interest due to prevalence[124] and potential association with working-life outcomes[54,57,124,151,248,249] were identified from the index: Anxiety/depression (yes/no) (ATC codes: N05BA01–N05BA56; N05BE01; N06AA01–N06AG02; N06AX01–N06AX11; N06AX13–N06AX26; and N06AX12) and pain (yes/no) (ATC codes: M01AB01–M01AX01; and N02AA01–N02AX99).

3.2.2.4 Statistical analyses

The study population was described by frequencies and percentages. Chi^2-tests investigated differences in the characteristics by MS year before merging into a single study cohort. Differences in proportions were observed regarding the number of comorbidities and anxiety/depression.

Sequence analysis methods were developed to find similar patterns in deoxyribonucleic acid, DNA, but are increasingly adopted in other research areas including social sciences because of the holistic approach of the method to analyse processes, such as the life course.[243,250-254] An explorative method that could compare a large number of individual sequences, identify patterns, and group the sequences that were most similar was required for this study.[254] Sequence analysis was conducted in three steps: first the individual sequences of the five possible annual activity states were constructed from Y_{-1} -Y_{+5} and described; second the differences between the sequences were calculated; and third, grouping of sequences was performed with cluster analysis. Accordingly, the algorithmic and data-driven method allowed for the development of a typology and assignment of individuals to their respective type. After which, the grouped sequences were further analysed to investigate patterns of membership and economic implications of the identified sequence types. A more detailed description of this novel method follows below.

First the individuals' sequences were constructed from the annual states defined above in 3.2.2.2.1. A sequence is an ordered list of states and episodes of successive identical states expressed on a time axis.[252-254] Three individuals had a single missing state which was imputed from the adjacent states. The characteristics of the individuals' sequences were described with aggregate measures regarding the duration and frequency of the states and number of state transitions.

After constructing the individual sequences, optimal matching algorithms were used to compare how far away one's sequence was from another's.[255] The dissimilarity measure (or edit distance) between the sequences was defined as the operation cost of the number of steps performed (operations) to transform one sequence into another when they are aligned.[253,254,256] This can be thought of as the minimum number of operations, or costs, to turn sequence A into sequence B. Different operations can be used: indel (insert or delete states) and substitution (substitute a state). The researcher sets the costs for the respective operations.[254] In Study II, a cost of 1 was set for indel operations and substitution operations were set to have data-driven costs derived from the observed state transition matrix (time independent transitions) (Table 3). The frequency of the specific transitions in the data defined the extent of similarity and the respective costs. Higher costs were assigned by the matrix to substitutions between states with rare transitions and lower costs for frequently occurring.[255] Variable substitution costs from the observed transitions are commonly used, and are recommended for career sequences.[257] The lowest cost is selected when there is more

than one solution to turn the sequences into one another.[254] The result of the pairwise optimal matching was a matrix (2595*2595) of the dissimilarity for each pair of sequences within the data.

Table 3: Data driven substitution cost matrix [a] of the people with MS (n=2595) for the five annual states.

	SA/DP	***Mixed: SA/DP 180+ days***	***Mixed: SA/DP 30-180 days***	***Activity***	***Other***
SA/DP to	0.00	1.70	1.91	2.00	1.98
Mixed: SA/DP 180+ days to	1.70	0.00	1.67	1.93	1.93
Mixed: SA/DP 30-180 days to	1.91	1.67	0.00	1.57	1.93
Activity to	2.00	1.93	1.57	0.00	1.75
Other to	1.98	1.93	1.93	1.75	0.00

[a] This matrix is derived from the transition matrix available in Study II (Table 1). 0.00 equates to no cost (i.e., to substitute to the same state as itself). The maximum value is 2.00 which is the equivalent cost to 1 deletion and 1 insertion. The range observed was 0.000 to 1.996. Accordingly, the values of 2.00 in the table above are due to rounding and represent very rare transitions.

Abbreviations: DP: Disability pension; MS: Multiple sclerosis SA: Sickness absence.

Then, similar sequences were grouped together using the dissimilarity measures with hierarchical cluster analysis with Ward's linkage algorithm.[254,255,257] This allowed for the identification of clusters of similar sequences that represented the types of working-life sequences among the newly diagnosed PwMS. Ward's linkage algorithm is widely used and often finds the most homogenous clusters.[255] A balance was sought in the cluster analysis, between retaining complexity and creating meaningful classification. Therefore, similar sequences were grouped while keeping the clusters as distinct as possible from one another. All sequences began on their own and at each iteration the most alike sequences (or clusters of sequences in later iterations) were merged.[231,257] Two to twelve final clusters were evaluated with commonly used measures of partition quality (e.g., Point Biserial Correlation, Hubert's Gamma, Average Silhouette Width).[231] The choice of the final number of clusters was also based on the hierarchical cluster tree diagram and membership sizes for the interest in including additional analytically meaningful clusters.[254]

Further analyses were conducted after assignment to the relevant cluster. In these analyses, the type of working-life sequence was treated as a meaningful unit. The membership characteristics of the six identified types of working-life sequences and characteristics of the sequences these types represented were described. Multinomial logistic regressions analysed the associations between the working-life sequence clusters and membership characteristics and were reported as crude and adjusted odds ratios (ORs) and 95% CIs. The *Stable High Activity* type was selected as the reference category for type of working-life sequence with mutual adjustment for sex, age, and year of MS diagnosis. Mean differences in annual incomes in Y_{+5} with those in Y_{-1}, in total and by type of sequence, were calculated with dependent t-tests.

3.2.3 Study III: Progression of the costs of MS before and after diagnosis

In Study III, *Cost-of-illness progression before and after diagnosis of multiple sclerosis: A nationwide register-based cohort study in Sweden of people newly diagnosed with multiple sclerosis and a population-based matched reference group*,[258] the progression of the socioeconomic burden of MS was quantified both before and after diagnosis with MS.

Annual excess costs of MS were from healthcare use (specialised outpatient and inpatient healthcare as well as drugs) and productivity losses owing to work disability (informed by SA/DP net days).

3.2.3.1 Design and study population

Study III was a longitudinal population-based COI study with a cohort design. The costs among working-aged PwMS diagnosed with MS in 2010-2012 were compared with those among a population-based matched reference group to isolate the costs attributable to MS. The magnitude of the socioeconomic burden of MS was described and translated from natural units into monetary terms by itemising, valuing, and summing the costs of MS.[2,179] Register data (NPR, LISA, CDR, SCR, SPDR, SMSreg, and MiDAS) were available in this study up until the end of 2016.

Newly diagnosed MS was again defined as the first ever recorded ICD code for MS in the NPR as a main or secondary diagnosis for inpatient or specialised outpatient healthcare. The diagnosis years included in Study III were 2010-2012 (n=3221) (Figure 3). Working age was defined as 19-55 years of age at baseline (Y_{-5}) which corresponded to 23-59 at MS diagnosis (n= 2465 included). Additional exclusions were again applied to assume the first identified diagnosis code in the NPR represented a newly established MS diagnosis and to confirm that the individual had MS (in total, n=441 excluded). In total, 2024 PwMS were identified (2010: n=621; 2011: n=720; 2012; n=683).

To compare the costs of PwMS with the expected costs without MS, a population-based matched reference group of four reference individuals per individual with MS were randomly selected from the LISA and matched at baseline (Y_{-5}) (n=8096). To isolate the excess costs of MS, I strived to have a reference group as alike the cohort of PwMS as possible, with one key exception, that the references were not diagnosed with MS. The reference individuals may therefore have had other diseases than MS. Exact matching was based on sex, age, type of living area, and country of birth (Figure 3).

Individuals were observed annually for nine years with a relative time scale from four years before (Y_{-4}) to four years (Y_{+4}) after the MS diagnosis year (Y_0). The study period spanned from 2006 to 2016. Individuals were censored from the year of death, emigration, or having SA/DP due to MS if a reference individual (PwMS: n=36; References: n=115). Accordingly, 98.5% were observed the entire study period and were included in the analyses (PwMS: n=1988, 98.2%; References: n=7981, 98.6%).

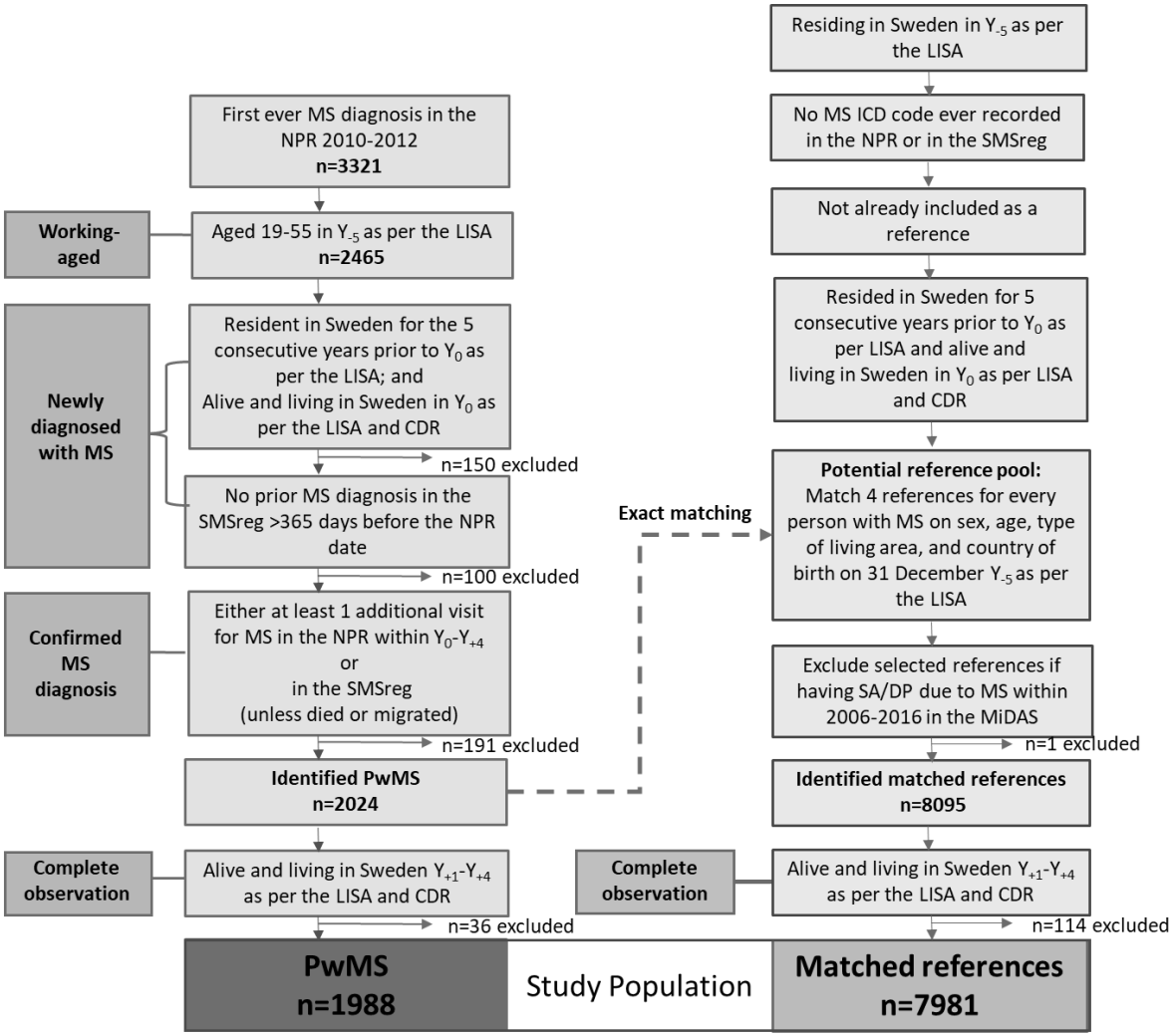

Figure 3: Study population flow chart for Study III of the PwMS (n=1988) and matched reference group (n=7981).

Abbreviations: CDR: Cause of Death Register; DP: Disability pension; LISA: Longitudinal Integration Database for Health Insurance and Labour Market Studies; MiDAS: Micro Data for Analysis of Social Insurances; MS: Multiple sclerosis; NPR: National Patient Register; PwMS: People with MS; SA: Sickness absence; SMSreg: Swedish Multiple Sclerosis Registry.

3.2.3.2 Outcomes

Since the aim of the study was to explore the progression of excess costs of MS before and after MS diagnosis, the study outcomes were the costs for healthcare use and productivity losses from work disability (Table 4). Annual all-cause costs were calculated from the societal perspective, including costs irrespective of who bore them.[180] Individual-level resource use was extracted from the registers. The costs were prevalence-based, including all costs incurred by the individuals within the respective calendar year,[178] to identify resource utilisation of PwMS (and the references) rather than utilisation in relation to MS.[259] Costs of respective resources were estimated through a bottom-up method of multiplying individual-level annual counts of register-informed resource use by unit costs from published sources (See *Study III, Table 1*).[178,180] The bottom-up approach is the most common among MS COI studies[8] and was facilitated by the individual-level resource use from the registers. Costs due to MS (excess costs of MS) were then calculated as the cost difference between the all-cause total costs among the PwMS and those among the reference group. For further discussion on costing methods and cost estimates, see 5.4.1.4. All costs were inflated to 2019 SEK using Eurostat's annual Harmonised Indices of Consumer Prices for healthcare.[260]

In addition, resource use was investigated to understand the excess cost findings, presented as the proportion of individuals with resource use in the respective year (yes/no).

Table 4: Summary of the costs included in Study III.

	Cost component	Resource	Resource source	Unit cost [1]	Unit cost source
Productivity losses	SA costs	Net days with SA (temporary work disability)	MiDAS	Average cost of labour (sum of gross salary and employer's social security contribution)	Statistics Sweden: Average gross salary across all sectors.[261] Swedish Tax Authority (Swedish: Skatteverket): Employers' social security contribution.[262]
	DP costs	Net days with DP (permanent or long-term work disability)	MiDAS		
Healthcare costs	Inpatient healthcare costs	Inpatient healthcare (hospitalisations)	NPR	DRG-based costs + patient OOP visit fee	Swedish Association of Local Authorities and Regions: Annual retrospective DRG weights, average annual costs per 1.0 DRG,[263] and patient OOP copayments.[264]
	Specialised outpatient healthcare costs	Specialised outpatient care (visits with a physician)	NPR	DRG-based costs + patient OOP visit fee	
	Drug costs	Drugs (prescribed drugs dispensed in pharmacies)	SPDR	Retail prices (patient OOP copayment & reimbursed portion) related to the substance type and quantity dispensed	SPDR

[1] All unit costs were inflated to 2019 SEK using annual Harmonised Indices of Consumer Prices for healthcare available from Eurostat.[260]

Abbreviations: DP: Disability pension; DRG: Diagnosis-related group; MiDAS: Micro Data for Analysis of Social Insurances; NPR: National Patient Register; OOP: Out of pocket; SA: Sickness absence; SEK: Swedish Krona; SPDR: Swedish Prescribed Drug Register.

3.2.3.2.1 Productivity losses

Productivity losses comprised the costs to society of the hypothetical lost production from temporary and permanent work disability (SA costs and DP costs). Work disability was informed by the individuals' net days of SA and DP calculated from the MiDAS data. For SA, only days with SA benefits from spells longer than 14 days were included to avoid introducing bias between employed and unemployed. For the included SA spells, the first 14 days of the spell were estimated and included. Productivity losses were calculated as the total net days of SA and DP, capped at the number of possible days in the respective year. Accordingly, there is a slight overestimation in the disaggregated SA costs (range: 0.3-1.7% of the cohort per calendar year). This is because the net days of work disability may sum to more than 100% if having part-time DP owing to partially reduced work capacity and simultaneous SA, due to the grade of SA benefits being based on usual work hours. Although the MiDAS contains the sums paid for the SA and DP benefits, these transfer payments to the individual represent a redistribution of wealth within society and are different to the productivity losses to society.[265] When an individual has work disability and is absent from work, society misses out on the potential output they would have otherwise produced.[180,265] Society's loss of production from work disability was valued according to the human capital approach at the cost of employment (mean gross salary across all sectors[261] and the employer social security contributions[262]).[178,180] Therefore, the average cost of labour was set as the average value of a month of production to estimate the cost of the months of lost production due to work disability.[137,178,180] The human capital approach is required by the Swedish Dental and Pharmaceutical Benefits Agency when applying for reimbursement[184] and enhanced comparability of the findings with previous MS COI studies which are mostly estimated with this approach.[181,187]

3.2.3.2.2 Healthcare costs

Healthcare costs comprised inpatient healthcare visits, specialised outpatient healthcare visits, and dispensed prescription drugs. Healthcare costs included the portions publicly financed by the respective county and the patient OOP costs in the form of visit fees or copayments for dispensed drugs. The patient OOPs were included within the respective cost.[264,266]

Healthcare visits were identified from the NPR, with costs for inpatient visits assigned to the year of discharge. The level of precision in healthcare costing can vary from microcosting to average per diem costs.[180] While original microcosting may be the most precise, practical limitations and interest in generalisability may result in practical alternatives. Using the average costs for a case-mix falls between the two end-points on the costing precision continuum.[180] The DRG classification is a commonly used measure of case-mix, aiming to provide clinically meaningful and homogeneous groups of patients in terms of resource use, and is available in the NPR.[267] The inpatient and specialised outpatient visit cost components were accordingly costed by using annual retrospective DRG weights for the DRG code classifying the visit and the annual unit cost per 1.0 DRG weight from the Swedish Association of Local Authorities and Regions (Swedish: Sveriges Kommuner och Regioner) [263] as well as the relevant patient OOP copayment in terms of visit fees.[264] Copayments were the mean fees across Sweden, and were set to 100 SEK per day for inpatient healthcare, with no maximum copayment ceiling, and 273 SEK per outpatient visit with a maximum annual

copayment ceiling of 1143 SEK.[264] The costs for inpatient and specialised outpatient healthcare visits, respectively, were then summed for each year for each individual.

The annual drug costs were extracted directly from the SPDR. These costs were the listed retail price for the substance and quantity dispensed at the pharmacy. Drug costs comprised of the patient OOP copayment, which varied based on previous dispensing,[111] and the remaining portion publicly financed.

3.2.3.2.3 Total societal costs

Total societal costs per person were calculated by summing the individuals' healthcare costs and productivity losses for the respective year. Total societal costs refer to the total sum of all cost components in the study rather than the method of costing (total or excess).

3.2.3.3 Covariates

The sociodemographic characteristics were obtained from the LISA for Y_{-5}. To construct the matched reference group the following variables were used:

- Sex (women/men);
- Age (years for matching, then categorised: 19-24, 25-34, 35-44, 45-55 years);
- Country of birth (Sweden; yes/no); and
- Type of living area (Stockholm/Södertälje, other large cities, medium-sized towns, rural areas). The coding of type of living area differed to previous studies. Information on the municipality of residence was used to identify individuals living in urban areas within Stockholm County. Accordingly, Norrtälje municipality remained classified within medium-sized towns, as in the previous studies, and the remaining municipalities within Stockholm County were separated from large cities and referred to as Stockholm/Södertälje.[234]

Additional sociodemographic characteristics further described the study population:

- Educational level (university/college, yes/no);
- Family composition dichotomised as married/cohabiting (yes/no) and living with children (yes/no); and
- Type of work (manager, office, manual labour, unclassified, not in paid work).

The modified Rx-Risk Comorbidity Index was constructed for Y_{-4} (0; 1-2; 3-4; 5+ comorbidity categories) as outlined in Study II (See 3.2.2.3). The index was originally developed to identify chronic diseases and predict the costs of healthcare,[245] and is recommended for assessing comorbidity when studying healthcare utilisation.[268] Disease modifying therapies available prior to 31 December 2016 were excluded (ATC codes: L03AB07, L03AB08, L03AB13, L03AX13, L04AA23, L04AA27, L04AA31, L04AA34, L04AC01, L01XC02, and N07XX09).

3.2.3.4 Statistical analyses

First, the study population's characteristics were described with frequencies and percentages. Statistical differences between the diagnosis year cohorts among the PwMS and then between the PwMS and matched references were assessed with chi^2-tests. No significant differences were observed between the diagnosis year cohorts before merging. The PwMS and matched

references were well-balanced after the exact matching and subsequent exclusions for the sociodemographic characteristics, with only differences regarding children living at home, type of work, and the variables related to comorbidity in Y_{-4} (depression/anxiety, pain, and comorbidity categories) observed.

Vastly different methods are used in the literature for estimating healthcare costs, which are characterised with skewness, excess zeros, and multimodality.[269] No single dominant method has emerged. Study III included several different cost estimates, summarised in Table 5, of which the main results refer to the excess costs of MS.[204,270] All individuals (PwMS=1988, matched references =7981) were included in the statistical analyses, including individuals with zero costs to get estimates for all, not just resource users.[271] The study design of relatively young and newly diagnosed PwMS, matched references, and the cost components included, all contributed to the relatively large proportions with zero costs. Considering the cost outcomes in all nine study years, 10% of healthcare costs and 64% of productivity losses among the PwMS were values of zero and the corresponding proportions for the references were 26% and 83%.

Table 5: Summary of the cost measures included in Study III for each cost component.

Type of cost estimate	Costing [270]	Statistical analysis	Estimate
Total costs among PwMS	Sum of the costs from all-cause resource use	Means of all costs stratified by MS status	*Estimate of the magnitude of all costs among PwMS (and references)* Annual mean per person, 95% CI
Excess costs of MS	Direct comparisons with a reference group	Two-tailed t-test comparing all-cause total costs among PwMS with those among the matched references	*Estimate of the magnitude of the costs of MS* Annual mean per person, 95% CI
	Regression	Regression models for the all-cause total costs fitted with GEE for estimates of the MS and MS*year interaction coefficients	*Estimate of the relative costs of MS* Incidence rate ratios (cost ratios), 95% CI

Abbreviations: CI: confidence interval; GEE: Generalised estimation equations; MS: Multiple sclerosis; PwMS: People with multiple sclerosis.

First, the all-cause total costs were compiled for both the PwMS and the references. Mean costs per person with 95% CIs were calculated for the PwMS and the matched reference group for each year. The estimated population mean is usually the statistic of interest in COI studies.[269] However, the data was skewed with a zero mass. Therefore, median values were also reported alongside the mean costs per person.[269]

By including a reference group without MS, matched on variables believed to influence the use of the resources, the costs directly and indirectly related to MS were estimated through both direct comparison and regressions.[269,270]

Excess (or incremental) costs of MS are the costs per person due to MS isolated by comparing total all-cause costs among the PwMS with those of a matched reference group without MS.[204] These are the additional costs on top of regular expenditure per individual due to MS. To estimate the magnitude of the excess costs of MS, mean differences with 95% CIs between the PwMS and references were calculated for each study year with two-tailed

Student's t-tests. The excess costs of MS from the t-tests were unadjusted mean values of the costs of MS across individuals irrespective of age or other basic characteristics.

Relative cost differences between the PwMS and the matched references were also estimated from regression models. Generalised linear models are often used for costs to accommodate the skewed data with heavy tails.[269] In this study, an extension of generalised linear models was applied to construct models with generalised estimating equations (GEE) to handle the deviation from independency from the repeated measurements across the study years. Poisson regression models were fitted with GEE to account for the within-individual correlation of the annually repeated cost measurements.[272,273] Gamma distributions are often used for modelling positive cost data, however, a non-normal model that retained individuals with zero costs in a year and one compatible with fitting GEE to account for dependency from the repeated cost measurements was needed. By using the Poisson distribution, individuals with zero costs were retained. Jones suggests that costs can be considered to follow a count distribution when they are generated by a count of the discrete episodes of care multiplied by the unit cost.[274] Full observation of the study population was required to prevent different or unpredictable parameter estimates with GEE because the missing cost data owing to emigration and death were not missing completely at random.[275]

Models were constructed separately for total societal costs, healthcare costs, and productivity losses, specifying a log link function and an autoregressive correlation matrix.[275,276] An autoregressive correlation structure was selected since the repeated measures had equal intervals and it is commonly used with longitudinal data to allow the correlations to diminish with time.[273,276] While theory grounded the choice of the autoregressive correlation structure, different options were tested (data not shown).[273]

To assess the association between MS and costs, three main effect models were built:

- Model 1a: MS (yes/no) and year (Y_{-4}-Y_{+4}).
- Model 2a: Covariates included in Model 1a, as well as the cohort (2010, 2011, 2012) and matching variables (sex, age, type of living area, country of birth).
- Model 3a: Covariates included in Model 2a, as well as educational level, married/cohabiting, living with children, and type of work.

To identify time trends in the progression of the excess costs of MS, the above models were repeated with an interaction term included between MS and the study year (Models 1-3b). All regression results were reported exponentiated as incidence rate ratios (IRRs) with 95% CIs from the robust standard errors.[276] The IRRs can be interpreted as cost ratios or multipliers of the average population response as an estimate of the relative difference in annual costs of a person with MS compared with their matched reference peers.[273,277]

A further model, Model 4a, was specified with comorbidity (0; 1-2; 3-4; 5+ categories) added to the covariates included in Model 2a to further investigate the contribution of comorbidity to the excess costs of MS. While the main analyses of excess costs of MS with the population-based references without MS indirectly controlled for expected levels of comorbidity as well as aging on the costs over follow-up, this model specification tested how much potential residual confounding remained. Ignoring comorbidity completely leads to overestimations of the costs (i.e., the total all-cause costs among PwMS), while over adjusting for comorbidity in situations where the condition was a consequence of or related to

MS would lead to misleading results, underestimating the costs of MS. Disentangling whether the comorbid condition is unrelated or connected as a symptom or consequence of MS is difficult conceptually as well as in practice, especially without further information, such as detailed patient journals.[42,48,270]

3.2.4 Study IV: Costs of MS in Stockholm

Study IV, *Excess costs of multiple sclerosis: A register-based study in Sweden*, was a development from Study III. This study included further cost categories of primary healthcare and MS DMTs among a prevalent cohort of PwMS. By focusing on Stockholm County, primary healthcare data from Region Stockholm could be used to include the costs from a wider range of healthcare contacts in accordance with the national MS care guidelines of access to a multidisciplinary team.[21]

3.2.4.1 Design and study population

This population-based COI study had a cohort design with one year of observation (2018) of prevalent PwMS of working ages and a population-based matched reference group. Register data (NPR, LISA, CDR, SPDR, SMSreg, MiDAS, and VAL) were available up until 31 December 2018.

