1

General introduction
Introduction

Multiple Sclerosis (MS) is one of the most common neurological diseases in adults.\(^1\,^2\) The term ‘multiple sclerosis’ refers to multiple sclerotic plaques that may occur anywhere in the brain or spinal cord.\(^2\) Nerves are protected by myelin, a fatty substance that promotes nerve transmission, and damage to the myelin sheath can lead to the distorted transmission of signals.\(^3\) Although the detailed pathogenesis is still not understood, MS results from a complex interplay of genetic susceptibility and environmental exposure.\(^2\,^3\) More information on the epidemiology of MS is detailed in Panel 1.1. Since neural damage can occur anywhere in the central nervous system, symptoms are widespread. Common MS symptoms include muscle weakness, spasms, poor balance, cognitive impairment, optic problems, pain, depression, and fatigue.\(^2\,^4\)

Panel 1.1  Epidemiology of MS

The estimated number of people living with MS worldwide is 2.3 million (2013), representing a global prevalence of 33/100,000. MS is found in every region of the world, although it is more frequent closer to the equator. The prevalence in Europe is 189/100,000, while the prevalence in Africa and East Asia is around 2/100,000.\(^1\) The estimated number of people with MS in the Netherlands is 16,000,\(^2\) corresponding to a prevalence of 80/100,000.\(^2\) While this is high compared to the global prevalence (33/100,000), it is lower than the European average.\(^1\) Whether these differences in prevalence are due to better diagnosis and reporting, or due to other causes is not clear.\(^1\,^2\)

The male:female ratio in MS is approximately 1:2. This difference is not yet understood. Although patients can be diagnosed at any age, diagnosis is usually in early adulthood at an average age of 30 years, a period when the patient is in the prime of life.\(^1\)

2  MS-ATLAS: Multiple Sclerosis International Federation, Dutch MS Research Foundation. 2013.

MS-related fatigue

One of the most frequent symptoms of MS is MS-related fatigue, which affects about 80% of patients.\(^5\,^6\) Fatigue is often experienced as a debilitating symptom, since it can interfere with many aspects of a person’s life, including home life and/or the workplace.\(^7\) MS-related fatigue can be the most prominent symptom in patients with otherwise minimal activity limitations.\(^1\) One patient (a participant at the start of the TREFAMS-CBT trial) described their MS-related fatigue as follows:
“Severe fatigue, without a prospect for improvement, slowly hollows out a person. When even pharmacological treatments fail to decrease this fatigue, one becomes desperate. My sense of humour, enthusiasm for things and even the energy for my favourite hobbies disappeared. Eventually it felt as if I was just surviving. At some point I even began to wonder what my motivation for surviving was…”.

Fatigue can have either a primary and/or secondary origin. Primary fatigue can be explained as a direct result of the MS disease process, for example due to demyelination or inflammation caused by MS. Secondary fatigue results indirectly from other symptoms of MS, such as mobility problems, depression, or respiratory problems. A number of pathophysiological mechanisms have been proposed to explain primary MS-related fatigue, although the exact mechanisms remain unknown. Possible mechanisms include dysregulation of the immune system, impaired nerve conduction, dysfunction of the central nervous system, neuro-endocrine/neurotransmitter dysregulation, the involvement of the autonomic nervous system and energy depletion.

Studying MS-related fatigue can be challenging due to the lack of a commonly used unambiguous definition. Whereas regular fatigue is a ubiquitous human experience, MS-related fatigue is a uniquely complex multifactorial phenomenon. It appears that MS-related fatigue differs from fatigue seen in healthy individuals and those with diseases other than MS. Fatigue is considered abnormal when it occurs under circumstances that should not produce it. Compared to Parkinson’s disease, cancer and HIV/AIDS, the nature of MS-related fatigue appears to be more complex, which is apparent in the dimension of prevalence, pathophysiology, contributing factors and subjective experience. Another problem with the concept of MS-related fatigue is that sometimes several types of fatigue are distinguished (e.g. physical, cognitive, and psychosocial functioning), while other times fatigue is approached as a one-dimensional concept. A recent article recommended that questionnaires on fatigue should include a disease-specific section that contains items related to physiological and clinical aspects of the underlying disease.

For the purpose of this thesis fatigue is defined according to Multiple Sclerosis Council for Clinical Practice guidelines 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’. Data from the North American Research Committee on Multiple Sclerosis (NARCOMS) study revealed that 81% of patients experience some degree of unexplained
fatigue during the first year after onset. The occurrence and severity increase with longer duration of disease. Due to the frequency and impact of MS-related fatigue, this symptom cannot be ignored.

Societal participation

The global and European average age of onset of MS is 29 years, the period in which most people are developing their career and starting a family. This timing means that MS significantly impacts the social and economic well-being of the individual and the people close to them, also referred to as societal participation. The World Health Organization’s International Classification of Functioning, Disability and Health (ICF) defines participation as ‘involvement in life situations in relation to health conditions, body functions and structure, activities, and contextual factors’. Societal participation is an important rehabilitation outcome and is considered an indicator of successful adjustment to chronic disease. A general definition for societal participation is not yet available. At the moment, the terms participation, social participation and societal participation are used interchangeably. In this PhD-thesis the term societal participation was mainly used.

