Summary
1. Cardiopulmonary exercise testing in patients with Multiple Sclerosis

Multiple Sclerosis (MS) can cause a variety of symptoms that include muscle weakness, spasms, pain, poor balance and fatigue. It is therefore understandable that many patients end up in a vicious cycle of deconditioning. Patients with MS are less physically active compared to healthy individuals and exercise therapy is known to have positive effects in MS patients. A measure frequently used to define the cardiopulmonary aerobic fitness of patients with chronic disabilities is cardiopulmonary exercise testing (CPET).

In Chapter 2, the feasibility and safety of CPET in patients with MS was studied using a systematic review format. After a systematic search of several literature databases, a total of 46 studies were included, comprising 1483 patients. A structured data extraction form was developed, with the following 10 feasibility items: age range, Expanded Disability Status Scale range, comorbidities, recent exacerbations, ability to perform CPET, whether permission was obtained from a physician, warming up, raise in Wattage, definition of VO\textsubscript{2max} and whether test abnormalities occurred. Adherence to safety guidelines was checked using the following 12 items: comorbidities, equipment calibration, room temperature and pressure, room humidity, patient preparation, whether a physician monitored CPET, 12-lead electrocardiogram, heart rate, blood pressure, pulse oximetry, whether a predefined endpoint for CPET was used, and whether adverse events were described. The feasibility and safety items combined led to a total of 22 possible quality points. The results showed that quality of reporting on CPET varied from 3 to 13 points. The percentage of reported test abnormalities in patients with MS (feasibility) was 10.0%, primarily due to an inability to maintain pedalling at a specific resistance. The percentage of adverse events (safety) was 2.1%. All adverse events had a temporary character. The results of this systematic review suggest that CPET is a feasible way to test a patient's aerobic system. Inevitably, the CPET modality needs to be tailored to the physical abilities of the patient. Moreover, CPET is safe in patients with MS, when the recommended precautions and safety measures are implemented according to ATS/ACCP guidelines.

Although CPET is considered the gold standard, the test-retest reliability and responsiveness of cardiopulmonary exercise testing outcomes in patients with MS have not been studied extensively. In Chapter 3 the test-retest reliability and responsiveness in terms of the smallest detectable change of CPET were determined in patients with MS with an Expended disease status scale (EDSS) score ≤6. Patients performed 2 maximal CPETs on a cycle ergometer within a period of one to three weeks. Thirty-two participants
suffering from severe MS-related fatigue performed CPET on a cycle ergometer until voluntary exhaustion was reached. The test-retest reliability was calculated in terms of the intra-class correlation coefficient, and the standard error of both individual and group levels. The results showed that at an individual level, CPET can be used reliably to assess physical fitness status, but less so to determine significant changes in terms of aerobic capacity, unless the test circumstances are rigorously controlled between tests (e.g. timing, temperature, food and beverage intake, etc.). This may also include subjective symptoms like fatigue. At the group level, CPET can be reliably used to determine physical fitness status and establish change.

2. MS-related fatigue and societal participation

MS-related fatigue is one of the most frequent symptoms in MS, occurring in about 80% of patients. The severity of fatigue increases with disease duration, and often interferes with a patient’s daily life. Difficulties caused by MS-related fatigue can ultimately impact the social and economic well-being of patients and the people close to them: i.e. societal participation is compromised.

