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A TWO-YEAR STUDY OF PEOPLE WITH MULTIPLE SCLEROSIS

*Aspects of disability, perceived impact,
needs and satisfaction with care*

Charlotte Ytterberg

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***ASPECTS OF DISABILITY, PERCEIVED IMPACT,
NEEDS AND SATISFACTION WITH CARE***

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*“Egentligen vet man något först när man nästan
ingenting vet. Tvivlet växer med kunskaperna.”*

Johann Wolfgang von Goethe

ABSTRACT

Background: Knowledge of the concurrent presence and longitudinal variations in disability in people with multiple sclerosis (MS) is lacking. Furthermore, the perceived impact of MS on health, which takes into account predictors of an increased impact, is not fully investigated. The variation in perceived needs of health-related services and satisfaction with care over time in people with MS has not been explored.

Aims: The overall aims of this thesis were to explore functioning and disability, perceived impact of MS on health, perceived needs and satisfaction with care, including variations over two years, in people with MS at an outpatient MS specialist clinic.

Methods: The 219 people with MS included were followed up every six months over a two-year period by means of tests and questionnaires regarding cognition, fine hand use, walking, energy, mood, activities of daily living and social activities. Furthermore, evaluation of perceived impact of MS on health was performed, as well as assessment of disease-related variables and contextual factors including sense of coherence, perceived needs and satisfaction with care.

Results: Among the people with MS, 49% had cognitive impairment; 76%, limitation in fine hand use; 43%, walking limitation; 67%, fatigue; 29%, depressive symptoms; 44%, limitations in activities of daily living and, in 47%, participation in social activities was restricted. Two or more disabilities were found in 81% and 24% had six or seven disabilities. During the study period, variations were found in the presence of disability and in nearly all functioning. The variations included improvements and declines but no general deterioration was found except for people with a primary progressive disease course. The perceived physical and psychological impact of MS on health also varied during the study period. A period of more than 10 years since diagnosis, cognitive impairment, fatigue and depressive symptoms were independent predictors of increase in perceived physical impact of MS. Weak or moderate sense of coherence, absence of immunomodulatory treatment, fatigue and depressive symptoms were independent predictors of increase in perceived psychological impact of MS. Individual variations were found in both perceived needs and satisfaction with care. People with severe MS had a greater perceived need for almost all health-related services and women experienced a need for psychosocial support and counselling to a greater extent than men. Among the different categories of health care staff, people with MS were most satisfied with nurses regarding all dimensions of care. They were least satisfied with the availability of psychosocial support and counselling; as well as of information on social insurance and vocational rehabilitation.

Conclusions: A high concurrent presence of disability was found, regardless of disease severity, which highlights the importance of making systematic assessments of the level of functioning, also in individuals with mild MS, in order to identify disabilities.

Knowledge of what are the predictors of increase in perceived physical and psychological impact may be used to identify the people with MS who are in need of special attention. Considering the variation in functioning over time, a regular and comprehensive assessment of functioning and disability is desirable, as well as flexibility in the supply of health-related services, and individualised interventions. Improved availability of rehabilitation services including an increase in the supply of psychosocial support and counselling, could probably improve satisfaction with care in people with MS.

SAMMANFATTNING

Bakgrund: Kunskap saknas om samtidig förekomst av funktionshinder och hur dessa varierar över tid hos personer med multipel skleros (MS). Dessutom är självskattad hälsopåverkan av MS otillräckligt undersökt liksom prediktorer för en ökad påverkan på hälsan. Variationer över tid i upplevda behov av hälsorelaterad service och tillfredsställelse med vård hos personer med MS har inte undersökts.

Syfte: Det övergripande syftet med denna avhandling var att undersöka och bedöma funktionstillstånd och funktionshinder, självskattad hälsopåverkan av MS, upplevda behov av hälsorelaterad service och tillfredsställelse med vård, samt hur dessa varierar under en 2-årsperiod, hos personer med MS vid en MS-mottagning.

Metod: De 219 inkluderade personerna med MS undersöktes var sjätte månad under två år med hjälp av tester och frågeformulär gällande kognitiv funktion, finmotorik, gång, energinivå, sinnesstämning, aktiviteter i dagligt liv och sociala aktiviteter. Dessutom undersöktes självskattad hälsopåverkan av MS, sjukdomsrelaterade variabler och kontextuella faktorer inklusive upplevda behov och tillfredsställelse med vård.

Resultat: Av samtliga personer med MS hade 49 % kognitiv funktionsnedsättning, 76 % begränsad finmotorik, 43 % begränsad gång, 67 % fatigue/trötthet, 29 % depressiva symtom, 44 % aktivitetsbegränsningar i dagligt liv och 47 % inskränkt delaktighet i sociala aktiviteter. Åttioen procent hade två eller fler funktionshinder och 24 % hade sex eller sju funktionshinder. Under två år varierade förekomsten av funktionshinder och nästan samtliga studerade aspekter av funktion, aktivitet och delaktighet.

Variationerna omfattade både förbättringar och försämringar men ingen generell försämring påvisades, förutom hos personer med en primärprogressiv sjukdomstyp. Även självskattad hälsopåverkan av MS varierade under studieperioden. Mer än 10 år sedan diagnos, kognitiv funktionsnedsättning, fatigue och depressiva symtom var oberoende prediktorer för en ökad självskattad fysisk påverkan av MS. Svag eller måttlig känsla av sammanhang, frånvaro av immunomodulerande behandling, fatigue och depressiva symtom var oberoende prediktorer för en ökad självskattad psykologisk påverkan av MS. Det fanns individuella variationer i upplevda behov och tillfredsställelse med vård och personer med svår MS uppgav ett större behov av nästan all hälsorelaterad service. Kvinnor angav behov av samtalsstöd och krisbearbetning i högre grad än män. Sjuksköterskor var den kategori av sjukvårdspersonal som personer med MS var mest nöjda med. De var minst nöjda med tillgången på samtalsstöd och krisbearbetning samt information i socialförsäkringsfrågor, arbetsrehabilitering och utbildning.

Slutsats: Samtidig förekomst av olika funktionshinder var hög oavsett svårighetsgrad av MS, vilket understryker betydelsen av att systematiskt undersöka och bedöma individens funktionstillstånd, även bland dem med mild MS, för att kunna upptäcka funktionshinder. Kunskapen om prediktorer för ökad självskattad fysisk och psykologisk hälsopåverkan av MS kan användas för att identifiera personer i behov av speciella åtgärder. Med tanke på variationerna i funktionstillstånd över tid är det önskvärt med regelbundna och allsidiga bedömningar, individualiserade åtgärder och flexibilitet i tillhandahållandet av hälsorelaterad service. En ökad tillgång på rehabilitering, inklusive samtalsstöd och rådgivning, skulle sannolikt kunna förbättra tillfredsställelsen med vård för personer med MS.

LIST OF PUBLICATIONS

- I. Johansson S, Ytterberg C, Claesson IM, Lindberg J, Hillert J, Andersson M, Widén Holmqvist L, von Koch L. High concurrent presence of disability in multiple sclerosis. Associations with perceived health. *J Neurol* 2007; 254: 767-73.
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- III. Ytterberg C, Johansson S, Widén Holmqvist L, von Koch L. Longitudinal variations and predictors of increased perceived impact of multiple sclerosis, a two-year study. *J Neurol Sci* 2008 Feb 21 [Epub ahead of print]
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LIST OF ABBREVIATIONS

ADL	Activities of daily living
BDI	Beck Depression Inventory
CI	Confidence interval
EDSS	Expanded Disability Status Scale
FAI	Frenchay Activities Index
FSS	Fatigue Severity Scale
HRQOL	Health-related quality of life
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile range
KI	Katz ADL Index Extended
MMSE	Mini Mental State Examination
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale
MRI	Magnetic resonance imaging
NHPT	Nine-Hole Peg Test
NICE	National Institute for Health and Clinical Excellence
OR	Odds ratio
PASAT	Paced Auditory Serial Addition Test
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SOC	Sense of coherence
T25FW	Timed 25-Foot Walk

1 INTRODUCTION

1.1 MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, progressive disease of the central nervous system, characterised by inflammation, demyelination and destruction of the axons within the brain and spinal cord [1]. MS is a relatively common disease in most of Europe, the United States, Canada, New Zealand and southern Australia [2], with a female-to-male ratio around 2-3:1 [3, 4]. Onset usually occurs between the ages of 20-40 years [1] and it is the leading cause of neurological disability in younger adults [4]. MS reduces life expectancy by approximately 10 years [5]. The prevalence of MS in Sweden has been reported to vary between 96/100 000 and 170/100 000 [6-8].

1.1.1 Pathogenesis and clinical signs

The cause of MS is not understood but it is considered to result from an interaction between genes and environmental factors [4]. The clinical course varies from episodes of symptoms with total resolution, to permanent severe symptoms [9]. The majority of people with MS start out with a relapsing-remitting disease course, in which worsening occurs in attacks – bouts/relapses, lasting for a minimum of 24 hours, with complete or partial recovery. After about 10 years, 50% enter a phase defined as secondary progressive MS, with the dominant pattern of a gradual worsening, with or without superimposed relapses [10]. Approximately 10-15% of people with MS have a primary progressive disease course, which is characterised by a gradually progressive clinical course directly from onset [11]. The disease results in a wide range of symptoms including fatigue; motor disturbances (weakness, spasticity, and ataxia); sensory disturbance; pain; cognitive dysfunction; mood disturbance; bladder, bowel, and sexual dysfunction [1].

1.1.2 Diagnosis

Diagnosis of MS is based on established clinical and laboratory criteria. The Poser criteria require at least two relapses in separate sites of the central nervous system and separated in time, by evidence from clinical examination and supported by findings from magnetic resonance imaging (MRI) or cerebrospinal fluid [12]. The more recent Mc Donald criteria also incorporate MRI findings as a means of revealing evidence of dissemination in time and space [13, 14].

1.1.3 Management of MS

There are no national guidelines for MS care in Sweden comparable to those provided by the National Institute for Health and Clinical Excellence (NICE) in the UK [15], but a proposal for a plan of action has been produced, stressing the need for frequent specialist neurological assessment including a multidisciplinary team [16]. Unfortunately, MS specialist teams are mainly located in the university hospitals, leading to large regional differences [16].

Medical therapy includes symptomatic management of e.g., pain; spasticity; depression; bladder and bowel dysfunction [17, 18], in addition to disease-modifying therapies, which mainly reduce the relapse rate, thereby slowing down the progression

of disability [19-22]. The philosophy current in neurological rehabilitation in MS emphasises the importance of involving the people with MS in a process of training and self-management, by which the individual acquires the knowledge and skills necessary for optimum physical, psychological and social function. This suggests a need for a multidisciplinary team with a thorough understanding of the MS disease process [17, 18, 23-25]. Evidence-based rehabilitation includes exercise therapy [26], multidisciplinary rehabilitation [27], and cognitive behavioural therapy in the treatment of depression, and in helping people adjust to, and cope with, having MS [28]. Instruction on energy conservation to decrease fatigue impact has shown promising [29] but as yet inconclusive results [30].

MS care in Stockholm County is mainly provided by the Departments of Neurology, Karolinska University Hospital, Huddinge; Karolinska University Hospital, Solna; Danderyd Hospital; and by the primary care sector. Home help service and other health services may be provided by the local authorities, or other organisations. Rehabilitation may be offered in different forms such as a stay at a rehabilitation centre, outside the hospital, or at hospital outpatient departments and within the primary care sector and the private sector.

