

# Work ability in multiple sclerosis

## The impact of immunomodulating treatments and adjusted working conditions

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# Abstract

**Background** Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease affecting the central nervous system (CNS) and is considered to be of autoimmune origin. The prevalence in Sweden is estimated to be about 1 in 500. The inflammation leads to demyelination as well as neurodegeneration and with time the patients often suffer from increasing neurological disability. The young age of onset makes MS one of the major causes of reduced ability to work in the Western society.

Several factors in the disease affect the work ability. One important factor is ongoing inflammatory activity conferring risk to develop tissue damage and disability. Previous studies have indicated that fatigue, mobility and cognitive problems are the primary symptoms preventing individuals with MS to remain in employment. However, the possibility to adapt both tasks and the workplace, the possibility for sedentary work and flexible working hours also have great influence to keep the individual in employment.

**The purpose** of the thesis was to investigate how factors in the disease, immunomodulating treatments and work requirements influence the ability to work and study in people with MS.

**Methods:** A MS specific questionnaire was used in one retrospective and one prospective study to compare the work ability before and after start of the second-generation immunomodulating drug natalizumab. The number of working hours per week and the degree of sick leave before and after one year of treatment was calculated. The effect of disease-specific and work-related factors on work ability was evaluated. The treatment effect on fatigue and walking ability was correlated to work ability. In addition, a health-economic calculation was performed to estimate the cost-benefit of the treatment.

The degree of sickness absence was evaluated in a cross-sectional study of two MS-populations; one historical that never was exposed to immunomodulating drugs and the other consisted of individuals with MS that was diagnosed after the introduction of immunomodulating drugs.

Furthermore, work ability was studied in two MS-populations, one southern and one northern cohort of Sweden, for the latter population more active immunomodulating treatment and work-promoting measures have been practiced. The data was collected using the instrument WAQ-MS.

**Results** Paper I: After one year of treatment with natalizumab the average working hours per week had increased with 3.3 hours, corresponding to an economic value of 3216 euro per person per year.

Paper II and III: After initiation of treatment with natalizumab, in an active phase of relapsing-remitting MS, the patients improved their working ability after one year from 31 % to 60 % ( $p < 0.001$ ) and reduced their sickness benefit correspondingly ( $p < 0.001$ ) in relation to their total employment rate. They also reported improved physical and cognitive ability in relation to their requirements. Short disease duration, younger age and lower Expanded Disability Status Scale (EDSS) grade at treatment onset predicted a positive effect on work ability and also improvement of walking ability correlated significantly with reduced sick leave.

Paper IV: The proportion of individuals without any kind of sickness absence was higher in the MS population being exposed to disease modifying drugs compared to the unexposed population (66 % vs 38 %) ( $p < 0.001$ ). In addition, the proportion of patients with full-time sickness absence was higher in the unexposed compared to the exposed population (32 % vs 16 %) ( $p < 0.001$ ). The median EDSS was lower in the exposed compared to the unexposed MS population ( $p < 0.001$ ).

Paper V: The proportion of MS patients who participated in the work force or studied was significantly higher in the northern cohort, where they had been exposed to more work promoting measures, compared with the southern cohort ( $p = 0.022$ ). MS patients in the northern cohort had significantly lower physical and cognitive requirements in their occupations, more adapted work conditions and could work more hours per week compared with the southern cohort. The EDSS level explained 12 % of the working ability in the northern cohort and 21 % in the southern cohort.

**Conclusion** Our results indicate that patients in the inflammatory phase of the disease may retain their work ability several years after disease onset if they are subjected to effective anti-inflammatory treatment regimens from disease onset. Furthermore, work ability may be additionally improved by adjusted working conditions even in the progressive phase of the disease. It is obvious that these results have implications in a socioeconomic perspective as well as for the individual patients as improved quality of life due to retained work-life participation. Long-term follow-up of our data is required to determine whether these positive effects are durable over longer time-periods.

## Abbreviations

CNS	Central nervous system
CWQ	Capacity for Work Questionnaire
DMD	Disease Modifying Drug
EDSS	Expanded Disability Status Scale
FSMC	Fatigue Scale for Motor and Cognitive functions
FS	Functional Systems
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
PP	Primary progressive disease
RA	Rheumatoid arthritis
RRMS	Relapsing-remitting disease
SMSreg	Swedish Multiple Sclerosis Register
SP	Secondary progressive disease
SPMS	Secondary progressive multiple sclerosis
WAQ	Work Ability Questionnaire
WAQ-MS	Work Ability Questionnaire – Multiple Sclerosis

## Original papers

The thesis is based on the following publications and manuscripts referred to in the text by their Roman numerals:

- I. Olofsson S, Wickström A, Häger Glenngård A, Persson U, and Svenningsson A. **Effect of Treatment with Natalizumab on Ability to Work in People with Multiple Sclerosis. Productivity Gain Based on Direct Measurement after 1 Year of Treatment.** *BioDrugs* 2011; 25: 299–306
- II. Wickström A, Nyström J and Svenningsson A. **Improved ability to work after one year of natalizumab treatment in multiple sclerosis. Analysis of disease-specific and work-related factors that influence the effect of treatment.** *Multiple Sclerosis* 2013;19: 622-630
- III. Wickström A, Dahle C, Vrethem M and Svenningsson A. **Reduced sick leave in multiple sclerosis after one year of natalizumab treatment. A prospective ad hoc analysis of the TYNERGY trial.** *Multiple Sclerosis* 2014;20:1095-1101.
- IV. Wickström A, Sundström P, Wickström L, Dahle C, Vrethem M and Svenningsson A. **Improved work ability in a contemporary MS population compared with a historic non-treated MS population in the same geographic area of Sweden.** *Multiple Sclerosis*. Submitted, April 2015
- V. Wickström A, Karlsson M, Wickström L, Sundström P, Dahle C, Vrethem M and Svenningsson A. **The impact of adjusted work conditions on the working ability, measured with Work Ability Questionnaire - Multiple Sclerosis (WAQ-MS).** *Manuscript*

# Svensk sammanfattning

**Bakgrund** Multipel skleros (MS) är en kronisk inflammatorisk sjukdom i det centrala nervsystemet (CNS) och anses bero på en autoimmun attack mot nervbanor och nervceller i hjärna och ryggmärg. Prevalensen i Sverige uppskattas till ca 1 på 500. Sjukdomen debuterar ofta i 20-40 års åldern vilket gör MS till en av de främsta orsakerna till nedsatt arbetsförmåga och medför avsevärda ekonomiska konsekvenser såväl för individen som för samhället i stort.

Det finns faktorer i sjukdomen som har stor påverkan på arbetsförmågan vid MS. En instabil sjukdom med återkommande inflammatorisk aktivitet kan resultera i vävnadsskador som medför olika typer och grader av funktionsnedsättning med nedsatt arbetsförmåga som följd. Studier har visat att fatigue, mobilitets- och kognitiva problem är primära symptom som hindrar personer med MS att arbeta. Faktorer som i sin tur ökar möjligheten att stanna kvar i arbetslivet är möjlighet till anpassade arbetsuppgifter och att arbeta i en anpassad arbetsmiljö med flexibla arbetstider.

**Syftet** med avhandlingen var att undersöka hur faktorer i sjukdomen, immunomodulerande behandling och krav i arbetet påverkar förmågan att arbeta och studera vid MS.

**Metoder** I en retrospektiv respektive en prospektiv studie jämfördes arbetsförmåga före och efter starten av andra generationens immunomodulerande behandling med natalizumab. Antalet arbetstimmar per vecka och även graden av sjukskrivning före och efter 1 års behandling beräknades. Effekten av hur sjukdomsspecifika och arbetsrelaterade faktorer påverkade arbetsförmågan utvärderades. Behandlingens effekt på trötthet och gångförmåga ställdes i relation till arbetsförmågan. Dessutom gjordes en hälsoekonomisk beräkning för att uppskatta behandlingens produktionsvinst. Dessutom har en tvärsnittsstudie genomförts för att utvärdera graden av sjukfrånvaro i två MS-populationer, varav den ena har och den andra inte har haft tillgång till bromsläkemedel. Arbetsförmåga har även studerats i två MS-populationer där man undersökte hur arbetskraven och flexibilitetsmöjligheterna i arbetet har påverkat förmågan att arbeta i förhållande till olika EDSS grader. Data samlades in med hjälp av frågeformuläret WAQ-MS.

**Resultat** Arbeta I: Efter ett års behandling med natalizumab hade arbetstiden per vecka i genomsnitt ökat med 3,3 timmar, vilket motsvarade ett ekonomiskt värde på 3216 euro per person och år.

Arbete II och III: Efter start av behandling med natalizumab, i en immunologiskt aktiv skovvis MS, ökade arbetsförmågan från 31 % till 60 % ( $p < 0.001$ ) av arbetad tid per vecka och grad av sjukpenning minskade på motsvarande vis ( $p < 0.001$ ) i förhållande till anställningen. Patienterna skattade även att deras fysiska och kognitiva förmåga hade förbättrats i förhållande till deras krav i arbetet. Kort sjukdomsduration, ung ålder och lägre funktionsnedsättning enligt Expanded Disability Status Scale (EDSS) predikterade för positiv effekt på arbetsförmåga. Även förbättring av gångförmågan korrelerade signifikant med minskad sjukfrånvaro.

Arbete IV: I MS populationen som hade exponerats för bromsläkemedel var andelen som inte hade någon form av sjukfrånvaro 66 % mot 38 % i den population som aldrig hade behandlats med bromsläkemedel ( $p < 0.001$ ). Dessutom hade andelen patienter med heltidssjukfrånvaro minskat från 32 % till 16 % ( $p < 0.001$ ). Median EDSS var lägre i MS populationen som var exponerad för bromsläkemedel ( $p < 0.001$ ).

Arbete V: I den norra MS-kohorten som hade haft tillgång till arbetsfrämjande åtgärder i större utsträckning, var signifikant större andel personer i arbete och i egna studier ( $p = 0.022$ ) än i den södra kohorten. De anställda i den norra kohorten hade signifikant lägre fysiska ( $p = 0.002$ ) och kognitiva ( $p = 0.046$ ) krav, större andel anpassade arbetsuppgifter ( $p = 0.006$ ) och kunde arbeta flera timmar per vecka ( $p = 0.007$ ) än motsvarande grupp i den södra kohorten. Arbetsförmåga kunde förklaras till 12 % av EDSS nivån i norra och 21 % i södra kohorten.

**Slutsats** Våra resultat visar att patienter som är i den inflammatoriska fasen av sjukdomen kan behålla sin arbetsförmåga flera år efter sjukdomsdebut, om de behandlas med effektiva bromsläkemedel från sjukdomsdebut. Vidare kan möjligheten att stanna kvar i arbete förbättras genom flexibla och anpassade arbetsförhållanden, även i den progressiva fasen då funktionsnedsättningen ofta är mer uttalad. Det är uppenbart att dessa resultat får konsekvenser i såväl ett samhällsekonomiskt som livskvalitets perspektiv. Långsiktig uppföljning av våra data krävs för att avgöra om dessa positiva effekter är hållbara över längre tidsperioder.



# 1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease affecting the central nervous system (CNS) and is considered to be of autoimmune origin [Compston et al., 2008]. It usually affects people 20-40 years of age. The prevalence in Sweden is estimated to be about 1 in 500 and a total of 18 000 people with MS were estimated to live in Sweden by 2011 [Ahlgren et al., 2011]. The inflammation leads to demyelination as well as neuronal loss and the patients usually suffer from increasing neurological disability by time. The young age at onset makes MS one of the major causes of reduced ability to work in the Western society [Putzki et al., 2009].

## Type of MS and working ability

The nature of the disease and the modern way to define MS in different phenotypes has importance on the ability to work and study. In a relapsing-remitting disease (RRMS) the disease can be classified as "not active" or "active" [Lublin et al., 2014] (Figure 1). Patients exhibit reversible or non-reversible neurologic disability because of inflammatory demyelination. Axonal loss also occurs in inflammatory demyelinating lesions during this phase of the disease, but is usually clinically silent and proposed to be related to the number of inflammatory demyelinated lesions [Mews et al., 1998]. The accumulation of disability leads to a progressive worsening of Expanded Disability Status Scale (EDSS) [Lublin et al., 2014].

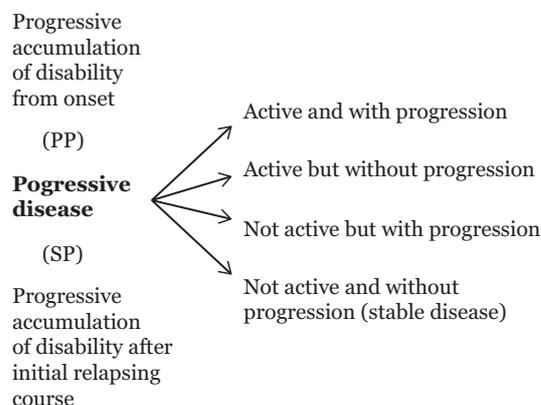
An active disease with ongoing inflammatory activity in the CNS leads to an unstable disease which is difficult to cope with, resulting in impaired cognitive and physical abilities, as well as MS-related fatigue [Multiple Sclerosis International Federation, 2010]. Control of inflammation and axonal preservation in active MS is of highest importance and should be considered as a therapeutic goal [Trapp et al., 1999].



**Figure 1.** Multiple sclerosis phenotype descriptions for relapsing-remitting disease. Adapted from Lublin FD et al. *Neurology* 2014;83:281-86.