Compared to fatigue in healthy controls, Krupp et al. (1989) reported a greater impact of fatigue on daily living and societal participation in patients with MS. Deteriorating societal participation is related to higher disability, greater economic consequences and a poorer quality of life resulting in a vicious circle. Research has demonstrated that MS-related fatigue and societal participation are affected by the way patients interpret and respond to their symptoms. MS is particularly challenging in terms of the wide range of resulting symptoms, and the unpredictable nature of the course of the disease in individual patients. This means that patients are more likely to focus on their symptoms and more likely to have a negative interpretation of the consequences of symptoms. Several studies have documented that the dysfunctional attribution of negative consequences to symptoms may lead to unhelpful behaviour such as excessive rest or an all-or-nothing behavioural pattern, i.e. overexerting themselves and then needing prolonged periods of rest, which itself creates a barrier to societal participation.
Treatment of MS-related fatigue

Although the pathogenesis of MS-related fatigue is still not understood, advances have been made in the treatment of MS-related fatigue. Current approaches include both pharmacological and non-pharmacological treatments, or a combination of these two approaches. Debate continues on the best strategies for the management of MS-related fatigue, although current pharmacological approaches to the treatment of MS-related fatigue are seldom evidence-based. In recent years, applied researchers and healthcare professionals have become increasingly interested in non-pharmacological approaches to treat MS-related fatigue. An extensive review concluded that non-pharmacological interventions (including exercise and psychological and educational interventions) reduce fatigue more effectively than commonly prescribed pharmacological treatments. Psychological interventions can thus be a feasible and cost-effective treatment for MS-related fatigue. An individualized multidisciplinary rehabilitation approach with a combination of therapies appeared not effective for the treatment of MS-related fatigue.

Building on encouraging literature relating to non-pharmacological interventions, multiple theories on how to alleviate MS-related fatigue can be distinguished. The first theory is that MS-related fatigue can be alleviated by improving aerobic capacity. Since patients with MS are less physically active compared to healthy individuals, a vicious circle of deconditioning might evolve. Improving physical capacity might positively influence anti-inflammatory function of the body, improve neuro-endocrine/neurotransmitter regulation and may protect the nerves and axons. Optimal measurement of physical capacity is crucial to gain insight into treatment effects in research and clinical practice. Today, cardiopulmonary exercise testing (CPET) is considered the gold standard measurement of aerobic capacity. Whether CPET is a feasible and safe way to measure aerobic capacity, and whether it is a reliable measure in patients with MS is not yet clear.

The second theory relates to coping with MS-related fatigue and how energy depletion can be prevented. Generally speaking, there are two common strategies. The first can be described as the conscious and effective use of available energy, an approach that often forms part of energy conservation management programmes. The goal is to conserve energy by analysing and modifying daily activities to reduce energy expenditure, balancing work and rest, examining and modifying standards and priorities, delegating activities, using the body efficiently, and organizing workspaces. The second strategy focuses on ignoring fatigue symptoms and not letting fatigue determine daily life.
is a constituent of cognitive behavioural therapies (CBT) that generally aim to identify, alter or manage any emotional, behavioural, cognitive and external factors that might contribute to MS-related fatigue. Literature supports a moderate positive effect of CBT over the short-term.\textsuperscript{45,46}

**Psychological models for MS-related fatigue**

Over the past two decades, a number of theoretical models have been developed to direct the focus of treatment development for MS-related fatigue.\textsuperscript{5,21,47-54} Vercoulen et al. (1998)\textsuperscript{48} concluded that a sense of control over one's own fatigue directly impacts the perceived severity of MS-related fatigue. In another psychological model, studied by van der Werf et al. (2003),\textsuperscript{50} it was concluded that both the chronic biological components of MS and emotional instability might lead to greater feelings of helplessness. In turn, this helplessness contributes to the perceived severity of MS-related fatigue. Building from these models, Strober and Arnett (2005)\textsuperscript{49} found that depression and sleep disturbance independently predicted MS-related fatigue. All of these models considered the influence of both biological and psychological factors. This insight led van Kessel et al. (2006)\textsuperscript{47} to develop a cognitive behavioural model. In this theoretical model, biological, cognitive and emotional factors are integrated and it is assumed that these factors can perpetuate or worsen the experienced fatigue. The model allows for interaction between factors and deals appropriately with individual differences, i.e. not every person with MS-related fatigue has the same cognitive or behavioural responses and consequently not every person suffers from secondary consequences, such as depression or sleep problems. Bol et al. (2010)\textsuperscript{53} studied the model developed by van Kessel et al. (2006)\textsuperscript{47} and concluded that both disease severity and depression predict the level of MS-related fatigue. More recently, Wijenberg et al. (2016)\textsuperscript{21} studied a model that included cognitive-behavioural factors and concluded that disease severity, depression and a fear-avoidance cycle play an important role in MS-related fatigue. Likewise, Morrison et al. (2016)\textsuperscript{54} also searched for factors related to MS-related fatigue and found that disease-related limitations that interfere with activities of daily living and role performance, together with depressive symptoms, are important predictors of MS-related fatigue. One of the conclusions that emerges from this chronological oversight of psychological models is that both cognitive and behavioural factors appear to influence MS-related fatigue. The insight that both cognitive and behavioural factors play a role in MS-related fatigue led to the development
of CBT specifically for MS-related fatigue. The aim of CBT in MS-related fatigue is to change dysfunctional emotions, cognitions and behaviours, and their interactions, and thereby decrease experienced fatigue. This involves challenging existing beliefs about fatigue and stimulating a gradual increase of physical and social activity.55