1.2 THEORETICAL AND EMPIRICAL BACKGROUND

1.2.1 The International Classification of Functioning, Disability and Health

A diagnosis is not sufficient to describe a health condition or the needs of the individual. The International Classification of Functioning, Disability and Health (ICF) is a framework which aims to provide a scientific basis and a common language for describing health and health-related states, and is also intended for studies of health care systems, in terms of outcomes and cost-effectiveness of services, needs assessment and consumer/patient satisfaction [31]. The ICF puts emphasis on how people live their lives in relation to their health conditions.

The ICF has two parts, each with two components. The first part is: Functioning, including the components: body functions/body structures, and activities; the execution of a task or an action by an individual and participation; involvement in a life situation. The second part is: Contextual Factors, including the components: environmental and personal factors. Functioning is a comprehensive umbrella term, encompassing body functions/body structures, and activities and participation. Similarly, disability is a comprehensive umbrella term, used for the impairments of body function/body structures, activity limitations and participation restrictions. Environmental factors make up the physical, social and attitudinal environment in which people live and they can have a hindering or facilitating impact. Personal factors are the particular background of an individual's life and living e.g: age, sex and coping styles. Contextual factors interact dynamically with functioning and disability, see Figure 1 [31].

The term: health condition (diseases, disorders, injuries, traumas) is not classified within the ICF but is associated with functioning and disability. An individual's

functioning is a complex relationship between the health condition and contextual factors. Thus, if the full health experience is to be described, it is important to collect data on all components independently and, thereafter, explore associations and causal links between them [31].

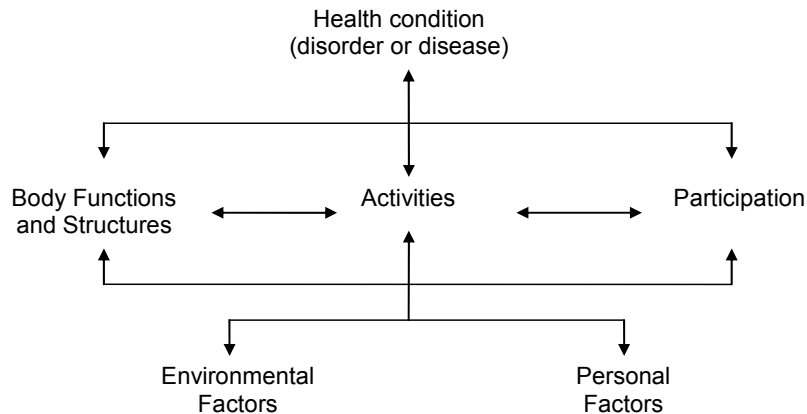


Figure 1. The theoretical model of the interactions between health condition and the components of the ICF

1.2.2 Functioning and disability

In this thesis, aspects of functioning and disability – with regard to cognition, fine hand use, walking, energy, mood, ADL and social/lifestyle activities – were studied.

Disabilities in these areas of functioning are known to occur commonly in people with MS [32]. The ICF was used as a framework and the variables were not classified in detail.

1.2.2.1 Cognition

Cognition can be defined as all forms of thinking – such as perception, learning, memory, problem solving and language activities [33]. Cognitive impairment affects an estimated 43–65% of people with MS [34, 35]. The cognitive domains most commonly impaired are: memory and learning, attention, executive functions and visuospatial abilities [35]. Cognitive dysfunction encompasses all phases of the disease and all types of disease course, and may develop at an early stage of the disease [36, 37]. However, the prevalence and the cognitive profile may vary in people with MS, in whom the course of the disease differs. In general, deficits are most severe in people with secondary progressive MS, followed by primary progressive MS and then relapsing remitting MS [38, 39]. Males with MS have proved to perform more poorly than females with MS in several tests [40]. Lower education level as well as limitations in a person's work and social activities are correlated with the extent of cognitive decline [34, 41, 42]. Some, [43-45] but not all [46], studies show an association between cognitive impairment and poor health-related quality of life (HRQOL).

Relatively little is known about the evolution of cognitive dysfunction in MS and longitudinal studies on cognitive functioning differ considerably in terms of the clinical characteristics of the participants and neuropsychological measurements used [41, 47, 48]. However, it is likely that, once cognitive dysfunction occurs, it may sometimes remain stable but is more often progressive and, in the long term, the likelihood increases that even persons with initial cognitive preservation may deteriorate [41, 48].

1.2.2.2 Fine hand use

There is limited research on fine hand use in people with MS in spite of the fact that upper extremity function plays an important role in the maintenance of functional independence [49]. More than 70% of people with MS in population-based studies have limited fine hand use [34, 50], and tasks such as cutting nails, using a hammer, peeling fruit or vegetables, buttoning clothes and shuffling and dealing cards are perceived as most difficult [51]. To my knowledge, no longitudinal study of fine hand use has been performed in people with MS.

1.2.2.3 Walking

Walking ability is often used by researchers and clinicians as a measure of disease progression in people with MS [52-54]. In population-based studies, at least 75% experience limitation in walking [34, 55], and only 23% have the walking speed needed to cross the street in Stockholm before the traffic lights have changed [34]. Walking problems increase the risk of falls [56], and changes of gait parameters such as reduced speed and stride length, and limited ankle motion have been detected even in the early phase [57, 58]. To my knowledge, no longitudinal study of walking has been performed in people with MS.

1.2.2.4 Energy

Lack of energy – fatigue – is defined as a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities [59]. The majority of people with MS report fatigue [60, 61], and more than one fourth consider it to be the most limiting symptom [60]. Fatigue is related to activity performance, but may be present even without preceding strain [62]. It influences the life situation of people with MS to a high degree [63]; limits the ability to maintain social roles [64] and is related to poor HRQOL [65-68]. In addition, it is a major determinant of change in work status in people with MS [69, 70] and may also predict change in disability status [71].

Longitudinal studies of fatigue in people with MS are scarce [72-75]. However, in a recent report almost half of an outpatient sample was shown to have persistent fatigue during an 18-month follow-up period [74].

1.2.2.5 Mood

Mood disorders comprise symptoms of inappropriate, exaggerated, or limited range of feelings [76]. Depression is the most common mood disorder in people with MS [77]. The diagnosis of major depression is based on the criteria in The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [76]. For major

depression, a person must have experienced at least five of the nine symptoms listed in the DSM-IV almost daily, for at least two weeks. One of the symptoms must be either depressed mood, or loss of interest. In clinical practice, screening for depression is often carried out with the help of questionnaires. The term, depressive symptoms, can be employed to describe what the questionnaires measure, since it is not possible to make the diagnosis of major depression merely on the results derived from questionnaires. The prevalence rates for depressive symptoms in people with MS range from 26% to 42% [78-80]. Depression in MS may be both a complication associated with MS, as well as a symptom of MS [81]. Depression has been found to be strongly associated with low HRQOL in several cross-sectional studies [44, 66-68, 79, 82] and associations between depressive symptoms and fatigue have also been reported [69, 83, 84].

Few longitudinal studies on depressive symptoms in people with MS have been performed. However, the results of a recent study revealed that global measures of depressive symptoms were quite stable over time when assessed twice, with a time lapse of three years. In contrast, mood symptoms varied considerably between the two assessments compared to other depressive symptoms [85].

1.2.2.6 Activities of daily living

Activities of daily living (ADL) are the things we do, including personal care and mobility activities, that are performed daily and are necessary for independent living [86]. The activities included in measures of ADL are not always the same, but basic ADL usually include bathing, dressing, eating, transfer from bed to chair, continence and toileting [86]. Another group of tasks that is more comprehensive is called Instrumental ADL [87]. These activities are not necessary for fundamental functioning, but enable the individual to live independently within a community. They include activities such as household activities and transportation [87]. In population-based studies, more than half of the people with MS have limitations in ADL [88, 89].

In a 10-year study on ADL trajectory in people with MS, significant changes occurred regardless of the number of years since diagnosis and relatively major decline began five years after diagnosis [90].

1.2.2.7 Social and lifestyle activities

Social/lifestyle activities are more complex activities regarding e.g., recreation and work that require some decision-making and organising on the part of the individual, both in the home and outdoors. For 38-65% of people with MS, participation in social/lifestyle activities is restricted [88, 89].

Results from a 10-year study on ADL trajectory in people with MS revealed a relatively low level of participation in social/lifestyle activities during the early phase of MS and a major decline ten years after diagnosis [90].

1.2.3 Personal factors

Personal factors included in this thesis comprise age, sex and Sense of Coherence (SOC). Some studies have reported that older people with MS are more likely to report a relatively good HRQOL than younger [91], whereas other studies have found no such association [82]. Results regarding the impact of sex are also conflicting, since some studies report that men have a better HRQOL than women [92], whereas other studies have found no differences in HRQOL with regard to sex [82].

1.2.3.1 Sense of coherence

Antonovsky introduced the salutogenic model, SOC, as a global orientation to view the world and the individual environment as comprehensible, manageable and meaningful, proposing that the way people view their lives influences their health [93]. The salutogenic approach is the search for the origins of health, described as an ease/disease continuum, rather than for the causes of disease [94]. An individual with a strong SOC, for instance, is thought to have more resources at hand to adjust successfully to living with a chronic disease such as MS. Weak SOC has recently been found to be associated with poor HRQOL and with depressive symptoms in people with MS [79, 95]. An individual's SOC is determined through childhood and early adulthood and is believed to be relatively stable after the age of 30 [93, 96], although changes in SOC over time have been reported [97].

1.2.4 Environmental factors

Environmental factors included in this thesis comprise: living with a partner, living with children, work status, immunomodulatory treatment and satisfaction with care. Some studies report a high divorce rate among people with MS [98], but the accuracy of these results is disputed [99]. One may assume that having children has a positive impact on quality of life but this might also be perceived as burdensome, due to the responsibility for support, for instance, but this has not yet been investigated in people with MS. Employment estimates for people with MS range from 23% to 44% [34, 95, 100-102] and unemployment increases with higher level of disability [102]. Several studies have revealed that not working is associated with poor HRQOL in people with MS [92, 95, 101]. The impact of immunomodulatory treatment on HRQOL is not clear since both a positive [103-105] and a negative impact have been reported [104, 106, 107]. There is some evidence for a beneficial effect of immunomodulatory treatment on cognitive function [108] and fatigue [109] although fatigue also has been reported as a side effect [110]. The possible association between immunomodulatory treatment and depressive symptoms is much debated and results are inconsistent [111].

1.2.4.1 Satisfaction with care

Health-related services are categorised in the component environmental factors of the ICF [31]. Satisfaction with care is not classified within the framework of the ICF but may be regarded as an environmental factor. It has been shown that patients' and physicians' perceptions of disability in MS differ [112] and people with disability and their nominated key providers have been found to perceive the needs for health-related services differently [113]. It is therefore important to identify the needs as perceived by the people with MS and to investigate their satisfaction with care. Satisfaction with care

is a complicated, multidimensional concept, including both affective and cognitive components [114]. It is related to quality of care [115, 116] and can provide health care providers with the means for improvement. Ware et al. have identified eight dimensions as the main sources of satisfaction with care: art of care, technical quality of care, accessibility, finances, physical environment, availability, continuity and efficacy/outcomes of care [117]. A number of studies have revealed that people with MS are dissatisfied with several areas of care, e.g. rehabilitation, psychosocial counselling, adaptations, coordination between services and advice concerning MS-related matters [118-124]. However, no study has explored the variation in perceived needs and satisfaction with care over time in people with MS. Furthermore, potential differences in subgroups, for instance with regard to sex and disease severity, are sparsely studied [119, 122, 124].