In the progressive type, the disease can still be active indicating a simultaneous inflammatory component of the disease, the activity manifesting as either relapses or new focal MRI lesions. The progression, on the other hand, is insidious and may also halt and retain a stable course for variable amounts of time [Lublin et al., 2014]. If the disease is active also in the progressive phase immunomodulatory treatment may be warranted. In

the case of the progressive, not inflammatory active type, axonal loss probably accounts for the progressive neurologic disability leading to increasing EDSS levels and an impaired work ability [Trapp et al., 1999, Gronning et al., 1990]. In this case immunomodulatory treatment is probably ineffective and thus physical rehabilitation and work-promoting measures are of importance. In one Swedish study of a mostly untreated MS population (n=307), the odds for full sick leave increased with increasing EDSS [Sundström et al., 2003].



**Figure 2.** Multiple sclerosis phenotype descriptions for progressive disease, both primary (PP) and secondary progressive disease (SP). Adapted from Lublin FD et al. *Neurology* 2014;83:281-87.

In the natural history of the disease, the majority of affected individuals will, after a period of approximately 15 years, develop a secondary progressive disease course (SP), characterised by an insidious worsening of neurologic disability [Weinshenker et al., 1989]. Preventing secondary progressive MS (SPMS) is important, because this phase of the disease accounts for the vast majority of neurologic disability in MS patients [Trapp et al., 1999]. A Swedish study comparing an untreated historical population with a contemporary treated MS-population, have shown that there was a convincing delay of the secondary progressive phase in the contemporary group compared to the data of the historical cohort. Immunomodulatory treatment is thus important in the active, inflammatory phase of the disease to delay secondary progression and to preserve work ability as long as no effective drugs for the progressive disease exists [Tedeholm et al., 2013].

### **Immunomodulatory treatment**

Important factors to remain in employment for MS patients are control of active disease and slowing down progression, altogether resulting in a more stable disease course [Multiple Sclerosis International Federation]. The first

generation immunomodulatory drugs were introduced in Sweden during the mid-90s, all with a clinical relapse reduction of about 30%. In 2006 and 2011 natalizumab and fingolimod were approved, respectively, offering more efficient control of inflammatory activity of approximately 55-70 % regarding relapse rate and a reduction of MRI activity of 80-90 %. Furthermore, since about 2010, rituximab has been used off-label as an immunomodulatory drug in MS.

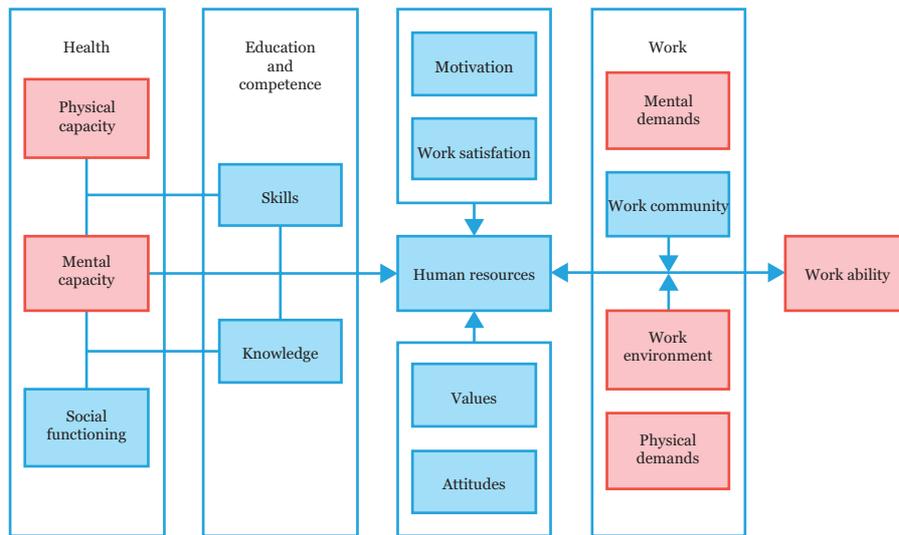
### **Disease-specific and work-related factors that influence the working ability**

Previous studies have indicated that fatigue, mobility- and cognitive problems are the primary factors preventing people with MS from remaining in employment [Multiple Sclerosis International Federation, 2010]. These symptoms have different impact on work depending on the requirements and the possibility of adapting the workplace, the possibility for sedentary work and flexible working hours and influence on the work content [Multiple Sclerosis International Federation].

MS patients with affected walking ability have about half the capacity to work compared to the general population [Berg et al., 2006]. A survey based on a Swedish study of a mainly untreated MS population aged 18-64 years (n=307), only one-third (34.5 %) were not sick-listed at all. Of all individuals of working age, 31 % had a full-time disability pension. If the disability is further increased, the risk for full time sick leave increases significantly [Sundström et al., 2003].

### **Theoretical framework**

Work ability is a central concept for this thesis and is based on Ilmarinen's theoretical model (Figure 3). The Work Ability Model, which is a theoretical model that offers a conceptual framework in which a person's physical and mental ability in relation to work requirements is central to define the person's ability to work. [Ilmarinen et al. 2001].



**Figure 3.** The Work Ability Model constructed by Ilmarinen, emphasises that individual work ability is a process of human resources in relation to work. Adapted from Ilmarinen J. *Occup Environ Med* 2001; 58: 549

### Work Ability Questionnaire - Multiple Sclerosis (WAQ-MS), the development of the instrument

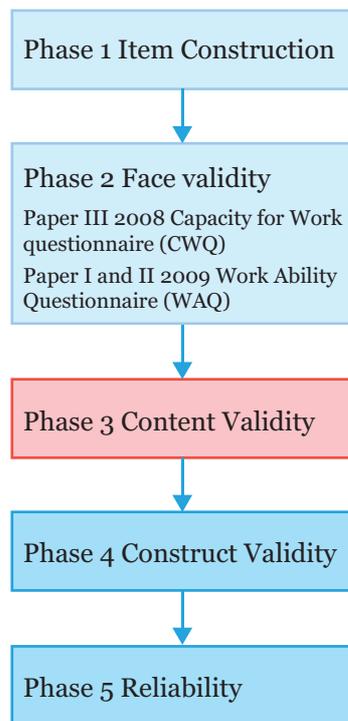
The various dimensions in work ability questionnaire, WAQ-MS originated from the Work Ability Model. WAQ-MS's purpose is to capture the MS specific dimensions that may particularly affect the work ability in persons with MS. The development of WAQ-MS has proceeded from literature review and a process of item constructing. The questionnaire was pretested in a pilot study and found to have high face validity and test-retest reliability. Previously it is used in three published studies [Olofsson et al., 2011, Wickström et al., 2013, Wickström et al., 2014] (Figure 4).

The disease-specific risk factors that may lead to sick leave or full-time disability pension are an active inflammatory disease and axonal loss that accounts for neurologic disability progression of the disease with worsening of EDSS. Especially work-related risk factors are high physical work demands, but also probably current legislation that controls the opportunities for work-oriented interventions [Gronning et al., 1990, Verdier-Taillefer et al., 1995]. However, research also shows that there are factors that enable people with MS to remain in study and work; stable disease, sedentary work, flexible working condition, higher education and salary [Messmer et al., 2009, Pompeii et al., 2005, Multiple Sclerosis International Federation, 2010]. Research also shows that people with MS who are in work are healthier, have a more stable economy, are socially more active and have higher quality of life [Johnson et al., 2004, Fernández et al.,

2011, Flensner et al., 2013]. These factors indicated the necessity of early and reliable evaluation of work ability. However, assessment of work ability is difficult because there are so many factors that influence the ability to work and MS-specific clinically useful measurement tools are still missing.

Since 2008 we have studied existing self-assessment questionnaires and found that the existing ones did not capture all important aspects needed to perform a valid analysis of work related problems in MS; no reporting of real work time, no estimation of ability to work in relation to the physical and cognitive demands of the job or did not measure the MS-specific problems in the workplace. Students or the unemployed were not accounted for in any of the existing questionnaires [Honan et al., 2012, Ilmarinen, 1997, Ilmarinen, 2009, McFadden et al., 2012, Raggi et al., 2015, Tuomi et al., 1998].

Given this background, there was a need for a clinically useful instrument to identify and quantify disease and work-related factors that predict inability to work in MS reliably and which is sensitive to changes. The instrument focuses on facts and information about the employment/study/unemployment and compensation forms, flexible work conditions, perceived physical- and cognitive work ability in relation to the requirements and work-related fatigue and estimation of future work. The development of WAQ-MS follows the Standards for Educational and Psychological Testing (1999) and Health Measurement Scales, a practical guide to their development and use (2008). In the paper V, content validity is presented. Phase 4 and 5 are ongoing and the whole validation process will be published shortly (Figure 4).



**Figure 4.** The instrument development chart of WAQ-MS

## **Economic burden**

### **General**

The cost of DMD was about 100 million euro in 2014 in Sweden. The disease greatly affects both the individual and the society, and the total cost of MS in Sweden 2005 was estimated to be 600 million euro per year, where one-third was indirect costs due to the productivity loss associated with the disease [Berg et al., 2006]. The total mean annual indirect cost per person with MS amounted to 17 151 euro in 2005. Ability to work was substantially lower for people with a higher EDSS score and costs were significantly correlated with EDSS scores. The ability to work among people with MS was about half that of the work ability of the general population [Berg et al., 2006].

### **Direct costs**

In economic evaluations costs are generally divided into three components; direct costs, indirect costs and intangible costs. Direct costs refer to health care costs for which payments are made, such as:

- ambulatory care visits to physician, physiotherapist, nurse etc.
- drugs, hospitalisation, surgery etc.

***Indirect costs***

Indirect costs are represented by loss of productivity due to sick leave or disability pension. This is of utmost importance in MS, since the ability to work is strongly associated with functional ability [Berg et al., 2006]. Different approaches can be made when calculating indirect costs. The most commonly used method is the human capital approach, which values the productivity of the individual as the gross income together with the employer's contribution, estimating the value of lost productivity during the entire time of absenteeism. The human capital approach assumes full productivity and may favour persons with higher salaries, thus being more cost effective for expensive treatments, and giving no value to unemployed, students and those retired with no salary [Schulper M., 2001].



## **2. Aims of the thesis**

The aim of the thesis was to evaluate if the use of immunomodulatory treatment and adjustment of work requirements increase the ability for individuals with MS to work or study.

The specific aims of the thesis were:

- I. To estimate the value of treatment with natalizumab in a socio-economic perspective by measuring the number of hours worked per week before and after one year of treatment with natalizumab.
- II. To evaluate the effects of treatment with natalizumab on ability to work in patients with MS and identify the influence of disease- and work-related factors.
- III. To prospectively evaluate the effect on sick leave of treatment with natalizumab and correlate the results to fatigue and walking ability.
- IV. To compare sickness absence in two MS-populations, one before and the other after the era of disease modifying drugs and investigate how inflammatory control of the disease and work-promoting measures, have influenced the results.
- V. To investigate how work requirements and flexible work conditions influence the ability to work in relation to different EDSS levels and to present content validity for the instrument Work Ability Questionnaire – Multiple Sclerosis.



## 3. Materials and methods

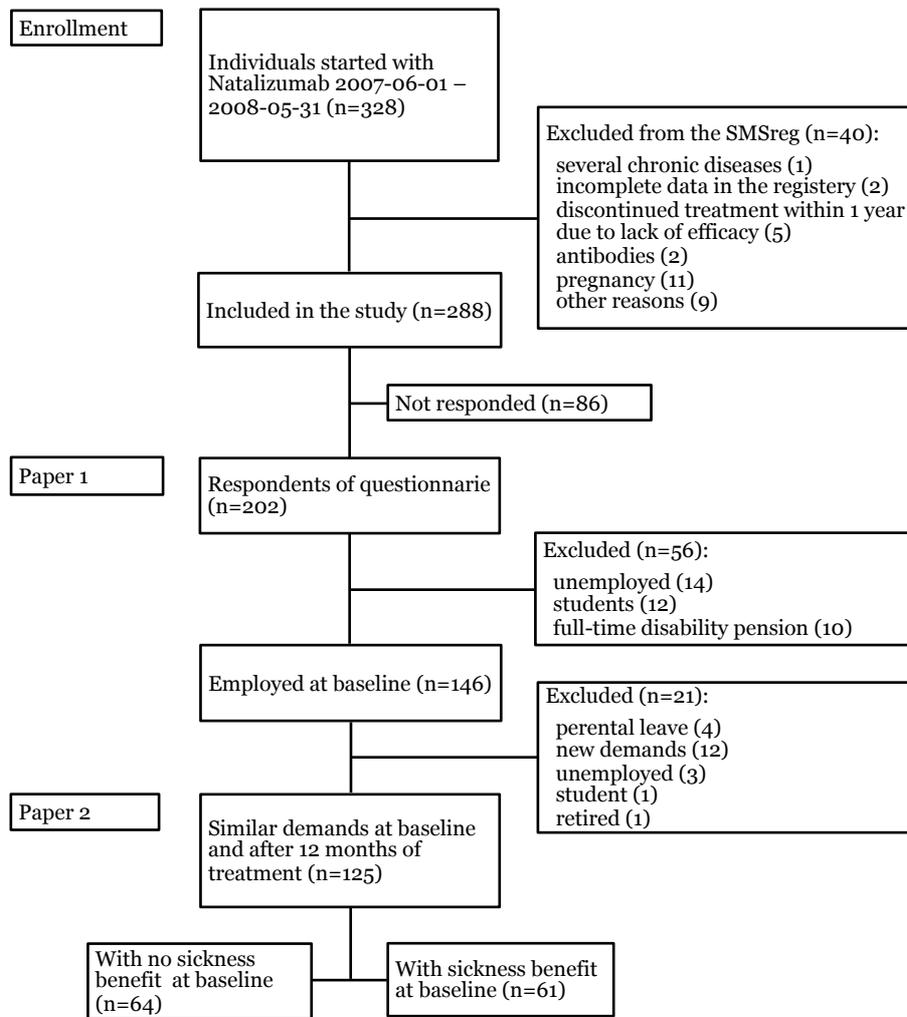
### 3.1 Study subjects

All patients were age 18-64 years of age and diagnosed with MS according to the McDonald criteria from 2001 [McDonald et al. 2001, Polman et al. 2005, Polman 2011] except in paper IV where the historical study population from 1997-2001 fulfilled the Poser criteria at the time for data collection [Poser et al. 1983, Poser et al. 1995].

