The Influence of Physiotherapy and Climate on Functioning in Multiple Sclerosis

Aspects of physical performance, fatigue and health-related quality of life

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Scientific environment

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To Olav

If the brain were so simple we could understand it, we would be so simple we couldn't.

Lyall Watson

Contents

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Abbreviations

ADL	Activities of daily living
AHUS	Akershus University Hospital
AUC	Area under the receiver operating characteristics (ROC) curve
BBS	Berg Balance Scale
Borg RPE Scale	Borg Rating of Perceived Exertion Scale
CGIC	Clinical Global Impression of Change
CIOPIMS	Climate Influence on Physiotherapy in Multiple Sclerosis
CIS	Clinically isolated syndrome
CNS	Central nervous system
CSD	Clinically significant difference
EBV	Epstein-Barr virus
EDSS	Expanded Disability Status Scale
ES	Effect size
FSS	Fatigue Severity Scale
GA	Glatiramer acetate
GLM	General linear models
HRQoL	Health-related quality of life
HUS	Haukeland University Hospital
ICC	Intraclass correlation coefficient
ICF	International Classification of Functioning, Disability and Health
IFN-ß	Interferon-beta
MCID	Minimal clinical important difference
MID	Minimal important difference
MRI	Magnetic resonance imaging

MS	Multiple sclerosis
MSIS-29	The Multiple Sclerosis Impact Scale
MSIS-29 NV	The Multiple Sclerosis Impact Scale, Norwegian Version
NRS	Numerical Rating Scale
PGIC	Patient Global Impression of Change
PPMS	Primary-progressive multiple sclerosis
PRMS	Progressive-relapsing multiple sclerosis
QoL	Quality of life
RMI	Rivermead Mobility Index
ROC	Receiver operating characteristics
RRMS	Relapsing-remitting multiple sclerosis
RVGA	Rivermead Visual Gait Assessment
SDC	Smallest detectable change
SEM	Standard error of measurement
SPMS	Secondary-progressive multiple sclerosis
SSED	Single-subject experimental design
TIS	Trunk Impairment Scale
TUG	Timed Up & Go
UVR	Ultraviolet radiation
VAS	Visual analogue scale
10MTW	10-metre timed walk
2MWT	2-minute walk test
6MWT	6-minute walk test

Abstract

Multiple sclerosis (MS) is a chronic, immune-mediated disease affecting the central nervous system (CNS), caused by interplay between predisposing genes and environment. The disease may result in a wide spectre of functional problems, best treated by a multidisciplinary team of professionals. Physiotherapy has shown to improve physical functioning related to mobility and has been advocated as a major component in rehabilitation in MS. The CNS has the ability to change its function and structure depending on demands, and this neuroplasticity also occurs after damage. The Bobath concept is one of the most used treatment approaches in neurological physiotherapy and is based on knowledge of neuroplasticity, aiming to relearn appropriate movement strategies after damage.

The thesis includes two intervention studies in MS. The first study is presented in Paper I. The second study (the climate study) is presented in Paper III. Data from the climate study are also used to investigate psychometric properties of a translated version of the self-reported health-related quality of life (HRQoL) questionnaire, the Multiple Sclerosis Impact Scale (MSIS-29) (Paper II), and to analyse associations between fatigue versus other variables (Paper IV).

A single-subject experimental design was used in the first intervention study (Paper I), investigating the effect of three weeks of individualized daily outpatient physiotherapy based on the Bobath concept, for two patients being their own controls. Twelve repeated measures were performed over a time period of 17 weeks, using a wide spectre of measurement-tools. We concluded that balance and gait were improved after physiotherapy for the two patients, and that effect of treatment should be further evaluated in a larger study.

In Paper II, the objective was to translate the MSIS-29 into Norwegian and to examine psychometric properties of the Norwegian version for use in the climate study. The questionnaire was answered by 64 patients prior to and at a screening session, and re-answered by 59 patients before and after four weeks of physiotherapy. Internal

consistency (Cronbach's α) was 0.92 for the physical- and 0.85 for the psychological subscale. Reliability by intraclass correlation coefficients were 0.86 for the physical- and 0.81 for the psychological subscale, smallest detectable change being 18.4 and 21.1, respectively. The physical- but not the psychological subscale demonstrated mostly satisfactory associations with other physical measures. Responsiveness by area under the receiver operating characteristics (ROC) curve was satisfactory, 0.83 and 0.76, respectively. As hypothesized, effect size was larger for the physical (1.01) than for the psychological (0.76) subscale after treatment. We concluded that MSIS-29, Norwegian Version demonstrated satisfactory psychometric properties.

In the main intervention study (Paper III) the objective was to examine climate influence on the effect of physiotherapy in MS by comparing the effect of inpatient physiotherapy in a warm (Spain) versus a cold (Norway) climate in a short- and long term perspective. Sixty patients with gait problems and without heat intolerance were included in a randomized cross-over study of 4-week inpatient physiotherapy. Two groups of 30 patients were treated the first year in either Spain or Norway, and switching treatment centre the year after. The 6-minute walk test (6MWT) as the primary outcome measure, and other physical performance and self-reported measures, were used at screening, baseline, after treatment and at three- and six months follow-up. Treatment effects were analysed by mixed models. All assessment tools demonstrated improvement after treatment in both warm and cold climate, but to different degrees. After treatment, the mean walking-distance had increased by 70m in Spain and 49m in Norway ($p=0.060$), and improvement in favour of a warm climate was demonstrated at six months follow-up, 43m (Spain) compared to 20m (Norway) ($p=0.048$). The patients reported less exertion after walking (6MWT) in favour of treatment in Spain at all time points ($p<0.05$). No significant differences in change were detected for the other physical performance measures. Most self-reported measures showed more improvement after treatment in Spain, but these improvements were not sustained at follow-up. The results indicate that MS patients without heat intolerance have additional benefits from physiotherapy in a warm climate.

In Paper IV, we also used data from the first part of the climate study. The aim was to investigate whether fatigue was associated with demographic-, clinical-, HRQoL- and physical performance variables, and whether change in fatigue after treatment was associated with changes in HRQoL and physical performance. Sixty patients were included for inpatient physiotherapy, and fifty-six completed the study. Fatigue (Fatigue Severity Scale; FSS), HRQoL (MSIS-29) and physical performance (walking ability and balance) were assessed at screening, baseline, after treatment and at follow-up after three and six months. We analysed possible associations between FSS and other variables at baseline by regression models, and between change in fatigue versus changes in HRQoL and physical performance variables after physiotherapy, by correlation analysis. We found that fatigue at baseline was associated with HRQoL (explained 21.9 % of variance), but not with physical performance tests. Change in fatigue was correlated with change in HRQoL, but not with changes in physical performance. All measures were improved after treatment ($p \leq 0.001$). While improvements in fatigue and HRQoL were lost at follow-up, improvements in physical performance were sustained for at least six months ($p \leq 0.05$). The findings suggest that fatigue in MS is not associated with physical performance as assessed in our study, but seemed to be associated with the patients' experience of HRQoL.

The results from both intervention studies indicate that physiotherapy based on the Bobath concept may cause improvement in physical performance in MS, in short- and long term perspectives. For patients without heat intolerance, there seems to be a favourable effect of treatment in a warm climate. The translated version of MSIS-29 demonstrated satisfactory measurement properties in line with the original English version and may therefore be recommended used as a measurement tool of HRQoL in patients with MS. If the aim of treatment is improvement of fatigue, a broader intervention, accounting for both physical and psychological aspects, seems necessary.

List of publications

The thesis is based on four papers, referred to by their roman numerals:

Paper I

Smedal T, Lygren H, Myhr KM, Moe-Nilssen R, Gjelsvik B, Gjelsvik O, Strand LI. Balance and gait improved in patients with MS after physiotherapy based on the Bobath concept. *Physiother Res Int* 2006;11(2):104-16.

Paper II

Smedal T, Johansen HH, Myhr KM, Strand LI. Psychometric properties of a Norwegian version of Multiple Sclerosis Impact Scale (MSIS-29). *Acta Neurol Scand* 2009; Epub ahead of print. DOI: 10.1111/j.1600-0404.2009.01298.x.

Paper III

Smedal T, Myhr KM, Aarseth JH, Gjelsvik B, Beiske AG, Glad SB, Strand LI. The influence of warm versus cold climate on the effect of physiotherapy in multiple sclerosis. *Acta Neurol Scand*, resubmitted after minor revisions.

Paper IV

Smedal T, Beiske AG, Glad SB, Myhr KM, Aarseth JH, Svensson E, Gjelsvik B, Strand LI. Fatigue in multiple sclerosis: Associations with health-related quality of life and physical performance. *Eur J Neurol* 2010; Epub ahead of print. DOI: 10.1111/j.1468-1331.2010.03090.x.

1. Introduction

Patients with gait and balance problems caused by disease or damage of the central nervous system (CNS) may profit from individualized physiotherapy. Intervention based on the Bobath concept (Gjelsvik, 2008; Graham et al., 2009) aiming to improve physical functioning through motor learning is frequently used. Knowledge of how the CNS responds to injury and how patients reacquire lost behaviours by training have brought promising new therapies for neurorehabilitation (Taub et al., 2002). The theoretical basis for treatment according to the Bobath concept is neuroplasticity referring to the ability of the CNS to change both its structure and function, as a response to changing demands (Nudo, 2003).

Evaluation of the effect of treatment has changed during the last ten years; from qualitative descriptions of the ability to move, to the use of more quantitative measurements related to limitations in physical functioning. Evidence-based medicine aiming to integrate individual clinical expertise and the best available clinical external evidence from systematic research (Sackett et al., 1996), is strongly advocated in clinical practise today. There may, however, be a conflict between the philosophy behind rehabilitation (in which physiotherapy is one part) and evidence based medicine, as the reductionism commonly employed in clinical trials may be insensitive to the individually tailored aims of rehabilitation medicine. To understand how to integrate new scientific evidence into clinical practice, we should find the correct balance between these two, which may be a challenge (Kesselring, 2004).

This challenge led us to design our first intervention study of this thesis (Paper I), aiming to investigate whether physiotherapy based on the Bobath concept would improve gait and balance in two patients with multiple sclerosis (MS). By using a single-subject experimental design, in which the patients are their own controls, and by using a wide spectre of outcome measures, we also aimed for finding appropriate measurement tools, applicable for a possible future study.

When planning for the second intervention study which was designed as a randomized cross-over study, the choice of measurement tools was partly based on experiences from the initial study. The climate influence on the effect of physiotherapy in MS was investigated, and as a part of this, we also discussed the change observed after physiotherapy, independent of the climate influence. This climate study, which should be considered the main work of this thesis, was carried out during approximately two years, including pre-screening and nine repeated test points over the time period (Paper III).

We choose the Multiple Sclerosis Impact Scale (MSIS-29) for evaluation of health-related quality of life (HRQoL) in the climate study (Hobart et al., 2001). This questionnaire was translated into Norwegian, and important psychometric properties of the Norwegian version were investigated, aiming to assess whether it was applicable for use in the climate study (Paper II).

Fatigue is one of the most frequent, but least understood symptoms in MS (Lapierre & Hum, 2007). The associations between fatigue and physical performance measures have previously scarcely been investigated. Data from the first part of the climate study were analysed for possible associations between fatigue and clinical- and demographical baseline characteristics as well as HRQoL and physical performance tests variables (Paper IV).

In our studies we have aimed to explore some important aspects of MS and treatment that may improve functioning.

1.1 Multiple sclerosis

MS is a chronic immune-mediated inflammatory demyelinating disease of the CNS and is the most common non-traumatic disabling neurological condition in young adults (Alonso & Hernan, 2008; Murray, 2006). The disease was first described in 1838, but the first extensive study and description of the disease was done by Jean-

Martin Charcot in 1868, and Joseph Babinski wrote his medical thesis about MS in 1885 (Compston et al., 2005b). The aetiology is still enigmatic, and there is no curative treatment. However, recent studies indicate that MS is triggered by environmental factors in individuals with complex genetic-risk profiles, and several disease modifying preparations have become available (Compston & Coles, 2008).

The patients may experience a variety of symptoms, with recurring themes and an unpredictable course (Compston & Coles, 2002). In most patients, the clinical manifestations indicate involvement of motor, sensory, visual and autonomic systems, in addition to many other symptoms and signs (Compston & Coles, 2008; Noseworthy et al., 2000). In addition to treatment of relapses and immunomodulatory treatments, symptomatic treatments are also important for MS patients. Effective management should require comprehensive and coordinated input from a multi-disciplinary team of professionals, and different settings may be required to best meet the individual's needs (Freeman, 2001). MS is a challenging disease to study, as the course is unknown, the pathophysiologic mechanisms are diverse, and the unpredictable course makes it difficult to determine whether an effect of treatment will sustain (Noseworthy et al., 2000).

1.1.1 Patophysiology

The myelin consists of a condensed membrane spiralled around nerve cells (axons) and forms the insulating segmental sheath needed for saltatory axonal conduction. Voltage-gated sodium channels cluster at the unmyelinated nodes of Ranvier, between the myelin segments. The action potential is propagated and spread passively down the myelinated nerve segment, triggering another action potential at the next node. Thus, the myelin contributes to ensure the high velocity of conducting nerve impulses, resulting in an effective system in bringing messages to and from the brain. In MS, inflammatory demyelination occurs and leads to reduced velocity of impulses. The symptoms of MS reflect the functional anatomy of the impaired conduction at the affected sites (Compston & Coles, 2002). The severity and duration of symptoms and

recovery after an exacerbation are dependant of the intensity and resolution of the process and possibly remyelination. In addition primary or secondary axonal degeneration have been demonstrated, leading to irreversible neurologic impairment (Trapp et al., 1998).

The sequence of events that initiates the disease remains unknown, but given a pathological heterogeneity, it may be that more than one pathological mechanism contributes to tissue injury (Noseworthy et al., 2000). It is presumed that genetic and environmental factors contribute to facilitate the movement of autoreactive T-cells and demyelinating antibodies from the systemic circulation and into the CNS through disruption of the blood-brain barrier. The injury to the myelin membrane results in denuded axons that are no longer able to transmit action potentials effectively within the CNS (Noseworthy et al., 2000). From considering MS as an intermittent disease with inflammatory breakdown of myelin in the white matter, it is now evident that the disease is more continues, with diffuse changes in the white and grey matter, breakdown of myelin and damage to axons (Murray, 2006). As a result of these pathological processes, all parts of the CNS may be affected, leading to the production of various neurological clinical symptoms (Noseworthy et al., 2000).

