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DISABILITY IN PEOPLE WITH MULTIPLE SCLEROSIS WITH FOCUS ON FATIGUE

Sverker Johansson

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Living with multiple sclerosis may be experienced as living in a whirl of several various consequences that are often demanding and difficult to cope with. A central prerequisite for an individual's capacity to participate in life areas of importance is her/his experience of an adequate energy level. Fatigue, a perceived lack of energy or energy loss, is commonly reported by people living with multiple sclerosis, thereby constituting a central threat against their ability to act and participate as desired. The cover page of this thesis is a detail from "The threat", painted by Lars Rading.

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ABSTRACT

Background: Knowledge of the concurrent presence of disabilities and of their association with the perceived physical and psychological impact of MS on health in people with MS is sparse. Fatigue is commonly reported and may cause limitations in daily life. Little is known regarding how fatigue varies over time and regarding which factors contribute to variations in fatigue. Dimensions of MS-related fatigue that can be modified by interventions need to be identified. Health services may alleviate the difficulties of living with a health condition, but the manner in which the presence or absence of fatigue is associated with the use of health services has not been explored.

Aim: To explore disabilities in people with MS and their association with the perceived physical and psychological impact on health; variations in fatigue and the capacity of selected factors to predict fatigue; the applicability of the Swedish Occupational Fatigue Inventory; and the use of health services in people with and without fatigue.

Methods: People with MS, outpatients at a specialist clinic were assessed every six months over the course of two years with tests and questionnaires, in order to collect data on disabilities (fatigue, depressive symptoms, cognitive impairment, limitation in walking and in fine hand use, limitation in activities of daily living, and restriction in social/lifestyle activities), contextual factors, disease-related variables, perceived physical and psychological impact of MS on health, and use of health services.

Results: Of the 219 people with MS included, 59% had mild MS. Two or more of the seven disabilities studied were found in 81%; 24% had six or seven disabilities. Fatigue and depressive symptoms were associated with both high perceived physical and high perceived psychological impact. During two years, 54% changed category of severity of fatigue and 27% had persistent fatigue. Depressive symptoms, weak/moderate sense of coherence, living with a partner and not working were independent predictors of increase in fatigue; people with moderate MS appeared at particular risk. The Swedish Occupational Fatigue Inventory appeared partly applicable for use in people with MS; it discriminated among dimensions and seemed to measure fatigue within a different construct than other frequently used scales. People with mild MS and fatigue used more outpatient health-care than people with mild MS without fatigue; few such differences were found in people with moderate/severe MS. Regardless of MS severity, higher proportions of people with fatigue than people without fatigue received informal care.

Conclusions: The high concurrent presence of disabilities in people with MS highlights the importance of systematic assessment of level of functioning in all states of the disease. In light of the variation of fatigue and the impact of depressive symptoms and contextual factors on fatigue, health services targeting people with MS should not only monitor disease-related variables but also apply a broad range of approaches to assess fatigue and provide appropriate interventions. The Swedish Occupational Fatigue Inventory might be a useful addition for the assessment of fatigue in MS, but development of the physical dimensions and the psychometric properties is needed. The generally higher use of health care in people with mild MS with fatigue suggests that a multi-professional team is best suited to provide services, even in the early phases of the disease. Health services should take the situation of partners and significant others into thorough consideration, regardless of MS severity, if fatigue is present. Authorities making decisions regarding the provision of salaried services in people with MS should always carefully consider the presence of fatigue.

SAMMANFATTNING

Bakgrund: Kunskapen om den samtidiga förekomsten av olika funktionshinder hos personer med MS och om sambanden mellan dessa hinder och upplevelsen av hälsa är bristfällig. Fatigue/trötthet är vanligt förekommande vid MS och begränsar förmågan att vara aktiv och delaktig i vardagen. Mer kunskap behövs om hur fatigue varierar över tid och vilka faktorer som förutsäger fatigue. Olika dimensioner av fatigue bör identifieras så att insatser som kan påverka fatigue kan utvecklas. Hälso- och sjukvårdsinsatser kan göra det lättare att leva med funktionshinder, men kunskap saknas om vilka insatser som personer med MS med och utan fatigue utnyttjar.

Syfte: Syftet med avhandlingen var att studera funktionshinder hos personer med MS och deras upplevelse av hur MS fysiskt och psykologiskt påverkar hälsan; hur fatigue varierar och vilka faktorer som förutsäger fatigue; användbarheten av The Swedish Occupational Fatigue Inventory för bedömning av fatigue vid MS; samt utnyttjandet av hälso- och sjukvårdsinsatser hos personer med MS med och utan fatigue.

Metod: Personer med MS vid en MS-mottagning bedömdes var sjätte månad under två år avseende förekomst av fatigue, depressiva symptom, kognitiv funktionsnedsättning, samt begränsning i gång och finmotorik, begränsning i det dagliga livets aktiviteter och i sociala/livsstilsaktiviteter. Data avseende kontextuella faktorer, sjukdomsrelaterade variabler, självskattad fysisk och psykologisk inverkan av MS, samt nyttjande av hälso- och sjukvård insamlades också.

Resultat: Av 219 inkluderade personer med MS hade 59 % en mild sjukdomsgrad. En hög samtidig förekomst av olika funktionshinder förelåg oavsett sjukdomsgrad. Både fatigue och depressiva symptom hade samband med upplevd omfattande fysisk och psykologisk påverkan av MS på hälsan. Under två år hade 27 % ihållande fatigue, medan 54 % varierade i sin skattning av fatigue. Depressiva symptom, svag/måttlig känsla av sammanhang, sammanboende och att inte arbeta var faktorer som förutsåg ökad fatigue, liksom måttlig grad av MS. The Swedish Occupational Fatigue Inventory kan delvis användas för bedömning av fatigue vid MS. Frågeformuläret särskilde dimensioner av fatigue och skulle kunna användas för bedömning av andra komponenter av fatigue än de som vanligtvis bedöms. Personer med mild MS och fatigue använde mer sjukvård än personer med mild MS utan fatigue, men nästan inga skillnader förelåg mellan personer med måttlig eller svår MS. Oavsett svårighetsgrad av MS-sjukdom hade en högre andel av personer med fatigue hjälp från närstående.

Konklusion: En hög samtidig förekomst av olika funktionshinder förelåg oavsett grad av MS, vilket understryker vikten av systematisk bedömning av funktions-tillstånd med specifika instrument oavsett sjukdomsgrad. Den stora variationen av fatigue, samt de depressiva symptomens och kontextuella faktorernas bidrag till ökad fatigue, antyder att hälso- och sjukvården bör ha ett vidgat arbetssätt vid bedömning av fatigue för att kunna utveckla och tillhandahålla lämpliga insatser. The Swedish Occupational Fatigue Inventory kan ge värdefull information angående fatigue utöver den som inhämtas med redan etablerade frågeformulär, men formuläret behöver utvecklas, särskilt dess fysiska dimensioner och psykometriska egenskaper. Det faktum att personer med mild MS och fatigue använder mer hälso- och sjukvård inom många områden antyder att ett multiprofessionellt arbetssätt bäst kan bemöta de behov som finns hos dessa individer. Om en person med MS har fatigue bör också de närståendes situation undersökas noggrant. Vid beslut om tilldelning av service bör beslutsfattare noggrant beakta om personen har fatigue, oavsett svårighetsgrad av MS.

LIST OF PUBLICATIONS

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CONTENTS

1	Introduction	1
1.1	Multiple sclerosis	1
1.2	Perceived impact of disease on health	2
1.3	The International Classification of Functioning, Disability and Health	3
1.4	Functioning and disability	4
1.4.1	Perceived energy level	4
1.4.2	Mood	5
1.4.3	Cognitive functions	6
1.4.4	Walking	6
1.4.5	Fine hand use	6
1.4.6	Activities in daily living	6
1.4.7	Social/lifestyle activities	7
1.5	Contextual factors	7
1.5.1	Sex; Age	7
1.5.2	Sense of coherence	7
1.5.3	Living with a partner; Living with children; Work status; Immunomodulatory treatment	7
1.5.4	Use of health services	8
1.6	Care and rehabilitation	8
1.7	Physiotherapy	9
1.8	Properties of measurements	9
1.9	Rationale	10
2	Aims	11
3	Methods	12
3.1	Design	12
3.2	Study population and procedures	12
3.3	Assessment of disability	13
3.3.1	Fatigue	13
3.3.2	Depressive symptoms	13
3.3.3	Cognitive impairment	14
3.3.4	Limitation in walking	14
3.3.5	Limitation in fine hand use	15
3.3.6	Limitation in activities of daily living	15
3.3.7	Restriction in social/lifestyle activities	15
3.4	Assessment of personal factors	15
3.4.1	Sex; Age	15
3.4.2	Sense of coherence	16
3.5	Assessment of environmental factors	16
3.5.1	Living with a partner; Living with children; Work status; Immunomodulatory treatment	16
3.5.2	Use of health-care services	16
3.5.3	Use of other health services	16
3.6	Assessment of disease-related variables	16
3.6.1	Disease severity; Disease course; Time since diagnosis	16

3.7	Assessment of perceived impact of MS on health	17
3.8	Categorisation of variables	17
3.9	Statistical analysis	19
3.10	Ethical approval	20
4	Results	21
4.1	Sample characteristics	21
4.2	Paper I.....	21
4.2.1	Presence of disability.....	21
4.2.2	Perceived impact of MS on health	23
4.2.3	Associations of disability with perceived impact of MS on health	23
4.3	Paper II	23
4.3.1	Variations in fatigue	23
4.3.2	Predictors of variations in fatigue.....	23
4.4	Paper III.....	25
4.4.1	Internal consistency and item-total correlations.....	25
4.4.2	Factor loadings	27
4.4.3	Correlations	27
4.5	Paper IV.....	27
4.5.1	Hospital outpatient care and primary care.....	27
4.5.2	Hospital inpatient care.....	28
4.5.3	Other health services	28
5	Discussion	29
5.1	Main findings	29
5.2	Disability and perceived impact of MS on health	29
5.2.1	Presence of disability.....	29
5.2.2	Fatigue.....	30
5.2.3	Perceived impact of MS on health	32
5.3	The Swedish Occupational Fatigue Inventory	32
5.4	Use of health services.....	33
5.5	Methodological considerations.....	36
5.5.1	Study sample	36
5.5.2	Design and procedure.....	36
5.5.3	Ethical considerations.....	40
5.6	Conclusions and clinical implications	40
5.7	Future studies.....	42
6	Acknowledgements.....	43
7	References.....	46
8	APPENDICES	59
8.1	Appendix 1	59
8.2	Appendix 2	60
8.3	Appendix 3	61

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
ICF	International Classification of Functioning, Disability and Health
IQR	Inter quartile range
KI	Katz ADL Index Extended
MMSE	Mini Mental State Examination
MS	Multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale
NICE	National Institute for Clinical Excellence
NHPT	Nine Hole Peg Test
OR	Odds ratio
PASAT	Paced Auditory Serial Addition Test
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SOC	Sense of coherence
SOFI	Swedish Occupational Fatigue Inventory
T25FW	Timed 25 Foot Walk

1 INTRODUCTION

In my work as a physiotherapist I have met people living with a wide range of disabilities due to neurological diseases/injuries. Such meetings have brought about an understanding that the situation of these people is often complex and influenced by many factors, for example the social context in which they live and how they manage to cope with a life situation in which several disabilities interplay. Multiple sclerosis (MS) is a particularly complex disease, due to its undecided origin; to its unpredictable onset early in life; to the wide range of possible disabilities that vary between individuals as well as within an individual over time; and to its progressive phase, which will eventually afflict most people with MS. The point of departure for this thesis has been to increase the understanding of the life situation of people with MS.

1.1 MULTIPLE SCLEROSIS

MS is a chronic inflammatory disease affecting the central nervous system and is believed to be mediated via autoimmune processes; inflammatory factors play an important role in the breakdown of myelin sheaths and axons, which leads to neuronal loss within the brain and the spinal cord [1, 2]. MS is thought to be caused by the interplay of genetic and environmental factors [1, 2]. The genetic influence can be illustrated by the fact that a monozygotic twin whose co-twin has MS has a 25% risk of developing MS, whereas the risk is 5% in dizygotic pairs and 3% in non-twin siblings [3]. The correlation between MS prevalence and latitude illustrates the environmental influence: prevalence figures rise closer to the Arctic/Antarctic Circles. MS is relatively common in geographical areas such as northern and central Europe, the United States, Canada, New Zealand and southern Australia [4]. The prevalence of MS in Sweden varies between 96/100 000 and 170/100 000 [5-7].

The MS diagnosis is based on clinical neurological examination as well as laboratory investigation. The Poser criteria require at least two bouts/relapses, in separate sites of the central nervous system and separated in time, found in the clinical examination and supported by findings from cerebrospinal fluid analysis or magnetic resonance imaging [8]. The McDonald criteria add evidence based on the development in magnetic resonance imaging and require a minimum of two attacks affecting more than one anatomical site. However, assuming an initial presentation suggestive of multiple sclerosis, the second lesion need not necessarily be clinically expressed [9, 10].

MS typically presents between 20 and 40 years of age [1] and is the leading cause of neurological disability in younger adults [11]. The disease reduces life expectancy by 5 to 10 years [1, 12]. MS is at least twice as common among women as men [1, 13]. Persistent disability is acquired through incomplete recovery from bouts, neurodegeneration and disease progression [2]. In about 85% of people with MS, the disease starts with a relapsing-remitting course, in which bouts evolve over a period of several days (minimum 24 hours), stabilise, and then improve, completely or partially. In about 15%, the course is progressive from onset, characterised by an unrelenting clinical decline [1]. The majority of people with a relapsing-remitting course will over time [1, 14] proceed into a secondary progressive course, with progression of disability with or without occasional bouts, minor remissions and plateaus [1]. An estimate for the median time from disease onset to reach secondary progression is 19

years [1]. The location of inflammatory lesions in the central nervous system varies and as a consequence there is a substantial variation in the symptoms experienced by different individuals. A wide range of disabilities are represented: motor disturbances (weakness, spasticity, ataxia); balance disturbances; sensory impairment; temperature sensitivity; pain; cognitive impairment; fatigue; emotional changes; mood impairment; bowel, bladder and sexual dysfunction; and visual impairment [1].

Although there is a substantial variation in disabilities experienced by people with MS, fatigue is one of the most frequently reported and affects an estimated 55% to 83% [15-20]. People with MS describe their fatigue as a time-consuming and all-absorbing phenomenon that can involve the body and the whole human being, and which can lead to emotional distress and a sense of dependency and being restricted in life [21]. The breadth of experiences of fatigue as perceived by people with MS cannot easily be related to objective signs of neurological impairment [16]. The fact that fatigue in itself is a subjective experience that might be invisible [22] and hidden [23] to others, can make it difficult for other people to understand its impact. It has been reported that health-care professionals as well as relatives sometimes do not understand the experiences of disability among people with MS [22, 24], including experiences of fatigue [22]. In this thesis the view of fatigue in people with MS has its starting point in a consensus definition, according to which fatigue in people with MS is a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities [25].