#### *Paper I and II*

The sample were identified through the SMSreg and consisted of all patients who had started treatment with natalizumab in Sweden during the period June 2007–May 2008, and had continued treatment for at least 1 year (a total of 288 patients). Of the 288 patients who were asked to participate in the study, information was obtained from 202 respondents (70 %). Of the 202 respondents, 146 had employment at treatment start, 14 were unemployed, 30 had full disability pension, and 12 were students. The average age was 37.5 years and 141 (70 %) were women. The average EDSS score was 3.08, the duration of the disease was about 10 years on average, and 130 (64 %) had part-time or full-time sickness absence and/or disability pension before treatment start.

Paper I included all 202 patients (Figure 5). Paper II included only those who had an employment. According to our hypothesis, the efficacy of natalizumab could only be evaluated within employment with stable working conditions during the study period of one year. Of the remaining 146 individuals with employment at baseline, 21 individuals were excluded because unstable working condition. The remaining 125 patients were divided in two groups, patients who had full or part-time sickness benefit (n=61) and patients who had no sickness benefit (n=64) at the start of natalizumab treatment. A flow chart of the selection criteria and groups are shown in Figure 5.

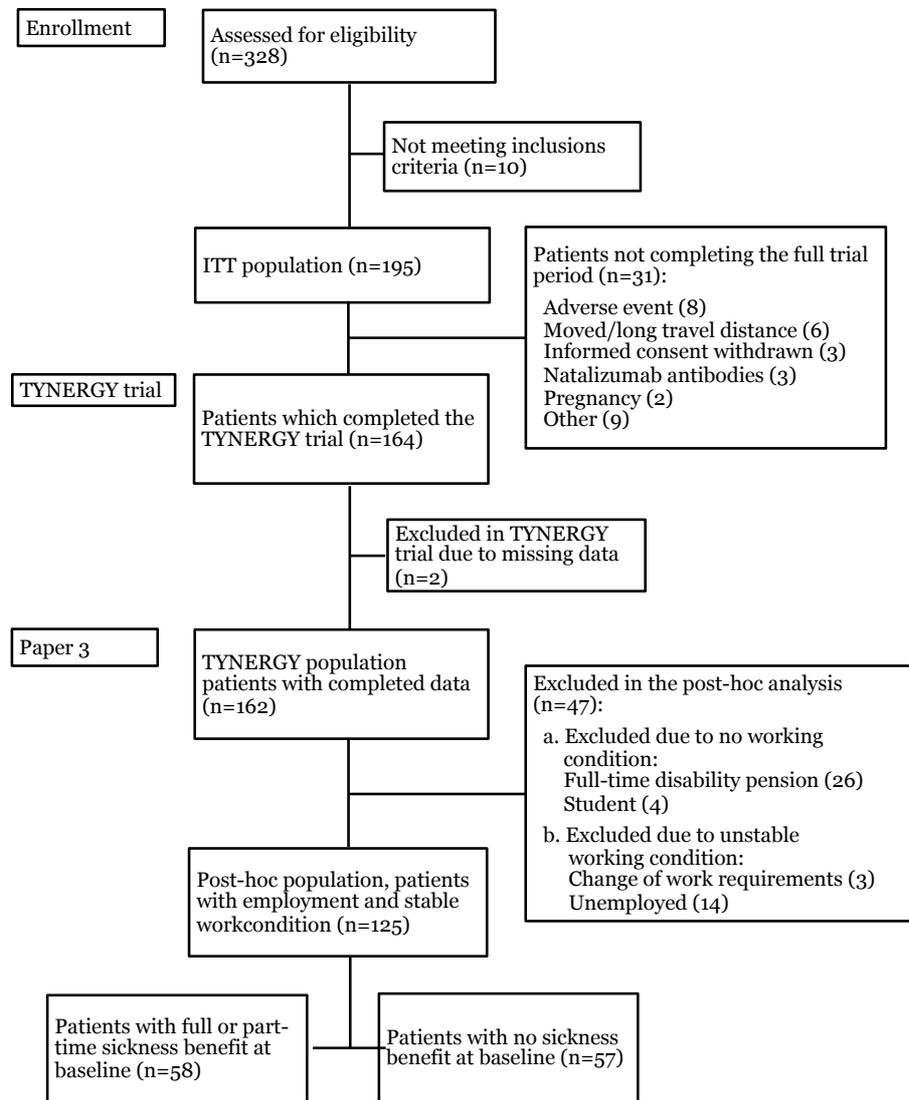


**Figure 5.** Flow chart of patient selection in paper I and II.

### **Paper III**

The post-hoc population studied came from the TYNERGY trial, which was a multicentre study that was performed at centers in Sweden, Norway, Austria and Denmark. All data were collected between 23 March 2009 and 30 June 2011. The primary endpoint was to evaluate the effects on fatigue after 12 months of treatment with natalizumab in patients with RRMS [Svenningsson A et al., 2013]. The TYNERGY trial showed a significant improvement of MS-related fatigue measured with the validated instrument Fatigue Scale for Motor and Cognitive functions (FSMC) [Penner A et al., 2009]. From the original 162 individuals, the study population in paper III was restricted to those with any type of employment at the onset of the study and stable working conditions over the trial period (n=115). The post-hoc

population was divided into two groups based on whether they obtained any degree of sickness benefit (n=58) or were working 100 % of their employment (n=57) (Figure 6). The demographic characteristics; the average age was 39.4 years and 85 (74 %) were women. The average EDSS score was 3.0 and the duration of the disease was about 9 years on average.



**Figure 6.** Flow chart of patient selection in paper III.

### Paper IV

This paper compares two prevalence populations in Västerbotten County, northern Sweden, a historical population from 1997 with a contemporary prevalent population from 2013.

The historical population, which was virtually unexposed to immunomodulatory drugs, was based on a prevalent population from 1997-12-31 (n=399). In this study only patients with a disease onset between 1982-01-01 – 1997-12-31 (16 years) were included (n=202). Information was obtained from 190 patients (Figure 7) with the following demographic characteristics: 64% were women and the average age was 40 years, the duration of the disease was about 7 years on average, and the median EDSS score was 2.5.

The contemporary population, based on the prevalent MS population 2013-12-31, was identified through SMSreg (n=416). In this study only patients with a disease onset between 1998-01-01 – 2013-12-31 (16 years) were included (n=240). 233 of the 240 individuals were included in the analyses (Figure 7). The demographic characteristics of the 233 individuals were: 69 % were women, the average age was 41 years, the duration of the disease was about 7 years on average, and the median EDSS score was 2.

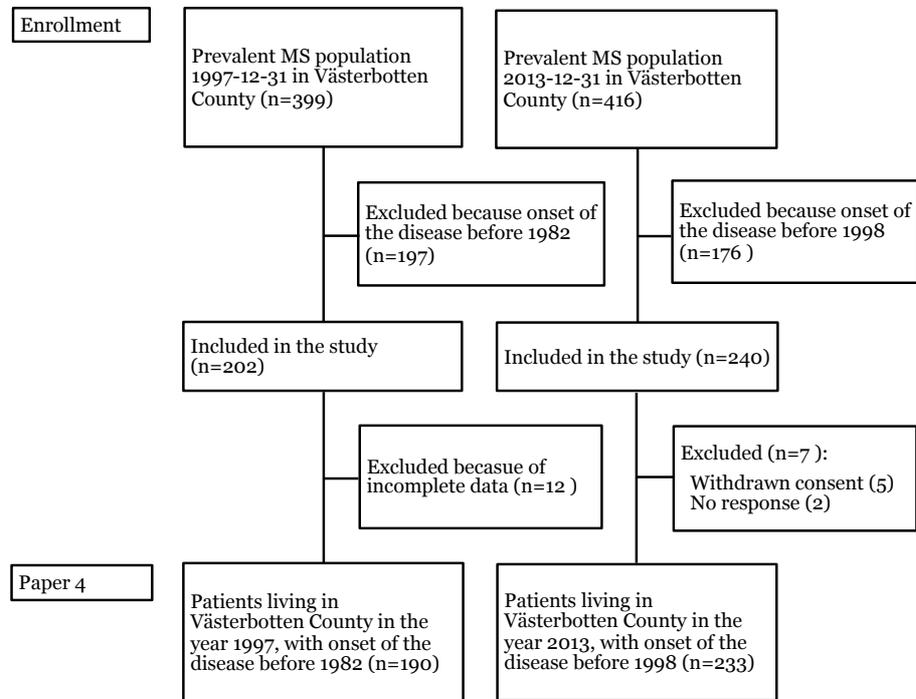


Figure 7. Flow chart of patient selection in paper IV.

### ***Paper V***

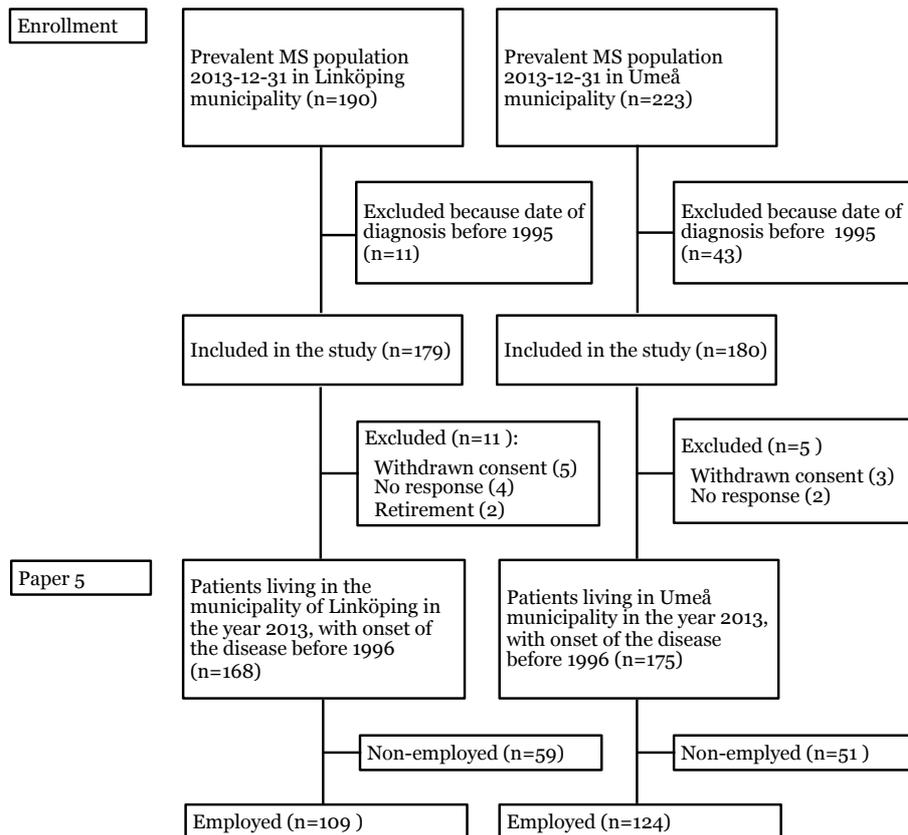
From two geographically different areas with similar demographic structure of jobs and sick leave, two comparable MS populations in Sweden were defined.

We identified 190 patients with MS living in the municipality of Linköping 2013-12-31, the southern cohort. Of these, 11 were excluded because the data of diagnosis was before 1995. Of the remaining 179 patients, 5 were excluded because of withdrawn consent, 4 gave no response and 2 because of early retirement (Figure 8).

The northern cohort, which had been exposed for more work promoting measures, was based on the prevalence population 2013-12-31 in the municipality of Umeå, containing 223 patients. Of these 43 were excluded because the data of diagnosis was before 1995. From the remaining 180 patients, 3 were excluded because of withdrawn consent and 2 patients gave no response (Figure 8).

The two populations did not differ significantly regarding basic demographic features besides disease duration, which was significantly ( $p=0.011$ ) lower in an average of two years in the northern cohort.

When limited to those with an employment there were no significant differences in basic demographic features. The demographic characteristics of the 109 individuals in the southern cohort were: 77 % were women, the average age was 43 years, the duration of the disease was about 13 years on average and the median EDSS score was 1.5. The demographic characteristics of the 124 individuals in the northern cohort were: 85 % were women, the average age was 42 years, the duration of the disease was about 11 years on average and the median EDSS score was 1.5.



**Figure 8.** Flow chart of patient selection in paper V.

## 3.2 Procedures

### 3.2.1 Disease severity scale (paper I, II, III, IV, V)

In all papers the Expanded Disability Status Scale (EDSS) was used to rate the degree of disease. EDSS is widely used as a measure of disability in MS and was revised to the present form 1983 [Kurtzke J.F., 1983]. It is composed of eight Functional Systems (FS), including pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (or mental), and other deficits. Other deficits can include paroxysmal symptoms. The sum of all FS scores defines the EDSS score (Table 1). EDSS 0-4.5 refers to fully ambulatory patients and requires a thorough neurological examination, whereas EDSS 5.0-9.0 is defined as the impaired ambulation.