1.1.2 Epidemiology

About 2.5 million people are affected of MS worldwide (Compston & Coles, 2002). A systematic review of incidence studies of MS published in Medline between 1966 and 2007 indicate an overall incidence rate of 3.6 cases per 100.000 person-years in women and 2.0 in men (Alonso & Hernan, 2008). The prevalence varies considerably around the world (Compston & Confavreux, 2005), and MS is considered a place-related acquired disease with a predilection for whites (Kurtzke, 1995). Earlier studies have demonstrated that the incidence of the disease increased with the distance from the equator (Acheson et al., 1960; Miller et al., 1990), but the latitude gradient presented in older incidence studies seems to be decreasing (Alonso & Hernan, 2008). The highest prevalence of MS is seen in the Northern Europe, southern Australia and

in the northwest of the United States and southern parts of Canada (Compston & Confavreux, 2005; Kurtzke, 1995). African Americans develop MS less frequently than Caucasian Americans (Kurtzke et al., 1979), but African Americans seem to have a more aggressive disease course (Cree et al., 2004). Caucasians from Scandinavian and Scottish origin seem to be especially susceptible to the disease (Hogancamp et al., 1997; Page et al., 1993; Rothwell & Charlton, 1998), and it has even been suggested that the distribution of MS may be a result of Viking raids in the Middle Ages (Poser, 1995). The prevalence in Norway is around 150/100.000, but somewhat lower in the northern parts of the country (Gronlie et al., 2000; Grytten et al., 2006; Torkildsen et al., 2007). The Norwegian MS population is estimated to around 7000 (prevalence) (Torkildsen et al., 2007), with an incidence of about 5-6/100.000 (Celius & Vandvik, 2001; Dahl et al., 2004; Grytten et al., 2006) in recent years. The incidence has been estimated increased from 1.8 per 100.000 in 1953 to 1957, to 6.0 per 100.000 in 1993 to 1997 (Grytten et al., 2006).

Both incidence and prevalence are approximately twice as high among woman as in men (Hirtz et al., 2007; Noseworthy et al., 2000). An increase in the female/male incidence ratio has been reported in recent decades for both Canada (Orton et al., 2006), northern Sardinia (Pugliatti et al., 2009) and northern France (Debouverie et al., 2007), and a recent systematic review conclude that the female-to-male ratio incidence has increased over time from an estimated 1.4 in 1955 to 2.3 in 2000 (Alonso & Hernan, 2008).

The mean age of MS onset is approximately 30 years, and few cases are diagnosed before the age of 15 or after the age of 50 (Hirtz et al., 2007).

1.1.3 Aetiology

Although MS has been described for more than a century, the cause of the disease is still unknown. Epidemiologic studies support both genetic and environmental components, and the most accepted theory is that MS is an immune-mediated disease

with genetic susceptibility requiring an additional environmental factor (Ascherio & Munger, 2007b; Ascherio & Munger, 2007a; Compston & Coles, 2008; Kahana, 2000; Pugliatti et al., 2008).

1.1.3.1.Genetic factors

Most MS cases occur sporadically, but about 20 % of patients have at least one affected relative, indicating that there is evidence for genetic factors in MS (Kahana, 2000; Nielsen et al., 2005). As early as 1972, human leukocyte antigen genes were found to be associated with MS (Jersild et al., 1972). Recently, several other immune related genes have been identified, amongst them IL2RA and IL7RA (Hafler et al., 2007), and numbers are increasing (MSGene, 2010).

1.1.3.2 Environmental factors

An observed change in the attenuation of the latitude gradient also suggest that in addition to genetic determinants, one or more environmental factors may play a role in the aetiology of MS (Alonso & Hernan, 2008). Migrants, who move from an area where MS is common into an area where it is rarer, show a decrease in rate of disease, while people who migrate in the opposite direction tend to retain the low risk of their country of origin (Gale & Martyn, 1995). Age of migration within the first two decades of life has been considered important in determining MS (Alter et al., 1978; Dean & Kurtzke, 1971). However, similar prevalence of MS in individuals who migrated before the age of 15 and those who migrated at older age has been demonstrated (Hammond et al., 2000), which may indicate that the environmental exposures may operate over a wide range of ages within the latent period (Pugliatti et al., 2008). A recent study was performed trying to identify the cause of increased incidence of MS in French West Indies. The following environmental modifications were suggested: return-migration from the mainland France and changes in lifestyle including less sun exposure and improved hygiene (Cabre, 2009).

Today, the most plausible environmental risk factors in MS seem to be: Epstein-Barr virus (EBV) infection (Ascherio & Munger, 2007a), vitamin D/sun exposure deficiency (Kampman et al., 2007; Kampman & Brustad, 2008) and smoking (Ascherio & Munger, 2007b; Riise et al., 2003).

The role of EBV in the aetiology of MS has been indicated in several studies (Myhr et al., 1998; Nielsen et al., 2007; Sumaya et al., 1985), and the EBV is the only infection agent which has been found to be a risk factor. Risk of MS is about 10 times grater among individuals who experienced an undiagnosed EBV infection in childhood, and at least 20 times greater among individuals who developed mononucleosis, which is often the expression of EBV infection during adolescence or adulthood (Ascherio & Munger, 2007a). The risk of MS may be increased soon after infectious mononucleosis and persists for at least 30 years after the infection (Nielsen et al., 2007).

Vitamin D has been shown to suppress the immune response mediated by T-cells, which are known to be important in the MS disease process (Gorman et al., 2007). There is indication that a functional variant of the vitamin D receptor gene interacts with the sun exposure in childhood to influence the risk of MS (Dickinson et al., 2009), and the role of vitamin D/sun exposure has been demonstrated in several studies. Higher sun exposure during childhood and early adolescence seems to be associated with a reduced risk of MS, and insufficient ultraviolet radiation (UVR) may influence the development of MS (van der Mei et al., 2003; Dalmay et al., 2010). Even north of the Arctic Circle, summer outdoor activities in childhood and adolescence may be associated with a reduced risk of MS, and supplemental cod-liver oil may be protective when sun exposure is less. This suggests that both climate and diet may interact to influence MS risk at a population level (Kampman et al., 2007; Kampman & Brustad, 2008). Interestingly, the MS prevalence in Norway does not increase with latitude (Kampman et al., 2007) and may be explained by the tradition of extensive fish diet in a location with low solar UVR (Kampman & Brustad, 2008). A tendency of more indoor activities and a diet containing less vitamin D, may account for the increasing incidence of MS in Norway, and also in the indigenous Sami (Pugliatti et al., 2008). In general, changes in lifestyle may be associated to decreased sun

exposure, resulting in lower synthesis of vitamin D, and this may partly explain the attenuation of the latitude gradient (Alonso & Hernan, 2008). The relationship between MS, geographic distribution, sunlight exposure and vitamin D is also discussed in a review article of Ascherio and Munger (2007b), concluding that sun exposure/vitamin D may reduce the risk of MS. Considering that vitamin D is associated with MS, protection could possibly be achieved with doses of vitamin D supplements (Ascherio & Munger, 2007b; Myhr, 2009; Niino et al., 2008; Smolders et al., 2008). An association between risk of MS and the season of birth, has been described (Bayes et al., 2010; Salzer et al., 2010; Willer et al., 2005), and a deficiency of active vitamin D due to reduced sun exposure during the pregnancy, may play a role, but should be further investigated (Salzer et al., 2010). For people who have developed MS, season variations of relapse rate and active MRI lesions have been reported in some studies, (Auer et al., 2000; Bamford et al., 1983; Ogawa et al., 2004), but not confirmed in others (Killestein et al., 2002; Rovaris et al., 2001). In summary, the complex interrelationship between ultraviolet radiation, vitamin D, infections and relapse rates require further investigation (Tremlett et al., 2008).

Cigarette smoking seems to be a risk factor for MS (Ascherio & Munger, 2007b), and a Norwegian study demonstrated that the risk of developing MS among individuals who smoked, was nearly twice as high as in never-smokers (Riise et al., 2003). Furthermore, an acceleration in transition from relapsing-remitting MS (RRMS) to secondary progressive MS (SPMS) has been demonstrated in smokers (Hernan et al., 2005). The relation between smoking and risk of MS, may, in part explain the recently reported increase in the female/male ratio in MS incidence (Ascherio & Munger, 2007b).

1.1.4 Diagnosis

MS is a clinical diagnosis, based on a careful neurological examination, and the patient history is essential in the diagnostic process. There is no pathognomonic test for MS, and the diagnostic criteria have changed according to new knowledge and technology.

Since the early 1980s, the Poser criteria were used. MS was indicated if the patient had at least two relapses and there were evidence of involvement in white matter in more than one cite in the CNS (Murray, 2006; Poser et al., 1983). When clinical criteria were not met, paraclinical abnormalities within the CNS made it possible to supplement the clinical evidence of the disease. Imaging, electrophysiology and cerebrospinal fluid examinations for oligoclonal bands were used as supplements. The McDonald criteria is a newer system of classification which also incorporate magnetic resonance imaging (MRI), aiming to demonstrate dissemination of disease both in time and space (McDonald et al., 2001). These criteria allow an accurate diagnosis of MS before the appearance of a second attack, enabling earlier decision about starting disease modifying therapies, and a further revision of the McDonald criteria was published in 2005 (Polman et al., 2005).

1.1.5 Course of the disease and prognosis

The clinical course of MS in an individual patient is largely unpredictable and may follow a variable pattern over time (Noseworthy et al., 2000). The most common courses are either episodes of acute periods of worsening (relapses, exacerbations, attacks), or a more gradual progressive deterioration, or combinations of both (Lublin & Reingold, 1996). Relapsing-remitting MS (RRMS) is defined as “clearly defined disease relapses with partial or full recovery; periods between relapses characterized by a lack of disease progression (Lublin & Reingold, 1996). About 80-85 % of patients present with a RRMS form, and a first attack is categorised as a clinically isolated syndrome (CIS) (Murray, 2006; Noseworthy et al., 2000). About 15 % of patients with MS show a slowly progressive pattern without relapses, and this course is classified as a primary-progressive MS (PPMS). The definition of PPMS is ”a disease progression form onset with occasional plateaus and temporary minor improvements allowed” (Lublin & Reingold, 1996). PPMS may be suggested clinically by a progressive course that lasts longer than six months, but laboratory studies are advised to obtain supportive evidence (Noseworthy et al., 2000). A few of the patients with PPMS may

later relapse, called progressive-relapsing MS (PRMS) (Lublin & Reingold, 1996; Murray, 2006). Classification of MS is important, as the disease modifying drugs have shown benefit only in the RRMS and not on PPMS (Murray, 2006). It has been suggested that within 25 years duration of disease, the majority (90 %) of patients with RRMS will develop a secondary-progressive MS (SPMS) (Weinshenker et al., 1989) defined as "initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus" (Lublin & Reingold, 1996). Clinical subtypes of MS are presented in Figure 1.

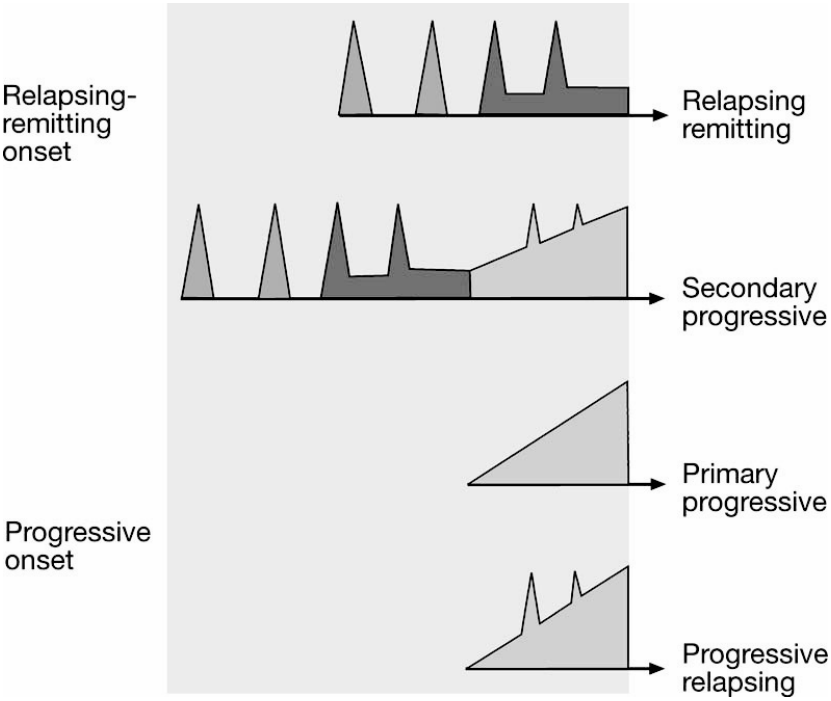

Figure 1. *Clinical subtypes of MS. The figures show the four main courses of MS. (Adapted from Figure 4.7, page 195 in: Compston et al., 2005a)* .

The clinical severity can be divided into "benign " and "malign" MS. Benign MS has been defined as a "disease in which the patient remains fully functional in all

neurologic systems 15 years after disease onset", while malign MS is characterized by "a rapid progressive course, leading to significant disability in multiple neurological systems or death in a relatively short time after disease onset" (Lublin & Reingold, 1996).

The median survival time from onset has been estimated approximately 10 years shorter for patients with MS than for the age-matched general population (Bronnum-Hansen et al., 2004). Female patients and patients with young onset seem to have longer median time to death, but higher relative risk of dying compared with the corresponding population. Patients with PPMS have demonstrated both shorter median time to death from onset and a higher relative risk of dying (Grytten et al., 2008).

1.1.6 Clinical symptoms

MS is characterised by symptoms which are mainly determined by the location of the plaques in the brain and the spinal cord (CNS), the burden of the lesion and the effectiveness of repair and compensatory mechanisms. The disease may result in movement difficulties including gait- and balance problems due to muscular weakness, spasticity, ataxia and tremor. Other common manifestations are: visual and sensory disturbances, pain, fatigue, speech and swallowing difficulties, bladder-, bowel- and sexual dysfunctions, cognitive and mood changes and hypersensitivity to external and internal temperature increases (Alusi et al., 2001; Boissy & Cohen, 2007; Noseworthy et al., 2000; Ponichtera-Mulcare, 1993; Vazirinejad et al., 2008).

1.1.6.1 The International Classification of Functioning, Disability and Health

The clinical symptoms of MS influence on functioning in different ways, and when assessing the effectiveness of drugs and rehabilitation programmes, the overall functioning should be taken into account (Asano et al., 2009). The World Health Organization's International Classification of Functioning, Disability and Health (ICF)

(World Health Organization, 2001) defines a common language for describing the impact of disease at different components of functioning (Khan & Pallant, 2007). The ICF is a comprehensive and integrated system for describing functioning and disability for a person and is considered a bio-psychosocial model of functioning (Mills et al., 2010). The model (Figure 2) includes Body Functions and Structures and Activities as well as Participation. In addition, Personal and Environmental factors are included as contextual factors. Functioning is a term including all body functions, activities and participation, while disability serves as a term for impairments, activity limitations or participation restrictions (Stevenson & Playford, 2007). Dimensions of functioning are affected by interactions between health conditions and contextual factors (environmental and personal). These components (except for personal factors) contain more than 1400 ICF categories (Kesselring et al., 2008). The ability of the ICF categories to describe the spectrum of functioning and disability as well as environmental factors in MS has been demonstrated (Holper et al., 2010). "Core Sets" are lists of ICF categories considered to be most relevant for patients having a particular health condition, and development of Core Sets for MS is now in process (Kesselring et al., 2008).

