Understanding and Optimising activity pacing to promote a physically active lifestyle in people with multiple sclerosis

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ABSTRACT

The way in which an individual habitually approaches physical activity has long been thought to have an impact on his/her daily functioning, with both underactivity and overactivity linked to disability. The experience of fatigue draws adaptations such as underactivity and periods of overactivity in people with multiple sclerosis. This emphasises the need to explore ways to facilitate physically active lifestyle in this population. Activity pacing is a novel goal-directed behavioural process of dividing activities into small manageable pieces to lessen the effect of symptoms, which then allows gradual progressive increases in activity. However, activity pacing as a potentially adaptive behaviour to stimulate physically active lifestyle has not been researched. This thesis consequently explored this. A literature review and meta-analysis were done to evaluate the influence of activity pacing on fatigue and physical activity, and potential moderator effects. Findings revealed activity pacing had beneficial but varied effects on fatigue and physical activity; suggesting that individual or intervention characteristics may have moderated effects. Consequently, we explored relations between activity pacing, fatigue, physical activity and health-related quality of life in daily life and found fatigue was related to low health-related quality of life. Also, engagement in pacing and perceived risk of overactivity were associated with low activity and high activity respectively. These findings suggest that people with multiple sclerosis might benefit from individualised guidance on efficient approach to activity and adequate fatigue management. These insights were used to develop and evaluate the efficacy of a tailored activity pacing intervention based on individual's attitudes towards physical activity and fatigue experience. Results revealed the approach effectively increased activity level and reduced activity variability without exacerbating fatigue. These findings provide the basis to incorporate tailored activity pacing approach in standard care to manage fatigue and promote longitudinal engagement in physical activity among people with multiple sclerosis.

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Abbreviations

BMI Body mass index

CI Confidence interval

d; g; ES Effect size

IQR Interquartile range

M Mean

MS Multiple Sclerosis

PDDS Patient Determined Disease Steps

ReSpAct Rehabilitation, Sports and Active lifestyle;

SD Standard deviation

SMD Standardised Mean Difference

CHAPTER 1

Introduction

1.1 Introduction

The burden of non-communicable chronic diseases is rapidly increasing worldwide. As of 2012, about half of all adults, that is 117 million people, had one or more chronic health conditions such as cancer, cardiovascular disease or respiratory disease (World Health Organization, 2002). By 2020, chronic diseases are expected to contribute to 73% of all death and 60% of the global burden of disease (Ward et al., 2012). The importance of habitual physical activity for attaining optimal health and minimising risk factors associated with the development of a broad spectrum of non-communicable chronic health conditions has been extensively documented (World Health Organization, 2010).

Conversely, engaging in an active lifestyle is often challenging for people with chronic health conditions, as they often report fatigue complaints and low energy (Seves et al., 2018). Therefore, to engage these populations in an active lifestyle, it is crucial to explore strategies for ameliorating the adverse impact of fatigue on physical activity behaviours. A particular group which experiences high levels of fatigue is people with multiple sclerosis (MS) (Merkelbach et al., 2011; Bakshi 2003; Amato et al., 2001; Simmons et al., 2004). MS affects approximately 2.5 million persons worldwide and over 100,000 persons in the UK (Multiple Sclerosis Trust, 2018).

MS is a chronic and unpredictable inflammatory demyelinating disease of the central nervous system (Compston and Coles, 2002). The clinical symptoms of MS are diverse and can include loss of function or sensation in the limbs, loss of bowel or bladder control, sexual dysfunction, blindness, loss of balance, pain, cognitive dysfunction, emotional changes, and fatigue (Compston and Coles, 2002; Mohr and Cox, 2001). Ultimately, this disease process can result in functional limitations, disability, and reduced quality of life (Motl et al., 2006).

Although there is substantial variation in the symptoms experienced by people with MS, up to 97% of persons with MS report that fatigue is most common, and one of their more disabling symptoms (Merkelbach et al.,200; Amato et al., 2001; Branas et al., 2000; Mohr and Cox, 2001; Fisk et al., 1994). Fatigue can severely affect persons with MS activities of daily living, ability to work and socialize, and quality of life (Amato et al., 2001; Branas et al., 2000; Bakshi, 2003; Motl et al., 2006). Thus, engagement in physical activity is difficult for people with MS as fatigue worsens throughout the course of the day and has a profound impact on activities of daily living, which subsequently perpetuate fatigue severity and physical disability (van den Berg-Emons et al., 2010; Motl et al., 2005; 2006).

There are four main types of MS – relapsing remitting, secondary progressive, primary progressive and progressive relapsing. In about 85% of people with MS, the disease begins with a relapsing remitting stage (Hooper, 2011). Relapsing remitting MS is characterised by temporary periods called relapses, flare-ups or exacerbations, when new symptoms appear, followed by periods of partial or complete recovery (remissions) (Multiple Sclerosis Trust, 2018; Hooper, 2011). During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. However, there is no apparent progression of the disease during the periods of remission.

After this relapsing remitting phase, most patients enter a secondary progressive phase and accumulate irreversible neurological deficits (Kuhlmann et al., 2002; Le Page et al., 2008; Hooper, 2011). In secondary progressive MS, symptoms worsen more steadily over time, with or without the occurrence of relapses and remissions (Multiple Sclerosis Trust, 2018). Conversely, primary progressive MS is characterized by slowly worsening symptoms from the onset and accumulation of disability, with no periods of relapses or remissions, though there may be periods where the condition appears to stabilise (Multiple Sclerosis Trust, 2018; Hooper, 2011). This type of MS is seen in about 10 - 15% of people with MS. Progressive-Relapsing MS is a rare form of MS, affecting about 5% of people diagnosed with MS, and is characterized by a steadily worsening disease state from the onset, with acute relapses but no remissions, with or without recovery (Hooper, 2011).

Because there is, as of yet no cure for MS, increasing attention is being directed toward treating the disease and managing its symptoms (Motl et al., 2006). Various disease modifying therapies have been shown to decrease the frequency of relapses and to delay disease progression. These include medications such as interferon beta, azathioprine, natalizumab, methotrexate, teriflunomide, dimethyl fumarate, fingolimod, glatiramer acetate and mitoxantrone (Hartung et al., 2002; Kappos et al., 2006; Le Page et al., 2008; Hooper, 2011; Multiple Sclerosis Trust, 2018).

Additionally, a physically active lifestyle is recommended to manage symptoms and improve health, mobility, participation and wellbeing of people with MS (Haskell et al., 2007; Motl et al., 2005). However, the unpredictable illness trajectory and symptoms inherent in MS bring challenges specific to this population and to engagement in physical activity (Kayes et al., 2011). Subsequently, there is increasing evidence that people with MS engage in significantly low physical activity level and spend considerably more time in sedentary behaviour compared with the general population and other diseased populations (Merkelbach et al., 2011; Motl et al., 2005; Motl et al., 2006; van den Berg-Emons et al., 2010). Disparately, literature on how to advise people with MS to engage in an active lifestyle is scarce. Therefore identification of interventions to help this population remain and/or become active is essential.

In this context, activity pacing could be a promising approach to manage fatigue and increase overall activity in people with MS (Antcliff et al., 2015; National Institute for Health and Clinical Excellence, 2007; Nielson et al., 2001). Activity pacing is defined as a strategy in which people learn to lessen the effect of fatigue on activity by dividing daily activities into smaller, more manageable pieces, and alternating activity and rest periods (Andrews et al., 2012; Birkholtz et al., 2004). However, activity pacing as an intervention with the aim of stimulating engagement in an active lifestyle for people with a chronic condition suffering from fatigue has not yet been tested. In addition, existing literature on how to impose activity pacing is limited and inconclusive (Andrews et al., 2012; Murphy and Kratz, 2014; Antcliff et al., 2015). There is the need for further exploratory and interventional studies on how to adapt, tailor and optimise activity pacing for people with MS. This underscores the need for a closer inspection of the dimensionality of activity pacing and its relations to physical activity behaviour, health-related quality of life and symptoms of fatigue. A better understanding of this is particularly relevant to physical rehabilitation therapy and could provide greater strategies and possible interventions to help persons with MS manage their fatigue and optimise their activities of daily living. Consequently, this research aims to explore possibilities of activity pacing and provides more insight into how to optimise, tailor and adapt activity pacing. Programmes that incorporate this design may help to reveal the efficiency and beneficial effect of activity pacing in stimulating a physically active lifestyle and improving health and quality of life.

1.2 Aims of the research

This research aims to explore possibilities of activity pacing, and obtain more insight into the relations between fatigue, activity pacing, physical activity and health-related quality of life; and use this knowledge to adapt, tailor and optimise activity pacing in persons with MS; a condition with frequent and disabling fatigue symptoms. This could help guide treatment efforts aimed to manage fatigue and promote physical activity important for health in people with MS.

In this context, the research concurrently address some of the key pitfalls in literature:

- The effect of activity pacing intervention and potential moderating factors in chronic fatigue.

- The pacing behaviour people with MS enact in daily life and how it impacts fatigue, physical activity behaviour and quality of life.
- The effectiveness of a tailored activity pacing approach based on person's fatigue experience and attitudes and behaviour towards physical activity in improving physical activity behaviour, fatigue and health-related quality of life in people with MS.

Empirical evidence regarding activity pacing (both use of pacing naturally and after pacing instruction) is limited and conflicting (Nielson et al., 2001; Murphy et al., 2008; Murphy et al., 2012). There is a lack of clarity in the direction of the relationship between activity pacing behaviour and symptom outcome, such as do persons engage in more pacing behaviour in daily life due to an increase in perceived symptoms (symptom-contingent) or do persons engage in more pacing behaviour and thereby reduce their perceived symptoms (symptom-reduction) (Nielson et al., 2001)? Also, most of the very few published study designs on activity pacing focused on symptom reduction with little or no emphasis on how it impacts on physical activity behaviour (White et al., 2011). Considering that activity pacing directly relates to altering physical activity patterns, it is necessary to understand how this affects physical activity behaviour. Without tangible change in physical activity behaviour, the impact of activity pacing strategies is likely to be insignificant and it is imperative to consider current physical activity behaviour and attitudes towards physical activity when designing an activity pacing intervention. In adding to the methodologically limited body of scientific knowledge relating to this matter, it is anticipated that this research could inform clinicians and physical rehabilitation professionals about how to appropriately tailor and adapt activity pacing advices. A schematic of the schedule of studies can be seen in Figure 1.1.

Literature review: A review of relevant literature revealed gaps in current knowledge.

• Despite the growing evidence of physical inactivity in persons with disabling conditions such as MS, pitfall exist on how to advice this population to remain or become active whilst managing their fatigue symptoms.

• Although activity pacing could be a useful tool in this regard, different conceptual traditions and definitions currently exist of activity pacing across clinical settings, and this has important implications on the implementation and subsequent effectiveness of activity pacing.

• A qualitative review was inadequate in determining the effect of activity pacing in chronic fatigue; mainly whether activity pacing could improve fatigue and physical activity, and potential moderators of effects.

• This necessitated the carrying out of a meta-analysis to determine activity pacing effects in chronic fatigue.

Meta-analysis: To examine activity pacing intervention effect on fatigue, physical functioning and physical activity in chronic fatigue, and examine potential moderator effects.
Results: Medium (SMD= 0.50) and marginal (SMD = 0.34) effects were found for fatigue at post-treatment and follow-up respectively. Inconsequential effects were found for physical functioning and activity (SMD = 0.08 to 0.30) at both assessment points. Minimal patient-provider contact had effect on fatigue comparable in magnitude to more intensive contact.
Conclusion: Activity pacing may be useful tool in fatigue management. Studies must concurrently examine natural pacing behaviour and perceived risk of overactivity, the impact of the behaviour and the context in which the behaviour occurs.

Cross-sectional study: To explore relations of naturalistic pacing with fatigue and physical activity.
Results: Hierarchical regression models showed no associations between activity pacing and fatigue (β = .20; p = .16), and physical activity (β = -.24; p = .12). Yet, fatigue was related to low health-related quality of life (β = -.34; p = .01)
Conclusion: The lack of relations between activity pacing, and fatigue and physical activity suggests that without interventions, there is no clear strategy amongst persons with MS to manage fatigue and improve physical activity

Longitudinal study: To explore how activity pacing affect the development physical activity and health-related quality of life over time.
Results: Multilevel modelling found no relations between activity pacing and physical activity (β = -.01; p = .89) and health-related quality of life (β = -.15; p = .09). Fatigue was related to low health-related quality of life (β = -.33; p < .001). Perceived risk of overactivity moderated the fatigue-physical activity (β = -.19; p = .02) and fatigue-health-related quality of life (β = -.13; p = .03) relationships.
Conclusion: An efficient approach to activity may be beneficial to manage fatigue and improve health

Observational study: To examine a within daily analysis of actual physical activity behaviour.
Results: Lower activity level was related to higher engagement in pacing (β = -.438, *t* = -2.66, *p* =.024). Higher activity level was associated with higher perceived risk of overactivity (β = .494, *t* = 2.84, *p* = .018). No associations were found between activity variability and engagement in pacing (β = -.225, *t* = -.96, *p* = .361) and between activity variability and perceived risk of overactivity (β = .149, *t* = .599, *p* = .562).
Conclusion: Individualised approach to guidance on optimal use of pacing may be beneficial for persons with MS and improve their physical activity behaviour.

Interventional study: To evaluate the effectiveness of an individualised approach to activity pacing based on persons' attitudes towards pacing, fatigue experience and physical activity patterns.
Results: Compared to the control group the tailored activity pacing group demonstrated increased activity counts per minute (22.79 ± 44.70 vs. -18.11 ± 36.07; p =.03) and decreased activity variability (-.10 ± .53 vs. .53 ± .80; p =.04).
Conclusion: Adopting an individualised approach to activity pacing was effective in improving activity levels and reducing activity variability without exacerbating fatigue in adults with MS. This pilot study provides the basis to incorporate activity pacing intervention in health promotion programs for persons with MS to manage fatigue and improve physical activity important for health.

Figure 1.1 Schematic of thesis structure

1.3 Outline of Literature review - Optimising activity pacing to promote a physically active lifestyle in persons with a disabling or chronic condition: A review

This review identifies declining levels of physical activity in persons with disabling conditions, considers how fatigue interacts with such conditions and also influences physical activity behaviour. It also discusses the potential of a practical strategy to stimulate a physically active lifestyle for persons with disabling condition by using a new clinical concept called activity pacing which is a novel goal-directed behavioural process of decision-making and planning over how and where to distribute available energy over daily activities. Currently, different conceptual traditions and definitions exist of pacing across sport and clinical settings and this has important implications for the implementation and subsequent effectiveness of activity pacing for persons with disability. The application of activity pacing has mostly focused on symptom-reduction in a rehabilitation context to improve self-regulatory behaviour and less on physical activity stimulation for health and wellbeing. There is the need for further exploratory and interventional studies on how to adapt, tailor and optimise activity pacing to make it successful and beneficial. The potential of activity pacing to increase physical activity and lessen fatigue could be a powerful tool to help fight the growing incidence of physical inactivity, particularly in persons with disabling conditions associated with high fatigue complaints.

1.4 Outline of Study 1 – Effects of activity pacing in patients with chronic conditions associated with fatigue complaints: A meta-analysis

To be able to further explore possibilities of activity pacing in the context of an active lifestyle, we first need to review results and outcomes of current interventions involving activity pacing in persons with high fatigue complaints. This chapter therefore presents the findings of a meta-analysis to (1) determine the effect of activity pacing interventions on fatigue, physical activity and physical functioning in patients with chronically fatiguing conditions, and to (2) examine potential moderator effects of trial characteristics (type of intervention, amount of patient-provider contact, type of condition and gender type of the sample). Six studies (N = 563) were eligible for inclusion. Relevant content of the studies was extracted and rated on methodological quality. Random-effects modelling was used to pool data across studies. Medium (standardised mean difference = 0.50) and marginal (standardised mean difference = 0.34) effects were found for fatigue at post-treatment and follow-up respectively. Inconsequential effects were found for physical functioning and activity (standardised mean difference = 0.08 to 0.30) at both assessment points. Minimal patient-provider contact had effect on fatigue comparable in magnitude to more intensive contact. Effects were larger when pacing was combined with graded exercise and/or cognitive behavioural therapy. This meta-analysis of activity pacing in patients with fatigue complaints suggests that activity pacing might have sustained beneficial effects on fatigue management, in particular on fatigue reduction for which medium effects were found. The divergence in the effects for all outcomes suggests that alternative ways such as tailoring advice to individual's behaviour towards physical activity may be more successful.

1.5 Outline of Study 2 – Associations between activity pacing, fatigue and physical activity in adults with multiple sclerosis: A cross sectional study

To now take the next step on how to tailor advice to stimulate an active lifestyle in specific populations, we need to explore person's engagement in pacing, fatigue experiences and physical activity. Understanding this is important to help guide treatment efforts for persons with MS. This study examined persons with MS engagement in pacing, fatigue experience and physical activity using self-report measures. This was a secondary analysis of data collected within a large longitudinal study (Rehabilitation, Sports and Active lifestyle; ReSpAct) to evaluate the effect of a nationwide multi-centre programme in the Netherlands, aimed at stimulating and promoting an active lifestyle in rehabilitation. 80 adults with MS filled in questionnaires on their engagement in pacing (5-point Activity Pacing and Risk of Overactivity Questionnaire), fatigue (7-point Fatigue Severity Scale), physical activity (time spent on activities using the adapted Short Questionnaire to Assess Health-enhancing physical activity) and Health-related quality of life (RAND-12) post rehabilitation. The results of hierarchical regressions showed no associations between engagement in pacing and fatigue ($\beta = .20$; $p = .16$) and activity level ($\beta = -.24$; $p = .12$). However, higher fatigue was significantly related to lower health-related quality of life ($\beta = -.34$; $p = .01$). These findings suggests that without interventions, there is no clear strategy amongst persons with multiple sclerosis to manage fatigue and improve physical activity. This demonstrates the complexity of naturalistic pacing behaviour, and the importance to explore this behaviour in relation to what we know from literature to help guide treatment efforts for persons with MS. Adequate management of fatigue might be crucial to promote health and well-being. As behaviours to manage problematic symptoms may be adaptive in the short term, but may become maladaptive in the long term, exploratory studies examining activity pacing effects on physical activity over longer periods of time are warranted.