**Table 1.** *The Kurtzke Expanded Disability Status Scale with description of EDSS scores [Kurtzke J.F., 1983].*

0.0	Normal neurological examination
1.0	No disability, minimal sign in one FS
1.5	No disability, minimal sign in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory.
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others.
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters.
4.5	Fully ambulatory without aid up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters, disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities.
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting.
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting.
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about wheelchair some 12 hours a day.
7.5	Unable to take more than few steps; restricted to wheelchair; may need aid in transfer, wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair.
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day, retains many self-care functions, generally has effective use of arms.
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self-care functions.
9.0	Confined to bed, can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow.
10.0	Death due to MS

### **3.2.2 Work Ability Questionnaire–Multiple Sclerosis (paper I, II, III, IV, V)**

At the start of the first section of WAQ–MS the patient selects category: employed, student, unemployed, (full-time disability pension or retired), then continue with level of education, country of birth and citizenship. Facts about work and studies are reported: the numbers of hours worked per week, percentage of studies and levels of disability pension and sick leave.

In the second section the patient estimates a number of self-rated levels of flexible work conditions, physical and cognitive abilities in relation to the work requirements and perceived fatigue during the workday. A 5-point Likert scale, "not at all", "small extent", "partially", "largely", "completely" (0–4 in table 1) is used for each self-rating questions and compiled at the group level as WAQ-MS mean score 0–4. The questions regarding physical and cognitive requirements are the only ones which are rated on a 4-point Likert Scale from "not at all"–"largely" (0–3 in table 1) and compiled at the group level as WAQ mean score 0–3. Finally, the patient estimates his or her future working ability. The questionnaire refers to conditions present the last two weeks, unless otherwise stated. The questionnaire is presented in Table 2.

**Table 2.** Overview of the Work Ability Questionnaire – Multiple Sclerosis (WAQ-MS).

Category	Employed	Student	Unemployed
<b>Section 1: Self reported data</b>			
<i>1. Facts and information</i>			
Level of education	Four options	Four options	Four options
Country of birth	Four options	Four options	Four options
Citizenship	Two options	Two options	Two options
Hours employed/study tempo/hours unemployed	0–40 hours/week	0–100%	0–40 hours/week
Hours worked/studied/ hours job seeking	≥0 hours/week	≥0%	0–40 hours/week
Disability pension	0%–100%	0%–100%	0%–100%
Activity compensation	0%–100%	0%–100%	0%–100%
Sickness benefit	0%–100%	0%–100%	0%–100%
Other reasons for absence	0%–100%	0%–100%	0%–100%
Unemployed	0%–100%	0%–100%	0%–100%
Studying	0%–100%	0%–100%	0%–100%
Profession	Profession	Study orientation	Trained as/profession
Shifts, eg day shift, two shifts	Four options		
Form of employment	Five options		
<b>Section 2: Self rating data</b>			
<i>2. Flexible work conditions</i>			
Opportunities to work at home	0–4		
Influence working hours	0–4		
Opportunity to influence the pace of work	0–4		
Opportunities to take breaks	0–4		
Work undisturbed	0–4		
Tasks adapted to the disease	0–4		
Work environment adapted to the disease	0–4		
<i>3. Physical requirements/ability</i>			
	<i>Requirements/ability to cope with own requirements during workday</i>	<i>Requirements/ability to cope with own requirements during study day</i>	<i>Ability to cope</i>
Dexterity	0–3/0–4	0–3/0–4	0–4
Sedentary working	0–3/0–4	0–3/0–4	0–4
Work standing	0–3/0–4	0–3/0–4	0–4
Being mobile	0–3/0–4	0–3/0–4	0–4
Walk inside	0–3/0–4	0–3/0–4	0–4
Walking outside	0–3/0–4	0–3/0–4	0–4
Lift and carry	0–3/0–4	0–3/0–4	0–4
Run, jump and climb	0–3/0–4	0–3/0–4	0–4
Visual acuity	0–3/0–4	0–3/0–4	0–4
<i>4. Cognitive requirements/ability</i>			
	<i>Requirements/ability to cope with own requirements during workday</i>	<i>Requirements/ability to cope with own requirements during study day</i>	<i>Ability to cope</i>
Attention and concentration	0–3/0–4	0–3/0–4	0–4
Attention and concentration in a noisy environment	0–3/0–4	0–3/0–4	0–4
Multitask	0–3/0–4	0–3/0–4	0–4
Remember things you decided to do later	0–3/0–4	0–3/0–4	0–4
Reading, understanding and use of new information	0–3/0–4	0–3/0–4	0–4
Working under time pressure	0–3/0–4	0–3/0–4	0–4
Solve problems, draw conclusions and make own decisions	0–3/0–4	0–3/0–4	0–4
<i>5. Work/study-related physical fatigue</i>			
Worsening visual, eg get more blurred or double vision	0–4	0–4	0–4
Worsening ability to walk or move	0–4	0–4	0–4
Worsening ability to move when it's hot	0–4	0–4	0–4
<i>6. Work/study-related cognitive fatigue</i>			
Worsening attention and concentration	0–4	0–4	0–4
Worsening to multitask	0–4	0–4	0–4
Worsening ability to think when hot	0–4	0–4	0–4
<i>7. Future ability to work/study</i>			
3 months	Numbers hours/week	Percentage	Numbers hours/week
12 months	Numbers hours/week	Percentage	Numbers hours/week

A 5-point Likert scale is used for each self-rating questions, from "not at all"–"completely"=0–4 in table, except for the questions regarding physical and cognitive requirements which is rated on a 4-point Likert Scale from "not at all"–"largely"=0–3.

### **3.2.3 The Swedish Multiple Sclerosis Register (paper I, II, IV, V)**

SMSreg is a Swedish Quality Register containing data concerning clinical course, magnetic resonance imaging, laboratory assessments and MS treatment (ref [www.neuroreg.se](http://www.neuroreg.se)). About 70 % of the Swedish MS population is registered in the SMSreg. The data in the register, alongside with other data, have been used to conduct studies about the clinical outcome and epidemiology of MS in Sweden.

### **3.2.4 Immunomodulatory drugs (paper I, II, III, IV, V)**

The first generation immunomodulatory drugs were introduced in Sweden during the mid-90s, all reducing the number of clinical relapses with about 30 %. In 2006 and 2011, respectively, natalizumab and fingolimod were approved, both offering a more efficient control of the inflammatory disease activity by reducing the relapse rate with 55-70 % and the MRI activity with 80-90 %. Furthermore, since about 2010, rituximab has been used off-label as an immunomodulatory drug in MS.

### **3.2.5 Work-promoting measures (paper IV, V)**

In the mid 90ies, a more systematic approach regarding clinical work-oriented team-based measures were introduced, and a comprehensive rehabilitation course for individuals with early MS was established in Västerbotten. The aim of the course was to increase knowledge about the disease, DMD and factors affecting studies and work ability and also to equip the patients with tools to influence their own work and study situation [Wickström et al., 1996, Wickström, 1997]. Since early 2000s the MS team at the northern neurology department in Västerbotten has put strong focus on detecting early signs of work-related inability and included these questions in the continuous team evaluations.

## **3.3 Content validity of the questionnaire, WAQ-MS**

The content validity was analysed to ensure that each item in the questionnaire, WAQ-MS, was representative and clear, was matched with a particular part of the field and reflected a complete range of attributes describing the concept of working ability in MS. The content validity test was done by using panels of content experts as groups of neurologists (5 persons), neuropsychologists (4 persons), physiotherapists (4 persons), and in final lay experts (8 patients in two groups). A packet with a cover letter together with a Content Validity Index (CVI) was sent to the experts [Mc Gartland et al., 2003, Lynn, 1996]. By using the CVI each expert independently rated the relevance of each item on the WAQ-MS to the conceptual framework using a 4-point Likert scale (1=not relevant (remove), 2=somewhat relevant (major revisions of the item is needed), 3=relevant

(minor revisions of the item is needed), 4=very relevant) and the clarity of each item using a 4-point Likert scale (1=not clear, 2=somewhat clear (item needs major revisions to be clear), 3=clear (item needs minor revisions to be clear), 4=very clear). The CVI was used to estimate the validity of the items [Mc Gartland et al., 2003]. The proportion of items rated 3 or 4 gives the CVI score for the instrument. A score of 0.80 or better indicates good content validity [Mc Gartland et al., 2003]. The CVI for the relevance and clarity of the items deemed good Content validity measured by experts and lay experts.

### **3.4 Statistical methods**

In the papers baseline characteristics, data were analysed by descriptive statistics (number, percentage, mean, standard deviation (SD), median and interquartile range (IQR)). Differences in disease-related baseline characteristics between groups were analysed in paper I, III, IV and V with independent samples t test for parametric variables and with Pearson Chi-Square, Fisher's Exact Test for the non-parametric variables or Wilcoxon's rank sum test.

#### ***Paper I and II***

Changes of variable data before (at baseline) and after one year of natalizumab treatment were analysed with the paired samples t test. In paper I a method to calculate the economic value of the changes in productivity was then used. The productivity loss and gain per week was extrapolated to 1 year. The economic value of the change in productivity was calculated by multiplying the change in hours worked per week with 48 (weeks per year) with the corresponding sex- and age-specific productivity value, where  $hw_1$  = hours worked per week at baseline;  $hw_2$  = hours worked per week at follow-up; and  $wAS$  = age- and sex-specific productivity value per hour:

$$((hw_2 - hw_1)wAS) \times 48 = \text{annual productivity gain}$$

In paper II the Pearson's correlation was used to analyse the relation between disease and work related factors. Linear regression and multivariate linear regression was used to analyse the direction and degree of explanatory power. Locally weighted scatterplot smoothing (LOESS) was used to analyse the occurrence of inhomogeneity in the regression line.

#### ***Paper III***

Changes of outcome variables: sickness benefit in percentage, 6MWT in meters, and fatigue in FSMC total score before (at baseline) and after one

year of natalizumab treatment, were analysed by paired-samples t test. Pearson's correlation was used for correlation between net percentage change of sickness benefit and change in walking distance in 6MWT expressed in meters and change in MS-related fatigue expressed in FSMC total score. Linear regression was performed to analyse the age-dependency regarding the net percentage change in sickness benefit and change in walking distance in 6MWT after one-year of natalizumab treatment [Goldman, 2008, Salzman, 2009].

#### ***Paper IV***

Changes of outcome variables: no sickness absence, part-time sickness absence and full time sickness absence between the populations 1997 and 2013, were analysed by Pearson's Chi-squared test with Yates' continuity correction or Fisher's Exact Test for Count Data.

#### ***Paper V***

Changes of outcome variables between the southern and northern cohort, were analysed with independent samples t test for parametric variables and with Pearson's Chi-squared test with Yates' continuity correction or Fisher's Exact Test for Count Data for non-parametric variables. Locally weighted scatterplot smoothing (LOESS) was used to analyse the occurrence of inhomogeneity in the regression line.

In all papers a  $\alpha$ -level of 0.05 was selected for determining statistical significance.

### **3.4 Ethical considerations**

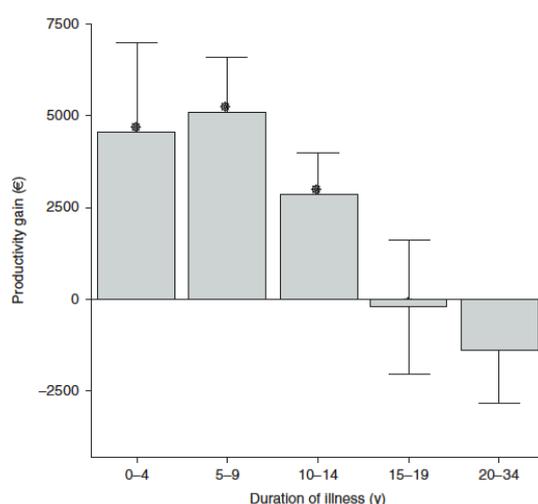
All studies included in this thesis were approved by The Regional Ethics Committee in Umeå. Written consent was obtained from all patients.

## 4. Results

### Paper I

This study showed that after 50 weeks of treatment with natalizumab, people with MS on average increased their productivity by 3.3 hours per week ( $p < 0.01$ ), corresponding to an economic value of 3216 euro per person per year (year 2007 values). When restricting the analysis to the employed subgroup with some degree of sickness benefit or disability pension at baseline ( $n=71$ ), the productivity gain increased to 8185 euro per person per year.

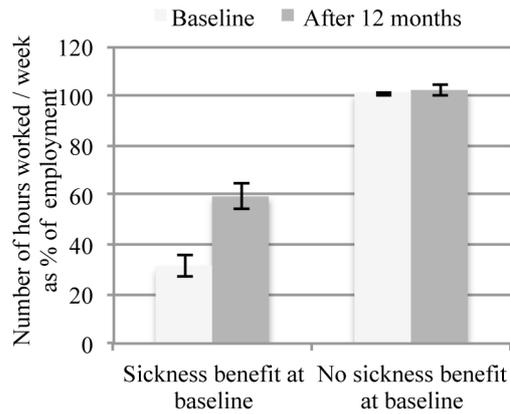
A shorter disease duration (<10-14 years) or being younger (age 25–35) was significantly associated with a greater productivity gain ( $p=0.025$  and  $p=0.002$ , respectively; Figure 9). By contrast, EDSS score did not show a significant correlation with the productivity gain ( $p = 0.464$ ).