To form the study population, working-aged Stockholm residents were identified from the LISA as alive and living in Stockholm County in both 2017 and 2018 (n=1,354,161) (Figure 4). Individuals 19-64 years of age on 31 December 2017 were considered to be of working age.

From the identified working-aged Stockholm residents, the prevalent MS group was identified. MS was identified by inclusion in the SMSreg in Study IV, in contrast with the other studies in this thesis. Region Stockholm has relatively high reporting rates to the register.[218,278] From the Stockholm residents included in the SMSreg (n=3400), those with an MS diagnosis date recorded up to and including 31 December 2017 were identified (n=2994). Individuals with paediatric onset MS were then excluded because of potential differences in the clinical course (n=188).[279] In total, 2806 PwMS were included.

The population-based matched reference group was selected from the working-aged Stockholm residents never included in the SMSreg (n=1,350,761). A broader definition of not having MS was applied because of the voluntary nature of the SMSreg, the changing diagnostic criteria with earlier set MS diagnoses, and a single year of observation.[11] At least 85% of PwMS have earlier had an isolated optic neuritis, brainstem syndrome, or partial myelitis.[11] Accordingly, individuals were excluded from the pool of potential references if ever having diagnosis codes (main or secondary) for MS or other demyelinating diseases in the NPR, VAL or MiDAS,[280-282] or an MS DMT dispensed according to the SPDR[281,282] (in total, n=2066 excluded).

Different methods can be used to mimic randomisation when comparing outcomes based on real-world data. Propensity score matching was used in Study IV to compare the costs among PwMS with those among population-based references. From the pool of potential references (n=1,348,695), the matched reference group was formed with the Greedy nearest neighbour method without replacement, optimising the most matches, and a calliper width of 0.25.[283] For each person with MS, 10 references were selected. The propensity score represents the

estimated probability of assignment to the PwMS group, conditional on the selected observed covariates.[283] The propensity score was estimated with a logistic model using the following information from 31 December 2017 with MS (yes/no) as the response variable and the explanatory variables: Sex (women, men); age (years); birth country (Sweden, yes/no); educational level dichotomised as university education (yes/no); municipality of residence within Stockholm County categorised by the degree of urbanisation[284] as binary variables for each of the three levels (Cities: densely populated areas; Towns and suburbs: Intermediate density areas; and Rural areas: thinly populated areas); and the dichotomised family composition information as living with children (yes/no) and cohabiting/married (yes/no). The covariates, were selected for the propensity score due to a priori likely association rather than relying on statistical tests for variable inclusion.[285]

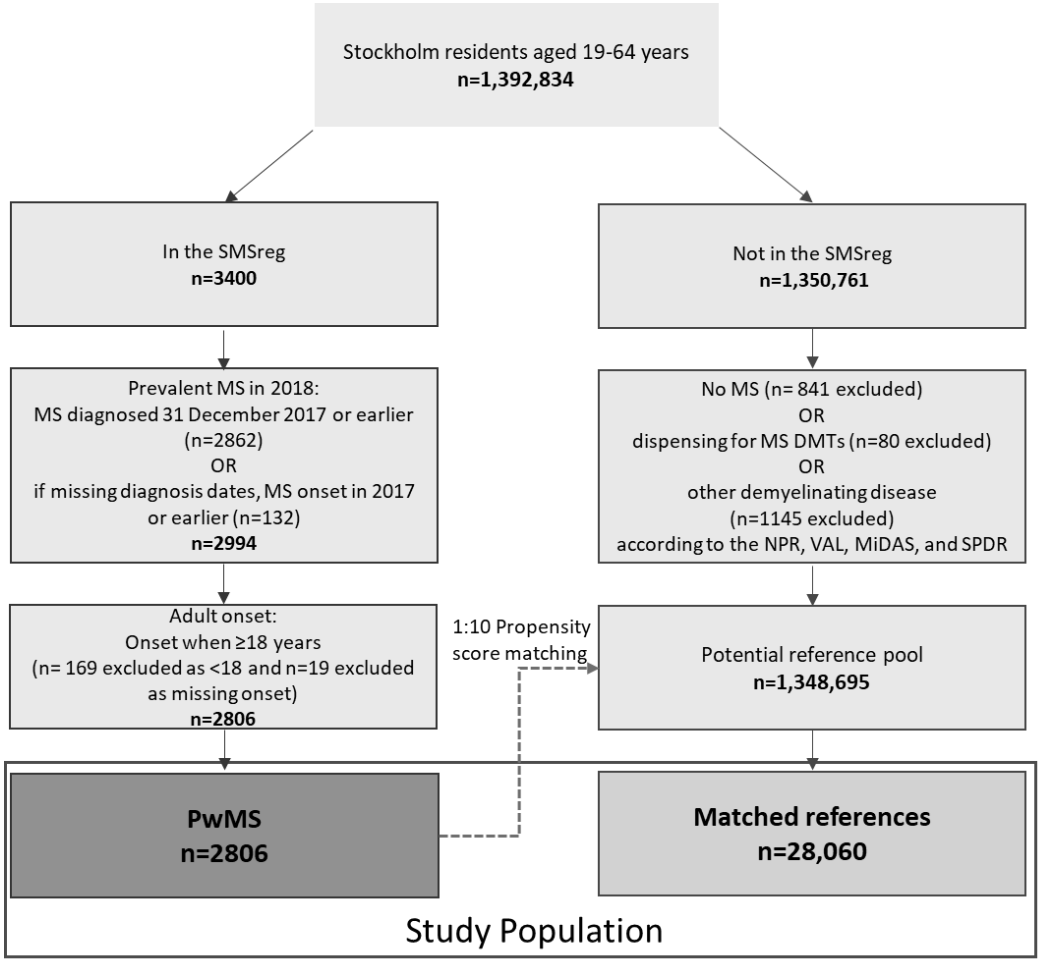

Figure 4: Study population flow diagram for Study IV of the n=2806 PwMS and n=28,060 matched references.

Notes: MS (ICD-10 G35 ICD-8/9 340) and other demyelinating diseases (ICD-10: G36 Other acute disseminated demyelination, G37 Other demyelinating diseases of central nervous system, H46 Optic neuritis, or ICD-9: 340, 377, 367, 323, 341) were identified in the NPR, VAL, or MiDAS. MS DMTs were identified from the SPDR (ATC codes: L03AB07, L03AB13, L03AB08, L03AX13, L04AA27, N07XX09, L04AX07, L04AA31, L04AA40, L04AC01, L01DB07, L01XC02, L01XC10, L04AA34, L04AA36, and L04AA23).

Abbreviations: ATC: Anatomical Therapeutic Chemical Classification System; DMTs: Disease modifying therapies; ICD: International Statistical Classification of Diseases and Related Health Problems; MiDAS: Micro Data for Analysis of the Social insurance; MS: Multiple sclerosis; NPR: National Patient Register; PwMS: People with multiple sclerosis: SMSreg: Swedish Multiple Sclerosis Registry; SPDR: Swedish Prescribed Drug Register; VAL: Region Stockholm's healthcare database.

Before conducting the matching, the covariate balance at baseline of each explanatory variable used in the propensity score between PwMS and the pool of potential references were assessed by standardised mean differences. These are the differences in the mean covariate values between the PwMS and the potential pool of references, scaled by the covariate's standard deviation.[286] A threshold level of 0.1 was implemented.[287,288] Some differences were observed in the sociodemographic compositions of the PwMS and potential reference pool prior to matching, with most variables well within the standardised mean difference threshold of 0.1 except for the propensity score, age, sex, country of birth, and cohabiting/married (Figure 5). The standardised mean differences by MS status were then reassessed for the references selected in the matching procedure (n=28,060). After matching with the propensity score, covariate balance was achieved with all included baseline factors having standardised mean differences <0.1.

In addition, common support was confirmed by observing overlap of the propensity score distributions of the PwMS and the resulting matched reference group as well as ensuring that the propensity score observations among the PwMS were available across the range of the propensity scores within the reference pool (See *Study IV, Supplementary Figure 1*).[283]

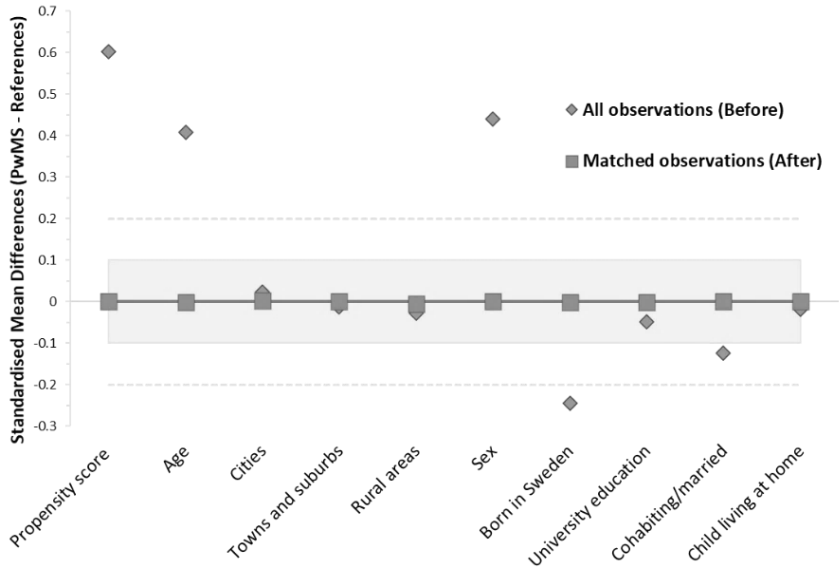

Figure 5: Standardised mean differences between the PwMS and the references without MS before (diamond) and after (square) propensity score matching to the nearest neighbour.

Notes: Grey shaded area corresponds to an effect size of 0.1 indicating well-balanced groups and dotted grey lines with an effect size of 0.2.

Abbreviations: MS: Multiple sclerosis; PwMS: People with multiple sclerosis.

3.2.4.2 Outcomes

The annual per person healthcare costs and productivity losses were also the main outcomes in Study IV. The costs were calculated from healthcare use and work disability occurring in 2018 with largely the same methods as in Study III. Although, additional cost categories were included in this study. Namely, the costs for primary healthcare and MS DMTs (Table 6). A reference year of 2020 was used whenever possible for unit prices,[180,289] measured in SEK. Inflation to 2020 prices was performed when an earlier unit cost was used owing to the extensive changes in healthcare organisation in 2020 due to the Corona Virus Disease-2019 pandemic.[260]

Table 6: Summary of included costs in Study IV from resource use in 2018.

	Cost component	Resource	Resource source	Unit cost [1]	Unit cost source	Comparison to Study III
Productivity losses	SA costs	Net days with SA.	MiDAS	Average cost of labour.	Statistics Sweden: Average gross salary across all sectors.[261] Swedish Tax Authority: Employers' social security contribution.[262]	✔ Included in Study III. Study IV adjusted SA for simultaneous DP.
	DP costs	Net days with DP.				
Healthcare costs	Inpatient healthcare costs	Inpatient healthcare (hospitalisations).	NPR	DRG-based costs + patient OOP visit fee.	Swedish Association of Local Authorities and Regions: Annual retrospective DRG weights, average annual costs per 1.0 DRG,[263] and the patient OOP copayments.[290,291] National Board of Health and Welfare: Prospective nationwide DRG weights if missing a retrospective weight.[292]	✔ Included in Study III. Study IV used prospective weights if no retrospective weight for the DRG code in 2018.
	Specialised outpatient healthcare costs	Specialised outpatient care (visits with physicians).				
	Primary healthcare costs	Primary healthcare (contacts with physicians and other healthcare professionals, at the clinic, home, or distance).	VAL	Average unit cost + patient OOP visit fee.	Swedish Association of Local Authorities and Regions: Unit cost for a visit with a physician at a primary healthcare clinic, with a ratio for different types of healthcare professionals and healthcare contacts,[293] as well as the patient OOP copayments.[290]	**!** New cost in Study IV.
	Drug costs	Prescribed drugs dispensed at pharmacies.	SPDR	Retail prices (patient OOP copayment & reimbursed portion) for the substance type and quantity dispensed.	SPDR.	✔ Included in Study III.
		MS DMTs administered within healthcare.	SMSreg	Retail prices based on average dosing and recommended dosing intervals for each drug.	Retail prices and dosing: Fass[294,295] or the Swedish Dental and Pharmaceutical Benefits Agency.[296-298] Additional dosing information from the Swedish MS Association (Swedish: Svenska MS-sällskapet) and the data.	**!** New cost in Study IV.

[1] All unit costs were inflated to 2020 SEK values using the annual Harmonised Indices of Consumer Prices for healthcare available from Eurostat.[260]

Abbreviations: DMT: Disease modifying therapy; DP: Disability pension; DRG: Diagnosis related group; MiDAS: Micro Data for Analysis of Social Insurances; NPR: National Patient Register; OOP: Out of pocket; SA: Sickness absence; SEK: Swedish Krona; SMSreg: Swedish Multiple Sclerosis Registry; SPDR: Swedish Prescribed Drug Register; VAL: Region Stockholm's healthcare database.

Resource use pertaining to the cost categories was again investigated as the proportion of individuals with resource use (yes/no).

3.2.4.2.1 Productivity losses

Productivity losses were calculated with the same methods as outlined for Study III, from the net days with SA and DP benefits. The only difference in Study IV was that the net days of SA within the year were adjusted for simultaneous DP, to avoid the slight overestimations of the disaggregated SA costs as in Study III. The unit cost for a month of lost production (whether due to SA or DP) applied in Study IV was 47,443 SEK, the product of the mean monthly gross salary (36,100 SEK)[261] and the employer social security contributions (31.42%) in 2020.[262]

3.2.4.2.2 Healthcare costs

Healthcare costs were calculated by summing the primary, specialised outpatient, and inpatient healthcare, as well as the drug cost components (DMT and non-DMT drug costs).

Study IV included primary healthcare costs from register-informed resource use. Primary healthcare contacts in 2018 identified in VAL were counted by type of visit (primary healthcare visit at the clinic, at home or offsite, and distance contacts) and type of healthcare professional (physician, nurse, or other healthcare professional). Primary healthcare costs comprised an average cost for primary healthcare contacts financed by Region Stockholm and the patient OOP copayment.[290,293] A retrospectively derived unit cost of 1879 SEK for the average cost per primary healthcare visit with a physician within general medicine at a clinic was used provided by the Swedish Association of Local Authorities and Regions.[293] From this base cost, a ratio for the other types of visits and healthcare professionals was applied.[293,299,300] A home or offsite visit corresponded to the cost of two clinic visits and a distance contact was one third of the cost of a clinic visit, while visits with a healthcare professional other than a physician equated to 40% of the cost of the respective visit with a physician.[293] The cost for all professionals listed for the contact (maximum of five) was calculated. The relevant patient copayment in Region Stockholm for the first recorded healthcare professional (100 or 200 SEK) was applied with a maximum copayment amount set to 1150 SEK.[290] The costs presented by healthcare professional excluded the OOP payments and were assigned to the first registered professional, with 91.9% of primary healthcare contacts having a single registered healthcare professional.

The costs for specialised outpatient visits and inpatient visits (with a discharge date in 2018) were again derived from information in the NPR as well as the relevant OOP patient copayment. The unit cost applied for a DRG weight of 1.0 in 2018 was 56,356 SEK in 2020 values.[263] For inpatient healthcare the same copayment as in Study III was applied (100 SEK per day) but was capped at 365 days for longer stays.[291] For specialised outpatient visits, the list copayment of 350 SEK per visit to a physician in specialised outpatient settings for Region Stockholm was applied, with a maximum annual copayment set to 1150 SEK.[290] However, not all DRG codes in the NPR had a retrospective weight for 2018 due to regular updating of the DRG definitions. Several DRGs in the data were split in the retrospective weight lists to include complication grades, for example, n=6264 individuals had O99Q (Physician visit for gynaecological disease in outpatient care). Accordingly, for the 355 inpatient visits and 19,248 outpatient visits observed without a retrospective DRG weight for

2018, the prospective nationwide DRG weights for 2018 from the National Board of Health and Welfare were applied to be able to cost all visits.[292]

The drug costs included the costs for prescribed drugs dispensed in pharmacies from the SPDR like in Study III. In addition, the costs of MS DMTs were included in Study IV. The costs for months on treatment with MS DMTs were estimated for rituximab, natalizumab, ocrelizumab, ofatumumab, and alemtuzumab with information from the SMSreg on the start and end dates of treatment of these drugs administered within healthcare. Average unit costs per month on treatment were applied based on the average dosing and recommended dosing intervals for each of the drugs (See *Study IV, Table One*). Extra costs were applied for the initial doses of rituximab and alemtuzumab, if starting the respective treatment in 2018, owing to the recommended initiation doses differing to the maintenance doses.[301,302] Drug costs are presented as total drug costs (including costs from both the SPDR and the SMSreg), DMT costs (from either the SMSreg or the SPDR), and non-DMT drug costs (all ATC codes in the SPDR except for the DMTs).

3.2.4.2.3 Total societal costs

Total societal costs for an individual were calculated as the sum of productivity losses (SA and DP costs) and healthcare costs (inpatient, specialised outpatient, and primary healthcare costs, as well as the total drug costs).

3.2.4.3 Covariates

Sociodemographic variables in Study IV were extracted from the LISA for 2017 and were used in the propensity score matching (sex; age; birth country; educational level; degree of urbanisation of the municipality of residence; and family composition).

Among the PwMS, time since diagnosis was measured representing the time in years between the year of diagnosis with MS and the observation year 2018.[303] Time since diagnosis was categorised as 0-4; 5-9; 10-14; and 15+ years. This was considered a proxy for disease progression and included to facilitate discussion with the findings for early MS from Study III.[303]

3.2.4.4 Statistical analyses

Descriptive statistics of the cost components and resource use were calculated for PwMS and the references. As in Study III, all individuals were included to enable inference on the whole study population, including those with zero costs.[271] Differences in the proportions with resource use between the PwMS and the matched references were tested with chi^2-tests.

The study design with propensity score matched references allowed for relatively simple analyses of the excess costs of MS.[283] Regression modelling was not considered necessary to remove residual confounding after the propensity score matching, as none of the observed covariates had an imbalance in standardised mean differences above the threshold of 0.1.[288] The excess costs of MS were again calculated with two-tailed Student's t-tests as the mean differences between the PwMS and the matched references for each cost component. Next, based on the Central Limit Theorem, that an aggregated measure (e.g., mean) in a large data set is approximately normally distributed around the true population estimate when a variable is sampled multiple times from the same population,[237] bootstrapping was performed to

produce 95% CIs.[304] The medians of the sampling distributions differed from the means, therefore, bias-corrected percentile CIs were calculated from 2000 replications.[304]

In addition, subgroup analyses were conducted by time since MS diagnosis. First, in group differences of the proportions of characteristics and users of resources were examined among the PwMS with chi^2-tests by the time since diagnosis categories. Excess costs of MS were then calculated for the PwMS compared with their reference peers, stratified by time since diagnosis. These additional analyses were not adjusted for structural differences between the strata, for example, age profiles and cohort effects from changing diagnostic criteria and treatments available when first diagnosed with MS.

3.3 ETHICAL CONSIDERATIONS

The project has been approved by the Regional Ethical Review Board, Stockholm, Sweden (reference numbers: 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).

The principles of autonomy and integrity of the person were balanced in this register-based research against the value of increased knowledge that the research could provide. The new knowledge from the project could have a positive effect on individuals with MS in line with the principal of beneficence. However, the time lag between data collection from routine practice and dissemination of the study findings may reduce the direct benefit to individuals whose data was used to inform the findings. This is especially so in Studies I-III, which investigated the wider outcomes of newly diagnosed PwMS.

Considerations on how to avoid harm or non-maleficence to the individuals are also important. The data infrastructure of linked register data allowed for the combination of clinical, economic, and sociodemographic information and the study of these personal, sensitive data over time. Overall, the imposed risks were few and balanced by the numerous benefits of using register data. Benefits include the large and population-based study cohorts, independent data collection, and minimal direct burden on participants owing to use of routinely collected data.

The main ethical consideration of register-based research concerns the possible violation of personal integrity. Safeguarding the personal integrity of participants is a mandatory prerequisite for using sensitive personal data in research.[305] We as a research group have actively undertaken many precautions to minimise the risk eventuating and established good governance systems that are in place for our use of the pseudonymised sensitive data in research.

In register-based research, informed consent from the individual study participants is rarely requested. Individuals neither consent to inclusion in the administrative registers nor for the use of such data for research. Nonetheless, the relevant ethical board has considered that the research project this PhD project is a part of is of ethical standard, in line with the Helsinki Declaration, to access such sensitive and personal data. Informed consent for the studies would have required identifiable data to provide an option to deselect, as well as be cumbersome and costly to implement. However, PwMS with data in the voluntary SMSreg did provide consent to their neurologist, as part of the registry's own process, prior to inclusion of data into the register for the purpose of research and allowing data extraction to researchers.[217] In return, individuals are benefited by inclusion in the SMSreg, as the portal

facilitates continuity of care and enables opportunities to monitor the clinical course. Individuals can always withdraw their consent and opt out from further data being prospectively recorded in the SMSreg or being made available for research.[306] Nonetheless, there remains a minimal risk that the neurologist is in a position of power that could influence how freely consent is provided.

Regarding the potential conflicts of interest or biases of the researchers, the project was partly funded, in terms of researcher salaries, by unrestricted researcher-initiated research grants from a pharmaceutical company with MS-related products. While the company did have an opportunity to comment on the manuscripts prior to submission to scientific journals, they did not direct the study questions or results.

Lastly, the findings of the four studies also raise ethical considerations. Accurate cost estimates are an important input for economic evaluations. However, there is a risk that further use of the estimates in economic evaluations could contribute to resource allocation decisions not in the PwMS' best interests, albeit maximising health gains for society. Normative judgments are embedded explicitly and implicitly in the cost estimates. In this project, productivity losses were estimated with the widely-used human capital approach, which estimates the opportunity cost of morbidity to society in hypothetically lost productivity. Beyond the narrow view of the value of health in this approach,[307] reducing human life and the value of health to one's ability to earn income or to be productive, including productivity losses can also be discriminatory against non-productive groups.[179,183] That said, a wider definition of work was applied in the productivity loss calculations, with students, active job seekers, and individuals on parental leave all included in the SA costs if experiencing reduced work capacity. Furthermore, Krol et al., argue that while such distributional consequences of including productivity losses are important to consider in decision-making, they do not justify excluding them in COI studies as exclusion may result in a misrepresentation of the actual costs.[183] The ethics surrounding the use of individualised wages has been questioned as it can identify individuals with lower incomes and create an inbuilt preference for treating those with higher incomes.[92] Therefore, there is a preference for average earnings rather than actual earnings to value lost productivity in population studies.[92,180,307] Average salaries were used to cost the days on SA/DP, rather than sex-specific, so that the presented productivity loss estimates valued women and men's productivity equally. These methodological choices were made in consideration of the study populations' age and the unequal sex-distribution of MS. The contribution of insurance medicine alongside COI studies added focus not only to the "burden" from work disability among PwMS in monetary terms, but also in other metrics to gain knowledge on the working lives of PwMS, underpinned by the importance of work for the individual.

4 RESULTS

Study I-III involved newly diagnosed cohorts of PwMS identified across Sweden. In Study IV, a Stockholm-specific cohort of people with prevalent MS was created where individuals had varying times since their diagnosis with MS (range 1-44 years). Not unexpectedly, the newly diagnosed PwMS in Study I-III were younger than the prevalent PwMS. In all studies, the study populations were predominantly women (68.6-70.2%) and born in Sweden (80.3-89.0%). Among incident PwMS in Study I-III, 36.2-41.1% had a university education and this proportion was 51.4% in Study IV among the prevalent PwMS.

The results from these four cohorts of PwMS are presented below, study by study.

4.1 STUDY I: ECONOMIC SITUATION AND WORK DISABILITY

4.1.1 Economic situation of people newly diagnosed with MS

Findings from Study I indicated diversity in the economic situation of 1528 newly diagnosed PwMS regarding the trajectories of DI, earnings, and work disability. The year of MS diagnosis was noticeable in the trends for annual earnings and work disability, marking a change in the respective trend. Inverse trends were observed between earnings and work disability, with increasing work disability in the years around MS diagnosis and a corresponding decrease in earnings and flatter development thereafter. In contrast, there was a rather smooth and steady increase in mean annual DI throughout the study with only small fluctuations. There was a mean increase in annual DI comparing the diagnosis year with the fourth year after MS diagnosis (19,800 SEK; 95% CI: 15,790-23,800).

The economic situation of newly diagnosed PwMS was further described after stratification by both age at MS diagnosis and sex. Women and men had similar trends, however, at different levels of annual income and net days. Men had higher annual means of DI than women for all study years, and both had increasing variation in DI by age group over follow-up. The trends for earnings among both women and men differed by age. Younger age groups at MS diagnosis had increasing earnings and a shallower decrease over MS diagnosis, while older age groups had a sharper decrease at MS diagnosis and either had flattened or decreasing earnings in the years following. A steep increase in work disability was observed for PwMS of all ages. There were higher levels of work disability among older than younger PwMS and among women than men.

4.1.1.1 Diversity in the trajectories of disposable income among people with MS

High diversity was observed in the development of DI around MS diagnosis. The seven trajectory groups identified with group-based trajectory modelling are numbered in descending order from highest to lowest mean DI for the first study year (Figure 6). Of the trajectories, four were increasing (in total 39.0% of the cohort), two were flat and at relatively low levels (50.7%) and one was decreasing (10.3%). The largest group was Group Six (36.7%), a flat trajectory at a relatively low level of DI. The group memberships of the four increasing DI trajectories were all relatively small, indicating wide diversity in how DI develops regarding levels and gradients. Two clusters of trajectory groups (Groups Two, Three and Four along with Groups Five and Six) started with similar DI levels but diverged over the 12-year study period.