1.6 Outline of Study 3 – A longitudinal study of associations between activity pacing, physical activity behaviour and health-related quality of life in adults with multiple sclerosis

This study examined the associations between activity pacing and development of physical activity and health-related quality of life one year after discharge from rehabilitation in a sample of adults with MS ($N = 68$) using data collected within the Rehabilitation, Sports and Active lifestyle study (brief description given in the preceding outline). Physical activity was assessed with an adapted Short Questionnaire to Assess Health-Enhancing Physical Activity; activity pacing and risk of overactivity were assessed with an Activity Pacing and Risk of Overactivity

Questionnaire; fatigue was assessed with the Fatigue Severity Scale; health-related quality of life was assessed with the RAND-1 Health Survey. Using multilevel modelling, no associations were found between activity pacing and physical activity (β = -.01; p = .890), and between activity pacing and health-related quality of life (β = -.15; p = .085) over time. Fatigue was related to low health-related quality of life (β = -.33; p < .001) and perceived risk of overactivity moderated the associations between fatigue and physical activity (β = -.19; p = .021), and between fatigue and health-related quality of life (β = -.13; p = .040). This study findings suggests that there is no clear strategy for using physical activity to ameliorate fatigue symptoms and advance quality of life amongst people with MS, and that those with increased perceived risk of overactivity and low physical activity and health-related quality of life in the context of increased fatigue may benefit from goal-directed interventions to manage their fatigue and improve longitudinal engagement in physical activity. As self-report measures are susceptible to biases, investigations of how activity pacing impacts objective physical activity behaviours is now needed. Further examination that looks at moment to moment associations between activity pacing and objective physical activity behaviour would help provide a better understanding of natural use of pacing and how it influences physical activity behaviour.

1.7 Outline of Study 4 - A within daily analysis of actual physical activity behaviour and natural use of pacing and perceived risk of overactivity in adults with multiple sclerosis

To provide a better understanding of how activity pacing affects actual physical activity behaviour in adults with MS, this study thus explored a within daily analysis of physical activity behaviour using accelerometry, and engagement in pacing and perceived risk of overactivity in persons with MS. 21 adults with MS from MS-UK and MS Society, Colchester, Essex, wore an accelerometer for 7 days to assess physical activity behaviours and filled in questionnaires on their engagement in pacing and risk of overactivity (5-point Activity Pacing and Risk of Overactivity Questionnaire), fatigue (7-point Fatigue Severity Scale), and Health-related quality of life (RAND-12) as baseline measures. Physical activity behaviours were assessed by examining activity variability (highest activity counts per minute each day divided by activity counts per minute on that day, and averaged over 7 days) and activity level (7-day average activity counts per minute). Using hierarchical regression models, lower activity levels was related to lower engagement in pacing ($\beta = -.438$, $t = -2.66$, $p = .024$). Higher activity level was associated with higher perceived risk of overactivity ($\beta = .494$, $t = 2.84$, $p = .018$). No associations were found between activity variability and engagement in pacing ($\beta = -.225$, $t = -.96$, $p = .361$) and between activity variability and perceived risk of overactivity ($\beta = .149$, $t = .599$, $p = .562$). The results indicates that those with lower activity levels may have worsening symptoms with respect to physical disability, and may be more inclined and aware to pace their activities. Conversely, those with higher activity levels may experience less disruption through fatigue in daily life and may resort to the execution of too long periods of activity which may cause overactivity. With both underactivity and overactivity associated with functional debility, individualised guidance on optimal use of pacing may be beneficial for persons with MS to help them approach activity effectively and improve their physical activity behaviour.

1.8 Outline of Study 5 - Effect of a tailored activity pacing intervention on fatigue, physical activity and health-related quality of life in adults with multiple sclerosis: A pilot study

Our previous exploration of physical activity behaviour and activity pacing demonstrated variations in the effect of activity pacing (both use of pacing naturally and after pacing instruction). This provides valuable insight that a tailored approach to activity pacing based on persons' attitudes to pacing, activity engagement and expectation and experience of fatigue is necessary for more successful outcomes.

However, there is a gap in literature in support of tailored activity pacing for persons with MS. Consequently, this pilot study presents the effectiveness of a tailored activity pacing intervention based on personalised report of attitude towards pacing, fatigue experience and physical activity patterns in improving fatigue, physical activity and health-related quality of life in adults with MS. 21 adults with MS were randomly allocated to tailored activity pacing group (n = 11) or control group (n = 10). All participants wore an accelerometer for 7 days and repeatedly reported engagement in pacing, physical activity, and fatigue via questionnaires at baseline and 4-week follow-up. Outcome measures were objective physical activity assessed with ActiGraph accelerometer and reported engagement in pacing and perceived risk of overactivity, leisure time activity, health-related quality of life, fatigue severity and expectation assessed with the Activity Pacing and Risk of Overactivity Questionnaire, adapted Self Questionnaire to Assess Health-enhancing physical activity, the RAND-12, the Fatigue Severity Scale and a self-reported questionnaire respectively. Using ANOVA, the tailored activity pacing group had increased activity counts per minute (+19.28 ± 42.98 vs. -4.05 ± 48.26; p =.048) and decreased activity variability (-.01 ± .02 vs. +.03 ± .06; p =.018) compared to the control group. No significant group differences in fatigue severity (-.13 ± .84 vs. .29 ± .54; p =.300), expectation of fatigue (-.36 ± .67 vs. .00 ± .67; p =.829), health-related quality of life (+3.95 ± 9.38 vs. -4.60 ± 9.55; p =.375), leisure time activity (679.09 ± 1745.51 vs. 1464.00 ± 2067.80; p =.225), perceived engagement in pacing (-.18 ± .42 vs. .02 ± .68; p =.413) and risk of overactivity (-.05 ± 1.04 vs. .30 ± .09; p = .566) were found. Tailoring activity pacing based on attitudes towards pacing, physical activity and fatigue experience was effective in improving activity level and activity distribution through the day more equally without exacerbating fatigue in adults with MS. This suggest that a tailored approach to activity pacing based on this design can be feasibly incorporated into standard care to promote physical activity and manage fatigue in persons with MS.

1.9 Outline of conclusion and summary

In the last chapter of this thesis, the novel insights into the optimisation of activity pacing to promote physical activity is summarised, and possible implications for practice of these findings are suggested. Finally, the limitations of the thesis and recommendations for future works in the context of this thesis are also presented.

CHAPTER 2

Optimising activity pacing to promote a physically active lifestyle in persons with a disabling or chronic condition: A review

Citation

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Abstract

It is a well-known principle that regular physical activity can improve both physiological performance and psychological wellbeing, but while compelling evidence exists for its efficacy in healthy individuals, data on how to help special populations to become or remain active is scarce.

This narrative review describes the declining levels of physical activity in persons with disabling conditions, and conceptually considers how fatigue interacts with such conditions influencing physical activity behaviour. It also discusses the potential of a practical strategy to integrate existing medical and sports medicine approaches to promote and manage physical activity by stimulating a physically active lifestyle for persons with disabling condition. This is suggested to be optimally achieved by using a new clinical concept called activity pacing which is a novel goal-directed behavioural process of decision-making and planning over how and where to distribute available energy over daily activities.

Currently, different conceptual traditions and definitions of pacing and effort distribution exist across sport and clinical settings with important implications for the implementation and subsequent effectiveness of activity pacing for persons with disabling conditions. The application of activity pacing is a medically derived concept that has mostly focused on symptom-reduction in a rehabilitation context to improve self-regulatory behaviour, and less on physical activity stimulation for health and wellbeing.

There is the need for further exploratory and interventional studies on how to adapt, tailor and optimise activity pacing to make it successful and beneficial. The potential of activity pacing to increase physical activity and lessen fatigue could be a powerful tool to help fight the growing incidence of physical inactivity, particularly in persons with disabling conditions associated with high fatigue complaints.

2.1 Introduction

Worldwide public health data clearly demonstrate physical activity levels are low across the general population, but worryingly this is even more prevalent in persons with disabling conditions (World Health Organization, 2002), further impacting on the wellbeing, health and functioning of vulnerable populations (Miles, 2007). There are many causal elements behind this observation, but engaging in regular physical activity depends on successfully managing and distributing physical efforts across daily activities. However, this can be particularly challenging to those with disabling conditions due to varying degrees of physical impediments, in addition to reduced confidence to exercise, exercise tolerance and self-awareness of one’s physical limits (Durstine et al., 2000; Barnett et al., 2012). Worryingly, studies investigating the effect of exercise in people with disabling conditions report a high number of dropouts, and identified that participants struggle to continue engaging in activity post-intervention (Roehrs and Karst, 2004; Brurberg et al., 2017).). This indicate that the way exercise is introduced, delivered and/or undertaken can influence its long-term adoption within a physically active lifestyle.

The importance of habitual physical activity for attaining optimal health and minimising risk factors associated with the development of a broad spectrum of health conditions has been extensively documented (Kayes et al., 2011; Lee et al., 2001; Motl et al., 2005). Notably, regular participation in physical activity is well known to improve quality of life and promote independence across the lifespan (Rimmer and Marques, 2012; Roehrs and Karst, 2004). Persons with disabling conditions such as multiple sclerosis, chronic fatigue syndrome, fibromyalgia, and osteoarthritis often struggle with mobility and consequently sedentary behaviours are common; however, this makes engagement in physical activity of even greater importance to increase health, mobility and participation in daily life (Kayes et al., 2011). Increasing physical activity positively impacts on health, energy, participation and longevity (Paterson et al., 2007), with an estimated gain of 4.5 years of life compared with being inactive (Moore et al., 2012). Thus strategies to promote physical activity ought to be a primary goal to support the quality of life and lifespan of persons with disabling conditions. It is therefore essential to explore ways to particularly promote active lifestyles for those with disabling conditions to optimise quality of life and to also reduce the economic burden associated with disabilities in the long term (Motl et al., 2005).

Several approaches have been successful in stimulating an active lifestyle in persons with disabling conditions (Alingh et al., 2015; Plotnikoff et al., 2013; Jensen et al., 2012; Pinto et al., 2013) but not much is yet known on the overarching principles of how to achieve this for a wide range of persons with disabling conditions based on their physical activity choices and behaviours. In addition, existing programmes (such as graded exercise therapy and cognitive–behavioural therapy) to promote physical activity in persons with disabling condition are typically expensive, resource-intensive and not widely accessible (Castell et al., 2011). The present review will therefore focus on the emergence of a pacing-based approach to self-regulation, overviewing literature related to physical activity behaviour and condition-induced fatigue management in persons with disabling conditions. It will explore the potential of better promoting self-regulatory behaviour through activity pacing, a recent medical concept to aid self-regulatory decision-making by having the confidence to engage in physical activity and accurately distribute available energy throughout the day (Smits et al., 2014). With appropriate education and experience, this process of fatigue management may be a practical, wide-scale strategy to facilitate persons with diverse disabling conditions becoming and/or remaining active, improve self-confidence and longitudinal engagement in an active lifestyle.

2.2 Physical activity in persons with disabling conditions

As regular physical activity has the potential to ameliorate the extent of functional impairment from disability, it is important to further explore current physical activity levels and practices in persons with a disabling condition. An estimated 10.2%–46.1% of the world's population have moderate to severe disabilities and experience significant functional difficulties (World Health Organization, 2004a). However, there is a dearth of physical activity data available on persons with disabling conditions (World Health Organisation, 2004a; Murray and Lopez, 1997). A disturbing statistic is that physical activity levels among people with a disabling conditions are significantly lower across all age groups compared to non-disabled people (Durstine et al., 2000).

Consequently, many persons with disabling conditions do not achieve the recommended amount of physical activity required for maintaining health (Graber et al., 2011; van den Berg-Emons et al., 2010). Therefore, the greater time spent in sedentary behaviour compared with the general population means that a population, often already with limited physical functionality, has a compounded problem exacerbated by an inactive lifestyle (Van den Berg-Emons et al., 2008). Consequently, physical function in persons with disabling condition is often impaired leading to a more severe impact of the disability and a lower quality of life (Afari and Buchwald, 2003; Boutron et al., 2008).

Several studies rightly emphasised that the lack of physical activity and excessive resting found in persons with disabling conditions can result in further physical deconditioning (Bakkum et al., 2013; Afari and Buchwald, 2003; Boutron et al., 2008; Clark and White, 2005). This consequently perpetuate early-onset fatigue when active and compound the physical disability impacting even more on mobility and participation in activities of daily living (ADLs), work, and other meaningful activities causing a downwards spiral (Grotle et al., 2008; Sutbeyaz et al., 2007; Theis et al., 2007; World Health Organisation, 2001).

Continuous or recurring symptoms of fatigue are among the most frequently reported (Anderson et al., 2012; Goudsmit et al., 2012; van Koulil et al., 2010; Power et al., 2008), and strongest predictors of functional debility (Wolfe, 1999; Deale et al., 1997) in persons with disabling conditions. The next section thus explored the association between fatigue and physical activity in persons with disabling conditions.

2.3 Associations between fatigue and physical activity behaviour in persons with disabling conditions

The sensations of fatigue can be disabling symptoms in which physical and cognitive function are limited by interactions between performance fatigability and perceived fatigability (Enoka and Duchateau, 2016). Performance fatigability is the decline in an objective outcome measure such as walking distance covered over a distinct period of time when tired; and perceived fatigability refers to changes in the sensations that regulate the effort and physical tolerance of the performer (Enoka and Duchateau, 2016). Fatigue therefore incorporates self-reported sensations of weariness, exhaustion, increasing sense of effort, such as mismatch between effort expended and actual performance (Deluca, 2005; Eldadah, 2010) where a person applies maximal effort while performance simultaneously deteriorate. This has also been proven to be associated with decreased daily functioning and disability that can persist for years (Richardson et al., 2004; Ament and Verkerke, 2009; Hardy and Studenski, 2008; Chou et al., 2011; Simonsick et al., 2004; Vestergaard et al., 2009). Fatigue is therefore not restricted to a single physical task, its effects are retained for long periods after exercise and consequently impacts on subsequent activities, meaning that particularly among people with physical disability managing effort should be considered not simply on a single task basis, but at a macro level encompassing their planning and management of effort across daily tasks (Edwards and Noakes, 2009).

Fatigue while performing daily activities has been examined in persons with a disabling condition, and has been found to profoundly impact physical and mental capacity (Amato et al., 2001). Disabling detriments associated with fatigue include, but are not limited to, cardiovascular disease (Rockwood et al., 2001) and depression (Bakshi et al., 2000; Bixler et al., 2005). Among otherwise healthy individuals, feeling of fatigue sensation is common and has been reported as the most common cause for physical inactivity (Avlund et al., 2006; Gill et al., 2001). Furthermore, fatigue has been found to be more severe and more strongly associated with decrements in physical activity levels than pain sensations in persons with chronic pain conditions (Murphy et al., 2008). This suggests that adequate management of fatigue in respect to performance of activities of daily living may also be important to target in designing interventions and treatments for persons with pain-related conditions, again highlighting the important role fatigue plays in disabling conditions.

The functional impairment associated with perceived fatigability commonly found in persons with disabling conditions may be explained by persons' perceptions and expectations with respect to symptom exacerbation as a consequence of physical exertion. This can lead to fear of engaging in physical activity (Clark and White, 2005; Nijs et al., 2008) and therefore may explain subsequent reductions in levels of physical activity (Nijs et al., 2011). Conversely, the lifestyle of these persons is often characterized by periods of extreme fluctuations such as overactivity (when feeling good) and as a consequence of that, feeling overtly fatigued afterwards, followed by long extensive rest periods to recover from residual symptoms or prevent any symptoms re-occurring (van der Werf et al., 2000). In this way, adequate ‘management’ of perceptions and expectations with respect to symptoms associated with physical activity are crucial in the stimulation and promotion of an active lifestyle, in particular in special populations with high fatigue complaints. Guidance towards a more evenly distributed pattern of activities throughout the day could be the key to a more active lifestyle.

Knowing the health-enhancing impacts of regular participation in physical activity, such as positive effect on mobility and quality of life (Haskell et al., 2007; Hollmannet al., 2007; Puetz, 2006; Rimmer and Marques, 2012) inevitably mean a physically active lifestyle is strongly recommended for persons with a disabling condition (Galea, 2012; Ginis et al., 2012; Plotnikoff et al., 2013). Consequently, the promotion of active lifestyle has been considered to be an important behaviour in the management of disabling conditions (National Institute for Health and Clinical Excellence, 2007).

2.4 Activity pacing as potential intervention to manage fatigue and promote an active lifestyle in persons with disabling condition

Currently, the most common clinical techniques to promote physical activity in persons with disabling conditions are graded exercise therapy and cognitive–behavioural therapy (Castell et al., 2011; Nijs et al., 2008; Marques et al., 2015). Graded exercise therapy involves a gradual increase in aerobic exercise in order to avoid overexertion and cognitive behavioural therapy usually incorporates changes in physical activity and rest behaviour. Studies have demonstrated that graded exercise therapy results in improved engagement in physical activity and increased likelihood of exercise adherence in people with disabling conditions compared to usual care, both in the short- and long-term (Marques et al., 2015; Pisters et al., 2010). Similarly, cognitive-behavioural therapy have been shown to result in increases in physical activity as well as reduction in fatigue (Castell et al., 2011; Wiborg et al., 2010). The UK National Institute for Clinical Excellence (NICE) recommends that cognitive-behavioural therapy and/or graded exercise therapy should be offered to people with disabling conditions (NICE, 2007; 2014). However, most cognitive–behavioural therapy and graded exercise therapy interventions are typically resource-intensive and require specialist clinics and considerable direct provider-patient contact (Malouff et al., 2008; Castell et al., 2011). In addition, the availability of these interventions for patients in many countries is limited which is problematic for a public health issue (Nijs et al., 2009).