**Figure 9.** Average productivity ( $\pm 1.0$  standard error of the mean) gain after 1 year of treatment with natalizumab per person per year, according to disease duration (2007 values)

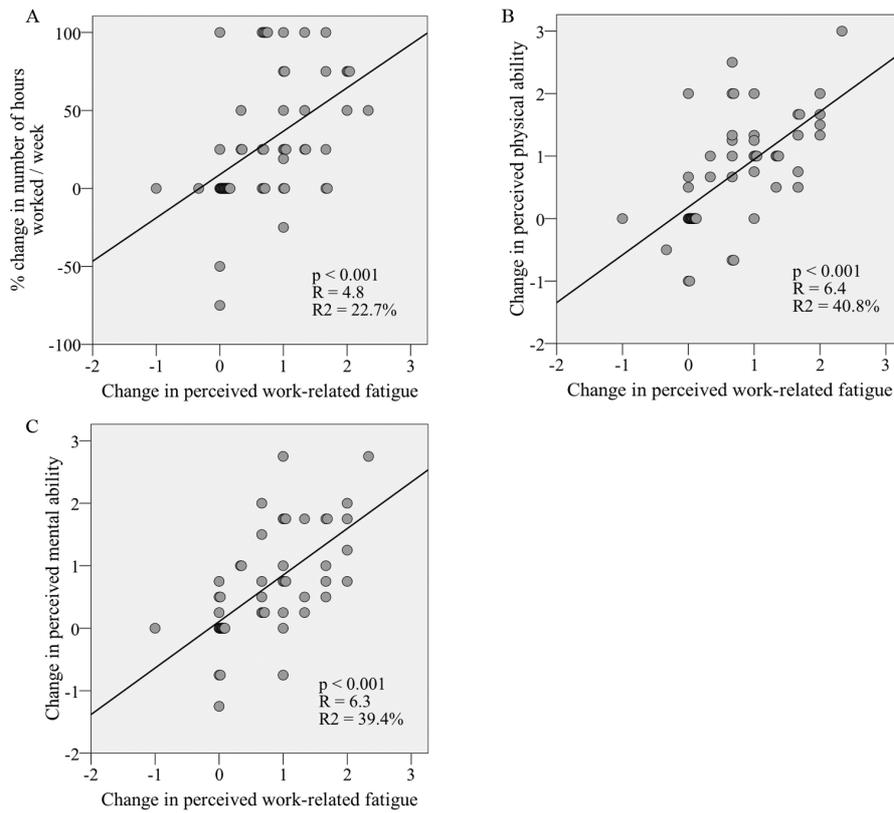
### Paper II

MS patients receiving some level of sickness benefit at baseline almost doubled their work amount after one year of natalizumab treatment, from 31% to 60 % ( $p < 0.001$ ; Figure 10). They decreased their percentage of sickness benefit from 62 % to 21 % ( $p < 0.001$ ) while those who worked full-time at baseline retained full work ability after one year.



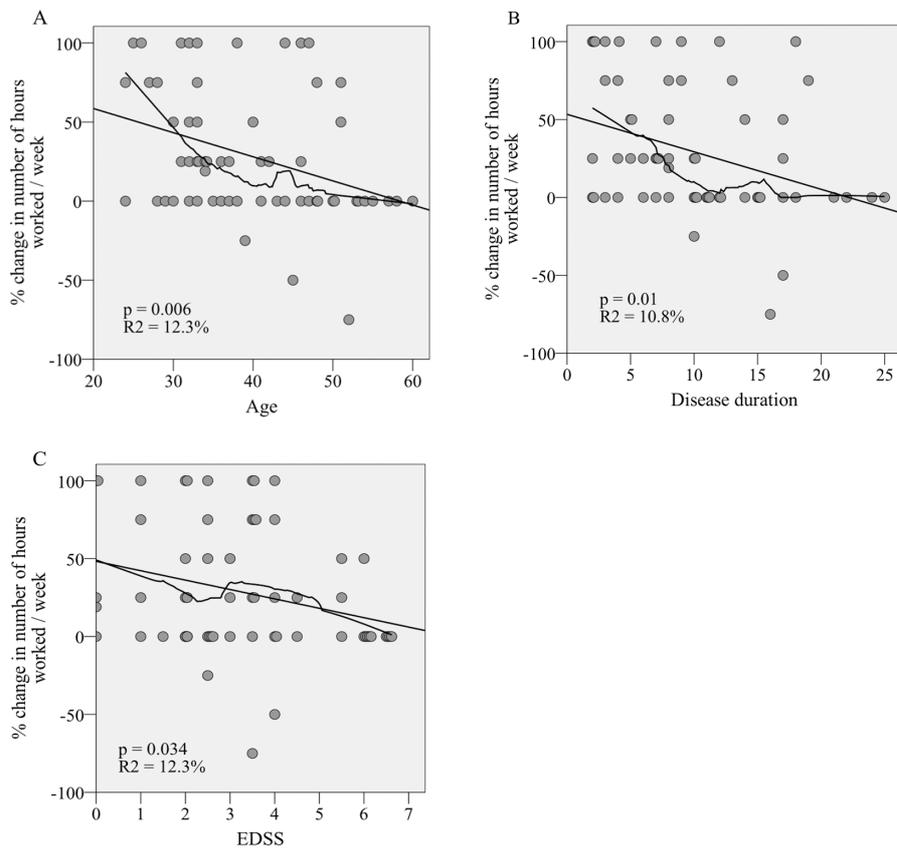
**Figure 10.** Mean number of hours worked in per cent of the level of full employment. The work level increased from 31 % to 60 % during the 12 month natalizumab treatment for the group with sickness benefit at baseline and was stable for the group with no sickness benefit at baseline. Error bars show standard error of the mean.

The analyses of the patients' ability to cope with work-related requirements and perceived fatigue during workday showed a significant improvement after one year of treatment with natalizumab, and that the improvement was independent of the previous level of employment. There were significant correlations between improved work-related fatigue and improved work ability reflected as increased number of hours worked and perceived mental and physical ability to cope with work requirements after one year of natalizumab treatment (Figure 11 A–C).



**Figure 11.** The panel shows that improvement in work-related fatigue strongly correlates with improvement in all other domains of work ability (A–C), including hours worked at employment (D). Change in perceived physical and mental ability and work-related fatigue was measured with WAQ mean scores. Each point represents one patient.

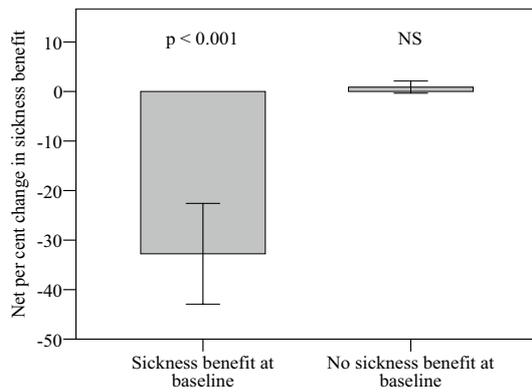
Short disease duration, younger age and lower EDSS at start of treatment onset were significant predictors for positive effect on work ability (Figure 12 A-C).



**Figure 12.** The panel shows regression between age (A), disease duration (B), EDSS (C) and percentage change in number of hours worked per week at employment. The linear regression shows that these three factors have significant impact on the effect of natalizumab treatment on the ability to work. The locally weighted scatterplot smoothing (LOESS) lines display that the impact is highest for young individuals early in the disease course while the EDSS effect is evenly distributed over the whole measured range.

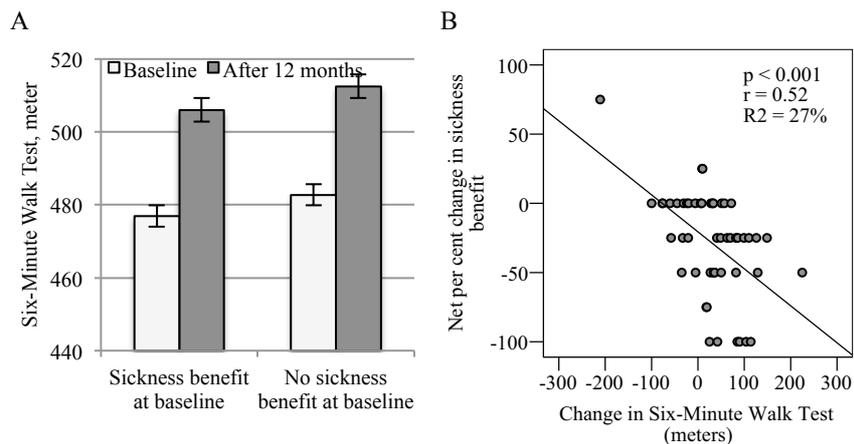
### Paper III

In the subgroup of MS patients with some degree of sickness benefit at baseline a reduction of sickness benefit from 57 % to 24 % ( $p < 0.001$ ) was found after one year of treatment with natalizumab. Patients without sickness benefit at baseline retained their full working ability (i.e. working 100 % of their employment) throughout the study (Figure 13).



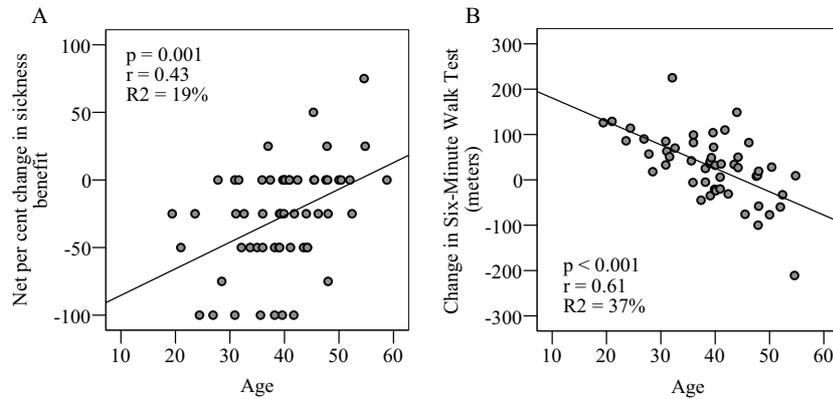
**Figure 13.** Sickness benefit as per cent of the employment was reduced with a net change of 33 % after the 12-month treatment with natalizumab in the group with some degree of sickness benefit at baseline whereas the group with no sickness benefit at baseline remained stable. Error bars show 95 Confidence Interval.

We found a significant increase in the 6MWT after one year of treatment in both the groups with and without sickness benefit at baseline (Figure 14 A). In the subgroup of MS patients with some degree of sickness benefit at baseline ( $n=58$ ), improvement in walking distance correlated with decreased level of sickness benefit ( $R^2=27\%$ ,  $p < 0.001$ ) (Figure 14 B). Furthermore, fatigue measured by the Fatigue Scale for Motor and Cognitive functions (FSMC) were decreased by natalizumab treatment. However, this did not correlate with the amount of sickness benefit.



**Figure 14.** Walking distance in meters, at baseline and after 12 months for the group with sickness benefit at baseline and no sickness benefit at baseline\* (A). Change in sickness benefit correlated with change in walking distance\*. Only patients with some degree of sickness benefit at baseline were included in the analyses ( $n=58$ ). Each point represents one patient (B). \*Patients from Denmark ( $N=7$ ) did not participate in the 6MWT. Error bars show standard error of the mean.

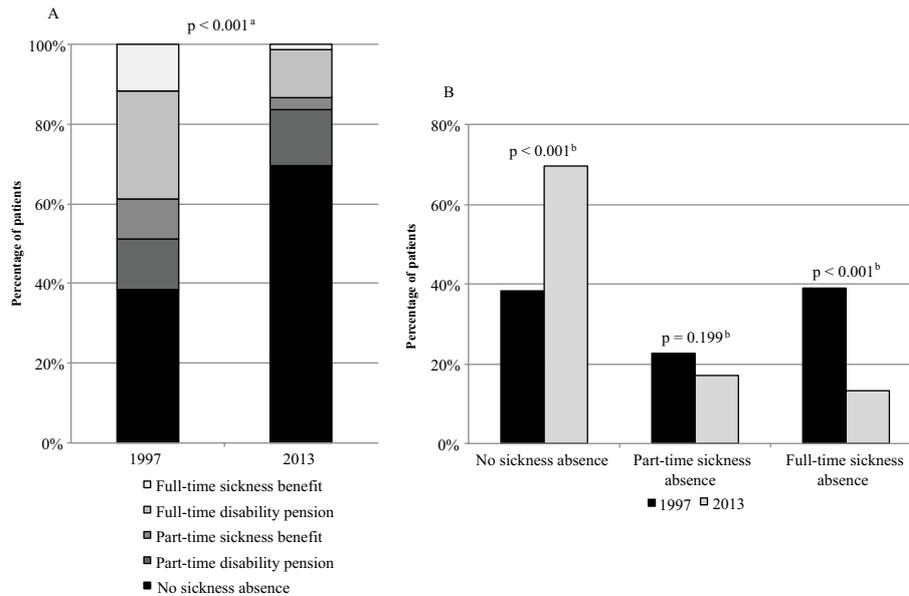
In the subset of individuals with sickness benefit at baseline (n=58), regression analysis showed that younger age correlated significantly with reduction of sick leave ( $R^2=19\%$ ,  $p<0.001$ ) and also with improvement of walking ( $R^2=37\%$ ,  $p<0.001$ ; Figure 15 A and B).



**Figure 15.** Regression analysis between age of onset of natalizumab treatment and change of sickness benefit as per cent of employment (A) and change in walking distance (B)\*. Younger individuals tend to improve their work ability more than older individuals after one year of natalizumab treatment (A). Also walking distance improves more for young individuals starting natalizumab therapy (B). Each point represents one patient. \*Patients from Denmark (n= 7) did not participate in the 6MWT.