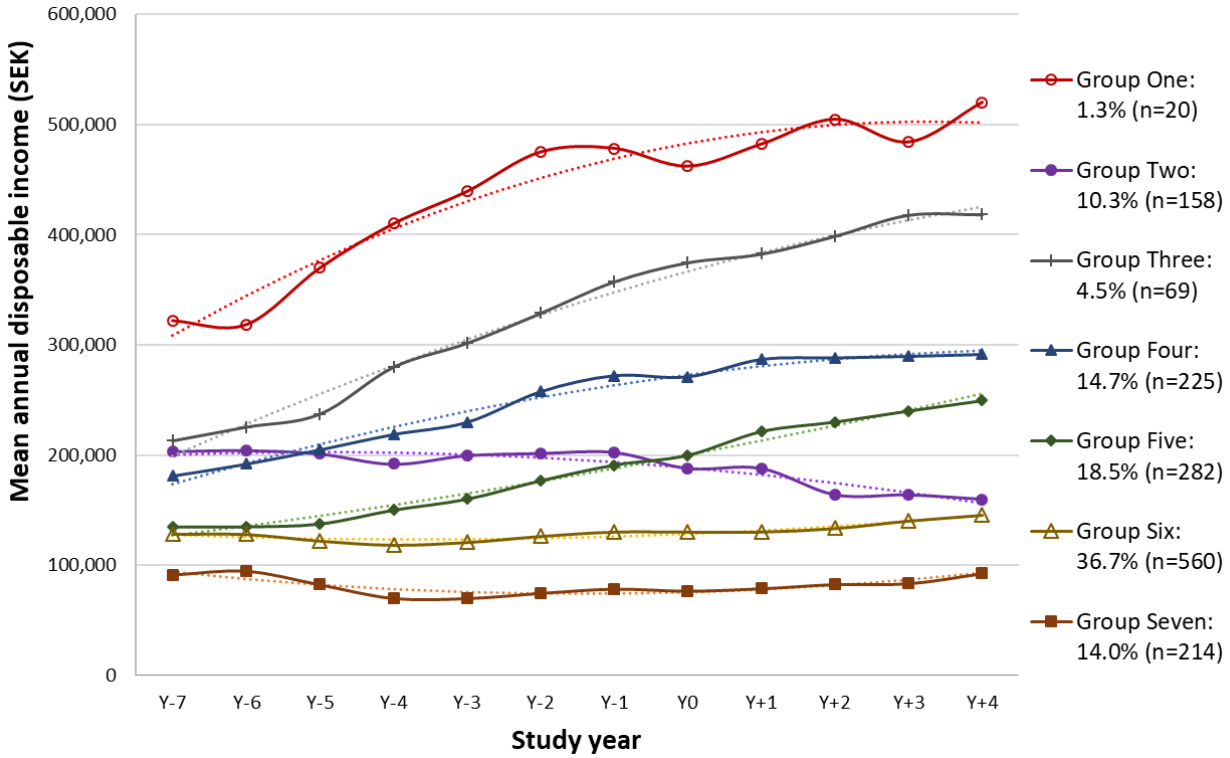

Figure 6: The observed mean annual DI values (solid line with markers) and model estimates (dotted line) of the seven DI trajectories from Y_{-7} to Y_{+4} identified from group-based trajectory modelling among the cohort with newly diagnosed MS (n=1528).

Note: Y_0 indicates the year of diagnosis with MS.

Abbreviations: DI: Disposable income; MS: Multiple sclerosis; SEK: Swedish Krona.

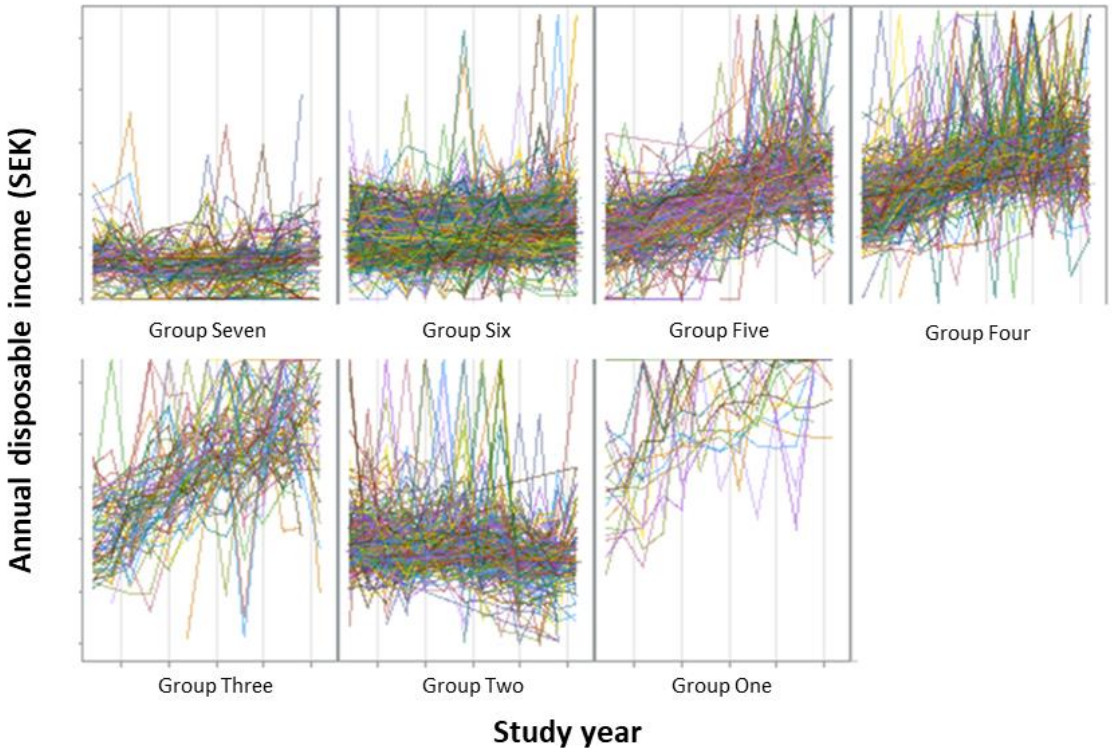

Figure 7: Spaghetti plots of annual DI by the seven identified trajectory groups.

Abbreviations: DI: Disposable income; SEK: Swedish Krona.

The spaghetti plots of DI illustrate the variation within each of the trajectory groups and provided support for the distinctiveness of the trends and levels of DI for the identified trajectory groups (Figure 7). There were clear differences between the trajectory groups despite the large spread. Variation in DI was observed both between individuals and within individuals over time, reflecting the dynamic nature of economic situation and highlighting the benefit of considering trends.

The seven identified DI trajectory groups had different profiles. All included characteristics were statistically significant in the analyses ($p< 0.05$). The Nagelkerke R^2 for full model was 0.33, with none of the characteristics independently asserting strong effects on the full model (Diff R^2 range: 0.01-0.06). The Diff R^2 indicated that age-group (0.06) and sex (0.05) had the highest explanatory powers and on DP in Y_0 (0.01) had a relatively weak influence.

Trajectory group membership differed by sociodemographic characteristics. Most groups were comprised of >90% of individuals born in Sweden, except Group Seven and One which had >15% born outside of Sweden. The decreasing trajectory, Group Two, was characterised by individuals of older ages, less university education, and living with a partner. University education was less common in the consistently low flat trajectories. These low flat trajectory groups also had higher proportions of women, living in rural areas, and younger age-profiles. In contrast, increasing trajectories had older age-profiles and higher proportions of men.

Work disability characteristics also differed across the trajectory groups. The decreasing and constantly flat trajectory groups had the smallest proportions without work disability in the diagnosis year (38% in Group Two and Six, 48% in Group Seven). In contrast, the increasing trajectory groups had higher proportions of members without work disability, for example, Group Three had >62% of members without work disability in the diagnosis year.

4.2 STUDY II: WORKING LIFE, WORK DISABILITY, AND ECONOMIC SITUATION

4.2.1 Working life of people newly diagnosed with MS

The diversity in the working-life sequences followed in the years around MS diagnosis of 2595 newly diagnosed PwMS was explored in Study II as well as the economic implications of these sequences.

Similar to Study I, PwMS overall had increasing mean annual DI as well as income from activity and earnings, comparing the last study year (Y_{+5}) to the first (Y_{-1}) (p-values <0.05). Earnings were the largest and most common source of income from activity. Among the 2071 PwMS with income from activity in Y_{+5}, on average 93% of their income was from earnings and 1482 of the PwMS had all of their annual income from activity comprising of earnings.

4.2.1.1 Individuals' sequences of working life

There were 633 unique working-life sequences identified spanning the seven study years (Y_{-1} to Y_{+5}). The most frequent sequence, followed by a third of the cohort of newly diagnosed PwMS, was to have the *Activity* state throughout (Figure 8). The three most common sequences accounted for 43.7% of all the individuals' sequences.

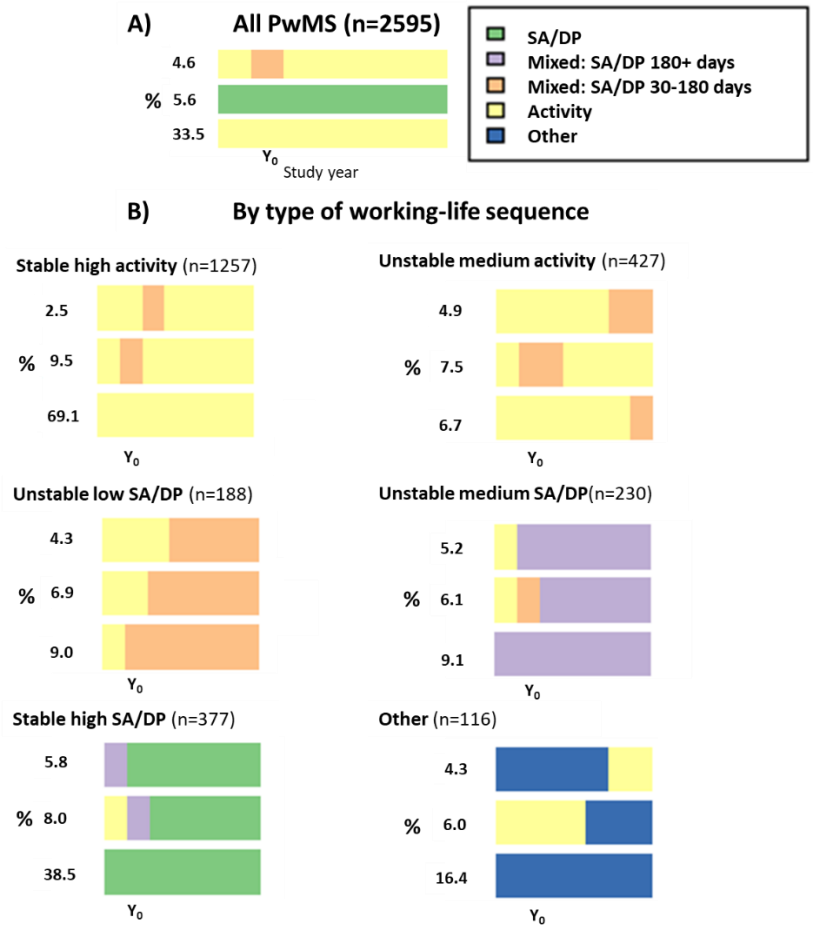

Figure 8: The three most common working-life sequences from Y_{-1} to Y_{+5} among A) newly diagnosed PwMS (n=2595) and B) within each of the six identified types of working-life sequences.

Note: Y_0 indicates the year of diagnosis with MS. Percentages indicate the proportion of individuals who followed the presented sequences.

Abbreviations: DP: Disability pension, MS: Multiple sclerosis; PwMS: People with multiple sclerosis; and SA: Sickness absence.

Overall, individuals were most likely to continue in the same state in the following year. Individuals with the *Mixed: SA/DP 30-180 days* state were more likely to transition in the following year to *Activity* than to the *Mixed: SA/DP 180+ days* state, representing an increased extent of work disability (See *Study II, Table 1*). Hence, the sequences visualised return-to-work processes as well as progression in the extent of work disability early in the disease. There was a mean of 1.42 transitions between states within the sequences (Table 7).

The timing of the states within the sequences was important. Overall, PwMS were in *Activity* 4.2 years out of seven, although these years were not necessarily consecutive. The *Activity* state was the most frequent state in all study years but decreased over the study period (annual proportions with the *Activity* state ranged 0.76-0.54) (Table 8). Conversely, work disability increased over the study period with the *SA/DP* and the two mixed activity and SA/DP states increasing in frequency. Accordingly, over time individuals were increasingly likely to transition between states. The entropy index increased from 0.54 in Y_{-1} to 0.79 in Y_{+5}, where a value of 0 would indicate that all PwMS were in the same state in that position

of the sequence. Thus, increasing diversity was observed in the states present within the later years of the sequences.

Table 7: Durations within the states and transitions between the states within the working-life sequences of newly diagnosed PwMS, in total, and by the six identified types of working-life sequences.

		Type of working-life sequence					
	All PwMS	*Stable High Activity*	*Unstable Medium Activity*	*Unstable Low SA/DP*	*Unstable Medium SA/DP*	*Stable High SA/DP*	*Other*
Mean duration (years) in….							
SA/DP	0.95	0	0.36	0.16	0.64	5.5	0.47
Part-time activity and some SA/DP net days							
180+	0.71	0.03	0.66	0.97	4.46	0.7	0.29
30-180	0.89	0.28	1.79	4.17	1.02	0.39	0.35
Activity	4.2	6.61	4.11	1.68	0.8	0.33	1.75
Other	0.25	0.07	0.09	0.02	0.08	0.09	4.14
Number of transitions (total)							
Mean	1.42	0.6	2.64	2.62	2.49	1.39	1.91
Median	1	0	3	3	2	1	2
n	**2595**	**1257**	**427**	**188**	**230**	**377**	**116**

Abbreviations: DP: Disability pension; PwMS: People with multiple sclerosis; SA: Sickness absence.

Table 8: The proportion of the newly diagnosed PwMS in each of the states by study year (position of the sequence).

State	Y_{-1}	Y_0	Y_{+1}	Y_{+2}	Y_{+3}	Y_{+4}	Y_{+4}
SA/DP	0.08	0.09	0.14	0.14	0.15	0.18	0.19
Mixed: SA/DP 180+ days	0.04	0.10	0.11	0.11	0.11	0.11	0.12
Mixed: SA/DP 30–180 days	0.08	0.20	0.13	0.12	0.12	0.12	0.12
Activity	0.76	0.57	0.58	0.60	0.58	0.56	0.54
Other	0.04	0.04	0.04	0.03	0.04	0.03	0.03

Abbreviations: DP: Disability pension; PwMS: People with multiple sclerosis; SA: Sickness absence; Y_0: the year of MS diagnosis.

4.2.1.2 The different types of working-life sequences

Individuals' sequences were grouped with cluster analysis into six clusters representing the types of working-life sequences. Figure 8 also displays the three most common sequences within each of these six sequence types. The types of working-life sequences describe different patterns of activity, an increasing extent of work disability in terms of net days of SA/DP in a year, and sequence stability. The largest cluster of working-life sequences was the *Stable High Activity* type (48.4%, n=1257). There were three types of sequences with varying durations and levels of mixed activity and work disability that were characterised by state instability: *Unstable Medium Activity* (16.5%, n=427) with most in activity but with some work disability, *Unstable Low SA/DP* (7.2%, n=188) mostly with *Mixed: SA/DP 30-180 days* states, and *Unstable Medium SA/DP* (8.9%, n=230) mostly with *Mixed: SA/DP 180+ days* states. The *Stable High SA/DP* type (14.5%, n=377) was characterised by full-time work disability throughout. In addition, 4.5% (n=116) belonged to *Other*.

The extent of similarity of the members' working-life sequences differed across the six types. The *Stable High Activity* and *Stable High SA/DP* types of sequences were more homogenous. This homogeneity is reflected in how many individuals were represented by the three most frequent sequences in the respective type (Figure 8). Furthermore, these types had more

stable trajectories, with fewer transitions on average than the three unstable sequence types (Table 7).

4.2.1.2.1 Membership characteristics of the different types of working-life sequences

The association of characteristics, including the modifiable characteristics education and type of work, differed across the six types of sequences. Men, individuals with university education, and office work were associated with *Stable High Activity* sequences and less likely to be in sequence types characterised with work disability and instability. The odds of being in manual labour compared with office work were higher for *Unstable Medium Activity, Unstable Medium SA/DP,* and *Stable High SA/DP* sequences than for the *Stable High Activity* sequences (p-values <0.05).

The *Stable High Activity* working-life sequences were associated with less morbidity. Having a higher number of comorbidities, pain drugs, or anxiety/depression, were all associated with having a sequence type other than *Stable High Activity*. Those with *Stable High SA/DP* sequences were less likely than those with *Stable High Activity* sequences to be on MS DMTs in Y_0 (OR 0.61; 95% CI: 0.47-0.78), and conversely, those with *Unstable Low SA/DP* sequences were more likely (OR 1.51; 95% CI: 1.08-2.11).

4.2.1.2.2 Economic implications of the different types of working-life sequences

The economic implications of the six different types of working-life sequences were also investigated. Similar trends for income from activity and earnings were observed, comparing the last study year (Y_{+5}) with the first (Y_{-1}). While the *Stable High Activity* sequences had an increase in mean annual income from activity (105,911 SEK; 95% CI: 99,739 to 112,082), the *Unstable Low SA/DP, Unstable Medium SA/DP,* and *Stable High SA/DP* types all had lower mean annual income from activity in Y_{+5} than in Y_{-1} (p-values <0.05). Nonetheless, a balancing of income sources for most PwMS was again observed with DI. All types of working-life sequences had significant increases in mean annual DI, except for *Stable High SA/DP* sequences (4669 SEK; 95% CI: -1892 to 11,230). Increases in mean annual DI were observed among types of working life sequences even though they had non-significant changes (*Unstable Medium Activity*) or even significant decreases in income from activity (*Unstable Low SA/DP* and *Unstable Medium SA/DP*) (p-values for DI <0.05).

4.3 STUDY III: PROGRESSION OF THE COSTS OF MS BEFORE AND AFTER DIAGNOSIS

4.3.1 Progression of the costs among people with MS around diagnosis

In Study III, the costs of MS to society were quantified. The annual costs per person with MS were higher after MS diagnosis than before (Figure 9). The three cost components consuming the most resources among PwMS before MS diagnosis were SA, DP, and inpatient healthcare. After MS diagnosis, the three largest cost components among PwMS were SA, DP, and drugs.

Productivity losses were the largest cost component in all studied years for the working-aged PwMS (comprising 63-86% of the total estimated societal costs) and matched references (81-86%). The proportions of PwMS with work disability were higher in the period after MS diagnosis (>45% in each year from Y_0). The relative contribution of SA and DP to the

productivity losses of PwMS changed over time; SA-related productivity losses peaked in the diagnosis year and DP costs increased thereafter.

The healthcare costs among PwMS peaked in the year after the MS diagnosis year. Almost all PwMS had annual healthcare costs after MS diagnosis (>98% per year) and healthcare costs contributed a larger proportion of the total societal costs of the PwMS (14% in Y_{-4} and 31% in Y_{+4}). This was largely due to the drug costs after MS diagnosis (>60% of healthcare costs).

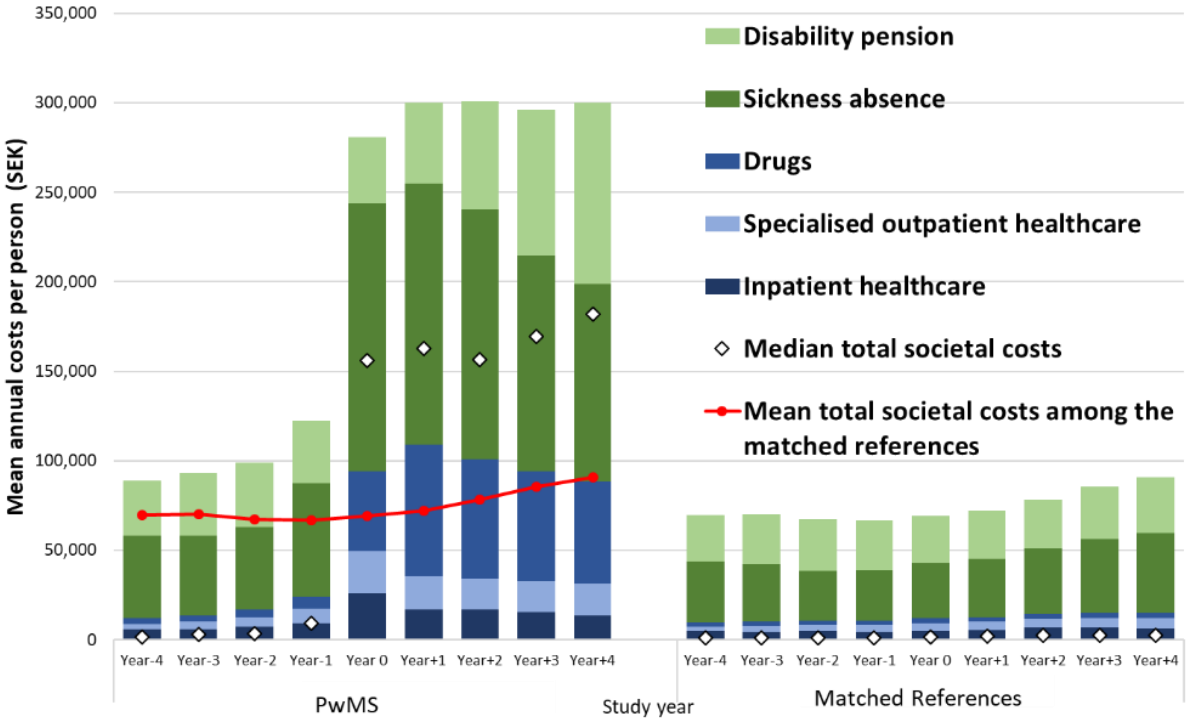

Figure 9: Annual mean costs per person by cost component among the PwMS (n=1988) and the matched reference group (n=7981).

Note: Green indicates productivity losses and blue indicates healthcare costs. Costs are presented in 2019 SEK values. Year 0 represents the year of diagnosis with MS.

Abbreviations: MS: Multiple sclerosis; PwMS: People with Multiple Sclerosis; SEK: Swedish Krona.

4.3.2 Excess costs of MS

To isolate the costs among the PwMS that were due to MS, the excess costs of MS were calculated with comparison to a reference group. Excess costs of MS were observed already before MS diagnosis, from both the t-tests considering the magnitude and the regression estimates of the relative excess costs. Among this newly diagnosed cohort, larger relative costs of PwMS were observed for healthcare costs than for productivity losses. However, the magnitudes of the excess costs of MS from productivity losses were larger than those for healthcare.

4.3.2.1 Magnitude of the excess costs of MS

Excess costs of MS were observed for both healthcare costs and productivity losses already prior to the MS diagnosis (Figure 10). The magnitude of which increased thereafter.

A mean excess healthcare cost of MS of 2285 SEK (95% CI: 613-3956) per person with MS was observed already four years prior to MS diagnosis. The excess healthcare costs of MS

peaked in the year after MS diagnosis (96,465 SEK; 95% CI: 93,733-99,197). The excess costs of MS for healthcare somewhat decreased thereafter but remained elevated throughout the study period after MS diagnosis.

The magnitude of the excess costs of MS from production losses were larger than for healthcare consumption. A mean excess productivity loss of 16,310 SEK (95% CI: 8980-23,640) per person with MS was observed already four years prior to MS diagnosis. The mean annual excess productivity losses of MS peaked at 127,326 SEK (95% CI: 119,282-135,370) per person with MS in the MS diagnosis year and remained elevated thereafter.

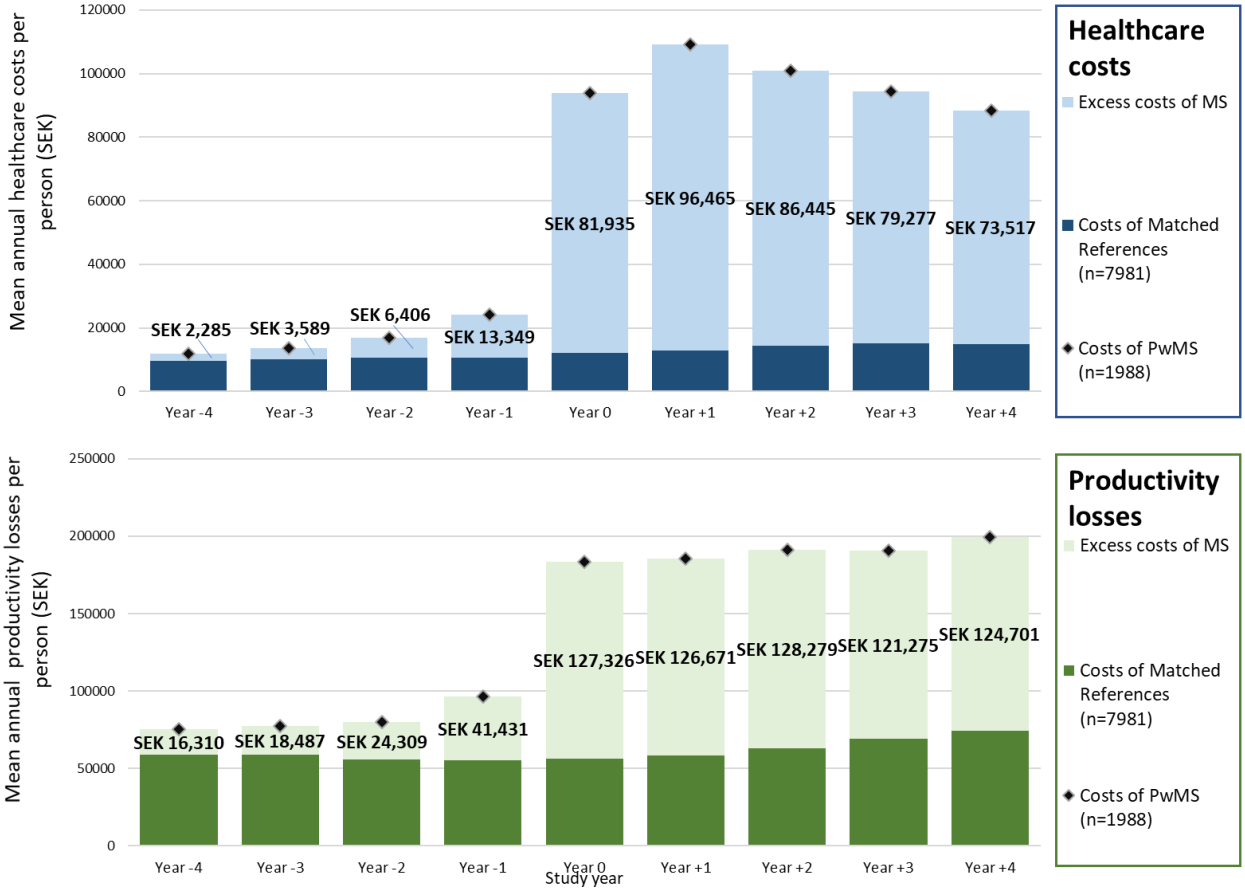

Figure 10: Annual mean excess costs of MS per person for healthcare consumption and productivity losses, as well as the sum of all-cause costs of PwMS and those of their matched references without MS for each study year.