Multiple rehabilitation programs and treatments exist to alleviate MS-related fatigue. To effectively guide and evaluate rehabilitation and clinical research, it is valuable to understand fatigue as a key outcome. Most research studies use questionnaires to measure fatigue. This approach has some limitations. Firstly, recall bias is inherent to questionnaires. Secondly, diurnal fluctuations are not measured and since individuals tend to focus on high levels of fatigue when using recall questionnaires, results might be biased. An alternative approach to fatigue measurement is the use of real-time digital assessment of fatigue, a method that avoids the limitations of questionnaires. In Chapter 4, patterns of MS-related fatigue during the day are analysed. Furthermore, the relation between three conventional, commonly-used questionnaires (Checklist Individual Strength [CIS] fatigue subscale, Modified Fatigue Impact Scale [MFIS], and Fatigue Severity Scale [FSS]) and the real-time digital assessment of fatigue is studied. Factors that confound the relation between real-time fatigue scores and conventional fatigue scores are also analysed. A sample of 165 ambulant participants of the TREFAMS-ACE trial received four text messages on a predefined day at set times of 9 am, 1 pm, 5 pm and 9 pm with the following question: How fatigued do you feel at this moment? Please rate your fatigue from 0 (no fatigue whatsoever) to 10 (severe fatigue). Latent class growth mixed modelling was used to determine diurnal patterns of fatigue. Regression analyses
were used to assess the association between the mean real-time fatigue score and the CIS fatigue subscale, MFIS, and FSS. Significant associations were tested for candidate confounders (e.g., EDSS, work status, daytime sleepiness). The results revealed four significantly different fatigue profiles, a stable high pattern (n=79), an increasing fatigue pattern (n=57), a stable low pattern (n=16) and a decreasing pattern (n=13). The conventional fatigue questionnaires correlated poorly (r<.30) with the real-time fatigue scores. No conclusions could be drawn about possible clarifications. It might work either way: real-time measured fatigue might not be a valid measure for MS-related fatigue because of the lack of convergent validity with conventional questionnaires or, the conventional fatigue measures do not assess the day-to-day fatigue experience. Moreover, the results suggest that severity of sleepiness is an important confounder to take into account in the assessment of fatigue.

Societal participation is a frequent rehabilitation target. Better insight into factors related to societal participation is a prerequisite for the improvement of rehabilitation strategies. In Chapter 5, appraisal, coping style and societal participation are studied in patients with MS-related fatigue. The relation between appraisal and societal participation was studied in 265 participants of the TREFAMS-ACE trial, together with the influence of coping styles on this relationship. Appraisal, a latent construct, was created from the General Self Efficacy Scale and the helplessness and acceptance subscales of the Illness Cognition Questionnaire. Coping styles were assessed using the Coping Inventory Stressful Situations (CISS21), and societal participation was assessed using the Impact on Participation and Autonomy. A multiple mediator model was developed to simultaneously study coping styles. This model was tested by structural equation modelling on cross-sectional data. We corrected for confounding by disease-related factors. Mediation was determined using a product-of-coefficients approach. The results showed a robust relation between appraisal and societal participation, indicating that when patients perceive their ability to deal with a situation positively, they are more likely to have better societal participation. It appeared that coping styles did not mediate this relationship: appraisal is related to coping styles, but remarkably, coping styles were not related to societal participation.

3. Cognitive Behavioural Therapy for MS-related fatigue

Multiple pharmacological and non-pharmacological approaches exist to treat MS-related fatigue. A recent focus has been the non-pharmacological treatment CBT.
To provide an overview of available literature on the effectiveness of CBT on MS-related fatigue, a systematic review and meta-analysis was performed in Chapter 6. An extensive literature search was performed to identify and include randomized controlled trials (RCTs) in which fatigue was a primary outcome measure and CBT was delivered to patients with MS. The search was performed by two independent reviewers, and three CBT experts determined whether interventions could be considered CBT. Data on patient and study characteristics and fatigue were systematically extracted using a standardized data extraction form. Two independent reviewers assessed the risk of bias using the Cochrane Collaboration risk of bias tool. In the event of disagreement, a third reviewer was consulted. In total, 4 RCTs were included in the meta-analysis, comprising 193 patients who received CBT and 210 patients who underwent a control treatment. Meta-analyses of these studies showed that CBT treatment had a positive post-treatment effect on fatigue (standardized mean difference [SMD]=-0.47; 95% confidence interval [CI] -0.88 to -0.06). In addition, three studies showed a long-term positive effect of CBT (SMD=-0.30; 95% CI -0.51 to -0.08). This review found that the use of CBT for the treatment of fatigue in patients with MS has a moderately positive short-term effect. However, this effect decreases with cessation of treatment. The included RCTs differed extensively in the way CBT was provided (e.g. face to face vs. internet guidance; group vs. individual guidance, the type of therapist (e.g. physiotherapists and qualified CBT therapists) and the intensity (i.e. the duration and number of sessions). In addition, the control conditions varied widely (e.g. from usual care to relaxation training).