Most people with MS will live with an unpredictable and progressive disease with both physical and psychosocial consequences for a period of many years [11, 26]. Adjustments to disabilities challenge the individual's ability to cope with a life situation that may change during periods of time when bouts are present, or when disabilities remain persistent or progress. High levels of anxiety and distress in the early disease phase has been reported in people with MS [27, 28], which might reflect the uncertainty of and misgivings related to living with a disease like MS. General health status as perceived by the individual, a concept related to health-related quality of life, has been reported to be lower in people with MS compared with the general population [29], also early in the disease [30, 31]. In addition, quality of life has been reported to be lower in people with MS compared with people with other chronic diseases [32], underlining the high perceived impact of MS on health.

1.2 PERCEIVED IMPACT OF DISEASE ON HEALTH

The terminology for outcome measurements for individuals' perspectives on their health is not agreed upon. Several related concepts are used – for example, quality of life, health-related quality of life, health status, functional status, performance status, and functional well-being [33] – a variety which reflects the differences of emphasis between instruments. Some instruments are concerned with physical function and activities of daily living without reference to social and psychological factors; others ask global questions about health; still others focus on the impact of health or a health condition on a broad spectrum of aspects of life, for example family life and life satisfaction [33]. Quality of life is defined by the World Health Organization 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” [34]. Health-related quality of life is a narrower concept that intends to capture the physical, psychosocial, social and emotional aspects of quality of life [35-37], and health status focuses more on physical than mental functioning [38]. Generic instruments measuring perceived health might detect areas of the impact of a disease that may not be obvious from the clinical view and that enable comparisons with the general population and other disorders [39]. Disease-specific instruments assessing perceived health, on the other hand, address clinically important aspects of the impact of a specific health condition, implying greater sensitivity [39-41].

1.3 THE INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH

In order to understand the situation of an individual, the complex relationship between a health condition and the background of the individual needs to be understood. The International Classification of Functioning, Disability and Health (ICF) [42], which attempts to synthesise biological, individual and social perspectives into a coherent view of different perspectives of health, has been used as a frame in this thesis (see Figure 1). The ICF defines two sets of components: 1) Functioning and Disability, encompassing body functions and body structures, and activities and participation; and 2) Contextual Factors, encompassing environmental factors and personal factors. Functioning and disability are used as umbrella terms. Functioning describes non-problematic or neutral aspects of health and health-related states related to body functions, body structures, activities and participation. Disability describes problems that influence health or health-related states: impairments in body functions and structures, activity limitations and participation restrictions. Environmental factors make up the physical, social and attitudinal environment in which people live and conduct their lives. The basic construct of environmental factors is their facilitating or hindering impact on features of the physical, social and attitudinal world. Personal factors are the particular background of an individual’s life, comprising features of the individual that are not part of a health condition – for example, age, gender and coping styles – but that might influence functioning and disability.

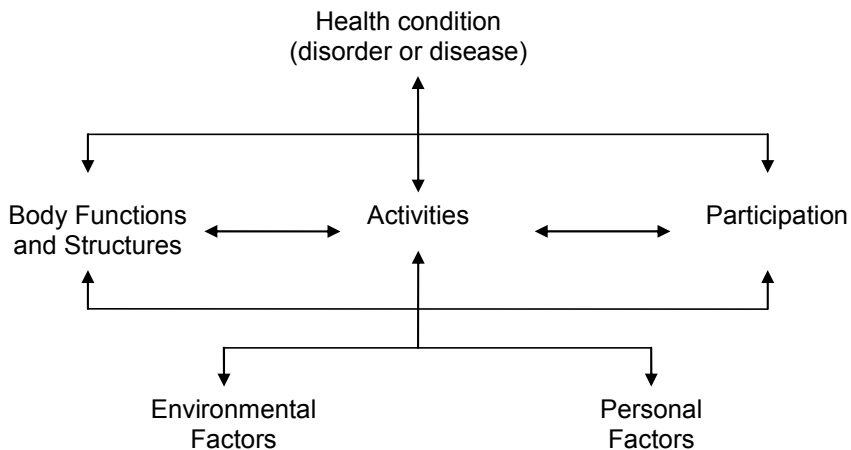


Figure 1. The theoretical model of the interactions between a health condition and the components of the International Classification of Functioning, Disability and Health

The ICF [42] does not classify a health condition (diseases, disorders, etc), but it can be systematically grouped within the domains associated with functioning and disability. An individual's functioning is a complex relationship between the health condition and contextual factors (see Figure 1). According to the ICF, the different components involved in an individual's functioning interact dynamically; thus, if the full health experience is to be described, it is important to collect data on various components independently and to then explore associations and causal links between them.

1.4 FUNCTIONING AND DISABILITY

Knowledge regarding the complex relationship between MS and the situation of the individual and her/his close family is limited. Studies that explore the complexity of the concurrent presence of disabilities and their associations with the perceived impact of MS on health, or that explore variations in disabilities over time, are sparse, as is knowledge of what health services people with MS actually use. In this thesis, disabilities commonly occurring in people with MS, as well as which health services people with MS use, were studied, with a particular focus on fatigue.

1.4.1 Perceived energy level

Energy and fatigue are related concepts. Energy is in the ICF [42] described in relation to an individual's management of her/his activity level. Furthermore, energy level is defined as a mental body function that produces vigour and stamina. Fatigue is in the ICF mentioned only in the context of body functions related to exercise tolerance, including functions of physical endurance, aerobic capacity, stamina and fatigability [42]. Though, the conceptual meanings of energy and fatigue vary [43]. Energy refers to both positive and negative aspects and constitutes as a disposable resource in daily life and may be connected with perceived health, while fatigue describes only the deficit in energy level and is thereby a problematic phenomenon [43].

Fatigue in MS is difficult to conceptualise and understand. One commonly used definition describes fatigue 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 [25]. This definition accentuates the fact that fatigue is subjectively perceived, that it refers to lack of either mental or physical energy or both, and that it interferes with desired activities. Using the ICF [42], fatigue is, according to the definition described above, related to the component body functions as well as to the component activities and participation. Other described characteristics of MS-related fatigue is that it comes on easily, prevents sustained physical functioning, is worsened by heat, interferes with responsibilities and causes frequent problems [16]. Fatigue in MS is related to activity performance but can be present even without preceding strain [44]. Fatigue has been described in terms of dependency and restrictions of life in general that interfere with vital goals in life [21] and as influencing all decisions regarding how to perform activities and responsibilities, both in leisure and work [21, 22]; indeed, it is a major determinant of change in work status [45, 46]. Fatigue limits the ability to maintain social roles [16, 47] and is associated with low health-related quality of life [44, 48-54].

In cross-sectional studies 55% to 83% of people with MS report fatigue [15-20], and 28% consider it to be the most limiting symptom [16]. Longitudinal studies of fatigue

in MS are scarce [55-57]; however, 37% to 48% of people with MS have reported persistent fatigue over a period of 18 to 24 months [55, 57].

Several approaches are used in order to measure MS-related fatigue. Performance-based, objective tests measuring decline during sustained motor [58-60] or cognitive activity [61-64] have been used in order to assess motor and cognitive fatigue. Such tests are useful for the assessment of certain muscle groups or aspects of cognitive function. However, the associations of self-reported fatigue with motor decline [60] and cognitive decline [61, 64] are often weak. One reason may be that self-reported measures mirror the perceived effort required to maintain a given level of sustained performance. The perceived effort may be higher for people with MS than for healthy people although there maybe not is any observable difference in the objective measurement of fatigue during the performance of the test [65]. Subjective measures of fatigue are appropriate since the definition of fatigue is based on experiences of the individual. These scales are sometimes criticised for being subjective, due to the risk for rater bias and since the ratings are retrospective [66]. Several self-report scales are used to capture MS-related fatigue. The most frequently used scales are probably the Fatigue Severity Scale (FSS), which grades the severity of fatigue in relation to its impact on daily functioning [67], and the Fatigue Impact Scale and its modified version, which measure the impact of fatigue on quality of life via its effect on cognitive, physical and psychosocial functioning [25, 68]. Other scales used are the Multidimensional Fatigue Inventory [69], the Fatigue Descriptive Scale [70], the Functional Assessment Instrument [71], and the Checklist of Individual Strength [72]. The scales predominantly measure fatigue within the ICF component activities and participation; in some scales aspects of body functions are also covered.

The causes of fatigue in MS are little understood. Primary fatigue may be the result of immune dysregulation, for example changed levels of cytokines [73-76]. Fatigue has not been found to correlate with active inflammation in the central nervous system; it might rather be linked to inflammation in the peripheral nerve system [77, 78]. Neuroendocrine dysregulation might also contribute to fatigue [75, 79-81], as might processes within the central nervous system, for example demyelination, reduced or delayed muscle innervation perhaps with a body temperature raise, but results are inconclusive [82-89]. Fatigue may also arise secondarily; several studies have reported an association with depressive symptoms [15, 45, 54-56, 90-93]. Other factors suggested to play a role in MS-related fatigue are impaired sleep [19, 53, 93], physical inactivity [94-96], medications [97-99] and personal factors [47, 100-102]. Results regarding the associations of fatigue with disease severity are inconclusive: absence [15, 89] as well as presence [20, 54, 92, 93] having been reported. Results regarding the associations of fatigue with disease course are indecisive: absence [91] and presence [17, 92, 103] having been reported. Studies on the associations of fatigue with disease duration have also reported both absence [90, 91] and presence [17, 92] of associations.

1.4.2 Mood

Depression and other symptoms of inappropriate, exaggerated, or limited range of feelings are included in mood disorders [104]. A diagnosis of major depression can, according to the Diagnostic and Statistical Manual of Mental Disorders IV [104], be made when five of nine symptoms (depressed mood, reduced interest in activities, sleep

disturbance, reduced energy level or energy loss, loss of appetite, self-accusation and feelings of guilt, changed motor function, difficulties in concentrating and making decisions, and suicidal thoughts) has been present daily during the past two weeks. One of these symptoms must be either depressed mood, or reduced interest in activities. The prevalence rates for depressive symptoms in people with MS range from 26% to 42% [105-107]. Associations of depressive symptoms with fatigue in people with MS have been reported [15, 45, 54-56, 90-93], as well as associations of both depressive symptoms and fatigue with aspects of health-related quality of life [48, 50].

1.4.3 Cognitive functions

Cognitive functions can be defined as all mental activities that are associated with thinking, knowing and remembering [108]. Memory, learning, conceptual reasoning, information processing speed, reaction time, attention, concentration, and executive function may be affected in people with MS, whereas recognition memory, implicit learning and speech comprehension usually remain intact [109]. The prevalence rates for cognitive impairment in people with MS range from 43% to 65% [110, 111]. Cognitive impairment also early in the disease has been reported [112]. Different courses of MS result in different cognitive profiles; impairments are more severe in people with a secondary progressive course, compared to primary progressive and relapsing-remitting courses [113]. It has been reported that cognitive impairment, independently from degree of physical disability, is associated with limitation in the ability of people with MS to work and take part in social activities [114, 115].

1.4.4 Walking

Walking ability is frequently used as a component in assessment of progression in MS [116, 117]. It has been reported that people with mild MS without evident signs of motor involvement have limitation in walking in terms of reduced speed and stride length and prolonged double support phase [118, 119]. Gait altered by disease has been linked to increased energy costs, fatigue and reduced capacity [120]. At the same time, the correlation between performance in the six-minute walk test and fatigue has been found to be only modest in people with mild or moderate state of MS [121]. On the other hand, people with mild or moderate MS rate their fatigue significantly worse in the afternoon compared to the morning, but exhibit no change in gait speed during the day [122]. The large majority of people with MS experience limitation in walking [110, 123] and the ability to walk without aid/support is associated with independence in activities in daily living (ADL) and normal frequency of social/lifestyle activities [124].

1.4.5 Fine hand use

Upper extremity disability in MS is seldom solely the result of muscle weakness but is compounded by ataxia and sensory impairment, which may lead to disability in various areas of functioning related to ADL [1]. Fine hand use in MS is more strongly associated with pinch strength than with grip strength [125]. At least 65% of people with MS in population-based studies experience limited fine hand use [110, 126].

1.4.6 Activities in daily living

Basic self-care activities such as bathing, dressing, transferring from a bed or chair, using the toilet, and eating are referred to as personal ADL [127, 128]. Instrumental ADL are more demanding tasks that might be required to enable participation in

domestic life and community activities, for example household chores, shopping and transportation [129]. In a recent Swedish population-based study, 28% of people with MS were dependent in personal ADL and 70% in instrumental ADL [124].

1.4.7 Social/lifestyle activities

Social/lifestyle activities refers to more complex activities related to participation in, for example, work/leisure and outdoor activities that require more initiative, organisation and decision-making on the part of the individual [130]. In previous studies, 38% to 65% of people with MS have been reported to be restricted in the ability to participate in social activities [124, 131].

1.5 CONTEXTUAL FACTORS

Personal factors studied in this thesis are sex, age and sense of coherence (SOC). Environmental factors studied are living with a partner, living with children, work status, immunomodulatory treatment, and use of health-care and other health services.

1.5.1 Sex; Age

Studies report that the proportions of women and men with MS experiencing fatigue do not differ [17, 45, 103]. Results regarding the associations of age with fatigue in MS are more inconclusive: absence [45, 47, 83] as well as presence of associations [17, 103] having been reported, the presence was however reported only for people with a primary progressive course in one study [17].

1.5.2 Sense of coherence

According to the ICF, coping style is a personal factor that contributes to how an individual perceives the impact of a health condition [42]. SOC, stemming from the salutogenic model, is a global orientation that describes an individual's ability to use her/his general resistance resources in the handling of stressful situations [132, 133]. The resistance resources assist a person in constructing coherent life experiences that are of importance for the successful handling of such situations. SOC grades the capacity of the individual to view the situation as meaningful, comprehensible and manageable [132, 133], which is of importance for the ability to cope successfully with the situation [134]. It has been proposed that SOC remains relatively stable over the adult life course [132]; however, changes over time have been reported [135, 136]. Weak SOC has been found to be associated with depressive symptoms in people with MS [106], but the influence of SOC on the perceived energy level of people with MS has not yet been explored.

1.5.3 Living with a partner; Living with children; Work status; Immunomodulatory treatment

Living with a chronic, progressive disease brings about changes for the individual with MS, but also for her/his partner, children and significant others. Few studies have explored the associations between the family situation and MS; a high proportion (30%) of divorces among people with MS has been reported [137], but these results have been questioned [138], and another study has reported the proportion of divorces as similar to the general population (13%) [139]. Living with children can be assumed as being strenuous and tiring but, on the other hand, it may instead be stimulating and

energising. However, no study has investigated the association between living with children and fatigue in people with MS. The proportion of people with MS working full-time or part-time varies from 23% to 50% [18, 55, 140-142]. It has been reported that the ability of people with MS and fatigue to continue working is associated with the individual's capacity to cope with her/his fatigue by reducing the working hours [46]. Reports on the effects of immunomodulatory treatment on quality of life in people with MS show conflicting results [143-145]. Fatigue has been reported as a side-effect of immunomodulatory treatment [97, 99, 146].