For all these reasons, studies examining the potential benefits of accessible, less resource-intensive treatments and/or strategies are warranted. Activity pacing is one such therapeutic intervention that has the potential to stimulating an active lifestyle by lowering fatigue and increasing physical activity in persons with a disabling condition. Activity pacing as defined in medical settings, is a strategy to educate and develop individuals' self-regulatory skills to divide one's daily activities into smaller, more manageable portions, in a way that should not exacerbate their symptoms, which then allows gradual progressive increases in activity (Andrews et al., 2012).

The concept of pacing has long been established in a sporting context (Hettinga et al., 2017), mostly in endurance activities, whereby physical capabilities are managed by an athlete in order to finish a race or event in an optimal performance time, depending on the goal of the athlete. Several researchers (Smits et al., 2014; Edwards et al., 2011) have examined the balance of performance and recovery periods holistically, and have stressed the importance of self-regulatory skills for effective pace-regulation particularly in longer exercise tasks involving fatigue, both within a race as well as en route towards the long term goal of athletic excellence (Elferink-Gemser and Hettinga, 2017; Brick et al., 2016). Several different theoretical frameworks on pacing in sports have in some way suggested that competition between psychological, physiological and/or social factors is essential for decision-making regarding the regulation of exercise (Smits et al., 2014; St Clair et al., 2017; Marcora, 2008; Renfree et al., 2014; Konings and Hettinga, 2018; Venhorst et al., 2017), with fatigue as a crucial factor. Pacing decisions have been suggested to be the outcome of the interplay between the sensation of fatigue and exercise expectations (Noakes et al., 2005; Tucker, 2009). In addition, planning and self-regulation skills have been identified as essential (Elferink-Gemser and Hettinga, 2017).

Self-regulation during exercise was postulated by Ulmer, 1996 who theorized the existence and functioning of a feedback control system for optimal adjustment of performance during exercise and the relevance of consideration of the finishing point (teleoanticipation). He provided a framework for examining extracellular regulation of muscular metabolic rate during exercise. This exquisitely regulated metabolic turnover system optimises perception or teleoanticipation along with feedback so that catastrophe is avoided and task is complete within physiological capacity (Marino, 2014). Based on previous experiences, the pacing process can be learned and optimised (Foster et al., 2009), and a distinction has been made between pre-planned deliberate strategic elements that determine optimal pacing, and more intuitive adaptations that occur while engaging in activities (Micklewright, et al., 2017).

Though the relevance of understanding the regulation of exercise intensity for a broader audience of exercisers has been highlighted (Smits et al., 2014), the majority of pacing research has tended to be limited to managing and describing competitive performances. However, the principles underlying pacing and the regulation of exercise intensity also apply in medical and clinical contexts, extending well beyond the maintenance of physical efforts in a single task. By self-managing and spreading physical efforts across multiple daily tasks, it is possible for individuals to have greater confidence to engage in many activities they may not have previously thought possible, which accumulatively represent a more active, fulfilling lifestyle, of greater physical engagement. This can be achieved by employing better strategies to manage fatigue symptoms and distribute the limited available energy resources to prevent overactivity causing periods of subsequent inactivity. Therefore, the concept of activity pacing postulates that by perceiving an increase in physical activity without exacerbation of symptoms, patients are likely to feel more in control of their fatigue and focus less on fatigue, which can lead to positive effects such as task enjoyment, better fatigue management and physical function (Chalder et al., 2015).

The rationale for activity pacing as an intervention to stimulate engagement in physical activity can also be found elsewhere in literature (Nijs et al., 2011). In rehabilitation practice, several activity engagement strategies have been observed in daily lives of persons with disabling conditions. This include reduced activity levels resulting from and in anticipation of fatigue (Clark and White, 2005; Nijs et al., 2009; Nijs et al., 2011), activity peaks followed by very long rest periods (van der Werf et al., 2000), and the ability to perform short periods of light to moderate activity without exacerbating symptoms (Cook et al., 2005). However, activity pacing as a potential treatment, stimulating engagement in an active lifestyle, for persons with disabling conditions has not been fully explored (Amato et al., 2001). The next section will overview the literature regarding activity pacing and its potential to stimulate a physically active lifestyle.

2.5 Activity pacing as a concept to influence physical activity behaviour

The fatigue-related decline that is commonly seen in physical activity levels in persons with a disabling condition might be an adaptive response to conserve energy and to lessen the energetic requirements of activities of daily living after periods of physical strain (Amato et al., 2001). However, by focusing only on conserving energy during relatively long recovery periods, beneficial effects associated with physical activity such as improvements in health, fitness levels, mobility and participation may be neglected. To avert such energy conserving behaviour that is associated with fatigue after periods of heavy strain, activity pacing is a reasonable approach. Activity pacing could help alter inefficient activity patterns such as being overactive, resulting in high fatigue sensation and subsequent prolonged inactive periods, or being underactive because of anxiety of physical activity and the associated fatigue symptoms (Antcliff et al., 2015).

Being underactive in general could be associated with fear of experiencing fatigue symptoms. However, fatigue itself is a symptom of physical activity and so education of how to self-manage fatigue could lead to better health outcomes, delay the onset of fatigue, prevent periods of inactivity associated with overactivity and improve confidence to exercise. Consistently low levels of physical activity are related to lower fitness levels, causing any exercise related fatigue responses that might occur after daily life activities to be even more pronounced (Bakkum et al., 2013; Clark and White, 2005; World Health Organization, 2001). As such the premise that both underactivity and overactivity are linked to physical activity decline and its further negative consequences, gives further basis towards the introduction of activity pacing as a potential positive coping strategy to prevent major symptoms of fatigue to occur while maintaining sufficient physical activity levels (Andrew et al., 2012; Butler et al., 2003).

Within the concept of activity pacing in rehabilitation, a distinction can be made between '*naturalistic pacing*' and '*programmatic pacin*g'. Naturalistic pacing comprises the level of activity pacing that persons implement in daily life without a specifically instructed activity pacing programme (Nielson et al., 2013). This is a similar and associated concept to the well-known self-paced behaviour (Smits et al., 2014; Edwards and Polman, 2012) that has been described and researched in the field of sport sciences. The main difference between concepts is that in rehabilitation it is applied to the pacing of activities over a day instead of the pacing of a single race or exercise bout in sports. An important difference therefore is that pacing a race is very much oriented towards the relatively straightforward goal of setting the best performance and using all the available energy as efficiently as possible, whereas in pacing activities over a day the key challenge is more complex: engaging in physical activity behaviour to improve fitness and mobility, while at the same time preventing too severe symptoms of fatigue that will have their impact on any subsequently planned physical activity. It is therefore more of a lifestyle strategy.

Within the concept of naturalistic activity pacing there is a lack of clarity in the direction of the relationship between activity pacing behaviour and symptom outcome, such as do persons engage in more pacing behaviour in daily life due to an increase in perceived symptoms (symptom-contingent) or do persons engage in more pacing behaviour and thereby reduce their perceived symptoms (symptom-reduction) (Antcliff et al., 2015; Nijs et al., 2008)? More insight in relations between physical activity, fatigue and pacing behaviour in this naturalistic context could provide greater strategies and possible interventions to help persons with high fatigue complaints manage their fatigue by the so-called programmatic pacing.

In programmatic pacing, patients receive a specific treatment with pacing instructions to learn and stimulate optimal activity pacing behaviour. The specific goals of this training vary depending on the theoretical orientation of the treatment and may include pain reduction, lessening of fatigue, and/or increased overall activity (Nielson et al., 2001). It is more of an instructional and educational pacing strategy where individuals may learn to become more naturalistic in their approach to their pacing of life activities.

While several studies support links between programmatic pacing and lower levels of fatigue and physical functioning (Van Koulil et al., 2010; Kos et al., 2015; Nielson and Jensen, 2004), a number of studies show no association (Nijs et al., 2009; Wallman et al., 2004; Murphy et al., 2010). In a sample of people with chronic fatigue syndrome, programmatic pacing was associated with low fatigue severity, high leisure time physical activity, improved personal activity goal progress and health related quality of life (Marques et al., 2015).

Conversely, Murphy et al., (2010) reported in their study that programmatic pacing had a positive effect on fatigue. Though not statistically significant, participants in a study of programmatic pacing demonstrated increased physical activity and physical functionality (Murphy et al., 2008). Similarly, van Koulil et al., (2010) found reduction in fatigue severity and a trend towards improvement in physical function related to concurrent programmatic pacing and exercise training.

Contrariwise, White et al., (2011) showed that programmatic pacing did not improve fatigue and physical functioning compared to graded exercise therapy and cognitive behavioural therapy. Additionally, Nielson et al., (2013) reported that increased pacing was associated with higher levels of pain and fatigue and suggested that future research should be based on a clear theoretical foundation and consider the context in which the behaviour occurs. This may suggest that programmatic pacing may be an important tool to develop a more self-directed naturalistic pacing approach to lifestyle management which would aid longitudinal engagement in physical activity.

In a study to measure naturalistic pacing behaviour in 30 women with osteoarthritis, Murphy et al., (2008) reported that naturalistic activity pacing was related to lower physical activity. Furthermore, when compared with low pacing, high pacing persons had more severe, escalating symptoms. Alternatively, Murphy et al., (2012b) in their study on associations between symptoms, coping strategies, and physical activity in adults with OA reported that naturalistic pacing moderated the relationship between fatigue and physical activity. Those with high levels of activity pacing have the smallest association between fatigue and physical activity. Also, with decreasing use of pacing, the association between fatigue and physical activity becomes increasingly negative.

Contrariwise, Murphy and Kartz, (2014) studied naturalistic pacing in 162 adults with osteoarthritis and reported that activity pacing was associated with higher subsequent levels of fatigue and that naturalistic pacing seemed symptom-contingent and not reinforced by symptom reduction. They further stated that naturalistic pacing may be distinct from programmatic pacing in terms of outcomes. Similarly, Andrews et al.,

(2012) reported that an increase in disability relating to naturalistic pacing may reflect either the ineffectiveness of pacing if not used to gradually increase an individual's activity level. They also suggested that people with better psychological functioning but more disruption through fatigue in daily life are more inclined to pace their activity.

While not the focus of this review, some interesting works has been done on self-paced and imposed pace exercise in sports. Together, they demonstrates that imposed paced exercise presents a significantly greater physiological challenge than self-paced exercise (Edwards et al., 2011; Lander et al., 2009). However, the ability to dynamically self-pace effort is an important behavioural response to homeostatic challenges. In this way, the individual is able to down regulate effort when necessary and up regulate when feeling strong. Knowing physical limitations is an important part of self-regulated exercise and so developing these skills in programmatic pacing would be an important strategy to aid further independent self-regulation. This suggest that programmatic pacing or imposing a pacing strategy, has a downside: it is physiologically less challenging than self-paced exercise.

From the preceding paragraphs, most of the few studies on activity pacing focused on programmatic pacing with little emphasis on naturalistic pacing (Antcliff et al., 2015; Nielson et al., 2001). Together, these findings demonstrate that despite the frequent use and theoretical benefits of activity pacing, there is dearth of and conflicting empirical evidence regarding activity pacing effects (Nielson et al., 2001: Jones et al., 2015), although its application to clinical and rehabilitation contexts appears promising.

2.6 Overactivity vs. underactivity

Most interventional designs of activity pacing focused on symptom-reduction and in particular on preventing overactivity. Instructions are based on limiting or avoiding those activities that exacerbate symptoms. While some studies advised patients not to undertake activities that demanded more than 70% of their perceived available energy levels (White et al., 2011), others advised activity duration 25%–50% lower than the capacity participants reported (Kos et al., 2015). The evidence that overactivity may perpetuate fatigue and subsequent functional decline may have contributed to this phenomenon of focusing mostly on symptom reduction and preventing symptom exacerbation by curtailing overactivity.

This may however represent a pitfall in literature as also underactivity has been evident to link to functional impairment (Birkholtz et al., 2004). It is possible that the current inconclusive findings on activity pacing may be accounted for by variation in characteristics such as illness duration (years since illness diagnosis), physical activity behaviour and attitudes towards both naturalistic as well as programmatic activity pacing. Studies that reported poor outcomes may have sampled from persons with prior underactive behaviour for whom instructions regarding prevention of overactivity is likely to be non-beneficial, while positive outcomes may have been obtained in an overactive sample of the population. It can thus be inferred that interventions modelled based on the assumption that overactivity needs to be prevented are less likely to be effective in underactive persons. An individualised approach, based on characteristics that are unique to that person, related to the outcome of interest, and have been derived from an individual assessment (Rimer and Kreuter, 2006), is therefore needed.

Very few studies have been conducted to investigate the effects of tailored activity pacing in different patient populations and these are mostly focused on symptom reduction (Murphy et al., 2010; Nijs et al., 2009; Kos et al., 2015; Murphy and Kratz, 2014). However, with activity pacing related to activity management, it is imperative to consider the physical behaviour and attitudes towards physical activity of individuals when delivering an intervention (Murphy et al., 2008). This emphasises the need to tailor interventions not only on patients' symptom profiles but also on their physical behaviour and attitudes towards physical activity. Thus persons need guidance more specifically adapted to their needs.

In addition, the existence of different concepts and definitions of activity pacing which translate into its implementation may have contributed to the current lack of clarity about the nature and impact of activity pacing. While some studies described activity pacing as adjusting to one's condition and staying within limited amounts of energy by alternating activities and incorporating rest periods (White et al., 2011; Murphy et al., 2010), others described activity pacing as involving goal setting, and speeding up activities (Nielson et al., 2013; Nijs et al., 2011). These were consistent with theoretical understanding of pacing as a goal directed process of decision-making on how and when to distribute energy in pursuit of optimal performance (Smits et al., 2014).

Some studies also described activity pacing as modifying behaviour by going slower, taking breaks, maintaining a steady pace and splitting tasks into manageable pieces, managing symptoms whilst reducing relapses and gradually increasing activity (Antcliff et al., 2015; Murphy and Kratz, 2014). However, guidance for persons with disabling conditions are scant and further specific guidelines on managing physical activity are required. While some studies encourage an increase in activities (Kos et al., 2015; Nijs et al., 2008), others clearly restrict patients to stay within their limits (White et al., 2011). There is growing consensus for the need of a clear definition of activity pacing (Antcliff et al., 2012; Birkholtz et al., 2004) based on a clear theoretical concept and considerations of the context in which the behaviour occurs (Nielson et al., 2001). This would allow activity pacing studies to be more easily replicated, and would provide more clarity on how to optimise the effectiveness of activity pacing interventions.

2.7 Recommendations for future research

Although, a number of recent studies have supported the effectiveness of activity pacing as a clinical intervention, there were considerable variations in responses

(Murphy and Kratz, 2014; Nielson and Jensen, 2004). While some patients demonstrated lowered fatigue and higher physical activity levels (Murphy and Kratz, 2014), others demonstrated lower fatigue and no change in physical activity level (Nijs et al., 2009) or vice versa (Murphy et al., 2011). Given that different activity profiles (underactivity, overactivity and uneven spread of activity) exist between patients, an individualised approach to activity pacing should be considered in future interventional studies. Thus persons with disabling conditions associated with high fatigue may need to be advised differently constructed on their activity profile. This type of tailored-activity pacing techniques appear warranted to manage fatigue and stimulate physically active lifestyle, to improve health and increase participation of patients.

Although studies, support the efficiency of self-paced exercise in sports (Lander et al., 2009; Edwards et al., 2011; Edwards and Polman, 2012), little remains known about how persons naturally pace their activities and how it relates to fatigue, quality of life and physical activity in the context of daily life. Further research that investigates the nature of pacing is warranted. Insight into this will contribute to better understand and explain the current considerable variation in response to activity pacing. Additionally, this will help tailor, adapt and optimise activity pacing interventions in disability and rehabilitation to make this to make it more efficient.

There is also a need for further evidence-based validity studies of current measures of activity pacing as an intervention strategy to positively influence behavioural engagement in physical activity. A number of measures of activity pacing are recent and have undergone limited validity testing (McCracken and Samuel, 2007; Antcliff et al., 2015). Given the variance in definition and implementation across studies, there may be a need to develop new measures or refine existing ones. For example, it may be worthwhile to develop a measure that detects risk of overactivity and underactivity as dimensions of pacing behaviour. With both underactivity and overactivity linked to disability, exploring risk of underactivity and overactivity may offer valuable insights into how to tailor activity pacing interventions to help persons with disabling conditions remain or become physically active. Results will be particularly relevant to incorporate in activity stimulation programmes aimed at providing tailored advice to promote an active lifestyle in those with disabilities or chronic diseases (Plotnikoff et al., 2013).

2.8 Conclusion

Physical inactivity and fatigue are prevalent in persons with disabling conditions and are associated with deconditioning and disability. A physically active lifestyle is of utmost importance to improve quality of life and participation in daily life in persons with a disabling condition. Activity pacing may be a useful adaptive strategy to stimulate a physically active lifestyle in persons with a disabling condition. However, most studies on activity pacing focused on symptom reduction and curtailing overactivity and further empirical work is now required to further explore this strategy.

Considering that both underactivity and overactivity are linked to disability, it is necessary to adopt an individualised approach to activity pacing intervention to provide extra and optimal guidance and support for those with high fatigue complaints. Given the efficiency of self-pacing in sports, there is a need for further exploratory studies on the use of naturalistic pacing in persons with disabling conditions within the context of daily life. Additionally, encouraging persons with disabling conditions to learn to ‘listen’ to their symptoms and develop a performance template based on previous experience in pursuit of optimal performance may be an efficient way to manage fatigue and stimulate an active lifestyle. This could further improve the effectiveness of activity pacing intervention.

The current limited evidence on activity pacing calls for closer inspection of the dimensionality of pacing as it is currently operationalized and its relations to physical activity and fatigue in daily life. Future research on activity pacing and physical behaviour will be welcome to fully understand the link between activity pacing and disability. This will play a key role in the management of disabling conditions and fight the growing incidence of physical inactivity in persons with disabling conditions.