#### Paper IV

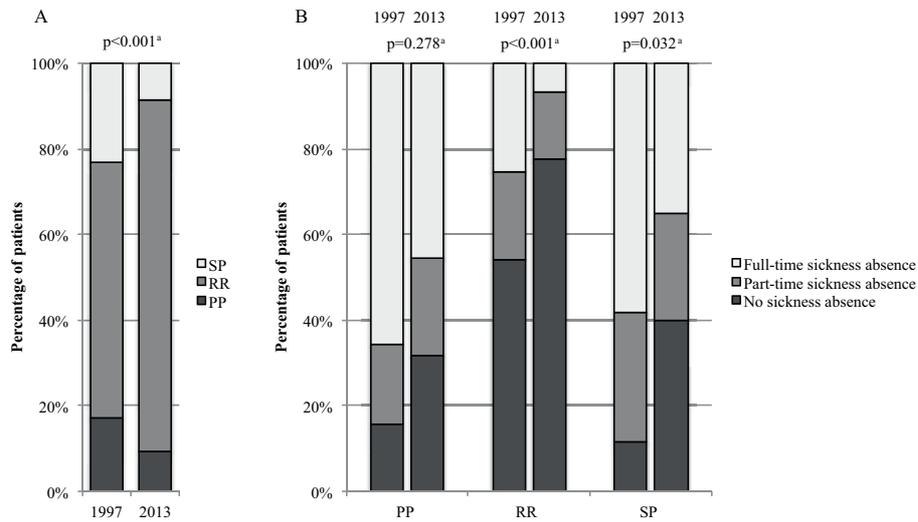
The proportion of MS patients in the workforce or studies was higher in the contemporary MS population being exposed to disease modifying drugs compared to the virtually untreated historic population (66 % vs 38 %;  $p<0.001$ ). The proportion of MS patients with full-time disability pension decreased from 27 % to 13 % ( $p<0.001$ ; Figure 16 A). The analyses showed also that the proportion of people belonging to the work force without any kind of sickness absence increased from 38 % to 70 % ( $p<0.001$ ) from 1997 to 2013 and the proportion of patients with full-time sickness absence decreased from 39 % to 13 % ( $p<0.001$ ; Figure 16 B).



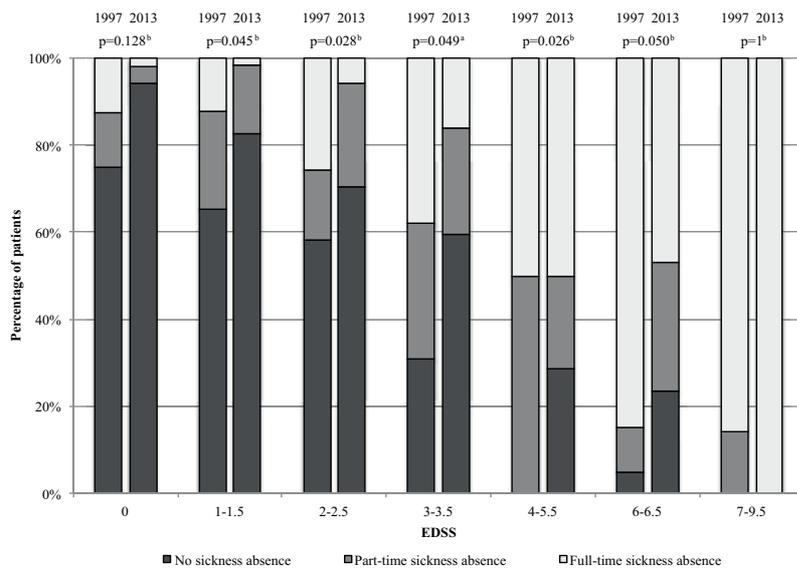
**Figure 16.** A comparison of two MS-populations in Västerbotten County in the year 1997 and 2013 with a disease onset 1982 – 1997 and 1998 – 2013, respectively. The proportions of different degree of sickness benefit and disability pension are presented in panel A. In panel B, the proportions of patients with no sickness absence, part-time sickness absence and full-time sickness absence in 1997 and 2013 are presented. <sup>a</sup>Pearson's Chi-squared test with Yates' continuity correction, <sup>b</sup>Fisher's Exact Test for Count Data.

We also analysed the distribution of the disease courses relapsing-remitting (RR), secondary progressive (SP) and primary progressive (PP) MS between the 1997 and 2013 populations and found a significant difference in the distribution ( $p < 0.001$ ; Figure 17 A). In particular, the proportion of patients in the RRMS phase increased from 60 % in the 1997 cohort to 82 % in the 2013 cohort. Within the RRMS and SPMS populations the sickness absence decreased significantly from 1997 to 2013 while there was no significant change in sickness absence within the PPMS group (Figure 17 B).

The contemporary population displayed a significantly lower median EDSS level compared with the historic population ( $p < 0.001$ ). There was a significant decrease of sickness absence in several individual EDSS grades (Figure 18).



**Figure 17.** Both the disease course and the sickness absence in relation to disease course differed between 1997 and 2013. The distribution between the different clinical courses of MS, eg primary progressive (PP), relapsing-remitting (RR), and secondary progressive (SP), differed significantly between the two occasions (A). Most notably, patients remained in RR to a higher degree 2013 compared with 1997. Both patients in RR and SP could work to a higher extent in 2013 compared with 1997. <sup>a</sup>Pearson's Chi-squared test with Yates' continuity correction. In the 1997 population four patients were excluded because of missing data.



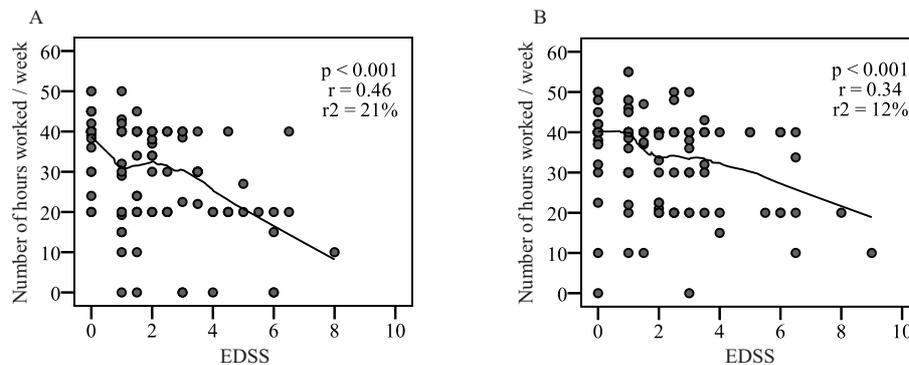
**Figure 18.** A comparison regarding degree of sickness absence between people with MS in Västerbotten County in the year 1997 and 2013 in relation to different EDSS groups. Within the EDSS groups 1- 6.5 the level of sickness absence decreased in 2013 compared with 1997. <sup>a</sup>Pearson's Chi-squared test with Yates' continuity correction, <sup>b</sup>Fisher's Exact Test for Count Data.

## Paper V

The proportion of MS patients belonging to the work force or studied were significantly higher in the northern cohort, where they had been exposed to more work promoting measures, compared with the southern cohort ( $p=0.022$ ). The analyses showed that the proportion without any kind of sickness absence was higher in the northern cohort (62 % vs 46 %). The prevalence of full-time disability pension was 25 % in the southern cohort and 14 % in the northern cohort.

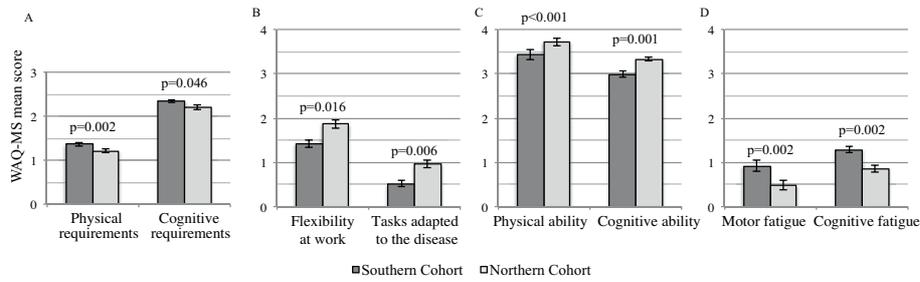
In the next step we wanted to study how the working ability was influenced by different requirements and flexible work conditions and restricted the analyses to those with an employment.

In order to investigate how EDSS predict work ability, regression analyses were performed. With EDSS as the independent variable, and number of hours worked per week as the dependent variable, the analyses indicated that 21% of the number of worked hours per week could be explained by the EDSS in the southern cohort, and 12% in the northern cohort (Figure 20 A and B).



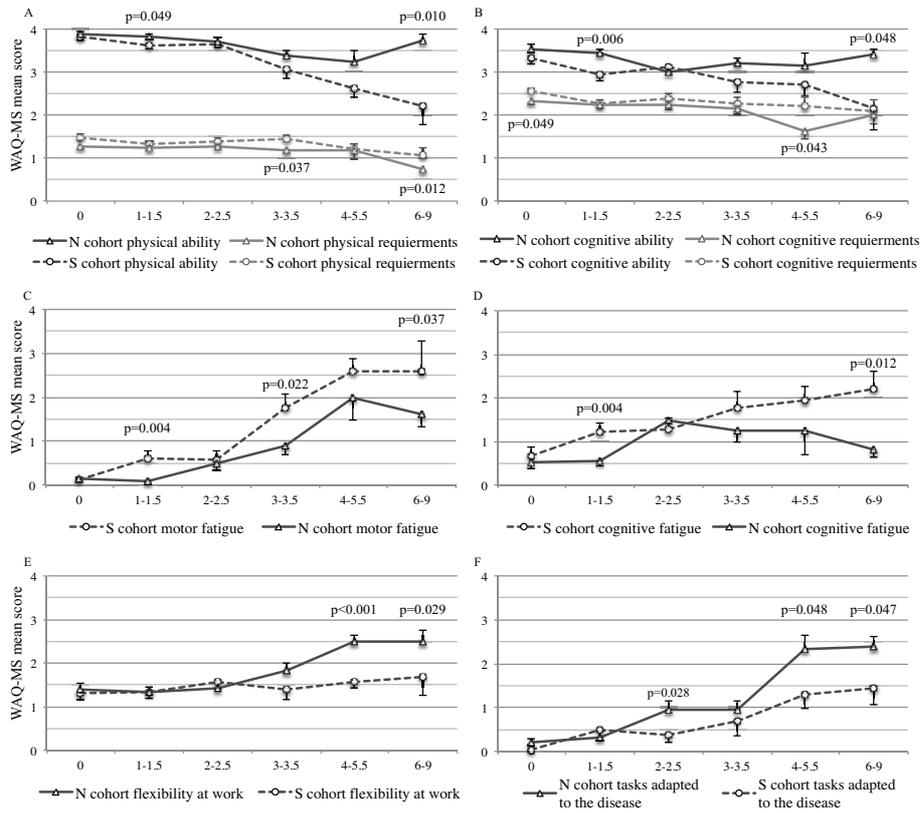
**Figure 20.** Regression analysis between EDSS and number of hours worked per week in subgroups analyses of the employees in the two MS cohorts, the southern (A) and the northern (B). The EDSS levels explained 12 % of the working ability in the northern cohort and 21 % in the southern cohort. The locally weighted scatterplot smoothing (LOESS) lines display that the impact of EDSS starts at level 2 in the southern cohort and at level 3,5 in the northern cohort and then affecting the distribution to level 8 respectively 9.

The employees in the northern cohort had significantly lower requirements, greater flexible work conditions and adapted tasks to the disease and estimated higher perceived physical and cognitive ability to cope with work requirements and lower level of MS-related fatigue both motor and cognitive during the workday compared to the southern cohort (Figure 21 A–D).



**Figure 21.** WAQ-MS mean score for perceived physical and cognitive requirements (A), flexibility at work and tasks adapted to the disease (B), physical ability and cognitive ability (C), and motor and cognitive fatigue (D) in one southern and one northern MS cohort. Error bars show standard error of the mean.

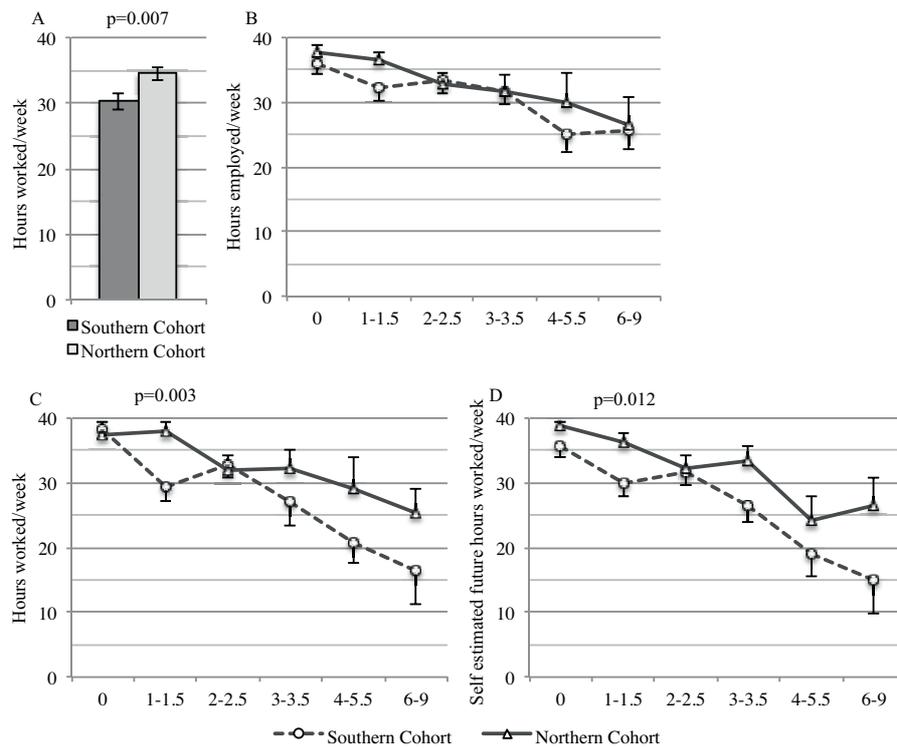
In a next step, we studied how the outcome was distributed in different EDSS groups. In the northern cohort the "physical requirements" were starting to become lower at EDSS 4-5.5 and became significantly lower in relation to the southern cohort at EDSS 6-9.5. This reduction was reflected by an improved "physical ability" (Figure 22 A). The "cognitive requirements" were equal between the cohorts until EDSS 4-5.5 and thereafter the northern cohort showed lower requirements in favour of maintaining the ability. Also for the "cognitive abilities", there was a significant difference between the groups at EDSS 6-9.5 (Figure 22 B). The items "motor fatigue" and "cognitive fatigue" during the workday was higher in the southern compared to the northern cohort. In both cohorts the motor fatigue peaked at EDSS 4-5.5 after which it declined in the northern cohort and were unchanged in the southern cohort (Figure 22 C and D). The items "flexibility at workplace" and "tasks adapted to the disease" was better provided in the northern cohort compared with the southern cohort at EDSS 4-9.5 (Figure 22 E-F).