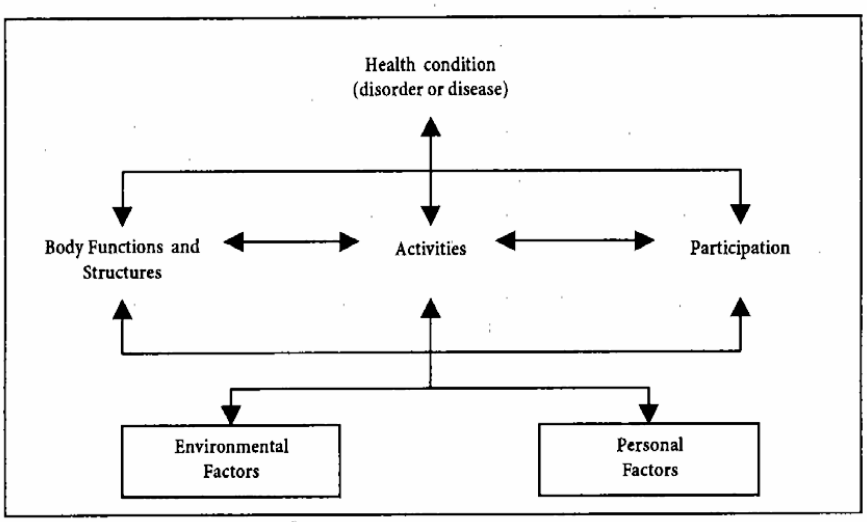

Figure 2. *Interactions between the components of ICF (From Figure 1, page 18 in: World Health Organization, 2001).*

The wide spectrum of clinical symptoms in patients with MS, may affect the different functional components in the ICF model. A multidisciplinary rehabilitation should therefore focus on all components in the ICF model in the context of both environmental and personal factors (Stevenson & Playford, 2007). The main focus in our intervention studies was motor problems, mainly investigated at the Body Functions and Structures and the Activities components. Consequently, these aspects will be highlighted through the thesis. However, the importance of other symptoms should be emphasized, also having in mind how a patient copes with different problems, also influenced by socio-cultural-, psychological,- economic,- and environmental factors (Freeman, 2001).

1.1.6.2 Motor symptoms

Lesions in the pyramidal tracts (motor system) as well as brainstem, cerebellum and vestibular nuclei, may lead to disorders related to motor control. Symptoms like spasticity, ataxia, tremor, muscular weakness, fatigue and sensory disturbances may lead to reduced movement control (McDonald & Compston, 2005). When treating movement disturbance in patients with MS, it is important to explore which CNS systems that are affected by the disease and the functional consequences for the patient. Treatment should be adjusted accordingly.

Gait- and balance disturbances due to weakness, spasticity and ataxia are commonly seen in patients with MS (Olgiati et al., 1988; Rodgers et al., 1999; Soyuer et al., 2006; Thompson, 2001). Patients report gait as one of the most valuable functions (Heesen et al., 2008). Factors reported to cause increased risk of accidental falls in MS are changed gait pattern, limited walking ability, impaired proprioception and vision, spasticity, divided attention, reduced muscular endurance, fatigue and heat sensitivity (Nilsagard et al., 2009). The ability to maintain balance in standing seems to be a marked problem (Frzovic et al., 2000), and low scores on balance and gait tests have been reported as significant predictors of perceived difficulties or dependence in activities of daily living (ADL) (Paltamaa et al., 2007). After 15 years, the probability

of managing without walking assistance is estimated to about 60 % and managing without a wheelchair, about 76 % (Myhr et al., 2001).

1.1.6.3 Other symptoms

Severe reduction in visual activity may follow serial episodes of optic neuritis or may be a result from progressive visual loss. Visual disturbances may also relate to diplopia due to brain stem lesions. Vertigo, dysarthria and dysphagia may be other disabling brainstem symptoms (Thompson, 2001).

Involvement of the autonomic nervous system is frequently observed in MS (McDonald & Compston, 2005), and in particular bladder disturbances are known to have an important impact on quality of life (QoL). In addition, sweating, gastrointestinal and cardiovascular disturbances may cause serious complaints, and it is hypothesised that the autonomic dysfunction may not only be a consequence of the disease, but may in itself affect the course of MS (Flachenecker, 2007). Cardiovascular and sudomotor autonomic abnormalities may not be explained by a lesion at any one site within the CNS, but be due to wide spread abnormalities of the CNS (McDougall & McLeod, 2003). Respiratory insufficiency is another symptom, resulting from respiratory muscle weakness or aspiration (Thompson, 2001).

A high number of persons with MS suffer from “invisible” symptoms, such as fatigue, depression and cognitive dysfunction during both early and late stages of the disease (Stuke et al., 2009).

Fatigue is one of the most frequent, but least understood symptoms in MS (Lapierre & Hum, 2007; Putzki et al., 2008; Stuke et al., 2009) and has been reported as the symptom that interferes most with daily life activities (Kesselring, 2004; Paltamaa et al., 2006). The syndrome of fatigue is characterised by uncontrollable apathy, exhaustion, fatigability and lack of energy which has not been experienced to the same extent before onset of the disease (Zifko, 2004). There is no universally accepted definition of fatigue, but it may be defined as an overwhelming sense of tiredness, lack of energy or feeling of exhaustion (Comi et al., 2001). More recently fatigue has been

defined as “reversible motor and cognitive impairment with reduced motivation and desire to rest. It could appear spontaneously or may be brought on by mental or physical activity, humidity, acute infection and food ingestion” (Mills & Young, 2008). As fatigue seems to be a multidimensional, complex and highly subjective symptom, it is likely that several factors play a role in the origin. Primary fatigue may result from centrally mediated processes like: brain lesions, axonal damage, functional cortical reorganization, immunological and neoroendocrine factors and peripheral mechanisms at muscle level (Kos et al., 2008). In general, patients with MS appear to recruit a more extensive neural network, often bilateral, to maintain proper motor output. This may explain some aspects of the phenomenon of fatigue (Morgen et al., 2004). It has also been suggested that impaired central motor activation is due to interruption of the cortico-subcortical motor circuits involving the motor cortex (Andreasen et al., 2010) and that fatigue could be due to a higher brain working load required to perform a mental or physical activity, or to an internal overestimation of such load (Leocani et al., 2008). Secondary factors, which may lead to fatigue, are sleep disorders, reduced activity, psychological factors and depression. Due to the heterogeneity of the fatigue symptom, both primary and secondary fatigue can be present in one individual, and they may also have an impact on each other (Kos et al., 2008). Fatigue and depression in MS have been found to be unrelated to disease progression and seem to persist at about the same level over time (Koch et al., 2008). However, fatigue in MS has shown inverse correlation with self-esteem, suggesting that fatigue may interfere with the way in which patients value themselves (Fragoso et al., 2009). It has also been suggested that physical activity is indirectly associated with QoL through pathways that include fatigue, pain, social support, and self-efficacy in individuals with MS (Motl & McAuley, 2009), but the effects of exercise on fatigue are inconsistent (Heesen et al., 2006). The first step in managing MS-related fatigue may be to identify and try to eliminate any secondary causes (Zifko, 2004), and it has been suggested that treatment of fatigue requires a multidisciplinary approach (Kesselring, 2004).

Anxiety and depression is a more frequent problem for patients with MS as compared to the general population, which has recently been confirmed in two Norwegian studies (Dahl et al., 2009; Beiske et al., 2008). There seems to be a need of greater focus also on these aspects to establish appropriate treatment.

Cognitive impairments like deficits of attention, memory and executive function are commonly seen in patients with MS and have great effects both on the patients and their families and friends (McDonald & Compston, 2005). Cognitive rehabilitation strategies have demonstrated some positive effects, but there is a need of larger studies with more standardized treatment and outcome measures (Messinis et al., 2010).

Also pain and sensory complaints are frequent problems in patients with MS and found to be independent of age, gender, and course and duration of the disease. There is a need of determining how these symptoms affect functioning in order to choose the appropriate treatment (Beiske et al., 2004). Pain symptoms have been divided into three categories; tendinoskeletal-, psychogenic- and neurogenic, and pain has been suggested to be more often of neurogenic origin than caused by secondary tendinoskeletal disorders (Vermote et al., 1986). Presence of pain has a negative impact on both QoL and ADL and seems to be an issue that warrants more attention (Grasso et al., 2008).

1.1.7 Health-related quality of life

Quality of life (QoL) embraces all aspects of well being and includes social, emotional, economic and cultural facets of our lives. The term “health-related quality of life” (HRQoL) captures those aspects of life quality or function which are influenced by health status (Benito-Leon et al., 2003). Clinicians focus on HRQoL, although all aspects of life can be health-related in an ill or diseased patient, and two patients with the same clinical criteria may often have completely different responses on HRQoL (Guyatt et al., 1993). HRQoL studies represent a rather new field in MS research, with the first study published in 1992 (Rudick et al., 1992), finding that

patients with MS had the lowest HRQoL as compared to patients with rheumatoid arthritis and inflammatory bowel disease. Impaired mobility and symptoms like fatigue, pain, depression and spasticity seem to be important factors related to reduced QoL (Zwibel, 2009). QoL and HRQoL are multidimensional concepts, based on subjective experiences, and may vary over time and in different situations. The validity of using quantitative instruments to measure a qualitative phenomenon, could be questioned (Torkildsen, 2008). However, there is an increasing understanding that global wellbeing of patients with MS is a valuable outcome in therapeutic trials as it emphasizes neuropsychiatric and social complications as well as impairment and disability components, and therefore may give important information (Benito-Leon et al., 2003).

1.1.8 The effect of heat and climate in MS

A generally accepted opinion is that persons with MS may be sensitive to heat and experience increased MS related symptoms due to increased temperatures. Decreased tolerance for high temperatures has been frequently reported (Simmons et al., 2004). However, the magnitude of increase in temperature that is necessary to precipitate symptoms, appears to be unique to each person, and the relationship between endogenous and exogenous sources of heat versus MS symptoms remains unclear (Ponichtera-Mulcare, 1993). Animal studies have indicated reversible conduction block with increased temperature in partly demyelinated nerve fibres (Rasminsky, 1973), while Uhthoff (1890) described a temporary worsening of vision with increasing core body temperature in patients with optic neuritis. With increasing core temperature, all activities in the body go quicker, and re-myeliniated nerve fibers may have reduced function, leading to temporary increase in symptoms with increased body temperature, such as after exercise or hot bath (Compston & Coles, 2008; Ponichtera-Mulcare, 1993). Scholl et al. (1991) concluded that Uhthoff's symptom was a prognostic indicator for the early development of MS, and for many years, the "hot bath test" (Davis, 1966) was used to diagnose MS. A person suspected of having MS

was immersed in a hot tub of water, and watched to see if neurological symptoms appeared or got worse, which would earn them a diagnosis of MS. The aetiology of the heating reactions may be multifactorial, including heat itself, effects of serum calcium, blockade of ion channels, circulatory changes, heat shock proteins and unidentified humoral substances (Guthrie & Nelson, 1995). On the other hand, cooling therapy has been associated with measurable, but modest improvement in motor and visual function (Schwid et al., 2003).

A study has indicated seasonal variation in MS exacerbations with significantly more attacks in the warmest and coldest months in Japan (Ogawa et al., 2004). However, limited impact on relapses was demonstrated in connection with a summer heat wave in France in 2003 (Tataru et al., 2006). The authors hypothesize that the adverse symptoms associated with high temperature, may require rapid rise in ambient or internal body temperature.

Norwegian patients with MS, who do not experience heat intolerance, have anecdotic reported less stiffness and that it is easier to move in a warm climate.

1.1.9 Medical treatment

There is no curative treatment for MS. However, medical treatment strategies are given in three main areas of intervention: 1) relapses (attack or exacerbation), 2) disease-modifying treatment (first-, second- and third line treatment) and 3) symptomatic treatment of common complaints in MS. The first two aim to influence the inflammation to reduce secondary tissue damage (Myhr, 2008). Relapses usually have a subacute onset and may appear as either new nervous system deficits or as worsening of previous ones, and last for at least 24 hours (McDonald et al., 2001).

Relapses are treated with intravenous or oral methylprednisolone, aiming to speed up the recovery, but there is no evidence for long term effects on the degree of recovery or risk of new relapses (Myhr, 2008; Sellebjerg et al., 2005). A combination of steroids

with planned comprehensive multidisciplinary team care has been suggested to be superior to standard therapy (Craig et al., 2003).

Disease-modifying therapies aim to minimize disease activity to prevent the progression of disability, and four different modifying compounds are available: interferon-beta (IFN-ß), glatiramer acetate (GA), natalisumab and mitoxantrone. Patients with CIS, who have substantial changes in MRI and/or serious functional loss, are treated with first-line treatment; IFN-ß or GA. Patients with RRMS who recently had an attack, should also be treated. Patients with SPMS, but still having some attacks, should be considered for treatment with IFN-ß. Both IFN-ß and GA seem to reduce the relapse rate by about 30 % and MRI disease activity by 50-75 % and seem to slow down the development of permanent loss of function. With high disease activity despite adequate first-line therapy with IFN-ß or GA, patients should be considered for second-line treatment; natalizumab. With still a high activity, third-line treatment with mitoxantrone should be considered. SPMS patients with clinical or MRI evidence of inflammatory disease activity, may be treated with mitoxantrone, independent of previous treatment (Myhr, 2008).

In addition to medical treatment of relapses and disease-modifying treatment, it is also important to evaluate patients with MS for treatment of symptoms like spasticity, pain, depression and bladder dysfunction (Myhr, 2008).

1.2 Rehabilitation in MS

While disease-modifying therapies aim to influence the degree of disability, the relapse rate and clinical progression (Noseworthy et al., 2000), the aim of rehabilitation is to ease the burden of symptoms by improving self-performance and independence (Kesselring, 2004).

Rehabilitation has been defined as a reiterative, active, educational problem solving process focusing on a patient's behaviour (disability), and the following components

are involved: assessment, goal setting, intervention and evaluation. The rehabilitation process aims to maximise the patient's participation in his or her social setting, to minimize the pain and distress experienced by the patient, and to minimize the distress on the patient's family and carers A rehabilitation service comprises a multidisciplinary team of people working together towards common goals for each patient, involving and educating the patient and family (Wade & de Jong, 2000). A multidisciplinary team may include the following professionals; a neurologist or rehabilitation physician, a rehabilitation or MS nurse specialist, physiotherapist, occupational therapist, speech and language therapist, psychologist, psychiatrist, family doctor, neuropsychologist, social worker, urologist and internist. In addition, other specialists may be involved when needed (Cabrera-Gómez, 2007; Stevenson & Playford, 2007). Neurological rehabilitation should be a continuous process throughout the development of the disease and should take place both at specialized centres and in the community (Cabrera-Gómez, 2007). When managing MS, the aim should be to enable each patient to do as well as possible with regard to the disability and symptoms, by treating the disease, the symptoms and the person who has the disease (Schapiro, 2009).

In rehabilitation settings, the ICF model can be used to identify a patient's impairment in body functions and structures, limitations in activity, and participation restriction. Management of these problems may be linked in with the psychosocial and environmental factors (Khan & Pallant, 2007). Using the ICF model in rehabilitation of patients with MS, therefore seems to be a suitable and practical way of organizing the rehabilitation (Khan & Pallant, 2007).