Note: Green indicates productivity losses and blue indicates healthcare costs. Please note the different scales for the respective costs. Costs are presented in 2019 SEK values. Year 0 represents the year of diagnosis with MS. The labelled values refer to the excess costs of MS, calculated in comparison with the propensity-score matched reference group as the mean difference between the two groups.

Abbreviations: MS: Multiple sclerosis; PwMS: People with Multiple Sclerosis; SEK: Swedish Krona.

4.3.2.2 Relative costs of MS

People with MS had on average 2.93-times (95% CI: 2.77-3.09) higher total societal costs, 5.25-times (95% CI: 4.97-5.55) higher healthcare costs, and 2.38-times (95% CI: 2.24-2.54) higher productivity losses compared with the matched references throughout the nine study years (Table 9). The estimates of MS from the GEE models were very stable across the models with different included covariates.

Table 9: Summary of the adjusted MS main effect estimates[1].

	IRR[2]	95% CI
Total societal costs		
MS (ref = no MS)	**2.93**	**(2.77-3.09)**
Healthcare costs		
MS (ref = no MS)	**5.25**	**(4.97-5.55)**
Productivity losses		
MS (ref = no MS)	**2.38**	**(2.24-2.54)**

For all estimates from the models, please see Study III, Electronic Supplementary Material Table 4.
[1] Model 2a: Cost = MS + year + matching variables (age + sex + country of birth + living area) + cohort.
[2] The exponentiated coefficients as IRRs can be interpreted as multipliers or cost ratios.

Abbreviations: CI: Confidence interval; IRR: Incidence rate ratio; MS: Multiple sclerosis; ref: Reference group in regression model.

The PwMS were observed to have higher proportions with comorbidity than the references, four years prior to MS diagnosis. While the excess cost estimates with a reference group were used to adjust for expected consumption, further investigation of the possible influence of comorbidity on the costs of MS was conducted by including comorbidity in the regression models. Increasingly higher relative healthcare costs and productivity losses were observed for an increasing number of comorbidities, compared with no comorbidity. The estimates of the excess cost ratios of MS for both healthcare costs and productivity losses lessened slightly to 5.06 (95% CI: 4.79-5.34) and 2.25 (95% CI: 2.12-2.39) when including comorbidity.

Table 10: Summary of the adjusted estimates for the MS*study year interactions[1].

		IRR[2]	95% CI
Total societal costs			
MS*Year	Y_{-3}*MS (ref = Y_{-4} & no MS)	1.05	(0.96-1.14)
	Y_{-2}*MS	**1.18**	**(1.06-1.30)**
	Y_{-1}*MS	**1.50**	**(1.35-1.68)**
	Y_0*MS	**3.44**	**(3.09-3.84)**
	Y_{+1}*MS	**3.59**	**(3.21-4.01)**
	Y_{+2}*MS	**3.27**	**(2.93-3.65)**
	Y_{+3}*MS	**2.88**	**(2.58-3.22)**
	Y_{+4}*MS	**2.74**	**(2.46-3.06)**
Healthcare costs			
MS*Year	Y_{-3}*MS (ref = Y_{-4} & no MS)	1.11	(0.94-1.31)
	Y_{-2}*MS	**1.33**	**(1.08-1.66)**
	Y_{-1}*MS	**1.93**	**(1.60-2.33)**
	Y_0*MS	**6.65**	**(5.57-7.94)**
	Y_{+1}*MS	**7.28**	**(6.07-8.74)**
	Y_{+2}*MS	**5.90**	**(4.92-7.08)**
	Y_{+3}*MS	**5.33**	**(4.41-6.44)**
	Y_{+4}*MS	**5.07**	**(4.22-6.09)**
Productivity losses			
MS*Year	Y_{-3}*MS (ref = Y_{-4} & no MS)	1.03	(0.94-1.13)
	Y_{-2}*MS	**1.14**	**(1.03-1.27)**
	Y_{-1}*MS	**1.41**	**(1.26-1.59)**
	Y_0*MS	**2.75**	**(2.44-3.09)**
	Y_{+1}*MS	**2.74**	**(2.44-3.09)**
	Y_{+2}*MS	**2.63**	**(2.34-2.96)**
	Y_{+3}*MS	**2.32**	**(2.06-2.61)**
	Y_{+4}*MS	**2.25**	**(2.00-2.53)**

For all estimates from the models, please see Study III, Electronic Supplementary Material Table 5, Model 2b.
[1] Cost = MS + year+ MS*year + matching variables (age + sex + country of birth + living area) + cohort.
[2] The exponentiated coefficients as IRRs can be interpreted as multipliers or cost ratios.

Abbreviations: CI: Confidence interval; IRR: Incidence rate ratio; MS: Multiple sclerosis; ref: Reference group in regression model; Y_0: the year of MS diagnosis.

Time was meaningful for the excess cost ratios of MS (Table 10). Significant excess costs among the PwMS compared with the matched references were observed from Y_{-2} with Y_{-4} as the reference year, with the largest cost ratios observed around MS diagnosis.

4.4 STUDY IV: COSTS OF MS IN STOCKHOLM

4.4.1 Excess costs of MS

In Study IV, the excess costs of MS were estimated among a prevalent cohort of PwMS in Stockholm, including the costs for primary healthcare and further MS DMTs (Figure 11).

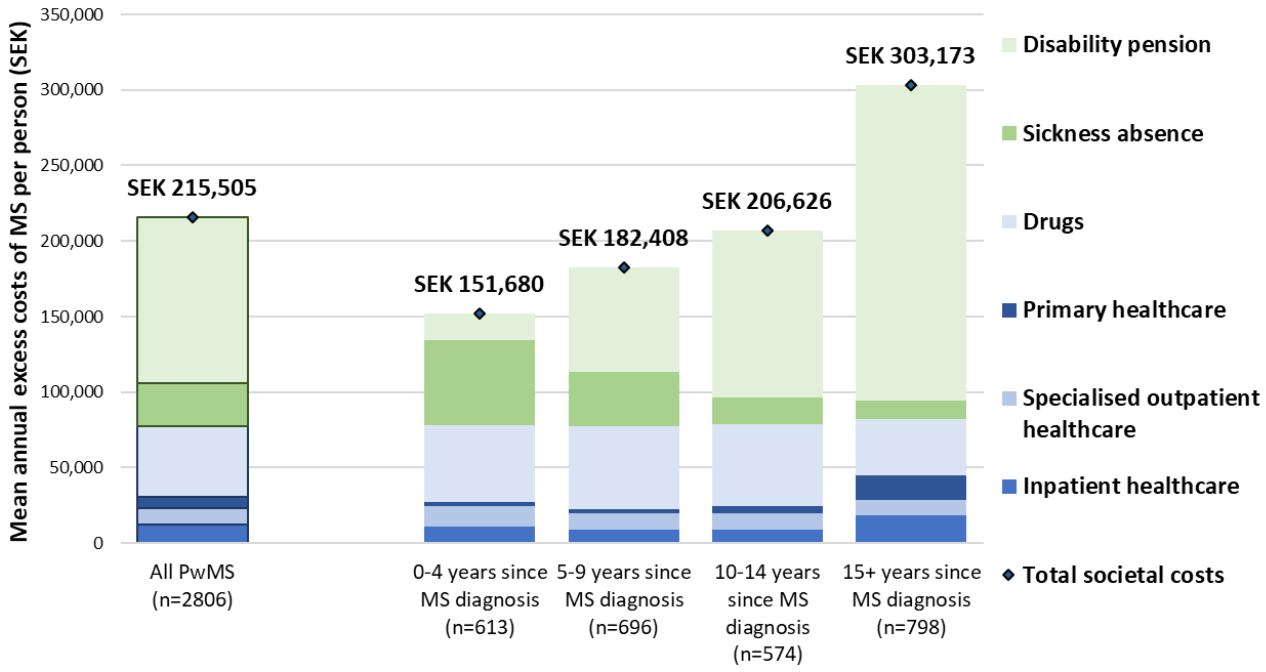

Figure 11: Mean annual excess costs of MS per person, for all and by time since MS diagnosis.

Note: Blue indicates healthcare cost components and green productivity losses. Excess costs were calculated for the PwMS in comparison with a propensity-score matched reference group as the mean difference between the two groups. Costs are presented in SEK in 2020 values. Only PwMS (n=2681) with a recorded MS diagnosis date and their reference peers (n=26,810) are included in the stratified analyses, as n=132 were included based on onset date and inclusion within the SMSreg (with subsequent exclusions for onset when aged <18 years).

Abbreviations: MS: Multiple sclerosis; PwMS: People with multiple sclerosis; SEK: Swedish Krona; SMSreg: Swedish Multiple Sclerosis Registry.

The mean annual healthcare costs were 100,599 SEK (95% CI: 96,347-104,851) per person with MS and 23,215 SEK (95% CI: 22,501-23,930) for the matched references. This equated to a 4.3-fold higher healthcare cost for PwMS. Accordingly, there was an annual excess healthcare cost of MS to society of 77,384 SEK (95% CI: 73,299-81,950) per person with MS, indicating the magnitude of the increase in costs associated with the disease (Table 11). People with MS had a higher percentage of their total annual healthcare costs publicly funded (96.8% versus 90.4%) than the references. However, as PwMS had higher healthcare costs than the references, there was an estimated annual mean excess cost of MS for healthcare fees and drugs paid OOP of 957 SEK (95% CI: 766-1123).

Table 11: Excess costs of MS[1] with 95% bootstrapped confidence intervals for all PwMS and by time since diagnosis[2] from mean differences in comparison with propensity score matched references.

	All PwMS (n=2806)		**0-4 years since MS diagnosis (n=613 PwMS)**		**5-9 years since MS diagnosis (n=696 PwMS)**		**10-14 years since MS diagnosis (n=574 PwMS)**		**15+ years since MS diagnosis (n=798 PwMS)**	
	Users (%)	Excess costs (95% CI)	Users (%)	Excess costs (95% CI)	Users (%)	Excess costs (95% CI)	Users (%)	Excess costs (95% CI)	Users (%)	Excess costs (95% CI)
Total societal costs	98.29	215,505 (204,995-225,936)	99.02	151,680 (132,022-170,554)	98.28	182,408 (162,009-201,337)	97.74	206,626 (185,135-228,619)	98.75	303,173 (281,474-326,127)
Healthcare costs	97.93	77,384 (73,299-81,950)	99.00	77,990 (69,114-88,918)	98.10	77,302 (69,242-85,415)	97.60	78,842 (70,401-88,409)	97.70	82,403 (74,245-91,768)
Inpatient	15.47	12,153 (9728-14,612)	14.52	11,165 (6654-16,395)	13.07	8915 (4452-14,570)	14.11	9107 (4943-13,647)	20.43	18,438 (13,251-24,241)
Specialised outpatient	79.62	10,987 (10,050-11,881)	79.77	13,401 (11,496-15,270)	80.03	10,790 (9059-12,834)	79.09	10,773 (8873-13,015)	80.20	10,281 (8664-11,904)
Primary	75.91	7287 (6135-8719)	72.10	2949 (1991-4012)	71.55	2468 (1510-3598)	74.91	4970 (2762-9831)	83.58	16,188 (12,995-19,834)
By professional[3]										
Physician	66.46	903 (693-1118)	62.97	826 (428-1247)	61.78	505 (152-917)	63.76	580 (126-1070)	74.94	1542 (1147-1984)
Nurse	25.41	2074 (1530-2631)	16.97	137 (-91-485)	19.25	308 (58-719)	24.04	650 (200-1432)	37.47	6101 (4435-8195)
Other	41.80	4161 (3408-5172)	38.01	1870 (1229-2653)	36.35	1557 (931-2410)	41.81	3622 (1860-7936)	49.62	8304 (6480-10,575)
Drugs	95.69	46,957 (44,284-50,006)	97.55	50,475 (43,911-59,199)	96.26	55,129 (49,322-60,415)	95.64	53,992 (47,594-60,766)	95.11	37,496 (33,062-42,093)
DMTs[4]	68.18	44,681 (42,274-47,200)	87.44	47,061 (41,872-52,192)	76.44	54,373 (48,761-59,773)	68.47	51,983 (46,330-57,788)	52.13	34,199 (30,210-38,759)
Non-DMT drugs	88.13	2276 (1126-4087)	84.99	3414 (-147-10,779)	86.93	756 (-453-2409)	86.93	2009 (38-6501)	93.23	3297 (2062-5246)
Productivity losses	48.86	138,121 (129,224-146,985)	35.07	73,691 (58,536-87,550)	41.09	105,106 (89,027-121,599)	49.13	127,784 (109,736-145,779)	65.66	220,770 (202,384-239,440)
SA	23.13	28,595 (23,884-33,406)	30.67	56,600 (45,237-68,976)	24.71	36,106 (26,924-47,154)	20.91	17,672 (9721-27,141)	19.42	11,714 (5015-18,832)
DP	31.29	109,527 (101,027-117,496)	6.69	17,090 (7554-26,764)	21.12	69,001 (55,231-82,966)	34.32	110,112 (92,034-127,760)	54.64	209,057 (190,743-227,531)

[1] Calculated as mean differences between PwMS and their respective propensity score matched references in independent t-tests. Costs are presented in SEK in 2020 values.
[2] Time since diagnosis measured on 31 December 2017. Only those n=2681 PwMS (and respective reference peers) with a recorded MS diagnosis date are included, as n=132 were included in the main analyses based on onset date and inclusion within the SMSreg, with subsequent exclusions for onset when aged <18 years (n=125 with missing diagnosis dates).
[3] The first registered healthcare professional per contact is used. Primary healthcare costs by type of healthcare professional are presented excluding the patient OOP copayment in the form of visit fees. The mean cost per person for primary healthcare copayments among all PwMS were estimated to be 550 SEK and 401 SEK for the references.
[4] DMTs from either SPDR or SMSreg (ATC codes: L03AB07, L03AB13, L03AB08, L03AX13, L04AA27, N07XX09, L04AX07, L04AA31, L04AA40, L04AC01, L01DB07, L01XC02, L01XC10, L04AA34, L04AA36, and L04AA23).

Abbreviations: ATC: Anatomical Therapeutic Chemical Classification System; CI: Confidence interval; DMT: Disease modifying therapy; DP: Disability pension; MS: Multiple sclerosis; OOP: Out of pocket; PwMS: People with multiple sclerosis; SA: Sickness absence; SEK: Swedish Krona; SMSreg: Swedish Multiple Sclerosis Registry; SPDR: Swedish Prescribed Drug Register.

Like in Study III after MS diagnosis, drug costs were the largest contributor to the excess healthcare costs of MS (60.7%). The excess drug costs of MS were mostly (95.2%) from DMTs, with 68.2% of PwMS having DMTs in 2018. Excess costs of MS were still observed when considering the costs for non-DMT drugs (2276 SEK; 95% CI: 1126-4087). Inpatient healthcare was more prevalent among the PwMS than the references (15.5% versus 7.4%, p-value <0.05), comprising 15.7% of the excess healthcare costs of MS. People with MS also had higher proportions with specialised outpatient healthcare (79.6% versus 48.9%, p-value <0.05), with specialised outpatient care contributing 14.2% of the excess healthcare costs of MS. Primary healthcare was the most common healthcare setting for references (65.5%) but there were still more PwMS with primary healthcare within the year (75.9%, p-value <0.05). Higher proportions of PwMS had primary healthcare visits at the clinic (74.3% versus 65.3%) or in the home (13.8% versus 1.2%, p-values <0.05) but no differences were observed for distance contacts (3.8% versus 3.4%, p-value 0.92). Primary healthcare stood for 9.4% of the excess healthcare costs of MS, with an annual excess cost of 7287 SEK (95% CI: 6135-8719) per person with MS. Having MS was associated with an annual excess cost of 903 SEK (95% CI: 693-1118) for primary healthcare contacts with physicians. Larger cost excesses of MS for primary healthcare were observed for visits with healthcare professionals other than physicians.

The magnitude of the costs from productivity losses was larger than from healthcare consumption for both the PwMS (177,420 SEK per person, 95% CI: 168,817-186,022) and the matched references (39,298 SEK, 95% CI: 37,830-40,766), with an average 4.5-fold higher productivity loss for a person with MS. A higher proportion of the PwMS had productivity losses than among the matched references (48.9% versus 15.4%, p-value <0.05). People with MS had a mean of 113.8 (95% CI: 108.2-119.3) net days of work disability in the year, the corresponding number of days among the matched references was 25.2 (95% CI: 24.3-26.1). This resulted in 88.6 (95% CI: 82.9-94.1) more days on average per person with MS. An excess productivity loss of MS of 138,121 SEK (95% CI: 129,224-146,985) per person with MS was observed. The excess productivity losses of MS were predominately (79.3%) from permanent reductions in work capacity (DP) among this prevalent MS cohort.

4.4.2 Excess costs of MS by time since diagnosis

There was a mean time of 11.1 years (95% CI: 10.8-11.3) since diagnosis with MS among this prevalent cohort of PwMS. The cohort was stratified by time since MS diagnosis (Table 12). The time since diagnosis strata had different sociodemographic characteristics. Variations across the strata by sex, age, country of birth, educational level, and family composition were observed (p<0.05).

With these differences in mind, the excess costs of MS stratified by time since diagnosis were calculated to indicate how the excess costs changed in magnitude and composition. Estimates of the excess costs of MS are contained in Table 11 and summarised in Figure 11.

The magnitude of the excess costs of MS from productivity losses became larger with increasing time since MS diagnosis. The composition of cost components changed by time since diagnosis, with increasing excess costs of MS from DP costs and the excess SA costs decreasing by time since diagnosis.

In comparison to the excess productivity losses of MS, the excess healthcare costs of MS were more stable (overlapping CIs) by time since diagnosis. However, there were substantial differences observed regarding the healthcare cost components. More recently diagnosed PwMS had excess healthcare costs of MS primarily driven by DMTs. Individuals with a longer time since MS diagnosis incurred higher excess costs of MS for inpatient healthcare and primary healthcare. Excess primary healthcare costs of MS were increasingly due to visits with healthcare professionals other than physicians, indicating the wide range of healthcare services and multidisciplinary care that PwMS require.

Table 12: Time since MS diagnosis for the PwMS (n= 2681).[1]

	n	%
Time since MS diagnosis		
0-4 years	613	22.86
5-9 years	696	25.96
10-14 years	574	21.41
15+ years	798	29.77

[1] Variable measured on 31 December 2017. Only those n=2681 with a recorded MS diagnosis date were included, as n=132 were included in the study based on an onset date and inclusion within the SMSreg, with subsequent exclusions for onset when aged <18 years (n=125 with missing diagnosis dates).

Abbreviations: MS: Multiple sclerosis; PwMS: People with multiple sclerosis; SMSreg: Swedish Multiple Sclerosis Registry.

5 DISCUSSION

5.1 MAIN FINDINGS OF THE SOCIOECONOMIC BURDEN OF MS

This thesis contributes with further knowledge on the socioeconomic burden of MS, especially related to work disability around MS diagnosis. Work disability, in terms of SA and DP, among PwMS was observed in the four population-based studies to have implications for the individual's working life and economic situation as well as result in excess costs to society from productivity losses. Nonetheless, most newly diagnosed PwMS of working ages in Sweden are in work. The main results of Study I and II indicate that despite the wide heterogeneity observed in working life with many having work disability, most PwMS in Sweden do not experience a decline in economic resources in the early stages of their MS. However, work disability was observed to increase around MS diagnosis and was associated with low or decreasing DI trajectories in addition to less stable working-life sequences. The identified DI trajectories and working-life sequences differed by sociodemographic characteristics, work disability, and comorbidity. The socioeconomic burden associated with MS begins early. Excess costs of MS from productivity losses and healthcare consumption were observed already before MS diagnosis in Study III. The excess costs of MS increased with time, with a steep increase around MS diagnosis. The excess productivity losses of MS were largest in magnitude, but there was a larger relative cost for healthcare among PwMS in comparison with the matched references in Study III. In contrast, in Study IV with a prevalent cohort of PwMS, the relative costs for healthcare and productivity losses were of a similar factor in comparison to references. The level and composition of the excess costs of MS differed by time since diagnosis.

The first aspect of the socioeconomic burden of MS in the following discussion relates to work disability in PwMS' working lives, then continuing with the implications of work disability for their economic situation, and afterwards regarding the societal costs of MS.

5.1.1 Working life of people newly diagnosed with MS

Working life has several stages, including labour market entry, maintenance, and eventual retirement.[91] As highlighted with this thesis, within working life there may also be temporary periods of absence or early withdrawal due to work disability. This can occur in early MS and at low levels of MS disability.[133,139] Study II observed patterns of work disability somewhere between presumed entry into and retirement from the labour force. Six different types of working-life sequences were identified following MS diagnosis, differing by the extent of activity and work disability as well as stability. Conventional binary categories of employment or work disability can obscure nuanced information of the fluctuating and progressive aspects of MS.[135] Furthermore, return-to-work is best understood as an evolving process with incremental milestones as a worker moves between phases and the outcomes of interest change,[88] providing further reason to move beyond binary classifications or point estimates and to investigate trajectories or sequences.

5.1.1.1 Work disability among people newly diagnosed with MS

Not all PwMS experience work disability resulting in SA or DP in the early stages of their MS. Rather, most people with early MS (48% in Study II) were observed to have working life

largely characterised by having stable and high levels of activity. Activity, mostly paid work, was also frequent among other identified sequence types. This is unsurprising for a chronic, progressive disease among a population with many potential years of working life ahead but is often obscured by focus on outcomes of withdrawal from the labour force. Earnings have previously been found to be the predominant income source among a prevalent cohort of PwMS.[308] However, larger differences in earnings compared with matched references were observed with time, where PwMS had 15% lower earnings than matched references in the diagnosis year with this gap increasing to 38% among PwMS with at least five years since their MS diagnosis.[308] While earnings indicate work participation, it is unclear how much of the observed reduction is because of reduced work participation or other factors such as underemployment. Nonetheless, disease worsening through both disease activity and disability progression seem to be key factors underlying findings of work outcomes.[133,144] One important characteristic of PwMS' working life not possible to directly capture, is that PwMS work part-time to a high extent, with the number of hours worked negatively associated with EDSS scores.[124,133,134,139-141] This is particularly so in Sweden,[124,140] with the possibility of combining part-time work and partial social insurances for work disability to leverage the remaining work capacity.[135,309] Accordingly, most newly diagnosed PwMS in Sweden are in work.

Nonetheless, the studies in this thesis all indicated that a high proportion of PwMS have work disability and have a higher extent of work disability with time. This is in line with the chronic and progressive aspects of MS and consistent with previous research that there are higher levels of work disability among PwMS than references and that this difference increases with time from diagnosis.[55,130,133-135,145,147]

More PwMS experience work disability than references without MS. The work disability findings of this thesis were skewed among PwMS, although to a lesser extent than among the matched references. Within the year of observation in Study IV, 48.9% of PwMS had work disability versus 15.4% of the matched references. In Study III, studying early MS in the four years before and after the diagnosis year, there was more spread in the annual proportions of PwMS with work disability, ranging between 20.4%-49.7%. These levels are consistent with previous Swedish findings covering the same period around MS diagnosis.[55] Regarding work disability resulting in DP, the proportion among the general population aged 19 to 64 with a DP was just under 5% in December 2019.[171] The corresponding proportions in Study IV with productivity losses from days with DP benefits in 2018 were 31.3% among the PwMS and 4.7% among the matched references. One study with up to 20 years of observation before MS diagnosis identified differences in the prevalence of SA already 15 years before MS diagnosis and three years before for DP in comparison with references without MS in Sweden.[130] Moreover, not all PwMS had states involving work disability in their working-life sequence spanning seven years in the early stages of MS. Heterogeneity characterises MS and this is accentuated by the various possible combinations of determinants of work disability.

PwMS have higher levels of work disability than references without MS.[55,126,130,134,135,145,147] This is also reflected in Study III and IV with the excess costs of MS from production losses. In Study IV, there was on average 88.6 additional net days with SA/DP benefits within the year among the prevalent PwMS than their references. Previously among newly diagnosed PwMS, the mean difference in net days of SA/DP among PwMS compared with references

have been observed to increase from 10.3 additional days four years before MS diagnosis to 68.9 days four years after MS diagnosis.[55] Therefore, there are high levels of work disability in terms of prevalence and extent in early MS and thereafter.