**Figure 22.** WAQ-MS mean score for perceived physical ability and physical requirements (A), cognitive ability and cognitive requirements (B), work related motor fatigue (C), work related cognitive fatigue (D), flexibility at work (E) and tasks adapted to the disease (F) in relation to EDSS (0, 1-1.5, 2-2.5, 3-3.5, 4-5.5, 6-9.5) in one southern and one northern MS cohort. Error bars show standard error of the mean.

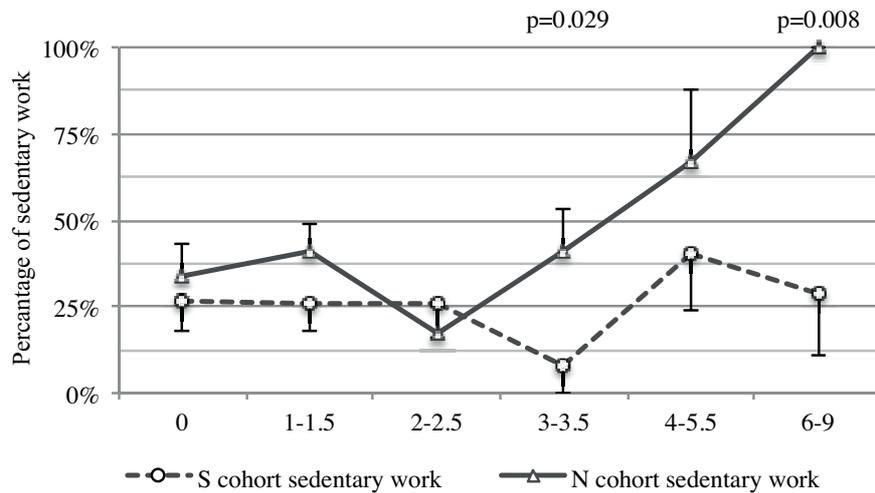
In the northern cohort MS patients worked an average 34.5 hours per week and in the southern 30.2 hours per week, which was a significant difference ( $p=0.007$ ). With increasing EDSS the number of hours worked per week decreased. At the high EDSS levels 6-9.5, the patients could work an average of 25.4 hours per week in the northern cohort and 16.4 hours per week in the southern cohort. Number of hours employed and hours worked were virtually identical in the northern cohort while number of hours worked compared to hours employed were lower in the southern cohort, because of higher number of patients receiving short-term sickness benefit in the southern cohort. The self estimation of future work showed that patients in both the northern and southern cohort estimated their future work amount to be more or less identical looking twelve months ahead. This indicates that patients in the southern cohort do not believe themselves to break their sick

leave and return to full working hours within their present employment (Figure 23 A–D).



**Figure 23.** Mean number of hours work per week (A) in one southern and one northern MS cohort. Mean number of hours employed per week (B), mean number of hours worked per week (C) and mean number of self estimated future hours worked per week (D) in relation to EDSS (0, 1-1.5, 2-2.5, 3-3.5, 4-5.5, 6-9.5) in one southern and one northern MS cohort. Error bars show standard error of the mean

Finally, we compared the proportion of people who worked sedentary in the two cohorts. We found that the proportion of people with sedentary work increased with increasing level of EDSS in the northern cohort compared with the southern cohort. A sedentary work was defined as having requirements to work sedentary, with or without shorter periods of standing or walking indoors.



**Figure 6.** The percentage of patients who worked sedentary in relation to EDSS (0, 1-1.5, 2-2.5, 3-3.5, 4-5.5, 6-9.5) in one southern and one northern MS cohort. Error bars show standard error of the mean.

### Paper V Content validity of the questionnaire, WAQ-MS

The development of WAQ-MS included a literature review followed by a process of item constructing. The questionnaire was then pretested in a pilot study and found to have high face validity and test-retest reliability. Previously it is used in three published studies [Olofsson et al., 2011, Wickström et al., 2013, Wickström et al. 2014]. The content validity was analysed to ensure that each item in the questionnaire was representative and clear, was matched with a particular part of the field and reflected a complete range of attributes describing the concept of working ability in MS. A score of 0.80 or better indicates good content validity [Mc Gartland et al., 2003]. The CVI for the relevance and clarity of the items deemed good Content validity measured by experts and lay experts (Table 3). The total content validity was good with a total CVI of 0.97.

**Table 3.** The Content Validity Index of the Work Ability Questionnaire – Multiple Sclerosis (WAQ-MS)

CVI	Content Experts		Lay experts	
	Relevance	Clarity	Relevance	Clarity
Facts and information	1.00	1.00	1.00	1.00
Flexibility possibilities	1.00	0.98	1.00	0.98
Physical requirements/ability	1.00	1.00	1.00	1.00
Cognitive requirements /ability	0.98	0.90	0.98	0.93
Physical fatigue	0.93	1.00	0.92	1.00
Cognitive fatigue	0.89	1.00	0.88	1.00
Future work ability	0.86	1.00	0.85	1.00
CVI	0.95	0.99	0.96	0.97
Total CVI	0.97			



## 5. Discussion

### The effect on work ability by DMD treatment

Our data show that patients with active RRMS improved their ability to work in several different aspects one year after start of treatment with natalizumab. The number of hours worked per week in the same position was almost doubled in individuals that had some form of sickness benefit at baseline, and those who were working full-time at baseline remained at this level after one year of treatment. The majority (88 %) of the patients started treatment with natalizumab due to insufficient inflammatory control with the first line treatment *i.e.* interferon-beta or copaxone.

Paper III supports our earlier observations that initiation of natalizumab treatment in patients with an active RRMS may be associated with improved ability to work. Furthermore, this study had a prospective design, eliminating the possible recall bias that could diminish the validity of our previous retrospective observations.

One important finding in the retrospective study was that natalizumab improved work ability more effectively in younger patients and in patients with short disease duration. This observation could then be confirmed in the prospective TYNERGY trial. We could in both studies see that the improvement in work ability was primarily found among younger compared with older individuals. One explanation for this may be that the inflammatory component in MS appears to be highest among young individuals [Khademi et al., 2013, Tortorella et al., 2005], and thus making it plausible that a more potent inflammatory control has a stronger effect on the overall well-being. The same type of observation was done regarding walking ability as a higher degree of improved mobility in younger individuals after initiation of natalizumab treatment.

Mobility is an important factor in many different types of employment, and poor walking ability results in a higher degree of motor fatigue during the workday and may confer lower work ability defined as the number of working hours. In the TYNERGY trial we have previously shown that the walking distance, as measured by the 6MWT was significantly improved after one year of treatment with natalizumab [Svenningsson et al., 2013]. We could now show that improvement in walking ability also correlated with reduced sickness benefit. That supports the significance of 6MWT as method to evaluate community ambulation, as walking at work [Kiseier et al., 2012].

The WAQ do not only bring information about number of hours employed and worked hours but also about how the individuals estimated their perceived physical and cognitive work ability in relation to the work requirements and perceived MS-related fatigue during the working day. The

individuals reported that they could cope with the physical and mental requirements of their work significantly better after one year of treatment with natalizumab and this was regardless of whether the individual had sickness benefit before start of treatment or not. It is therefore reasonable to assume that even if it was not possible to detect an increase in worked hours for those individuals that already worked full-time before the treatment started, the perception of coping better with work-related requirements will make it likely for them to keep their full-time working situation.

### **Health economics effects of DMD**

Health economic calculations show that after one year of treatment with natalizumab, the increased productivity corresponded to an economic value of 3216 euro per person per year. When restricting the analysis to those having an employment and sickness benefit or disability pension at baseline (n=71), the productivity gain increased to 8185 euro per person per year. It was also shown that patients with shorter disease duration had a higher probability of increasing their productivity, and that shorter disease duration was associated with a greater productivity gain.

Our findings are in line with those of Augustsson et al. who found that treatment with modern biological drugs in patients with rheumatoid arthritis was associated with increased work ability [Augustsson et al., 2010]. Individuals with rheumatoid arthritis, in line with individuals with MS, typically experience a decreasing ability to work as the disease progresses. Kobelt et al. have estimated the cost effectiveness by using natalizumab for the treatment of MS in Sweden by using a modeling approach with inputs from the study by Berg et al. as well as a randomised clinical trial of natalizumab compared with placebo in relapsing MS [Berg et al., 2006, Kobelt et al., 2008, Polman et al., 2006].

### **Work ability in a contemporary MS-population compared with a historical MS-population not exposed to immunomodulating drugs**

In paper IV, it was found that the proportion of individuals with any degree of sickness absence or disability pension was significantly reduced in the MS population that had been exposed to immunomodulating drugs compared to an MS population that had never been exposed to these treatments. Furthermore, the MS population that had been subjected to immunomodulatory treatments also had access to more systematic work-promoting measures.

In Sweden, disease-modifying drugs have been available from 1995 but during the first 5–10 years the prescription of these drugs were quite

restrictive reserving it for patients with high inflammatory disease activity. It was not until natalizumab was introduced in 2006 that disease-modifying treatment appeared to demonstrate the stabilization of the disease more profoundly [Polman et al., 2006]. Apart from a more prominent effect on the inflammatory activity, less side effects and a positive effect on MS-related fatigue may have contributed to this observation [Svenningsson, 2013; Iaffaldano, 2012].

Our data showed that EDSS once again was one of the main predictors for reduced work ability, the higher EDSS the less likelihood for retained work ability. However, there were still differences in work ability in relation to different EDSS levels when comparing the 2013 and 1997 populations. Between EDSS 1-6.5 a higher proportion of patients without or with part-time sickness absence were seen in the 2013 population. This emphasises that, systematic work-promoting interventions and different vocational rehabilitation interventions probably are of great importance to preserve work ability.

### **The impact of immunomodulating treatments and adjusted work conditions on the working ability**

In our last study two otherwise similar urban Swedish MS populations were shown to differ significantly in the overall degree of sickness absence. Possible explanations for this may be differences in the use of DMD in patients with active disease as well as successful adaptation of work requirements for the patients with disability. The comprehensive instrument used to investigate the ability to work in relation to work requirement, WAQ-MS, seems to be of high validity for collecting such data.

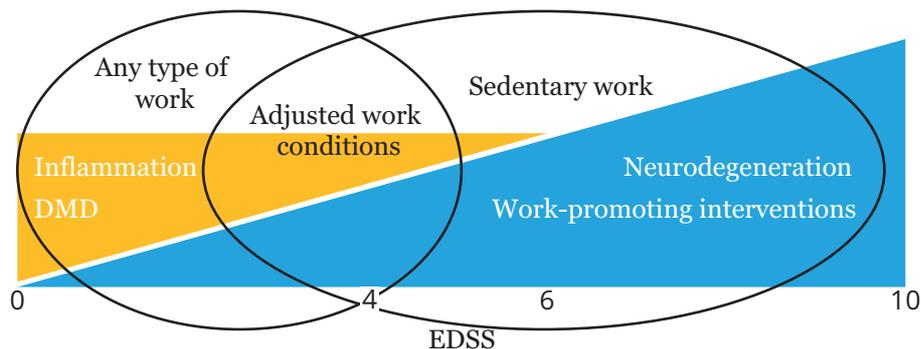
The proportion of individuals with MS who belonged to the work force or were studying was significantly higher in the northern compared with the southern cohort. The two municipalities are comparable regarding job structures, proportion of unemployed and sickness absence. In both areas all patients with RRMS are offered treatment with DMD in early stages of the disease. However, at the northern clinic there has been a systematic strategy for use of the second-generation DMDs as first-line treatment in the early stages of the disease. This strategy will likely yield a more stable disease without side effects of the first-line injectable treatments.

This approach also means that patients can be maintained in RR phase for a longer time. In paper IV, we compared an untreated historical population with a treated population from the same area and found that the proportion of patients with RR disease course increased. We also found that sickness absence decreased overall within the RRMS group from 1997 to 2013. This points towards a positive effect of DMD, with a more stable disease without

side effects, on the work ability. A recently published Norwegian study showed that people with MS in RR phase had greater opportunity to remain in employment [Boe Lunde et al., 2014].

Besides delaying disease progression by treatment with DMD, work ability is influenced by the specific requirements regarding physical and mental ability that is specific to each type of employment. Our study shows that the work tasks in the northern cohort involved significantly less physical demands compared with the southern cohort. This may be one of the reasons why these patients retained their work ability significantly more than in the southern cohort, also when they due to axonal loss accounts for progressive neurologic disability progression of the disease with increasing EDSS levels. This was seen whether or not they had reached the progressive stage of the disease and was irrespective of grade of EDSS.

In paper IV we showed that there were differences in work ability within several EDSS groups when comparing the 2013 and 1997 populations. Within lower EDSS levels the inflammation and tissue damage was effectively reduced making the disease more stable, which may have an impact of the working ability. In the EDSS levels 2-6.5 an increased proportion of patients with no sickness absence and sickness absence on part-time were seen in the 2013 population, indicating that it is possible to adapt the work situation for people at median EDSS levels so that they can study or work to a higher degree. This emphasises that, besides slowing the underlying disease process to maintain as low EDSS as possible, systematic work promoting interventions may further improve work ability.