1.5.4 Use of health services

Use of health-care services and other health services is, according to the ICF, an environmental factor that might have impact on functioning and disability, thereby making living with a health condition easier or more difficult [42]. Thus it is of great importance to gain knowledge concerning the use of health services. In a population-based study of people with MS in Stockholm, Sweden, covering a period of three years, 92% of the sample had been in contact with outpatient neurology departments, 76% with other hospital outpatient departments and 54% with primary care [147]. No study that describes the manner in which the presence or absence of fatigue in people with MS is associated with the pattern of contacts with health services has been found.

1.6 CARE AND REHABILITATION

With the access to disease modifying drugs, diagnostic criteria in MS has been revised to allow an early diagnosis [9] and people with MS are cared for in MS specialist clinics, an established model of care in Europe, Canada and the United States [148]. There are no national guidelines for MS care in Sweden, but a Swedish manual for MS care [148] stresses that every individual with MS should have access to a neurologist if needed and that a multi-professional team should be available in order to develop health-care and support individual care providers. This is however a reality only in areas where the university hospitals are located [148]. According to the National Institute for Clinical Excellence (NICE), a British organisation responsible for providing guidelines on the promotion of health and on appropriate treatment, care and rehabilitation of people with diseases such as MS, specialist neurological health-care and rehabilitation services should be available to every individual with MS [149].

Disease-modifying pharmacological therapies are available since the 1990s; their effects are mainly related to a reduction of the relapse rate, thereby slowing down the progression of disability [150-152] as assigned with the Expanded Disability Status Scale (EDSS) [117]. However, they do not cure people with MS. Other symptomatic pharmacological treatments used in MS aims to treat for example pain, spasticity, bladder and bowel dysfunction, and depression [153, 154]. Pharmacological agents used with the aim to diminish fatigue are primarily amantadine and modafinil, however, studies have shown that the effects are only modest [155-157].

Rehabilitation in MS is regarded as a necessary component of comprehensive, quality health-care for people with MS, at all stages of the disease [158]. According to the NICE, a multidisciplinary team that involves both the person with MS and the family will achieve a better outcome [149], and a multidisciplinary approach with goal-

oriented programmes which include the perspective of the individual is recommended [159]. Rehabilitation is an active process of education and enablement, aiming to improve independence and quality of life by maximising ability and participation [153, 154]. Rehabilitation might be effective in reducing impairment, but its focus is to reduce activity limitations and participation restrictions, through holistic interventions, which include personal and environmental factors [149]. Evidence-based rehabilitation in MS, reviewed by The Cochrane Collaboration include exercise therapy [160], occupational therapy [161], psychological interventions [162], and multidisciplinary rehabilitation [163]. Regarding the rehabilitative effects on fatigue, results are not yet conclusive. It has been reported that fatigue can be alleviated by multidisciplinary inpatient [164] and outpatient [165] rehabilitation in people with mild and moderate MS, and by specific interventions, e.g., energy conservation courses [23, 166], aerobic exercise [167-169], yoga [170] and cooling therapy [171]. The difficulties in finding effective treatment for fatigue are probably at least in part due to poor understanding of the causes of fatigue [94, 98], the unpredictable and progressive nature of MS, the fact that each person with MS experiences combinations of disabilities that often are unique for the individual, and the fact that the disabilities are likely to vary over time [172].

1.7 PHYSIOTHERAPY

According to an early definition, physiotherapy is “the science of pathokinesiology and the application of therapeutic exercise for the prevention, evaluation and treatment of disorders of human motion” [173]. Carr & Shepherd stressed the focus on movement by describing physiotherapy as an applied movement science [174]. The World Confederation of Physical Therapy [175] has stated that functional movement is central to what it means to be healthy; the nature of physiotherapy is to provide services to people in order to develop, maintain and restore movement and functional ability throughout the life span, when movement and function are threatened by ageing, injury, disease or environmental factors. The concern is to maximise quality of life and movement potential within the spheres of promotion, prevention, intervention, habilitation and rehabilitation, with an aim to attaining physical, psychological, emotional, and social well-being. Physiotherapy involves the interaction between physiotherapist, patients, health professionals, families, caregivers, and communities in a process where movement potential is assessed and goals are agreed upon [175].

1.8 PROPERTIES OF MEASUREMENTS

Reliability is the extent to which an instrument measures something in a consistent and reproducible way, maximising the true score and minimising both the random and the systematic error inherent in the instrument [176, 177]. A reliable instrument should be stable, internally consistent and equivalent [177]. Internal consistency reflects the degree of inter-correlation or homogeneity between items [176]. Validity is the extent to which an instrument measures what it purports to measure. Instrument testing often does not completely prove the validity of the instrument but rather supports it by accumulating evidence of a number of aspects of validity [176, 177]. When an instrument developed for usage in one population is considered for use in a new population, tests of reliability as well as validity are needed, in order to clarify that the instrument’s construct and scalability is valid in the new population.

Most patient-based outcome measures consist of several items. If all items aim to measure a single aspect of a phenomenon (a latent factor) then the scale is unidimensional; if several aspects are covered then the scale is multidimensional. When the aim is to measure one or several more complex factors, several items are needed in order to cover all aspects of the particular factor. A major consideration when designing such scales is the determination of how consistently the items within a proposed factor (or dimension) hang together [178]. Furthermore, the item scores should demonstrate good variability and span the full scale range [179], and floor- and ceiling effects should be avoided [180].

1.9 RATIONALE

Comprehensive knowledge of the health experience of people with MS is limited. Contributing to the difficulties in understanding the effects of MS is the fact that the disabilities and their progression vary to a great extent between individuals, and also within an individual over time. In addition, it has been reported that there is a risk that disabilities remain unidentified [181]. There is a lack of studies that take into account the presence of concurrent disabilities in people with MS. In addition, there is a need for studies on disability and the perceived impact of MS on health focusing on people with MS cared for in MS specialist clinics.

Fatigue is commonly reported by people with MS [15-20]. Fatigue may be an extra challenge for the individual when coping with daily activities, or fatigue may in itself bring about activity limitations and participation restrictions which might threaten the roles and occupations of the individual in important areas of life [16, 21, 22, 46, 47]. A range of studies have reported the presence of fatigue in various samples of people with MS, but little is known of how the energy level varies over time [55-57], both on group level and individual level. Furthermore, little is known of which factors contribute to fatigue in people with MS.

Disability is, according to the ICF [42], a complex relationship between body functions and body structures; activities and participation; and environmental factors and personal factors. The dynamic interactions between these components make up the state of health of people with MS. Instruments frequently used to measure fatigue [25, 67, 68] emphasise the perceptions of people with MS regarding the impact of fatigue on their daily activities. The negative impact of fatigue, leading to activity limitations and participation restrictions in daily life highlights the need to identify components modifiable by interventions. Thus, an instrument that assesses fatigue within, for example, body functions, and that can discriminate between different dimensions of fatigue is needed and should be tested in people with MS.

Use of health services is an environmental factor that may have impact on functioning and disability, by facilitating or hindering the individual to live with a health condition [42]. Thus it is of great importance to gain knowledge concerning the use of health services and its association with various disabilities. No study has explored the manner in which the presence or absence of fatigue is associated with the pattern of use of health services.

2 AIMS

The overall aim of this thesis was to explore – with a particular focus on fatigue – aspects of disability, perceived physical and psychological impact of MS on health, and use of health services, in people with MS at an outpatient MS clinic who were followed over the course of two years.

The specific aims were to:

- I. explore functioning and the concurrent presence of disabilities – concerning perceived energy level, mood, cognition, walking, fine hand use, ADL and social/lifestyle activities – with regard to disease severity; to describe the perceived physical and psychological impact of MS on health; and to investigate the associations between disabilities and the perceived physical and psychological impact of MS on health;
- II. describe variations in fatigue in people with MS over the course of two years and to explore the predictive value on variations in fatigue of the following factors: sex, age, sense of coherence, living with a partner, living with children, work status, immunomodulatory treatment, mood, disease severity, disease course, time since diagnosis and time;
- III. investigate the applicability of the Swedish Occupational Fatigue Inventory and its ability to identify various dimensions of fatigue in people with MS;
- IV. explore and compare the use of health services in people with MS with and without fatigue during the study period.

3 METHODS

3.1 DESIGN

Papers I, II, III and IV are based on data collected in a prospective, longitudinal study of people with MS, who were outpatients at an MS specialist clinic and followed every six months over the course of two years. Of 255 eligible people with MS, 36 declined and 219 were included in the study. Table 1 gives an overview of how the collected data were used in the four papers at the different points of data collection and reports the number of people included at the five points of data collection. The studies have a descriptive, explorative and/or comparative design.

Table 1. Overview of how data collected at different time points were used in Papers I, II, III and IV, and the number of people still included at the various points of collection

Point of data collection	People with MS, n	Paper			
		I	II	III	IV
Inclusion	219	X	X	X	X
6 months	214		X		X
12 months	205		X	X	X
18 months	203		X		X
24 months	200		X	X	X

3.2 STUDY POPULATION AND PROCEDURES

All people with MS diagnosed according to the Poser criteria [8] were eligible 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 of Karolinska University Hospital, Huddinge, in Stockholm, Sweden. The people with MS received written and oral information regarding the study and were, after informed consent, included in the study at the appointment with the senior neurologist. In conjunction with the appointment, the included individual met an investigator, one of five research physiotherapists specialised and experienced in the field of neurology, or an appointment was made for data collection on another day. After inclusion, the people with MS were followed up at 6, 12, 18 and 24 months, primarily in conjunction with their regular appointments with the senior neurologist. Data collection at 24 months was finished on July 8, 2004, for the final individual. Data collection was carried out in the hospital, except for 10 occasions on which the data was collected in the individual's home or work place.

The senior neurologist determined disease course and assigned disease severity at the appointments. The remaining data were collected with tests and questionnaires by the research physiotherapists, for each individual primarily by the same physiotherapist at the same time of the day for all points of data collection. A research physiotherapist who had previously treated an individual with MS in the clinic did not carry out data collection on that individual. Formal tests of inter-rater reliability were not carried out, but before the study started and at regular intervals during the study period, the research physiotherapists were trained together in order to perform tests and to behave similarly during data collection. At each point of collection, the individual

with MS filled in the questionnaires and the research physiotherapist remained present, in order to administrate the tests and to explain the questionnaires if needed.

Using the ICF [42] as a framework, a range of standardised measurements were employed to collect data reflecting aspects of disability known to commonly occur in MS. In addition, data on the perceived physical and psychological health impact of MS, on SOC, on use of health services, on other contextual factors, and on disease-related variables, were collected. Selection of the measures was based on recognised reliability and validity, recommendations in the literature and previous good experience, with respect to feasibility for people with MS in a Swedish population-based study [106, 110, 124, 141, 147]. In sections 3.3 to 3.7 the methods employed are presented.

3.3 ASSESSMENT OF DISABILITY

3.3.1 Fatigue

3.3.1.1 The Fatigue Severity Scale

The FSS was used to assess perceived energy level, reflecting the severity of fatigue and aspects of its impact on daily functioning [67]. The FSS contains nine statements rated on a Likert scale, ranging from 1 (strong disagreement) to 7 (strong agreement). The people with MS were asked to rate the statements according to their experience during the last 6 months. The FSS score is the mean of all statement scores. High internal consistency [17, 55, 67, 182], strong correlation with other fatigue scales [20, 182] and test-retest reliability [182] have been shown. The FSS was developed for people with MS [67] and has been widely used to assess fatigue in people with chronic conditions [67, 182, 183] and in the general population [184]. In Appendix 1, the items of the FSS are categorised in relation to components of the ICF [42].

3.3.1.2 The Swedish Occupational Fatigue Inventory

The Swedish Occupational Fatigue Inventory (SOFI) was originally developed to measure subjective dimensions of work-related fatigue in people from 16 occupational settings who rated 95 verbal expressions on a Likert scale [185-187]. The SOFI consists of 20 items in which feelings of being tired are graded from 0 (not at all had such feelings) to 6 (had such feelings to a very high degree) [188], see Appendix 2. The items can be interpreted as *Lack of energy* (items: *worn out, spent, drained, overworked*), *Physical exertion* (items: *palpitations, sweaty, out of breath, breathing heavily*), *Physical discomfort* (items: *tense muscles, numbness, stiff joints, aching*), *Lack of motivation* (items: *lack of concern, passive, indifferent, uninterested*) and *Sleepiness* (items: *falling asleep, drowsy, yawning, sleepy*). *Lack of Energy* is defined as a general latent factor, and the other four factors are assumed to represent unique dimensions in various states of fatigue [188]. The applicability of the SOFI has been studied in patients with cancer undergoing radiotherapy treatment [189]. In Appendix 3, the items of the SOFI are categorised related to ICF components [42].

3.3.2 Depressive symptoms

3.3.2.1 The Beck Depression Inventory

The Beck Depression Inventory (BDI) [190] was used to assess depressive symptoms. The BDI consists of 21 items. The respondent rates 20 items from 0 (absent) to 3 (severe) and one item from 0 (absent) to 2 (severe). In total, the scale ranges from 0 to 62 points; mild to moderate depression 10 to 18 points; moderate to severe depression

19 to 29 points; and severe depression 30 to 62 points [191]. The BDI has been used in studies of people with MS, both the original version [190], and a version where three items (work difficulty, fatigue and concerns about one's own health), believed to falsely inflate the rate of depression in people with MS, are removed (BDI-18) [192]. Both versions were calculated. The reliability and validity are considered good [128].

3.3.3 Cognitive impairment

Three instruments were used to cover aspects of cognitive functioning.

3.3.3.1 The Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) was used for screening of general cognitive performance [193]. The MMSE is widely used in clinical settings [194, 195]. Of 11 items, a first section asks for verbal responses to questions measuring orientation, memory and attention, and a second section requires the ability to read and write and deals with the ability to name, follow verbal and written commands, write a sentence and copy a polygon. The scale ranges from 0–30 points. Reliability and validity are considered good [128], but low sensitivity for people with MS has been reported [196].

3.3.3.2 The Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) was applied to assess complex scanning and visual tracking [197]. The test assesses the capacity to direct attention quickly and accurately. A key made up of pairings of digits and geometrical symbols is presented, and the individual is asked to substitute numbers for the various geometric symbols according to the key during a period of 90 seconds. The SDMT score is the number of correct substitutions. The SDMT was primarily administered in written form, but was administered verbally for people with severe upper extremity dysfunction. Enlarged font size was used for individuals with visual problems. The SDMT has been recommended as a sensitive cognitive screening test in people with MS [198, 199].

3.3.3.3 The Paced Auditory Serial Addition Test

The Paced Auditory Serial Addition Test (PASAT) was used to assess information processing speed and flexibility, as well as calculation ability [200]. The PASAT is presented on audiotape. Single digits are presented every three seconds during a period of three minutes. The individual is asked to add each new digit to the one immediately prior to it and verbally present the result of each addition. The result is the number of correct sums given out of 60 possible sums. To minimise familiarity with stimulus items, two alternative forms of the PASAT have been developed; these were presented alternatively at the various points of data collection in the present study. The PASAT is reliable and valid [201]; but learning effects have been described [62, 201, 202], and the test can be stressful for the individual which might cause drop-outs [201, 202].