1.2.5 Perceived impact of MS on health

Health is defined by the World Health Organization (WHO) as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [125]. Quality of life is a multidimensional concept, defined by the WHO as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” [126]. HRQOL is a narrower concept focusing on those aspects that are affected by disease, usually encompassing the perceived impact on physical, emotional and social functioning [127], whereas health status is thought to focus mainly on physical functioning [128]. The different terms are ambiguous [129] but all of them incorporate the perspective of the individual. Patient-based outcome measures of general health status or HRQOL are important when evaluating the impact of MS on the individual and may even predict change in disability status [130, 131]. Several studies have shown that people with MS experience poorer HRQOL in comparison with the general population and compared to those diagnosed with other chronic diseases e.g., inflammatory bowel disease, and rheumatoid arthritis, even early in the disease process [132-134].

In people with MS, depressive symptoms have been found to be strongly associated with poor HRQOL in several cross-sectional studies [44, 66-68, 82, 95], whereas results concerning the impact of disease-related characteristics, e.g. duration, course and severity [66, 68, 82, 91, 95, 132, 135], fatigue [66-68], and cognition [44], are partially insufficient and contradictory. The impact of personal factors, e.g. sex and age [82, 91, 92], and environmental factors e.g., immunomodulatory treatment [103, 136], on HRQOL in people with MS is not fully explored and results are inconsistent.

Some longitudinal studies on self-reported general health status or HRQOL in people with MS have been performed [46, 130, 131, 137-140], but few studies have follow-up periods of more than six months [130, 131, 137, 138].

1.2.6 Longitudinal design

Longitudinal studies may be performed retrospectively or prospectively. In a prospective longitudinal study, data are collected with a specific aim and this design is the most effective research design to describe how individuals change over time [141].

Results of prospective longitudinal studies can identify similarities or differences in intra-individual and inter-individual change and the relationships of independent and dependent variables between time periods [142]. When the aim is to explore long-term outcome, longitudinal studies with few follow-ups may be appropriate. However, keeping in mind that MS is a heterogeneous and varying disease, it may be necessary to apply a longitudinal design with frequent follow-ups to describe the course of the disease. Measurement of change and interpretation of the clinical relevance of change are key issues in longitudinal research. Statistical significance tests tell us whether a difference can be attributed to chance, but indicate little about the magnitude of the difference and nothing about the clinical relevance. One way of interpreting difference is to present the percentage of individuals above or below a certain cut-off value based on population-based norms [127]. The magnitude of the difference can be interpreted by determining the minimal clinically important difference, which is the smallest difference in score that the patient perceives as important and which would cause clinicians to consider a change in the patient's management [127]. One way of determining the size of the minimal clinically important difference is to use an anchor-based method and examine the relationship between scores on the instrument whose interpretation is under question and some independent anchor measure [143]. When such information is unavailable, a distribution-based method may be used to calculate effect sizes, for example [127, 143].

1.2.7 Rationale for the thesis

The majority of people with MS live with the disease for most of their lives and experience various needs for health-related services over a period of many years. Consequently, knowledge concerning the presence and longitudinal variations in disability, in groups as well as in individuals with MS, is crucial when planning and organising health-related services. This knowledge will assist health care providers to supply timely and adequate services.

The natural history of MS has been described using the Expanded Disability Status Scale (EDSS) [54], as assessed by clinical examination or by self-report, for the assessment of disability [144-150]. Longitudinal studies using more specific instruments, with recommended cut-offs, to assess impairments, activity limitations and participation restrictions in people with MS are scarce [41, 47, 48, 73, 74, 85, 90]. Furthermore, previous longitudinal studies have assessed one disability at a time regarding, for example, energy [73, 74], cognition [41, 47, 48], mood [85] and ADL [90]. No study has made a longitudinal assessment of a number of concurrent disabilities in people with MS. Few longitudinal studies on self-reported health status or HRQOL in people with MS, with follow-up periods of more than six months, have been performed [130, 131, 137, 138] that take into account factors of importance for long-term outcome of the perceived impact of MS. Moreover, there is little or no knowledge concerning the longitudinal variations in disability and perceived impact of MS in subgroups as well as in individuals with MS.

With the access to disease-modifying drugs, people with MS are diagnosed at an early stage and many are cared for in MS specialist clinics, an established mode of care in Europe, USA and Canada [16]. There are few longitudinal studies on disability [47, 74]

and perceived impact on health [138] that focus on people with MS cared for in such clinics. Furthermore, it has been reported that there is a risk that disabilities in people with MS remain unidentified [151]. Hence, knowledge concerning the presence and course of various disabilities and of the perceived impact of MS has important clinical implications for health care providers, who see people with MS on a regular basis, as well as scientific implications for study design and the interpretation of results. Longitudinal studies are also necessary in order to explore predictors of change.

Considering the extensive costs of MS in terms of public spending, it is crucial that the health-related services supplied are effective and in accordance with needs as perceived by the people with MS. No study has explored the variation in perceived needs and satisfaction with care over time in people with MS and potential differences in subgroups, with regard to sex and disease severity, for instance, are sparsely studied [119, 122, 124]. This knowledge is important for the planning of health-related services for people with MS to meet perceived needs and optimise patient satisfaction.

2 AIMS

The overall aim of the thesis was to explore functioning and disability, perceived physical and psychological impact of MS on health and perceived needs and satisfaction with care, including variations over a two-year period, in people with MS at an outpatient MS specialist clinic.

Specific aims were to explore:

- I. Functioning and the concurrent presence of disabilities – concerning cognition, fine hand use, walking, energy, mood, ADL and social/lifestyle activities – with regard to disease severity, in people with MS; and to explore the perceived physical and psychological impact of MS on health, as well as the associations between disabilities and the perceived impact of MS.
- II. Variations over time in functioning and disability – with regard to cognition, fine hand use, walking, energy, mood, ADL and social/lifestyle activities – in people with MS, during a two-year period.
- III. Variations in the perceived physical and psychological impact of MS during a two-year period and to explore the capacity of selected factors – contextual factors (sex, age, SOC, cohabiting with a partner, living with children, work status, immunomodulatory treatment), disease-related characteristics (disease severity, disease course, time since diagnosis, bouts), cognition, fatigue, mood and time – to predict an increase in the perceived physical and psychological impact of MS, over a period of two years.
- IV. The perceived needs and satisfaction with care of people with MS during a two-year period, taking sex and disease severity into consideration.

3 MATERIALS AND METHODS

3.1 PARTICIPANTS AND PROCEDURES

Those eligible were all the people with MS, diagnosed according to the Poser criteria, [12], who, during the period from February 1, 2002 to June 12, 2002, were scheduled for an outpatient appointment with either of two of the senior neurologists at the MS Centre of the Department of Neurology, Karolinska University Hospital, Huddinge, in Stockholm, Sweden. The people with MS received written and oral information regarding the study and were included after informed consent. They were followed up every six months for two years, primarily in conjunction with the regular visits to their senior neurologist, or an appointment was made for data collection on another day. During inclusion and at 6, 12, 18 and 24 months, the people with MS met an investigator, one of five research physiotherapists, primarily the same investigator and at the same time of day on all occasions. The research physiotherapists were specialists and experienced in the field of neurology and co-trained before and during the study. Data were collected by means of tests and questionnaires.

3.2 MEASUREMENTS

Using the ICF [31] as a framework, a range of standardised measurements was employed to collect data reflecting aspects of seven areas of functioning and disability. In addition, data on perceived physical and psychological impact on health, from the perspective of the people with MS, were collected, as were data on disease-related variables and contextual factors, including perceived needs and satisfaction with care. Selection of instruments was based on recognised reliability and validity, recommendations in the literature and previous good experience with respect to feasibility for people with MS from a population-based Swedish study, the Stockholm MS Study [34, 79, 88, 95, 118]. The instruments were presented to each individual in a preset order, see Table 1.

3.2.1 Disease-related data

The senior neurologist determined disease course, registered occurrence of bouts during the preceding six months and assessed disease severity by means of the EDSS [54]. The remaining data were collected by the research physiotherapists. Data on the time lapse since diagnosis were collected from the medical records or, if not registered, by interview.

3.2.1.1 The EDSS

The EDSS [54] was originally developed to evaluate disability in people with MS. The scale includes assessment of pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual and mental functions, as well as assessment of walking distance and ambulation. The overall score for disease severity is then determined, ranging from 0 to 10, where 10 represents death due to MS. The validity and reliability of the EDSS has been questioned [152-154].

Table 1. Tests and questionnaires in order of performance

Tests and questionnaires	Points of data collection, months					Paper			
	0*	6	12	18	24	I	II	III	IV
1. Timed 25-Foot Walk	√	√	√	√	√	x	x	x	
2. Nine-Hole Peg Test	√	√	√	√	√	x	x	x	
3. Paced Auditory Serial Addition Test	√	√	√	√	√	x			
4. Mini Mental State Examination	√					x			
5. Symbol Digit Modalities Test	√	√	√	√	√	x	x	x	
6. Fatigue Severity Scale	√	√	√	√	√	x	x	x	
7. Sense of Coherence Scale†		√	√				x	x	
8. Multiple Sclerosis Impact Scale	√		√	√	√	x		x	
9. Questions concerning contextual data	√					x	x	x	x
10. Katz ADL Index Extended	√	√	√	√	√	x	x		
11. Frenchay Activities Index	√	√	√	√	√	x	x		
12. Beck Depression Inventory	√		√		√	x	x	x	
13. Questionnaire on perceived needs and satisfaction with care	√	√	√	√	√				x
14. Questions concerning medication	√	√	√	√	√	x	x	x	x

* inclusion

† data collected at 6 or 12 months

3.2.2 Functioning and disability

3.2.2.1 Cognition

Three instruments were used to cover different aspects of cognitive functioning.

3.2.2.1.1 The Mini Mental State Examination

The Mini Mental State Examination (MMSE) is widely used in clinical settings for screening general cognitive performance [155]. The MMSE includes 11 items, divided into two sections; the first requires verbal responses to orientation, memory, and attention questions. The second section requires reading and writing and covers ability to name, follow verbal and written commands, write a sentence, and copy a polygon. The total-sum score ranges from 0 to 30. Reliability and validity are considered good [86], although low sensitivity has been reported in people with MS [156].

3.2.2.1.2 The Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) was applied to assess complex scanning and visual tracking [157]. A key made up of pairings of numerical digits and geometric symbols is presented. The respondent is asked to substitute numbers for as many as possible of the various geometric symbols verbally, according to the key. The score is based on the number of correct responses made within 90 seconds. The SDMT was primarily administered in written format, but for those unable to write, the test was administered verbally. Enlarged font size was used for persons with visual problems.

The SDMT has been recommended as a sensitive cognitive screening test for people with MS [158, 159].