**Figure 24.** Proposed model for different strategies to preserve work ability in different stages of MS. Our studies emphasise the importance of anti-inflammatory treatments with a low profile of side effects in the inflammatory phase. When non-reversible neurologic disability occur there is need for adjusted work conditions even for patients with lower EDSS. In the degenerative stage with progressive neuronal loss and higher EDSS, sedentary work or energy saving mobility devices, such as wheel chair or seated segway, are required. Inspired of Kuhlmann et al. *Brain* 2002; 125: 2202-12, Palillo et al. *J Neurol* 2004; 251: 42-9.

The instrument WAQ-MS appeared to give valuable and relevant information regarding key elements of work-related conditions and thereby indicating its potential usefulness in a clinical setting. Especially when reaching EDSS grades 3 or more, the two investigated populations displayed significant differences regarding both work requirements and perceived capacity to cope with them. Since this information appeared to correlate with actual ability to remain in work, the WAQ-MS should be used already at low EDSS levels, so that warning signs for inability to work may be detected in time in order to start work-related interventions in time to prevent long-term sickness absence.

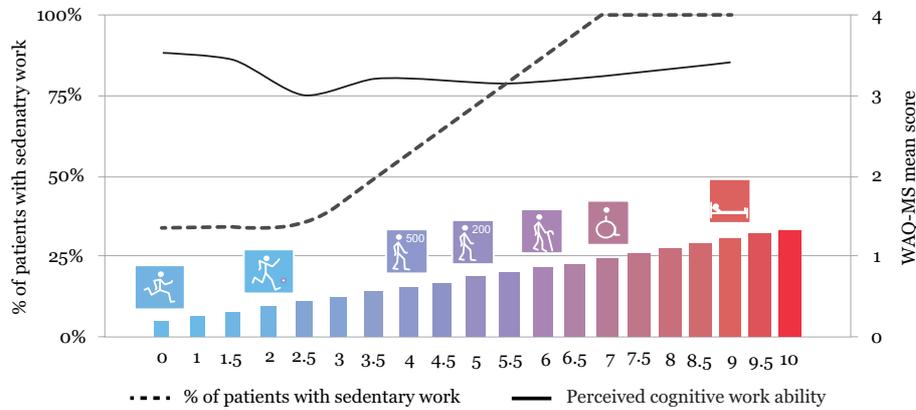
In our last study the content validity of WAQ-MS was analysed to ensure that each item in the questionnaire was representative and clear and describing the concept of working ability in MS. The CVI for the relevance and clarity of the items deemed good Content validity measured by experts and lay experts (Table 3). The total content validity was good with a total CVI of 0,97. This reinforces WAQ-MS clinical usability in a clinical setting but it requires further development and psychometric testing.

Specific rehabilitation efforts probably also play an important role for work ability. In the mid 1990s a comprehensive rehabilitation course for people with early MS was established at the northern neurology department. The aim of the course was to increase knowledge about the disease, DMD and factors affecting studies and work ability and also to equip the patients with tools to influence their own work and study situation [Wickström et al., 1996, Wickström, 1997]. 72 % of the northern cohort had participated in this course. To understand the symptoms of the disease and their management for the individual patient in relation to their workplace, pointed out as an important factors in a recently published study for MS patients who were unstable in their work [Bronwyn 2014]. The multidisciplinary professional team at the department has also focused on detecting early signs of work-related inability and included these questions in the continuous team evaluations.

The southern clinic offered since several years a brief information course for patients early in the disease. The clinic has also started a systematic work-promoting approach, but not yet with effects on group level.

Analysis of perceived ability in relation to different EDSS levels, showed a good workability at EDSS 0, even in full-time work. The proportion with sedentary work at this EDSS level was about 30 % and in total, the southern and northern cohorts were equal when comparing different work related factors. The disease affected perceived work ability due to fatigue and decreased cognitive ability already from EDSS 1-2.5. At EDSS 3-3.5 the proportion with sedentary work increased linearly with worsening of EDSS

in the northern cohort. The change in work condition seems to result in an improved physical and cognitive ability. In the northern cohort the tasks were more frequently adapted to the disease and the adaptation was more pronounced at higher EDSS. Several studies pointed out inadequate cognitive ability as a problem during workday in MS [Boe Lunde et al., 2014, Multiple Sclerosis International Federation, Ruet et al., 2013]. Interestingly, it seems that patients in the northern cohort, perceived good cognitive ability at different EDSS levels even at high EDSS levels.



**Figure 25.** The illustration shows how patients in the northern cohort perceived their cognitive ability in different EDSS levels. Due to transition to sedentary work and energy saving mobility devices, even those with progression of EDSS, could maintain a good perceived cognitive work ability (WAQ-MS mean score more than 3). The illustration is based on analyses from paper V, the employees of the northern cohort. The broken line shows percentage of patients with sedentary work and the solid line shows WAQ-MS mean score of perceived cognitive work ability. The EDSS is adapted from Kurtzke JF. *Neurology* 1983; 33: 1444-52.

It seems that work-related physical requirements will affect the possibility to work more pronounced when the patient reach a higher disability. It is important to note, however, that our data show associations and it is therefore not possible to draw firm conclusions regarding causality. There are several confounders that may have influenced the results e.g. differences in the labour market and acceptance of sickness absence by the Social Insurance Agency, both of which may vary over time and geographically.

## **6. Conclusion and future perspectives**

This thesis supports that the majority of Swedish MS patients aged 18-64 years are able to work or study, but that this requires systematic efforts from the health care as well as employers. Optimal immunomodulating therapy from disease onset as well as adapted working conditions, when the work ability does not correspond to the demands, is of great importance. Also from a health economic perspective our studies support the use of modern disease-modifying drugs. Future studies need to address the question of long-term effects on work ability from immunological and work-promoting treatment interventions. We intend to apply WAQ-MS prospectively in a cohort of MS patients in order to further assess its value in clinical practice.



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## 8. References

- Ahlgren C, Odén A, Lycke, L. High nationwide prevalence of multiple sclerosis in Sweden. *Mult Scler*, 2011 17: 901-8.
- American Educational Research Association APA, and National Council on Measurement in Education. 1999. Standards for educational and psychological testing. Washington, DC.
- Augustsson J, Neovius M, Cullinane-Carli C, et al. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). *Ann Rheum Dis* 2010; 69: 126-31.
- Berg J, Lindgren P, Fredrikson S, et al. Costs and quality of life of multiple sclerosis in Sweden. *Eur J Health Econ* 2006; 7: 75-85.
- Boe Lunde HM, Telstad W, Grytten N, et al. Employment among patients with multiple sclerosis - A population study. *Plos One* 2014; 9: e103317.
- Bronwyn J, Sweetland J, Riazi, et al. Staying at work and living with MS: a qualitative study of the impact of a vocational rehabilitation intervention. *Disability and Rehabilitation* 2014; 36: 1594-9.
- Compston A, Coles A. Multiple sclerosis. *Lancet* 2008; 372: 1502-1517.
- Fernández O, Baumstarck-Barrau K, Simeoni MC, et al. Patient characteristics and determinants of quality of life in an international population with multiple sclerosis: Assessment using the MusiQoL and SF-36 questionnaires. *Mult Scler* 2011; 17: 1238-49.
- Flensner G, Landtblom AM, Söderhamn O, et al. Work capacity and health-related quality of life among individuals with multiple sclerosis reduced by fatigue: a cross-sectional study. *BMC Public Health* 2013; 13: 224.
- Goldman M, Marrie R, Cohen J. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Mult Scler* 2008; 14: 383-90.
- Gronning M, Hannisdal E, Mellgren S. Multivariate analyses of factors associated with unemployment in people with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1990; 53: 388-90.
- Honan C, Rhonda F, Donald W, et al. The Multiple Sclerosis Work Difficulties Questionnaire. *Mult Scler* 2012; 18: 871-80.
- Iaffaldano P, Viterbo R, Paolicelli D, et al. Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis: a prospective, open-label, two years observational study. *PloS one* 2012; 7: e35843.
- Ilmarinen J. Aging and work - coping with strengths and weaknesses. *Scandinavian Journal of Work, Environment & Health* 1997; 23: 3-6

- Ilmarinen J. Aging workers. *Occup Environ Med* 2001; 58: 546-52.
- Ilmarinen J. Work ability – a comprehensive concept for occupational health research and prevention. *Scandinavian Journal of Work, Environment & Health* 2009; 35: 1-5.
- Johansson G, Lundberg O, Lundberg I. Return to work and adjustment latitude among employees on long-term sickness absence. *J Occup Rehabil* 2006; 16:185-95.
- Khademi M, Dring A, Gilthorpe J, et al. Intense inflammation and nerve damage in early multiple sclerosis subsides at older age: a reflection by cerebrospinal fluid biomarkers. *PLoS One* 2013; 8: e63172.
- Kieseier BC and Pozzilli C. Assessing walking disability in multiple sclerosis. *Mult Scler* 2012; 18: 914-24.
- Kobelt G, Berg J, Lindgren P, et al. Modeling the cost-effectiveness of a new treatment for MS (natalizumab) compared with current standard practice in Sweden. *Mult Scler* 2008; 14: 679-90.
- Kuhlmann T, Lingfeld G, Bitsch A, et al. Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. *Brain* 2002; 125: 2202-12.
- Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444-52.
- Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; 83: 278-86.
- Lynn, M. Determination and quantification of content validity. *Nursing Research* 1986; 35: 382-385.
- McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; 50:121-7.
- McFadden E, Horton MC, Ford HL. Screening for the risk of job loss in multiple sclerosis (MS): development of an MS-specific Work Instability Scale (MS-WIS). *Mult Scler* 2012; 18: 862-70.
- McGartland R, Berg-Weger M, Tebb S, et al. Objectifying content validity: conducting a content validity study in social work research. *Social Work Research* 2003; 27: 94-104
- Messmer Uccelli M, Specchia C, Battaglia MA, et al. Factors that influence the employment status of people with multiple sclerosis: a multinational study. *J Neurol* 2009; 256: 1989–96.
- Mews I, Bergmann M, Bunkowski S, et al. Oligodendrocyte and axon pathology in clinically silent multiple sclerosis lesions. *Mult Scler* 1998; 4: 55-62.
- Multiple Sclerosis International Federation. MSIF survey on employment and MS. Global survey: Multiple Sclerosis International Federation 2010 April. <http://www.msif.org/wp-content/uploads/2014/10/Survey-on-employment-and-MS.pdf>.

- Paolillo A, Piattella MC, Pantano P, et al. The Relationship between inflammation and atrophy in clinically isolated syndromes suggestive of multiple sclerosis; A monthly MRI study after triple-dose gadolinium-DTPA. *J Neurol* 2004; 251: 432-9
- Penner IK, Raselli C, Stöcklin M, et al. The Fatigue Scale for Motor and Cognitive Functions (FSMC): Validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* 2009; 15: 1509–17.
- Polman C, Reingold S, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald criteria”. *Ann Neurol* 2005; 58: 840-6.
- Polman C, O’Connor P, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 899-910.
- Polman C, Reingold S, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292-302.
- Pompeii L, Moon S, McCrory D. Measures of physical and cognitive function and work status among individuals with multiple sclerosis: a review of the literature. *J Occup Rehabil* 2005; 15: 69-84.
- Poser C, Paty D, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; 13: 227-31.
- Poser C. Onset symptoms of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1995; 58: 253-4.
- Putzki N, Fischer J, Gottwald K, et al. Quality of life in 1000 patients with early relapsing–remitting multiple sclerosis. *Eur J Neurol* 2009; 16: 713-720.
- Ruet A, Deloire M, Hamel D, et al. Cognitive impairment, health-related quality of life and vocational status at early stages of multiple sclerosis: a 7-year longitudinal study. *J Neurol* 2013; 260: 776-84.
- Salzman S. The 6-min walk test: Clinical and research role, technique, coding, and reimbursement. *Chest* 2009; 135: 1345-52.
- Schulper M. The role and estimation of productivity costs in economic evaluation. In: Drummond M, McGuier A, editors. *Economic evaluation in health care*. Oxford: Oxford University Press, 2001.
- Steiner, D.L. & Norman, G.R. 2008. *Health measurement scale. A practical guide to their development and use*. (4<sup>nd</sup> ed). Oxford. Oxford University Press.
- Svenningsson A, Falk E, Celius E, et al. Natalizumab treatment reduces fatigue in multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. *PLoS One* 2013; 8: e58643.
- Sundström P, Nyström L, Svenningsson A, et al. Sick leave and professional assistance for multiple sclerosis individuals in Västerbotten County,

- northern Sweden. *Mult Scler* 2003; 9: 515–520.
- Tedeholm H, Lycke J, Skoog B, et al. Time to secondary progression in patients with multiple sclerosis who were treated with first generation immunomodulating drugs. *Mult Scler* 2012; 19: 765-774.
- Tortorella C, Bellacosa A, Paolicelli D, et al. Age-related gadolinium-enhancement of MRI brain lesions in multiple sclerosis. *J Neurol Sci* 2005; 239: 95–9.
- Trapp B, Ransohoff R, Rudrick R. Axonal pathology in multiple sclerosis: relationship to neurologic disability. *Curr Opin Neurol* 1999; 12: 295-302.
- Tuomi K, Ilmarinen J, Jahkola A, et al. AFM-indexet: en metod att bedöm och uppfölja arbetsförmåga. Helsinki: Finnish Institute of Occupational Health, 1998.
- Verdier-Taillefer M, Sazdovich V, Borgel F. Occupational environment as risk factor for unemployment in multiple sclerosis. *Acta Neurol Scand* 1995; 92: 59-62.
- Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. *Brain* 1989; 112: 1419-28.
- Wickström A, Ekstedt J. Armament for the future. Neurological Rehabilitation, Newcastle upon Tyne, UK 1996
- Wickström A. Rusta-rapporten. Tidig rehabilitering för personer med multipel skleros inom rehabilitativ neurologi. The Department of Community Medicine and Rehabilitation, Umeå University, Umeå, 1998. (in Swedish)