While setting the agenda for rehabilitation in MS, it has been advocated that rehabilitation needs to focus beyond ambulation and also address the "hidden" disabilities, like the interaction between fatigue, depression and cognitive impairments and how these problems may impact on participation in daily life (Mayo, 2008). Nevertheless, various forms of physical training may be one important part of rehabilitation (Wiles, 2008). In a population based survey of people with MS, ADL and social/lifestyle activities were found to be affected in two-thirds, and the most

affected items were items that could be classified as mobility-related and physically demanding. These results highlight the importance of adequate exercise treatment and rehabilitation aiming to improve independence (Einarsson et al., 2006).

Several studies have investigated the effect of inpatient and outpatient rehabilitation, also including various forms of physical training. However, many lack a clear description of the intervention, and in general, the long term effect is scarcely investigated (Wiles, 2008). It may be a challenge to demonstrate the effect of an intervention that is "all-inclusive" and often poorly defined, for a patient group in which mechanisms of disability are poorly understood. Nevertheless, such studies are important and feasible, but demand that trial methodology and choice of outcome measures have been carefully considered (Thompson, 2000).

1.2.1 Neuroplasticity and possible implications for rehabilitation

Although considerable changes in the brain may be detected at MRI, the lesions are often associated with limited clinical symptoms; the so-called "clinico-radiological paradox" (Pelletier et al., 2009). One suggested explanation for this is the neuroplastic mechanisms mediated by various processes, among them; a cortical reorganization process. Functional and structural changes take place in the cerebral cortex after injury and are shaped by the sensorimotor experiences. Undamaged parts of the brain are remodelled during the recovery (Nudo, 2003). This neuroplastic processes may reduce the clinical expression of motor disorders during the early stage of MS, and rehabilitation strategies should be based on specific training to enhance these mechanisms (Pelletier et al., 2009).

1.2.2 Physiotherapy and physical training in MS

The knowledge of brain plasticity gives optimism and supports the use of rehabilitative training as a tool to improve brain reorganization and functional outcome (Kleim & Jones, 2008).

Physical training can be addressed in different ways, using different methods. Previously, patients with MS were recommended not to exercise, because symptoms might worsen with an elevated body temperature. Inactivity may, however, result in increased fatigue, weakness and health risks (Heesen et al., 2006), and muscular weakness may be a consequence not only of altered central motor drive, but also of disuse (Gallien et al., 2007). Recent studies suggest that patients with a stable disease and moderate disability (Expanded Disability Status Scale; EDSS score $\leq$ 6.0) (Kurtzke, 1983) can improve their physical fitness from exercise with supervision, without adverse effects (Heesen et al., 2006; Rietberg et al., 2004). In a review study, no evidence was found in favour of specific exercise programmes compared to others in improving activities and participation. Also, no evidence was provided for the effect of exercise therapy on fatigue (Rietberg et al., 2004). Resistance training has recently been demonstrated to improve muscle strength and functional capacity in moderately impaired patients (Dalgas et al., 2009). More research is needed to define the nature of physical training that provides health benefits without exacerbating underlying inflammatory stress associated with disease pathology (Ploeger et al., 2009). There is also a need to establish a stronger evidence base to support the use of physical activity and exercises for various subgroups of adults with physical disabilities (Rimmer et al., 2010).

When the patients experience motor and sensory disorders, physiotherapy may be implemented as an important part of the rehabilitation process. Depending on the stage of the disease, different aspects of functioning are emphasized, and over time, the importance of improving or maintaining physical performance seem to be central (Stevenson & Playford, 2007). Physiotherapy has been suggested implemented early to influence gait (Boissy & Cohen, 2007). In addition to being important for daily

functioning, a walking patient is less likely to develop problems like contractures, decubitus ulcers, venous thrombosis, osteoporosis, as well as bowel and bladder complications (Kelleher et al., 2009). Physiotherapy is commonly given to patients with MS, but limited scientific evidence of effect or non effect exists. However, it has been demonstrated that specialized neurological physiotherapy helps to improve mobility, balance, walking, wellbeing and mood (Wiles et al., 2001), indicating that physiotherapy may be one appropriate way of influencing neuroplasticity in order to enhance motor control. In this study, the physiotherapists used a facilitation approach, which seems to be similar to the Bobath concept.

Also other studies have demonstrated positive effects of physiotherapy in MS. A pilot study indicated improved gait ability, gait quality and balance after treatment, comparing a facilitation approach with a more task oriented approach. There was no significant difference in improvement between the two approaches (Lord et al., 1998b).

Another study has compared the effect of neurophysiologically based physiotherapy including individual facilitation techniques, with the effect of only aerobic training and a third group with a combination of these two modalities, as well as a comparison group of patients who did not change their training habits (Rasova et al., 2006). The patients who participated in one of the training programmes, showed a significant improvement in the examined parameters as compared to those who did not change their training habits. The neurophysiologically based physiotherapy had the greatest impact on the EDSS, while the aerobic training had the greatest impact on spirometric and spiroergometric parameters. The authors conclude that it is important for patients to undergo a physiotherapeutic programme that should be specifically tailored to each patient (Rasova et al., 2006).

A recent review reports benefit from both physiotherapy, rehabilitation and other specific and non-specific techniques (Wiles, 2008). Interestingly, there is now an ongoing two strand multi-centre trial evaluating which form of physical activity optimises outcome for people with MS, in which the patients are stratified according to

mobility. In this study different interventions like; yoga, physiotherapy led exercise class, fitness instructor led class, one on one physiotherapy and control groups will be compared (Coote et al., 2009).

Taken together, limited evidence makes it difficult to conclude regarding prescription of exercises and modalities of physiotherapy. Irrespective of such evidence for groups of patients, treatment should be tailored to the individual's need, as also suggested by Asano et al. (2009); "the aim of gathering evidence would be to match intervention to individuals' needs and lifestyles".

1.2.2.1 The Bobath Concept

The Bobath concept is presently described as a problem-solving approach to the assessment and treatment of individuals with disturbances of function and movement due to a lesion of the CNS (Gjelsvik, 2008; Graham et al., 2009). It was developed by the physician Karel and physiotherapist Bertha Bobath in the 1950s and has been called a neurofacilitation approach along with other treatment approaches developed in the same time period (Rood, Brunnstrøm and Proprioceptive Neuromuscular Facilitation; PNF) (Shumway-Cook & Woollacott, 2007). The current theories of motor behavior have been developed from systems theory (Shumway-Cook & Woollacott, 2007), and the organization of motor behavior is seen as a nonhierarchical, self-organizing system driven by multisensory input. An important issue is also that motivation is necessary for motor learning. The motor processes interact with cognitive and perceptual processes, and movement should be understood in a task-oriented context, as goal-directed actions which are based on past experiences and the environment. The Bobath concept is based on knowledge about plasticity and how the CNS responds to injury. Function of the CNS may be altered on a synaptic level by external influences, and use and repetition is necessary for establishing new skills. The use of facilitation during intervention has been a key feature of the Bobath concept since its inception, and facilitation techniques are used when considered necessary to

initiate movement and/or improve quality of performance (Gjelsvik, 2008; Graham et al., 2009).

The aim of treatment is to facilitate the recovery process, to regain and (re)learn motor control, aiming to help the patients move as efficiently as possible. The CNS learns how we move, and due to plasticity, the CNS may change its function depending on experiences. In other words; learning by doing. The facilitation of postural control, specifically core stability through trunk, pelvis and hip control, is considered a main focus in treatment. Optimizing body alignment and maintaining range of movement is seen as a prerequisite for more efficient movement control. Analysis of movement in functional activities determines which component of dysfunction (impairment) that seems likely to cause activity limitation. When possible, the aim is to guide the patient towards efficient movement strategies for task performance. In intervention, the focus is on all three components in the ICF model; Body Functions and Structures, Activity and Participation, and there is no single recipe for treatment. However, in the treatment sessions the therapist and patient work mostly on the components of Body Functions and Structures, and Activity. Assessment, goal setting, treatment planning and implementation of treatment are individualized and tailored to each patient (Gjelsvik, 2008; Graham et al., 2009).

2. Aims of the study

The aims of the study were to explore the effect of physiotherapy, based on the Bobath concept, on individuals with MS, and to examine whether the climate had an impact on the effect of physiotherapy. In order to assess change in quality of life, the MSIS-29 was applied in the climate study after being translated into Norwegian and examined for measurement properties. In addition we also aimed to examine the impact of HRQoL and physical performance on fatigue.

The work consists of four studies with specific aims:

1. To evaluate the effect of physiotherapy based on the Bobath concept for patients with balance and gait problems due to MS, and to evaluate the ability of different functional tests to demonstrate change (Paper I).

2. To translate the Multiple Sclerosis Impact Scale (MSIS-29) into Norwegian, and to examine psychometric properties of the Norwegian version (MSIS-29 NV) (Paper II).

3. To compare the effect of inpatient physiotherapy in a warm (Spain) versus cold (Norway) climate in a short- and long term perspective, for patients with gait disturbances due to MS (Paper III).

4. To investigate whether fatigue was associated with demographic-, clinical-, health-related quality of life (HRQoL)- and physical performance variables, and whether change in fatigue after treatment was associated with changes in HRQoL and measures of physical performance (Paper IV).

3. Materials and methods

The four papers were based on studies of patients with gait disturbances due to MS. Information about the number of patients, gender, study design and statistics applied in each of the four papers, are shown in Table 1.

Table 1. *Overview of participants, gender, designs and applied statistics in the four papers*

Paper	Patients		Design	Statistics
	n	Women/men		
I	2	1/1	Single-subject experimental design	Descriptive Statistics 2 SD band Effect size
II	64	39/25	Repeated measurements; - test-retest - longitudinal	Descriptive Statistics Cronbach's alpha (α) ICC (1,1) SEM SDC (2.77 x SEM) Pearson correlation Spearman rank correlation Area under the ROC curve Effect size
III	60	36/24	Randomized cross-over design	Descriptive Statistics Independent t-test Paired samples t-test Mann-Whitney test Chi-square test Mixed model SDC (2.77 x SEM)
IV	56	33/23	Cross-sectional and longitudinal design	Descriptive Statistics Univariate regression Stepwise regression GLM Paired samples t-test Pearson correlation

2 SD band = ±2 standard deviations of baseline scores, carried forward, evaluating data points outside this band; ICC = Intraclass correlation coefficients; SEM = Standard error of measurement; SDC = Smallest detectable change; Area under the ROC curve = area under the receiver operating characteristics curve; GLM = General linear models

3.1 Patients

Two patients were included in the first, and sixty in the second intervention study (the climate study). For inclusion and execution criteria in the first study, see Paper I. Paper II, III and IV are based on data from the climate study, including mostly the same patient group.

In the test-retest analysis at screening (Paper II), we included data collected from 64 who underwent screening, although some dropped out at baseline.

In paper III, the analyses are based on data from the 60 included patients who started treatment. Inclusion criteria for participation in the study were gait problems with moderate disability equivalent to an EDSS score of 4.0-6.5. For further information about inclusion and exclusion criteria, see Paper III.

In study IV, one patient dropped out during the treatment period, and three patients dropped out after treatment. One patient was not tested physically at six months follow-up due to a bone fracture, and mean change of the total group was added to the previous test values for this test point. However, results were similar also when excluding data from this patient. Thus 56 patients were therefore available for analysis in Paper IV.

Participation was based on written informed consent, and the studies were approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Social Science Data Services.

3.2 Measurement tools

Outcome measures used in each of the papers and suggested components of functioning according to the ICF model are presented in Table 2. The data were analysed using the SPSS version 14 and 15, Stata version 10 and Excel.

Table 2. *Outcome measures used in each of the four papers, and suggested captured components of the ICF model*

		Paper			
Test	**ICF component**	**I**	**II**	**III**	**IV**
GAITRite®	BFS, Activity	X			
Rivermead Visual Gait Assessment	BFS, Activity	X			
Berg Balance Scale	Activity	X	X	X	X
Timed Up & Go	Activity	X		X	X
Visual Analogue Scale; gait	Activity	X			
Rivermead Mobility Index	Activity	X			
Borg Rating of Perceived Exertion Scale	BFS	X		X	
Patient Global Impression of Change	Functioning overall	X		X	
Clinical Global Impression of Change	Functioning overall	X			
Semi-structured interview	BFS, Activity, Participation	X			
6-minute walk test	Activity		X	X	X
10-metre timed walk	Activity			X	X
Trunk Impairment Scale	BFS			X	X
Expanded Disability Status Scale	BFS, Activity		X		
Multiple Sclerosis Impact Scale (MSIS-29)	BFS, Activity, Participation		X	X	X
Fatigue Severity Scale	BFS, Activity, Participation			X	X
Modified Health Assessment Questionnaire	Activity, Participation		X	X	
Numerical Rating Scale; gait and balance	Activity		X	X	
Numerical Rating Scale; pain	BFS			X	

ICF = International Classification of Functioning, Disability and Health
BFS = Body Functions and Structures

3.3 Intervention

The intervention studies were based on physiotherapy treatment according to the Bobath concept, described in chapter 1.2.2.1. The treatment in the first study (Paper I) was performed by two specialized physiotherapists. The treating physiotherapists in the second study (Paper III) received a 4-day course on treatment based on the Bobath concept.

To clarify the contents of treatment according to the Bobath concept, a description of a hypothetical treatment session is included:

A 40 years old woman with gait and balance problems due to MS, uses a unilateral walking aid. Observation demonstrated a wide-stepping gait, stiff and flexed legs, flexed posture, reduced weight transfer during stance, ataxia with mild distal hypertonia and hyperreflexia of lower legs and feet, immobile head and staring eyes. Through clinical reasoning it was hypothesized that her balance and walking problems were due to: reduced postural stability, mobility and endurance of the trunk, pelvis and hips combined with reduced mobility and adaptability of the feet during weight bearing, with hyperreflexia of the calf muscles. It was hypothesized that her CNS received disturbed somatosensory information due to impairments of tonus, mobility, stability, coordination and alignment. In addition she compensated for reduced balance by using visual feed-forward and cognitive strategies. The treatment aimed at improving gait and balance. Through handling by the therapist, the mobility of legs and feet was treated (in sitting and supine). The coordination of hips and pelvis was facilitated through specific bridging exercises (in supine) in relation to the improved adaptability of the feet. In sitting, her thoracic spine was mobilised into more extension, and postural stability was facilitated. In standing, weight transference through the feet in both anterioposterior and lateral directions, was facilitated by the therapist, to improve the coordination through her body. In standing, guided by the therapist, she further worked with going up and down on her toes, to increase postural control, strength and endurance. She also worked with coordination of the pelvis, feet and trunk in the activity of sitting to standing and to one-legged standing in preparation for stepping and walking. In addition she practised standing with her eyes closed, aiming to improve the perception of her body in space over more adaptable feet. This was done to reduce overuse of visual and cognitive strategies. The patient experienced walking with improved alignment and coordination, first through facilitation by the therapist and then independently.

This treatment session demonstrates the combination of interventions on the Body Functions and Structures, and Activity components of the ICF, and how the therapist uses handling to improve motor control when necessary.

3.4 Paper I

One 32 years old man and one 48 years old woman with gait- and balance problems and relapsing-remitting MS in a stable phase were included in this study. We used a single-subject experimental design (SSED) with ABAA phases; A: at baseline, B: during treatment, A: immediately after treatment and A: after two months. In this design the patients are considered their own controls. The tests were performed 12 times, three at each phase, with one week between the tests. The treatment was given for three weeks and was based on the Bobath concept. The outcome measures are listed in Table 2. Due to the aim of evaluating the usefulness of different functional tests, we did not consider one special test as the primary outcome measure prior to the study start. We also used semi-structured interviews three times; immediately after treatment and three as well as eleven weeks after treatment. By the interviews we aimed to capture the patients' experiences regarding bodily functioning, ADL and comments from family and friends.