3.2.2.1.3 The Paced Auditory Serial Addition Test

The Paced Auditory Serial Addition Test (PASAT) was used to assess information-processing ability [160]. Administration of the PASAT involves presenting an audio-recorded series of single-digit numbers, where the two most recent digits must be added together. The digits are presented every three seconds during a period of three minutes. The PASAT score is the number of correct sums given by the respondent, where 60 is the maximal score. To minimise familiarity with stimulus items, two alternative forms of the PASAT have been developed. Presentation alternated between these forms at the various points of data collection. The PASAT is increasingly used in the cognitive evaluation of people with MS and is one of three components of the Multiple Sclerosis Functional Composite (MSFC) [53], which has been used as an outcome measure in clinical trials in MS [161]. The PASAT is valid and reliable but a learning effect has been proved and, furthermore, the test can be experienced as very stressful, which might cause dropout [162].

3.2.2.2 *Fine hand use*

3.2.2.2.1 The Nine-Hole Peg Test

The Nine-Hole Peg Test (NHPT) was used for assessment of fine hand use [163]. The instructions for the NHPT is, with one hand, to pick up and insert pegs, one by one, into each of nine holes in a board, and then to remove the nine pegs, one at a time, and put them back into the tray. The task of completing the sequence is timed with a stopwatch and the time in seconds is recorded. The mean time recorded for two trials with each hand is recorded. The NHPT is widely used in people with various neurological disorders and has proved to be valid and reliable [164]. It is one of the three components of the MSFC [53] and has been recommended for assessment of people with MS [159]. A mean change in scores of more than 20% has been proved to be a minimal clinically important difference [165].

3.2.2.3 *Walking*

3.2.2.3.1 The Timed 25-Foot Walk

The Timed 25-Foot Walk (T25FW) at maximum speed was used to assess walking ability [52]. Before the T25FW is performed, the individual is shown the 25-foot course, clearly marked on the floor in the testing area. The individual is instructed to walk as fast as possible, yet safely, not risking falling and not to slow down before passing the mark on the floor. Walking aids are allowed. A stopwatch is used to time the walk and the time needed to complete the walk in seconds is recorded. Trial 2 is performed immediately after completing trial 1 by walking the same distance again, back to the starting point. The mean time for two trials of the T25FW is recorded. The T25FW is one of the three components of the MSFC [53] and has been found to be valid and reliable for people with MS [166, 167]. A mean change in scores of more than 20% has been proved to be a minimal clinically important difference [165].

3.2.2.4 *Energy*

3.2.2.4.1 The Fatigue Severity Scale

Perceived level of energy – fatigue – was assessed using the Fatigue Severity Scale (FSS), reflecting the severity of fatigue and aspects of its impact on daily functioning [168]. It contains nine statements rated on a scale, ranging from 1 (strong disagreement) to 7 (strong agreement). The FSS score is the mean of all statement scores. The people with MS were asked to rate the statements according to their experience during the last six months. The FSS has been frequently used in studies of people with MS [60, 61] and other chronic conditions [168, 169], as well as in the general population [170], and has been found to be valid and reliable [168, 169].

3.2.2.5 *Mood*

3.2.2.5.1 The Beck Depression Inventory

The Beck Depression Inventory (BDI) was employed to assess mood – depressive symptoms [171]. Many of the symptoms listed in DSM-IV [76] are included in the BDI, being one of the most widely used self-report measures of depressive symptoms, which has been recommended as a screening measure for depression in people with MS [172]. It consists of 21 symptoms related to depression, each of which is self-rated from 0 (absent) to 3 (severe), and one item: 0 (absent) to 2 (severe). The ratings for each item make up the total score, ranging from 0 to 62; mild to moderate depression: 10-18, moderate to severe depression: 19-29, severe depression: 30-62 [173]. The BDI items can be grouped into three categories dealing with mood, evaluative and somatic/vegetative symptoms [174]. In the BDI-18, three items confounded by MS-related symptoms – work difficulty, fatigue, and concerns about health – are removed [175]. Both versions were calculated. Validity and reliability are considered good [86].

3.2.2.6 *Activities of daily living*

3.2.2.6.1 The Katz ADL Index

The Katz ADL Index Extended (KI) was used to assess ADL [176]. The KI is widely used and contains six personal activities: feeding, continence, transfer, going to the toilet, dressing and bathing, and four instrumental activities: cooking, transportation, cleaning, and shopping. The items were scored: 0 (dependent) or 1 (independent) and the sum score was used in the analyses as an ordinal scale. The reliability and validity of the KI has been found to be sufficient [177].

3.2.2.7 *Social/lifestyle activities*

3.2.2.7.1 The Frenchay Activities Index

The Frenchay Activities Index (FAI) was used to assess the frequency of social/lifestyle activities [178]. The scale consists of 15 items measuring activities in categories of domestic chores, leisure/work and outdoor activities. The items deal with activities that require some decision-making and organising on the part of the individual, both in the home and outside. The FAI scoring is based on the frequency with which an activity has been performed and ranges from 0 (inactive) to 45 (highly active). The FAI was originally developed for use in the stroke population, but has also been used in other

samples including people with Guillain Barré Syndrome [179] and people with MS [88]. Reliability and validity are considered good [178, 180].

3.2.3 Personal factors

Data on age were collected from the medical records.

3.2.3.1 SOC

3.2.3.1.1 The Sense of Coherence Scale

To assess SOC, the 13-item version of the SOC-scale was used [93]. The items are constructed as statements, which are rated by the respondent on a Likert scale from 1 to 7. The SOC-scale is considered valid and reliable and has been used in studies of people with various diseases including stroke [181], MS [79] and other chronic disorders [182], as well as in the general population [96].

3.2.4 Environmental factors

Information on cohabitation with a partner, living with children, work status and medication were collected by means of interviews.

3.2.4.1 Perceived needs and satisfaction with care

3.2.4.1.1 Questionnaire on perceived needs and satisfaction with care

Data regarding perceived needs and satisfaction with care during the past six months were collected using a questionnaire that has previously been used in studies of people with stroke [183], Guillain-Barré syndrome [184] and MS [118]. The questionnaire is based on the taxonomy of Ware [117], and includes the dimensions: art of care (engagement/sympathy, kind treatment), accessibility, technical quality of care, finances, availability, continuity and efficacy/outcomes of care. In addition, items dealing with diagnosis-related information, information about the disease and participation in planning care were included. The questionnaire consisted of 22 statements, which the people with MS were asked to agree or disagree with on a 5-grade scale. The alternative “not applicable” was also presented.

3.2.5 Perceived impact of MS on health

3.2.5.1 The Multiple Sclerosis Impact Scale

The disease-specific Multiple Sclerosis Impact Scale (MSIS-29) [185] was used for assessment of the perceived physical and psychological impact of MS on health, from the perspective of the people with MS. The MSIS-29 consists of two ordinal subscales, of which one assesses the physical impact and the other, the psychological impact of MS. The physical subscale contains 20 items and the psychological subscale, nine items. The items are constructed as questions “How much has your MS limited your ability to ...?” or “How much have you been bothered by...?” with a five-point response option (1 = not at all; 5 = extremely). The time frame for all questions is the preceding 2 weeks. The MSIS-29 has been psychometrically developed for people with MS and has proved to be valid and reliable [185-187]. A change in physical score of ≥ 7 in people with MS with an EDSS score of 0.0-5.0 and a change in physical score of \geq

8 in people with MS with an EDSS score of 5.5-8.0 has been proved to be a minimal clinically important difference [138].

3.3 CATEGORISATION OF VARIABLES

Criteria for the categorisation of variables are presented in Table 2. Age was categorised according to the mean age of the sample. When analysing work status, people with MS ≥ 65 years of age, the customary age for retirement in Sweden, were excluded. EDSS-scores were categorised according to the Swedish MS-register [188]. Recommended cut-offs were used for categorising the presence of weak or moderate versus strong SOC and the presence of disability in cognition, fine hand use, walking, energy, mood and social life/style activities. In Paper II, The BDI items were also grouped into three categories dealing with mood, evaluative and somatic/vegetative symptoms [174]. In the absence of a recommended cut-off for the KI, the criterion: dependent in one or more items was considered as indicating presence of disability. In addition, when deciding the number of disabilities per person (Paper I), and when exploring the variation in the presence of disabilities (Paper II), persons unable to perform the NHPT were assigned the score: 0 pegs/second, and were categorised as having limitation in fine hand use. Furthermore, persons unable to perform the T25FW were assigned the score: 0 metres/second, and were categorised as having limitation in walking. The perceived physical and psychological impact of MS, according to the MSIS-29, was categorised according to the quartiles of its distributions in the sample at inclusion; 1st category $< 25^{\text{th}}$ percentile, 2nd category $\geq 25^{\text{th}}$ to $< 50^{\text{th}}$ percentile, 3rd category $\geq 50^{\text{th}}$ to $< 75^{\text{th}}$ percentile, and 4th category $\geq 75^{\text{th}}$ percentile. According to this categorisation, the 1st category represents the lowest perceived impact and the 4th category represents the highest perceived impact. Satisfaction with care was dichotomised into satisfied (1-2 on the scale) or not satisfied (3-5 on the scale).

3.4 STATISTICAL ANALYSIS

Descriptive statistics, analysed in Statistica 7, were used in Paper I-IV. A probability value of equal to or less than 0.05 was considered statistically significant.

In Paper I, logistic regression employing proportional odds models was used to identify the associations of disabilities – concerning cognition, fine hand use, walking, energy, mood, ADL, and social/lifestyle activities – with the perceived physical and psychological impact according to the MSIS-29. Software used was SAS[®] System 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

In Papers II-III, analyses of statistically significant changes in scores during the study period were performed using Repeated Measures ANOVA for ratio data and Friedman ANOVA for ordinal data. As an estimation of the magnitude of variations, effect size was calculated by dividing the mean two-year change in score by the initial standard deviation [189]. Aiming to detect learning effects, effect size was also calculated using data from inclusion and at 12 months, and compared with effect size, which had been calculated using data from 12 months and 24 months (Paper II). Effect size was interpreted using Cohen's arbitrary criteria (0.2 = small, 0.5 = moderate and 0.8 = large) [190]. In addition, the mean/median change in score for each functioning was determined for all the people with MS.

In Paper III, the individual change in score during the study period was determined for the MSIS-29 physical and psychological subscales respectively. In the absence of established minimal clinically important difference in the psychological score, arbitrary intervals of five were used. Generalized Estimating Equations employing proportional odds models were used to explore the capacity of the independent variables (contextual factors, disease-related characteristics, cognition, energy, mood and time) to predict an increase in the perceived physical and psychological impact of MS. Interactions between time and the independent variables were controlled for, as were interaction between SOC and mood; SOC and level of energy; disease severity, disease course and time since diagnosis respectively; and between level of energy, cognition and mood respectively. People with MS with fatigue, depressive symptoms or cognitive impairment at one or more points in time were categorised as having fatigue, depressive symptoms or cognitive impairment. People with MS who had experienced one or more bouts during the study period were categorised as having bouts. Software used was SAS[®] System 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

In Paper IV, the Cochran Q test was performed for analyses of changes occurring during the study period, in proportions of people with MS with perceived needs regarding different health-related services. Chi square statistics were used for analyses of differences in sex and disease severity between individuals with perceived need for different health-related services and those with no perceived need, and between individuals who were satisfied with availability and those who were not.