3.3.4 Limitation in walking

3.3.4.1 The Timed 25 Foot Walk

The Timed 25 Foot Walk (T25FW) at maximum speed was used to assess walking ability [203]. The individual is directed to one end of a clearly marked 25-foot course

(7.62 m) and is instructed to walk 25 feet as quickly as possible, but safely, and not to slow down until having passed the marked line on the floor 25 feet away. The task is repeated by asking the individual to walk back the same distance. If needed, a preferred assistive device is allowed. The examiner walks along with the individual when administering the test. The mean time of two trials is recorded (time limit 180 seconds per trial). Validity [204] and reliability [205] in people with MS have been confirmed.

3.3.5 Limitation in fine hand use

3.3.5.1 The Nine Hole Peg Test

The Nine Hole Peg Test (NHPT) was used for assessment of fine hand use [206]. A board, consisting of a container beside nine holes and anchored on a solid table is used. The individual picks up nine pegs from the container, with one hand only and only one peg at a time, and inserts the pegs into the holes of the board. Then, without pausing, the nine pegs are removed, one at a time and returned to the container. The mean times of two complete trials for each hand are recorded, starting with the dominant hand. The individual is asked to perform the task as fast as possible. The NHPT is recommended for the assessment of people with MS [199] and is considered valid and reliable [207].

3.3.6 Limitation in activities of daily living

3.3.6.1 The Katz ADL Index Extended

The Katz ADL Index Extended (KI) was used to assess personal and instrumental ADL [208]. The KI consists of ten items measuring independence/dependence in six personal and four instrumental activities. The personal activities are feeding, bathing, dressing, continence, toileting and transfer; the instrumental activities are cooking, cleaning indoors, transportation and shopping. The items were dichotomised to 0 (dependent) or 1 (independent), and the sum score was used in the analysis as an ordinal scale. The reliability and validity of the KI have been found to be sufficient [209].

3.3.7 Restriction in social/lifestyle activities

3.3.7.1 The Frenchay Activities Index

The Frenchay Activities Index (FAI) was used to assess frequency of social/lifestyle activities [210]. The FAI consists of 15 items, graded from 0 (inactive) to 3 (highly active), relating to general activities that require initiative and organising on the part of the individual. Ten items assess the frequency during the past three months of domestic tasks, leisure activities and outdoor transportation. Five items assess the frequency during the past six months of outings, gardening, household and car maintenance, reading books and gainful work. The maximum score of 45 indicates a high frequency of social/lifestyle activities. The FAI was developed for evaluation in people with stroke [210], but has also been used in people with disorders such as MS [124] and Guillain-Barré syndrome [211]. The reliability and validity are considered good [130].

3.4 ASSESSMENT OF PERSONAL FACTORS

3.4.1 Sex; Age

Data on age were collected from the medical records.

3.4.2 Sense of coherence

3.4.2.1 The Sense of Coherence Scale

The short version of the SOC scale was used to assess SOC [133]. The 13 items are all constructed as statements, which the respondent is asked to rate on a Likert-type scale ranging from 1 to 7, representing anchoring responses (for example, never and very often). The reliability and validity are considered good [133, 212].

3.5 ASSESSMENT OF ENVIRONMENTAL FACTORS

3.5.1 Living with a partner; Living with children; Work status; Immunomodulatory treatment

Data were collected by interview. Work status was applied for people with MS younger than 65 years of age, the customary age for retirement in Sweden.

3.5.2 Use of health-care services

Data on the use of health-care services, in the context of hospital outpatient care and primary care (the total number of contacts at different departments), as well as inpatient care periods (hospital stay in number of days), were obtained from the computerised register at the Stockholm County Council. This register contains information regarding all health-care contacts with care providers organised within the County that results in documentation of care in the medical records. The type of outpatient contacts recorded includes visits, telephone consultations, home visits and other matters. Total outpatient care included both hospital outpatient care and primary care and was categorised as medical care (contacts with physicians, nurses and nurse aids) or as rehabilitation (contacts with welfare officers, psychologists, occupational therapists, physiotherapists, dieticians, and speech and language therapists). Searches were carried out for the whole period during which data on fatigue was collected, in total a period of 30 months. A similar methodology has previously been used in a population-based study of people with MS in Stockholm County [147].

3.5.3 Use of other health services

Data on the use of other health services – home-help services; salaried personal assistants; salaried help from others; unsalaried informal care from spouses/partners and others; access to safety alarm systems; transportation service for the disabled; and periods of intense rehabilitation services at rehabilitation units – during the previous six months, were collected by interview according to a protocol [147] at each point of data collection, thus covering a period of 30 months. Informal care was categorised as assistance with personal or instrumental ADL according to the Katz ADL Index Extended [208], or as assistance with other matters (e.g., gardening and paying bills).

3.6 ASSESSMENT OF DISEASE-RELATED VARIABLES

3.6.1 Disease severity; Disease course; Time since diagnosis

3.6.1.1 The Expanded Disability Status Scale

The Expanded Disability Status Scale (EDSS) was used to assign disease severity [117]. The EDSS includes clinical examination of eight ordinal scales representing functional systems of the CNS: pyramidal functions, cerebellar functions, brain-stem functions, sensory functions, bowel functions, bladder functions, visual functions and mental functions. Scores for the various functional systems and other measures of function such as walking distance, need of aid when ambulating and dependence on

carers are used to determine an overall score for MS severity, ranging from 0 (normal neurological exam) to 9.5 (totally helpless) and to 10 (death due to MS). The EDSS is probably the most widely used instrument for quantifying disease severity in MS, but limitations in its scientific rigour have been described [213, 214].

Disease course was determined by the neurologist. Information about time since diagnosis was collected from the medical records or, if not registered, by interview.

3.7 ASSESSMENT OF PERCEIVED IMPACT OF MS ON HEALTH

3.7.1.1 The Multiple Sclerosis Impact Scale-29

The Multiple Sclerosis Impact Scale (MSIS-29) [215] was used for assessment of the perceived impact of MS on health from the perspective of people with MS. This patient-based, disease-specific instrument consists of two ordinal subscales: one physical subscale consisting of 20 items and one psychological subscale consisting of nine items. The items are constructed as questions regarding how much MS during the previous two weeks has limited or bothered the individual – “How much has your MS limited your ability to ...” or “How much have you been bothered by...” The items range from 1 (not at all being limited or bothered) to 5 (being extremely limited or bothered). The MSIS-29 has been psychometrically developed specifically for people with MS and has proven to be valid and reliable [215-217].

3.8 CATEGORISATION OF VARIABLES

All variables and instruments employed, as well as categorisation criteria, are presented in Table 2, in which the use of variables in Papers I, II, III and IV is also described. Fatigue was in Paper I categorised according to the original categorisation [67] and in Papers II, III and IV according to a revised categorisation which has been recommended in more recent studies [15, 17, 20]. Recommended cut-offs were used for categorising the presence of weak or moderate versus strong SOC [218]. Age was categorised according to the mean age of the sample. People unable to perform the NHPT and the T25FW were categorised as having limitation in fine hand use and in walking, respectively. The EDSS was categorised as normal (0), or as a mild (1.0 to 3.5), a moderate (4.0 to 5.5) or a severe (6.0 to 9.5) state of MS according to the Swedish MS Registry [219]. The perceived physical and psychological impact of MS on health, according to the MSIS-29, was categorised according to the quartiles of its distributions in the sample: 1st category < 25th percentile, 2nd category \geq 25th to < 50th percentile, 3rd category \geq 50th to < 75th percentile, and 4th category \geq 75th percentile. According to this categorisation, the 1st category represents the lowest perceived impact and the 4th category the highest perceived impact. The tests and questionnaires were presented to each individual in a preset order in order to minimise the effect of tiresome tests: T25FW, NHPT, PASAT, MMSE, SDMT, FSS, SOC, MSIS-29, KATZ, FAI, SOFI, BDI. The assessments were employed at all points of data collection, except for the following: the SOC was employed at 6 or 12 months; the MSIS-29 was employed at inclusion and at 12, 18 and 24 months; and the BDI was employed at inclusion and at 12 and 24 months.

Table 2. Variables; Instruments; Categorisation criteria; Use of variables in Paper I–IV.

Variables	Instruments Criteria for categorisation	Paper			
		I	II	III	IV
Energy level	<i>The Fatigue Severity Scale</i> non-fatigue ≤ 4.0 , fatigue > 4.0 [67]	X			
	non-fatigue ≤ 4.0 ; 4.0 < borderline fatigue < 5.0 ; and fatigue ≥ 5.0 [15, 17, 20]		X	X	X
Energy level	<i>The Swedish Occupational Fatigue Inventory</i>			X	
Mood	<i>The Beck Depression Inventory</i> $\geq 10^1$ [191] or $\geq 13^{2*}$ [220]	X	X ²		
Mood	<i>The Beck Depression Inventory-18</i>	X			
Walking	<i>The Timed 25 Foot Walk</i> Meter/second, age-/sex-related norms, -1 SD [221]	X			
Fine hand use	<i>The Nine Hole Peg Test</i> Seconds, age-/sex-related norms, $+1$ SD [206]	X			
Cognition	<i>The Mini Mental State Examination</i> < 28 [222]	X			
Cognition	<i>The Symbol Digit Modalities Test</i> Age-related norms, written/oral reply, -1.5 SD [197]	X			
Cognition	<i>The Paced Auditory Serial Addition Test</i> Norms for first test (2.4 sec), -1 SD [200]	X			
Activities of daily living	<i>The Katz ADL Index Extended</i> Dependent in one or more items	X			
Social/ lifestyle activities	<i>The Frenchay Activities Index</i> Age-/sex-related norms, $<$ lower quartile [130]	X			
Sex	Female/male		X		
Age	< 47 years / ≥ 47 years †		X		
Sense of coherence	<i>The Sense of Coherence Scale</i> Sex-related norms; weak/moderate < 76 /Strong ≥ 76 [218]		X		
Living with partner	Yes / No ‡		X		
Living with children	Yes / No ‡		X		
Work status	Working full- or part-time / Not working		X		
Immunomodulatory treatment	Yes / No	X	X		
Health-care services	Use of services, number of contacts				X
Other health services	Received/not received other health services				X
Disease severity	<i>The Expanded Disability Status Scale</i> Normal/Mild(1.0-3.5)/Moderate(4.0-5.5)/Severe(6.0-9.5)[219]	X	X	X	X
Disease course	Relapsing-remitting/Primary or secondary progressive	X	X		
Time since diagnosis	≤ 10 years / > 10 years		X		
Impact of MS	<i>The Multiple Sclerosis Impact Scale</i> 1 (low)–4 (high), per quartile of the distributions in the sample	X			

*Categorised as depressive symptoms if at any time during the study the BDI score was ≥ 13 , [220] otherwise categorised as no depressive symptoms (n = 198)

†Age: categorised as either below the mean age of the sample, or equal to and above this age

‡Considered a partner if 18 years of age or older and a child if younger than 18 years of age

3.9 STATISTICAL ANALYSIS

In Papers I, II and III, all people with MS under study were included in the analyses. In Paper IV, the analysis was based on those individuals who completed the two-year study and were residents within the Stockholm County, and who during the whole study period persistently had fatigue or non-fatigue.

The statistical methods used are summarised in Table 3. Probability values of 0.05 or less were considered statistically significant in all analyses. Software used was SPSS versions 13.0, 14.0 and 15.0 (SPSS Inc., Chicago, Illinois, USA), and SAS[®] System 9.1, (SAS Institute Inc., Cary, NC, USA).

Table 3. Statistical methods used in Papers I, II, III and IV

Paper I	Paper II	Paper III	Paper IV
Descriptive statistics	Descriptive statistics	Descriptive statistics	Descriptive statistics
Logistic regression	Chi-squared test	Cronbach's alpha	Mann-Whitney U test
	Friedman test	Item-total correlation	Chi-squared test
	Generalised estimating equations	Explanatory factor analysis	Fisher Exact test
	Bonferroni correction	Spearman rank correlation	

In Paper 1, logistic regression employing proportional odds models was used to identify the associations of disabilities regarding perceived energy level, mood, cognition, walking, fine hand use, ADL, and social/lifestyle activities, with the perceived physical and psychological impact of MS on health. Stepwise forward selection criterion for the entering of variables was employed.

In Paper II, a chi-squared test was employed for univariate analyses and the Friedman test for changes in FSS scores. Generalised estimating equations employing proportional odds [223-225] were used to explore the capacity of contextual factors, disease-related variables and mood to predict increase and decrease in fatigue. People with MS with at least one FSS score and complete data for the independent variables were included. Data regarding all independent variables were collected at inclusion, except SOC, which was collected at 6 or 12 months. Interactions between time and the independent variables were controlled for, as were interaction between SOC and mood, and between disease severity, disease course and time since diagnosis. Stepwise backward selection was employed. Pair-wise comparisons were adjusted for multiple comparisons with the Bonferroni correction. Separate generalised estimating equations were performed with the disease-related variables removed.

In Paper III, the internal consistency was calculated with Cronbach's alpha [226]. In case of alpha values lower than 0.70, analyses were performed to explore if the internal consistency could be improved by removing one or two of the items of the dimension at a time. Item-total correlations were calculated; item-total correlations higher than 0.30 were considered satisfactory [227]. Internal consistency and item-total correlations were analysed with regard to the whole sample and to disease

severity at inclusion. Explorative factor analyses using polychoric correlations [228] and promax rotation [229] were performed, to determine presence of underlying dimensions in the SOFI and factor loadings of the items included in the SOFI for people with MS. Factors with eigen values higher than 1 in the extraction phase were selected. Items with factor loadings higher than 0.50 and loading distinctly on one factor only were considered satisfactory. Correlations between the different dimensions arrived at in the final factor analysis, as well as correlations between the dimensions of the SOFI and the FSS, were assessed by the Spearman rank correlation coefficient with the a priori hypothesis that the correlations would be at most low. Coefficients from 0 to 0.25 were considered as “little if any correlation”; from 0.26 to 0.49 as “low correlation”; from 0.50 to 0.69 as “moderate correlation”; from 0.70 to 0.89 as “high correlation”; and from 0.90 to 1.0 as “very high correlation” [230].

In Paper IV, the use of health services during 30 months was analysed with regard to disease severity at inclusion, categorised as either mild or moderate/severe disease. People with and without fatigue in the same category of state of MS were compared with regard to use of services. The Mann-Whitney U test, a chi-squared test and the Fisher Exact test were used in order to analyse differences between groups with regard to continuous and categorical data, respectively.

3.10 ETHICAL APPROVAL

Ethical approval for the study, Papers I–IV, was obtained from the ethics committee of Karolinska Institutet in Stockholm (Dnr 449/01).

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 individuals, data were collected within 5 weeks on average. Contextual and disease-related characteristics at inclusion are summarised in Table 4. A total of 14 individuals were not residents in the Stockholm County. At 24 months, 200 people with MS had completed the study; seven (3.5%) had died and twelve (5.5%) had withdrawn. Data at 24 months were collected within two weeks before or after the 24 months had passed for 147 of the 200 people with MS, and within, on average, four weeks before or after, for the remaining 53. Seven people died: six were women, the mean age at inclusion was 52 years, and one, one and five individuals had, respectively, mild, moderate and severe MS. Twelve people declined further participation: eight were women, the mean age at inclusion was 44 years, and six, two and four individuals had, respectively, mild, moderate and severe MS.