The effect of the intervention was examined using the 2 SD band method based on the baseline data. A statistically significant change is indicated if at least two consecutive data points after the baseline phase fall outside the 2 SD range (Nourbakhsh & Ottenbacher, 1994). To compare the amount of change and thus sensitivity to change in the different measures, we calculated the effect size (ES). To obtain a more representative value of variability of data expressed by the SD, we included all data points at baseline and at follow-up to compute a common SD. The following procedure was used: [mean change (follow-up ÷ baseline)] / [(SD follow-up + SD baseline)/2]. The ES is a unit-less term allowing direct comparison of change between

the measures. We also presented mean scores and SD for all time points and made a summary of the semi-structured interviews.

3.5 Paper II

We chose the Multiple Sclerosis Impact Scale (MSIS-29) to evaluate self-reported HRQoL in the climate study. The questionnaire was originally generated from interviews with patients with MS, opinions from multidisciplinary experts on MS and from literature reviews, and resulted in a 29-item questionnaire with two subscales. Twenty items address the physical domain with questions regarding ambulation, mobility, physical symptoms and functioning, while 9 items address the psychological domain with questions about mood, role limitations and autonomy (Hobart et al., 2001). For each item there are 5 alternative levels for estimating the degree of the problem, and the higher the score, the more is the impact of the disease on the patient's daily life (MSIS-29: see Appendix 3).

MSIS-29 was translated into Norwegian (MSIS-29 NV; Norwegian Version) in agreement with Dr. J Hobart (Appendix S1 in Paper II). We made a forward and backward translation procedure according to guidelines for translation and cross-cultural adaptation (Beaton et al., 2000; Meadows et al., 1997; Sartorius N & Kuyken W, 1994). The intention was to establish a Norwegian version which was conceptually equivalent to the original questionnaire and culturally relevant to the target population in Norway. The original English version was translated by three physiotherapists, being independent and bilingual translators, whose first language was Norwegian. The three translated drafts were used to develop a first joint Norwegian version. An expert panel discussed the version, resulting in a slightly adjusted questionnaire. Three MS patients, two males and one female were then asked to fill in the questionnaire. In a group setting they were asked to consider the relevance of the different questions, whether the questions were easy to understand, and whether the questionnaire was user friendly. Finally, the backward translation was done by a bilingual Norwegian

physiotherapist and researcher. Particular problems encountered during the process of translation, and how they were solved, are outlined in chapter 5.2.1.

After the translation process, psychometric properties of the translated version were examined. Repeated measurements, from 64 patients that underwent screening for the intervention study, were obtained, and test-retest reliability was calculated, estimating both relative and absolute reliability. Relative reliability is based on the assumption that if a measurement is reliable, individual measurements within a group will maintain their position within the group on repeated measurement. (Domholdt E, 2005). Relative reliability was calculated by intraclass correlation coefficient (ICC). Absolute reliability indicates to what extent a score varies on repeated measurements and is expressed by standard error of measurement (SEM). The smallest detectable change (SDC) is an estimate of measurement error in two repeated measurements of the same individual, (2.77SEM) for 95 % of pairs of observations (Bland & Altman, 1996). Knowing the SDC of a measure helps the rehabilitation professionals or researcher to evaluate whether a change is above measurement error in individual patients.

Internal consistency by Cronbach's alpha tells whether multiple items of a questionnaire measure a single underlying concept. Internal consistency was calculated for each subscale separately. The homogeneity of both subscales was evaluated by correlating the scores of each item and the respective total subscale score (item-total correlations). The alpha value of each subscale was also examined when each of the items were deleted (alpha if item deleted) (Streiner & Norman, 2008), but these results were not included in Paper II. Construct validity was assessed by examining predefined hypothesis as recommended by Terwee et al. (2007). Responsiveness is considered the ability of a questionnaire to detect clinically important change over time, even if these changes are small (Guyatt et al., 1989). The receiver operating characteristics (ROC) curve is a graph depicting the true positive (sensitivity) versus false positive (1- specificity) values for each cut-off points in score change. The area under the curve (AUC) is a measure of responsiveness, being a measure of the ability of an assessment tool to distinguish patients who have, and have not changed, using an

external criterion of change (Deyo & Centor, 1986). In our study of responsiveness, we used treatment versus no treatment as an external criterion and expected that a period with treatment would demonstrate a change, while a period without, would not. We also evaluated responsiveness by testing a predefined hypothesis that ES of change after intervention would be larger for the physical than for the psychological subscale of the MSIS-29, since the focus of treatment was on physical functioning.

3.6 Paper III

In this study we compared the effect of inpatient physiotherapy in a warm versus cold climate in a short- and long term perspective, for patients with gait disturbances due to MS.

Based on information from patient records at the Neurological Departments at Haukeland and Akershus University Hospitals, possible participants were contacted by telephone and asked if they would like to participate in the study. Some also contacted the departments asking for participation after having heard about the study. Possible participants were then pre-screened at the hospital by a neurologist, physiotherapist and nurse. They underwent a neurological examination, were tested on the primary outcome measure, the 6-minute walk test (6MWT) (Enright, 2003) and checked for inclusion and exclusion criteria. A randomized cross-over design was used, and the patients were the first year randomized for individualized physiotherapy based on the Bobath concept at a treatment centre in either a warm (Spain) or a cold (Norway) climate, and switching treatment centre the year after. The patients went through a comprehensive test battery (Table 2). The 6MWT was prior to study start defined as the primary outcome measure. The test has been found reliable for patients with MS (Paltamaa et al., 2005), and has been used as an outcome measure in MS studies (Goldman et al., 2008; Paltamaa et al., 2008). The 6MWT is discussed more in detail in chapter 5.1.3.1.

Data collection was performed at screening before randomization to the two treatment cites, and also at baseline, after treatment and at three and six months follow-up for both treatment periods, giving data at nine time points over a period of about 19 months. To account for possible effects of period and sequence of the treatment as well as differences in carry-over effects, mixed model was used in the analysis of different effects of treatment (Brown & Prescott, 2006). Data from the screening were not included in these analyses. For definition of the different variables included in the model, see Table 3.

Table 3. *Definition of the different variables included in the mixed model analysis, using an example for the 6-minute walk test*

Variable	Description	Values	Type
6MWT	6-minute walk test (primary outcome)	The measured values	Dependent
Patient number	The number for each patient	1-60	Random
Time	Defines the time point of the measured value of 6MWT. This variable is not included in the model but is used to define the rest of the included fixed variables.	1=baseline-I 2=after first treatment period 3=3 months after first treatment period 4=6 months first treatment period 5=(12 months) baseline-II 6=after second treatment period 7=3 months after second treatment period 8=6 months after second treatment period	Fixed
Sequence	Where they got treatment first (same as group)	1 - Spain first (SN) 2 - Norway first (NS)	Fixed
Period	Measures the period effect	1 - time=6 to 8 0 - otherwise	Fixed
Effect Spain after treatment	Effect in Spain	1 - time=2 or 6 0 - otherwise	Fixed
Addition Norway after treatment	Effect in Norway in addition to the effect in Spain (if negative, Spain has best effect for the physical tests, and opposite for the self-reported measures).	1 - time=2 and sequence=2, or time=6 and sequence=1 0 - otherwise	Fixed
Effect Spain 3 months after treatment	Effect 3 months after treatment in Spain	1 - time=3 or 7 0 - otherwise	Fixed
Addition Norway 3 months after treatment	The effect in Norway in addition to Spain after 3 months	1 - time=3 and sequence=2, or time=7 and sequence=1 0 - otherwise	Fixed
Effect Spain 6 months after treatment	Effect 6 months after treatment in Spain	1 - time=4 or 8 0 - otherwise	Fixed
Addition Norway 6 months after treatment	The effect in Norway in addition to Spain after 6 months	1 - time=4 and sequence=2, or time=8 and sequence=1 0 - otherwise	Fixed
Carry-over effect Spain 12 months after baseline-I	Effect 12 months after treatment in Spain (measures carry-over/wash-out)	1 - time≥5 0 - otherwise	Fixed
Addition Norway 12 months after baseline-I	The effect in Norway in addition to Spain after 12 months (measures carry-over/wash-out)	1 - time≥5 and sequence=2 0 - otherwise	Fixed
Period x Sequence	Interaction between period and group (excluded if not significant)	1 - time=6 to 8 and sequence=1 0 - otherwise	Fixed

To estimate the gait distance at baseline-I for the two different groups, Constant + Sequence for Spain and Constant + 2x Sequence for Norway were calculated.

Reporting the proportion of patients achieving improvement that is beyond measurement error, is said to be an informative method of describing effects of intervention (Haley & Fragala-Pinkham, 2006). Standard error of measurements (SEM) on the 6MWT was calculated based on scores from screening and baseline-I, and SDC (2.77SEM) was calculated. The number and per cent of patients who scored above this level in connection with treatment, was calculated and compared, without taking into consideration the cross-over design.

In addition to focusing on the climate effect, we have also analysed the change in test scores over the whole study period (19 months) for all participants by paired samples t-tests, and did also calculate the change in scores for the patients treated in Norway the first year, using general linear model (GLM) and Bonferroni-adjusted t-tests.

Assessment procedure

A standardized test procedure was strictly followed, and the sequence of physical tests was the same from time to time (Trunk Impairment Scale; TIS, Timed Up & Go; TUG, Berg Balance Scale; BBS, 10-metre timed walk; 10MTW and 6MWT). Before performance of the two last tests, the patients had a break of 10 minutes, and between the two last tests, a break of two minutes. The patients were examined by the neurologist, then the physiotherapists and finally the nurse. One of three neurologists registered the neurological status (EDSS), medications and physical conditions. Three of six physiotherapists did the physical performance tests, and one of three nurses collected the self-reported measures and responded to questions from the patients. We aimed for assessment at about the same time of day, the patients using the same walking aids and footwear from time to time. We also aimed for using the same assessors, specifically trained for particular tests. However, due to illness during the study period, two testers were replaced by three trained physiotherapists to collect data from the 6MWT and TIS. An overview of test points and data collected in the climate study is presented in Table 4.

Table 4. *An overview of test points and data collected in the climate study*

The flow of the study	Pre-screening June 2006	Screening August 2006	Baseline-I (Mnth 0) 2006	Mnth 1 2006	Mnth 4 2007	Mnth 7 2007	Baseline-II (Mnth. 12) 2007	Mnth 13 2007	Mnth 16 2008	Mnth 19 2008
Written informed consent (N)	X									
Demographic data (N)	X	X								
Inclusion criteria (N)	X	X	X							
Exclusion criteria (N)	X	X	X							
Medical history, not MS related (N)	X	X	X	X	X	X	X	X	X	X
Neurological history related to MS (N)	X	X	X	X	X	X	X	X	X	X
Vital status (N)	X	X	X	X	X	X	X	X	X	X
Physical examination (N)	X	X	X	X	X	X	X	X	X	X
Medications (N)	X	X	X	X	X	X	X	X	X	X
Expanded Disability Status Scale (N)	X	X	X	X	X	X	X	X	X	X
Randomization (ST)			X							
6-minute walk test (P)	X	X	X	X	X	X	X	X	X	X
Timed Up & Go (P)		X	X	X	X	X	X	X	X	X
10-metre timed walk (P)		X	X	X	X	X	X	X	X	X
Berg Balance Scale (P)		X	X	X	X	X	X	X	X	X
Trunk Impairment Scale (P)		X	X	X	X	X	X	X	X	X
Borg Rating of Perceived Exertion Scale (P)		X	X	X	X	X	X	X	X	X
Multiple Sclerosis Impact Scale, Norwegian Version (NU)		X	X	X	X	X	X	X	X	X
Fatigue Severity Scale (NU)		X	X	X	X	X	X	X	X	X
Modified Health Assessment Questionnaire (NU)		X	X	X	X	X	X	X	X	X
Numerical Rating Scale; gait, balance, pain (NU)		X	X	X	X	X	X	X	X	X
Patient Global Impression of Change (NU)				X				X		
Satisfaction with aspects of the stay at the centres (NU)				X				X		

N=Neurologist; ST = Statistician; P = Physiotherapist; NU = Nurse

3.7 Paper IV

In this study we aimed to explore possible factors with impact on fatigue. Of special interest was the association between fatigue and scores on physical performance measures, as there seems to be limited knowledge regarding this association. We used data from the first period of the climate study, including data from screening, baseline-I, immediately after treatment and at three and six month follow-up. As there were no differences in fatigue between the two groups neither at baseline nor at follow-ups, we analysed the data as one cohort.

Fatigue as measured by the Fatigue Severity Scale (FSS) (Krupp et al., 1989) was included as the dependant variable in a multivariate regression model. In the initial univariate analysis, we investigated associations of fatigue with demographic-, clinical-, HRQoL- and physical performance variables at baseline. Further, we used stepwise regression to identify possible factors with independent effect on the FSS. We used the squared coefficient of correlation (R^2) to measure the explained variance in the regression models. Of demographic variables, gender, age, work status and rehabilitation centre were included. Course of disease and duration of MS were included as clinical variables, and data from the MS specific self-reported questionnaire MSIS-29 were included as a measure of HRQoL. All the physical performance measures which were used in the climate study (6MWT, TUG, 10MTW, BBS and TIS) were included as the physical performance variables. Correlation in changes of scores between fatigue versus HRQoL,- and physical performance variables were demonstrated by graphs and by Pearson correlation coefficients. In addition, the same correlations were calculated for change from before to after treatment and from after treatment to six months follow-up. To investigate change over time in variables, GLM and Bonferroni-adjusted t-tests were used.

4. Summary of results

4.1 Paper I

Balance and gait improved after three weeks of physiotherapy based on the Bobath concept. Improved balance was demonstrated by BBS in both patients, and improved quality of gait was indicated by Rivermead Visual Gait Assessment (RVGA). Among the physical performance tests these two measures demonstrated the highest change, both regarding the 2 SD band graphs and the ES. For the 2SD band graphs, variability at baseline for some of the other variables resulted in a broad band, giving less data points outside the 2 SD range. An overall positive trend was demonstrated while inspecting the graphs, indicating improvement also in most of the other variables. Improvement of balance and gait was also demonstrated by satisfactory ES on the TUG for both patients. Improved maximum gait velocity as measured by the electronic walkway GAITRite® was indicated by ES, but not at follow-up for Mr B. Other gait parameters recorded by the GAITRite®, changed, but differently in the two patients. The patients also reported improved balance and gait function in the interviews and scored their general condition after treatment and at follow-ups as "much improved" on the Patient Global Impression of Change (PGIC), also confirmed by the therapist's evaluations using the Clinical Global Impression of Change (CGIC). Treatment seemed to improve components of Activity and Participation, as well as components of Body Functions and Structures (ICF).

4.2 Paper II

The forward and backward translation of the MSIS-29, according to guidelines for translation, resulted in a Norwegian version of the questionnaire (Appendix S1 in Paper II). During the different steps of translation, discrepancies between the various versions were adjusted in a dialog with the measurement developer Dr Hobart, and special issues regarding this, are presented in chapter 5.2.1.