3.5 ETHICAL APPROVAL

Ethical approval for all studies was obtained from the ethical committee of the Karolinska Institutet in Stockholm, Sweden.

Table 2. Criteria for categorisation of variables

Variable	Criteria
Time lapse since diagnosis	≤ 10 years since diagnosis / > 10 years since diagnosis
Bouts	No bouts / Bouts
Disease course	Relapsing remitting / Secondary progressive / Primary progressive
Disease severity	<i>The Expanded Disability Status Scale [54]</i> Normal (0) / mild (1.0-3.5) / moderate (4.0-5.5) / severe (6.0-9.5) [188]
Cohabiting with a partner	Cohabiting with a partner ≥ 18 years of age / Living alone
Living with children	Living with children < 18 years of age / Not living with children
Work status	Working, full-time or part-time / Not working
Immunomodulatory treatment	Immunomodulatory treatment / No immunomodulatory treatment
Sex	Women / Men
Age	< 47 years / ≥ 47 years
Sense of Coherence	<i>The Sense of Coherence Scale [93]</i> Sex-related norms: SOC weak or moderate: < 76 / SOC strong: ≥ 76 [191]
Cognition	<i>The Mini Mental State Examination [155]</i> < 28 [192] <i>The Symbol Digit Modalities Test [157]</i> Age-related norms, written or verbal reply, - 1.5 SD [157] <i>The Paced Auditory Serial Addition Test [160]</i> Norms for first test (2.4 sec), -1 SD [160]
Fine hand use	<i>The Nine-Hole Peg Test [163]</i> Seconds, age-/sex-related norms, +1 SD [163]
Walking	<i>The Timed 25-Foot Walk [52]</i> Meter/second, age-/sex-related norms, -1 SD [193]
Energy	<i>The Fatigue Severity Scale [168]</i> > 4 (Paper I-II) [168] ≥ 5 (Paper III) [83]
Mood	<i>The Beck Depression Inventory [171]</i> ≥ 10 (Paper I) [173] ≥ 13 (Paper II-III) [172] <i>The Beck Depression Inventory-18 [175]</i> ≥ 10 (Paper I) [173]
Activities of daily living	<i>The Katz ADL Index Extended [176]</i> Dependent in one or more items
Social/lifestyle activities	<i>The Frenchay Activities Index [178]</i> Age-/sex-related norms, < 25 th percentile [194]

4 RESULTS

4.1 SAMPLE CHARACTERISTICS

Of 255 eligible people with MS, 36 declined and 219 were included in the study. Data were collected within two weeks after the outpatient appointment for 204 of the 219 people with MS. For the 15 remaining persons, data were collected within 5 weeks, on average. Contextual and disease-related characteristics on inclusion are summarised in Table 3.

During the study period, seven persons died and 12 withdrew, leaving 200 to be followed for two years. Of those who died, the mean age was 52 years and six were women. One had mild MS, one had moderate and five had severe MS. Of those who withdrew, the mean age was 45 years and eight were women. Six had mild MS, two had moderate and four had severe MS. At 24 months, data were collected within two years \pm two weeks after inclusion for 147 of the 200 people with MS and, for the 53 remaining individuals, within two years \pm 4 weeks, on average. During the study period, 84% to 91% received immunomodulatory treatment and 23% had bouts.

Table 3. Contextual and disease-related characteristics on inclusion

Sample, n	219
Women, n (%)	149 (68)
Mean age, years (SD, range)	47 (12, 20–75)
Cohabiting with partner, n (%)	152 (69)
Living with children, n (%)	64 (29)
< 65 years of age*, working full or part time, n (%)	117 (58)
Disease severity, n (%)	
EDSS normal, 0†	1 (0.5)
EDSS mild, 1–3.5	129 (59)
EDSS moderate, 4–5.5	37 (17)
EDSS severe, 6–9.5	52 (23.5)
Years since diagnosis, mean (SD, range)	14 (10, 0–44)
Disease course, n (%)	
Relapsing remitting	127 (58)
Secondary progressive	83 (38)
Primary progressive	9 (4)
Immunomodulatory pharmacological treatment, n (%)	182 (83)
Symptomatic pharmacological treatment of:, n (%)	
Flu-like symptoms‡/pain	184 (84)
Spasticity	55 (25)
Depressive symptoms	49 (22)
Urogenital problems	41 (19)
Fatigue	23 (10)
Insomnia	21 (10)
Constipation/diarrhoea	8 (4)

* n = 201

† The results for the one person with EDSS normal is reported within EDSS mild

‡ Side effects associated with the immunomodulatory pharmacological treatment

4.2 PAPER I

4.2.1 Presence of disability

The proportions of people with MS able to complete the tests, functioning and presence of disabilities for those who completed the tests, regarding cognition, fine hand use, walking, energy, mood, ADL and social/lifestyle activities on inclusion are presented in Table 4. In the sample, 45 persons had no signs of cognitive impairment in any of the three cognitive instruments used. Using the BDI, 29.5% had mild, 10.5% moderate, and 2% severe depressive symptoms. Corresponding figures using the BDI-18 were 21.5% mild, 7% moderate and 0.5% severe depressive symptoms. The disabilities studied were more common among people with severe MS according to the EDSS, except for fatigue and depressive symptoms, which were most common among people with mild MS. The PASAT was completed to a lesser extent than the MMSE and the SDMT: only 48% completed the PASAT in the EDSS severe category.

In the sample, 19% had no (n=17) or one (n=25) disability, all with EDSS mild, whereas people with six or seven disabilities, 24% of the sample, were found in all EDSS categories. Seven of these, 3% of the sample, had EDSS mild. Two or more disabilities were found in 81% of the sample.

4.2.2 Perceived impact of MS on health

The largest proportion with low physical impact of MS was found in the EDSS mild category. Nevertheless, 10% experienced a high physical impact of MS (\geq 3rd quartile) in EDSS mild. The results concerning psychological impact indicated that people with mild and, in particular, moderate disease severity, had larger proportions with high impact (\geq 3rd quartile) compared with people in the EDSS severe category.

4.2.3 Associations between disabilities and perceived impact of MS on health

Results derived from the logistic regression analyses showed that fatigue (*odds ratio [OR] 12.47, confidence interval [CI] 6.21 to 25.02*), depressive symptoms (*OR 2.76, CI 1.49 to 5.14*), walking limitation (*OR 4.01, CI 1.96 to 8.23*), limitation in fine hand use (*OR 3.59, CI 1.60 to 8.08*) and limitation in ADL (*OR 3.66, CI 1.79 to 7.50*) were significantly associated with high perceived physical impact, whereas fatigue (*OR 5.77, CI 3.20 to 10.40*) and depressive symptoms (*OR 4.96, 2.69 to 9.17*) were significantly associated with high perceived psychological impact of MS. Fatigue and depressive symptoms were associated with both high physical and high psychological impact, and fatigue, common in all EDSS categories, had the strongest associations with both.

Table 4. Proportions of the sample and of EDSS categories able to complete the tests, functioning and proportions with disability on inclusion

Test	All n=219		EDSS mild n=130		EDSS moderate n=37		EDSS severe n=52	
	Completed the test %	Median (IQR) Mean (SD)*	Completed the test %	Disability %	Completed the test %	Disability %	Completed the test, %	Disability %
Mini-mental State Examination	99	27 (26-29)	100	38	100	62	96	74
Symbol Digit Modalities Test	96	35.5 (14.2)*	98	34	100	68	88	76
Paced Auditory Serial Addition Test	77	38.5 (14.2)*	88	35	78	72	48	56
Nine-Hole Peg Test †	93	32.6 (28.6)*	99	71	100	92	73	97
Nine-Hole Peg Test ‡	91	32 (23.4)*	98	64	100	95	67	100
Timed 25-Foot Walk	84	8.3 (12.8)*	100	22	100	89	35	100
Fatigue Severity Scale	99	5 (3.5-6)	99	60	100	95	96	64
Beck Depression Inventory Total	94	8 (5-14)	98	39	95	46	85	50
Beck Depression Inventory -18	94	6 (3-10)	98	25	95	40	85	30
Katz ADL Index - personal	100	6 (6-6)	100	4	100	22	100	69
Katz ADL Index - instrumental	100	4 (1-4)	100	15	100	59	100	96
Frenchay Activity Index	100	28 (17-35)	100	21	100	73	100	96

† dominant hand, ‡ non-dominant hand

4.3 PAPER II

4.3.1 Variations in functioning over time

During the study period, there were statistically significant variations in all functioning studied (cognition, fine hand use, walking, energy, mood, ADL and social/lifestyle activities), except in the total BDI score. Significant variations were found in the BDI category: mood symptoms, $p = 0.04$, but not in evaluative, $p = 0.18$, or somatic/vegetative symptoms, $p = 0.39$. When calculating the BDI using a cut-off ≥ 13 and the BDI-18 using a cut-off ≥ 10 , all the same persons but one were categorised as having depressive symptoms.

The effect size for the SDMT, based on data from inclusion and at 12 months (0.20), represented an improvement and was markedly larger than the effect size based on data from 12 months and 24 months (0.01). The effect size regarding the T25FW represented a decline and was large in the EDSS severe category and moderate in people with a primary progressive disease course. The effect size regarding the KI instrumental was large and, regarding the FAI, moderate in people with a primary progressive disease course, which represented declines. The other effect sizes were minimal or small (≤ 0.2).

During the study period, the largest mean change in scores with regard to the SDMT was found in people with bouts, in the EDSS mild category and in people with a relapsing remitting disease course. The smallest mean change in scores with regard to the NHPT and the T25FW were found in people with bouts, in the EDSS mild category and in people with a relapsing remitting disease course. There were no other apparent differences in mean/median changes in scores during the study period either between the whole sample and subgroups of people with or without bouts, or between men and women. Regarding the T25FW, 99 (63%) and, regarding the NHPT, 84 (46%) demonstrated $> 20\%$ mean change, including both improvements and declines.

4.3.2 Variations in disability over time

Proportions that varied over time regarding the presence of disability; proportions with disability at all times (inclusion, 6, 12, 18 and 24 months); and never, are presented in Table 5. Five persons (2.5%) had no disability, whereas 60% had limitation in fine hand use and 9%, depressive symptoms, throughout the study. During the two-year study period, the level of variation within the disabilities studied was 3% to 13%.

Table 5. Proportions of people with MS that varied regarding the presence of disability; proportions with disability at all times (inclusion, 6, 12, 18 and 24 months); and never

Disability (n)	Varied, %	All times, %	Never, %
Cognition (186)	32	24	44
Fine hand use * (198)	28	60	12
Walking * (197)	15	43	42
Energy (197)	36	44	20
Mood (185)	33	9	58
Activities of daily living – personal (198)	26	14	60
Activities of daily living – instrumental (198)	15	31	54
Social/lifestyle activities (197)	26	36	38

* Persons unable to perform the test due to MS are included

4.4 PAPER III

4.4.1 Variations over time in perceived impact of MS on health

Complete data on the MSIS-29 were collected at all points of data collection from 194 people with MS. During the two-year study period, there were no statistically significant variations in the physical subscale, $p = 0.12$, but variations were found in the psychological subscale, $p < 0.001$. The proportions of people with MS in the different categories were similar at all points in time. Regarding the physical subscale, 127 (65%) persons changed category one or more times during the study, whereas 67 (35%) remained in the same category: 29 in the 1st category, 8 in the 2nd category, 9 in the 3rd category and 21 in the 4th category. Regarding the psychological subscale, 149 (77%) persons changed category one or more times during the study, whereas 45 (23%) remained in the same category: 23 in the 1st category, 8 in the 2nd category, 4 in the 3rd category and 10 in the 4th category.