Table 4. Contextual and disease-related characteristics at inclusion

Sample, n	219
Women, n (%)	149 (68)
Mean age, years (SD, range)	47 (12, 20–75)
Living 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 (%)	
Normal clinical examination, 0	1 (0.5)†
Mild state of MS, 1.0–3.5	129 (59)
Moderate state of MS, 4.0–5.5	37 (17)
Severe state of MS, 6.0–9.5	52 (23.5)
Time since diagnosis, years (SD, range)	14 (10, 0–44)
Disease course, n (%)	
Relapsing remitting	127 (58)
Secondary progressive	83 (38)
Primary progressive	9 (4)
Immunomodulatory treatment, n (%)	182 (83)

*< 65 years of age, n = 201

†The one person with a normal state is reported within a mild state of MS

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 at inclusion are shown in Table 5. In the sample, 45 people, 21%, had no cognitive impairment, according to any of the three cognitive tests 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 were more common

Table 5. Proportions of the sample and of categories of state of MS able to complete the tests, functioning and proportions with disability at inclusion

Test (range)	All n=219		Mild MS n=130		Moderate MS n=37		Severe MS n=52	
	Completed the test, %	Median (IQR) Mean (SD)*	Completed the test, %	Disability %	Completed the test, %	Disability %	Completed the test, %	Disability %
Fatigue Severity Scale, (0-7)	99	5 (3.5-6)	99	67 [§]	100	95	96	64
Beck Depression Inventory (0-62)	94	8 (5-14)	98	42	95	46	85	50
Beck Depression Inventory -18 (0-53)	94	6 (3-10)	98	29	95	40	85	30
Mini-mental State Examination (0-30)	99	27 (26-29)	100	50	100	62	96	74
Symbol Digit Modalities Test	96	35.5 (14.2)*	98	49	100	68	88	76
Paced Auditory Serial Addition Test (0-60)	77	38.5 (14.2)*	88	45	78	72	48	56
Timed 25 Foot Walk	84	8.3 (12.8)*	100	43	100	89	35	100
Nine Hole Peg Test †	93	32.6 (28.6)*	99	79	100	92	73	97
Nine Hole Peg Test ‡	91	32 (23.4)*	98	76	100	95	67	100
Katz ADL Index - personal (0-6)	100	6 (6-6)	100	22	100	22	100	69
Katz ADL Index - instrumental (0-4)	100	4 (1-4)	100	42	100	59	100	96
Frenchay Activity Index (0-45)	100	28 (17-35)	100	48	100	73	100	96

† dominant hand, ‡ non-dominant hand

§ Proportions with fatigue when using the revised categorization of the Fatigue Severity Scale (applied in Paper II, III and IV): in the sample 50%, in mild MS 43%, in moderate MS 81%, and in severe MS 46%

among people with severe MS, except for fatigue and depressive symptoms which were most common among people with moderate MS. In the sample, 19% had no (n=17) or one (n=25) disability, all categorised with mild MS; consequently, 81% of the sample had at least two disabilities. Fifty-two people, 24% of the sample, had 6 or 7 disabilities. They were found in all categories of MS severity, 7 of these had mild MS.

4.2.2 Perceived impact of MS on health

As expected the largest proportions with low physical impact of MS (< 1st quartile) were found in people with mild disease severity. Nevertheless, about 10% of people with mild MS experienced a high physical impact of MS (\geq 3rd quartile). Regarding psychological impact of MS, people with a severe state of MS had the largest proportion with low impact. The largest proportion with high psychological impact of MS was found in people with a moderate state of MS; a high proportion in this group also had high physical impact of MS.

4.2.3 Associations of disability with perceived impact of MS on health

Fatigue was associated with high physical impact of MS (odds ratio [OR] 12.47, 95% confidence interval [CI] 6.21 to 25.02) as well as with high psychological impact of MS (OR 5.77, CI 3.20 to 10.40). Depressive symptoms was also associated with both high physical impact of MS (OR 2.76, CI 1.49 to 5.14) and high psychological impact of MS (OR 4.96, CI 2.69 to 9.17). The other disabilities associated with high physical impact of MS were limitation in walking (OR 4.01, CI 1.96 to 8.23), in fine hand use (OR 3.59, CI 1.60 to 8.08) and in ADL (OR 3.66, CI 1.79 to 7.50). No more associations with high psychological impact of MS were found.

4.3 PAPER II

4.3.1 Variations in fatigue

The FSS was completed by 98.5% to 100% of people with MS at the five points of data collection. For people with FSS scores at all points of data collection (n=197), the scores varied significantly ($p = 0.02$). Proportions per FSS category at the various time points varied from 32% to 39% for non-fatigue, from 14% to 18% for borderline fatigue and from 45% to 52% for fatigue. During the study, 106 people with MS (54%) changed FSS category one to four times, while 91 (46%) remained in the same FSS category; 53 of the latter (27%) had fatigue and 38 (19%) had non-fatigue.

4.3.2 Predictors of variations in fatigue

The probability of belonging to a certain FSS category did not change over time; time did not interact with the other variables, nor did SOC with mood. Disease severity interacted with time since diagnosis and disease course. Independent predictors of increase in fatigue were depressive symptoms, weak or moderate SOC, living with a partner and not working, see Table 6. Regarding disease-related variables, a moderate state of MS in conjunction with a period of more than 10 years since diagnosis predicted increase in fatigue, when compared to both a mild and a severe state of MS, as well as a moderate state of MS in conjunction with a progressive disease course, when compared to a mild state of MS, see Table 6. Reciprocal categories of the same variables predicted a decrease in fatigue and displayed similar predictive values: no depressive symptoms, strong SOC, living alone and working. Furthermore, a mild and

a severe state of MS in conjunction with a period of more than 10 years since diagnosis compared to a moderate state of MS predicted decrease in fatigue, as did a mild state of MS in conjunction with a progressive disease course compared to a moderate state of MS.

Table 6. Proportional odds for increase in fatigue in people with MS (n = 193); odds ratios (OR), 95% confidence intervals (CI) and p values

Independent variable	Variable categorisations	Increase in fatigue OR (CI)	P value
Mood	Depressive symptoms	2.73 (1.65 to 4.51)	< 0.0001
	No depressive symptoms	1	
Sense of coherence	SOC weak or moderate	1.90 (1.12 to 3.20)	0.017
	SOC strong	1	
Living with a partner	Living with a partner	1.92 (1.09 to 3.39)	0.025
	Living alone	1	
Work status†	Not working	1.78 (1.01 to 3.15)	0.0047
	Working	1	
>10 years since diagnosis/ Disease severity	Moderate state of MS	13.39 (2.03 to 88.47)	0.001
>10 years since diagnosis/ Disease severity	Mild state of MS	1	0.0234
	Moderate state of MS	19.49 (1.27 to 303.03)	
Progressive course / Disease severity	Severe state of MS	1	0.001
	Moderate state of MS	37.83 (3.12 to 459.00)	
Disease severity	Mild state of MS	1	

†Work status: applied for people with MS younger than 65 years of age (n = 177)

The independent predictors of increase in fatigue when disease-related variables were removed were depressive symptoms, weak or moderate SOC, living with a partner and age higher than or equal to 47 years, see Table 7. Reciprocal categories predicted decrease: no depressive symptoms, strong SOC, living alone and age lower than 47 years.

Table 7. Proportional odds for increase in fatigue in people with MS, disease-related variables removed from the model (n = 193); odds ratios (OR), 95% confidence intervals (CI) and p values

Independent variable	Variable categorisations	Increase in fatigue OR (CI)	P value
Mood	Depressive symptoms	2.51 (1.54 to 4.10)	0.0002
	No depressive symptoms	1	
Sense of coherence	SOC weak or moderate	1.79 (1.04 to 3.06)	0.0342
	SOC strong	1	
Living with a partner	Living with a partner	1.76 (1.04 to 3.00)	0.0357
	Living alone	1	
Age	≥ 47 years	1.75 (1.10 to 2.79)	0.0184
	< 47 years	1	

4.4 PAPER III

The proportion of people with MS who completed the SOFI at inclusion and at 12 and 24 months varied from 97% to 99%. The whole range (0 to 6) was used in all items. Floor effects were found. In two items (*palpitations* and *breathing heavily*) more than half of the sample, and in ten items (*lack of concern, falling asleep, sweaty, passive, stiff joints, indifferent, out of breath, drained, aching* and *uninterested*) more than one fourth, scored zero at each point of data collection. In two items (*numbness* and *overworked*) more than one fourth scored zero at least once. When the dimensions were ranked by their median score, *Lack of energy* had the highest ratings at all points of data collection, while *Physical exertion* had the lowest, see Table 8.

Table 8. Mean scores, standard deviations (SD), median scores, interquartile ranges (IQR) and ranges in five dimensions of the Swedish Occupational Fatigue Inventory (20 items); n = 195, people who completed the SOFI at inclusion, 12 and 24 months

Dimension	Inclusion	12 months	24 months
	Mean (SD)	Mean (SD)	Mean (SD)
	Median (IQR) [Range]	Median (IQR) [Range]	Median (IQR) [Range]
<i>Lack of energy</i>	2.7 (1.7)	2.5 (1.7)	2.5 (1.7)
	2.8 (1.3–4.3) [0–6]	2.5 (1.0–3.8) [0–6]	2.3 (1.0–3.8) [0–6]
<i>Physical Exertion</i>	1.3 (1.2)	1.2 (1.2)	1.3 (1.3)
	1.0 (0.3–2.3) [0–5.3]	1.0 (0.3–2.0) [0–5.0]	0.8 (0.3–2.0) [0–5.3]
<i>Physical Discomfort</i>	2.4 (1.5)	2.3 (1.4)	2.3 (1.5)
	2.30 (1.0–3.5) [0–6]	2.30 (1.0–3.3) [0–6]	2.30 (1.0–3.3) [0–6]
<i>Lack of Motivation</i>	1.9 (1.5)	1.7 (1.5)	1.6 (1.5)
	1.8 (0.5–2.8) [0–6]	1.3 (0.5–2.8) [0–6]	1.3 (0.3–2.8) [0–6]
<i>Sleepiness</i>	2.6 (1.5)	2.3 (1.4)	2.3 (1.6)
	2.5 (1.3–3.8) [0–5.5]	2.3 (1.0–3.3) [0–5.8]	2.0 (1.0–3.5) [0–6]

4.4.1 Internal consistency and item-total correlations

Internal consistency and item-total correlations for the whole sample, for a mild state of MS and for a moderate/severe state of MS, are presented in Table 9. At each point of data collection, the internal consistency and the item-total correlations in the whole sample, in a mild state of MS, and in a moderate/severe state of MS, were satisfactory in three dimensions: *Lack of energy*, *Lack of motivation* and *Sleepiness*. In two dimensions, *Physical exertion* and *Physical discomfort*, the internal consistency and item-total correlations did not reach a satisfactory level at all points of data collection, neither in the whole sample nor in the subgroups. Items with the lowest item-total correlations were *palpitations* and *numbness*. Further analyses revealed that in the whole sample, in a mild state of MS and in a moderate/severe state, the most satisfactory internal consistency in *Physical exertion* was achieved with *palpitations* and *sweaty* removed. In *Physical discomfort* the most satisfactory internal consistency in the sample and in a mild state of MS was achieved with *numbness* removed, while this removal did not result in satisfactory levels in a moderate/severe state of MS.

Table 9. Internal consistency in the dimensions of the SOFI and item-total correlations in the items of the SOFI; the ranges represent values from inclusion, 12 and 24 months

Dimension Item	Whole sample		Mild disease		Moderate/severe disease	
	Internal consistency	Item-total correlation	Internal consistency	Item-total correlation	Internal consistency	Item-total correlation
<i>Lack of energy</i>	0.87–0.91		0.88–0.92		0.85–0.91	
worn out		0.76–0.79		0.80–0.82		0.71–0.74
spent		0.70–0.84		0.70–0.84		0.69–0.85
drained		0.71–0.82		0.75–0.85		0.68–0.78
overworked		0.71–0.78		0.73–0.76		0.68–0.82
<i>Physical exertion</i>	0.69–0.79		0.70–0.79		0.63–0.81	
palpitations		0.23–0.47		0.32–0.50		0.06–0.43
sweaty		0.44–0.57		0.46–0.54		0.40–0.63
out of breath		0.60–0.70		0.56–0.70		0.59–0.71
breathing heavily		0.61–0.69		0.61–0.67		0.62–0.75
<i>Physical exertion, (palpitations and sweaty removed)</i>	0.81–0.84		0.76–0.84		0.84–0.86	
out of breath		0.68–0.72		0.62–0.72		0.74–0.76
breathing heavily		0.68–0.72		0.62–0.72		0.74–0.76
<i>Physical discomfort</i>	0.68–0.75		0.70–0.76		0.65–0.75	
tense muscles		0.53–0.61		0.53–0.58		0.51–0.65
numbness		0.33–0.43		0.38–0.43		0.28–0.44
stiff joints		0.53–0.58		0.49–0.56		0.56–0.59
aching		0.48–0.58		0.55–0.65		0.36–0.53
<i>Physical discomfort (numbness removed)</i>	0.70–0.75		0.70–0.76		0.67–0.75	
tense muscles		0.55–0.62		0.54–0.61		0.53–0.62
stiff joints		0.56–0.61		0.50–0.60		0.56–0.64
aching		0.46–0.54		0.53–0.59		0.35–0.50
<i>Lack of motivation</i>	0.88–0.92		0.89–0.92		0.86–0.91	
lack of concern		0.73–0.77		0.78–0.82		0.61–0.72
passive		0.67–0.78		0.68–0.79		0.67–0.77
indifferent		0.79–0.88		0.80–0.88		0.78–0.88
uninterested		0.74–0.81		0.77–0.81		0.69–0.84
<i>Sleepiness</i>	0.81–0.86		0.86–0.86		0.71–0.87	
falling asleep		0.55–0.67		0.62–0.63		0.43–0.73
drowsy		0.65–0.74		0.70–0.75		0.54–0.73
yawning		0.58–0.68		0.69–0.72		0.36–0.60
sleepy		0.71–0.76		0.74–0.77		0.62–0.78

4.4.2 Factor loadings

Five factors with initial eigen values of 0.42, 0.10, 0.07, 0.06 and 0.05, in total 0.70, were identified. After promax rotation, 17 items had loadings higher than 0.50 distinctly located in five factors. *Palpitations* loaded close to 0.5 in two factors (0.57 and 0.43), thus implying indistinct belonging. *Numbness* and *sweaty*, did not load satisfactorily in any factor. The explained variance was in the rotated model in total 0.43. Additional analyses revealed that the most satisfactory loadings in five factors were achieved when *palpitations*, *numbness* and *sweaty* were removed, the explained variance of the remaining 17 items was in total 0.47.

4.4.3 Correlations

The correlations between the five dimensions of the SOFI based on the 17 items with satisfactory loadings were low, except for moderate correlations found between *Lack of energy* and both *Lack of motivation* (0.60) and *Sleepiness* (0.62), as well as between *Lack of motivation* and *Sleepiness* (0.61).