For the Norwegian version of MSIS-29, the sum scores on the 0–100 point physical subscale ranged from 6.3 to 78.8 (mean 41.4, SD 18.1), and on the psychological subscale from 2.8 to 80.6 (mean 29.6, SD 18.4). Missing data from the separate items were low. Internal consistency (Cronbach's α) was 0.92 for the physical- and 0.85 for the psychological subscale, and item-total correlation ranged between 0.26 and 0.78 for the physical items and between 0.30 and 0.77 for the psychological. Most items contributed to increase the total alpha. Reliability by ICC was 0.86 for the physical- and 0.81 for the psychological subscale. SDC was estimated to 18.4 and 21.1, respectively. The physical- but not the psychological subscale demonstrated mostly satisfactory associations with other physical measures. Responsiveness by the area under the ROC curve for the physical subscale was 0.83. The optimal cut-off point of change providing the highest sensitivity (0.78) as well as specificity (0.81) was an improvement of 8.1 points on the 0-100 scale. The area under the curve for the psychological subscale was 0.76. The optimal cut-off point of change providing the highest sensitivity (0.73) as well as specificity (0.80) was an improvement of 5.6 points on the 0-100 scale. As hypothesized since treatment primarily addressed physical performance, the ES was larger for the physical (1.01) than for the psychological (0.76) subscale after treatment.

4.3 Paper III

After treatment, the mean walking distance as measured by the 6MWT, had increased more in Spain than in Norway ($p=0.060$). The improvement was 70m in Spain and 49m in Norway. At 6 months follow-up, the improvement was significant larger ($p=0.048$) after treatment in Spain (43m) as compared to Norway (20m). After walking (6MWT), the patients reported larger decrease of exertion on the Borg Rating of Perceived Exertion Scale (Borg RPE scale) after treatment in Spain as compared to Norway at all time points ($p<0.05$). No significant differences between treatment in a warm and cold climate were detected for the other physical performance measures. The proportion of patients that had an improvement above

SDC on the 6MWT was larger after treatment in Spain as compared to Norway (34 % and 17 %, respectively). After three months, 19 % versus 12 % scored above SDC, and after six months, 18 % versus 12 %, respectively. Most self-reported measures showed more improvement after treatment in the warm climate, but the improvements were not sustained at follow-up. The PGIC scored immediately after treatment, demonstrated significant more improvement in Spain than in Norway ($p= 0.006$). Fifteen patients (27 %) scored “Very much improved” after treatment in Spain, compared to five (9 %) after treatment in Norway.

In addition to focusing on the climate effect, we have also analysed the change in test scores over the whole study period (19 months) for all participants (Table 5).

Table 5. *Mean scores and differences from baseline-I to 6 months after the second treatment (19 months) for those who completed the whole study (n=50)*

Test	Baseline-I	19 months	Difference (95%CI)
High scores are best			
6MWT; m	314	345	31 (8, 55)*
BBS; scale 0-56	45.2	45.8	0.6 (-1.0, 2.3)
TIS; scale 0-23	13.7	15.7	2.0 (1.3, 2.7)*
TUG; m/s	0.56	0.59	0.03 (-0.01, 0.07)
10MTW; m/s	1.12	1.18	0.06 (-0.02, 0.15)
Low scores are best			
Borg RPE Scale; 6-20	13.4	14.5	1.1 (0.2, 2,0)*
MSIS-29, Physical scale; 0-100	39.9	45.3	5.4 (1.0, 9.9)*
MSIS-29, Psychological scale; 0-100	25.6	31.2	5.6 (1.6, 9.6)*
FSS; scale 1-7	4.89	5.22	0.33 (-0.05, 0.70)
MHAQ; scale 0-3	0.45	0.58	0.13 (0.01, 0.25)*
NRS; gait; scale 0-10	5.6	5.9	0.3 (-0.3, 1.0)
NRS; balance; scale 0-10	5.2	5.3	0.01 (-0.6, 0.7)
NRS; pain; scale 0-10	3.2	3.8	0.6 (0.01, 1.3)*

6MWT = 6-minute walk test; BBS = Berg Balance Scale; TIS = Trunk Impairment Scale; TUG = Timed Up & Go; 10MTW = 10-metre timed walk; Borg RPE Scale = Borg Rating of Perceived Exertion Scale; MSIS-29 = Multiple Sclerosis Impact Scale; FSS = Fatigue Severity Scale; MHAQ = Modified Health Assessment Questionnaire; NRS = Numerical Rating Scale.
* = significant difference ($p \leq 0.05$) from baseline to six months after the second treatment.

4.4 Paper IV

Fatigue at baseline was associated with HRQoL (explained 21.9 % of variance), but not with physical performance tests. Change in fatigue correlated with change in HRQoL, but not with changes in physical performance. All measures were improved after treatment ($p \leq 0.001$). While improvements in fatigue and HRQoL were lost at follow-up, improvements in physical performance were sustained for at least six months ($p \leq 0.05$).

5. General discussion

5.1 Intervention studies, Paper I & III

The climate study is considered the main study of the thesis, and Paper III will therefore be discussed first. Nevertheless, physiotherapy based on the Bobath concept was less addressed in this paper, and is therefore discussed in chapter 5.1.2 along with the discussion of results from Paper I.

5.1.1 The climate influence on the effect of physiotherapy

From the climate study, we concluded that physiotherapy in a warm climate had additional benefit. After 6 months, the improvement on the primary outcome after treatment in Spain was statistically significant better than after treatment in Norway. Also immediately after treatment the difference was close to being significant. However, not only statistical, but also clinical significance should be addressed. The methods of calculating clinical significance differ, and several terms are used, like: minimal important difference (MID), minimal clinical important difference (MCID) and clinically significant difference (CSD) (Haley & Fragala-Pinkham, 2006). However the amount of change needed to be clinically relevant, should be considered in relation to the study population accounting for diagnosis, age and disability level, and in addition the duration of the intervention. In fact, in patients with progressive diseases, stabilization (no decline) over time could be considered a clinically significant result. We have not found reference values of clinically significant improvement estimated on a similar population as ours, for the tests used in our study.

The difference after treatment between the two centres was especially demonstrated by the primary outcome measure (6MWT). Taking into account the limited walking distance at baseline, we consider a difference of 23 m after 6 months to be clinically important. In addition, we find it interesting that the patients also perceived less

exertion at all time points after having walked for a longer distance, after treatment in a warm as compared to a cold climate. This may imply that the patients will experience reduced restrictions in physical activities during the day, but this aspect was not specifically investigated in our study. Also the results from the PGIC, demonstrated significant better improvement immediately after treatment in a warm as compared to a cold climate. For instance, 15 patients reported to be "Very much improved" after treatment in Spain, while five patients reported that much improvement after treatment in Norway, also indicating a clinically important difference.

The proportion of patients, who scored better than SDC, was largest after treatment in Spain. The estimated SDC value in our study may seem large (77 m for individual patients) and could have been influenced by the long time interval between test and retest (screening and baseline-I), and also by the fact that the test situation had changed after travelling to the rehabilitation centres. However, another study on patients with MS, demonstrated a SEM value of about 31 m (Paltamaa et al., 2005), giving a SDC of 86 m.

Treatment at the rehabilitation centre at Tenerife was compared to treatment at MS-Senteret Hakadal, which is a specialized MS rehabilitation centre in Norway. We therefore suppose that the patients received the best available treatment in Norway. However, the results indicate that the warm climate in Spain provided additional benefits. The reason for this is not straight forward to explain. Many of the patients reported that the warm climate "did them well". The warm temperature might have had a relaxing effect, giving a feeling of less stiffness in muscles and joints. In addition, when lightly dressed, it is easier to move and to be physically active. This might have made the patients more receptive for treatment and reduced their feeling of exertion after walking. In addition, the patients reported less exertion after the 6MWT, after treatment in Spain as compared to Norway at all test points, also after returning to Norway. This might contribute to the sustained improvement of gait.

The difference in effect of physiotherapy in warm and cold climate might have been affected by other factors than the warm climate alone. However, no differences were detected between the centres regarding satisfaction with the rehabilitation centres, the physiotherapy intervention, and social life during the study, assessed by the Numerical Rating Scale (NRS). Overall their satisfaction was very high at both places. The amount of physiotherapy and other organized physical activities during the whole study period, as well as change in physical condition (like relapses and other illness) were registered for each patient during the whole study period. Compatible data regarding these aspects were demonstrated between the two centres.

The climate was considered to be the main difference between the two rehabilitation centres, but we can not establish that the subtropical climate was the only difference. Change in lifestyle and being far away from home and daily duties, might as well have had an impact. Also, the sun-exposure might have given additional serum vitamin D, which might have influenced disease activity. Based on a recent study (Tremlett et al., 2008), it was suggested that vitamin D could modify the infection rate in patients with MS, as low ambient sunlight and low serum vitamin D are associated with clinical disease activity (Kesselring, 2008). We did not systematically register whether the disease activity changed after the stay in the warm climate by using MRI. Nevertheless, travelling to a warm and sunny area during the winter months in Norway may increase serum vitamin D levels and thereby influence the immune system (Falkenbach & Sedlmeyer, 1997).

5.1.2 Physiotherapy based on the Bobath concept

During prolonged clinical practice we have experienced that gait and balance tend to improve after physiotherapy based on the Bobath concept. To investigate this assumption scientifically, we carried out the first study (Paper I).

We concluded that balance and gait in the two patients did improve after the treatment. Improved functioning at the Body Functions and Structures component

(ICF) was demonstrated by the RVGA. Also the GAITRite® measures functioning at the Body Functions and Structures component, being a more objective measurement tool. Results from the GAITRite® demonstrated that the two patients changed their gait pattern, but in different ways. While interpreting these results we found it necessary to take each patient's problems into consideration. Mrs A, who had an ataxic gait, increased her double stance phase, which might indicate a positive change with a more stable and less ataxic gait, allowing her to use more time in double stance. On the contrary, Mr B, who demonstrated more imbalance in walking at baseline, increased his double stance phase slightly after treatment, but at early and late follow-ups, it was somewhat decreased. Due to his gait problems a decreased double stance might indicate less need of standing on two feet during walking, and for him indicate an improved gait. However, these results should be interpreted with caution as no reference values exist. There seems to be a need to examine how gait patterns change in MS in a larger group of patients.

Treatment according to the Bobath concept, imply a focus on quality of movement. Specifically impaired movement components, considered influential on performance of activities, are treated and put together in functional activities. Improved movement control within the component of Body Functions and Structures is hypothesized to make functioning at the Activity component easier. Other physiotherapy treatment concepts, like the Motor Relearning Programme, focus more directly on performance of activities, and less on skill and quality of movement. Whether one of the treatment approaches are superior to the others, has not been demonstrated (Lord et al., 1998b; Paci, 2003; van Vliet et al., 2005).

In our first study, it may not be a surprise that functioning at the Body Functions and Structures component improved after treatment, taking the focus of treatment according to the Bobath concept into consideration. Interestingly, however, improvement was also demonstrated at the Activity component of the ICF, by the TUG, which is a measure of gait and balance ability and by the BBS, which is a measure of balance in functional activities. Measurement error by SEM has been estimated to be 0.83 for the BBS in patients with MS (Paltamaa et al., 2005), meaning

that SDC for an individual is 2.3 (2.77 x SEM) (Bland & Altman, 1996). A change for a single patient should be larger than this to indicate a real change. Both patients in the study scored above this level at all follow-ups after treatment. In addition, they improved their low scores from below the limit of increased risk of falling (45) to scores higher than this limit (Bogle Thorbahn & Newton, 1996), also indicating a clinically important change. Improvement after treatment was also shown at the Participation component of the ICF, as the patients reported better gait and balance in ADL activities, and improvement in overall functioning (PGIC). These subjective reports from the patients further validate the results from the physical performance tests. Based on experiences from clinical practise and results from this first study, we also chose treatment according to the Bobath concept in the climate study to improve gait and balance in patients with MS.

The main focus in the climate study was to examine whether there was a difference in effect of physiotherapy in a warm compared to a cold climate (discussed in chapter 5.1.1). Nevertheless, despite not having a control group who did not receive any treatment, we also considered the change in test scores after treatment, independent of treatment place, to be a topic for discussion. The study design made it possible to compare change after a time period without physiotherapy (screening and Baseline-I) and time periods after physiotherapy. The patients could then be their own controls. GLM analysis demonstrated change in all measures across the time points ($p<0.05$). There were no differences in scores between screening and baseline-I, except for a decline in the TIS. Immediately after the first treatment period, the improvement for patients treated in Norway, was significant ($p<0.05$) for all measures except for fatigue, indicating an effect of the treatment itself, also without the climate effect. The mean improvement was 45m for the 6MWT. After 3 months, the improvement was significant for 6MWT (41m, $p=0.002$), and for 10MTW ($p=0.025$), and for TIS ($p< 0.001$), and after 6 months still for TIS ($p< 0.001$). The p-values were Bonferroni adjusted for the five different time periods.

In a progressive disease like MS, no decline in physical functioning over time may be of clinically relevance. From start of the study to after 19 months, the patients as a

whole group, walked significantly longer (mean 31m) (Table 5). In a population based study of 118 people with MS and median EDSS of 2, gait distance was shown to be reduced with about 10m over a period of two years without treatment (Paltamaa et al., 2008). The improved gait distance for the patients in our study over a period of 19 months therefore seems to be of clinically importance. Interestingly, the TIS, which captures aspects of Body Functions and Structures, was also significantly improved (Table 5) which might be explained by treatment focusing on impairments aiming to improve Activity and Participation (ICF). When the change scores from baseline-I to 6 months after the second treatment for TIS (Body Functions and Structures) and 6MWT (Activity) were correlated, we found in fact a correlation of 0.65, meaning that 42 % of the variance of change scores of 6MWT was explained by change scores on the TIS.

Over this long period, none of the five physical performance tests demonstrated decline. The climate study indicated, accordingly, a positive effect of treatment according to the Bobath concept. However, we can not say that this approach is better than other physiotherapy approaches in treating patients with MS.

Improvement of the self-reported measures did not sustain, and most of them demonstrated a significant decline over the time period of 19 months (Table 5) (data not included in paper III). In patients with acute low back pain, it has been suggested that self-reported assessments are more influenced by the patients' psychological status than performance based assessments are (Wand et al., 2009), and perhaps this may be the case also for our patient group. A recent effect study of multidisciplinary rehabilitation in MS (Khan et al., 2008) demonstrated improvement in the physical performance as measured by the Functioning Independence Measure, but no improvement in HRQoL. The authors argue that a response shift could be a possible explanation for this. A response shift refers to a change in the meaning of the patient's self-evaluation of their target construct (Schwartz & Sprangers, 1999; Sprangers & Schwartz, 1999). The patients in our study might have changed their internal standard or values as a result of having received inpatient physiotherapy together with other patients with MS. This might have resulted in making them

reassess how they perceived their limitations (Costelloe et al., 2007). A response-shift may be an important internal mechanism of mind whereby changes in QoL may not always parallel function. This phenomenon emphasizes the case for clearly separating QoL from functional assessment and attempt to make the latter as objective as possible (Wiles, 2008). In any case, self-reported and performance based measures seem to capture different aspects of functioning, and it therefore seems important to include both when planning for intervention studies.