The effect sizes for the whole sample were negligible (< 0.2) in both subscales but small effect sizes were found in the EDSS moderate category with regard to the physical subscale and in the EDSS mild category with regard to the psychological subscale. In individuals with an inclusion EDSS of 0.0-5.0, 110 (74%) experienced a change in the MSIS-29 physical score of ≥ 7 . In individuals with an inclusion EDSS of 5.5-8.0, 35 (80%) experienced a change in the MSIS-29 physical score of ≥ 8 . Regarding the psychological subscale, 139 (72%) persons experienced a change of ≥ 5 , 69 (36%) ≥ 10 and 23 (12%) ≥ 15 .

4.4.2 Predictors of increased perceived impact of MS on health

The results of the Generalized Estimating Equations, presented in Table 6a and 6b, revealed that the probability of belonging to a certain category of the MSIS-29 did not change significantly over time, neither did time interact with the other independent variables. There were no interactions except between disease severity and disease course with regard to physical impact. A period of more than 10 years since diagnosis, cognitive impairment, fatigue and depressive symptoms were independent predictors of increase in perceived physical impact of MS. Mild disease severity in combination with a progressive disease course compared to a relapsing remitting disease course predicted an increase in physical impact as did a relapsing remitting disease course in

combination with moderate disease severity compared to mild disease severity. Weak or moderate SOC, no immunomodulatory treatment, fatigue and depressive symptoms were independent predictors of increased perceived psychological impact of MS.

Table 6a. Proportional odds for increase in perceived physical impact in people with MS (n=185); odds ratios (OR), 95 % confidence intervals (CI) and p values

Independent variable	Variable categorisation	Increase in perceived physical impact, OR (CI)	P value
Years since diagnosis	> 10 years since diagnosis	2.01 (1.23 to 3.28)	0.005
	≤ 10 years since diagnosis	1	
Cognition	Cognitive impairment	2.41 (1.49 to 3.90)	< 0.001
	No cognitive impairment	1	
Energy	Fatigue	10.60 (6.18 to 18.20)	< 0.001
	No fatigue	1	
Mood	Depressive symptoms	2.28 (1.42 to 3.65)	< 0.001
	No depressive symptoms	1	
EDSS mild / Disease course	Progressive	3.58 (1.23 to 10.46)	0.011
	Relapsing remitting	1	
Relapsing remitting / Disease severity	EDSS moderate	4.83 (1.95 to 11.95)	< 0.001
	EDSS mild	1	

Table 6b. Proportional odds for increase in perceived psychological impact in people with MS (n=185); odds ratios (OR), 95 % confidence intervals (CI) and p values

Independent variable	Variable categorisation	Increase in perceived psychological impact, OR (CI)	P value
Sense of coherence	SOC weak or moderate	2.32 (1.39 to 3.86)	0.001
	SOC strong	1	
Immunomodulatory treatment	No immunomodulatory treatment	1.64 (1.02 to 2.64)	0.04
	Immunomodulatory treatment	1	
Energy	Fatigue	4.50 (2.81 to 7.21)	< 0.001
	No fatigue	1	
Mood	Depressive symptoms	4.71 (3.01 to 7.36)	< 0.001
	No depressive symptoms	1	

4.5 PAPER IV

4.5.1 Perceived needs and satisfaction with care on inclusion

All the people with MS preferred an early diagnosis but only approximately half were satisfied with the situation in which the diagnosis was received. Most people with MS were satisfied in areas concerning information on the disease, art of care (engagement/sympathy, kind treatment), and accessibility, although fewer were satisfied with contacts with psychologists and the accessibility of physicians. Among the professional health care staff, the people with MS were most satisfied with nurses regarding all dimensions of care. For the majority, all the expertise needed had been

available, but most of those who perceived a need for information regarding social insurance/vocational rehabilitation and half of those who perceived a need for psychosocial support/counselling and rehabilitation periods had not received these services to the extent that they perceived necessary. High proportions perceived a need for physiotherapy (61%); occupational therapy (41%); and rehabilitation periods (a defined time-period of more intense rehabilitation at special rehabilitation units or in day care) (42%). However, more than one third of those who perceived a need were not satisfied with these areas of rehabilitation. The costs of care were considered onerous by 75%. The vast majority wanted to participate in planning their care but only 63% of those who perceived a need to participate were satisfied. Regarding continuity and efficacy/outcomes of care, the majority were satisfied.

4.5.2 Variations over time in perceived needs and satisfaction with care

On a group level, there were no statistically significant variations in the proportions of people with MS who had perceived needs concerning different health-related services, during the study period. Individual variations in perceived needs as well as in satisfaction with care were found regarding most health-related services. Few people perceived a persistent need of a specific health-related service during the study period but many perceived a need at least once but not throughout the entire study period. However, the majority perceived a need for rehabilitation (physiotherapy – 85%, occupational therapy – 62%, rehabilitation periods – 60.5%), assistive devices (69%), transportation service for the disabled (62%), psychosocial support/counselling (60%) and information on social insurance/vocational rehabilitation (56%) at all times or sometimes. Of those who perceived a need at all times or sometimes, the people with MS were most satisfied with the availability of assistive devices; workplace adaptation; home adaptation; and transportation services for the disabled. They were least satisfied with the availability of psychosocial support/counselling; and information on social insurance/vocational rehabilitation. Among those who perceived a persistent need, the transportation service for the disabled was the only item where more people were satisfied at all times than sometimes.

4.5.3 Perceived needs and satisfaction with care with regard to sex and disease severity

Women experienced a need for psychosocial support/counselling to a greater extent than men ($p = 0.04$). Severe MS, according to the EDSS, was associated with a greater perceived need and mild MS was associated with a smaller perceived need for availability in almost all the health-related services studied: physiotherapy ($p = 0.004$), occupational therapy ($p = 0.01$), rehabilitation periods ($p = 0.008$), assistive devices ($p = 0.002$), home adaptation ($p = 0.04$), transportation service for the disabled ($p = 0.002$) and home help/personal assistants ($p < 0.001$). However, there were no associations between disease severity and perceived need for psychosocial support/counselling and information on social insurance/vocational rehabilitation; nor were there any associations between satisfaction with care and sex or disease severity.

5 DISCUSSION

5.1 MAJOR FINDINGS

The results derived from this thesis contribute to the base of knowledge concerning the course of concurrent disabilities in MS and illustrate the fact that considerable variations in functioning and disability occur, including improvement and decline, in a relatively short period of time. The majority of the people with MS in the present thesis had mild MS according to the EDSS, yet a high concurrent presence of disability was found. Nearly all functioning studied varied significantly during the study period but there was no general deterioration in the sample. Variations were also found when using cut-offs to categorise the presence of disability. Furthermore, the perceived impact of MS varied, and predictors of an increase in physical and psychological impact were identified. Individual variations were also found in both perceived needs and satisfaction with care. Key services demanded by people with MS were identified, as well as areas with a potential for improvement with regard to satisfaction with care. The results presented in this thesis may be used in the planning of health-related services and could supply health care providers with ways to achieve improvement.

5.1.1 Functioning and disability

Although the majority of those studied had mild MS, the presence of cognitive impairment, limitation in fine hand use and depressive symptoms were similar to those reported in population-based studies [34, 35, 50, 78-80]. The presence of limitation in walking, fatigue and limitation in ADL was, however, lower [34, 55, 60, 88, 89]. The reasons for these similarities and differences are not clear since previous studies have not presented the presence of disability in subgroups of disease severity. However, the results in this thesis imply that the largest differences between subgroups of disease severity are found with regard to limitation in walking, fatigue and limitation in ADL, which might be one possible explanation. Even in EDSS mild, the majority had fatigue and limitation in fine hand use; one third had cognitive impairment; 25%, depressive symptoms: 20 %, limitation in walking and 15%, limitations in instrumental ADL. The majority, 81% of the sample, had two or more of the disabilities studied. These results imply that a composite score, like the EDSS, might be inadequate to detect disabilities in MS and may need to be complemented by disability-specific measures.

In line with our findings, long-term individual variability in cognitive functioning including both improvements and declines has been found [41, 48] but, to my knowledge, short-term variations have not previously been illustrated with the use of frequent follow-ups every six months. Eighty percent had fatigue at least at one point in time, whereas 44% remained fatigued during the whole study period, and 36% varied. This result is comparable with previous longitudinal studies of fatigue [73, 74]. No significant variation was found in the total BDI score but when the different BDI categories were analysed, mood symptoms varied significantly, similar to findings in a previous study [85]. The reasons for this result are not clear but one may speculate whether depression in MS differs from major depression, and that symptoms dealing with evaluative and somatic/vegetative symptoms of depression may be equally attributable to the MS disease [77], whereas symptoms dealing with mood are not. Our

results regarding significant variations in ADL and social/lifestyle activities are in agreement with a 10-year study on ADL trajectory in MS, in which significant changes occurred regardless of the number of years since diagnosis [90]. However, the more frequent follow-ups in the present thesis, compared to the 10-year study, demonstrate that variations occur also at shorter intervals.

The fact that people with MS with a primary progressive disease course are especially susceptible to rapid deterioration was reflected in the moderate and large effect sizes in this subgroup, which represented declines. However, the results concerning the primary progressive subgroup should be interpreted with caution since it consisted of only eight individuals. The effect size for the SDMT, based on data from inclusion and at 12 months was markedly larger than the effect size based on data from 12 months and 24 months, probably reflecting a practice effect. Notable was the fact that the largest mean change in score with regard to the SDMT was found in the EDSS mild category, possibly implying a considerable practice effect in this category. Similar mean/median changes were found in the subgroup with bouts and the EDSS mild category, probably reflecting the fact that the majority in the sample that experienced bouts had a mild degree of disease severity. Surprisingly, there were no other apparent differences in mean/median changes in scores between the whole sample and subgroups, with or without bouts, during the study period, suggesting that the variations cannot entirely be ascribed to bouts. The influence of bouts on disability progression is disputed since some studies suggest an association between bouts and worsening of disability [195], while other studies have found that disability progression is not obviously influenced by bouts [196]. As many as 63%, with regard to walking, and 46%, with regard to fine hand use, demonstrated > 20% mean change, which has been proved to be the minimal clinically important difference [165]. Concerning the other instruments included in this study, the minimal clinically important difference has not yet been determined, thus needing to be explored in future studies.

The variations in functioning and disability included both improvements and declines and no general deterioration could be found in the sample. Despite the fact that MS is a progressive disease, two years is a relatively limited period of time and probably too short to detect patterns of deterioration, except in the subgroup of people with a primary progressive disease course. The results suggest a need for a systematic and regular long-term assessment of functioning and disability in people with MS, in order to identify individuals at risk of deterioration.