The levels and type of work disability among PwMS were dynamic. Changes in functional capacities in early MS may explain the changes in the levels and types of work disability. An increase in the states representing an increasing extent of work disability became more frequent in later study years of Study II. Consistently, increasing excess costs of MS from productivity losses, especially from DP, and proportions of PwMS with these costs, were observed with time from MS diagnosis in Study III and IV. However, there was a sharp spike in work disability around MS diagnosis, mostly from SA, observed in Study I-III. Even PwMS who otherwise had working life characterised by high levels of activity often had a state representing an extent of SA/DP proximate to MS diagnosis. This pattern of high SA proximate to MS diagnosis can relate to the clinical course with more PwMS in relapsing-remitting phases as well as SA in relation to disease activity and healthcare to diagnose MS.[55,165] Relapses are likely a more important contributor of SA in early MS, with a short spell of SA recommended if a relapse leads to reduced working capacity.[120,165] Nonetheless, there are also increases in the extent of work disability over time for PwMS. The transition from work disability being from temporary reductions in work capacity (SA) to reductions more permanent in nature (DP) observed after MS diagnosis in the excess costs in Study III has also been observed in previous studies focusing on work disability.[55,130,147]. Previously, a higher risk for a new DP in the four years following MS diagnosis was observed in comparison to references, including for DP due to other diagnoses than MS.[55] Accordingly, the extent and type of work disability differs in MS.

By investigating working-life sequences in the years proximal to MS diagnosis, aspects of return-to-work were also observed, with the transition of many PwMS back into activity after the peak of work disability at diagnosis. People with MS with 30–180 days of work disability in a single year were observed to transition to activity or maintain the same extent of work disability to a higher degree than to increase the extent of work disability in the next year. This is similar to Björkenstam et al.'s findings of a decreasing work disability trajectory followed by 5% of PwMS in the five years following MS diagnosis.[155] Accordingly, support and interventions to return-to-work when absent as well as those to stay at work could be relevant for early MS as employment is dynamic[136] and to prevent more PwMS following a trajectory of increasing work disability. A study using data from the Australian MS Longitudinal Study in 2015-2019 investigated inter-individual changes in work productivity (composite of self-reported absenteeism and presenteeism) among employed PwMS, observing that nearly 40% of respondents had stable work productivity over time at a high level of productivity, with no change when assessed 12-months or five years apart.[248] Another group of about 30% reported higher work productivity compared with 12-months prior.[248] Thus reiterating that not all PwMS have work disability and that in some situations, including among PwMS with longer times since MS diagnosis, there can be improvements. As discussed further below, work disability led to excess costs of MS with the progression of productivity losses following the same pattern as described here. Productivity losses were the cost driver in Study III and IV, already before MS diagnosis and increasingly so with time from diagnosis. Therefore, there could be potential economic savings from combining early

detection and treatment initiation with early, responsive support to maintain the work capacity or facilitate a timely, safe return-to-work among PwMS.[1,66,72,73,144]

The heterogeneity of work disability trajectories of PwMS alluded to have been studied with the group-based trajectory methods employed in Study I.[148,155,310] When considering the diversity among prevalent cohorts of PwMS, studies from both Sweden and Australia indicate that PwMS tend to follow one of three reasonably stable linear-shaped trajectories of work disability (or work productivity) at different levels.[148,310] This relative stability of the respective trajectories contrasts with the trends of work disability observed when focusing only on early MS around diagnosis. A sharp mass at diagnosis at the group level was observed in this thesis. This dynamic nature of work disability is highlighted in a previous study investigating trends among newly diagnosed PwMS in Sweden.[155] Björkenstam et al. identified five trajectories of work disability with vastly different trends and shapes of the curves in the periods five years before and the five years following MS diagnosis.[155] These findings are also complemented with the sequences in Study II where differences in work disability were observed both between PwMS with the different types of working life sequences, and over time for the same individual. Accordingly, one can speculate that these descriptive studies of the heterogeneity of work disability, highlight the importance of intervening early to support PwMS to settle on a stable low trajectory, before individuals settle on a particular trajectory.

Work disability among PwMS is associated with higher physical disability.[41,133,160] However, changes to employment, work capacity, and work productivity occur early,[1,208] as also observed in this thesis. This suggests that wider aspects of the disease than solely physical disability affect work capacity among PwMS.[1] The literature has increasingly highlighted the impact of invisible symptoms of MS, such as reduced cognitive function, pain, or fatigue, on work-related outcomes.[1,56,124,139,141,160,165-168,208,249,310,311] These symptoms can help explain findings where standard measures, like EDSS, indicate that the individual is doing well despite work outcomes suggesting otherwise.[139] Many invisible symptoms are prevalent even among PwMS with mild disability or early MS.[1,34] Yet, invisible symptoms are not so easily recognised or measured and are often underreported in registers based on clinician-reported outcomes.[34,139] Clusters of MS symptoms, regarding difficulties with walking in addition to balance and spasticity, have been observed to be most strongly associated with labour force participation among PwMS in Australia.[311] However, among the PwMS within the labour force, the clusters of fatigue and cognitive symptoms as well as pain and sensory symptoms were most strongly associated with MS-related work productivity loss.[311] Similarly, in Study II, pain was associated with a working-life sequence other than *Stable High Activity*. For this reason, change of employment[139] and longitudinal information on earnings as well as SA/DP benefits[40,134] have been suggested to be comprehensive proxies of the global functional abilities of PwMS, capable of encompassing aspects of the disease such as fatigue and cognition even for mild MS. Therefore, an individual's working-life sequence may have wider interpretations.

While the studies in this thesis did not directly compare DMT treated and not, or early versus late initiation of a DMT, the study cohorts had increasing DMT options available to them to manage their MS. Appropriate treatment with DMTs can likely maintain, prolong, and even improve the work capacity of PwMS [40,53,140,144,163,164] in addition to the well

documented improvements in clinical outcomes for the individual.[11,44,62,67-71] In Study II, DMT use within the MS diagnosis year was associated with the observed sequence types. The *Stable High SA/DP* sequences were less likely than *Stable High Activity* to be prescribed MS DMTs in the diagnosis year (OR: 0.61). This combination of no DMT and a sequence with constant high extent of work disability could indicate that the individuals with these types of sequences had more progressive MS and were not on a DMT or had a DMT delivered via an infusion, which was not captured in the SPDR data. Clinically stable MS has been observed to be associated with a lower risk for both loss of earnings and receiving a DP among Danish PwMS on DMTs.[144] Therefore, highlighting the importance of the underlying disease for work disability outcomes among PwMS.[83,312]

In addition to disease-related factors, differences in the unique work situations of the PwMS may also partially explain the diverse work disability patterns observed.[93] Job demands regarding the physical and mental abilities required, as well as workload and time pressures, may negatively influence work retention and be associated with work disability.[135,140,148,312] Job resources such as flexible work conditions, autonomy, and social support may provide tools to maintain work and retain work capacity notwithstanding invisible symptoms of MS.[140,312] Interventions to equip PwMS with work-promoting tools and to increase self-efficacy may also aid in retaining work capacity.[140] Transitioning to more seated work at higher EDSS levels has been observed among PwMS who stay in work.[140] Accordingly, there are a range of potential ways to adapt to MS within one's working-life which will affect the work disability patterns observed.

This thesis observed aspects of work disability related to absences from work. Among PwMS in paid work, lost work time from presenteeism has been estimated to be around 3.2-times greater than work disability resulting in absences.[311,313] Higher proportions of employed PwMS in Australia self-reported problems affecting productivity while at work than absences (52% versus 18%).[311] Although the opposite was self-reported among employed PwMS in Canada with early MS (24% versus 44%), resulting in 5% and 7% of usual working time lost due to reduced productivity at work and absences due to health problems in the preceding three months, respectively.[168] These estimations regarding work disability from absences among employees underestimate long-term SA or DP. However, the studies provide further insights into PwMS' working lives and call for supporting PwMS in work before work disability results in an absence.

5.1.1.2 Sociodemographic characteristics of people with MS with work disability

In addition to disease and job-related characteristics, sociodemographic characteristics can also contribute to the observed heterogeneity in work disability among PwMS. The seven identified DI trajectories and six types of working-life sequences had different sociodemographic profiles. The general trends of being a woman, less educated, and of older ages, being associated with work disability and resultant productivity losses reflect the wider trends in Sweden[170,171] and previous findings among PwMS.[55,140,145,155]

Age is an important factor for both working life outcomes and MS.[173] Older age at MS diagnosis was associated with increasing DI, perhaps due to possible associations of age with work experience and career growth.[173] Nonetheless, patterns of higher age and higher levels of work disability were observed in Study I and II. These findings were not surprising given

the age gradient observed in SA/DP in general.[171,172] Multiple sclerosis specific studies follow the same trend,[55,140,145,155] which can be expected from the baseline trends as well as the relationship of age and MS.[314-316] The aging process of PwMS is complex, with an interaction of the MS disease and normal aging, including increasing comorbidities and likely reduced efficacy of DMTs with age.[11,317] Age could also be a proxy for a higher degree of disability, progressive phase, or a longer disease duration.[312,318] However, the associations have been observed to remain after controlling for time since diagnosis[312] and were also observed in Study I-III constructed relative to the MS diagnosis year. Hence, age is critical for understanding the working life and work disability among PwMS.

Similarly, the sex distribution differed across the identified DI trajectories and types of working-life sequences. Men were less likely than women to be in sequence types other than *Stable High Activity*. The associations of sex and work disability could also relate to the gender stratification on the labour market, where occupations with higher risks for SA often have higher proportions of women.[115] Women with MS have largely been observed to have more SA/DP than men with MS,[53,145,155] reflecting the wider trends in Sweden regarding proportions with SA/DP.[170,171] However, men with MS have previously been found to have a higher risk than women to reach MS disability milestones,[25,32,314] emphasising the importance of both work situation and morbidity in assessing work capacity.

Educational level is a potentially modifiable factor that may provide opportunities and tools to adapt and maintain work notwithstanding MS. The observed associations of lower educational levels and sequence types characterised by work disability follows previous SA/DP-specific findings for PwMS.[135,140,155,167] People with MS in Sweden with university education have previously been observed to have a higher proportion with part-time DP rather than full-time DP five years after MS diagnosis.[135] In addition to the skills to adapt that may come with a higher education, there may also be more assistance and latitude provided to individuals with knowledge or skills perceived as in demand or difficult to replace.[139,141,319] This could include flexibility and autonomy to modify their work to match their MS-related needs such as the ability to cut back hours, work from home, or reconfigure their positions.[141,319] Accordingly, the skills and the positions higher educational levels enable may facilitate adjustments to utilise remaining work capacity to a higher extent, including alongside part-time DP.

Occupation was included with a broad categorisation. While specific job demands or workplace characteristics cannot be commented on, differences regarding work disability were observed. People with MS with manual labour jobs were observed to have higher odds for having sequence types other than *Stable High Activity* compared with office workers, adding to the growing literature that manual labour jobs are associated with higher levels of work disability among PwMS. Previous research has shown a high degree of heterogeneity in the extent of work disability of PwMS by occupation.[135,148] People with MS who were office workers or managers had higher proportions of part-time DP five years after MS diagnosis than PwMS who were manual labourers, who had more full-time DP.[135] This could reflect the nature of physical work demands or broader aspects of the work relationship such as lower degree of flexibility to adjust that lead to higher rates of full-time DP. More nuanced categories of occupation regarding the sector of employment were recently studied among a prevalent cohort of PwMS, with an increase of SA/DP observed over time for all

occupational groups.[148] People with MS with administrative occupations had higher levels of SA/DP. Although these PwMS also had higher proportions with a more than 20 years since diagnosis, suggesting that administration roles may provide opportunities for work adaptions when functional limitations do arise as well as the lower levels of physical exertion than manual labour occupations enables PwMS to maintain these roles.[148,319] Occupation is therefore an important factor when considering the sustainability of PwMS' working life.

The combination of findings regarding educational level and type of occupation suggest that the ability of individuals with early MS to adapt to their MS symptoms and disability as well as to maintain or utilise remaining work capacity may differ at least in part by modifiable characteristics.[135] Nonetheless, there may be differences in the characteristics associated with PwMS being in work and those associated with work disability[311] or cutting back hours[141] among PwMS in work. Older age and lower educational level of PwMS in Australia have been previously associated with not being in the labour force, while MS symptom clusters were found to be more determinative of work disability among the PwMS in the labour force.[311] Similarly, the factors predictive of work disability do not always correspond to those for return-to-work.[158] These subtle differences should be considered in future research and when designing interventions to assist PwMS to continue their working lives.

5.1.2 Economic situation among people newly diagnosed with MS

This thesis contributed further to the body of knowledge that the economic situation and consumption potential of PwMS in Sweden is relatively unaffected by early MS. Variations in annual DI levels were observed both between individuals with the seven identified DI trajectories and within individuals over time in Study I, reflecting the dynamic nature of economic situation. This highlights the need to consider trends in addition to point estimates.

The majority of PwMS in Study I and II were observed to maintain or have increasing levels of mean annual DI around MS diagnosis. Previously we observed increasing mean annual DI among PwMS at diagnosis, with no statistical differences and parallel development of DI among PwMS and matched references, both before and after MS diagnosis.[138] This suggests a degree of balancing of any reduction in earnings by the SA and DP benefits in situations of work disability in early MS. People with MS in Sweden have higher levels of SA and DP benefits and lower earnings than references without MS.[9,134,138,308] The balancing of income sources was observed visually in Study I with contrasting trends of annual earnings and work disability days. The findings from Study I and II regarding increasing annual mean DI in the years following MS diagnosis have support from previous findings from Sweden and Denmark that MS is not associated with declining economic situation for the individuals, at the group level, in the years directly following MS diagnosis.[9,128,138] Similar findings of lower earnings but no differences in DI between people with a somatic diagnosis and references without have been observed in Sweden, for example, following a spontaneous subarachnoid haemorrhage[320] or inflammatory bowel disease diagnosis.[177] However, people with bipolar disorder have been observed to have lower DI than references.[321] More generally, in several European countries, including Sweden, the equivalised household income from households with a person self-assessed as having a disability reached around 95% of the income of households without a disabled person, and this dropped to 70-80% for other European countries.[309] The report highlights that the relative economic wellbeing of households with a person with a disability is correlated with the structure of the social insurances as well as the

benefit level paid.[309] Accordingly, systems like Sweden, with full population coverage and high public expenditure on earnings-related benefits, have the highest relative incomes. Overall, the social protections in Sweden in situations of work disability appear to substantially compensate PwMS for their loss of earnings and play an important role in guaranteeing income security.

However, there are potential limits to this responsiveness already in early MS. In Study I, a decreasing DI trajectory was followed by 10.3% of the cohort. Accordingly, some PwMS are already potentially at risk for a reduction in available economic resources and may experience economic hardship. Previous Swedish findings with a longer follow-up observed that among PwMS diagnosed in 2001-2011, mean annual DI was comparable to references' DI up until nearly a decade after the diagnosis.[9] This was despite observing increasing differences in earnings between PwMS and references earlier in the follow-up.[9] Similar findings have also been observed in Denmark where after around ten years from MS onset, the personal income among PwMS began to decline and was no longer comparable to references, largely due to higher proportions of PwMS transitioning from paid work to early pension and the lower rates of early pension.[128]

Accordingly, there is a potential risk with further time from diagnosis that more PwMS have a higher extent of work disability and correspondingly lower earnings. This situation is likely to lead to a decrease in economic resources and potential economic hardship, especially among PwMS who already had relatively low levels of DI before experiencing work disability. Study I and II investigated only early MS. It is therefore likely with further observation that differences do appear both within individuals with MS over time as well as in comparison with references without MS. This thesis adds further support to such cautions as higher levels of work disability were observed among the members following decreasing and relatively low DI trajectories as well as the non-increasing mean annual DI of individuals following working-life sequences characterised with full-time SA/DP throughout. This is partly due to the design of the social insurances where compensation is less than 100% of previous earnings and the lower rates of compensation from DP than SA benefits. The latter is particularly important for PwMS who tend to progress from SA to DP benefits.

The use of social insurances has been observed in a sensitivity analysis by Wiberg et al. to not fully explain the lower levels of subsequent DI among individuals with previous SA in Sweden.[175] An additional potential mechanism raised by the authors is the bidirectional relationship, whereby future health could be influenced by income.[175] Another contributing factor to the divergence of DI levels of PwMS from the references with time could be underemployment. A smaller premium on earnings among PwMS remaining in work would be consistent with truncated careers and underemployment.[139,141] Therefore, suggesting that the retention of PwMS in work despite work disability, especially for PwMS with higher qualifications, comes at a price as one may not experience the expected career growth.[128,139,141] Such mechanisms are only speculative and were not investigated in this thesis, as they would likely slowly develop rather than manifest immediately at diagnosis. Future employment may also be subsequently impacted owing to stigma and hesitation among employers related to MS or previous SA, as well as long spells of work disability potentially resulting in a worker falling behind with changes and developments in the

workplace.[175] Accordingly, the reimbursement levels of SA and DP benefits may not be the only explanation behind progressive changes to the DI levels of PwMS.

In addition to potentially lower available material resources, a higher proportion of DI may be spent by PwMS on additional expenditures related to their MS. Although Study IV did not include all possible OOP expenditures, PwMS had annual excess OOP costs for healthcare fees and drugs of 957 SEK more than the references. There are specific allowances available to help cover other additional costs of living and daily activities due to a disability, with previous research indicating that PwMS have higher annual levels of income from disability allowances than references in Sweden without MS.[126] Nonetheless, OOP costs may have meaningful consequences for PwMS, especially for individuals with relatively low DI levels.

Overall early MS does not seem to be associated with economic hardship at the group level in Sweden. However, MS probably is associated with risk of economic hardship to a larger extent in the long-term, at later stages of MS, notwithstanding the social protections in situations of work disability. That said, PwMS with relatively low DI at diagnosis and high levels of work disability in early MS are at particular risk for economic hardship from decreases in economic resources. Long-term decreases as well as temporal fluctuations in DI in connection with work disability may result in present economic hardship as well as in the future through reductions in savings including old-age pension contributions.

5.1.3 Cost of illness

The increasing DMT options available to reduce disease activity and postpone MS disability have sparked interest in the overall costs of MS as well as the costs at different stages.[189] Substantially higher costs among PwMS than among references were observed from the excess healthcare use and days of production lost due to work disability among PwMS in Study III and IV.[322] However, the cost findings alone provide no direct guidance of how resources should be allocated. Rather, the findings point to the importance of the consequences of MS, both for the individuals and society. This thesis adds to the dialogue advocating for early intervention and highlights the importance of productivity losses from work disability to both society and the individual.[189]

5.1.3.1 Excess costs of MS

Excess costs in early MS, including already before the diagnosis with MS, as well as progression and changes to the patterns of the costs were observed. This thesis adds updated population-based estimates of the magnitude of the excess costs of MS to the literature. In Study IV, the mean annual total excess costs of MS to society were estimated to be 215,505 SEK per person with MS on top of the expected costs. The excess costs of MS are a considerable sum given that there are approximately 20,000 working-aged PwMS in Sweden,[19] in addition to children and adults of older ages with MS, who may have different costs and cost compositions. The cost per person also likely varies among the observed PwMS depending on MS severity and relapses.[7,8,205,322]

The mean annual excess productivity losses of MS due to work disability related absences were estimated in Study IV as 138,121 SEK per person with MS. The mean excess healthcare costs of MS for primary, specialised outpatient, and inpatient healthcare visits as well as prescribed drugs dispensed in pharmacies and MS DMTs, incurred within the year were

estimated at 77,384 SEK more per person with MS than per matched reference individual. The magnitude of the excess costs attributable to MS from productivity losses were higher in absolute terms per person in both Study III and IV than the healthcare costs of MS, except among PwMS with 0-4 years since MS diagnosis in Study IV, where there were overlapping CIs. Therefore, reinforcing the substantial socioeconomic burden incurred from the high levels of work disability observed among PwMS, especially with time from diagnosis. The excess costs of MS were generally in line with the previous estimates from Sweden, among working-aged PwMS in 2006, 2009, and 2012.[198] That study observed higher excess costs of MS for drugs and outpatient care in 2012 than in 2006, with all other cost components observed to be lower in 2012 than in 2006. The annual mean excess costs of MS for both healthcare and lost production in 2018 in Study IV, were slightly lower again, despite including additional costs. Therefore, there is a suggestion that with modern DMTs and care, MS may be becoming less costly. The potential cost offsets of DMTs and other early interventions are further discussed below (See 5.2).

Study IV is the first population-based COI study to include the costs of primary healthcare among PwMS in Sweden to the best of my knowledge. The excess healthcare costs of MS for primary healthcare were at the magnitude of 7287 SEK per person with MS and were concentrated among PwMS with a longer time since MS diagnosis. Excess costs for primary healthcare were observed to be not only for physicians but also other healthcare professionals, plausibly representing rehabilitation services sought. The excess costs of MS for primary healthcare were of a smaller magnitude than for the higher cost settings of specialised out- and inpatient healthcare, except among PwMS with 15 years or more since diagnosis, who had widespread primary healthcare utilisation.

The relative difference in the costs among PwMS to those among matched references differed with time from MS diagnosis. Among newly diagnosed PwMS in Study III, summarising the four years before to four years after the MS diagnosis year, PwMS had on average 5.3-times higher annual healthcare costs and 2.4-times higher annual productivity losses than matched references. Costs due to healthcare tend to correspond to a greater proportion of the costs at a lower severity level,[8] so the elevated healthcare costs compared with references were to be expected. Summarising the eight years before and after diagnosis of PwMS of all ages diagnosed in 1998-2006 in Denmark, drug costs were three-times higher for PwMS, inpatient care costs two to three-times higher, and total healthcare costs (including primary healthcare) more than twice as high.[10] With further DMT options available and a condensed follow-up over diagnosis in Study III, higher cost ratios for healthcare costs in early MS could be expected. The unadjusted cost ratio in Study IV for healthcare costs was somewhat less than observed in Study III, with on average 4.3-times higher mean annual healthcare costs among prevalent PwMS. In addition, there was on average 4.5-times higher productivity losses among PwMS than among references. Therefore, highlighting that the excess costs can change with time.

5.1.3.2 Progression of the excess costs of MS

Multiple sclerosis was associated with higher societal costs already before the individuals received their clinical diagnosis. Study III indicated that there were excess costs of MS already four years prior to the MS diagnosis at a magnitude of 2285 SEK for healthcare costs and 16,310 SEK for productivity losses. The excess costs of MS prior to MS diagnosis are

consistent with previous research of higher SA/DP levels and healthcare consumption among PwMS in comparison with references.[55,130,147,281,282,323] Previous research has observed differences between PwMS and references prior to MS diagnosis,[130] including physician and hospital encounters prior to the first demyelinating claim or symptom onset.[323] Therefore, excess costs of MS are likely incurred even earlier than observed in Study III.

The pattern of the excess costs of MS changed with time, as indicated with the progression of costs over the years around MS diagnosis (Study III) and the differences in the cost contributors when stratified by time since diagnosis (Study IV). Therefore, providing further support that increasing costs of MS involve changes in the distribution of costs.[181] Healthcare costs, especially from MS DMTs are important contributors in early MS.[8,181] Both the findings of drug costs driving the COI among recently diagnosed PwMS, which one can assume have relatively lower severity levels and the productivity losses among PwMS with longer disease durations especially from permanent reductions in work capacity are in line with previous findings.[8,189] Accordingly, as MS disability escalates an increasing share of the costs of MS are borne outside of the healthcare system, for example, productivity losses or informal care.[7,8,181,187,189] The progression of costs and the changing patterns of the cost categories within healthcare costs and productivity losses are discussed in turn below.

5.1.3.2.1 Healthcare costs

The excess healthcare costs of MS were observed to peak in the year after the MS diagnosis year in Study III and remain elevated thereafter. This pattern of progression is in line with previous findings from Denmark and reflect a cohort largely comprised of RRMS.[10,156,162] A Swedish study on the COI progression among working-aged PwMS in the five years following MS diagnosis identified 63.9% of PwMS followed a total all-cause healthcare cost trajectory that increased in the year after diagnosis and thereafter decreased somewhat.[156] This established spike in healthcare costs, with more than seven-fold costs among PwMS compared with references the year after MS diagnosis observed in Study III, is likely due to the need for healthcare visits arising from disease activity and investigations to diagnose MS in combination with the subsequent initiation of DMTs.[22,59] In Study IV, 68.2% of the PwMS had DMT costs within the year, with 43.3% using rituximab. Rituximab is used off-label for MS, with a high rate of use in Sweden especially among PwMS with active disease.[63,302] Importantly it has a relatively low unit cost compared with other DMTs. Therefore, the magnitude of these costs may be higher if those treated with rituximab switched DMT. The proportion of the COI attributable to DMTs varies in the literature due to different patterns of use across countries.[181] Sweden has comparatively high proportions of DMT use and has had a treatment strategy to initiate on more efficacious DMTs as the initial treatment.[62] The sustained excess healthcare costs post-diagnosis are likely a combination of more PwMS requiring ongoing healthcare, DMTs, and related monitoring.[21,59,281]

When stratifying the excess costs in Study IV by time since diagnosis, the magnitude of the excess healthcare costs was reasonably stable across the strata, but with different cost compositions. Differences in resource use could be from cohort effects. Disease modifying therapies comprised a larger proportion of the excess healthcare costs among the more recently diagnosed (60.3% of excess healthcare costs among PwMS 0-4 years since MS diagnosis compared with 41.5% among those with 15+ years), in line with previous research.[8,137,156] In contrast, PwMS with longer time since MS diagnosis had higher costs

from inpatient healthcare and primary healthcare, especially from contacts with healthcare professionals other than physicians. Specialised multidisciplinary and individualised care is often needed and is recommended due to the complex and chronic nature of MS with a wide range of symptoms.[21,324] Primary healthcare contributed 9.4% of the excess healthcare costs for all PwMS. However, among PwMS with 15 years or more since MS diagnosis, primary healthcare contributed 19.6% of the costs. A significantly higher mean cost per person with MS among those with severe MS disability than those PwMS with no or moderate disability has also been reported in a Spanish COI study to be due to higher primary healthcare utilisation.[325] Studies from Sweden also suggest high levels of primary healthcare utilisation among PwMS, especially with nurses, physical therapists, and occupational therapists.[124,193,324,326,327] Among 121 PwMS in Stockholm with ten-year follow-up (baseline 1999-2002), primary healthcare comprised the largest component of healthcare contacts, with 40% of the primary healthcare contacts with nurses.[206] This is reflected in the increasing excess costs of MS for contacts with nurses and other healthcare professionals by time since diagnosis. Notably, the excess costs for specialised outpatient healthcare in both Study III after MS diagnosis and Study IV by time since diagnosis were relatively stable. These excess costs could reflect the regular annual recommended follow-ups, as well as treatment for acute relapses.[21,162]

5.1.3.2.2 Productivity losses

The relatively young age of PwMS with the potential for many more years in their working life elevates the potential for high productivity losses.[7] The excess costs of MS for productivity losses were mostly of a higher magnitude than the excess healthcare costs throughout Study III and IV. Accordingly, excluding these costs related to health-related changes in productivity would lead to a substantial misrepresentation of the costs to society of MS. A number of studies report work disability and the associated productivity losses among PwMS, and that these costs represent an economic burden to individuals with MS, employers, and society, however the rates and associated costs of work disability vary between the studies, likely due to study methodology as well as differences in the studied contexts.[92,187] Nonetheless, the higher rates of work disability result in excess productivity losses of MS. This is similar with other chronic diseases among people of working ages, such as Crohn's disease[328] and rheumatoid arthritis.[92] The excess costs of MS from productivity losses in early MS can be interpreted as indicating challenges that PwMS face to maintain work capacity and remain in or return to work. Challenges begin early and are likely indicating unmet needs among PwMS regarding morbidity as well as work adaptations.