The results of the TREFAMS-CBT trial are presented in Chapter 7. The goal was to evaluate the effectiveness of CBT in improving fatigue and societal participation in severely fatigued patients with MS. The TREFAMS-CBT trial was a multicentre, assessor-masked, randomized controlled trial performed in three Dutch healthcare institutions. Ambulatory participants with severe MS-related fatigue were assigned to CBT or the control treatment. The CBT study group received twelve individual face-to-face sessions with a certified psychologist trained in CBT, while the control intervention consisted of three individual consultations with a MS nurse, both delivered over 16 weeks. Assessments took place at baseline and at 8, 16 (i.e. post-intervention), 26 and 52 weeks post-baseline. Primary outcomes were the Checklist Individual Strength-fatigue subscale (CIS20r fatigue) and the Impact on Participation and Autonomy questionnaire (IPA). Data were analysed on the basis of the intention-to-treat principle using Mixed Model Analysis. Between December 2011 and August 2014, 91 patients were included, of whom
44 were randomly allocated to CBT and 47 to the MS nurse. The between-group analysis showed a positive post-intervention effect for CBT on CIS20r fatigue (T16: -6.7 [95% CI -10.7 to -2.7] points) that diminished during follow-up (T26: -3.5 [95% CI -7.4 to 0.5]; T52: 0.5 [95% CI -3.6 to 4.4]). Post-intervention (T16), 22 out of 39 patients in the CBT group and 9 out of 37 patients in the control study group showed a clinically relevant improvement of 8 points or more on the CIS20r fatigue, leading to a number needed to treat of 3.3 (95% CI 1.9 to 10.6). No clinically relevant effects were found on societal participation. In conclusion, CBT can effectively reduce severe MS-related fatigue in the short-term. More research is needed on how to maintain this effect over the long-term.

Cognitive behavioural therapy effectively reduces fatigue directly following treatment in patients with Multiple Sclerosis (MS), but little is known about the process of change during and after CBT. In Chapter 8, a first step was made to unravel which factors mediate the positive treatment effect of CBT, and which factors are related to the period after cessation of treatment. All 91 TREFAMS-CBT participants were included in the mediation analysis. Mediation during CBT treatment was studied using assessments at baseline, 8 and 16 weeks. Mediation of the change in fatigue from post-treatment to follow-up was separately studied using assessments at 16, 26 and 52 weeks. Studied mediators included changes in illness cognitions, general self-efficacy, coping styles, daytime sleepiness, concentration and physical activity, fear of disease progression, fatigue perceptions, depression and physical functioning. Mediators were separately analysed according to the product-of-coefficients approach. It appeared that during treatment improved fatigue perceptions, increased physical activities, less daytime sleepiness, less helplessness, and improved physical functioning mediated the effect of CBT on the decrease in fatigue. Focusing on these factors might improve the effectiveness of CBT. After treatment, the changes in fatigue levels were mediated by reduced physical activities, reduced concentration, and increased sleepiness. Maintaining treatment effects might be helped by using treatments that target long-term maintenance of acquired habits regarding physical activities, concentration and daytime sleepiness.

In Chapter 9, the results of the studies presented in this thesis are discussed. We provide an overview of the knowledge gained regarding cardiopulmonary exercise testing, fatigue and societal participation in patients with MS. Furthermore, the effectiveness of cognitive behavioural therapy for MS-related fatigue is described and mediators in the process of change of cognitive behavioural therapy are unravelled.