Rehabilitation typically includes multiple simultaneous therapies and treatments in a "treatment package". It may therefore be difficult to document specific treatment effects that are due to only one therapy (Figoni, 1990). However, the intervention in the climate study was not a multidisciplinary rehabilitation programme, but physiotherapy according to the Bobath concept, aiming to improve movement control and ambulation. Recent recommendations for treatment of patients with MS, focus on different aspects of training, including exercises in general, resistance training, aerobic training, aquatic exercise, endurance training, as well as functional training. The importance of fitness has also been underlined (Dalgas et al., 2008; Gallien et al., 2007; Heesen et al., 2006; Rietberg et al., 2004). Physiotherapy according to the Bobath concept does not focus on fitness and endurance training specifically, but rather on improving motor control of impaired movements, with the overall aim to improve functional activities. We hypothesize, however, that improved ability to walk, may lead to a better opportunity to stay active and thereby also improve fitness, but we did not investigate this aspect specifically. In the climate study, improved walking distances (6MWT) was demonstrated over a period of 19 months, indicating that the patients had improved their ambulation ability independent of treatment place. Interestingly, Rogers et al. (1999) did not find improvement of gait, although aerobic fitness improved. Rather a reduction in gait velocity and range of motion during walking was demonstrated after a 6-month aerobic programme with cycling. We therefore hypothesize that training focusing on motor control in relation to performance of activities, may be valuable in the attainment of improved activities, such as walking in the climate study.

5.1.3 Outcome measures, designs and methodological considerations

5.1.3.1 Outcome measures

When planning for the intervention studies, the feasibility and applicability of outcome measures was an important consideration. When choosing outcome measures for the first study, we aimed to capture the main components in the ICF model. Functioning at the Body Functions and Structures component was examined by the RVGA (Lord et al., 1998a), the Borg RPE Scale (Borg, 1970) and the electronic walkway (GAITRite®) (Bilney et al., 2003). The GAITRite® captures footfall data providing both spatial and temporal gait parameters. We did not find any earlier studies on patients with MS in which this walkway had been used, and the results were therefore analysed based on our clinical experience of gait problems in patients with MS, and of how gait may change in connection with treatment. However, the lack of reference values for patients with MS, resulted in a decision of not using the GAITRite® as an outcome measure in the climate study. This study would also imply much travelling between different centres, both in Norway and Spain, which would have been rather strenuous with the GAITRite® equipment. The RVGA is a measure of gait quality, in which 20 different components in the gait cycle as well as upper limb position are evaluated subjectively by the assessor. Scores are graded as “normal” or “mild”, “moderate” or “severe” deviations and are based on guidelines for each item. The RVGA had demonstrated satisfactory measurement properties for patients with MS, and was said to be relatively easy to learn (Lord et al., 1998a). Prior to start of the first study, two physiotherapists scored seven patients with different neurological disorders in addition to the two included in the study. The scoring was done independently by the two therapists at the same time point, and the results were discussed. We needed time to agree on how to interpret the different items of the test and how to score abnormality. The test is based on a subjective judgement, and since the assessor was not blinded, we decided not to use this test in the climate study.

In the first study, the BBS (Berg et al., 1989) and TUG (Podsiadlo & Richardson, 1991) were used as outcome measures at the Activity component of the ICF. Prior to the first study, two physiotherapists discussed and practised scoring patients on the BBS, and we experienced that it was easier to achieve agreement. Satisfactory test-retest and inter-rater reliability have been demonstrated for the BBS (Paltamaa et al., 2005) and test-retest reliability has been demonstrated for the TUG (Nilsagard et al., 2007). Both these tests were found sensitive to change in the first study and were considered applicable for use in the climate study in which change was also demonstrated. However, regarding the BBS, the mixed model analysis demonstrated a ceiling effect, and the results were therefore of less value in the climate study.

The Rivermead Mobility Index (Collen et al., 1991) did not demonstrate any change in the two patients in the first study, and a ceiling effect was indicated, resulting in the decision of not including this test in the climate study.

In the first study, the patients were asked to score the Borg RPE Scale after having walked on the GAITRite®. This activity did not seem to have been very strenuous to any of the patients, and the change on the Borg RPE Scale after treatment was only trivial. The Borg RPE Scale was used as an outcome measure also in the climate study, but the rating was done after a more strenuous activity (6MWT). Previously, the Borg RPE Scale has mostly been used during exercises to guide the degree of exertion. However, in our two studies, we were interested in the experience of exertion after having walked on the GAITRite® and performed the 6MWT, respectively. When the patients in the climate study as a group graded the 6MWT as less exhausting and at the same time walked a longer distance, we interpreted these results to be positive for the patients.

In both studies we aimed to explore the patients' overall impression of perceived change in their physical condition after treatment, assessed by the PGIC (Farrar et al., 2001). As the result from this test was in line with results from the other self-reported measures in the climate study, and due to limited space, information about this test

was omitted from Paper III. However, it demonstrated a significant larger improvement after treatment in a warm as compared to a cold climate.

In the climate study, the outcome measures were selected aiming to capture common physical problems seen in patients with MS, and we chose outcome measures considered to be sensitive to the expected change according to the intervention. Also in this study, we aimed to cover the consequences of disease as defined by the World Health Organization, regarding the components of Body Functions and Structures, Activities and Participation (World Health Organization, 2001). However, the main focus of attention was on physical performance, especially related to gait, and 6MWT was chosen as the primary outcome measure (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories., 2002; Enright, 2003). For elderly people the 6MWT seems to be more a measure of general mobility and physical functioning than a specific measure of cardiovascular fitness (Lord & Menz, 2002). Persons with cerebral palsy, who also have a disturbance of the CNS, describe problems with stiffness in their legs rather than cardiorespiratory problems as the main reason for reduced walking distance (Andersson et al., 2006). In addition, habitual walking performance seems to be best reflected by longer walking capacity tests, such as either the 6MWT or the 2-minute walk test (2MWT) in patients with MS (Gijbels et al., 2010), supporting our choice of primary outcome. A measure of walking distance could therefore give valuable additional information about motor control and movement ability, than simply walking distance. The test demands ability to balance during walking and turning every 30 m. We expected that a possible improvement in motor control and gait functioning would be reflected in a longer walking distance as captured by the 6MWT. In addition to the 6MWT, we used the 10MTW (Wade, 1992), and TUG to assess walking speed and balance. By using all these tests, we considered important aspects of gait to be sufficiently covered. However, including an ambulant accelerometer-based ambulatory monitoring over a longer time period, could have given additional information regarding habitual walking. (Gijbels et al., 2010).

In the climate study, we still wanted to capture functioning at the Body Functions and Structures component, in spite of having decided not to use the RVGA or the GAITRite®. The recently developed TIS measures aspects of trunk performance, and test scores have been found to be associated with gait and functional ability scores in stroke patients (Verheyden et al., 2006b). As patients with MS commonly have reduced trunk control (Lanzetta et al., 2004) and treatment focused on this aspect, we included the TIS, which has also been found reliable and valid in patients with MS (Verheyden et al., 2006a). Together with using the Borg RPE Scale, we considered important aspects of the Body Functions and Structures to be captured.

The EDSS (Kurtzke, 1983) is composed of eight subscales, each measuring a specific function within the CNS. The total EDSS index of severity of MS is ranging from 0 (normal) to 10 (death). Scores lower than 4 address impairments (Body Functions and Structures components of the ICF), and scores from 4 to 7 address limitations in ambulation (Activity component of the ICF). The EDSS is one of the most common neurological outcome measures for patients with MS (Hoogervorst et al., 2003). However, based on recent critical comments regarding standardisation and marginal sensitivity to change (Balcer, 2001; De Souza, 1999; Hoogervorst et al., 2003), we decided to use the EDSS only as a classification variable, as also suggested by Hoogervorst et al. (2003).

By using self-reported questionnaires in the climate study, we aimed to capture different components of the ICF related to HRQoL, fatigue, ADL and experienced problems of gait, balance and pain. We found the MSIS-29 (Hobart et al., 2001) applicable for investigating important aspects of HRQoL. This test is discussed in more detail in chapter 5.2. The ADL was examined by the Modified Health Assessment Questionnaire (Uhlig et al., 2006). We have not found MS studies in which this questionnaire has been used, but considered the questions to be relevant in our study. The FSS was chosen in the climate study to capture perceived fatigue, and this test is more thoroughly described in chapter 5.3. From the first study, we found it appropriate to assess the patients' self-reported experience of gait problem by using the Visual Analogue Scale (VAS). However, the 11-point NRS has been

recommended more feasible to use than the VAS (Jensen MP & Karoly P, 2001), and we therefore decided to use the NRS in the climate study to capture experienced problems related to gait, balance and pain.

In summary, the use of a wide spectrum of outcome measures in the two intervention studies has given valuable information about change in different functional components of the ICF.

5.1.3.2 Study design

Both intervention studies imply repeated measurements over a time period, giving valuable information about variation in the patients' condition over time.

In the first study, a SSED was used. Several registrations before and during treatment make it possible to evaluate whether treatment has an effect beyond normal variability in the condition over time. The patients are, accordingly, their own controls (Figoni, 1990). In group designs, results can be generalized to a defined population, but may not necessarily be applicable to each individual in the group. Contrary, when using a SSED the findings may not be generalized to a broad population, but related to subjects with similar characteristics as those in the study. A detailed description of the participant(s), the testing procedure and the treatment should therefore be emphasized (Figoni, 1990). We found the SSED relevant for use in the first study and experienced that it gave valuable information about the two patients and about the use of different outcome measures.

In the climate study, a randomized cross-over design was used, aiming to investigate differences in treatment effect due to climate influence for a larger population. When using this design, the patients are also their own controls, resulting in a need of fewer participants as compared to when using a parallel group design (Altman, 1991). Another advantage may be that all participants received the same treatment in Norway and Spain although in different years, which might have given a high motivation for participation and for completing the study. A cross-over design is

applicable when investigating patients with a chronic and rather stable disease, not expecting a substantial decline during the study period (Jones & Kenward, 2003; Wang et al., 2006). The patients in our study had a chronic, often progressive disease, but included rather stable patients, and the decline during the relatively short study period was expected to be only minor. Thus we therefore found the design applicable. A possible disadvantage of such a design, is the risk of drop-outs due to the longer study durability (Wang et al., 2006). We found the drop-out of 9 out of 60 (15 %) to be acceptable. Using mixed models allows for missing data, and we could therefore include measured data from all patients in the analysis. A possible carry-over effect, meaning that the second treatment is influenced by the first, may be a problem in cross-over trials. The best way of preventing this, is to ensure an adequate washout period (Wang et al., 2006). We considered eleven months to be a sufficient washout period; not too long in case of a possible decline, and not too short in case of a possible carry-over effect. Only a short-term effect of outpatient physiotherapy given two times a week over a period of eight weeks was demonstrated in a previous cross-over trial on patients with MS (Wiles et al., 2001). In this study, a period of eight weeks between the treatment periods was applied, and no carry-over effect was demonstrated. The authors concluded that the use of a cross-over design seems applicable for patients with MS. In our study, one year between the two treatment periods was necessary, to ensure as similar conditions regarding climate as possible the two subsequent years. Possible differences in carry-over effect were controlled for in the mixed model, implying that this was not considered a methodological problem.

By testing the patients with the complete test-battery two times before start of the first treatment, we aimed to reduce the learning effects. Anyway, we presume that a possible learning effect would not differ between the two groups and would therefore not influence the results regarding differences between effects at the two places. By testing at screening before randomization, we also had the possibility to compare these scores with those at baseline-I after the patients had been randomized and travelled to the different places. Overall, scores from screening to baseline-I, were compatible.

The data in the climate study were analysed using mixed models. In an ordinary regression analysis, the independent variable (on the x-axis) is of a constant value and not associated with uncertainty, while the value on the Y-axis may vary, being the dependant variable. In a mixed model we also permit the variable on the x-axis to be associated with uncertainty. In our model, this was the participant number. By using the mixed model, we were able to take into account the sequence of treatment, the two different treatment periods and possible differences in carry-over effects (Table 3). As we prior to study start had chosen a primary outcome measure, and the different tests seemed to capture different aspects of the same function, the p-values were not Bonferroni adjusted (Bland & Altman, 1995). Such an adjustment would be too strict. However, when interpreting the results, it should be taken into consideration that the use of many tests increases the risk of false significant results.

5.1.3.3 Other methodological considerations

In the SSED study (Paper I), we included only two patients since this design focus on in depth knowledge of few individuals. However, it is realized that inclusion of more patients would have made the study results more robust. At least three data points are required at baseline as well as at the other study phases (Figoni, 1990). It can be questioned whether this is sufficient to demonstrate a stable level or trend in each period, but we considered it to be too strenuous for the patients to be exposed for additional testing. Another limitation is the lack of blinding. The assessor knew that the patients participated in an intervention study, and did also know in which phase of the study period they were tested. This might have influenced the results. However, results from the more objective measures like the GAITRite® and the TUG also indicated improvement, and the positive subjective expressions from the patients supported the results.

In Paper I, Table 1, below the column “Test”, the “Double stance phase” and “Step-length” should have been specified more precisely. “Step-length (m) at 0.4 m/s” was estimated for Mrs A and should be followed by “for Mrs A and at 1 m/s for Mr B”.

This information should also have been included in connection with “Double stance phase (%)” in the same table, as the step-length and double stance phase were estimated at 0.4 m/s for Mrs A and at 1 m/s for Mr B. In Table 2, the heading “Change in Mr B”, should have been placed above “Treatment” and not above “Late follow-up”.

The awareness of being under observation, may influence the way a person behaves (the Hawthorn effect) (De Amici et al., 2000). The Hawthorn effect might have influenced the treatment effects in both intervention studies, but should not have influenced the differences in effect between the two centres in the climate study.

We found it necessary to limit the study population to an EDSS between 4 and 6.5, making it possible to select appropriate measurement-tools for the target group and also to tailor treatment focusing on gait functioning. Since gait has a direct impact on ambulation, it appears to be important for an independent lifestyle. As participation would imply laborious travelling and demand a great amount of testing, we did not consider patients with an EDSS larger than 6.5 to be relevant for participation in the study. The results should therefore primarily be considered for patients with similar functional levels as those included in the study. However, we hypothesize that also patients without heat intolerance and lower EDSS than 4 might benefit from physiotherapy in a warm climate.

5.2 Norwegian version of MSIS-29, Paper II

Research regarding development of HRQoL outcome measures for use in clinical trials is increasing (Meadows et al., 1997), and there is also an increase in multinational and multicultural research (Beaton et al., 2000). Most of the questionnaires are developed in English-speaking countries resulting in a need of translating the questionnaires into new languages, also including a cross-cultural adaptation (Beaton et al., 2000; Meadows et al., 1997). A poor translation process may result in an instrument not equivalent to the original, which may imply limited

comparability across populations from different cultures and countries (Beaton et al., 2000).