CHAPTER 3

Effects of activity pacing in patients with chronic conditions associated with fatigue complaints: A meta-analysis

Citation

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Abstract

A meta-analysis was conducted to (1) determine the effect of activity pacing interventions on fatigue, physical functioning and physical activity among patients with chronic conditions associated with fatigue complaints, and to (2) examine potential moderator effects of trial characteristics (components of intervention and amount of patient-provider contact). Six studies were included in the meta-analysis. Relevant content of the studies was extracted and rated on methodological quality. Random-effects modelling was used to pool data across studies. Medium (standardised mean difference = 0.50) and marginal (standardised mean difference = 0.34) effects were found for fatigue at post-treatment and follow-up respectively. Inconsequential effects were found for physical functioning and activity (standardised mean difference = 0.08 to 0.30) at both assessment points. Subgroup analyses revealed components of intervention and amount of patient-provider contact were not source of variance. Minimal patient-provider contact had effect on fatigue comparable in magnitude to more intensive contact. This meta-analysis of activity pacing in patients with fatigue complaints suggests that activity pacing might have sustained beneficial effects on fatigue management, in particular on fatigue reduction. The divergence in effects for all outcomes suggests that alternative ways such as tailoring advice to individual's behaviour towards physical activity may be more successful.

3.1 Introduction

Promoting physical activity is essential to preserve the health, quality of life and physical functioning of healthy individuals and those with chronic diseases (Blair et al., 2001; Nijs et al., 2011; Lee and Skerrett, 2001). Post-exertional fatigue is a normal perceptual response in healthy humans but may be exacerbated in patients with chronically fatiguing conditions such as chronic fatigue syndrome, cancer, fibromyalgia and osteoarthritis (Mitchell, 2010; Murphy et al., 2008; Nijs et al., 2013). Feelings of fatigue (subjective sensations of weariness) is a common symptom in chronically fatiguing conditions (Mitchell, 2010; Murphy et al., 2008; Nijs et al., 2013). Post-exertional fatigue may be a barrier to physical activity and explain activity avoidance in patients with chronically fatiguing conditions (Nijs et al., 2013).

Fatigue may result in cycles of overactivity followed by periods of fatigue-induced inactivity (Sutherland and Andersen, 2001) and activity avoidance, negatively affecting patients' physical health and quality of life of patients with chronically fatiguing conditions (Nijs et al., 2013; Andrews et al., 2012). Fatigue management is therefore paramount when programming physical activity for patients with conditions characterised by heightened perceptions of fatigue or pain (Birkholtz et al., 2004).

Activity pacing is a strategy to divide one's daily activities into smaller, more manageable, portions, in a way that should not exacerbate their symptoms, which then allows gradual progressive increases in physical activity (Andrews et al., 2012; Butler and Moseley, 2003; Nicholas et al., 2006). The goals of activity pacing are to disentangle the symptom experience from the activity experience, prevent over-exertion, attenuate fluctuations in physical activity patterns and avert the detriment associated with fatigue-induced inactivity (Andrews et al., 2012). While activity pacing is a highly endorsed clinical treatment strategy in chronic pain (Birkholtz et al., 2004), it remains poorly researched with very little literature in chronic fatigue.

The results of the few studies on activity pacing effects in chronic fatiguing conditions have been conflicting. While one study supported links between pacing and lower levels of fatigue and higher physical functioning (van Koulil et al., 2010), a number of studies have found no association (Murphy et al., 2010; Kos et al., 2015; White et al., 2011). Consideration of these findings highlights uncertainty and confusion about the effect of activity pacing on fatigue, physical functioning and activity in chronic fatigue.

The aims of the meta-analysis are thus: 1) To review literature on activity pacing interventions and to determine the overall effect of activity pacing interventions on fatigue, physical functioning and activity; both at post-treatment and follow-up, among patients with chronic conditions associated with fatigue complaints; 2) To examine possible moderators such as components of intervention arm, provider-patient contact frequency, the type of condition and gender type of the sample.

3.2 Methods

This meta-analysis was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Liberati et al., 2009).

3.2.1 Inclusion criteria

Types of participants

Studies were included if they were conducted in a participant group of adults (≥16years), with a chronic condition associated with fatigue complaints and fatigue was measured before and after the intervention.

Types of interventions

Studies had to include a construct of activity pacing that measured patient behaviour, targeting fatigue management, physical activity and/or physical functioning.

Outcome measures

Studies had to present statistical data allowing the calculation of effect sizes in the published study or provided by the author(s) upon request, on at least one of the following outcomes; fatigue, physical activity and/or physical functioning, measured at baseline (pre-treatment) and post-treatment and/or at follow-up.

Study Design

Studies had to include a control condition, consisting of usual care, waiting list control, or another type of intervention (e.g. relaxation).

Studies were included if they were randomized controlled trials published in peer review journals in English. There were no restrictions with respect to the type of diagnostic criteria used, setting, format and source of delivery of the intervention, as well as with respect to the length of the intervention and assessment point(s).

3.2.2 Search strategy

Initially, electronic databases MEDLINE, PubMed, PEDro, CINAHL, Cochrane Database of Clinical Trials, PsychINFO and Web of Science were searched for relevant articles up to July 2017. A comprehensive search strategy was used. Key words ‘‘activity pacing’’ and ‘‘fatigue’’ were combined using an ‘‘and’’ statement. Key words related to physical activity (‘‘exercise,’’ “physical function,” ‘‘physical fitness,’’ ‘‘exercise therapy,’’ ‘‘activities of daily living,’’ ‘‘therapeutic exercise,’’ ‘‘functional status,’’ and ‘‘rehabilitation”) were combined using an ‘‘or’’ statement and then combined with the previous search using an ‘‘and’’ statement. The searches were limited to ‘‘English language,’’ ‘‘humans,’’ and ‘‘all aged 16 and older.’’ References and bibliographic lists of retrieved articles were also hand searched to find additional studies.

3.2.3 Study selection and Data Extraction

Two reviewers independently scanned all the titles and abstracts and identified potentially relevant articles to be retrieved using a custom-designed screening form. Where there was uncertainty, full-text copies of papers were obtained. Studies were considered eligible if they were randomized controlled trials; included patients with chronic conditions associated with fatigue complaints and assessed fatigue before and after intervention; involved activity pacing (activity pacing alone or in combination with psychosocial or exercise interventions [cognitive behavioural therapy and/or graded exercise therapy]) programme undertaken in a primary, secondary, or tertiary setting; and comprised a control group that did not receive any form of structured activity pacing but that could include usual or standard treatment.

Outcomes included the following: fatigue, physical functioning and physical activity, assessed by recognized and validated measures.

Two reviewers independently selected trials to be included: disagreements were resolved by consensus. Two reviewers independently extracted the data once the trials were formally included in the review.

The following information was extracted from each selected study: 1) bibliographic information (authors, year of publication, country and reference); 2) type of chronic condition (chronic fatigue syndrome, fibromyalgia, other; 3) sample characteristics (sample size, gender, age); 4) provider (psychologist/psychotherapist, exercise physiologist, physical therapist, nurse, occupational therapist, other); 5) outcomes assessed (fatigue, physical activity, physical functioning); 6) measures used to assess outcomes (type and name of measure); and 7) assessment points (baseline, post-treatment — after the termination of the treatment, follow-up —an additional measurement taken at a later point in time after the termination of the trial); 8) type of care provided to the intervention group (activity pacing and/or graded exercise therapy and/or cognitive behavioural therapy); 9) type of care provided to the control group (passive control—waiting list control, treatment as usual, other; active control: relaxation/flexibility, counselling, other); 10) length of intervention and number of patient–provider sessions. Tables 3.1 show the characteristics of the included studies.

Table 3.1. Characteristics of Included studies

Study Intervention Led	Sample size (Male/Female) Age in years (Mean ±SD) Condition Diagnosis	Intervention Condition (Control condition)	Structure of Session & Assessment (weeks)	Measure tool	Outcome
Van Koulil et al., 2012 Cognitive Behavioural Therapist	84 (6/78) 41.7 ± 10.9 Fibromyalgia	Pacing + CBT + GET (Waiting List)	16 group sessions/2x8 weeks + 1 booster session Post-treatment = 10 Follow-up = 24	CIS IRGL	Fatigue Physical function
Wallman et al., 2004 Physiologist	61 (14/47) NA(16-74) Chronic Fatigue Syndrome	Pacing + GET (Relaxation/flexibility)	1 face to face session + 6 telephone calls/12 weeks Post-treatment = 12	Chalder Fatigue Questionnaire Older Adult Exercise Status Inventory	Fatigue Physical activity
Sandler et al., 2017 Clinical psychologist Exercise physiologist	46 (3/43) 51.2 ± 9.5 Post Cancer Fatigue	Pacing + CBT + GET (Education)	11-13 face to face sessions/12weeks Post-treatment = 12 Follow-up = 24	SOMA of SPHERE Short Form-36 IPAQ	Fatigue Physical function Physical activity
Kos et al., 2015 Occupational Therapist	33 (0/33) 39.3 ± 11.4 40.8 ± 11.1 Chronic Fatigue Syndrome	Tailored Pacing (Relaxation)	3 face to face/1x3 weeks Post-treatment = 3	CIS & CFSSL Short Form Physical Function subscale	Fatigue Physical function
Murphy et al., 2010 Occupational Therapist	32 (8/24) 61.9 ± 7.9 Hip/Knee Osteoarthritis	Tailored Pacing (General Pacing)	2 face to face/1x2 weeks Post-treatment = 10	Brief Fatigue Inventory	Fatigue
White et al., 2011 Occupational Therapist	319 (76/243) 38 ± 12 Chronic Fatigue Syndrome	Adaptive Pacing + Specialist Medical Care (Specialist Medical Care)	14 face to face and telephone / 23 weeks Post-treatment = 24 Follow-up = 52	Chalder Fatigue Questionnaire Short Form Physical Function subscale	Fatigue Physical function

CBT: Cognitive Behavioural Therapy; CIS: Checklist Individual Strength; CFSSL: Chronic Fatigue Syndrome Symptom List; GET: Graded Exercise Therapy; IRGL: Impact of Rheumatic Diseases on General Health and Lifestyle Instrument; SOMA of SPHERE: Somatic subscale of the Somatic and Psychological Health Report

3.2.4 Quality and risk of bias assessment

The methodological quality of the included trials was assessed using a 14-item modified version of the Downs and Black checklist (Downs and Black, 1998). The scale assesses characteristics of reporting, internal and external validity of trials. Each item is scored 0 (not done and/or not reported) or 1 (done and/or reported). Total scores range from 0 to 14; higher scores indicate higher methodological quality. The Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011) was used to assess risk of bias in included studies. Risk of bias (high/low/uncertain) was classified based on the following items from this scale: Selection bias —random sequence generation and concealment of allocation; detection bias — blinding of participants and assessors; attrition bias (incomplete outcome data) — information on attrition and inclusion of drop-outs in analyses and selective reporting. Discrepancies in quality rating were resolved by consensus between the two coders. Overall, inter-rater agreement on the items of the methodological quality and risk of bias scales was satisfactory (Cohen's kappa = 0.68)

3.2.5 Data Synthesis

Effect sizes were the standardized mean difference [(mean a −mean b / pooled change standard deviation)] with Hedge's g correction for small samples (Hedges, 1981). To calculate effect sizes for selected outcomes, we extracted sample sizes and baseline, post-treatment and/or follow-up means and standard deviations for the intervention and control groups. Authors of included studies were contacted when necessary to retrieve missing data in published reports. When reported in the original trials, we used data from intention-to-treat analyses. When several measures were used for the same outcome (e.g. physical functioning), we chose the measure most frequently used across the studies included. This was the case in one study (Kos et al., 2015), and in this instance the Checklist Individual Strength measure was used for the effect of the intervention on fatigue, as this was the tool most frequently used across the included studies.

3.2.6 Data Analysis

Analyses were conducted using the Review Manager (RevMan) Software Version 5.3 (RevMan, 2014). Main effects were calculated for each outcome (fatigue, physical activity and physical functioning) at post treatment and at follow-up.

Main effects were weighted using the inverse variance method and aggregated using a random effects model, in which the summary effect is an estimate of the mean of a distribution of effect sizes (Borenstein et al., 2009). Effect sizes were interpreted according to Cohen's guidelines (values of 0.20, 0.50 and 0.80 correspond to small, medium/moderate and large effect sizes) (Cohen, 1992). The confidence intervals (CI) and corresponding p-values were considered as indicator of the significance of the effect. We also inspected the standardized residuals (i.e. how much each study differs from the overall effect) for outliers (>1.96).

We quantified between-study heterogeneity using I^2 statistic (Higgins et al., 2003) that assesses the proportion of observed dispersion that is due to real differences in the true effect sizes. The I^2 ranges from 0 to 100%, with values of 25%, 50% and 75% reflecting low, moderate and high heterogeneity (Higgins et al., 2003). Whenever heterogeneity of effect sizes was observed (I^2 ≥50%), subgroup analyses were conducted (where applicable) to examine whether effect sizes varied according to the potential moderators.

Studies were grouped according to the following characteristics: i) activity pacing alone intervention vs. activity pacing combined with cognitive behavioural therapy and/or graded exercise therapy intervention; ii) minimal face-to-face individual/group patient(s)-provider contact (≤ 3sessions) vs. more contact (>10sessions) and iii) fatigue-related condition vs. pain-related condition. Between-groups Q statistic was used to compare the standardised mean effect post-treatment between subgroups, when there were at least three studies in each subgroup.

3.3 Results

3.3.1 Description of included studies

A total of 79 potentially relevant articles were identified in the literature search and additional hand searches. The abstracts of all the articles were scanned to identify studies meeting the inclusion criteria. After the screening of abstracts 68 studies were excluded. Common reasons for exclusion were nonrandomized designs (n = 15), inappropriate interventions (n = 12), inappropriate sample groups (n = 28), and inappropriate outcome measures (n = 9). A total of 11 full-text articles were retrieved. Three articles (Murphy and Kratz, 2014; Murphy et al., 2008; Murphy et al., 2012) were not intervention studies and one further study (Nijs et al., 2009) did not include a control group and so were also excluded. Two articles reported data from the same study (Murphy et al., 2010; 2012) and were therefore grouped together for analysis. Two authors of full articles were contacted to obtain additional data; however, only 1 provided the necessary data for inclusion (Sandler et al., 2017). This resulted in 6 studies (van Koulil et al., 2010; Murphy et al., 2010; Kos et al., 2015; White et al., 2011; Sandler et al., 2017; Wallman et al., 2004) eligible for inclusion in the meta-analysis (Table 3.1). The process of data screening is shown in Figure 3.1.

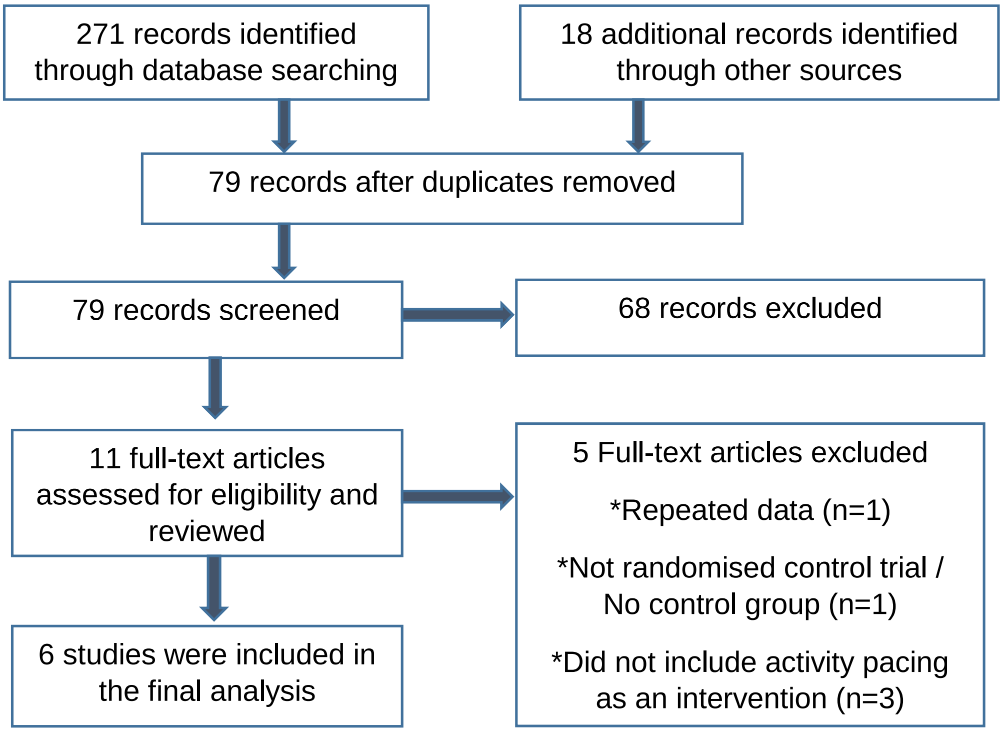


Figure 3.1 Flow diagram of data screening.

3.3.2 Study characteristics

Three studies were activity pacing only and three were activity pacing combined with graded exercise therapy and/or cognitive behavioural therapy. The majority of the trials were conducted in Europe (the United Kingdom, the Netherlands and Belgium) (3 studies, 50%). The remaining studies were conducted in Australia (2 studies, 33%) and the United States of America (1 study, 17%), in secondary–tertiary care settings (e.g. specialized clinics). Study sample sizes varied widely from 32 to 319 patients (median, 54 patients), with a median intervention duration of 10 weeks (range, 2 to 23 weeks) and individual or group sessions varied from 1-16 face to face contacts (median, 7.5). The longest available median post-treatment period was 18 weeks (range, 3 to 52 weeks) with a median short term assessment point of 12 weeks (range, 3 to 24 weeks) and a median long term assessment point of 24 weeks (range, 10 to 52 weeks).

At baseline, the intervention group and the control group in the included studies were similar in terms of fatigue, physical functioning and physical activity ($p > 0.05$). Reported baseline fatigue (mean and standard deviation or range) in the intervention groups and control groups were comparable across the studies.