Except for moderate correlations between *Lack of energy* and the FSS (0.53 to 0.61) at the three points of data collection, the correlations were low between the dimensions of the SOFI and the FSS: *Physical exertion* (0.32 to 0.42), *Physical discomfort* (0.36 to 0.49), *Lack of motivation* (0.40 to 0.52) and *Sleepiness* (0.43 to 0.52).

4.5 PAPER IV

Of the 200 people with MS who completed the two year study, 197 had FSS scores at all points of data collection. Of these, 10 people were residents outside the Stockholm County and further 103 people varied FSS category one or several times, thus leaving a total of 84 people with MS who were residents within the Stockholm County and who had either fatigue (n = 48), borderline fatigue (n = 0) or no fatigue (n = 36) persistently during the period of the study. In Paper IV the analysis was based on these 84 people, of whom 46 people had a mild state of MS, 17 with and 29 without fatigue. An additional 38 people had a moderate/severe state of MS, 31 with and 7 without fatigue.

4.5.1 Hospital outpatient care and primary care

In people with a mild state of MS, contact with outpatient health-care services was more common in people with fatigue than in people without fatigue in the following areas: primary care in total (94% vs. 66%, [p = 0.04]; rehabilitation in total (76% vs. 41%, [p = 0.03]); emergency rooms (59% vs. 24% [p = 0.03]); welfare officers in hospital outpatient care (53% vs. 21% [p = 0.05]); physicians in primary care (88% vs. 58%, [p = 0.05]); welfare officers in primary care (12% vs. 0, [p = 0.05]); and occupational therapists in primary care (18% vs. 0, [p = 0.04]). The total number of all outpatient care contacts for people with a mild state of MS with fatigue was on average almost twice as large as for people with a mild state of MS without fatigue (40.8 vs. 21.4, [p = 0.02]). People with a mild state of MS with fatigue also had on average a higher number of contacts than people with a mild state of MS without fatigue regarding hospital outpatient care in total (27.9 vs. 16.4, [p = 0.01]); primary care in total (12.8 vs. 5.0, [p = 0.01]); medical care in total (31.3 vs. 16.8, [p = 0.02]); and rehabilitation in total (9.5 vs. 4.7, [p = 0.02]). Regarding type of departments, people

with a mild state of MS with fatigue had on average a higher number of contacts than people with a mild state of MS without fatigue at: neurology departments (13.6 vs. 9.3 [p = 0.04]) including contacts with neurologists (11.1 vs. 7.3 [p = 0.01]); emergency rooms (1.3 vs. 0.3 [p = 0.01]); welfare officers in hospital outpatient care (4.2 vs. 1.5, [p = 0.02]), occupational therapists in primary care (0.6 vs. 0, [p = 0.02]); and physiotherapists in primary care (1.5 vs. 0.6, [p = 0.05]). In contrast, people with a mild state of MS without fatigue had on average a higher number of contacts with psychologists in hospital outpatient care (1.6 vs. 1.3 [p = 0.04]).

Proportions of people with moderate/severe MS with or without fatigue in contact with outpatient health-care services did not differ in any area. The average total number of all outpatient care contacts in people with moderate/severe MS did not differ between people with and without fatigue (77.1 vs. 76.9 [p = 0.56]). Nor did the number of contacts differ significantly when analysed as hospital outpatient care and primary care in total, or as medical care and rehabilitation in total. Regarding type of department, the only difference in number of contacts between people with moderate/severe MS with and without fatigue, were that people without fatigue had on average a higher number of contacts with occupational therapists in primary care (8.3 vs. 2.2, [p = 0.05]).

4.5.2 Hospital inpatient care

The length of hospital stay for all 84 people with MS was, on average, 2.0 days (median 0 days, range 0–49 days). Differences between groups with and without fatigue were not statistically significant.

4.5.3 Other health services

Few people with a mild state of MS received salaried services in total; there were no significant differences in proportions between people with and without fatigue (24% vs. 10%, [p = 0.40]). A higher proportion of people with a mild state of MS with fatigue received informal care in total from spouses/partners compared to people with a mild state of MS without fatigue (94% vs. 52%, [p < 0.01]), specifically regarding instrumental ADL (71% vs. 21%, [p < 0.01]) and assistance with other matters (94% vs. 48%, [p < 0.01]). Furthermore, a higher proportion of people with a mild state of MS with fatigue received transportation service for the disabled (24% vs. 3%, [p = 0.05]) and underwent intensive rehabilitation periods (41% vs. 7%, [p = 0.01]).

In people with a moderate/severe state of MS, a higher proportion of people without fatigue received salaried services in total compared to people with fatigue (100% vs. 39%, [p < 0.01]), specifically regarding help from salaried personal assistants (57% vs. 13%, [p = 0.02]) and others (57% vs. 10%, [p = 0.01]). A higher proportion of people with a moderate/severe state of MS with fatigue received informal care from spouses/partners in total (100% vs. 71%, [p = 0.03]), whereas people without fatigue more often had safety alarm systems (86% vs. 23%, [p < 0.01]). There were no differences regarding transportation service for the disabled or intensive rehabilitation periods.

5 DISCUSSION

5.1 MAIN FINDINGS

A high concurrent presence of disability was found in people with MS regardless of disease severity. Fatigue as well as depressive symptoms were associated with both high perceived physical impact and high perceived psychological impact of MS on health. Fatigue had the strongest associations with both types of impact.

High proportions of people with fatigue were found in all states of MS severity; the proportion was particularly high in people with a moderate state of MS. The majority of people with MS changed category of severity of fatigue during a two-year period and every fourth individual had persistent fatigue. Depressive symptoms, weak or moderate SOC, living with a partner and not working were independent predictors for increase in fatigue. People with a moderate state of MS appeared at particular risk for increase.

The SOFI appears partly applicable for use in people with MS as a measure of fatigue within the component body functions, since *Lack of energy* and the mental dimensions *Lack of motivation* and *Sleepiness* were valid for the identification and assessment of such dimensions of fatigue in MS. However, the two physical dimensions were not valid for use in their original version and the functioning of rating scale categories should be improved; thus the SOFI needs further development.

People with a mild state of MS with fatigue used more hospital outpatient care and primary care including rehabilitation compared to people with a mild state of MS without fatigue, but there were few such differences in people with a moderate/severe state of MS. Regardless of state of MS severity, a higher proportion of people with fatigue received informal care compared to people without fatigue.

5.2 DISABILITY AND PERCEIVED IMPACT OF MS ON HEALTH

5.2.1 Presence of disability

The people with MS studied in this thesis covered the whole range of disease severity according to the EDSS, although the majority were categorised with a mild state of MS. In the cross-sectional study (Paper I) a high presence of disability was found, regardless of MS severity. Even in people with mild MS, 71% had limited fine hand use, 43% fatigue, 34% cognitive impairment, 25% depressive symptoms and 22% limited walking ability, while 15% were dependent in instrumental ADL. The presence of concurrent disabilities was high in all states of MS: of all people included, 81% had two or more disabilities of the seven disabilities studied. It has been proposed that it is unlikely that a single assessment strategy will work for all purposes in all people with MS [213], and that there is a risk that disabilities with less apparent features remain unidentified [181]. Our results imply that the number and type of disabilities are not fully captured by a summed score like the EDSS. Thus, instruments that specifically relate to various areas of functioning should be employed. In addition, in order to identify disabilities in people with MS and to provide individualised health-care interventions, systematic assessments of various areas of functioning are needed, also in a mild state of the disease.

5.2.2 Fatigue

High proportions of people with fatigue were found in all states of MS; however, the proportion of people with fatigue was markedly higher in those categorised with a moderate state of MS. The proportions of people with MS categorised with non-fatigue, borderline fatigue and fatigue in the sample were quite persistent during the study period (Paper II): at the different points of data collection the proportions of people categorised with fatigue in the sample varied from 45% to 52%, when the revised cut-off score ($FSS \geq 5.0$) was used. These proportions are 10% to 15% lower than proportions of people with fatigue reported in cross-sectional studies having used the same cut-off score for categorisation, in which the proportions varied from 55% to 65% in the different studies [15, 17, 20]. Disparities with regard to disease-related or psychosocial characteristics of the samples [17] or methods used [15, 17, 20] might have contributed to such differences. In our study the FSS scores varied significantly over time (Paper II). Substantial individual variations in fatigue were also found when using the revised cut-off score to categorise presence of fatigue. As many as 54% changed FSS category when followed every six months during a two-year period, whereas 27% had persistent fatigue and 19% had no fatigue. The figure of 54% for people who changed category is markedly larger compared to figures reported in other longitudinal studies having used the FSS: at most 35% of people with MS were reported to vary with regard to fatigue category when assessed twice during on average 18 months [57], and 38% varied when assessed three times during a period of 24 months [55]. It is likely that more frequent assessments, such as five times during the course of two years as in our study, better detect variations in fatigue. Our results suggest that both the presence of and the variations in fatigue need to be considered by health-related services, for the planning and implementation of proper intervention.

Today studies on fatigue in people with MS focus mainly on the ICF component activities and participation. The results from data collected with the FSS mainly describe perceptions regarding the extent to which fatigue have an impact on daily activities. In this thesis fatigue is defined [25] as a subjective lack of physical and/or mental energy – which relates to the ICF component body functions – that is perceived by the individual or caregiver to interfere with usual and desired activities – which relates to the ICF component activities and participation. According to the ICF [42], different components involved in an individual's functioning interact dynamically and, in order to fully understand a health condition, all components are useful. It can be argued that there is a need to explore if and how aspects of fatigue belonging to body functions are related to aspects of fatigue belonging to activities and participation, and, if appropriate, to implement the results into assessments and interventions in the clinic.

Several variables were independent predictors of increase in fatigue in people with MS (Paper II). The strongest independent predictor was depressive symptoms, which is in line with a recent two-year study [55] and with a study in which depressive symptoms predicted physical but not mental fatigue over one year [56]. The relationships found in these three longitudinal studies strengthen the associations between depressive symptoms and fatigue previously found cross-sectionally [15, 45, 54, 90-93], thus supporting the notion that fatigue and depressive symptoms should be seen as related phenomena in people with MS. Among contextual factors, weak or moderate SOC independently predicted increase in fatigue, results implying that a strong SOC might

have a favorable impact on the perceived energy level in people with MS. The association between SOC and fatigue has not previously been explored in people with MS, but SOC has been reported to contribute to the variability of fatigue in people with other chronic disorders [231-234]. Our results regarding SOC are in line with previous findings in MS, where fatigue has been found to be associated with a low sense of environmental mastery [47], feelings of helplessness [102], and an individual's ability to interpret and behaviorally respond to symptoms [101]. In addition, low SOC and depressive symptoms were recently found to be associated in people with MS [106], but in the present study no such interactions were found. Living with a partner was also a predictor of increase in fatigue, which has not previously been described. However, an association between living with a partner and the presence of fatigue has been reported in people with MS [235] and in patients with advanced cancer [236]. One might hypothesise over reasons for why the odds for increase in fatigue rise for people living with a partner. It might be related to fewer opportunities to rest when needed due to responsibilities to others: but, on the other hand, people living together should have more opportunities to assist one another. However, the assistance from others might lead to fewer opportunities to be physically active in, for example, household chores, thereby contributing to physical deconditioning and plausibly to an increase in fatigue. Comparisons with the partner and feelings of being a burden or holding the partner back might also contribute to an increase in fatigue. The fact that people with MS who were not working were more likely to be fatigued is in accordance with results previously reported [45, 55]. It has been suggested that for people with MS the ability to continue working might be related to an individual's capacity to cope with her/his fatigue by reducing the working hours [46]. The results from our study support this association, since not working as well as weak/moderate coping capacity as measured with the SOC were predictors for increase in fatigue. An age higher than or equal to the mean age of the sample was a predictor of increase in fatigue when the disease-related variables were removed from the analysis. The result from our study suggests that age and the disease-related variables are interacting and that, when included together in the analysis, the capacity of age to predict increase in fatigue is diminished. This might also explain why the association of fatigue with age is inconsistent in cross-sectional studies [17, 45, 47, 83, 103]. To summarise, depressed symptoms and several personal and environmental factors were found to be independent predictors of increase in fatigue in people with MS. These results point to the importance for health-care services targeting people with MS not only of monitoring disease-related variables but also of taking a broader perspective when assessing fatigue, with an aim to providing preventive care and appropriate interventions. Furthermore, this knowledge should be distributed also to other services, for example, to social services and informal caregivers, in order to deepen the understanding of the great impact that the more psychosocial variables might have on an "invisible" disability such as fatigue.

People with a moderate state of MS were particularly at risk for increase in fatigue, in conjunction with a time period since diagnosis greater than 10 years or with a progressive course (Paper II). There is still no agreement concerning the influence of disease severity [15, 20, 54, 89, 92, 93], disease course [17, 91, 92, 103] and disease duration [17, 90-92, 103] on fatigue. The substantially shorter staying time that has been reported at EDSS scores between 3.0 and 5.0 [237], indicate that this period might bring about evident and a more pronounced deterioration compared to earlier during the

route of the disease. One may speculate that among the reasons why people with a moderate state of MS are particularly vulnerable to be fatigued is the fact that they to a greater extent struggle to keep up their activities and responsibilities in their everyday lives, which requires great efforts that easily bring about physical and/or mental fatigue.

5.2.3 Perceived impact of MS on health

Cross-sectional analyses of the perceived impact of MS on health from the individual's perspective revealed that, in people with a mild state of MS, a high physical impact (\geq 3rd quartile) was present in almost 10% (Paper I), which is in agreement with results from other studies [29, 30]. People with mild and moderate MS had larger proportions with high psychological impact (\geq 3rd quartile) compared to people with severe MS, a result which might be related to the fact that stressful experiences in conjunction to receiving the MS diagnosis may lead to vulnerability [238], or experiences of a more rapid deterioration in the moderate state [237]. The higher proportions with low psychological impact found in people with severe MS might be a sign of adaptation, response shift, in this category. Response shift refers to how an individual changes her/his health-related quality of life, as a result of a change in her/his internal standards and values [239]. The high proportion with low impact in people with severe MS may also be explained by a higher proportion of cognitive impairment in this group. The results regarding the associations between degree of disease severity and health-related quality of life are not conclusive in previous studies [48, 52, 53, 141, 240]. There was a tendency in this study for the highest proportions of physical impact and psychological impact to be found in people with a moderate state of MS, which may be related to the relatively faster changes occurring in disability in this group [237].

Fatigue and depressive symptoms were both associated with high physical and high psychological impacts of MS (Paper I), which highlights the impact of fatigue and depressive symptoms on the lives of people with MS. Fatigue, common in all states of MS, had the strongest associations with both high perceived physical impact and high perceived psychological impact, replicating the associations found between fatigue and health-related quality of life in previous studies [44, 48-54]. Depressive symptoms were also associated with both types of impact, which is also in line with previous studies [48, 50, 52, 53]. Fatigue and depression have been reported to have stronger associations with health-related quality of life than disability as assigned with the EDSS [48]. In a recent study of the population studied in this thesis both fatigue and depressive symptoms were predictors of increase in physical and psychological impact of MS over time [241]. Consequently, it can be argued that fatigue and depressive symptoms should be systematically assessed in MS, in order to provide services with the aim of improving the life of people with MS.