TREFAMS-CBT

The TREFAMS-ACE research programme was developed to study three individual non-pharmacological therapies for the treatment of MS-related fatigue. TREFAMS-ACE (TREating FAtigue in patients with MS) studies the effectiveness of Aerobic training, Cognitive behavioural therapy, and Energy conservation management. Both the effectiveness and the mechanisms underlying each intervention are studied and analysed using the same design, allowing a one-on-one comparison. The TREFAMS-CBT trial focused on primary MS-related fatigue, meaning that the treatment targets fatigue that results directly from the MS disease process, and not fatigue that can be attributed to symptoms of MS (secondary fatigue), such as fatigue caused by depression or nocturnal spasms. This thesis will focus on the effectiveness of cognitive behavioural therapy (i.e. the TREFAMS-CBT trial) on MS-related fatigue and societal participation.

The Expert Centre for Chronic Fatigue has developed a CBT protocol for the treatment of Chronic Fatigue Syndrome. Following promising results in this patient group, the protocol was modified for the treatment of MS-related fatigue. The main goal of this TREFAMS-CBT intervention was to reduce patient fatigue and lessen debilitation due to fatigue, rather than accepting their fatigue as it is. In the field of rehabilitation, this approach is new to many health professionals, patients and caregivers. A theoretical model was developed to substantiate this approach (Figure 1.1). In this model there is a distinction between factors that cause fatigue, the disease MS, and factors that perpetuate fatigue, dysfunctional cognitions, emotions and behaviours. This CBT approach is based on the assumption that disease factors cause primary MS-related fatigue and that certain unintentionally developed cognitions and behaviours perpetuate or even worsen fatigue. Based on literature the following perpetuating factors for MS-related fatigue were identified: disturbed sleep-wake cycle, less physical activity, all-or-nothing behaviour, dysfunctional cognitions about fatigue, strong focus on fatigue, problems with coming to terms with a chronic unpredictable disease, pain and dysfunctional social support. Therefore, the TREFAMS-CBT protocol focuses on these factors.
Due to the presumed relation between fatigue and societal participation, one hypothesis of the TREFAMS-ACE study predicted that as fatigue declines in prominence, societal participation will improve. The aim of TREFAMS-CBT was therefore twofold, 1) improve MS-related fatigue, and 2) improve societal participation. Furthermore, using data obtained from the TREFAMS-CBT trial, it may be possible to identify the underlying mechanisms of CBT in MS-related fatigue.

**Aims and outline of this thesis**

The research described in this thesis was part of the TREFAMS-ACE study. Since MS-related fatigue is such a frequent and debilitating symptom, the overall aim for this thesis was to examine and explain MS-related fatigue and in particular the influence of cognitive behavioural therapy on MS-related fatigue and participation, with an additional sub focus on CPET.
This thesis consists of three parts. **Part 1** describes CardioPulmonary Exercise Testing (CPET) in patients with MS. In **Chapter 2** a systematic review is performed to study the feasibility and safety of CPET in patients with MS. **Chapter 3** describes the test-retest reliability and responsiveness of CPET in patients with MS. **Part 2** is dedicated to MS-related fatigue and participation, which are the primary treatment goals of the TREFAMS-CBT trial. **Chapter 4** describes the relation between conventional self-reported questionnaires of fatigue and the real-time digital measurement of fatigue. Furthermore, patterns of MS-related fatigue during the day are outlined. **Chapter 5** describes the role of appraisal and coping style in relation to participation in patients with MS-related fatigue. To study this a theoretical model was developed and tested. **Part 3** focuses on the effectiveness of CBT for the treatment of MS-related fatigue. In **Chapter 6** a systematic review and meta-analysis was performed to summarize the effectiveness of randomized clinical trials of CBT for the treatment of MS-related fatigue. In **Chapter 7** the results of the TREFAMS-CBT trial will be elaborated. Subsequently, in **Chapter 8** we go into detail about the working mechanisms of CBT for MS-related fatigue. Finally, this thesis ends with a general discussion in **Chapter 9**, the interpretation of the findings from the above mentioned studies and the implications of this PhD-thesis for further research and future treatment of patients with MS-related fatigue.
References


15. Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. Mult Scler. 2006 Aug;12(4):367-8.