3.3.3 Assessment of outcome and measures

Fatigue was the outcome measured in six trials, and was assessed with the Chalder Fatigue Scale (Chalder et al., 1993) in two trials (White et al., 22011; Wallman et al., 2004), the Checklist of Individual Strength (Vercoulen et al., 1999) in one trial (van Koulil et al., 2010), while both the Checklist of Individual Strength and the Chronic Fatigue Syndrome Symptom List 100 mm Visual Analogy Scale (Vercoulen et al., 1999; Nijs et al., 2008) were used in another trial (Kos et al., 2015). Of the remaining trials, one (Murphy et al., 2010) used the Brief Fatigue Inventory (Mendoza et al.,1999) to assess fatigue and the other (Sandler et al., 2017) used the Somatic subscale of the Somatic and Psychological Health Report (Hickie et al., 1998)

Physical functioning was reported in four studies, and the Short Form Health Survey-36 physical function subscale (Ware et al., 1992) was used in three studies (Sandler et al., 2017; Kos et al., 2015; White et al., 2011). The Impact of Rheumatic Diseases on General Health and Lifestyle instrument (Evers et al., 1998) was used in the other study [12] to assess physical functioning. Of the two trials that reported physical activity (Wallman et al., 2004; Sandler et al., 2017) the Older Adult Exercise Status Inventory (O'Brien, 1996) was used in one trial (Wallman et al., 2004), while the International Physical Activity Questionnaire (Craig et al., 2003) was used in the other trial (Sandler et al., 2017).

Three studies (Murphy et al., 2010; Wallman et al., 2004; Kos et al., 2015) had only post-treatment assessment points, while the remaining three studies (Sandler et al., 2017; White et al., 2011; van Koulil et al., 2010) had both post-treatment and follow-up assessment points.

3.3.4 Participant characteristics

In total, 561 participants with chronic conditions associated with fatigue were included in this meta-analysis, with ages ranged from 16-74 years; approximately 82% were women. Patients with chronic fatigue syndrome diagnosed according to the Oxford (Sharpe, 1991) or the Centres for Disease Control and Prevention (Fukuda et al., 1994) criteria, were recruited in three trials. The essential characteristics of chronic fatigue syndrome according to the Oxford and the Centres for Disease Control and Prevention criteria are clinically evaluated, unexplained, persistent or relapsing fatigue not alleviated by rest and a cluster of symptoms that include chronic fatigue, sore throat, lymph node pain, post-exertional malaise, memory/concentration problems and unrefreshing sleep. The remaining trials recruited either exclusively post cancer fatigue patients diagnosed with the Somatic subscale of the Somatic and Psychological Health Report (Hickie et al., 1998) of which clinically-significant fatigue is an essential feature; or fibromyalgia patients diagnosed according to the American College of Rheumatology criteria (Wolfe et al., 1990) with the essential characteristics of unexplained, persistent widespread pain and symptoms of fatigue, cognitive problems and waking unrefreshed; or hip or knee osteoarthritis patients as evidenced by radiograph of osteoarthritis in that joint and a pain score of ≥ 4 out of the 5 items on the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale (Goggins et al., 2005).

3.3.5 Intervention characteristics

In two studies (van Koulil et al., 2010; Sandler et al., 2017), the intervention arm included activity pacing, cognitive behavioural therapy and graded exercise therapy. The activity pacing intervention sought to encourage patients to avoid exacerbations of their symptoms by planning daily and weekly schedules of activities and rest breaks, and segmenting tasks into short time blocks. Cognitive behavioural therapy was aimed at diminishing the daily perceived cognitive, behavioural, emotional, and social consequences of illness and accompanying symptoms in order to optimise adherence to treatments. The graded exercise therapy component consisted of aerobic activities adapted to the individual's physical capacity assessed at baseline taking into account a gradual increase in the duration and frequency of exercise sessions. The trials were delivered by clinical psychologists and exercise physiologists. The number of sessions ranged from 11 to 16 sessions, weekly or fortnightly, lasting for 8-12 weeks.

In one trial, the intervention group received graded exercise therapy incorporating a pacing construct, which consisted of individualized aerobic exercise based on baseline assessment and taking into account a gradual increase in the duration and intensity to reduce fatigue and increase activity (Wallman et al., 2004). Activity was gradually increased and rest was reduced, step by step as tolerance developed. Patients were recommended not to exceed the levels of exercise agreed upon beforehand by the therapist and patient, and to reduce their activity levels if symptoms got worse. The number of sessions was 12, once a week, lasting for 12 weeks, consisting of 1 face-to-face and 6 telephone contacts.

Two studies (Murphy et al., 2010; Kos et al., 2015) included tailored activity pacing programmes delivered via an educational module on activity pacing. The module outlined general principles of activity pacing as they apply to one's condition and included the preplanning and prioritizing of activities, and alternating active and rest periods before a symptom exacerbation. Patients were advised to prevent overactivity. The focus was on a personalised report that summarised and visually depicted each person's symptom-activity relationship based on their physical activity and symptom data collected during a home monitoring period. Specific examples of where symptoms seemed to affect activity were highlighted within and across the days from the home monitoring period, and individual goals for pacing were formulated. The treatment also included an educational support manual and a log book to monitor coping strategies. The number of sessions ranged from 1 to 17 sessions, once or twice weekly, lasting for 3-10 weeks.

The trial conducted by Kos et al., (2015) consisted of a stabilization phase and a grading phase. The stabilization phase focused on coaching clients in how to perform activities of daily living within the limits of their actual capacity. The activity duration advised within the programme was 25%–50% below self-reported capacity, to account for any overestimations. Each activity block was interspersed with breaks, with the length of the break equating to the duration of the activity. Once clients were able to control their activities of daily living without excessive feelings of fatigue, the grading phase was started during which activity level was increased gradually. Participants conferred with a cognitive behavioural therapist to set relevant and achievable personal physical activity goals, based on prioritized activities.

Adaptive pacing therapy was used in the trial by White et al., (2011). Therapeutic strategies consisted of identifying links between activity and fatigue by the use of a daily diary. Patients were encouraged to plan activities to avoid exacerbations, develop awareness of early warnings of exacerbation, limit demands and stress, regularly plan rest and relaxation, and alternate different types of activities, with advice not to undertake activities that required more than 70% of participants' perceived energy envelopes. Increased activities were encouraged, if the participant felt able, and as long as they did not exacerbate symptoms.

In summary, the theoretical models informing and guiding activity pacing intervention in the included studies are operant theory and energy conservation (Nielson et al., 2013; Fordyce, 1976). The operant theory-based interventions aimed to limit the extent to which activity is symptom-contingent (example, reduce excessive resting when fatigue or pain are high) in order to achieve predetermined activity goals (Murphy et al., 2010; Kos et al., 2015; Wallman et al., 2004). The energy based interventions, on the other hand, sought to preserve energy for completing valued activities while reducing overall symptoms (Sandler et al., 2017; White et al., 2011; van Koulil et al., 2010).

3.3.6 Quality of the studies and risk of bias

The Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011) was used to assess risk of bias in included studies. Methodological quality of each study was then assessed using a modified Downs and Black checklist (Downs and Black, 1998). Table 3.2 shows the quality of the trials and risk of bias. The trial by Sandler et al., (2017) showed the highest quality and lowest risk of bias. The trial conducted by Wallman et al., (2004) showed the lowest quality and presented an uncertain risk of bias on three criteria. The trials by van Koulil et al., (2010) and Murphy et al., (2010)] presented uncertain risk of bias on two and three criteria respectively. The trial by Murphy et al., (2010) presented a high risk of bias on selective reporting. In relation to attrition bias, most studies presented adequate drop-out information and inclusion (intent to treat analysis). Two trials (Murphy et al., 2010; White et al., 2011) reported an adequate method of concealment, one presented high risk of bias (van Koulil et al., 2010) and two studies did not report details on blinding of assessors (van Koulil et al., 2010; Wallman et al., 2004).

Table 3.2: Classification on methodological quality, risk of bias and moderators of included interventions.

Study ID	Methodological Quality Rating (0-14)	Random sequence generation	Allocation concealment	Blinding of participant and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other: Dropout information
van Koulil et al., 2012	13	Low	High	Unclear	Unclear	Low	Low	Low
Wallman et al., 2004	11	Low	Unclear	Unclear	Unclear	Low	Low	Low
Sandler et al., 2017	13	Low	Low	Low	Low	Low	Low	Low
Kos et al., 2015	11	Low	Low	Unclear	Low	Low	Low	Low
Murphy et al., 2010	12	Unclear	Unclear	Unclear	Low	Low	High	Low
White et al., 2011	11	Low	Low	High	High	Low	Low	Low

3.3.7 Synthesis of results

Table 3.3 shows the overall results of the effect of activity pacing on fatigue, physical functioning and physical activity at post-treatment and/or follow-up. The forest plots of the effects comprising of the main effects are presented in figures 3.2, 3.3 and 3.4. Table 3.4 presents the results of the subgroup analysis for effects on fatigue for the post-treatment assessment.

Table 3.3 Pooled mean estimates for change in outcomes assessed at post-treatment and at follow-up.

Outcome	Assessment point	*k*	*n*	Standardised Mean Difference [95%CI]	*Z*	*p*	I^2
	Post-treatment	6	563	0.50 [0.14, 0.86]	2.69	.007	70%
Fatigue	Follow-up	3	435	0.34 [-0.10, 0.77]	1.53	.13	71%
Physical	Post-treatment	4	470	0.08 [-0.36, 0.51]	0.35	.73	73%
functioning	Follow-up	3	435	-0.07 [-0.61, 0.48]	0.24	.81	82%
Physical	Post-treatment	2	107	0.30 [-0.08, 0.68]	0.44	.66	0%
activity	Follow-up	1	46	n/a	n/a	n/a	n/a

k = number of studies

3.3.8 Effects on fatigue

Six studies (Murphy et al., 2010; Wallman et al., 2004; Kos et al., 2015; Sandler et al., 2017; White et al., 2011; van Koulil et al., 2010) reported measures of fatigue at post-treatment (varying from 3 to 24 weeks). The pooled estimates showed moderate effect for fatigue at post-treatment (standardised mean difference = 0.49; 95% CI [0.08 – 0.90]) but results were heterogeneous between studies (I^2 = 70) (table 3.3).

Effects were larger when activity pacing was combined with graded exercise therapy or cognitive behavioural therapy (standardised mean difference = 0.68; 95% CI [0.28 – 1.08]) compared with activity pacing alone (standardised mean difference = 0.27; 95% CI [-0.12 – 0.67]). The pooled estimate for the three studies which included minimal patient contact was moderate (standardised mean difference = 0.49; 95% C1 [0.14 – 0.85]) and homogeneous (I^2 = 0%) and was comparable in magnitude to the differences in interventions with more patient contact which was also moderate (standardised mean difference = 0.51; 95% CI [0.14 – 0.86]) but more heterogeneous (I^2 = 87%) (table 3.4).

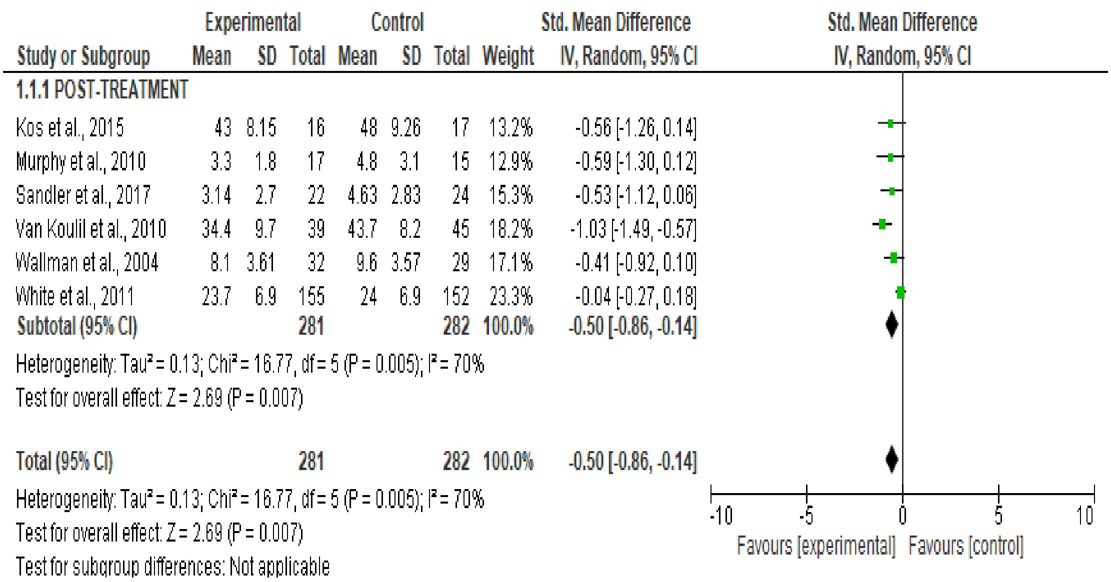
Table 3.4: Subgroup analysis assessing the effect of study characteristics upon fatigue at post-treatment.

Moderator		Fatigue				
		k	SMD [95%CI]	Z	p^1	I^2
Components of intervention arm	Pacing + GET + CBT	3	0.68 [0.28, 1.08]	3.35 (p = 0.0008)	0.16	44% (p=0.17)
	Pacing only	3	0.27 [-0.12, 0.67]	1.35 (p = 0.18)	I^2 =50.3%	45% (p=0.16)
Number of patient-provider contact	Minimal contact	3	0.49 [0.14, 0.85]	2.72 (p = 0.007)	0.96	0% (p=0.91)
	More contact	3	0.51 [-0.14, 1.17]	1.53 (p = 0.13)	I^2 = 0%	87% (p=0.0005)
Condition	Fatigue-related	4	0.28 [-0.01, 0.56]	1.90 (p = 0.06)	n/a	36% (p=0.19)
	Pain-related	2	0.49 [0.49, 1.30]	4.36 (p < 0.0001)		6% (p=0.30)

CBT = Cognitive Behavioural Therapy; GET = Graded Exercise Therapy; k = number of studies; p^1 = p-Values correspond to subgroup differences in effects; n/a = not enough interventions in the subgroup to allow for a comparison; SMD = Standardised Mean Difference

Three studies (Sandler et al., 2017; White et al., 2011; van Koulil et al., 2010) presented fatigue data at follow up (varying from 24 to 52 weeks after baseline). The pooled estimates showed marginal effect for fatigue at follow-up (standardised mean difference = 0.37; 95% CI [-0.10 – 0.77]), but results were heterogeneous between studies (I^2 = 71%) (table 3.3) The forest plots of effect sizes comprising the main effects of activity pacing on fatigue at both post-treatment and follow-up are illustrated in figure 3.2.

A



B

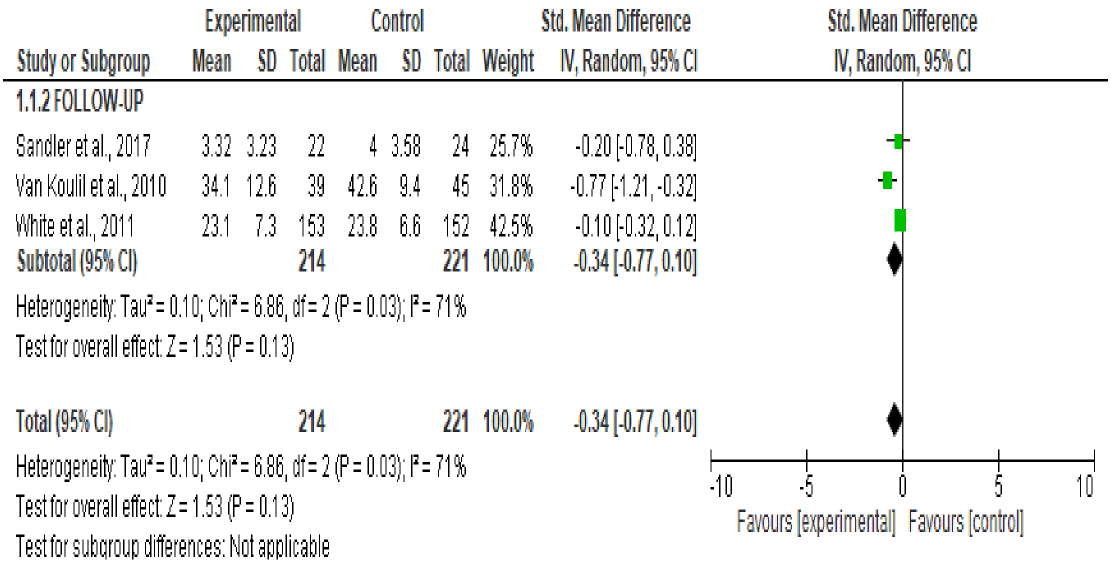
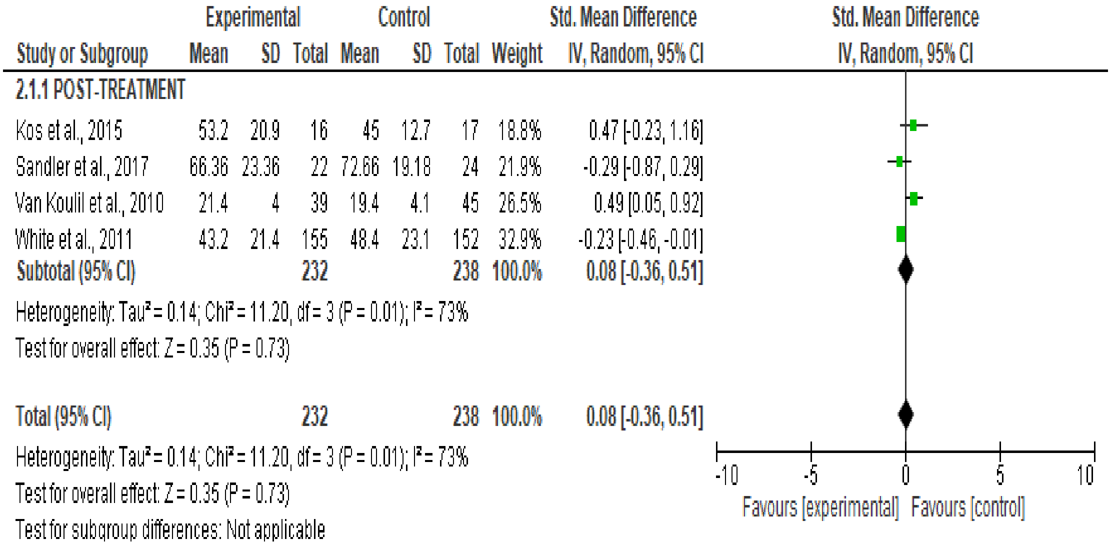


Figure 3.2 Forest plot of the activity pacing effects on fatigue at (A) post-treatment and (B) follow-up. The pooled standardised mean difference was .50 (95% CI [.14 – .86]) at post-treatment. The pooled standardised mean difference was .34 (95% CI [-.01 – .77]) at follow-up.