5.3 THE SWEDISH OCCUPATIONAL FATIGUE INVENTORY

The five dimensions of the SOFI reported in healthy people were present also in people with MS. Tests of internal consistency revealed that *Lack of energy*, *Lack of motivation* and *Sleepiness*, were valid for the identification of such dimensions of fatigue in MS, but not the physical dimensions. After removal of two items from *Physical exertion (palpitations, sweaty)* and one item from *Physical discomfort (numbness)*, alpha values and item-total correlations rose satisfactorily for all groups

except for people with moderate/severe MS. With these three items removed in the factor analyses, the loadings of the remaining 17 items were satisfactory, and the explained variance rose. The results imply that the 17 items are valid for use in people with MS, but that *palpitations*, *sweaty* and *numbness* do not coincide with experience of fatigue in this group and should be replaced. Other appropriate items reflecting physical aspects of fatigue as perceived by people with MS regardless of MS severity ought to be considered and tested for validity and then included in the SOFI. Such items should include experiences of physical functioning in people with MS, for example reduced endurance, physical deconditioning or low physical capacity. In addition, improvement of the scalability of the SOFI is warranted with the aim of decreasing the floor effects, particularly since low ratings have been found previously when the dimensions of the SOFI were studied in other populations [188, 189].

When developing an instrument that consists of several dimensions, the different dimensions should be separate from each other. This was the case for *Lack of energy*, *Lack of motivation* and *Sleepiness* in the analyses of factor loadings. Furthermore, if separate, the dimensions should have at most a low correlation, which was not the case for these dimensions when studied in people with MS. One possible explanation using the ICF [42] might be that, since *Lack of energy*, *Lack of motivation* and *Sleepiness* are, according to the ICF, associated mental aspects belonging to “global mental functions” within the component body functions, they are related and might be correlated, thus explaining the moderate correlations. Likewise, between instruments that are supposed to measure different constructs, the correlations should be low, giving evidence for validity. In the study the evidence for validity was supported by the low correlations found for four out of five dimensions of the SOFI with the FSS, implying that the major part of these instruments measure different constructs of fatigue. The moderate correlation of *Lack of energy* with the FSS is in concordance with the findings of Åhsberg [188], who proposes that *Lack of energy* should be defined as a dimension describing more general characteristics of fatigue, containing unique characters but also the common variance of other dimensions. Thus, it is likely that *Lack of energy* describes more general features of fatigue also in people with MS.

In summary, the SOFI might be a useful addition for the assessment of fatigue in MS, since it appears to measure fatigue within the ICF component body functions – that is, in a different construct than other frequently used scales – and, furthermore, since it can discriminate among dimensions. The psychometric properties of the SOFI need further development, particularly the physical dimensions, for which new items also need to be considered. When further developed, the SOFI might contribute to a more thorough understanding of fatigue in people with MS, thereby providing possibilities to develop tailor-made services for this group.

5.4 USE OF HEALTH SERVICES

People with mild MS and persistent fatigue used significantly more hospital outpatient care and primary care, including rehabilitation, than people with mild MS without fatigue (Paper IV). The fact that people with mild MS and fatigue had a larger use of several types of medical care and rehabilitation suggests that there was a general increase in use of health-care services rather than in a specific service. There

are several possible explanations to the higher use. On one hand an increased need of care related to problems associated with the presence of fatigue, such as depressive symptoms [15, 45, 54-56, 90-93], physical inactivity [94-96], pharmacological treatment [97-99], sleep disturbance [19, 93] and aspects related to coping capacity [47, 100-102], might contribute to a higher use. High levels of anxiety and distress in the early phase of MS has been reported [27, 28] and might be reflected in the higher number of contacts, for example, with welfare officers. In addition, it is plausible that the higher use might be due to a difference in health-care-seeking behaviour, for example, due to reduced capacity for self-care, reduced capacity for work, or to the fact that the experience of other symptoms might be perceived as more troublesome when fatigue is present. Furthermore, if people with MS with fatigue do not receive appropriate care to meet the perceived needs, additional services might be sought out.

The fact that almost no differences in use of outpatient health-care were found between people with moderate/severe MS with and without fatigue indicates that the amount of care used was to a lesser extent associated with the presence of fatigue. It is possible that, since people with mild MS and fatigue already early in the disease have more contacts with health-care services they might also receive services for the treatment of, for example, bladder impairment and balance dysfunction at the same time. Thus, people without fatigue might have a delayed rise in their consumption of health-care. Furthermore, the relative impact of fatigue might be less apparent in the later states of MS, when other disabilities are more prominent to the individual or to the health-care services. The only difference found regarding use of outpatient health-care was the occurrence of more contacts with occupational therapists in people with moderate/severe MS without fatigue; a tendency in the same direction also found for physiotherapists. The fact that people without fatigue in the moderate/severe group had higher EDSS scores compared to people with fatigue, may at least in part explain the higher use. One may also hypothesise that only people with moderate/severe MS without fatigue were considered able to benefit from rehabilitation or that only they had energy enough to participate in or ask for rehabilitation.

To our knowledge, no previous study has reported that people with MS and fatigue more commonly receive informal care than people with MS without fatigue, regardless of MS severity. Previous studies have reported that the amount of informal care [147, 242] and care burden [242, 243] increase with MS disease severity, and that the health-related quality of life of the informal caregivers at the same time decreases [49, 242]. The strain experienced by the informal caregiver has been found to be associated with lower perceived health-related quality of life in both the individual with MS and the caregiver, and with presence of depression in the individual with MS [243]. The fact that larger proportions of people with fatigue, compared to people without fatigue, receive informal care, while there at the same time are no differences in the proportions receiving salaried services, raises the question whether fatigue is taken into account in decisions regarding whether salaried services should be provided or not. It has previously been reported that disabled people and their nominated health and social care providers perceive the needs for health-related services differently [244]. It can be argued that authorities making decisions regarding the provision of salaried services in people with MS always should thoroughly consider the presence of fatigue and assess its impact. In addition, when fatigue is present, services should take the situation

of spouses/partners and significant others into particular consideration, regardless of MS severity, and provide services that target the specific needs of people with MS and their caregivers.

There is evidence, yet inconclusive, that fatigue can be alleviated by multidisciplinary rehabilitation in people with mild and moderate MS [164, 165], and by specific interventions, e.g., energy conservation courses [23, 166], aerobic exercise [167, 169], yoga [170], cooling therapy [171] and pharmacological treatment [156]. The difficulties in finding effective treatment for MS-related fatigue are probably due to poor understanding of the causes of fatigue [94, 98], the unpredictable and progressive nature of MS, the fact that each individual with MS experiences combinations of disabilities that often are unique for the individual and the fact that the disabilities are likely to vary over time [172]. It could be argued that a multi-professional team might be the best starting point, for a consideration of all aspects of the individual's situation and the coordination of comprehensive health-care interventions with an aim to diminishing fatigue. However, such interventions need to be further explored, taking into consideration the views of both people with MS, their significant others and health-care professionals. In addition, the appropriateness of interventions for MS-related fatigue should be evaluated in the context of cost-effectiveness both from a societal point of view [245] and from the individual perspective, since people with MS have reported higher costs and higher economic stress in the presence of fatigue [246].

According to the ICF, the behavioural patterns of an individual is a personal factor [42]. Little is known of how the trajectory of MS can be associated with the health behaviour on part of the individual. A recent study found that people with MS, who had a more frequent engagement in physical exercise and physical activity behaviour at baseline, had a slower accumulation of activity limitations when followed over the course of five years, compared to people with MS who less frequently were engaged in physical exercise and physical activity [247]. This result suggests that regular physical activity behaviour in individuals with MS should be promoted and initiated early in the disease. Furthermore, it has been suggested that a broadened view of rehabilitation, in which theories of change in health behaviour and rehabilitation practice are merged, is the best way to accomplish influence on functioning, health and well-being of an individual [248]. Interventions with a health promotion behavioural approach – energy conservation courses [23], cognitive behavioural therapy [249], and a recent study in which exercise therapy was combined with a self-efficacy enhancement intervention [250] – have shown promising results by reducing fatigue and/or increase the adherence to a health promoting behaviour in people with MS. Thus it can be presumed that physiotherapists and other health professionals working with rehabilitation of people with MS should, to a greater extent, learn to recognise and understand the behavioural pattern of the individual, and to implement this knowledge in individualised rehabilitation programmes so that also the behaviour pattern of the patient is taken into thorough consideration.

5.5 METHODOLOGICAL CONSIDERATIONS

5.5.1 Study sample

It has been recommended that all people with MS should have access to a specialist neurological service [149]. The present study demonstrates the presence of disability in people attending such a service. The use of clinical datasets may cause bias in estimates of functioning and disability if extrapolated to the population of people with MS. When compared to a population-based study of people with MS in Stockholm County, the present dataset had higher proportions of people with mild MS and a relapsing-remitting disease course, and the mean age was lower [106, 110, 124, 141, 147]. However, the aim of this study was to explore, with focus on fatigue, aspects of disability in people in contact with specialist MS care on a regular basis, and the sample is presumed to be representative for this group. It is probable, though, that difference may occur, between countries and between regions within the same country due to differences in organisation of health-care and other health services.

The results should be interpreted keeping 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 from the perspective of people with MS is not fully understood and needs to be explored. The fact that people with MS included in this thesis had access to the neurologist at the specialist clinic for regular appointments every six months might have influenced the number of contacts with neurology departments in Paper IV.

5.5.2 Design and procedure

The ICF seeks to synthesise biological, individual and social perspectives into a biopsychosocial perspective, a coherent view of health [42]. In this thesis several aspects of the various components were covered. The ICF was primarily used as a framework when designing the study and choosing which instruments would be employed. This thesis provides evidence of that the ICF model might be suitable for studies on associations between different variables belonging to various ICF components. In addition, in Paper III the ICF was used in order to classify two instruments, the SOFI and the FSS, in detail by categorising each item. The classification of the FSS gives an example of the difficulties that might appear also when a well-established and psychometrically tested instrument is to be classified within the ICF. The classification procedure revealed that the items of the FSS belong mainly to the component activities and participation, but in addition to the component body functions. The model in itself is so far not scientifically evaluated and should therefore be used with its shortcomings in mind. The associations between the different components are not verified. Another criticism of the model is that the concept of the will of the individual is absent [251-253]. Since will is a prerequisite for participation, the question whether participation should be included in the model has been raised [251, 252]. A development of the ICF has been suggested, in which among several suggested modifications the will of the individual is included as a personal factor [253].

Formal tests of inter-rater reliability were not performed, but before the study started and at regular intervals during the study period, the research physiotherapists calibrated their performance during administration of the tests. For each individual with MS data were primarily collected by the same physiotherapist and at the same

time of the day for all points of data collection. The application of the methods used appears to be feasible and useful. The low attrition rate, 5.5%, suggests that the experiences of the people with MS participating in the study were not too demanding.

A major strength of Paper IV was the use of data collected during an extended period of time, which implies that the variability of care used was taken into account. The use of a computerised register to identify health-care contacts allowed the identification of contacts independent of the individual's cognitive capacity. At the same time, the number of health-care contacts might have been underestimated, since contacts with vocational health services and complementary medicine was not registered. Data on the use of services other than health-care, on the other hand, were collected by interview and may have been biased by the individual's inability to accurately recall. The amount of informal care given has been reported to be lower when asking the individual with MS and higher when asking the informal caregiver, which indicate that our results regarding informal care might have been underestimated [254]. However, since we chose to report whether the people with MS had had informal care or not, not the amount of informal care they used, the risk for underestimation should be small.

Despite the fact that a high presence of disability was found in people with MS studied in this thesis, the number of disabilities is likely to be underestimated since some instruments were not completed by all participants, and other known disabilities, for example, balance disturbance [255], pain [256, 257], and bladder, bowel and sexual dysfunction [258], were not studied. Ongoing pharmacological treatment, for example, for fatigue and depressive symptoms may also have influenced the presence of disability.

Fatigue was assessed with the FSS, which grades the severity of fatigue in relation to its impact on daily activities. Among several instruments assessing fatigue, the FSS is probably the most widely used. Since the FSS is a unidimensional scale, it could be argued that a multi-dimensional scale could have been used in this study, such as the Modified Fatigue Impact Scale [25, 68]. However, the FSS and the Modified Fatigue Impact Scale have been shown to be correlated, which indicates that they measure related constructs [20, 90]. Since the FSS has recommended cut-offs for categorisation of fatigue, it was chosen for use in this thesis. In Paper I the original categorisation of the FSS was used; in Papers II, III and IV, the revised categorisation. In the revised categorisation a higher threshold is set for the FSS score for the categorisation of fatigue in order not to overestimate the presence of fatigue. The revised categorisation has been found to be more consistent with findings of fatigue in the general population of other Western countries based on other fatigue measures [184, 259, 260]; it thereby may enable comparisons with the general population. There is no stated length of time that should be covered when answering the items in the FSS. The people in this study were asked to rate the statements according to their experience during the last six months. This period of time was chosen in order to cover the whole period between follow-ups. It could be argued that it is difficult to remember details over such a long period, which might negatively influence the answers. The respondent will, on the other hand, by reflecting over a longer period of time, be given the opportunity to reflect on the fatigue and form an opinion about the whole period, and the reflection may not then

be influenced by extreme situations during the period or by the fatigue present at the moment.

The BDI was used in order to measure depressive symptoms. In Paper I the original version [190] was used as well as a version in which three items believed to falsely inflate the rate of depression in people with MS are removed [192]. A recommended cut-off of ≥ 10 was used in Paper I [191]. However, since newer recommendations supported the use of all BDI items in studies of people with MS [261], the original version was used in Paper II. In addition, the cut-off ≥ 13 was used, following recent recommendations [220].

The SDMT, which is recommended as a sensitive cognitive screening test in MS [198, 199], and the PASAT, which is frequently used in MS and considered valid and reliable [202] were used for the assessment of cognitive function. The SDMT was applied primarily in written form, which might have contributed to poorer results for cognitive function in people with limitation in fine hand use, and a resulting over-estimation of the proportion with cognitive impairment. However, the proportion with cognitive impairment found is in concordance with estimated prevalence rates in people with MS [110, 111]. For a detailed assessment of cognitive function, extensive test batteries are needed. Since not all aspects of cognitive function were tested, it is probable that the proportion with cognitive impairment might be underestimated.

Day-to-day variability in the individual maximum walking distance [117, 262] and walking time has been reported for people with MS [262]. In this study, walking ability was measured as walking speed, which is considered to be a more constant and reliable parameter and is recommended as the best single measure of limitation in walking in MS [199, 262]. It has been reported that, although fatigue in people with MS increases during the day, gait speed is not reduced [122]. However, in order to minimise the possible influences of fatigue from morning to afternoon, people were assessed primarily at the same time of day at all points of data collection.