The excess costs of MS due to productivity losses were incurred already before MS diagnosis. The excess costs to society from productivity losses were observed in Study III and IV to increase in magnitude with time and were increasingly due to permanent work disability. This shift from work disability characterised as temporary (SA) around MS diagnosis to permanent or long-term (DP) with time thereafter is discussed above (See 5.1.1.1). The trends for excess productivity losses of MS followed the same trend owing to relatively stable trends among the matched references. Accordingly, excess costs of MS for productivity losses increase with time due to changes in the functional ability and work capacity among a greater proportion of PwMS and within individuals to a greater extent. This

is observed with a transition from temporary work disability to more permanent situation of work disability, or SA to DP costs.

While excess productivity losses were substantial, not all PwMS were observed to have work disability as discussed above. In a study by Karampampa et al., 51.7% of newly diagnosed PwMS in Sweden followed two of four identified cost trajectories characterised with relatively low productivity losses in the first 5 years following MS diagnosis.[156] The authors suggested that this could be due to the use of MS DMTs where the early use can slow the accumulation of MS disability and postpone or reduce the need for SA or DP.[156] Nonetheless, an increase in these relatively low cost trajectories was observed later in the study period.[156]

There is a well-established association of higher MS disability levels and productivity losses.[7,187,208] High productivity losses have been documented in the literature especially among PwMS with low proportions on DMTs due to severe disability, progressive MS types, or among cohorts who did not have access to the highly effective but often costly DMTs, for example, older cohorts of PwMS.[7] These reasons could underlie the relatively low proportions on DMTs and comparatively higher excess costs for productivity losses among the PwMS with 15+ years since MS diagnosis in Study IV.

Work disability resulting in SA spells longer than 14 days and DP benefits were included and are indicative of a high extent of work disability of the individual. However, shorter absences and reduced productivity while at work likely also contribute to the total costs of MS, including in early MS.[168,208] MS COI studies tend to include productivity losses from absences from production but not reduced productivity at work.[187,311] Reduced productivity at work often precedes and follows spells of SA upon return to work.[265] Among the PwMS in Sweden participating the European burden of illness study, 78% of the employed PwMS reported that MS affected their productivity at work and 14% reported no problems.[124] Multiple sclerosis-related presenteeism (% impairment while at work because of one's health) has been reported by PwMS in paid work in both Australia and the United States to be around three-times more than the loss from absenteeism (% of work time missed because of one's health), in terms of both time and costs.[311,313] In another study with survey data from the United States, with propensity score matched references, the levels of absenteeism and presenteeism were 2.0 and 1.8-times higher among the employed RRMS group than references using the Work Productivity and Activity Impairment-General Health scale.[329] These production losses were estimated only among employed PwMS and the relative levels of presenteeism would likely be lower, if such information was available, for the studied cohorts in this thesis. Using the MS-specific version of the questionnaire, Chen et al. reported an average of 1.9 lost work days over a four week period due to MS-related presenteeism among employed PwMS in Australia.[311] Assuming similar hours are lost in Sweden among PwMS in work with the same balance of work disability resulting in absences and reduced productivity at work, the approximate annual productivity loss from 24.7 days of reduced productivity at work would be at the magnitude of 38,522 SEK per person with MS in paid work (2020 values). While a blunt estimation of the costs for PwMS in paid work, such costs are not negligible.

5.2 POTENTIAL COST OFFSETS OF EARLY INTERVENTION

PwMS have complex healthcare needs due to the wide range of potential symptoms to manage and to reduce MS disease activity. Accordingly, PwMS often have parallel use of healthcare services in different departments and types of healthcare.[326] Ultimately, healthcare expenditure is incurred with the aim to improve health outcomes of individuals. A 10% increase in annual healthcare costs for DMTs, DMT administration, and management, has been associated with a 1.1% reduction in 1-point EDSS worsening, a 0.7% reduction in reaching EDSS level 6.0, and a 1.0% reduction in conversion to SPMS, among an Italian cohort of people with RRMS newly diagnosed in 2001-2010 over a ten-year follow-up.[330] Thus, indicating that expenditure on DMTs among newly diagnosed PwMS is associated with improved short and longer term clinical outcomes.[330] Accordingly, it is important to remember the healthcare needs and potential positive outcomes resulting from some of the incurred costs. A discussion follows below regarding investment in DMTs and symptom treatment. Despite advances in MS care, there remains an unmet need to prevent worsening disability, progression, treat MS symptoms, and to facilitate the working lives of PwMS.[56]

Although Study III and IV did not directly examine the effects of DMTs on the COI progression, DMT costs were identified as a major cost driver, consistent with the literature.[7,8,137,181] In addition to the upfront expenditure for DMTs, additional monitoring of patients is required for some DMTs, such as natalizumab, which has been attributable to increased outpatient healthcare costs.[59,73,331] Treatment with MS DMTs aims to reduce the frequency of relapses as well as reduce and postpone the accumulation of disability.[59] In addition to better health outcomes, this could logically lead to lower subsequent costs, whether directly due to reduced healthcare consumption or wider effects. The association of relapses and increased costs is well established.[124,181,205] Furthermore, the literature contains suggestions of different patterns of healthcare use following DMT initiation. Treatment with a DMT has been associated with 24% lower hazard of subsequent hospitalisation (including day surgery but not infusions) compared with no DMT over a mean follow-up of 12-years in a large Canadian study spanning four provinces.[332] Such changes in healthcare utilisation could reasonably translate into corresponding changes in costs.

Cost-of-illness studies provide indications of changes in cost distributions; more recent COI studies indicate DMTs are large contributors of healthcare expenditure and older studies suggested that healthcare costs prior to DMTs were largely due to inpatient and outpatient healthcare.[181] The stratified analyses in Study IV reflect this, for example, higher proportions on DMTs and relatively lower excess costs of MS for inpatient healthcare. A comparison of early DMT treatment (before first documented MS code) versus delayed DMT treatment (DMT start after first MS code) found that early DMT use was associated with fewer hospitalisations.[72] Although no statistically different healthcare costs were observed between the early and late treatment groups. However, when excluding the DMT costs, the other healthcare costs were significantly lower among the early initiators, suggesting that at least part of the drug costs for early DMTs were offset by savings in other expenditures.[72] In another study from the United States, comparisons were conducted of the healthcare costs in the year before and after initiation of DMTs in 2012-2015.[66] Overall, DMT initiation was associated with reductions in relapses, inpatient, and emergency healthcare, however, healthcare costs after DMT initiation were observed to increase, again largely due to the DMT expenditure.[66] In a Swedish study under review, COI progression over eight years was

compared among RRMS with early treatment initiation (with six months of diagnosis) versus late (after six months).[203] In both groups, drug costs and DP were the cost drivers. While both groups had similar mean annual all-cause healthcare costs, the early initiating group had lower productivity losses over time with fewer early treated PwMS incurring DP costs.[203] Furthermore, a recent systematic review of MS COI reviews concluded that DMTs may increase healthcare expenditure but are offset, at least in part, by reduced relapse rates and disability progression facilitating PwMS to remain in work longer.[7] Accordingly, a raft of observational COI studies propose that DMTs, in addition to the improved clinical outcomes for PwMS, may help to reduce future costs associated with MS despite the upfront expenditure.[7,181]

The above COI studies indicate potential cost savings from DMTs in other cost categories. Economic evaluations are appropriate for further analysing these suggested cost offsets.[7,73,181] One economic evaluation so far has considered the cost-effectiveness of early treatment and found that early treatment with DMTs to reduce conversion from clinically isolated syndrome to MS was cost effective for society from various models across time-horizons and nations, including Sweden.[73] The longer the time horizon applied, the more cost effective early treatment to avert MS was in terms of decreased healthcare costs, increased savings for society, and quality-adjusted life years gained.[73] While this study considered averting MS, there may still be savings in delaying progression among PwMS. The wider benefits of DMTs to the Swedish state have also been modelled in terms of fiscal benefits, regarding higher tax revenue gains attributed to changes in lifetime productivity among DMT treated groups compared with placebo alongside savings from community services.[186] Accordingly, DMTs seem to be associated with reductions in long-term costs of MS from a societal [73] as well as a state payer perspective.[186] These studies emphasize that costs are incurred at different stages; DMTs are most costly at the early stages of the disease and the potential offsets in other cost categories accrue with time. This time aspect has implications for the treatment strategy of early high efficacy therapy in Sweden[62] which plausibly incurs higher upfront drug costs but could be associated with decreased long-term costs alongside improved outcomes for PwMS. Further research is required to investigate the potential cost offsets and the mechanisms behind the changing costs.

Similarly, MS symptom management may also have wider cost offsets in addition to reducing morbidity. MS symptoms have been associated with work outcomes including work disability.[131,166,202,248] Fatigue is associated with poorer employment outcomes among PwMS and resultant productivity losses, although the literature is conflicting as to whether fatigue is associated with higher healthcare costs among PwMS.[166,168] Likewise, the severity of spasticity was associated with higher MS-specific costs among PwMS in Sweden, especially costs for productivity losses, informal care, and personal assistance.[202] This COI study suggested that if spasticity could be reduced, the associated cost burden could plausibly be reduced.[202] However, there may be other barriers to re-entry apart from spasticity (or other symptoms) especially among individuals who have been out of work for a longer period of time. Therefore, early MS symptom management including in relation to work is required[131] and may prevent or delay costs. An Australian study investigating individual-level changes in work productivity (absenteeism and presenteeism) suggests that the observed changes in work productivity of PwMS in employment were determined largely by changes in symptom severity (fatigue, spasticity, walking difficulties, and feelings of depression) rather than the

baseline level of symptom severity.[248] This has the implication that there is potential for interventions that stabilise and improve MS symptoms to also improve work outcomes among PwMS.[248] In addition, flexibility to adjust to changing morbidity situations may also provide a non-medical support to maintain work. Accordingly, the excess costs of MS for productivity losses observed may represent unmet needs in relation to symptom management[56] as well as potential lack of opportunities to accommodate changes in symptom manifestation in the work environment or job role.

The resource use underlying the excess costs of MS can indicate potential unmet needs among PwMS and possibilities to intervene. The combined knowledge of excess costs of MS from productivity losses before MS diagnosis in Study III and other SA/DP studies[10,55,130] indicate there is a need to proactively intervene early regarding work. An early focus on sustaining employment among PwMS and to provide support before the barriers become too challenging is required.[136] Considering the excess costs of MS observed in this thesis, as well as with relapses[124,205] and increasing severity,[7,8,124,181,189] intervention to reduce disease activity and worsening, and manage MS symptoms, whether ameliorating the severity level or stabilising and preventing further deteriorations, may lead to improved health status, work outcomes, and potential cost savings elsewhere, reducing the overall socioeconomic burden of MS.[181] Investing in early diagnosis, prompt initiation of DMTs, and symptom treatment may incur healthcare costs upfront but at least a part of these expenditures is likely offset by savings for other healthcare costs as well as perhaps even reduced productivity losses by maintaining work capacity.[158] As suggested with the Arenas of Work Disability Model,[93] not all improvements in clinical factors associated with work disability necessarily lead to improved work outcomes.[158] Further research is required to investigate how, and which medical and non-medical interventions promote the maintenance of work capacity and minimise work disability among PwMS. Early medical and non-medical interventions tailored to promote the maintenance of work capacity and minimise the impact of MS are required to address this unmet need among PwMS[12] and the high costs to society.

5.3 IMPORTANCE OF WORK FOR THE INDIVIDUAL

Work disability has been highlighted throughout this thesis to have considerable socioeconomic consequences, both for the individual and for society. The substantial excess productivity losses of MS from work disability reflect the challenges that PwMS encounter to stay or return to work due to their morbidity. Accordingly, economic evaluations of MS that exclude productivity losses will underestimate the socioeconomic burden of MS. However, productivity losses are not just a cost to society, where potential savings could be made. Work is generally good for physical and mental health, as well as wellbeing.[76] Work is a central dimension of life for many adults and most value work and find it fulfilling, even among people with a medical condition.[81,82] Research supports the notion that quality of life among PwMS is associated with employment.[83,84,136,333] In a meta-analysis of self-report data from 22,864 PwMS, higher health-related quality of life ratings were observed among those employed, whether full or part-time.[83] In a Swedish study, not working was associated with lower health-related quality of life among PwMS, suggesting it is more preferable to reduce hours (mixed activity and SA/DP), than to leave work completely.[333] Moreover, work brings many benefits to the worker, including a source of income, identity, purpose, and social

opportunities.[76,78] It is reasonable to assume that most PwMS would like to continue their working lives for as long as possible.

Therefore, there is an imperative to support PwMS to sustain or return to decent work when their MS and work capacity permit it.[76,78,80,85] This can involve changes to one's role at work as well as their work environment. Sustainable working life for PwMS involves a well-functioning work-life balance because work among PwMS has been indicated to sometimes come at the cost of limitations and restrictions in other life areas.[334,335] Full-time paid work may not be the ultimate goal for all PwMS. It is therefore necessary to focus on person-centred approaches with the right types of supports, in the right way, at the right time, as each person with MS has unique needs. Receiving the diagnosis, a relapse, and experiencing progressive MS may all trigger the need for intervention to support PwMS to find, regain, or remain in work as well as access educational or other occupational opportunities.[131] Work interventions are diverse and vocational rehabilitation for job retention can offer support to improve performance, compensate for performance difficulties, or modify performance demands of PwMS to support them in keeping and advancing their work.[131,319] However, while interventions can be effective at improving symptoms and factors influencing work disability and the literature calls for vocational rehabilitation approaches for PwMS, the evidence from quantitative studies are inconclusive on work outcomes despite qualitative studies suggesting benefits of vocational rehabilitation.[136,158,335] Further research is therefore required regarding how to prevent as well as reduce work disability among PwMS and support PwMS to access or remain in work.[131,136,158,335] Early, proactive interventions to reduce the symptoms and disease activity of PwMS to reduce morbidity and postpone disability accrual as well as to directly support PwMS with work may lead to more than potential economic savings over time.

5.4 METHODOLOGICAL CONSIDERATIONS

The main strengths of the four studies of this thesis are the population-based designs and the study material being high-quality microdata from routine administrative and clinical practice.[19,123,212,213,216,336] The unique register data allowed for large study populations of PwMS, matched references in Study III and IV sourced from the registered population in Sweden, and rich longitudinal information of the included individuals. The relatively large MS study populations increased the precision of the estimates and enabled subgroup analyses examining heterogeneity with exploratory and innovative methods.[102]

The SMSreg is without comparison and this clinical register was linked with the rich population-based register data to investigate socioeconomic outcomes. Study I and II were based on individual income data with continuous coverage of the outcomes and regular annual measurement for all. This is unlike many clinical outcomes of chronic diseases, such as EDSS for PwMS, which are often collected irregularly and when changes in status are suspected.[40] Another strength was the use of net days of SA/DP to provide an estimation of the work disability reflecting the opportunities for part-time absences.

There was a trade-off in the studies between a longer follow-up and observing recent MS cohorts. The most recent register data available was utilised in each study to facilitate results reflecting the current wider context including MS care and social insurance regulations. This however reduced the opportunity to study later stages of MS and long-term outcomes.

Nonetheless, not all possible sources of bias were able to be prevented. Internal validity of a study is a prerequisite for the external validity of the findings. Methodological considerations of the studies regarding these two related aspects are discussed below.

5.4.1 Internal validity

Both random and systematic errors can lead to lower levels of internal validity of a study.

Random error is often summarised as random variation, or the opposite of precision.[337] One effect of the relatively large population-based study populations was more precise estimates. To produce the relatively large study populations, several cohorts of newly diagnosed PwMS were combined in Study I-III, respectively. Sociodemographic characteristics of the cohorts were checked for comparability before merging. In addition, separate trajectory analyses with the same specifications as the main results for Study I were also performed for the two cohorts (2008 and 2009) (data not presented). Visual comparisons revealed similar trends and proportions of membership per trajectory group, but with wider 95% CIs due to smaller numbers, highlighting the benefit of merging the cohorts and suggesting that this was not at the expense of introducing bias. Furthermore, the reporting in all studies of 95% CIs around the point estimates provided an interval of values, in recognition of random variation.[337]

Systematic biases result from the incorrect estimation of the association between the exposure and the outcome variables.[337] Such bias may be introduced when identifying and selecting study subjects, classifying the exposure or outcome variables, and analysing the data. The three main risks to internal validity, selection bias, information bias, and confounding,[337] are discussed in relation to the studies below and followed by considerations specific to costing.

5.4.1.1 Selection bias

Selection bias refers to distortions of the relationship between exposure and outcome introduced by factors influencing study participation or procedures to select participants.[337]

Selection bias from non-participation is generally not a large concern in research with population-based registers.[102] The universal coverage of the social insurance and healthcare systems reduces selection bias from non-participation and makes Sweden a particularly suitable setting to study the socioeconomic burden of MS. In respect to the work disability outcomes, the MiDAS and LISA contain SA and DP for all, rather than information of a self-selected group voluntarily enrolled based on perceived risk and risk adversity. Similarly, for healthcare consumption, the Swedish healthcare system is universal in coverage to residents with modest copayments. Only healthcare visits privately financed with private providers are not included in the NPR or VAL. The potential risk for selection is larger for types of primary healthcare which could be privately financed and provided, for example, private occupational health services. This unlikely contributes to a selection in observing MS exposure but may influence the completeness of costs in Study IV. Nonetheless, despite the high level of public funding and universal coverage of the healthcare system, inequities in healthcare access exist. Primary healthcare resource allocation, for example, has become less dependent on need and more dependent on patient demand since the 2010 reforms on patient choice of provider and freedom of establishment for private providers.[103] Therefore, there may be potential non-participation in the healthcare registers due to barriers in accessing care. This could affect MS exposure as one cannot be identified with MS if one is yet to receive the diagnosis.

Furthermore, among the included individuals, those who face barriers to accessing healthcare likely have different characteristics, patterns of resource use, and consequent costs and this could partially explain some of the observed heterogeneity among PwMS.

There is potential non-participation in Study IV that could have introduced some selection bias. Neurologists and patients voluntarily choose to use the SMSreg and input data, with improved coverage of providers and their patients over time.[218] The coverage was estimated to be 80.1% of all PwMS in 2019.[218] Individuals not regularly attending neurology clinics, despite recommendations for annual visits,[21] may be less likely to be included. These PwMS may not be on DMTs due to being in the progressive phase of MS and treat symptoms within primary healthcare to a higher extent, which could lead to systematic differences.[218] This may have affected the mean costs of MS in Study IV regarding the healthcare cost components and also possibly underestimated the productivity losses.

Turning to participant selection procedures, some selection was introduced by requiring stable residence in Sweden for inclusion in the study populations. This was required to solve other issues; either to assume the MS diagnosis was new or to require full observation for the statistical analyses. There could be systematic differences in the outcomes of those who were not included, for example, by age or country of birth. The potential consequences of which are further discussed below.

In Study II and III, complete observation of the seven and nine-year study periods were a trade-off with the analytical methods to provide more robust estimates. This potentially increased the selection already introduced by requiring residence in Sweden prior to the first MS diagnosis code registered. The potential consequences of this selection on the identified types of working-life sequences in Study II were tested after observing differences in the characteristics of the individuals included (n=2595) with those excluded from the main analysis cohort due to death or emigration (n= 57) regarding age, country of birth, child at home, married/cohabiting, type of living area, work, and MS drugs. The sequence analysis methods were repeated with six activity states (*Censor* state added) and 2652 PwMS. The findings with an additional state and the main results did not differ substantially, indicating a negligible effect on the interpretations by requiring full observation. With an additional state, the number of unique sequences was higher at 674 and more heterogeneity was introduced into the sequences. Nevertheless, the main findings of increasing diversity across the study period and the resulting six types of working-life sequences were like the main results. In Study III, given the short time frame of four additional years, and small numbers (27 people with MS died and nine emigrated, and the respective numbers among the references were 38 and 76), the impact on the findings by excluding these individuals was likely to be small. The risk of introducing bias from selection was balanced among this reasonably young cohort against the potential overestimation of costs incurred in later study years after diagnosis that could occur if imputing the observed elevated excess costs close to MS diagnosis in situations of attrition in the later years after diagnosis.[338] Similarly in Study IV, a full year of observation was required, but this requirement likely impacted the findings even less.

Attrition of the study population was possible in Study I, where individuals were included even if they died or migrated after Y_0. If the attrition was non-random and closely related to the outcome measure, biases of unknown size and direction could have been introduced, for example, low earnings preceding a death.[339] By the final study year Y_{+4}, 1.7% were lost to

attrition. This low percentage of this young cohort was fairly evenly spread across the seven identified trajectory groups (range 0-3.2%) in the short follow-up (four years). Some caution is required in interpreting the results because the group membership probabilities assumed that attrition and trajectory group membership were independent.[339] Although the level of distinctiveness of the trajectory groups indicates trajectory membership with less uncertainty and increases the robustness of the findings notwithstanding attrition. Therefore, with such low levels of attrition and distinct trajectories there was minimal bias introduced in Study I.

5.4.1.2 Information bias

Errors in either the exposure (MS) or the outcome variable measurement may lead to distortions in the measure of association.[337] The register data used in this thesis is in general of high-quality and reduced the risk of misclassification and measurement errors as exposure and outcome information were not subject to recall bias.[102] However, as largely based on routinely collected data, there could be non-differential misclassification from data input and coding errors which could have somewhat reduced the strength of associations observed.[274] This is not considered a major concern.

5.4.1.2.1 Exposure of MS

Misclassifications of the "exposure" MS from the MS ICD codes in the NPR were possible.[214] Additional criteria to observing an MS ICD code were developed across the studies to guard against misclassifications when classifying an individual as having MS (See 3.2, Table 1). These criteria strengthened the assumptions that the MS ICD code both represented an MS diagnosis (Study II and III), rather than a miscode (non-differential misclassification) and that it was a new diagnosis to prevent potential overestimation of outcomes associated with further progression of the disease (differential misclassification) (Study I-III) as the NPR does not record whether a diagnosis was newly established at the recorded visit.[214]

The NPR can be used to accurately identify PwMS.[19,340] Factors favouring the quality of MS diagnoses from the NPR include: In Sweden it is nearly always a neurologist that determines a diagnosis of MS; neurology departments are expected to use the current diagnostic criteria; the McDonald criteria were introduced in 2001 the same year as specialised outpatient visits were included in the NPR; and magnetic resonance imaging machines are well distributed throughout Sweden.[13] The validity of MS codes in the NPR in the years 2001-2013 have been investigated in a multi-register linkage study.[19] In this study, we found that 92.5% of individuals with an MS code could be corroborated with MS-specific information, from either additional visits in the NPR or information linked from other registers.[19] The remaining 7.5% did not have additional MS information in the available registers and the MS diagnosis was deemed to be uncertain.[19] More recently, in a comparison of PwMS identified in the NPR in 2001-2013 with medical records from Värmland County, a positive predictive value of 94.8% was found.[340] A case definition of MS of three or more MS codes in the NPR for in- or specialised outpatient healthcare was suggested to be best balanced in terms of sensitivity and specificity.[340] Similarly, in Study II and III, at least two visits in the NPR were required or one NPR visit and inclusion in the SMSreg. Having such procedures to identify PwMS when using register data have also been applied in Canada.[282,341] These requirements may have simultaneously introduced some selection bias as discussed above, however, I believe

that this is not a substantial problem as they are balanced against increasing the validity of the exposure. The completeness of MS diagnoses in the NPR has not been formally assessed to the best of my knowledge. People with MS at the two extremes of the severity spectrum may be missed if sourced from the NPR: PwMS with mild severity and low disease activity that do not seek medical care for their MS or only seek primary healthcare and PwMS with severe disability who either reside in long-term care or only receive care in primary healthcare settings.[340]

Similarly, the definition of no MS for a potential reference was also developed across Study III and IV to correctly identify people without MS and reduce the likelihood of differential misclassification of MS status. In addition to the residency requirements, people with previous healthcare visits due to MS or other demyelinating diseases, an MS DMT dispensing, or included in the SMSreg were excluded as potential references. Such criteria are often used in MS register-based research in defining reference groups without MS.[280-282]

5.4.1.2.2 Covariates

Misclassification of comorbidity from the ATC codes in Study II and III was possible. This may have contributed to measurement error as well as residual confounding from comorbidity not fully captured by the index. The SPDR does not contain information as to why a drug was prescribed, which could lead to some misclassification as to whether the drug represented a distinct comorbid condition to MS. Some antidepressants (Amitriptyline, ATC code: N06AA09, Nortriptyline: N06AA10, and Buspirone: N05BE01) are also used off-label to treat MS symptoms and in such situations they were incorrectly classified among PwMS as a comorbid condition.[57] In Study II, <6% of PwMS had these antidepressants and were classified as having anxiety/depression, representing an upper estimation of the potential misclassification.