3.3.9 Effects on physical functioning

Four studies (Sandler et al., 2017; White et al., 2011; van Koulil et al., 2010; Kos et al., 2015) reported measures of physical functioning at post-treatment (3–24 weeks) and three studies (Sandler et al., 2017; White et al., 2011; van Koulil et al., 2010) reported measures of physical functioning at follow-up (24–52 weeks). Combined effect sizes were inconsequential at post-treatment (standardised mean difference = 0.08; 95% CI [-0.36 – 0.51]) and at follow-up (standardised mean difference = d = -0.07; 95% CI [-0.61 – 0.48]), but effects varied between studies at both assessment points (I^2 = 73% and I^2 = 82% respectively) (table 3.3). The forest plots of effect sizes comprising the main effects of activity pacing on physical functioning at both post-treatment and follow-up are illustrated in figure 3.3.

C



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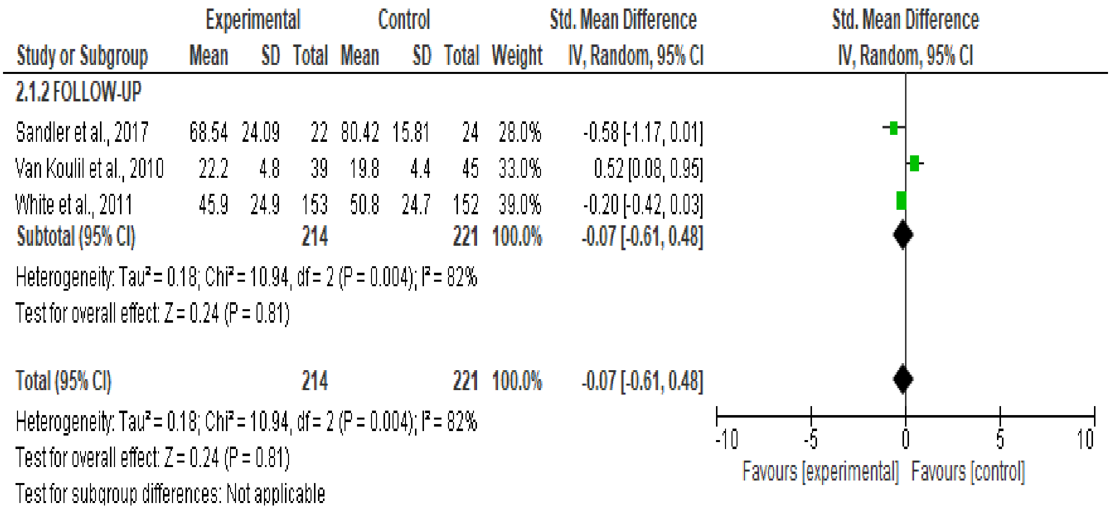


Figure 3.3 Forest plot of the activity pacing effects on physical functioning at (C) post-treatment and (D) follow-up. The pooled standardised mean difference was .08 (95% CI [-.36 – .51]) at post-treatment. The pooled standardised mean difference was -.07 (95% CI [-.61 – .48]) at follow-up.

Due to the limited number of studies presenting data for physical functioning no further potential moderator analyses were conducted.

3.3.10 Effects on physical activity

Post-treatment physical activity data (12 weeks) was available in only two studies (Sandler et al., 2017; Wallman et al., 2004). Only one study (Sandler et al., 2017) presented follow-up physical activity data (24 weeks). Overall main effect for physical activity at post-treatment was not significant (standardised mean difference = 0.30; 95% CI [-0.08 – 0.68]), with evidence of homogeneity between studies (I^2=0%) (table 3.3). For that reason, no further moderator analyses were conducted. The forest plots of effect sizes comprising the main effects of activity pacing on physical activity at post-treatment are illustrated in figure 3.4.

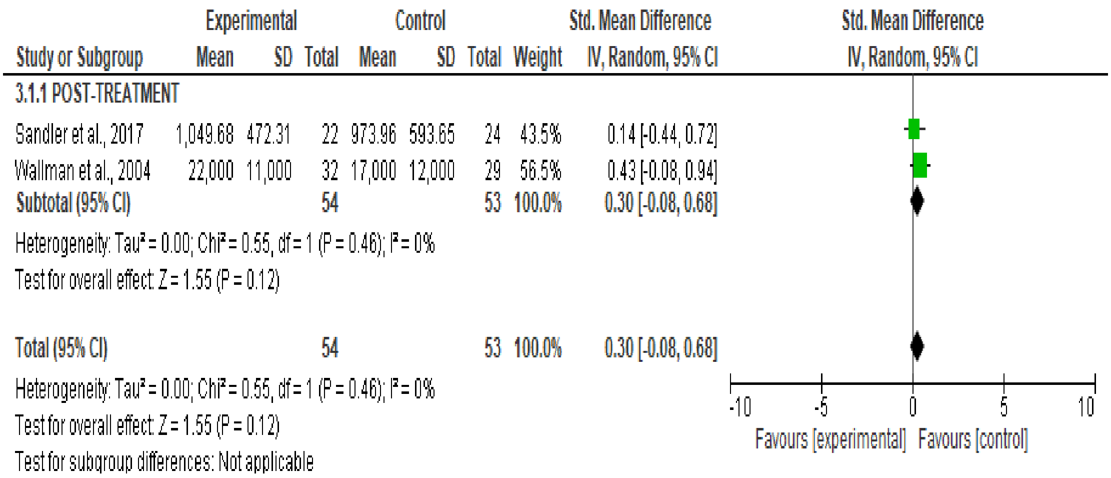


Figure 3.4 Figure 4. Forest plot of the activity pacing effects on physical activity for post-treatment. The pooled standardised mean difference was .30 (95% CI [-.08 – .68]) at post-treatment.

3.3.11 Sensitivity analyses

Primary analyses were repeated with the exclusion of the trial by White et al. (2011), which presented a high risk of bias and poor methodological quality (Table 3.2). Excluding this study led to an increase in the magnitude of treatment effects for fatigue at post-treatment from standardised mean difference = 0.50 to standardised mean difference = 0.67, and at follow-up from standardised mean difference = 0.34 to standardised mean difference = 0.51. And also led to an increase in the magnitude of treatment effects for physical functioning at post-treatment from standardised mean difference = 0.08 to standardised mean difference = 0.23, and at follow-up from standardised mean difference = -0.07 to standardised mean difference = -0.01 The exclusion of the trial conducted by Wallman et al., (2004) because of high/uncertain risk of bias in most categories and poor methodological quality, led to an increase in the overall point estimate for fatigue at post-treatment (from standardised mean difference = 0.50 to standardised mean difference = 0.52). Excluding both studies led to an increase in magnitude of treatment effects for fatigue at post-treatment from standardised mean difference = 0.50 to standardised mean difference = 0.75.

3.4 Discussion

To our knowledge, this is the first meta-analysis investigating the effectiveness of activity pacing on fatigue severity, physical functioning and physical activity in patients with fatigue complaints with a chronic condition. Six trials with baseline fatigue assessment and post treatment and/or follow-up assessment point(s) were included. In addition, this meta-analysis analysed the potential moderating effects of the following trial characteristics at post-treatment: whether the intervention arm was activity pacing only or activity pacing with behavioural and or exercise intervention and whether or not the intervention was a minimal (direct face to face) contact intervention.

This meta-analysis shows that activity pacing interventions have beneficial effects on fatigue at post-treatment (standardised mean difference = 0.50) and marginal effect at follow-up (standardised mean difference = 0.34) in chronically fatiguing conditions. Treatment effects varied widely between studies and subsequent subgroup comparisons revealed that components of intervention arm and amount of face-to-face contact were not significant moderators of the effect of the interventions on fatigue at post-treatment. The effect of minimal contact interventions on fatigue (standardised mean difference = 0.49) was comparable in magnitude to the effect of interventions of more intensive contact (standardised mean difference = 0.51). The finding is somewhat similar to that of a recent meta-analysis on effects of behavioural and psychological interventions that pointed at the beneficial effects of minimal contact interventions on fatigue (Marques et al., 2015). This makes a case for activity pacing as a plausible effective less resource intensive activity stimulation programme that could substitute for more resource intensive programmes such as cognitive-behavioural therapy and can be useful for patients presenting difficulties in regularly attending health care facilities (Antcliff et al., 2015). The lack of sustained beneficial effect at follow-up may be accounted for by the limited number of studies providing follow-up fatigue data. This highlights the need for future interventional studies on the long-term effect of activity pacing on fatigue.

The small overall effect sizes for intervention arms of activity pacing alone (effect size = 0.27) compared to intervention arms comprising of activity pacing combined with cognitive behavioural therapy and/or graded exercise therapy on fatigue (effect size = 0.68) may be accounted for by the clearly distinct features of each of the three activity pacing alone interventions studies included in our meta-analysis. One trial, was a tailored activity pacing intervention that focused on preplanning and prioritizing of activities, and alternating active and rest periods before a symptom exacerbation (Murphy et al., 2010), another was an activity pacing trial that focused on prioritizing of activities, and alternating active and rest periods, and gradually increasing activities to prevent exacerbation of symptom (Kos et al., 2015), and the last one was the adaptive pacing trial that restricted performance of activities within limits of 70% of actual capacity (White et al., 2011). The high heterogeneity found in this subgroup and the limited number of trials is a limitation to this finding. This suggests that there may be differences in the effect of activity pacing interventions on fatigue across other particular patient characteristics such as disease diagnosis, attitude towards physical activity, self-efficacy and stage of behavioural change. Further exploratory studies on this is needed.

Regarding physical function, inconsequential main treatment effects of activity pacing were found post-treatment (standardised mean difference = 0.08) and at follow-up (standardised mean difference = -0.07). However, considerable variation in response was observed at both assessment points. The small number studies included in this meta-analyses that reported activity pacing effects on physical functioning limited further analyses of potential moderators of the variance in activity pacing main effect. This points to the fact that there may be differences in the effect of activity pacing interventions on physical functioning across other particular patient and/or intervention characteristics. More research is clearly needed to analyse the effects of potential moderators.

Considering that activity pacing instruction directly relates to altering physical activity patterns, it was interesting to find that only a handful of studies (n = 2) evaluated the effect of activity pacing on physical activity in patients with high fatigue complaints. Although a small non-significant main effect (standardised mean difference = 0.30) of activity pacing on physical activity was found in this review, the responses were varied. The limited number of included studies reporting on the effect of activity pacing on physical activity could account for the small treatment effect found in this review and is a limitation to this finding. Previous exploration into the effects of activity pacing on physical activity has produced inconsistent findings. In some studies, pacing was associated with lower levels of physical activity (Murphy et al., 2010; van Koulil et al., 2010), while in other studies pacing was related to high physical activity (Murphy and Kratz, 2014; Murphy et al., 2008; Nielson et al., 2013).

These inconsistencies may in part be explained by study design and interpretation of activity pacing as observed in this review. While some studies described activity pacing as managing energy expenditure, aimed at staying within boundaries of physical limits by either focusing on symptoms or by including rest (Murphy et al., 2010; White et al., 2011; Sandler et al., 2017), other studies included activity progression as an aim of activity pacing (van Koulil et al., 2010; Kos et al., 2015; Sandler et al., 2017). This highlights the dearth of a standardized definition of activity pacing and may reflect the ineffectiveness of activity pacing if not used to gradually increase an individual's activity level (Butler et al., 2003).

Other features that could have moderated the findings are avoidance behaviour, naturalistic pacing behaviour (level of activity pacing that persons implement in daily life without a specifically instructed activity pacing programme) and perceived difficulty in preventing overactivity in daily life. With most of the studies aimed at preventing overactivity (Murphy et al., 2010; White et al., 2011; Sandler et al., 2017), superior improvement may have been observed in persons with high natural engagement in pacing and/or high perceived difficulty in preventing overactivity compared to persons with avoidance behaviour, low natural engagement in pacing and/or low perceived difficulty in preventing overactivity. Future studies exploring the impact of patients behaviour towards physical activity is of utmost importance.

The discrepancy that was found in this meta-analysis between the effects found for fatigue and for physical activity and physical functioning could indicate that the mere decrease of fatigue does not necessary lead to improved outcomes in terms of physical activity and physical functioning. This may point to the fact that alternative ways of promoting physical activity and physical functioning, e.g. flexibility in physical activity goals in the form of tailoring advice to individual's characteristics towards physical activity assessed at baseline and making use of motivational interview may be more successful in changing this health behaviour and equally managing fatigue. This provide further insight to help optimise tailored activity stimulation programmes.

3.5 Limitations and recommendations for future research

The limited number of eligible and included studies, coupled with the uneven distribution of studies in subgroups limited the analyses of subgroups effect sizes of activity pacing on fatigue, physical functioning and physical activity. Readers should therefore be cautious when interpreting the pooled effect sizes. Emphasis should instead be placed on the distribution in each category and the observed patterns in the data. Future studies should continue to explore potential moderators that can account for differences between trial results. Among these are patient and disease-related characteristics (e.g. illness duration, severity of disease, attitudes towards pacing) and treatment features (e.g. pacing alone, pacing + graded activity).

Most of the categorization of intervention characteristics was based on the intervention description provided in the articles. In many cases these descriptions were limited and the same accounts for the description of the content of manuals that were used in different interventions. Future studies should give a sufficiently detailed account of the content of the intervention/self-help manual offered to patients. Although most of the outcomes were assessed using validated measures, the way scores were calculated was not always clear. Future randomized controlled trials should pay more attention to the way statistical data are presented, making an effort to present effect sizes and raw data (means and standard deviations) for all outcomes and assessment periods.

The number of studies included in this meta-analysis that presented follow-up assessment data was limited and only available for a maximum period of 52 weeks. Hence, although activity pacing had beneficial effects on fatigue at post-treatment, and inconsequential effects on physical functioning and physical activity after data synthesis, more research is needed to understand long-term effects. More research on the impact of activity pacing on physical activity behaviour (assessed by examining both physical activity level/volume and physical activity pattern) using subjective and objective measures are needed.

There is the need to standardize activity pacing based on a clear theoretical concept and consideration of the context in which the behaviour occurs. There is also a need for further validity studies of measures of activity pacing to help streamline the construct. Additionally, studies on the effect of natural pacing behaviour and perceive difficulty in preventing overactivity on the effectiveness of pacing intervention are needed to help guide and refine treatment efforts.

3.6 Conclusion

This meta-analysis of activity pacing in patients with chronic diseases associated with fatigue complaints suggests that activity pacing might have sustained beneficial effects on fatigue management, in particular on fatigue reduction for which small-to-moderate effects were found. The finding that minimal contact interventions had similar effect compared to more intensive contact intervention is important. This provides valuable insight that activity pacing intervention can be feasibly implemented in standard health care and can be suitable for patients who do not need more intensive forms of treatment.

More importantly, findings of the study demonstrate the need to further explore moderators such as patient's behaviour towards physical activity assessed at baseline to help optimise the tailoring of activity stimulation programmes. All trials included in this meta-analysis had an initial face-to-face patient-provider contact with patients, which may have led to increased motivation of patients to engage in a behaviour change process. Notwithstanding the beneficial effects of activity pacing reported in this meta-analysis and the valuable indications about targets and format of future interventions, more research are needed to identify optimal features of activity pacing.

CHAPTER 4

Associations between activity pacing, fatigue and physical activity in adults with multiple sclerosis: A cross sectional study

Abstract

Activity pacing could alter inefficient activity patterns in persons with multiple sclerosis. However, little is known about how persons with multiple sclerosis naturally paces their activities to manage their fatigue and optimise their daily activities. The aim of this study was thus to explore relations of perceived activity pacing with fatigue and physical activity in persons with multiple sclerosis in rehabilitation.

80 adults with multiple sclerosis (median age= 44 ± 11 years) filled in questionnaires on their activity pacing (5-point Activity Pacing Questionnaire), fatigue (7-point Fatigue Severity Scale), physical activity (adapted Short Questionnaire to Assess Health-Enhancing Physical Activity) and health-related quality of life (RAND-12), collected within the Rehabilitation Sport and Active lifestyle (ReSpAct) study. The relationships between the variables were examined using hierarchical regression.

There was a positive non-significant association between activity pacing and fatigue (β= .20; t= 1.43, p= .16), and a negative non-significant association activity pacing and physical activity (β= -.24; t= -1.61, p= .12). Fatigue was related to low health-related quality of life (β= -.34; p= .01).

The lack of significant associations between activity pacing, and fatigue and physical activity suggests that without interventions, there is no clear strategy amongst persons with multiple sclerosis to manage fatigue and improve physical activity. Persons with multiple sclerosis may benefit from interventions to manage fatigue and optimise physical activity. The present study demonstrate the complexity of naturalistic pacing, and the importance to explore this behaviour in relation to what we know from literature to help guide treatment efforts for persons with multiple sclerosis. As behavioural strategies may be adaptive in the short-term but prove to be maladaptive longer term, studies exploring long-term effects of activity pacing are warranted.

4.1 Introduction

Continuous or recurring symptoms of fatigue are among the most frequently reported and strongest predictors of functional disability in persons with multiple sclerosis (MS) (Merkelbach et al., 2011; Branas et al., 2000; Bakshi, 2003). The experience of fatigue draws behavioural adaptations, such as limiting the engagement in activities resulting in underactivity, or a lifestyle characterized by periods of overactivity followed by long extensive rest periods (Amato et al., 2001; Johansson et al., 2007; Motl et al., 2006; Motl et al., 2005). However, both underactivity and overactivity are linked with disability (Hanson and Gerber, 1990).