5.1.2 Perceived impact of MS on health

In contrast to the negative linear relationship between disease severity and HRQOL that has been suggested in other studies [197], the results of the MSIS-29 indicated that the category of persons with mild and, in particular, moderate EDSS had larger proportions with a high psychological impact (\geq 3rd quartile) of MS compared with severe EDSS, which might be a sign of adaptation in the severe category. Similar findings have been reported in other studies [66, 68, 91, 95, 132] and might be the result of a response shift in those with severe MS, referring to a change in the meaning of one's self-evaluation of HRQOL, as a result of a change in internal standards, values, or conceptualisation [198]. Other possible explanations may be that important predictors of increased

psychological impact of MS e.g., fatigue and depressive symptoms, were less frequent in those with severe MS than in those with moderate MS. Furthermore, cognitive impairment was a predictor of increased physical impact of MS, but surprisingly not of increased psychological impact, suggesting that persons with cognitive impairment, which was more common among those with severe MS, perceive a physical rather than a psychological impact of MS. Some previous studies have found a relationship between cognitive impairment and poor HRQOL [43-45], whereas others have found no such association [46]. The fact that fatigue and depressive symptoms were independent predictors of an increase in both physical and psychological impact of MS, a result in line with other studies [44, 66-68, 82, 95], emphasises the importance of systematic and regular assessment of these areas of functioning, which have proved to be modifiable [28, 29]. In this thesis, disease duration of > 10 years since diagnosis was a predictor of increase in physical impact of MS. Previous results on the impact of long disease duration are conflicting since both a positive [91] and a negative impact [135] on HRQOL have been found. One possible explanation for these differences in results can be that different HRQOL measures have been used, focusing more or less on physical functioning. A negative impact of long disease duration was found for physical functioning using the Medical Outcome Study Short Form-36 and for mobility, self-care and social activities using the Disability and Impact Profile [135]. In contrast, a positive impact of long disease duration was found using the Leeds Multiple Sclerosis Quality of Life scale, which has no particular items related to physical functioning [91], and the positive impact may thus reflect an adaptation among those who have lived with the disease for a longer period of time, although the physical impact is still present. The predictive capacity of SOC has been sparsely explored but our results confirm those of a previous study, in which weak SOC was found to be associated with poor HRQOL [95]. However, we found weak or moderate SOC to be a predictor only of increased psychological impact. Absence of immunomodulatory treatment predicted an increase in psychological impact. This result might reflect either a lack of positive immunomodulatory treatment effect or, possibly, diminished hope in those who lack such treatment. Immunomodulatory treatment has proved mainly to reduce the number of relapses but one may speculate whether the treatment may positively influence other aspects of MS also, which, in turn, may have a positive impact on HRQOL. Previous findings on the impact of immunomodulatory treatment on HRQOL are conflicting since some studies report a positive impact [103-105, 137] while other have found a negative impact [106], at least partly due to adverse effects related to treatment [104, 107]. Somewhat surprisingly, occurrence of bouts did not predict an increase in the perceived impact of MS, in contrast to the findings of a previous study [197].

The effect sizes implied that the largest variations were found in the EDSS moderate category with regard to the physical subscale, and in the EDSS mild category with regard to the psychological subscale. In addition, despite the fact that no statistically significant variations were found in the physical subscale, as many as 74% of those with an EDSS score of 0.0-5.0 and 80 % of those with an EDSS score of 5.5-8.0 experienced a minimal clinically important difference [138]. Concerning the psychological subscale, we chose to present the changes in arbitrary intervals of five since the minimal clinically important difference for this subscale has not yet been determined, thus needing to be explored in future studies. A majority of the people with

MS experienced changes in psychological scores but we do not know whether they represent minimal clinically important differences. It is difficult to compare our results concerning variations with the findings of previous longitudinal studies since they differ considerably in terms of the clinical characteristics of the participants and study [46, 130, 131, 137-140] focus. To my knowledge few studies have follow-ups periods of more than six months [130, 131, 137, 138]. The aim of one previous study was to study changes over time and it found that the majority of people with MS experienced changes in scores on the MSIS-29 over a four-year study period [138].

5.1.3 Perceived needs and satisfaction with care

The majority preferred an early diagnosis, a result which tallied with previous studies [118, 199]. However, only around half were satisfied with the situation in which the diagnosis was received. This finding might reflect the fact that some persons in the sample received their diagnosis many years ago at a time when the diagnostic process was slower than today. The stress associated with receiving an MS diagnosis [200] may also have a negative impact on the degree of satisfaction. Nevertheless, some potential for improvements with regard to the diagnostic situation is likely to exist and should be further explored. Despite the fact that the people with MS met a neurologist every six months, as many as 35% of them were not satisfied with the accessibility of physicians, a result in line with a previous study [118]. This finding might reflect a need for more frequent visits or telephone contacts but may also illustrate the fact that physicians are gatekeepers to many health-related services. Previous studies have recognised the need for more effective care coordination [119, 201]. Future studies should identify the issues underlying the call for increased accessibility of physicians and explore how these needs could best be met e.g., by involving a multi-professional team or a designated care coordinator [15]. Among the professional health care staff, the people with MS were most satisfied with nurses regarding all dimensions. One possible explanation for this result may be that the majority received immunomodulatory treatment, entailing repeated contacts with nurses for instructions and assistance with the injections. This frequent contact may lead to the nurses becoming care coordinators. The results derived from previous studies revealing that people with MS exhibit high participation preferences [118, 202] were confirmed by the huge majority in the present thesis wanting to participate in planning their care. Involving people with MS in decision-making is included in the NICE guidelines [15] and in Sweden's Health and Medical Services Act [203].

On a group level, there were no statistically significant variations in proportions of people with MS with perceived needs concerning the health-related services studied during the study period. However, on the individual level, variations in perceived needs as well as in satisfaction with care were found. The reasons for these variations are not clear but might indicate that some needs are met or disappear while others vary as a consequence of the varying MS disease. All the same, the variations in needs and satisfaction with care agree with the variations found also regarding functioning and disability in people with MS. The results highlight the call for a flexible health care system that can provide services with a minimum delay and reduce the environmental barriers to optimised functioning. The majority perceived a need for rehabilitation, assistive devices, transportation service for the disabled, psychosocial

support/counselling and information on social insurance/vocational rehabilitation at all points in time or sometimes, suggesting that these are key services demanded by people with MS. Of those who perceived a need at all times or sometimes, the people with MS were most satisfied with the availability of assistive devices, workplace adaptation, home adaptation, and transportation service for the disabled, which indicates that the availability of these services may be regarded as reasonably satisfactory within the Swedish health care system. However, the people with MS were least satisfied with the availability of psychosocial support/counselling; and information on social insurance/vocational rehabilitation. Furthermore, the majority were burdened by the costs of care and one may assume that costs are especially onerous for the 42% of the sample not working. A flexible sick-leave system, an improved information service regarding social insurance issues and access to vocational rehabilitation services that respond to individual needs [204] might be facilitating environmental factors that could enable people with MS to work and might facilitate participation. The fact that the people with MS were not satisfied with the availability of psychosocial support/counselling possibly illustrates that this kind of service is in poor supply within the public social insurance system in Sweden but is mainly provided by private caregivers, entailing high costs for the individual. Another explanation may be that the concerns underlying the need for psychosocial support/counselling are less targeted than e.g. mobility problems. The cost of rehabilitation is relatively small. Nevertheless, a recent study of the costs of MS in Sweden revealed that the costs of rehabilitation were reduced from 8.6% in 1998 to 7.2% in 2005 [197]. Considering that large proportions reported a need for physiotherapy, occupational therapy, and rehabilitation periods and that more than one third were not satisfied, the rationale for the reduction in rehabilitation costs can be questioned. A regular and individualised review of the individual's care needs seems desirable, in accordance with the NICE guidelines [15]. One may assume that a comprehensive needs assessment is required, keeping in mind that less apparent disabilities, such as fatigue and depressive symptoms, are common in people with MS, and may be of importance for the individual's need of different health-related services, such as home-help service and psychosocial support/counselling.

As can be expected, a severe state of MS was associated with a greater perceived need for almost all the health-related services studied, a result in line with previous studies [119, 124]. However, the fact that persons with mild disease severity perceive a need for rehabilitation services to a lesser extent than those with a more severe state of MS might arise from expectations according to the way the health care system is structured, focusing on symptomatic treatment rather than on health promotion. The expectations and knowledge that people with MS have of the different health care providers' areas of expertise may have an impact on their perceived needs of different services as well as their satisfaction with care. Although a previous study revealed that surprisingly large proportions lacked information about appropriate exercises [122], maintaining the level of functioning with the assistance of e.g. a physiotherapist is perhaps not recognised as a need by persons with mild disease severity. People with MS risk a variety of secondary conditions, including physical deconditioning, weight problems and osteoporosis [205, 206], and a relationship between secondary conditions and health behaviour has been suggested [205, 207, 208]. Thus, a shift in focus, not only to include cure but also health promotion, would possibly be effective in terms of outcome

and costs, as has been shown in a previous study [209]. Health promotion programmes should be designed for people with MS.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Study sample

The aim of this thesis was to identify the presence of seven common disabilities in people with MS in contact with specialist MS care on a regular basis. The sample, with a majority of persons with mild MS according to the EDSS, is thought to be representative of such care and it is likely that our results regarding the presence of disability and variation in functioning over time can be extrapolated to other MS specialist clinics, keeping in mind that differences may occur between countries or regions in Sweden due to different structures of health care systems, for example. The use of clinical samples, as in this thesis, may cause a bias in estimates of functioning and disability if extrapolated to the population of people with MS. In comparison with a population-based study of people with MS in Stockholm County, the mean age of the present sample was lower; higher proportions had mild MS and higher proportions a relapsing remitting disease course [34]. The participants were recruited consecutively and a major strength was the low dropout rate.

The perceived needs and the level of satisfaction with care in the present thesis may be influenced by higher demands made by people with MS attending a specialist clinic. On the other hand, the potential for meeting the needs of the people with MS should be most advantageous at such a clinic and the opportunities for improvements e.g. enhanced availability of rehabilitation services, are excellent.

When interpreting the results, one should keep in mind that a large proportion of the sample received immunomodulatory treatment. The impact of such treatment and of other health care interventions on disability and perceived impact of MS is not fully understood and needs to be explored.

5.2.2 Design and procedure

Major strengths of this thesis were the longitudinal design with frequent follow-ups, and the exploration of seven concurrent areas of functioning and disability; perceived impact of MS and perceived needs and satisfaction with care, using valid and reliable tests and questionnaires in a standardised manner. Data were collected by five research physiotherapists, specialists and experienced in the field of neurology. No actual tests of inter-rater and test-retest reliability were performed. However, the research physiotherapists were co-trained before and during the study and, for each individual, data were collected primarily by the same physiotherapist and at the same time of day on all occasions. Although the presence of a health professional may have influenced the responses, one advantage, considering that cognitive impairment is common among people with MS, was the opportunity to explain the questionnaires. Furthermore, their presence ensured that the questionnaires were filled in by the people with MS and not by proxies, and the administration of the measurements as postal questionnaires would have caused ethical dilemmas.

The ICF is a consensus model and, so far, there is little scientific evidence for its validity. The associations between the different components are not verified and we lack suitable instruments to measure participation. Furthermore, it has even been questioned whether the component participation, should be included at all, since it presupposes the existence of a will, and the concept of will is lacking in the model [210, 211]. However, the use of the ICF as a conceptual framework was found to be helpful in offering a structure to study a combination of biological and psychosocial perspectives of the life situation of people with MS. The ICF [31] was only used for structure and the variables were not classified in detail, which might be seen as a shortcoming. On the other hand, the instruments used are valid and reliable and so far no valid and reliable instruments using the components of the ICF as a starting point have been developed.