5.4.1.2.3 Outcomes

Misclassification and measurement error in the outcomes were also possible in the register data and when simplifying complex phenomena to describe working life. The income and SA/DP information used in Study I and II was annual, without information on the distribution of incomes or work disability within the year. Study I and II both created typologies where individuals were classified (DI trajectory or type of working-life sequence). The methods summarised data to group individuals who may not be entirely homogenous, however, this data reduction was balanced against the creation of comprehensible descriptions over time.

The analytical approaches in Study I and II also required choices in specification by the researchers for the group-based modelling and sequence analysis process. These methods both focused on the whole trajectory to uncover groups of individuals with similar trajectories and group assignment allowed the possibility to subsequently explore the trajectory relationship with baseline covariates.[243] Both methods will create the requested number of groups, even if there is no meaningful structure in the data, so there was an element of researcher judgement, with a need for transparency and critical thought.[231,239,243,342] In both studies, a range of specifications were tested before determining the final classifications. The spaghetti plots in Study I (See 4.1.1, Figure 7) and index plots in Study II (*Study II, Figure 2*), illustrated the coherence of each group suggesting little misclassification. There was an assumption that these classifications were sufficient to describe the complexity within the

data when testing associations with the group assignments in further statistical tests. Notably, the subsequent analyses using the group assignments did not reflect the within-group heterogeneity[239,243] and the multinomial logistic regressions assumed that all groups were equally different from one another.[231]

Regarding Study II, there are no current precise guidelines for sequence analysis on appropriate sample size, minimum sequence length, or optimal number of states, beyond using the minimum required number of states. There was a possibility of overlapping working-life characteristics within a year. Therefore, the states were designed to be mutually exclusive, with all activities which one could be entitled to SA benefits in situations of work disability classified within the activity state and the state assignment conducted in a fixed order. Sequence analysis created a typology of working-life sequences, though grouping similar sequences, of the common temporal patterns of the states regarding when, what order and duration.[243] In doing this, small and negligible differences between individuals' sequences were ignored. The resultant cluster solution had an average silhouette width (coherence of assignments) of 0.50, where a number closer to one is a sign of high between-group distances and strong within-group homogeneity.[231] This value, which was like other tested cluster solutions (range: 0.46-0.54), indicated a weak to reasonable global structure.[231] The average silhouette widths were also calculated for each cluster separately to have a better understanding of the partition quality, as the reasonable global average silhouette width did not necessarily imply high levels of internal cohesion or homogeneity among all identified clusters.[243] The resultant values ranged from -0.12 for *Unstable Medium Activity*, indicating that there was low homogeneity within the group and the group structure could be artificial, to 0.77 for *Stable High Activity*, indicating a strong identified structure.[231] In a simulation study, the length of the sequence has been found to be largest determinant of incorrectly classifying individual sequences,[257] suggesting that a longer follow-up in Study II could have been preferable, not only to observe a longer segment of PwMS' working life.

The individualised household measure of DI could have been influenced by the underestimation in register data of cohabitating couples without children.[123,176] An alternative measure 'Individual DI' referring to the sum after tax and deductions of only the individual's personal income sources[176] was investigated, with information from 2004 onwards capped at the 99% level (708,997 SEK). Adults within the same household could have different individual DI values but would have the same individualised-household DI.[123] A visual comparison of the two DI formulations by plotting the annual means over follow-up by trajectory group assignment in Study I in revealed similar trends, with individual DI at slightly higher values (data not shown). Therefore, suggesting that the main findings of the trends and relative levels of the trajectory groups identified in Study I would not change substantially by the choice of DI formulation.

There was a lack of information in all studies on SA spells without benefits administered by the Social Insurance Agency. Accordingly, there should be caution in interpreting classifications of no (identified) work disability and as a consequence, there is also an underestimation of productivity losses.

5.4.1.3 Confounding

Confounding is a key consideration in observational studies. Confounding distorts the association between exposure and outcome when the study groups compared are imbalanced regarding other factors (confounders) which are associated with the outcome and do not fall in the causal pathway between the exposure and the outcome.[337] Contrary to selection and information bias, confounding could be potentially controlled for in the statistical analyses by comparing within appropriate strata of the identified and measured confounder. Confounding was handled differently across the studies. The use of linked microdata made it possible to control for several potential confounding factors in the analyses.

The classifications created in Study I and II were not adjusted for confounders. Rather the aim was to investigate the distribution of individuals across the exploratory classifications (DI trajectories and working-life sequences) in these largely hypothesis-generating rather than testing studies. Sociodemographic factors as well as comorbidity (Study II) were mutually adjusted for in the subsequent analyses of associations with the group membership.

In Study III and IV, sociodemographic confounders were considered in the design, as well as adjusted for statistically in Study III. Matching references without MS that are identical or nearly so to the MS cohorts with respect to the distribution of potentially confounding factors, provided improved efficiency in confounder control by increasing the precision of the adjusted estimates for the given study size.[337] In Study IV, double adjustment with statistical analyses to remove residual confounding was not deemed necessary after matching with propensity scores owing to standardised mean differences <0.1 for the observed sociodemographic factors.[288] Unadjusted excess cost estimates are presented for both Study III and IV, providing estimates for all PwMS rather than conditioned on a subgroup.

A given limitation of the studies stems from the lack of information in the registers on other relevant factors. The included outcomes are complex with many potential associated domains, for example, socioeconomic position, workplace, health status, and lifestyle factors. Accordingly, residual confounding may arise from other potential confounding factors which were not adjusted for in the analyses or adjusted for but not fully captured within the measure. Educational level was an indicator of socioeconomic position but only covered some aspects underlying socioeconomic stratification, so that unobserved differences in socioeconomic position may still influence the findings. Similarly, workplace factors were not included at all but may explain part of the observed associations with work disability. MS clinical factors were also not included as such information was not available for the full study cohorts. However, inclusion in Study I-III by diagnosis with relative time scales did somewhat control for progression.[303] Thus, inclusion of additional relevant factors may further explain part of the associations observed, although they must be balanced against inclusion of additional variables which could affect precision but not the bias (over adjustment).[343]

5.4.1.4 Isolating the costs of MS

Study III and IV provided estimates of the costs of PwMS as well as isolated the costs attributable to MS (excess costs of MS). Cohort and study design as discussed in the above sections are essential to underpin valid cost estimates. Considerations specific to costing with register data are further detailed below.

5.4.1.4.1 Methods to isolate the costs of MS

Costs also occur in the general population from healthcare consumption and production losses. Accordingly, not all identified costs among the PwMS were incurred because of their MS. The estimates of the sum of all-cause costs should be interpreted as costs of PwMS. These costs of PwMS are an overestimation of the true cost of MS. This thesis comprised register-based research, where it was not possible to limit the identified resource use of PwMS to consumption related to MS by asking them or consulting patient records. Studies of smaller samples of PwMS can quantify the costs of MS by asking individuals directly, however, this may introduce recall bias as well as variations in how people perceive symptoms to be related to MS or not. Excess costs of MS in this thesis were calculated with comparisons of the sums of all-cause costs among PwMS to those among population-based references without MS to remove the proportion of costs not likely to be due to MS.[204] The excess costs of MS should be interpreted as the costs per person attributable to MS that can be expected in addition to the usual costs. Accordingly, the excess costs of MS represent the hypothetical sum society could save if there was no MS.

Matching is a method of sampling from a pool of potential references to produce a reference group of adequate size in which the distribution of factors are similar to the distribution of the 'exposed' PwMS group.[283] While adjustment in regression models can also provide covariate balance, building covariate balance into the study design by matching allowed for simpler analyses and reduced the variance in the excess costs of MS.[283] The references without MS identified in Study III with exact matching and Study IV with propensity score matching were intended to reflect the PwMS in the respective studies except for not having MS. Accordingly, their cost estimates are not representative of the general population's. The excess cost methods with well-matched reference groups also accounted for personal factors which may influence resource consumption. By calculating the progression of excess costs with a reference group in Study III, possible changes in costs from wider societal changes and the cohort aging were incorporated.[147] Excess costs are also advantageous in that they are not conditioned on a very specific subgroup within PwMS, as with statistical adjustment, but are more generally applicable.

Excess cost approaches are particularly appropriate for investigating the costs of a chronic disease like MS. By use of the reference group, the excess costs incorporated costs related to comorbidity above the expected level in the population and isolated costs due to wider problems related to MS. Some of the excess costs can be directly related to MS, whereas other contributions to the excess costs may be less obvious especially when using register data. This is because MS may influence wider resource use, with MS either recorded as a side diagnosis or not at all. Previously, working-aged PwMS have been observed to have SA and DP certified with a main diagnosis other than MS to higher levels than reference peers, even after MS diagnosis.[55] Some comorbid conditions are independent from MS, others have shared risk factors, while others may stem from MS, for example, increased risk for cardiovascular disease among PwMS with reduced mobility.[42,48] Comorbidities may alter the clinical course of MS as observed with depression,[57] and consequently may lead to further MS-specific healthcare utilisation. Costs of MS will be underestimated if measuring only MS-specific costs among PwMS indicated by an MS code in the registers and overestimated if summing any resource use.[198] It can be difficult to assign resources to the correct disease in register-based research if not using excess cost or attributable fraction methods.

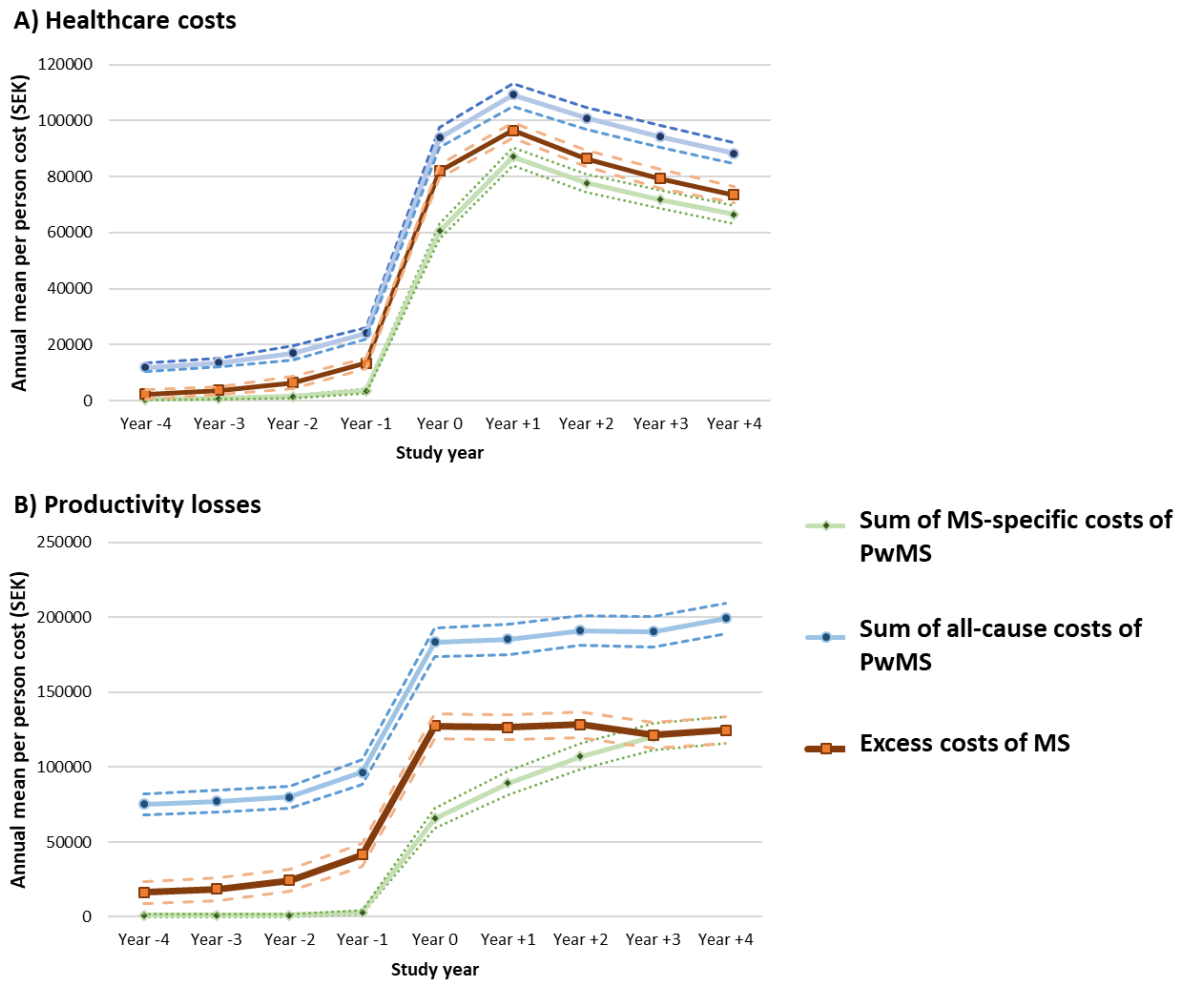

Figure 12: Mean annual healthcare costs (A) and productivity losses (B) with 95% confidence intervals from Y_{-4} to Y_{+4} among the PwMS (n=1988) comparing the excess costs of MS, the MS-specific costs, and the all-cause costs.

Notes: Y_0 indicates the year of diagnosis with MS. MS-specific costs were inferred from MS ICD-10 code G35 as the main diagnosis recorded for the healthcare visit or on the physician certificate for the SA/DP benefits, or an MS DMT. Excess costs were estimated as the mean difference in annual total all-cause costs between the PwMS and population-based matched reference group for the respective cost components. All-cause and excess healthcare costs also include the patient copayments for the visits to healthcare and for drugs. The copayments for healthcare visits could not be ascertained for MS-specific costs given the annual ceilings are irrespective of the main diagnosis for the visit.

Abbreviations: DMT: Disease modifying therapy; DP: Disability pension; ICD: International classification of diseases and related health problems; MS: Multiple sclerosis; PwMS: People with multiple sclerosis; SA: Sickness absence; SEK: Swedish Krona.

To illustrate the differences in possible cost estimates with register data, a visual comparison is presented in Figure 12 of the annual mean excess costs of MS from Study III, MS-specific costs of PwMS, and all-cause costs of PwMS. The figure indicates that despite increasing MS-specific costs over the study period, costs due to other diagnoses (main diagnosis coded with other ICD codes than G35) remained important cost contributors. With the wide range of symptoms of MS and issues attributing resources to the correct disease, there is a risk of underestimating the costs of MS in register-based research if identifying resource use with an MS ICD-code. Furthermore, slightly decreasing estimates for MS were observed in Study III for models also statistically adjusting for comorbidity. These estimates were likely over-adjusted but were of similar magnitude to those from the models without comorbidity. Hence,

suggesting that the excess costs were adequate, and that further adjustment risked underestimating the costs of MS.

5.4.1.4.2 Modelling the costs of MS

There are challenges in modelling costs. A small minority are often responsible for a high proportion of the costs, with the mean often above the median.[274] Alongside the often strongly right-skewed positive distribution from complications and comorbidities of severe patients, healthcare cost data also typically features a mass of zero observations.[236,269,274] The annual costs from productivity losses, in addition to the zero mass, also had a natural upper limit. Nonetheless, methods based on the normal distribution for inference of the sample mean are widely used to estimate mean costs.[269] Truncation by capping extreme values by assuming the high values are contaminated may provide more robust estimates of the mean, but the extreme values should be assumed to be a part of the cost distribution (i.e., noncontaminated) and included to avoid introducing bias in the cost estimates.[269] Rather, larger samples are recommended to reduce sparsity of the sampling distribution and the sway of a few values.[269] Hence, simple methods are preferred when sample size allows.[269] The excess costs, calculated as mean differences from independent t-tests, were on the scale of interest.[269] These estimates were also unadjusted estimates from real-life populations and are likely to be more useful than adjusted data from standardised trial populations. The excess cost estimates provided a mean value across all individuals, irrespective of age, sex, or other characteristics which were adjusted by design.

In Study III, regression estimates also isolated the cost of MS as a multiplier of the costs of PwMS compared with references. The estimates tested relationships of MS with other factors such as the progression of costs with time. A model that could maintain the zero observations, rather than conditioning estimates on positive expenditure, was desired to allow inference for all PwMS. Generalised linear models are the dominant approach to modelling mean costs. These methods with a single distribution, provide reasonably robust estimates of the mean despite outliers.[269,274] An extension of these models, GEE, enabled the modelling of repeated measures of the individuals over time with the log link implying a multiplicative effect of the included covariates on the mean costs.[276]

5.4.1.4.3 Costing methods

There are also several considerations regarding the precision and choice of unit costs applied in Study III and IV. Register-based resource use enabled observation of resource use over the full study period, rather than extrapolating the resource use from a shorter period.[328]

The level of precision used to cost the healthcare visits (gross- to micro-costing) was selected based on the level of resource data in the registers, availability of unit costs, and efficiency considerations. Costs for healthcare visits were based on retrospectively determined aggregate average unit costs from official sources and may not reflect the actual costs incurred. These widely-used averages fostered comparisons with other studies. To avoid temporal biases in Study IV from the vast rearrangements of healthcare owing to the pandemic, earlier unit costs for healthcare were used and inflated[344] to 2020 values. If the implemented routines continue and become standard, then the costs will be underestimated.

For the primary healthcare visits, an average unit cost for all categories of patients was applied.[180] The common unit cost options reported in the literature for costing primary healthcare in Sweden from regional register data are to either to use the retrospectively set unit cost and matrix from Swedish Association of Local Authorities and Regions [293] as in Study IV,[299,300] the prospectively set out-of-region price lists,[345] or disease-specific microcosting of the physician's time and average salary.[346,347] The register data sources made the latter less feasible. The retrospective average unit cost and matrix was selected as retrospectively set from cost data across Sweden. They also allowed costing of more detailed types of visits, retaining more of the available detail in the data, than the out-of-region price lists for all outpatient healthcare, for example, the average costs for a home visit.

Specialised outpatient and inpatient healthcare costs were based on an average cost for each category of case as defined by the DRG codes. This provides more detail than with primary healthcare visits and reflects the greater potential variation in resource use within these healthcare settings. Diagnosis-related group weights were used to cost the healthcare visits by grouping visits with a similar case-mix (clinically meaningful and homogenous resource use) and applying a unit cost for each group of cases.[180,267] The precision depends on the level of detail in specifying the types of cases and homogeneity of resource use within the groups. The DRG codes, weights, and cost per 1.0 DRG are updated annually.[267,344] Accordingly, the DRGs were increasingly split up into respective complication grades across the studied years with these refinements to increase within-group homogeneity and reflect clinical practice. Weighting was retrospectively based on the nationwide average resource use of visits with each specific DRG code from annually audited expenditure and should cover the standard treatment burden as the weights are adapted annually to reflect resource consumption with changes in care and technology.[267] Sweden, alongside England, have recently been assessed as benchmarks of good practice regarding DRGs and appropriate settings for using DRGs for costing for economic evaluations.[344] Nonetheless, the use of DRGs may have underestimated any visits with extreme costs and potentially the cost of visits due to diagnoses other than MS among PwMS, if the MS diagnosis required more resources than average.

There is also a slight overestimation of the OOP copayments with having separate caps for specialised outpatient and primary healthcare visits rather than one combined. The economic burden to PwMS from OOP costs in Study III and IV was limited to visit fees and costs for prescribed drugs. Other relevant costs often borne by the individuals, like utensils, transport, and home adaptations, were not included within the registers leading to underestimations.

In contrast to costs for healthcare visits, the drug costs from the SPDR were specific to the filled prescriptions. The public retail price for these and the MS DMTs may be overestimated. The actual prices are commercially sensitive and can be set in negotiations.[137,180] Nonetheless pharmacy retail prices are recommended when costing drugs.[184] While Study IV estimated the cost for the drug, the costs for administering the DMTs were not always captured in the data, leading to underestimations in the costs of being on DMTs.

There are different methods available for costing foregone production owing to morbidity. The two most common are the human capital and the friction cost approaches.[180,188] Productivity losses were estimated using the widely-used human capital approach,[187] as per the guidelines by the Swedish Dental and Pharmaceutical Benefits Agency.[184] The human capital approach valued lost production from the perspective of the individual, by counting

any net month with work disability (as a proxy of absence from production) as a month lost.[178,180] The alternative, friction-cost method, aligns more with the employer's perspective. This method would only count absences within the friction period, the time until another employee takes over the work and production can continue. Exact friction periods were unknown and would assume that the available replacement was not already actively producing elsewhere.[178] Furthermore, the friction period would restart with each recurrent SA spell. In the absence of further information, a period of three-months is suggested to be a reasonable base case for a friction period.[183] Therefore, the choice of approach only affects the costing of longer SA spells as well as DP. The reported productivity losses in Study III and IV are accordingly higher than if they were calculated with friction cost methods. However, as Rice argues, the reasoning that human capital approach overestimates costs simply because the individual could be replaced is contrary to wider public health principles and societal goals of valuing human health (and life).[179] In Study III and IV, the use of the average gross earnings of all sectors (as well as social security contributions) as the value of lost production, reflected the range of occupations within the labour market. Using this value of lost production, likely led to underestimations in the productivity losses to society, for example, in situations of team production or time-sensitive work output.[86] Use of an average salary as the value of lost production balanced efficiency and equity considerations when costing the net days of lost productivity.[86,180] Notably, the lost hypothetical production was valued the same irrespective of the sex of the individual with work disability, to prevent exacerbating situations of a pay gap between women and men in the labour market.[117]

5.4.1.4.4 Additional relevant cost categories

Costing involves identifying, measuring and valuing all resources used.[180] A societal analytic viewpoint requires that ***all*** relevant costs for treatment and morbidity should be identified, quantified, and valued, irrespective of who bears the costs (emphasis intended).[180,184] However, there are limitations to what cost categories are practicable and possible to quantify with the available data. The included costs expanded between Study III and IV, with the inclusion of costs for primary healthcare as well as widening drug costs to include MS DMTs administered within healthcare. For the cost components included in the registers, population-based estimates of the costs could be quantified from large cohorts with no recall bias. Nonetheless the following cost categories ideally should have been included for more complete estimates of the societal costs of MS:

- **Short-term SA.** Further aspects of "absenteeism", for example, spells of SA less than 14 days or absences in relation to attending healthcare.
- **Reduced productivity at work ("presenteeism").** With the focus on working-aged PwMS and utilising remaining work capacity in situations of changed functional abilities, this aspect of work productivity is particularly relevant. Reduced work capacity due to disease tends to onset prior to SA, potentially leading to reduced productivity at work, and can also continue during the return-to-work process.[88] The Swedish findings from the European burden of illness study found that workforce participation of PwMS in Sweden was relatively high despite older ages and progression among the Swedish study participants.[124] However, most PwMS participating in the Swedish workforce (78%) responded that MS affected their productivity while at work.[124] The main reasons reported in the Europe-wide results were fatigue (70%), cognitive difficulties (34%),

mobility (28%), and pain (21%).[137] In a recent Canadian study of employed people with early MS, with 97% with mild MS (EDSS scores 0-3.5), 24% reported presenteeism in the past three months, accounting for 5% of regular work time on average.[168]

- **Costs of community and social services.** Sweden has an encompassing personal assistance system available to support independent living at home. These services are often provided by municipalities, and not collected at a national level. In the Swedish findings from the European burden of illness study, one third of PwMS in the sample reported using community and social services in the past month.[124] While transportation services were the most frequently used service, personal assistants supported 13% of the sample at an average of 400 hours per month.[124] Use of services were observed to be concentrated among PwMS with higher EDSS levels. These costs would have been particularly relevant in Study IV with a prevalent cohort of PwMS.
- **Informal care.** The European burden of illness study observed 44% of the respondents from Sweden had help from family, with most reporting home help having higher EDSS levels.[124] Again, these costs would have been especially relevant in Study IV.
- **Other drugs, including drugs administered within healthcare.** The SPDR was estimated to contain 84% of the total volume of drugs and 77% of the total expenditure in Sweden in the second half of 2005.[221] The remaining drug expenditure in Sweden involved drugs administered within healthcare (14%), over-the-counter purchases (8%), and other (drugs in other healthcare facilities than hospitals such as dentistry or prisons) (1%).[221] While MS-specific DMTs administered within healthcare were estimated in Study IV from the SMSreg, other such drugs were unable to be identified and quantified.
- **Adaptations and utensils.** In the Swedish findings from the European burden of illness study, investments in equipment and devices to aid mobility were made for or by 34% of the PwMS during the past 12 months.[124]

This list is not exhaustive but contains key items. Importantly, these cost categories were missing for both the PwMS and references in Study III and IV and are seldom included in register-based studies. Many of these costs require other data sources to quantify, for example, questionnaire, which could introduce recall bias. The register data sources limited inclusion of several cost items often borne by the PwMS. Patient OOP costs are important in the context of patient-centred care.[270] It is rare for productivity losses from premature death to be included in MS COI studies.[8,181] Such costs were not included because both Study III and IV were limited to working-aged PwMS and the observations in Study III were close to MS diagnosis. When all relevant costs are considered, the true excess costs of MS are likely to be higher than those presented in Study III and IV.