This emphasises the need to encourage individuals, especially persons with recurrent fatigue symptoms to approach activity in an effective way to prevent deconditioning and poor health outcomes (Antcliff et al., 2015; Nijs et al., 2009). Activity pacing is a behavioural strategy that could help alter these often occurring inefficient activity patterns (Antcliff et al., 2015; Nijs et al., 2009; Birkholtz et al., 2004). It involves dividing one's daily activities into smaller, more manageable, pieces to manage symptoms of fatigue, and to maintain a steady pace, whilst reducing relapses (National Institute for Health and Clinical Excellence, 2014; Antcliff et al., 2015).

However, current literature on how people naturally pace activities in daily life is limited and inconclusive and no clear strategies are available to optimise activity pacing in order to improve overall engagement in physical activity (Abonie et al., 2018a; 2018b; Antcliff et al., 2015; Murphy and Kratz, 2014; Murphy et al., 2012; Murphy et al., 2008). For example, it is unclear if persons engage in more pacing behaviour in daily life due to an increase in perceived symptoms (symptom-contingent) or if persons engage in more pacing behaviour and thereby subsequently reduce their perceived symptoms (symptom-reduction) (Andrews et al., 2012; Murphy and Clauw, 2010). Furthermore, quality of life have been proposed to impact on activity pacing (Andrews et al., 2012).

It is notable that most of the reviewed works aimed to explore issues in a range of chronic disabling conditions, and did not focus on specific disabilities or chronic diseases such as MS. While findings from these studies can contribute to our understanding of naturalistic pacing behaviour, their broader focus with regards to multiple health behaviours and mixed populations may have resulted in failure to elicit key issues specific to engagement in physical activity for people with MS. Currently no study has explored people with MS natural approach to activity pacing, and it relations to fatigue and physical activity.

Understanding these associations might help guide treatment efforts for persons with MS and promote an active lifestyle in this population suffering from fatigue complaints. Therefore, the aim of this study was to examine engagement in pacing and how it relates to fatigue and physical activity in people with MS. Based on the expectation that activity pacing would be an adaptive strategy to manage fatigue and optimise daily activities (Abonie et al, 2018a; Murphy et al., 2008), we hypothesized that engagement in pacing would be associated with a decrease in fatigue and an increase in physical activity.

4.2 Materials and methods

4.2.1 Design

This study is part of a multicentre longitudinal study (Rehabilitation, Sports and Active lifestyle; ReSpAct) to evaluate the nationwide implementation of an active lifestyle programme (Rehabilitation, Sports and Exercise) among persons with a wide range of chronic diseases and/or physical disabilities in Dutch rehabilitation on organisation and patient level (Alingh et al., 2015). The current study uses a cross sectional study design based on the baseline measurement (3-6 weeks before discharge from rehabilitation) of pacing behaviours, fatigue severity, physical activity and health-related quality of life of persons with MS, selected from the ReSpAct dataset. The study procedures were approved by the ethics committee of the Center of Human Movement Sciences of the University Medical Center Groningen (reference: ECB/2013.02.28_1) and at participating institutions.

4.2.2 Sample

Participants were recruited upon referral to the participating rehabilitation institutions across the Netherlands. Potential participants received information on study rationale, potential benefits, and procedures, had questions answered and checked for the inclusion criteria. Participants were included in this study if they were; 18 years and older, had a multiple sclerosis diagnosis, received inpatient or outpatient rehabilitation care or treatment based on medicine consultation within one of the participating rehabilitation institutions and participates in the 'Rehabilitation, Sports and Exercise' programme. Participants were excluded from the study if they were not able to complete the questionnaires, even with help, or participated in another physical activity stimulation programme. Before participation in the study, diagnosis of MS was required from each participant. Information on the specific type of MS was not collected. Participants who were eligible and willing to participate signed an informed consent form.

4.2.3 Procedure

Enrolled participants were assessed through standardised baseline measurement. The baseline measurement consisted of three parts. Each part consisted of filling out a set of questionnaires. First, participants indicated which physical activities they perform in the context of the rehabilitation treatment and on their own initiative by filling out an adapted version of the short questionnaire to assess health enhancing physical activity (Wendel-Vos et al., 2003). Second, participants filled out short questionnaires on their pacing behaviour and fatigue (Alingh et al., 2015; Krupp et al., 1989). Last, participants filled out a questionnaire on their health-related quality of life (Selim et al., 2009). The questionnaires were completed on paper or digitally.

4.2.4 Measures

Participants age, gender and body mass index; calculated from participants measured body mass and height [body mass (kg) / height^2 (m^2)] were collected as background demographics data.

Engagement in pacing

Engagement in pacing was assessed with the Engagement in pacing subscale of the Activity Pacing and Risk of Overactivity Questionnaire (Alingh et al., 2015) (appendix 1). This questionnaire was developed for use in the ReSpAct study and provides insight into two different components: active engagement in pacing decisions (Items A, B, C, E and F) and perceived difficulty in preventing overactivity (Items D and G) (Alingh et al., 2015). The first component of the complete questionnaire reflected engagement in pacing within daily routines and was the primary outcome of the current study. The second component reflected perceived risk of overactivity within daily routines and was a secondary outcome of the current study. Participants were asked to score each of the 7 items of the questionnaire on a scale of 1–5 (1, never; 2, rarely; 3, sometimes; 4, often; 5, very often). The items in each component were averaged to calculate the subscale score that ranges from 1 to 5, with a higher score on the first component indicating high engagement in pacing. A higher score on the second component indicated a high perceived risk of overactivity.

Fatigue

Fatigue severity was measured using the Fatigue Severity Scale (Krupp et al., 1989) (appendix 2), a valid and reliable questionnaire to determine the impact of fatigue in persons with MS (Whitehead, 2009). The participants scored the nine items of the questionnaire on a scale of 1–7 (1, completely disagree; 7 completely agree). Mean fatigue score based on an average of the 9 items was used. The mean fatigue score ranged from 1 to 7, with a higher score indicating greater fatigue severity. A mean fatigue score ≥ 4 was adopted as the cut-off for severe fatigue (Smedal et al., 2011)

Physical activity

An adapted version of the Short Questionnaire to Assess Health-Enhancing Physical Activity (Wendel-Vos et al., 2003) (appendix 3) was used to assess perceived physical activity. The questionnaire is a self-reported recall measure to assess daily physical activity of healthy adults based on an average week in the past month. The original questionnaire has demonstrated good test-retest reliability and internal consistency and moderate concurrent validity in ordering participants according to their level of physical activity in an adult population (Wendel-Vos et al., 2003) and in several patient groups (Arends et al., 2013; Wagenmakers et al., 2008). The original Short Questionnaire to Assess Health-Enhancing Physical Activity was adapted to make it applicable for people with a chronic disease or physical disability. Within the domains 'commuting activities', 'leisure-time' and 'sports activities', the items 'wheelchair riding' and 'hand cycling' were added. Also, 'tennis' was modified as '(wheelchair) tennis'. Furthermore, the self-reported intensity was categorised as 'light', 'moderate' and 'vigorous', instead of 'slow', 'moderate' and 'fast'. Total minutes of physical activity per week was calculated by multiplying frequency (days/week) and duration (minutes/day) for each activity.

Health-related quality of life

Health-related quality of life was assessed by the RAND-12 Item Health Survey (Version 1.0) Questionnaire (Selim et al., 2009) (appendix 4). The RAND-12 Item Health Survey is a shorter version of the RAND-36 Item Health Survey (Hay et al., 1998) that assesses seven health domains; general health, physical functioning, role limitations due to physical health problem bodily pain, role limitations due to emotional problems, vitality/ mental health and social functioning. The RAND-12 was scored using the recommended scoring algorithm for calculating global health (Hays et al., 1998). The global health score which is a composite score of person's health-related quality of life ranged from 18 to 62. A higher global health score indicated better health-related quality of life. The RAND-12-Item Short Form Health Survey has been proven to be a valid and reliable measure of health-related quality of life (Ware et al., 1996).

4.2.5 Data analysis

Data were analysed using IBM Statistical Package for the Social Sciences (SPSS) software version 23.0 (IBM co., 2017). Data were checked for normality by visually inspecting frequency distribution. The data were generally normally distributed. All values were reported using descriptive statistics of means, standard deviations and interquartile ranges to summarize characteristics of participants. Bivariate Pearson correlations were conducted to examine basic between-person associations between demographic and study variables, prior to testing the study hypotheses to ensure there was no multicollinearity (variables are not highly correlated with each other, $r \geq .8$).

Hierarchical linear regression was used to test the study hypotheses. This statistical approach was optimal for adjustment for confounders; we are after relationships that remain after adjusting for confounders.

To examine how engagement in pacing was related to fatigue and physical activity, two hierarchical regression analyses were conducted with fatigue or physical activity as the dependent variable, and engagement in pacing as the independent variable of interest. Age, gender, body mass index, health-related quality of life and perceived risk of overactivity were entered as co-predictors.

These co-predictors were included in the models based on the fact that they are general demographic variables of interest in studies on physical activity behaviour and fatigue experience and on known associations with fatigue experience and physical activity behaviour (Murphy et al., 2008; 2012). We chose to analyse our data using these models based on the literature and our expectation that activity pacing may be a positive strategy to manage fatigue and optimise daily activities (Abonie et al., 2018a; 2018b).

In both models, at the first step, gender, age and body mass index were entered. At the second step, health-related quality of life and perceived risk of overactivity were entered, and at the third step engagement in pacing was entered. In both models, the variance inflation factors (VIFs) were examined for multicollinearity.

4.3 Results

Of the 89 participants included in the study, data for 9 participants were incomplete and were therefore excluded from the analysis. Characteristics of the sample (N = 80) are shown in Table 4.1. Of the sample, 75% were female (n = 60) and the mean age was 44 ± 11 years. Results indicated that the sample reported severe levels of fatigue (fatigue severity scale score $>$ 4). The sample was, on average, overweight according the World Health Organization standards (Body mass index ≥ 25.0kg/m^2).

Table 4.1 | Demographics of Participants

Variable	N	Mean ± SD	Interquartile Range*
Age (years)	80	44.48 ± 10.67	38.00–52.00
Body Mass Index (kg/m^2)	73	27.28 ± 6.91	23.04–32.41
Number of women	60		
Engagement in pacing	80	3.74 ± .71	3.30–4.20
Perceived risk of overactivity	79	3.73 ± .86	3.00–4.50
Fatigue severity	79	5.43 ± 1.11	4.78–6.17
Physical activity (minutes/week)	78	1585.64 ± 1103.51	780.00–2070.00
Health-related quality of life	66	34.35 ± 7.73	28.03–40.26

N = Sample size; SD = Standard deviation * = Interquartile range of the 25 percentile and the 75 percentile

Bivariate Pearson correlations (table 4.2) showed the variables were not generally highly correlated with each other, providing support for the decision to include them into the primary analyses. Fatigue and health-related quality of life had the highest correlation ($r = -.41$). The next highest correlations were between engagement in pacing and health-related quality of life ($r = -.27$), and between engagement in pacing and fatigue ($r = .27$). These were followed by the correlations between engagement in pacing and physical activity ($r = -.25$), and between engagement in pacing and age ($r = .24$). All other bivariate correlations were of modest magnitude ($r \leq \pm.22$).

Table 4.2 | Bivariate Pearson correlations of all variables in the hierarchical linear regression models

	2	3	4	5	6	7	8
1. Engagement in pacing	-.210	.270*	-.252*	-.271*	.241*	.049	-.202
2. Perceived risk of overactivity		.190	.137	-.162	-.098	-.042	.208
3. Fatigue			-.139	-.414**	.035	.040	-.016
4. Physical Activity				-.017	-.150	.075	.093
5. Health-Related Quality of life					.117	-.048	-.039
6. Age						-.218	-.168
7. Gender							-.119
8. Body mass index							1

* Correlation is significant at the 0.05 level ** Correlation is significant at the 0.01 level

Primary Analyses

Relationship between engagement in pacing and fatigue— In order to determine the extent to which engagement in pacing is related to fatigue when controlling for demographic variables (age, gender and body mass index), health-related quality of life and perceived risk of overactivity, a hierarchical regression analysis was conducted (Tables 4.3).

Table 4.3 | Hierarchical linear regression model showing the relationship between engagement in pacing and fatigue

Variable	β	B	SE	df	t	p
Age	.058	.006	.014	3, 55	.436	.664
Gender	.065	.155	.302	3, 55	.515	.609
Body mass index	-.011	-.002	.021	3, 55	-.086	.931
Health-related quality of life	-.341	-.049	.019	2, 53	-2.568	.013
Perceived risk of overactivity	.188	.243	.167	2, 53	1.454	.152
Engagement in pacing	.198	.307	.215	1, 52	1.431	.158

β = Standardised regression coefficients from the complete regression model accounting for all variables.

B = Unstandardised regression coefficients from the complete regression model accounting for all variables

df = Degree of freedom; SE = Standard error of B

Note: In this model, fatigue was the dependent variable, activity pacing was an independent variable, and the other variables were co-predictors.

In the final model with all variables entered, although not statistically significant, engagement in pacing was positively related to fatigue (β = .198; t = 1.43, p = .16). However, health-related quality of life was negatively related to fatigue (β = -.341; t = -2.57, p = .03). A higher health-related quality of life was associated with lower fatigue.

A visual inspection of the scatter plot (figure 4.1) revealed there was no particular pattern of engagement in pacing with respect to fatigue.

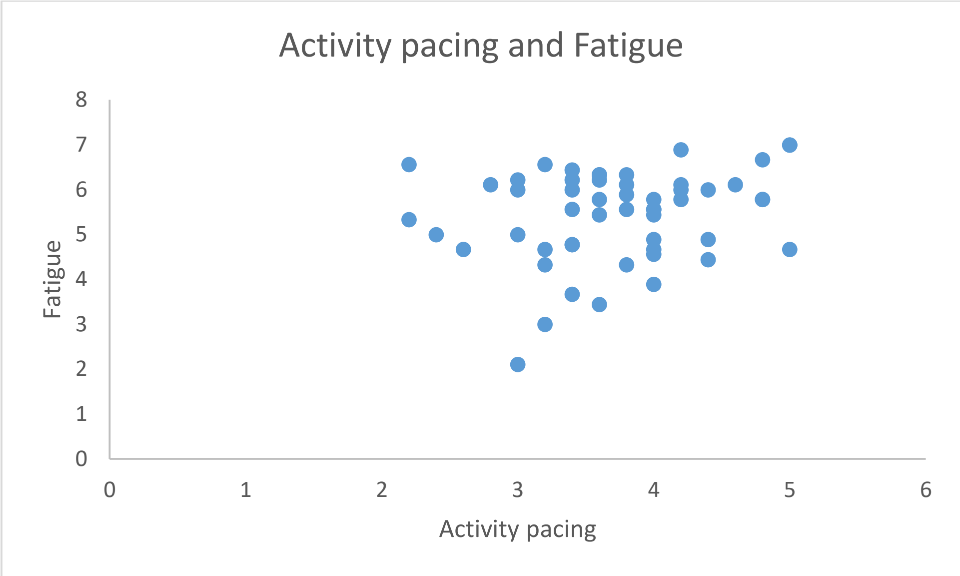


Figure 4.1. A scatter plot of the relationship between engagement in pacing and fatigue

Relationship between engagement in pacing and physical activity— In the model testing the association between engagement in pacing and physical activity (table 4.4), demographic variables (age, gender and body mass index), health-related quality of life and perceived risk of overactivity were co-predictors. Physical activity and engagement in pacing were the dependent and independent variable respectively.

Table 4.4 | Hierarchical linear regression model showing the relationship between engagement in pacing and physical activity

Variable	β	B	SE	df	t	p
Age	-.054	-5.555	15.028	3, 55	-.370	.713
Gender	.084	198.685	327.197	3, 55	.607	.546
Body mass index	.029	4.558	22.309	3, 55	.204	.839
Health-related quality of life	-.069	-9.827	20.678	2, 53	-.475	.637
Perceived risk of overactivity	.067	86.563	181.27	2, 53	.478	.635
Engagement in pacing	-.242	-3733.690	232.825	1, 52	-1.605	.115

β = Standardised regression coefficients from the complete regression model accounting for all variables.

B = Unstandardised regression coefficients from the complete regression model accounting for all variables

df = Degree of freedom; SE = Standard error of B

Note: In this model, physical activity was the dependent variable, activity pacing was an independent variable, and the other variables were co-predictors.

In the final model with all variables entered, although statistically insignificant, engagement in pacing was negatively related to physical activity ($\beta = -.242$; $t = -1.61$, $p = .12$). None of the co-predictors had a significant association with physical activity ($\beta \leq \pm .084$; $p \geq 0.05$).

A visual inspection of the scatter plot (figure 4.2) revealed there was no particular pattern of engagement in pacing with respect to physical activity.

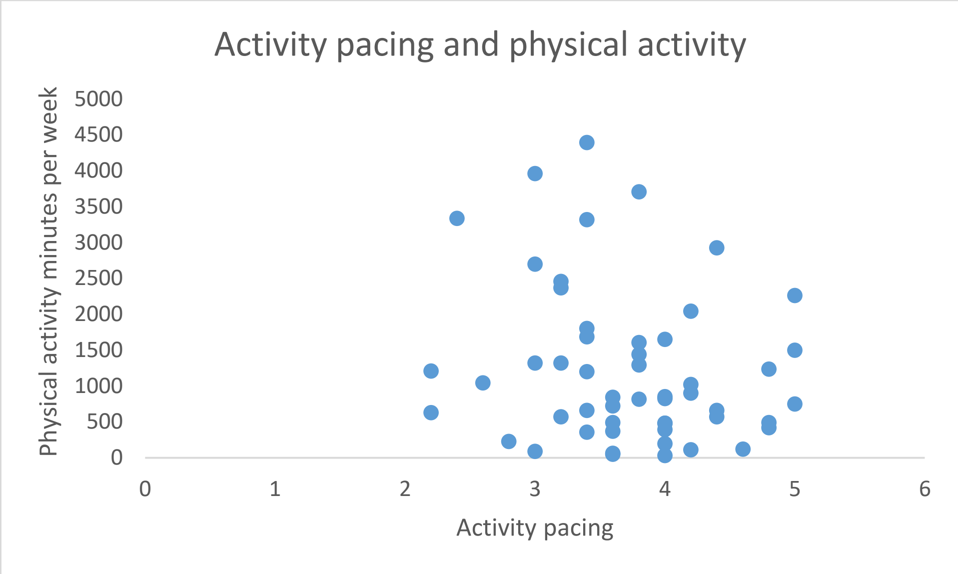


Figure 4.2. A scatter plot of the relationship between engagement in pacing and physical activity.