When choosing a health outcome measure, an important consideration is whether a generic or a condition-specific questionnaire should be used. A generic HRQoL measure allows us to contrast and compare the impact of a disease on HRQoL across different conditions, while a condition-specific instrument should be preferred when the aim is to measure the impact of one particular disease or to evaluate the effect of an intervention in a particular group (McColl E et al., 1997). Using condition-specific instruments in effect studies, enhances the chance for increased responsiveness, resulting from including only important test items relevant for the target population (Guyatt et al., 1993).

An optimal MS specific outcome measure should be multidimensional, but non-redundant, widely applicable across the full range of disease severity without floor or ceiling effects and be reliable, valid, responsive and practical in use (Fischer et al., 1999). In the climate study, condition-specific questionnaires like the Functional Assessment of Multiple Sclerosis (FAMS), the Multiple Sclerosis Quality of Life 54 (MSQOL-54) and the Multiple Sclerosis Quality of Life Inventory (MSQLI) were considered for possible use. However, based on the overall evaluation of the different measurement tools (Gruenewald et al., 2004), we chose the MSIS-29 for our study, as it has been found clinically useful and scientifically robust. The MSIS-29 takes about 15 minutes to complete (Benito-Leon et al., 2003). Items included in the two subscales contain questions regarding a broad range of HRQoL aspects like Physical, Emotional, Social, Cognitive, Fatigue, Mobility and Bladder/Bowel functioning. Questions regarding communication and sexual and sensory functions are, however, not included (Benito-Leon et al., 2003). A recent Rasch analysis of the MSIS-29 demonstrated satisfactory psychometric properties of the two subscales, and dimensionality testing indicated that it was not appropriate to combine the two subscales to calculate a total MSIS-score (Ramp et al., 2009).

The developer of the MSIS-29 did not name it a HRQoL questionnaire, but rather an instrument that measures the impact of MS (Hobart et al., 2001). However, in recent literature, it has been classified and used as a condition-specific HRQoL questionnaire (Benito-Leon et al., 2003; Gray et al., 2009; Gruenewald et al., 2004; Khan et al., 2008; Ramp et al., 2009). Nevertheless, it could be discussed whether using the term ”HRQoL” should be replaced with “self-reported health”, since it may be difficult to establish each individual’s quality of life, based on a general assumptions of the meaning of this phenomenon.

5.2.1 The translation process of the MSIS-29

The MSIS-29 was found to be an appropriate measurement tool of HRQoL in the climate study. Due to lack of a Norwegian version, we first translated the questionnaire into Norwegian and then examined reliability, validity and responsiveness of the translated version. The procedure of the translation process is described in chapter 3.5. Below follows an overview of particular problems encountered during the process of translation, and how they were solved:

Translating the five scoring-alternatives

In particular; the translation of the scoring alternatives 4 and 5 was discussed. Number 4: ”quite a bit” was translated into “mye” (much), and number 5: ”extremely” to “svært mye” (very much). Those answering–alternatives were suggested by the target group as being more appropriate to use in Norwegian, and these alternatives also seem to imply more even intervals between the 5 scoring-alternatives, although this is not specifically examined.

Item 13: Limitations in your social and leisure activities at home?

The last part of item 13, referring to limitations in social and leisure activities at home, was discussed. We chose to leave out “at home” as we found that it might limit the scope of the question to the individual’s house.

Item 17: Problems using transport (e.g. car, bus, train, taxi, etc.)?

There is a substantial difference between Norway and Great Britain when it comes to ”transport” for physically disabled persons. In Norway the political focus has mostly been to customize cars or other means of transport to individuals, while in Britain the focus has been more into developing the public transport. Both the expert panel and the target group advised us to change “transport” into “offentlig transport” (public transport) and then delete the examples.

Item 28: Lack of confidence

”Confidence” was probably the word we found most difficult to translate, and we contacted the developers of MSIS-29 (Dr. Hobart) to clarify the scope of the question. After many discussions and suggestions from the experts, the item was translated into ”mangel på selvtillit”. In Norwegian this is usually understood as “lack of self-esteem”.

The original version of MSIS-29 was considered to have validity in the Norwegian culture. A pragmatic approach was used in the translation process, aiming for equivalence and taking cultural differences into consideration (Sartorius N & Kuyken W, 1994). The translated Norwegian version was therefore not completely identical word by word to the source instrument, but well adopted for use in Norwegian patients and rather similar to the original version.

Our overall impression, after having used the Norwegian version of MSIS-29 in the climate study, is that the patients found the questionnaire easy to understand, and most of the patients completed the questionnaire without missing items.

5.2.2 Psychometric properties of the Norwegian version of MSIS-29

Reliability and validity are important measurement properties. When an assessment tool is used to assess outcome, responsiveness to change implying the extent to which

a change in status is reflected in a change of scores, should also be documented. Responsiveness to change depends on both reliability and validity (Domholdt E, 2005; Finch E & Brooks D, 2002).

Important quality criteria for measurement properties of health status questionnaires have been proposed by Terwee et al. (2007), and these were used as guidelines when evaluating psychometric properties of the translated version of the MSIS-29. Our intention was not to change the original MSIS-29 regarding contents and number of items or dimensions, but rather to obtain a similar questionnaire in the Norwegian language, with satisfactory psychometric properties. We examined internal consistency, construct validity, test-retest, reliability, responsiveness as well as floor and ceiling effects.

Overall, the psychometric properties were in accordance with the original version, as presented and discussed in Paper II. Test-retest reliability was examined as recommended by Terwee et al. (2007). We also calculated the SDC for an individual based on the SEM values, taking into consideration the measurement error at repeated measurement with 95 % CI. The proportion of patients in a group scoring above and below the SDC value can then be calculated and compared between groups. When also taking the systematic shift into consideration, the limits of agreement can be estimated. In the present study the upper limit was an improvement of 20.6 and the lower limit a decline of 16.2 on the physical subscale, and an improvement of 24.5 and a decline of 17.7 on the psychological subscale.

Internal consistency was examined for each subscale of MSIS-29. Terwee et al. (2007) also suggest that a factor analysis should be performed. The rationale for a two-dimensional model was not examined in the Norwegian version as the sample of patients was not large enough.

Construct validity was examined by testing predefined hypothesis, as also recommended by Terwee et al. (2007). The physical subscale of the MSIS-29 was expected to demonstrate a larger correlation with physical performance measures, than the psychological subscale. Among the physical performance measures used in

the climate study, only scores of the 6MWT and the BBS were applied in the present study as they were considered most related to the physical subscale of MSIS-29. In addition, we also included the EDSS classification scores in the validation. From our results, we concluded that construct validity was satisfactory, in accordance with our predefined hypothesis.

The ES is often used as an indicator of responsiveness to change of a measure, but it may rather be a measure of treatment effect. We therefore followed recommendations from Terwee et al. (2007) by predefining hypotheses regarding expected differences in change between "known groups". Taking the nature of treatment into consideration focusing on physical performance, the ES of the physical subscale of MSIS-29 was expected to be higher than the ES of the psychological subscale, which was shown in our study. Responsiveness of the Norwegian version of MSIS-29 was also indicated by satisfactory area under the ROC curve, demonstrating ability to differentiate between a period of expected stability (without treatment) and a period with expected change (treatment).

The sum scores on the physical subscale ranged from 6.3 to 78.8 and on the psychological from 2.8 to 80.6. The mean of the physical subscale was 41.4 (SD 18.1), and of the psychological 29.6 (SD 18.4). A good distribution of scores and no floor or ceiling effects were demonstrated for our study population.

The included patients in our study were restricted to an EDSS between 4.0 and 6.5, which may be a limit regarding the evaluation of psychometric properties. However, the results regarding measurement properties were in line with results from studies of the original version, including a broader range of patients.

In summary, we found important psychometric properties of the Norwegian version of the MSIS-29 satisfactory, and we therefore considered the questionnaire to be applicable for clinical and research purposes.

5.3 Fatigue study, Paper IV

In this study, we aimed to explore the phenomenon of fatigue in MS by analysing possible explanatory variables. Only HRQoL (MSIS-29) was found to be associated with fatigue at baseline, and only change in HRQoL was associated with change in fatigue after physiotherapy. No association was found between fatigue and the physical performance measures of gait and balance. Improvement of physical performance sustained over time, while improvement in fatigue and HRQoL did not. We therefore concluded that fatigue in MS was not associated with physical performance.

5.3.1 Associations between fatigue versus HRQoL and physical performance

The FSS is the most widely used measure of fatigue in cross-sectional and longitudinal studies of patients with MS (Bakshi, 2003). The scale was considered appropriate for our study, as it has a physical focus (Flachenecker et al., 2002) measuring the impact of fatigue on daily living (Comi et al., 2001). It may be argued that the scale should have been supplemented by newer multidimensional fatigue scales (Goldman et al., 2008). By including newer scales with validated sub-dimensions of fatigue, the impact of independent variables on the various aspects of fatigue might have been better explored.

Weak correlations have been found between different fatigue scales, and can best be explained by the fact that fatigue is a multidimensional symptom and available tests measure and weight different aspects of fatigue differently. A more exact definition of fatigue and more valid scales to quantify the various aspects of fatigue might have provided different results in the present study. It has been suggested that, due to the multi-dimensional nature of fatigue in MS, the role of fatigue should be explored in a broad perspective according to the bio-psychosocial ICF model (Mills et al., 2010).

Using scales with items selected to represent conceptually distinct domains of for example physical, cognitive and psychosocial functioning, may question whether it could be concluded that a total score measures a unidimensional construct of fatigue. The FSS has been defined as unidimensional (Comi et al., 2001). However, a recent Rasch analysis of the FSS indicated a reduction to a 5-item scale to provide a strictly unidimensional scale (Mills et al., 2008). A recently developed unidimensional assessment of fatigue (U-FIS), which was modified from the Fatigue Impact Scale (Meads et al., 2009) seems to capture a broader aspect of fatigue and has demonstrated satisfactory psychometric properties. Also a fatigue scale named The Neurological Fatigue Index (NFI-MS) has recently been developed (Mills et al., 2010), including a 10-item summary scale together with scales measuring the physical and cognitive components of fatigue. It remains to be seen whether these measures of fatigue will be more preferred than the FSS in future studies.

We found that fatigue was not associated with physical performance of gait and balance. Frzovic et al. (2000) found that despite an increase in self-rated fatigue from the morning to the afternoon in patients with MS, little change was found in balance from the morning to the afternoon, supporting our results. It may be questioned whether other physical performance measures than used in our study, would show similar results. We can only conclude that fatigue was not associated with the 6MWT, TUG, 10MTW, BBS and TIS.

Due to the multidimensional characteristics of fatigue, we also find it plausible that physiotherapy according to the Bobath concept, would not alone result in a reduction of fatigue. Other factors related to the treatment, like social well-being, support and staying away from home and daily duties, might have given a short term effect on the experience of fatigue. We suggest that the improvement of fatigue after physiotherapy in our study was related to other factors than improvement in physical performance of gait and balance.

In this study, we included patients from the climate study. They did not suffer from excessive fatigue that would preclude participation in the study protocol. However,

when analyzing the results, the patients in the study were comparable with other MS samples regarding fatigue severity, and the scores of fatigue using the FSS demonstrated a normal distribution and scores all over the scale. Fatigue did not differ between patients randomized to the two treatment sites, and we therefore found it appropriate to analyse the data as one cohort.

5.3.2 Suggestions for a broader startegy in treating fatigue

The results that fatigue was not associated to physical functioning, lead us to hypothesise that physiotherapy alone, focusing on physical performance, is probably not an adequate or sufficient remedy for improving fatigue, and a broader strategy seems to be needed.

However, regular physical activity has been found to improve fatigue, depression and QoL in persons with MS (Stroud & Minahan, 2009). In addition, physical activity has been found to be indirectly associated with improved QoL through pathways that include fatigue, pain, social support, and self-efficacy (Motl & McAuley, 2009).

Results from a recent study indicate that coping mechanisms are associated with depression, anxiety and fatigue in MS, and the authors suggest a cognitive behavioural therapy (Brajkovic et al., 2009). The results from this study support our theory about a need of a broader strategy in treating fatigue. Another multidisciplinary fatigue management programme demonstrated efficacy in reducing the impact of fatigue, but no differences were found as compared to a placebo intervention programme (Kos et al., 2007). The authors of the paper discuss whether the two programmes were too similar, suggesting that further research should also include a control group with no intervention. In addition, the intervention consisted of only 4 sessions of two hours spread over 4 weeks. Interestingly, a group-based intervention for the management of fatigue in MS has recently been developed, focusing on energy effectiveness and cognitive behavioural approaches. Preliminary

results of the effect look promising, and results from a randomized controlled trial will soon be published (Thomas et al., 2010).

Nevertheless, we argue that the effect of treatment on fatigue should be investigated over the long term. If improvement in fatigue is due solely to positive experiences of having attended a programme, we expect the improvement to decrease after the intervention, while a sustained effect may indicate that the treatment itself has given a more sustained and positive effect.

6. Conclusions and further research

Results from the climate study demonstrated improvement of physical performance, HRQoL, fatigue and ADL after physiotherapy. The improvement was larger for most self-reported measures and tended to be larger for the primary outcome (6MWT) after treatment in a warm climate (Spain). Over the long term, a significant additional effect was demonstrated on the primary outcome after treatment in Spain, indicating that patients with gait disturbances due to MS, not suffering from heat intolerance, may profit from physiotherapy in a warm climate. From the first intervention study we concluded that balance and gait were improved after physiotherapy based on the Bobath concept for the two patients, and from the climate study, we also found it plausible to suggest that physiotherapy improved physical performance.

The Norwegian translated version of the MSIS-29 demonstrated satisfactory psychometric properties and is recommended for use as a measurement tool of HRQoL in patients with MS.

Fatigue, which is a common problem for patients with MS, was found to be associated with HRQoL, but not with physical performance measures of gait and balance. Change in fatigue was associated with change in HRQoL, but not with changes in gait and balance. Fatigue might therefore not be related to how patients perform on physical tests, which should be taken into consideration in treatment of patients with MS and fatigue.

Suggestions for further research

Effect of physiotherapy based on the Bobath concept was indicated in the intervention studies, but we do not know whether treatment based on this concept has greater effect than other treatment approaches. We therefore suggest that a multicentre study should be conducted. The including centres should adhere to

different treatment approaches to ensure that the treatment is given by competent therapists within the different approaches.

When interpreting the results from the intervention studies, we looked for estimates of clinically important change in outcome measures for the target group. As such information was scarce, we suggest that this topic should be further investigated.

Regarding the investigated climate effect, we do not know whether a warm climate alone may have an effect on physical functioning. This aspect could be further investigated, by also including a control group living in a warm climate for four weeks, without receiving physiotherapy. A possible additional effect from vitamin D should also be considered, including serum analysis as well as registration of MS specific disease activity, including relapses and MRI lesions.

To improve fatigue, we have suggested including strategies that challenge cognitive interpretation and behavioural responses to symptoms. Further studies are needed to evaluate the effect of such an intervention.

A challenge in rehabilitation research in MS is to identify the main target for the intervention. It may be difficult to find the right balance between a holistic view and specific problems captured by each professional. In any case, the knowledge of plasticity of the brain should lead us to considering the brain as an important target for improving functioning (Mayo, 2008). This makes rehabilitation in general and physiotherapy, as part of rehabilitation, a demanding and optimistic challenge.

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Papers I-IV