5.4.2 External validity

An important aspect of the use of internally valid study findings is the representativeness of the study populations to wider populations of interest. The large population-based study cohorts, universal healthcare, and social insurances covering all residents in Sweden increase the generalisability in all four studies for working-aged PwMS in Sweden. However, there are limits to the generalisability of the results to other settings. The Arena of Work Disability Model highlights the importance of the legislative and insurance system, healthcare system, workplace system and personal systems for work disability.[93] Accordingly, these factors must be considered in generalising of the work disability findings, whether as SA/DP days,

prevalence, or productivity losses. The findings are best applied to other Nordic countries which have the most similarities in their social insurance and healthcare systems.

The comprehensiveness of social protections is a crucial consideration for the external validity of the results. Another consideration is that regulations can change over time, which could influence the generalisability of the study results in the future. Stricter rules were launched in 2008, which could lead to shorter SA durations and fewer DPs granted. Accordingly, there could be cohort effects and a change overtime in SA/DP outcomes for Study I, II, and III with study periods spanning the old regulations. Nonetheless, the main purpose of SA and DP benefits remained the same.

Similarly, the composition of the labour force is of importance in generalising the results to other countries. The Swedish labour market has a particularly high participation rate among women and among people of older ages.[113] Nonetheless, women work part-time in Sweden to a higher extent than men and like other countries, there is a gender pay gap.[117] The pay gap is generally smaller among younger individuals entering the labour market and tends to widen with age. These characteristics are relevant considerations for the findings related to the incomes and working life of the MS cohorts in Study I and II, that have high proportions of women and of younger ages, as well as work disability throughout the thesis.

The demographic composition is also relevant. Immigrants to Sweden receive a personal identity number if intending to stay for at least a year, therefore, some individuals (non-permanent residents) in Sweden are not included in the registers.[210] Furthermore, the MS populations in all four studies were working-aged at diagnosis. Extrapolating the findings should have this in mind as paediatric onset MS can have a different clinical course.[279]

Regarding the healthcare system, the observed resource utilisation patterns from register data and resulting healthcare costs reflect the healthcare organisation, medical traditions, and access of the study populations.[137] Sweden has a comparatively low average number of physician consultations, at 2.9 per person in 2016 compared with the European Union average of 7.5 consultations per person.[348] The comparatively low number of consultations with physicians could be partly attributable to the central role of nurses in primary healthcare, lessening the need for consultations with physicians.[349] The national unit costs increase the generalisability of Study IV from Stockholm to wider Sweden. But the regional financing of healthcare also potentially influences the utilisation patterns observed in Study IV for Stockholm and generalisability of the findings to the nation.[206,326,350] The average number of visits to physicians in primary healthcare in 2015 ranged across Sweden from 1.1 to 2.0 per person and 0.9 to 1.6 for visits to physicians in specialised healthcare.[350] Region Stockholm had considerably higher values for specialised healthcare. Stockholm County is a largely urban area with a university hospital, it is possible that the distribution of care differs compared to rural areas of Sweden as well as between Sweden and other countries.

Lastly, the MS-specific treatments and diagnosis procedures have changed over time, and they can also differ between countries. This is especially so with the level of DMT use and how they are used.[73] Individuals with RRMS in Sweden have to a higher extent initiated on more efficacious DMTs.[62] Differences in clinical outcomes at a national level have been observed between Denmark and Sweden, where the Swedish strategy of high-efficacy DMTs at treatment initiation was associated with a 29% reduction in the time to 24-week confirmed disability worsening than the Danish strategy of treatment escalation.[62] These treatment

differences may affect the DMT costs in Study III and IV, as well as have consequences for other findings in the four studies regarding wider costs and resulting work disability levels from the reduced disease activity and progression. Accordingly, MS care should also be considered when generalising the findings.

The generalisability of the findings from all four studies is, therefore, limited to settings with similar social insurance systems, healthcare systems, labour market regulations, as well as demographic structure. These features may influence the work disability findings, earnings especially among a group with a chronic disease, and level of DI as well as the consumption of healthcare resources and excess costs of MS. While the estimates of the magnitude of the excess costs may be more Swedish-specific, the ratios of costs of PwMS compared with those of references in Study III and IV may be more transferable.

6 CONCLUSIONS

The studies of this thesis contribute descriptive and detailed knowledge of the socioeconomic burden of MS among people of working ages in the dynamic period around their diagnosis with MS. Work disability among PwMS has implications for the individuals' incomes and results in excess costs to Swedish society from the productivity losses.

Most newly diagnosed PwMS are in work.

- Working life of the majority of newly diagnosed PwMS was characterised by activity and in all studies, work disability was not observed for all PwMS.
- However, with time from diagnosis, work disability increasingly affected more PwMS and individuals to a greater extent.

Work disability is heterogeneous among newly diagnosed PwMS.

- Six different types of working-life sequences were observed, differing by the extent of activity and work disability as well as skewed productivity losses among PwMS.
- The sociodemographic characteristics of PwMS, including the modifiable factor of educational level, differed between the seven DI trajectories and the six types of working-life sequences identified.

Most individuals in the early stages of their MS have stable or increasing economic resources.

- Seven DI trajectories were identified spanning the years directly before and after diagnosis with MS, with 39.0% with one of the four increasing trajectories, 50.7% in the two flat and relatively low trajectories, and 10.3% with a decreasing DI trajectory.
- Most PwMS were observed to maintain or have increasing levels of annual DI in the years around their MS diagnosis.
- Reduced earnings among newly diagnosed PwMS are usually balanced by the social protections of SA and DP benefits.

There is a potential risk with further time and disease progression that more PwMS will have a higher extent of work disability and experience a decrease in economic resources.

- Trajectories of DI with a decreasing gradient as well as stable but at relatively low levels were identified in early MS in addition to a working-life sequence, characterised with full-time SA/DP throughout, with non-increasing annual DI.

People with MS have substantially higher costs from lost production and healthcare use than references without MS.

- People with MS had on average 2.38-times higher productivity losses and 5.25-times higher healthcare costs than matched references in the years around their MS diagnosis.
- Among prevalent PwMS in Stockholm, there was on average 4.5-times higher productivity losses and 4.3-times higher healthcare costs than among matched references.
- The excess costs of MS from productivity losses are higher than those from healthcare. The mean annual excess productivity losses of MS due to work disability were 138,121 SEK per person with MS. The mean annual excess healthcare costs of MS for primary, specialised outpatient, and inpatient healthcare visits as well as drugs were estimated at 77,384 SEK per person with MS.
- Primary healthcare contributed 9% of the mean annual excess healthcare costs of MS, at 7287 SEK per person. Excess costs of MS were observed not only for contacts with

physicians but also with other healthcare professionals, indicating the importance of multidisciplinary care for rehabilitation services and to manage both MS symptoms and comorbidities.

Excess costs of MS from lost production and healthcare use are incurred already before MS diagnosis.

- The increasing excess costs of MS from productivity losses occur early and reflect unmet needs of PwMS regarding work capacity.

The pattern of the excess costs of MS changes with time.

- The excess productivity losses from work disability increased in magnitude with time from MS diagnosis and were increasingly due to DP.
- The annual excess healthcare costs of MS were reasonably stable with time since diagnosis, but the cost composition differed. More recently diagnosed PwMS had excess healthcare costs of MS largely from excess drug costs due to DMTs. In contrast, higher excess costs of MS from inpatient and primary healthcare were observed among the PwMS with longer times since their MS diagnosis.

Using large recent cohorts, this thesis highlights that most PwMS in Sweden are in work in the early stages of the disease. However, work disability is often and increasingly a part of PwMS' working life. Work disability is associated with decreasing or static and relatively low DI trajectories, in addition to unstable working life sequences. In this dynamic period, PwMS with work disability may also transition back to work whether by utilising remaining work capacity, improvements, or adjustments, as well as increasing the extent of work disability. Nonetheless, excess costs of MS from productivity losses in relation to work disability as well as healthcare use are incurred already before MS diagnosis. These early excess costs have important implications for the healthcare sector and the Social Insurance Agency. They can also indicate that there are unmet needs among PwMS regarding morbidity and work capacity and contribute to the body of knowledge calling for early intervention. Around MS diagnosis there is a key window of time to intervene to manage symptoms, reduce disease activity and disability accumulation, and support PwMS to maintain sustainable working lives. Earlier diagnosis with immediate initiation of appropriate treatment and proactive interventions may support PwMS, the costs of which may be partially offset by reduced future costs.

7 POINTS OF PERSPECTIVE

The consequences of disease, including work disability, can be studied from different scientific disciplines. An interdisciplinary approach was taken, which has led to some tensions in terminology and focus. However, this interdisciplinary approach is a strength of the studies investigating the multifactorial phenomenon of work disability and provided a wider range of tools and understandings. Strong epidemiological methods and a grounding in public health were important. The two main disciplines contributing theory, methods, and that the specific findings of this thesis contribute to are insurance medicine and health economics. To facilitate interpretation and the comparison of studies within insurance medicine, studies can be classified according to the modified structure[351] presented in Table 13.

Research questions regarding work disability can be posed from different perspectives, for instance, that of the patients, employers, or society. The perspective taken in each of the four studies was influenced by which discipline one was primarily standing in, with nuanced differences in perspective definitions and the appropriate analyses for the adopted perspective. From an insurance medicine perspective, all studies take the perspective of society by considering the social protections SA and DP and the wider context to support PwMS with work disability. Study I and II arguably align more with an individual perspective within health economics, considering the individual's economic situation and working life, irrespective of the source of income. A societal perspective was explicitly taken in the two COI studies, including the wider costs of MS to society, irrespective of who bore the costs.[178,180] Accordingly, the productivity losses to society were costed by use of the net days of SA/DP, rather than the sum of the transfer payments themselves. While the findings could also be important for healthcare (or the Social Insurance Agency), the main perspective taken in the analyses was a societal perspective rather than a healthcare payer perspective. The measure of DI incorporated the household's income, with the findings potentially also relevant for families and healthcare providers caring for PwMS.

Health economics introduces new concepts to medicine.[352] Excess costs, as the additional cost of MS, is no exception. The disease of focus was MS. Yet, the work disability outcomes were included irrespective of the diagnosis certifying the absence. This was consistent with the costing in Study III and IV through comparisons with a reference group to isolate the excess costs of MS. However, studying the specific morbidity directly attributed to the reduced work capacity or healthcare use, could further inform unmet needs as well as interventions to support PwMS to maintain work capacity. Previous research has identified a diverse range of diagnoses beyond MS that newly diagnosed PwMS have as the certifying diagnosis for their SA and DP benefits.[55] While the studies within this thesis do not offer guidance on how resources should be allocated, the estimates of the excess costs of MS offer a descriptive picture of resource use of PwMS, and costs incurred in real world clinical practice. These estimates can convey aggregate information of the socioeconomic burden of MS or be used in further analyses as inputs into economic evaluations for MS treatments, alongside additional information on effect. The findings from Study I and II can inform newly diagnosed PwMS and clinicians of non-clinical consequences of MS. In the era of early MS diagnoses and immediate initiation with DMTs, around the MS diagnosis is a critical period to study the broader consequences of MS.

Table 13: A modified version of the structure to categorize studies of sickness absence and disability pension by Alexanderson.[351] Relevant perspectives to the studies comprising this thesis are marked in bold.

What is studied regarding SA/DP?	**-Study design -Type of data -Analyses**	**Scientific discipline**	**Perspective taken in the research questions**	**Studied**	**Structural level of the data and/or the factors included in the analyses**	**Diagnoses** (of included and of SA/DP 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. *Socioeconomic* "Consequences" or "side-effects" of (being on) sickness absence/disability pension** 5. Sickness certification / assessment practices / processes 6. Methods, theories	**Study design** Cross sectional **Longitudinal** RCT, CT, etc. **Type of data** Interview Questionnaire **Register** Medical files Insurance files Certificates Documents Observations Video Other **Type of analyses** Qualitative **Quantitative**	**Economics (health economics,** macroeconomics, etc**)** **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: S**ociety** Insurance Healthcare Employer Colleagues Family **Patient/Individual with MS**	**General population** (references Study III & IV) Insured In paid work (general or special jobs/organisations) **Diagnosed with MS** Sickness absent/Disability pensioned Organizations Professionals Countries	International National Regional Municipality Worksite Healthcare Family **Individual**	**All diagnoses together** (SA/DP and healthcare utilisation) Mental Musculoskeletal Cancer **MS** (of included) Hearing Cardiovascular diseases Infections Injuries Diabetes Headache Other

Abbreviations: DP: Disability pension; MS: Multiple sclerosis; PwMS: People with multiple sclerosis; SA: Sickness absence.

8 FUTURE RESEARCH

Alongside answering the specific research questions, the hypothesis-generating studies in this thesis raised many further questions. Early MS is a critical period to study as well as intervene. However, further research will also be required to study the longer-term associations of MS and socioeconomic outcomes among PwMS treated early with DMTs.

This thesis highlights a risk that with further time from diagnosis that more PwMS may have a higher extent of work disability, have a decrease in economic resources, and be at risk of economic hardship. Accordingly, more research is required to understand the protective factors for work disability among PwMS at different stages of the disease. Further knowledge on the interactions of disease-related factors, especially invisible symptoms of MS, with the determinants of work disability are required. Research regarding the different arenas of work disability,[93] especially workplace factors for PwMS, requires different data sources than this thesis was based on. Linking data sources would allow deeper investigation into the personal and workplace factors that support sustainable employment among PwMS. Large surveys with linked register data would allow research regarding the impact of MS on work disability, workplace environment and adaptations, meaning of work, and symptoms or limitations on sustaining employment. Net days of SA/DP were combined, however, the use of part-time DP as a tool to manage MS warrants further investigation.[135] Focus on the modifiable characteristics of those who stay at work could help inform interventions to assist PwMS to maintain work.

The register-based nature of this thesis allowed for population-based research of incomes, however, limited opportunities to study wider aspects of employment such as being a source of identity and quality of life.[353] Accordingly, there are likely broader implications of the identified DI trajectories and working-life patterns that could be explored. Material resources were focused upon with DI, however, other aspects of economic hardship may be relevant for PwMS, such as financial worry or cost-related non-adherence. Furthermore, the experienced economic implications of work disability likely differ among PwMS by baseline DI.

Spells of SA <14 days and reduced work capacity while at work are also contributing to the socioeconomic burden of MS. These types of work disability require research with alternative data sources, as the patterns and characteristics associated with these aspects of work disability may well differ to those studied.

Further research on subgroups within this heterogeneous population is required. The working-life trajectories, ideally of longer duration, could be related to healthcare and treatment sequences or disease activity for example with multichannel sequence analysis (i.e., sequence analysis extended to multiple domains analysed simultaneously accounting for interdependencies). Similarly, the DI trajectory findings from Study I could be studied further, either by linking further information regarding disease and workplace characteristics or with group-based multi-trajectory modelling to identify latent groups of PwMS following similar trajectories across multiple outcomes of interest. Specific turning point events could be assessed in relation to these trajectories or sequences of working life, for example initiating or escalating DMT treatments, entering the labour market, or being granted DP.

Working life covers from labour market entry to exit. Study I-III were designed based on timing of MS diagnosis rather than work milestones. The timing of MS disability and career events are of importance as social protections are often based on prior earnings and legal protections are provided for employees against discrimination due to disability. Accordingly, future research should specifically consider outcomes of younger PwMS, PwMS entering the labour market, and PwMS with precarious employment. In addition, one could consider potential 'lock in' among PwMS already established within the labour market as well as motivations and meaning regarding work following an MS diagnosis.

It would also be interesting to perform Study I and II in settings with different social security systems.

Standardisation of costing methods and transparent reporting in future studies can aid comparisons. Future COI studies as well as economic evaluations will be critical to observe changes in resource utilisation further along the disease trajectory than can currently be observed and evaluate the potential offsets from early inventions. The cost estimates from this thesis could be combined with measures of effectiveness and other information. Mixing data sources in an economic evaluation could also allow for additional cost components.

Knowledge on the implications of early MS for the spouse and family is limited in Sweden regarding their working-life and their time spent for informal care. The resulting costs are likely more pronounced for care of PwMS with more severe MS or later after MS diagnosis. However, planning and changes could plausibly occur earlier. Similarly, the time the individual takes for their own self-care and management of MS outside of healthcare requires further research. MS management, as with any chronic disease, is a combination of healthcare and self-care.[354]

Further investigation of the details (diagnoses or procedure codes) for which the PwMS consume healthcare and underlying the changes in productivity in comparison to those without MS is needed to reflect the current treatment options.[206] Subgroup analyses among PwMS are also important to consider variations in access and need, and to understand parallel use of services. This could provide nuanced understandings of the excess healthcare costs of MS, whether the same but more or different patterns, and suggest where to intervene.

Broadening out from MS, further research is required focusing on the challenges faced within working life from work disability of people with chronic disease. This includes the role of inclusive and supporting work environments and self-management of symptoms.[83] The MS clinical course emphasises the need for timely interventions with a focus on sustaining work capacity, before barriers become too challenging.[136,158] While early intervention can improve MS symptoms and factors associated with work, the current evidence is mixed on improved work outcomes.[158] There is potential to maintain the working lives of PwMS and other groups with chronic disease, if there is a better understanding of the conditions enabling this. This knowledge, informed by the determinants of work disability,[93] is needed to fulfil the sustainable development goal that all, including people with disabilities, have full and productive employment and decent work.[80]

9 ACKNOWLEDGEMENTS

Thank you to the people living with MS in Sweden for sharing your data for research in the SMSreg.

I would like to thank the following people who have enriched my journey, contributed to this research with ideas, knowledge, review of materials, as well as helped and supported me throughout the years. The support and encouragement of the people mentioned below have all helped to lift me to reach this milestone and I am appreciative beyond what these words can capture. Dr Seuss may have stated "You can get help from teachers, but you are going to have to learn a lot by yourself, sitting alone in a room"[355] but he certainly underestimated teachers, support, collaboration, and Zoom. Perhaps a more apt quote is "The more that you read, the more things you will know. The more that you learn, the more places you'll go".[356] I apologise that Dr Seuss does not seem to be a household staple growing up in Sweden. My doctoral education has been a process and a journey, not just physically, in continuing to live on the opposite side of the globe to New Zealand, but a journey of growth as a researcher and as a person (and true, a lot of time seated learning).

Firstly, to my main supervisor Emilie Friberg. Thank you for having me as your doctoral student. You have been an irreplaceable and solid support throughout. I am so appreciative of your availability and commitment to me and my PhD project, as a person and a researcher. Thank you for sharing your knowledge and your patience in walking with me through the research world (and across borders) as my guide, supervisor, and in later years research group leader, but always making me feel as an equal.

To my cosupervisor, Kristina Alexanderson. I am thankful for your investment in me as a researcher and the opportunity to stay to work in academia within your research project SHoL after my master's project. You saw potential in me as a researcher, nurtured and fostered that potential. You have guided me with your wealth of expertise and experience ever since I first emailed you as the Head of the Division about a master's thesis project back in 2016. Thank you for providing me with this opportunity as well as constantly sharing your vast knowledge.

To my cosupervisor, Petter Tinghög. Thank you for sparking ideas and sharing your passion and enthusiasm for science with me. From a master's thesis to a full-blown PhD, you have encouraged and supported my curiosity and drive to contribute to improving public health. I hope we can continue our scientific discussions on the social determinants of health over a beer.

To my cosupervisor, Korinna Karampampa. Thank you for introducing me to the world of health economics. I thank you as a teacher, colleague, supervisor, and friend. Thank you for the opportunity to teach master's students alongside you. Your laughter and down to earth nature always inspires confidence in me and reminds me to chill, the project is all under control. Thank you for all your practical solutions along this journey.

I value the support from Ali Manouchehrinia, my mentor on life as an international researcher. Thank you for introducing me to the world of MS research, especially at ECTRIMS 2018.

This PhD project was conducted at the Division of Insurance Medicine at Karolinska Insitutet. Thank you to my research colleagues, past and present, at the Division for always being welcoming and available to share your knowledge and passion for research. Thank you to the current Head of the Division Ellenor Mittendorfer-Rutz, Pia Svedberg, Emilie, and Kristina and your respective research groups over the years! Thank you to all the past and present statisticians, especially Kerstin Nilsson, Pontus Josefsson, Linnea Kjeldgård, Mahbuba Haque, Nils Larsson, Jakob Bergström, Emma Pettersson, and Niklas Gustafsson, for taking the time to answer my questions about the data and statistical methods. Katarina Lönnqvist and Annika Evolahti, I am grateful for your kindness and administrative support throughout.

A particular thank you to the MS group and our collaborators over the years for sharing your knowledge and this experience with me, especially, Hanna Gyllensten, Jan Hillert, Alejandra Machado, Fitsum Sebsibe Teni, Michael Wiberg, Fei Yang, Greta Bütepage, Kyla McKay, Jenny Aspling, Astrid Bosma, Jessica Dervish, and Anna He. You have all been a part of my research home and I appreciate all the collaborations and discussions we have had. You have all taught me so much. Micke, you left some big shoes to fill as a PhD student in the MS group and I am ever so grateful for your patience in teaching me to open SAS and code. Ale, I appreciate our friendship and your support over the many after-lunch chocolate breaks.

A big thank you to my roommate, Rasmus Elrud, for the great company and book recommendation. Even after you defended your thesis and the office converted to a home office during the pandemic, you have been here with me on this journey.

A big thank you to all the opponents of my manuscript seminars: Ali Manouchehrinia, Linnea Kjeldgård, Syed Rahman, Ridwanul Amin, Hanna Gyllensten, and Victoria Arfuch Prezioso. Thank you also to all the participants at those seminars for your time and valuable feedback.

Kristin Farrants, thank you for facilitating the IM journal club and all the fika breaks.

Thank you to Annika Herr for being an opponent at the EUHEA PhD workshop 2020 as well as Cochrane Insurance Medicine and the EUPHA Section of Social Security, Work and Health for the opportunities to present my PhD project in person and online. Opportunities to present and discuss research externally are not to be dismissed, especially during a pandemic!

Sofia Sveréus, I appreciate you taking the time to share your knowledge of the Swedish healthcare system with me.

Nicky Dunn, Natasha Smyrke, and Deborah Mason, I thoroughly enjoyed our NZ-Sweden MS research collaboration.

Fellow current and former PhD students, thank you for inspiring me! Rasmus, Ridwanul Amin, Mirkka Söderman, and Domitilla Di Thiene, from the Division who have graduated before me and Linnea Kjeldgård and Fitsum Sebsibe Teni, who will after, as well as the guest PhD students, Samanta Lalic, Julio Hernando, Astrid Bosma, Filip Gedin, Amaya Ayala García, and Victoria Arfuch Prezioso. Thank you, Julio, for sharing your knowledge on sequence analysis and R to facilitate adapting this exciting method to our Swedish data. In addition, the PhD students at the LIME journal club including Olivia Ernstsson for inviting me, the Stockholm Stress Center PhD workshops, and fellow board members of the SHEA doctoral network, Frida Labori, Dominik Elsner, and Naimi Johansson. Nicky, thank you for your constant support, what a journey us kiwis have had in Stockholm! I look forward to

celebrating with you in the Town Hall and sharing a kiwi summer with you back home soon. Helena Honkaniemi, I am so grateful that we did our projects in parallel, sharing the ups and downs from start to finish, and for your cheerful encouragement throughout! I am also glad I got to share my PhD journey with the following phenomenal women: Jenny, Anna, Kelsi Smith, Margarita Ravinskaya, Hala Nasr, and Claire Honney. I have enjoyed following your research, learning from you, and sharing the doctoral student experience with all of you.

In preparing my thesis for the public defence, there are some specific thank-yous. A big thank you to Mark Belan, for sharing your passion for science and creativity in creating the cover illustration. Thank you to Kelsi, Anna, Julio, Astrid, Steven Karl, Olof Mogard, and Bjarne Albèr, for reviewing and posing questions to specific sections. Annika Evolahti, thank you ever so much for helping with the proof reading and formatting as well as handling logistics and preparations for my defence. Vibeke Sparring, thank you for your role in preparing me for the final defence by being my opponent in my final kappa seminar. To all the participants at my kappa seminar, thank you for your feedback and advice! Bjarne, Mahbuba, and Pontus, the "Party Planning Committee", thank you for checking in on me, maintaining my social life, and celebrating each milestone with me. Lastly, Ellenor Mittendorfer-Rutz, thank you for taking the time to chair my defence and for all your perceptive questions throughout my project in preparation for the big day.

Olof; thank you for starting this research journey with me! I recall fondly numerous missing semicolons as we learnt to code; our sloping review; and the companionship we had throughout our master's project!

Ann Mair, you sparked my interest in epidemiology and social sciences. I never thought back in high school that I would later attend lectures by Hans Rosling, cofounder of Gapminder.

I am so thankful for my fantastic family and friends! Whether your calling code is +64 or +46, you have all provided more understanding and support than I could have asked for with my PhD journey and living in Sweden. Thank you for always staying in touch and making the distance to NZ seem small, even amid border closures and travel restrictions. Dad, you may have read Dr Seuss and encouraged me on my learning journey, perhaps not foreseeing the path leading to Sweden… Mum, thank you for your endless support and the care packages of chocolate to get me through! My family, Adam, Jordan, Nanny and Dadda, Beth, Coralie, and Luke, I look forward to seeing you all Up North soon. Helen, Becca, Laura, Ali, Matt, Erin, Aubrey, Maryanne, Paul and Eva, Lillian och Jack, Fil, Ross, Tiina, Sarah, Celine, Annika, Kerstin, Alexandra, Richard, Paulina, Ragnhildur…the list goes on! Thank you all!

Bjarne 9, min sköldpadda, tack för allt! Your steady support and encouragement, your patience with my Swedish, refilling my energy, my fantastic matlådor, and for always listening. I am sure you are possibly best positioned to vouch for my development as a researcher. I look forward to our adventures together post-PhD!

This thesis was financially supported by grants from the Swedish Research Council for Health, Working life and Welfare, the Swedish Research Council, and unrestricted researcher-initiated grants from Biogen, the support of which is greatly acknowledged.

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