The ceiling effects found in the KI were expected since most people included had mild MS. The FAI was used in order to assess activities related to participation that require more initiative, organisation and decision-making. The FAI was developed for the assessment in people with stroke [210]; previous studies have reported that the FAI might not be valid among young people (16 to 24 years of age) and that activities such as sports should be included [130]. It has also been suggested that the FAI needs continuous modification in order to reflect changes in performance of social/lifestyle activities in society [124]. Since the mean age of the sample studied was 47 years it is likely that the present version of the FAI was applicable. The cut-off for the FAI was set to less than the lower quartile according to age- and sex-related norms, which implies that the proportion with restriction might possibly be underestimated.

One important finding reported in this thesis is the predictive capacity of SOC on fatigue in people with MS. SOC was originally presumed to remain relatively stable over the adult life course [132]. An instability related to onset of disease and increase in age has nonetheless been reported, but the significance of this instability remains unclear [135]. Furthermore, the results implied that people with lower levels on SOC

were at higher risk for instability [135]. In this thesis, data on SOC was collected at either 6 months or 12 months, while data on the other independent variables used in Paper II were collected at inclusion. Since SOC was categorised in two categories, it is not likely that the delayed data collection would have influenced the results.

Measures used in order to determine an overall score for disease severity in MS should be sensitive, but with regard to the EDSS, this has been questioned [213, 214]. Still, the EDSS is frequently used, which enable comparisons between studies. The high concurrent presence of disabilities among people with MS described in Paper I, based on data collected with standardised instruments, illuminates the limitations of the EDSS. These shortcomings are also illustrated in Paper IV, in which the results demonstrate that fatigue is not sufficiently reflected with the EDSS. A more recent example of a composite score test is the Multiple Sclerosis Functional Composite [116], in which three performance tests are used in order to calculate the composite score: the T25FW [203], the NHPT [206] and the PASAT [200]. However, in line with a previous report [202], quite a number of participants in our study did not perform the PASAT due to refusal; thus the Multiple Sclerosis Functional Composite could not be applied. Another disadvantage with this composite is that its scores are not immediately interpretable; thus they do not summarise the clinical picture as easily as the EDSS. In this thesis the EDSS has been used to categorise severity of MS in three broad categories. Severity, as determined with the EDSS, increases slowly over time in people with MS, as was described in a population-based cohort in which the change was on average one EDSS point over a 10-year period [263]. EDSS changes might have occurred over the two years of the present study, but since the EDSS scores were classified into three broad categories the possibility of changes was reduced.

For the assessment of perceived health, the disease-specific MSIS-29 [215] was used. One of the advantages of disease-specific instruments is that they address clinically important aspects of the impact of a specific disorder, implying a greater sensitivity [39-41]. Generic measures of health can on the other hand detect areas of disease impact that may not be obvious from the clinical situation and enable comparisons [39]. However, for the purpose of studying the associations of a number of disabilities with the perceived impact of MS on health, a disease-specific instrument was the preferred choice.

One difficulty regarding analysis of repeated-measures data is that observations within an individual are correlated; a difficulty which however can be handled by the analysis with generalised estimating equations (Paper II). Furthermore, in generalised estimating equations individuals are not required to have the same number of assessments, and linear as well as non-linear data can be analysed in the same analysis. In addition, interactions with time can be studied, to test whether a predictor's effect varies over time [223-225].

In order to analyse internal consistency of the dimensions of the SOFI, Cronbach's alpha and item-total correlations were calculated. Regarding Cronbach's alpha, values of 0.70 or higher are recommended for use in research contexts. However, for a clinical application, higher alpha values (0.90 to 0.95) are needed [226]. Regarding item-total correlations, various levels for correlations are suggested; however, in this

study values higher than 0.30 were considered satisfactory [227]. In order to provide evidence for validity, factor analyses were performed. Since the SOFI items are rated on an ordinal scale, factor analyses using polychoric correlations [228] and promax rotation [229] were performed. Polychoric correlations are appropriate when data consist of ordered rating levels; data are transformed with the assumption that the latent variable can be viewed as continuous. Promax rotation is applied due to the assumed correlation between factor loadings. For further study of validity, it was hypothesised that the correlations between the dimensions of the SOFI and the FSS would be at most low [230]. In addition, correlations between the different dimensions were analysed, also with the a priori hypothesis that the correlations would be at most low [230]. The results imply that further studies of the SOFI are needed in order to develop its psychometric properties. Studies on properties such as functioning of rating-scale categories, unidimensionality and hierarchy can preferably be performed with Rasch analysis [264].

5.5.3 Ethical considerations

All people with MS received written and verbal information regarding the study and were, after informed consent, included. Each individual could choose to decline further participation at any time during the study. Data collection was performed primarily in conjunction with regular visits to the neurologist, with the aim to minimise extra inconvenience for the individual. However, if preferred, data collection was performed on another day. In addition, data collection was primarily collected by the same investigator for each individual, thereby minimising the number of contacts. Some questionnaires included items which could be perceived as a threat to the individual's privacy. Furthermore, the regular assessments every six months may have made the individual aware of various difficulties. However, each individual was in regular contact with health-care services and should have been accustomed to discussing aspects related to her/his health status and other matters that might influence the present situation. In addition, since the time spent together with the investigator brought about extra attention, difficult matters could be discussed at the appointment. Even if such a situation could be perceived as strenuous, it might also have assisted people to develop ways to cope. Furthermore, if problems or difficult matters came up, the investigator could suggest where the individual could get in contact with appropriate services.

5.6 CONCLUSIONS AND CLINICAL IMPLICATIONS

People with MS studied in this thesis were outpatients at an MS clinic and covered the whole range of disease severity as assigned with the EDSS, but the majority were categorised with a mild state of MS. Regardless of disease severity, a high concurrent presence of disabilities was found in the majority of the sample, which highlights the importance of a systematic assessment of functioning in all states of MS, in order to identify disabilities. Standardised instruments specifically targeting the area of functioning under study should preferably be employed for the assessments.

The largest proportions with high psychological impact of MS on health were found in people with a moderate state and a mild state of MS. A high proportion of people with a moderate state of MS also perceived a high physical impact. The results

illuminate the importance for health services of taking the situation of people with MS into thorough consideration also in the early phases of the disease. Both fatigue and depressive symptoms were associated with high physical impact as well as high psychological impact of MS on health; fatigue had the strongest associations with both types of impact. The results illustrate that health-care professionals aiming to maximise the level of functioning in people with MS and to diminish the impact of MS should systematically identify disabilities, in particular fatigue and depressive symptoms, in order to provide individualised health services.

More than half of the people with MS changed category of severity of fatigue, and more than one fourth had persistent fatigue during the two-year study period. Depressive symptoms, weak or moderate SOC, living with a partner and not working were independent predictors of increase in fatigue. People with moderate MS appeared to be at particular risk for increase in fatigue. In light of the variation of fatigue and the impact of depressive symptoms and contextual factors, health services targeting people with MS should not only monitor disease-related variables but should also apply a broad range of approaches and systematically assess fatigue. Individualised, appropriate interventions and flexibility in the provision of health services are needed.

The Swedish Occupational Fatigue Inventory might contribute to a more thorough understanding of fatigue in people with MS and might be useful for clinical assessment of MS-related fatigue, in particular *Lack of energy* and the mental dimensions *Lack of motivation* and *Sleepiness*. However, the psychometric properties of the instrument need development, particularly the physical dimensions, for which new items also need to be considered.

People with a mild state of MS with fatigue used more outpatient health-care compared to people with a mild state of MS without fatigue, but there were few such differences between those with and those without fatigue in people with a moderate/severe state of MS. The generally higher use of health-care services among people with a mild state of MS with fatigue suggests that a multi-professional team that considers all aspects of the individual's situation is best suited to supply services and to coordinate tailor-made interventions with an aim to diminishing fatigue, which should be provided already in the early phases of the disease.

Regardless of MS severity, a larger proportion of people with fatigue received informal care compared to people without fatigue. At the same time, in people with a mild state of MS there were no differences in the proportions receiving salaried services. It can be argued that, when fatigue is present, health services should take the situation of spouses, partners and significant others into particular consideration, regardless of MS severity, and provide services that target the specific needs of people with MS and their informal caregivers. In addition, authorities making decisions regarding the provision of salaried services in people with MS should always thoroughly consider the presence of fatigue.

5.7 FUTURE STUDIES

Future studies should: 1) explore the association between the different disabilities and patterns of the variation over time; 2) investigate whether contextual factors and disease-related variables contribute to variations in disabilities; and 3) attempt to identify individuals with similar patterns in longitudinal changes.

The perceived physical and psychological impacts of MS were partly explained in this thesis. However, particularly with regard to the psychological impact, the explanatory variance was low. Future studies should explore plausible contributors to the perceived impact among other disease-related variables and contextual factors than those studied in this thesis.

This thesis demonstrates that depressive symptoms, weak or moderate SOC, living with a partner and not working predict increase in fatigue in people with MS, irrespective of the disease-related variables. Further exploration of the associations of these variables with different dimensions of fatigue is needed, in order to increase understanding of the mechanisms behind these variables' predictive capacity on fatigue. Future studies should also explore the predictive capacity on fatigue of other variables than those explored in this thesis, for example, cognition, sleep and physical functioning. In addition, the capacity of fatigue to predict factors such as depressive symptoms, SOC and living condition should be explored.

Depressive symptoms were, like fatigue, associated with both perceived physical and psychological impact of MS on health. Future studies should investigate the predictive value on variations in depressive symptoms of various environmental and personal factors, fatigue and disease-related variables.

In addition, qualitative studies with the aim of identifying characteristics of physical dimensions of MS-related fatigue in various states of the disease are needed.

For the further development of the SOFI, other appropriate items reflecting physical aspects of fatigue as perceived by people with MS regardless of degree of disease severity ought to be considered and tested for validity. Moreover, development of the psychometric properties, such as functioning of rating scale categories, unidimensionality and hierarchy, which could be performed with Rasch analysis, is warranted. Studies on the capacity of the SOFI to measure changes in fatigue over time are also needed for full validation of the instrument.

The reasons for differences in use of health services between people with MS with and without fatigue are not well understood and need to be further explored. Future studies should explore how caregiver activity and burden are influenced by the presence of fatigue in MS. Health-care interventions, pharmacological as well as non-pharmacological, with an aim to diminishing fatigue need to be further explored, taking into consideration the views of both people with MS, their significant others and health-care professionals. Such interventions should be evaluated in the context of cost-effectiveness, both from a societal point of view and from the individual perspective.

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8 APPENDICES

8.1 APPENDIX 1

Items of the Fatigue Severity Scale: categorisation within components of The International Classification of Functioning, Disability and Health (ICF)

Item	ICF code*	Description
My motivation is lower when I am fatigued	b130	b130 = Energy and drive functions
Exercise brings on my fatigue	b130 d570 b455	b130 = Energy and drive functions d570 = Looking after one's health b455 = Exercise tolerance functions
I am easily fatigued	b130	b130 = Energy and drive functions
Fatigue interferes with my physical functioning	b130 b455 d4; d5; d6	b130 = Energy and drive functions b455 = Exercise tolerance functions d4 = Mobility; d5 = Self-care; d6 = Domestic life
Fatigue causes frequent problems for me	b130 d175	b130 = Energy and drive functions d175 = Solving problems
My fatigue prevents sustained physical functioning	b130 b455 d4; d5; d6	b130 = Energy and drive functions b455 = Exercise tolerance functions d4 = Mobility; d5 = Self-care; d6 = Domestic life
Fatigue interferes with carrying out certain duties and responsibilities	b130 d2 d5; d6 d7 d8 d9	b130 = Energy and drive functions d2 = General tasks and demands d5 = Self-care; d6 = Domestic life d7 = Interpersonal interactions and relationships d8 = Major life areas d9 = Community, social and civic life
Fatigue is among my three most disabling symptoms	b130	b130 = Energy and drive functions
Fatigue interferes with my work, family, or social life	b130 d6 d7 d8 d9	b130 = Energy and drive functions d6 = Domestic life d7 = Interpersonal interactions and relationships d8 = Major life areas d9 = Community, social and civic life

* The ICF uses an alphanumeric system in which letters are used to denote Body Functions (b) and Activities and Participation (d). These letters are followed by a numeric code.

8.2 APPENDIX 2

Tänk på hur det känts de senaste sex månaderna. I vilken utsträckning kände Du det som nedanstående uttryck beskriver?

För varje uttryck, svara spontant och ringa in den siffra som bäst motsvarar hur det har känts. Siffrorna varierar mellan 0 (inte alls) och 6 (i mycket hög grad).

	inte alls						i mycket hög grad	
	0	1	2	3	4	5	6	
hjärtklappning	0	1	2	3	4	5	6	
oengagerad	0	1	2	3	4	5	6	
sliten	0	1	2	3	4	5	6	
spända muskler	0	1	2	3	4	5	6	
ögonen faller ihop	0	1	2	3	4	5	6	
domnande känsla	0	1	2	3	4	5	6	
svettig	0	1	2	3	4	5	6	
slut	0	1	2	3	4	5	6	
dåsig	0	1	2	3	4	5	6	
passiv	0	1	2	3	4	5	5	
stela leder	0	1	2	3	4	5	6	
likgiltig	0	1	2	3	4	5	6	
andfädd	0	1	2	3	4	5	6	
gäspar	0	1	2	3	4	5	6	
uttömd	0	1	2	3	4	5	6	
sömnig	0	1	2	3	4	5	6	
utarbetad	0	1	2	3	4	5	6	
värker	0	1	2	3	4	5	6	
flåsar	0	1	2	3	4	5	6	
ointresserad	0	1	2	3	4	5	6	

The Swedish Occupational Fatigue Inventory –20

8.3 APPENDIX 3

Items per dimension of the Swedish Occupational Fatigue Inventory: categorization within components of The International Classification of Functioning, Disability and Health (ICF)

Dimension	ICF code*	Description
Item		
<i>Lack of energy</i>		
worn out	b130	b130 = Energy and drive functions
spent	b130	
drained	b130	
overworked	b130	
<i>Physical exertion</i>		
palpitations	b460	b455 = Exercise tolerance functions
sweaty	b830	b460 = Sensations associated with
out of breath	b455; b460	cardiovascular and
breathing heavily	b455; b460	respiratory functions
		b830 = Other functions of the skin
<i>Physical discomfort</i>		
tense muscles	b735; b780	b735 = Muscle tone functions
numbness	b265; b270	b780 = Sensations related to muscles
stiff joints	b710	and movement functions
aching	b280	b265 = Touch function
		b270 = Sensory functions related to
		temperature and other stimuli
		b710 = Mobility of joint functions
		b280 = Sensation of pain
<i>Lack of motivation</i>		
lack of concern	b126; b130	b126 = Temperament and
passive	b126; b130	personality functions
indifferent	b126; b130	b130 = Energy and drive functions
uninterested	b126; b130	
<i>Sleepiness</i>		
falling asleep	b134	b134 = Sleep functions
drowsy	b130	b130 = Energy and drive functions
yawning	b134; b450	b450 = Additional respiratory functions
sleepy	b134	

* The ICF uses an alphanumeric system in which letters are used to denote Body Functions (b) and Activities and Participation (d). These letters are followed by a numeric code.