A major strength of the present thesis was the use of disability-specific measurements with recommended cut-offs, in contrast to the majority of other longitudinal studies, in which disability has been graded according to the EDSS [144-150]. The high concurrent presence of disability that was found, as well as the variations in functioning and disability, also among those with mild MS, suggest that composite scores of MS symptoms, such as the EDSS, may be insufficient when assessing functioning and disability and does not incorporate the views of the people with MS. In the present thesis, scores on the EDSS were categorised in three categories: mild, moderate and severe disease severity. Thus, it is not likely that changes in EDSS scores during the study period would have influenced the results.

Seven disabilities, known to occur commonly, were studied. However, the presence of disability is likely to be underestimated, since some instruments were not completed by all persons and other known disabilities among people with MS: bladder, bowel and sexual dysfunction [212, 213]; and pain [214-216], for instance, were not explored. Ongoing pharmacological treatment e.g. for fatigue and depressive symptoms, may also have influenced the presence of disability.

In the present thesis, the SDMT [157] was primarily used to assess cognitive function since it has been recommended as a sensitive cognitive screening test in MS [158, 159]. However, our results point to a plausible learning curve, which is likely to obscure the variation of cognitive functioning during the two years. Practice effects have been reported in the PASAT [217] but need to be further explored for the SDMT. Furthermore, since the SDMT was primarily administered in written format, possibly including some persons with limitation in fine hand use, the proportion with cognitive impairment might have been overestimated. On the other hand, there are many aspects of cognitive function and detailed assessment of people with MS requires extensive batteries of neuropsychological tests. Thus, it is also plausible that the proportion with cognitive impairment was underestimated. Cognitive impairment, assessed with the SDMT, was found to be a predictor of an increase in perceived physical impact. However, since the SDMT does not capture all aspects of cognitive function, it is possible that other types of cognitive impairment have a different impact.

Day-to-day variability in the individual maximum walking distance, which is included in the overall score for disease severity as per the EDSS [54], as well as in the

maximum walking time in people with MS has been reported [218]. The average walking speed, which was used in this thesis, is considered to be more stable [218]. An increase in fatigue in people with MS has been reported, from the morning to the afternoon, while walking speed remains constant [219]. Nevertheless, in order to minimise the possible influence of fatigue, and of fluctuations in disability during the day, data for each individual were primarily collected at the same time of day on all occasions.

The FSS [168] was used to assess level of energy and different cut-offs for fatigue were used. In Papers I and II, the original cut-off of > 4 [168] was used, but in Paper III the revised categorisation with a cut-off ≥ 5 [83] was employed in order not to overestimate the presence of fatigue. Since increased fatigue in people with MS has been reported, from the morning to the afternoon [219], data for each individual were primarily collected at the same time of day on all occasions in order to minimise the effects of fluctuations during the day.

Depression is the most common mood impairment in people with MS [77]. However, other psychiatric disorders that may occur in people with MS, such as euphoria, and psychological laughing and crying, were not explored [77]. Different cut-offs for depressive symptoms according to the BDI were used. In Paper I, BDI [171] and BDI-18 [175] were calculated and a cut-off ≥ 10 was employed since it has usually been the recommended cut-off for minimal depression [173]. In Papers II and III, only the original BDI was calculated since a recent study supported the use of all BDI items when measuring depressive symptoms in people MS [220]. Furthermore, a cut-off ≥ 13 was used along with current recommendations [172]. In the present sample, the BDI and a cut-off ≥ 13 led to almost identical proportions of depressive symptoms as the use of the BDI-18 and a cut-off ≥ 10 , which supported the use of the original BDI and a cut-off ≥ 13 .

As might be expected, the KI [176] had clear ceiling effects but was complemented with the FAI, which includes more complex social and lifestyle activities [178]. The FAI was originally developed for use in the stroke population and its validity for younger populations has been questioned. It has been suggested that items specific to younger people, such as sports, should be included [194] as well as activities relevant to the MS population, such as going out using a mobility scooter for the disabled [88].

Data regarding SOC were collected at one point in time (6 or 12 months). SOC is considered to be relatively stable after the age of 30 [93, 96] but instability related to onset of disease or increasing age has also been reported, particularly among people with low SOC [97]. In the present thesis, data regarding SOC were categorised in two categories; weak/moderate or strong SOC. Thus, it is not likely that changes in SOC over the study period would have influenced the results.

Aiming to explore the perceived impact of MS on health, including predictors of an increase in perceived impact, we chose the disease-specific MSIS-29, consisting of items that are specific and relevant to people with MS [185]. Although generic measures make comparisons with the general population and with other diseases possible, they do not capture certain disease-specific areas and may have limited

responsiveness [221, 222]. Hence, a generic instrument would have complemented the disease-specific MSIS-29 in presenting a more detailed understanding of the perceived impact in our sample. Other disabilities: e.g. in bladder, bowel and sexual function and pain, are known to have an impact on HRQOL [214, 223, 224], but were not included in the Generalized Estimating Equation analysis, which might have influenced our results. Furthermore, additional contextual factors may be of importance for outcome in HRQOL: self-efficacy [140] and education level [225], for example.

In this thesis, perceived needs and satisfaction with care were explored from the perspective of the people with MS and it is not known whether our results reflect the actual care received. However, one may argue that the care supplied should concur with the perceived needs of the people with MS and areas with a potential for improvement were identified. Major strengths were the fact that the questionnaire included questions on both perceived needs and satisfaction with care in different dimensions and the low drop-out rate, as opposed to many previous studies in which postal questionnaires have been used [119, 122-124].

5.2.3 Statistical analysis

Parametric statistics were used for ratio data and non-parametric statistics for ordinal data. A major strength of the present thesis was the fact that the results were analysed both on a group level and an individual level. Several statistical approaches were used to describe the variation over time in different areas of functioning and disability and in the perceived physical and psychological impact of MS. The minimal clinically important difference has been determined in previous studies with regard to the NHPT [165], the T25FW [165] and the MSIS-29 [138]. Concerning the other instruments included in our study, the minimal clinically important differences have not yet been determined. We chose, therefore, to present effect size, which has proved to be useful as an estimation of the magnitude of variations. However, one should keep in mind that effect sizes are based solely on the variability of the measurements and do not consider the values and opinions of people with MS or of clinicians [127]. Furthermore, effect sizes are calculated using parametric statistics; consequently, the characteristics of the ordinal scale are not considered. Traditionally, effect size of 0.20 has been considered small but some results indicate that even small changes may be subjectively important to the individual [226, 227].

Generalized Estimating Equations is a modern statistical method used to approach longitudinal data. The advantages of Generalized Estimating Equations are that it allows for linear as well as non-linear data in the same analysis; the individuals are not required to have the same numbers of assessments; it can identify temporal patterns in the data and it can include interactions with time to test whether a predictor's effect varies over time [228].

5.2.4 Ethical considerations

The assessments, made every six months, repeatedly made the participants aware of different shortcomings, which might have been perceived as discouraging by some individuals but may also have assisted them in developing coping strategies. Some questions included in the questionnaires may have been perceived as discouraging or as

violating integrity. However, one should keep in mind that the questions were put to persons in regular contact with health care, who are used to discussing their state of health, and the extra attention and time spent with each individual made it possible to bring up issues not normally dealt with during an ordinary appointment. When needed, the investigator informed the participant about where to turn for professional support in different matters. The experience of the follow-ups was that most individuals were willing and positive to being assessed and sharing their experiences of living with MS, thus contributing to the base of knowledge needed to organise and supply adequate health-related services that may be beneficial for people with MS. Data collection was performed primarily in conjunction with regular visits to the neurologist in order to minimise the inconvenience for the individual but for those who so preferred, an appointment was made for another day. Furthermore, data were mostly collected by the same investigator for each individual.

5.3 CONCLUSIONS AND CLINICAL IMPLICATIONS

This outpatient sample of people with MS covered the whole range of disease severity as per the EDSS although the majority had mild MS. A high concurrent presence of disability was found, regardless of disease severity, which highlights the importance of making systematic assessments of the level of functioning also in individuals with mild MS, in order to identify disabilities. The fact that a relatively high concurrent presence of disabilities was found also in individuals with mild MS indicates a need to complement the EDSS assessment with other more disability-specific measurements. Given the range of disabilities that may occur in people with MS, a multidisciplinary approach is probably necessary to minimise the risk that disabilities may remain unidentified.

The perceived impact of MS on health should be considered, regardless of disease severity, since the largest proportions of people where the psychological impact of MS was high were found among those with mild and moderate MS, and since some people with mild MS perceived a high physical impact.

Nearly all functioning studied varied significantly during the two-year study period but there was no general deterioration in the sample. Variations in the presence of disability were also found. Considering the variation in functioning over time, a regular and multidimensional assessment of functioning and disability in people with MS is desirable. Furthermore, the variations demand flexibility in the supply of health-related services, as well as individualised interventions. The fluctuation in functioning over time and the conceivable learning effect inherent in some instruments used should be taken into consideration when designing studies and interpreting the results.

During the study period, the majority had changes in the perceived physical impact of MS of established important magnitude and the psychological impact varied significantly. A longitudinal analysis revealed that: a period of more than 10 years since diagnosis, cognitive impairment, fatigue and depressive symptoms were independent predictors of increase in physical impact. Weak or moderate sense of coherence, absence of immunomodulatory treatment, fatigue and depressive symptoms were independent predictors of increase in psychological impact. The knowledge of what are

the predictors of increase in perceived physical and psychological impact may be used to identify people with MS in need of special attention.

Rehabilitation, assistive devices, transportation services for the disabled, psychosocial support/counselling and information on social insurance/vocational rehabilitation, seem to be key services demanded by people with MS. Improved availability of rehabilitation services including an increase in the supply of psychosocial support/counselling; and information on social insurance/vocational rehabilitation could probably improve satisfaction with care.

5.4 FUTURE STUDIES

The two-year study period in this thesis is a relatively short period of time, considering that many people with MS live with the disease during most of their lives; thus, there is a need for more extended longitudinal studies, which may provide knowledge of the long-term impact of the variations found in the present thesis.

Future studies need to explore plausible contributors, e.g. contextual and disease-related factors, to the variations in disability over time, as well as to identify individuals with similar patterns in longitudinal changes.

Although outside the scope of this thesis, knowledge concerning evidence-based interventions in different areas of disability in people with MS is limited. Considering that the occurrence of bouts did not have a major influence on the perceived impact of MS on health in the present thesis, there is need to apply a broad range of approaches in developing also non-pharmacological interventions with the aim of improving the life situation for people with MS.

Qualitative studies to identify what issues underlie the perceived need for different health-related services and level of satisfaction with care are needed. For example, it has been proved that the reasons for a perceived need for rehabilitation may differ at different stages of the MS disease [229]. Satisfaction with care is a complicated, multidimensional concept, and should be studied further, e.g. the impact of met/un-met perceived needs and level of satisfaction with care on functioning and HRQOL. Future research is also needed to explore how the different needs of people with MS best should be met in terms of outcome and cost-effectiveness and what levels of satisfaction with care can be considered as acceptable in different dimensions.

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