For all analyses, the variance inflation factors (VIFs) were low showing that there was no problem of multicollinearity (range: 1.04–1.30).

4.4 Discussion

This study explored relations of engagement in pacing with fatigue and physical activity, while controlling for demographics, health-related quality of life and perceived risk of overactivity in adults with MS and found no associations between engagement in pacing and fatigue, and physical activity. These findings were similar to the findings of Murphy et al., 2012 but did not support our hypothesis that engagement in pacing would be associated with low fatigue and high physical activity. Regarding the co-predictors, health-related quality of life was negatively related to fatigue. Descriptive statistics showed persons with MS demonstrated moderate-severe fatigue complaints—similar to studies evaluating fatigue in MS population (Murphy et al., 2008), high engagement in pacing and a high perceived risk of preventing overactivity.

Activity pacing could be a useful adaptive strategy to stimulating longitudinal engagement in physical activity (Abonie et al., 2018a), and studying the natural use of activity pacing within daily routines was thought to be a necessary step in understanding how to better develop, design and refine interventions for people with MS. The present results show there is a need to explore the potential of guiding and advising persons with MS on activity pacing and develop therapeutic interventions, as when no interventions are in place, no relations are found with fatigue or physical activity.

Bivariate correlation analysis conducted prior to the primary analyses showed a moderate negative association between fatigue and health-related quality of life, indicating high fatigue was associated with low health-related quality of life. Additionally, there was a weak positive association between engagement in pacing and fatigue, and a weak negative association between engagement in pacing and physical activity, indicating that high engagement in pacing was associated with high fatigue and low physical activity. These findings were similar to the findings of Murphy et al., (Murphy and Kratz, 2014; Murphy et al., 2008). Furthermore, there was a weak negative association between engagement in pacing and health-related quality of life, suggesting that high engagement in pacing was associated with low health-related quality life.

Together, these findings suggest the natural use of pacing to be a reactionary response to occurring fatigue related symptoms–and not a pre-planned strategy to manage fatigue and optimise performance of daily activities (Murphy and Kratz, 2014; Murphy et al., 2008) as would be taught in rehabilitation. This underscores the need to explore the potential of guiding and advising people with MS regarding optimal pacing behaviour and to develop therapeutic interventions. However, after controlling for age, gender, body mass index, health-related quality of life and perceived risk of overactivity, engagement in pacing was not related to fatigue, and physical activity. A visual inspection of the scatter plots showed no certain patterns of engagement in pacing with respect to fatigue and physical activity.

A possible explanation for the lack of associations between engagement in pacing, and fatigue, and physical activity, coupled with the moderate-severe fatigue found in this study may be multiplicity in persons' attitudes towards physical activity in relation to fatigue symptoms. Persons with MS who experience more disruption through fatigue in daily life may be consciously limiting their activities to prevent fatigue worsening, or exhibiting a lifestyle characterized by periods of overactivity (when feeling good) and as a consequence of that, feeling overtly fatigued afterwards, followed by long extensive rest periods to recover from residual symptoms or prevent symptoms re-occurring. For those consciously limiting their activities to prevent fatigue worsening, more active engagement in pacing will most likely result in less physical activity, where for those exhibiting a lifestyle characterized by periods of overactivity and prolong inactivity, more active engagement in pacing will most likely result in more physical activity, and thus when both attitudes are present in the subject population no relations between activity pacing and physical activity may be found.

This further highlights the importance to explore naturalistic pacing in relation to what we know from literature to help guide treatment efforts for persons with MS. Tailored advice and goal-directed interventions on how to approach activity effectively, such as guidance on optimal use of pacing, might be beneficial for person with MS. For example, people who avoid physical activity in anticipation to fatigue might score high on engagement in pacing but may need advice to engage more in physical activity and less in pacing, and could be provided with a graded consistent program of physical activity to increase their health, as well as be given information and strategies to help change their beliefs that "I should do less if I am tired" or "symptoms are always a sign that I am damaging myself." Similarly, people who have developed an all-or-nothing behaviour style might need advice to be more aware of anticipatory ways of engaging in pacing to develop a consistent pattern of paced activity and rest.

In addition, the sample size in this study was small (N = 80), which limits the ability to obtain precise estimates of the model parameters and may account for the lack of significant associations between engagement in pacing, and fatigue, and physical activity after controlling for confounders. It would therefore be useful to replicate these analyses in a larger sample. To our knowledge this is the first study to tap into the experiences of persons' with MS during their daily routines and explore the associations between engagement in pacing, fatigue, and physical activity. Adequate management of fatigue might be essential to improve health and wellbeing in persons with MS, based on the findings of this study and previous literature that revealed most persons with MS experience high levels of fatigue throughout the day (Heine et al., 2016).

To optimise generalizability within the population of persons living with MS, this study was conducted solely in persons with MS. Generalizability to other populations might therefore be limited, as findings may vary per condition (Murphy and Kratz, 2014). Similarly, because this sample was primarily Dutch, findings are limited in their generalizability to a more diverse population. Additionally, the lack of information on participants' MS type and disease severity in this study limits the ability to draw firm conclusions.

The inability of physical activity questionnaire to quantify physical activity patterns is a limitation of the study. The weak bivariate correlations between engagement in pacing and fatigue, and between engagement in pacing and physical activity found may have accounted for the lack of associations after controlling for demographics, health-related quality of life and perceived risk of overactivity, and is a limitation of this study. It is worth noting that although participants received rehabilitation treatment as part of the larger multicentre study, a structured activity pacing program was not included and we do not think this has influenced the findings of this study.

The findings that the sample reported engagement in pacing and perceived risk of overactivity scores near the possible upper limits may be more of a reflection of the parameters the Activity Pacing and Risk of Overactivity Questionnaire is able to measure than of how the individuals may be ultimately functioning. In addition, data were slightly skewed towards high engagement in pacing, perceived risk of overactivity and fatigue. These are limitations of the current study and further demonstrate the complexity of naturalistic pacing behaviour in the context of fatigue and physical activity behaviour.

Future studies should include larger sample size, quantify physical activity patterns and include information on MS type and disease severity. In addition, future studies should further explore how engagement in pacing and perceived risk of overactivity relate to performance of activities of daily living, to allow for firm conclusions and help advice persons with MS on how to engage in an active lifestyle. Additionally, further exploratory studies on how activity pacing behaviour might affect physical activity, fatigue and health-related quality of life over a longer period of time and whether advice on optimal activity pacing based on personalised report of attitudes towards pacing, physical activity and fatigue experience would lead to reduced fatigue, increased physical activity and increased health-related quality of life, are warranted.

4.5 Conclusion

In summary, this was a study to examine the relationships between engagement in pacing and fatigue and physical activity in persons with MS, while controlling for demographics, perceived risk of overactivity and health-related quality of life. No significant associations were found between engagement in pacing and fatigue, and between engagement in pacing and physical activity. We found that low health-related quality of life was associated with high fatigue. Persons with MS might benefit from targeted interventions to better manage their fatigue and improve their health and wellbeing. Ascertaining engagement in pacing may be important to help tailor advice on optimal pacing behaviour for persons with MS. There is a need to explore the potential of guiding and advising persons with MS on activity pacing and develop therapeutic interventions.

CHAPTER 5

A longitudinal study of associations between activity pacing, physical activity behaviour and health-related quality of life in adults with multiple sclerosis

Abstract

Literature on activity pacing effects on fatigue symptoms is scarce, with little known about how activity pacing strategies affect physical activity behaviour and quality of life over longer periods of time. The purpose of this study was to evaluate how activity pacing relates to development of physical activity and health-related quality of life a year after rehabilitation in adults with multiple sclerosis (MS).

89 adults with MS (mean age= 42 ± 11 years) filled in questionnaires on their engagement in pacing and perceived risk of overactivity (Activity Pacing and Risk of Overactivity Questionnaire), fatigue (Fatigue Severity Scale), physical activity (adapted Short Questionnaire to Assess Health-Enhancing Physical Activity) and health-related quality of life (RAND-12 Health Survey) at 14, 33 and 52 weeks post-rehabilitation. Multilevel models were used to analyse the associations between activity pacing and physical activity and health-related quality of life.

Engagement in pacing were 3.86 ± 0.64, 3.82 ± 0.64 and 3.84 ± 0.59; physical activity were 1990.32 ± 1395.06, 2029.47 ± 1311.07 and 1650.53 ± 1335.92; and health-related quality of life were 36.00 ± 8.61, 37.31 ± 8.30 and 38.47 ± 7.29 at 14, 33 and 52 weeks respectively. No associations were found between activity pacing and physical activity ($\beta = -0.01$; $p = 0.89$), and between activity pacing and health-related quality of life ($\beta = -0.15$; $p = 0.09$) over time. Fatigue was negatively related to health-related quality of life ($\beta = -0.33$; $p < 0.001$). Perceived risk of overactivity moderated the associations between fatigue and physical activity ($\beta = -0.19$; $p = 0.02$), and between fatigue and health-related quality of life ($\beta = -0.13$; $p = 0.04$).

These findings suggest that persons who experience decreases in physical activity and health-related quality of life with increased fatigue, are more likely to be engaging in ‘overactive’ behaviour. The lack of relations between activity pacing and physical activity, and between activity pacing and health-related quality of life suggests there is no clear strategy among persons with MS that is effective in improving physical activity and quality of life either in short or long-term when no interventions are introduced.

5.1 Introduction

For people with multiple sclerosis (MS), the experience of fatigue symptoms can greatly impair their quality of life (Merkelbach et al., 2011; Brañas et al., 2000; Amato et al., 2001). While a link between fatigue and measures of physical disability has been established in MS (Molt et al., 2005; Krause et al., 2013), less is known about how strategies to cope with fatigue such as activity pacing, influence physical activity on a day-to-day basis.

Activity pacing is a behavioural strategy in which people learn to lessen the effect of fatigue or pain related symptoms on engagement in an active lifestyle by dividing daily activities into smaller, more manageable pieces, and alternating activity and rest periods (Antcliff et al., 2015). The goal of activity pacing behaviours is to attenuate the “overactivity-underactivity” cycle in which excessive activity can lead to symptom flares that require a prolonged period of rest to recover (Antcliff et al., 2015; Nijs et al., 2009).

In our previous cross-sectional study exploring the relations between activity pacing and physical activity measured subjectively in persons with MS in rehabilitation (Abonie et al., 2018c), we found no associations between activity pacing and physical activity, despite their high engagement in pacing. This demonstrates the complexity of naturalistic pacing and the importance to explore this behaviour in relation to what we know from literature to help guide treatment efforts for persons with multiple sclerosis.

An interesting feature that has not yet been explored is the long-term influence of activity pacing on physical activity behaviour, symptoms and quality of life. Exploring this could provide valuable insights on the direction of the relations between activity pacing, physical activity and symptom outcome. For example, do persons engage in more pacing in daily life due to an increase in perceived symptoms (symptom-contingent) or do persons engage in more pacing behaviour and thereby reduce their perceived symptoms (symptom-reduction) or do persons engage in more pacing to reduce the influence of symptoms on activity and thereby optimise their daily activities (Antcliff et al., 2015; Nijs et al., 2008)?

Equally, the development of a strategy to cope with symptoms such as fatigue does not ensure that it is adaptive (a positive behaviour), as evident in the association between underactivity or avoidance behaviour and physical disability (Bakkum et al., 2013; Clark and White, 2005). Similarly, strategies may be adaptive in the short-term but prove to be maladaptive on the longer term if symptoms become chronic, as evident in the association between overactivity and physical disability (Hasenbring and Verbunt, 2010). These findings further underscore the need to explore how strategies such as activity pacing influence physical activity behaviour and quality of life over time.

Conversely, despite the known associations between underactivity-overactivity cycles and physical disability in the long term, how pacing behaviour of persons with MS affects their physical activity behaviour and quality of life in the long-term is unknown. An understanding of the natural use of pacing and how it contributes to physical activity behaviour and quality of life over time can establish the need for, and influence the design of effective treatments and interventions incorporating activity pacing to stimulate an active lifestyle.

This study addressed a pitfall in literature by examining how activity pacing relates to the development of physical activity and health-related quality of life in a sample of adults with MS a year after rehabilitation. Activity pacing was assessed with an Activity Pacing Questionnaire (Alingh et al., 2015) representing the areas of active engagement in pacing decisions.

Based on the expectation that activity pacing may be an adaptive strategy to manage fatigue and enhance longitudinal engagement in physical activity (Abonie et al., 2018a), we hypothesized that activity pacing would be associated with physical activity behaviour and health-related quality of life over time. We also hypothesized that activity pacing would moderate the associations between fatigue and physical activity, and between fatigue and health-related quality of life over time. Specifically, we expected that over time people who engage in activity pacing would display weaker associations between fatigue and activity, to reflect independence of activity and fatigue, compared to people with low levels of activity pacing.

5.2 Materials and methods

5.2.1 Design

This is a secondary data analysis of data from a larger longitudinal multicentre study in the Netherlands (Alingh et al., 2011). The goal of the current study was to examine how activity pacing related to the development of physical activity and quality of life in a sample of adults with MS. Data from 14 weeks, 33 weeks and 1 year follow-up assessment periods were used for these analyses. Ethical approval for this study was obtained by the Center of Human Movement Sciences of the University Medical Center Groningen (reference: ECB/2013.02.28_1) and at participating institutions.

5.2.2 Sample

Details about recruitment have been described in chapter 4. In brief, participants were included if they were age 18 years and older, self-reported MS diagnosis and receives inpatient or outpatient rehabilitation care or treatment based on medicine consultation within one of the participating rehabilitation centres or hospitals, participates in the ‘Rehabilitation, Sports and Exercise’ programme. Participants were excluded from the study if they were not able to complete the questionnaires, even with help, or participating in another physical activity stimulation programme. Written informed consent was obtained from participants who were eligible and willing to participate.

5.2.3 Procedure

Enrolled participants were assessed through standardised measurements after rehabilitation (14 weeks, 33 weeks and one year follow-up). At each assessment point, the measurement consisted of filling out a set of questionnaires on paper or digitally and was in three parts. First, participants filled out a short questionnaire on their daily physical activity (Wendel-Vos et al., 2003). The participants were asked to indicate which physical activities they perform in the context of the rehabilitation treatment and on their own initiative. Second, participants were asked to fill out short questionnaires on their pacing behaviour and fatigue (Alingh et al., 2015; Krupp et al., 1989). Last, participants filled out the RAND-12 Item Health Survey to assess their health-related quality of life (Selim et al., 2009)

5.2.4 Measures

Background demographics and personal variables included age, gender and body mass index; calculated from measured body mass (kg) / height^2 (m^2)].

Engagement in pacing

The active engagement in pacing decisions subscale of the Activity Pacing and Risk of Overactivity Questionnaire (Alingh et al., 2015) (appendix 1) was used to assess engagement in pacing. This new questionnaire was to evaluate how and based on which aspects participants modify their pacing behaviour over the day. The complete questionnaire provided insight into two different components of the concept of activity pacing: active engagement in pacing decisions and perceived risk of overactivity (Alingh et al., 2015). The active engagement in pacing decisions component indicated a person’s engagement in pacing routines and was a primary outcome of the current study. The perceived difficulty in preventing overactivity component indicated a person’s perceived risk of overactivity within their daily routines and was a secondary outcome of the current study. The participants scored the seven items of the complete questionnaire on a scale of 1-5 (1, never; 2, rarely; 3, sometimes; 4, often; 5, very often). This generated two subscales scores (engagement in pacing score and perceived risk of overactivity score) that ranged from 1 to 5.

Physical activity

Self-reported level of daily physical activity was assessed with an adapted version of the Short Questionnaire to Assess Health-Enhancing Physical Activity (Wendel-Vos et al., 2003) (appendix 3). The Short Questionnaire to Assess Health-Enhancing Physical Activity is a self-reported recall questionnaire to assess daily physical activity of healthy adults based on an average week in the past month. The Short Questionnaire to Assess Health-Enhancing Physical Activity was adapted to make it applicable for people with a chronic disease or physical disability. Within the domains 'commuting activities', 'leisure-time' and 'sports activities', the items 'wheelchair riding' and 'hand cycling' were added. In addition, 'tennis' was modified as '(wheelchair) tennis'. Last, the self-reported intensity was categorised as 'light', 'moderate' and 'vigorous', instead of 'slow', 'moderate' and 'fast'. Total minutes of physical activity per week was calculated by multiplying frequency (days/week) and duration (minutes/day) for each activity. The original Short Questionnaire to Assess Health-Enhancing Physical Activity has demonstrated good test-retest reliability and internal consistency and moderate concurrent validity in ordering participants according to their level of physical activity in an adult population (Wendel-Vos et al., 2003) and in several patient groups (Arends et al., 2013; Wagenmakers et al., 2008).

Health-related quality of life

Health-related quality of life was assessed by the RAND 12-Item Health Survey (Version 1.0) (Selim et al., 2009) (appendix 4), a validated and reliable questionnaire (Ware et al., 1996). The RAND-12 is a self-reported questionnaire that assesses seven health domains; general health, physical functioning, role limitations due to physical health problem bodily pain, role limitations due to emotional problems, vitality/ mental health and social functioning. The RAND-12 was scored using the recommended scoring algorithm for calculating global health (Hays et al., 1998). This generates the global health score which is a composite score of person's health-related quality of life. The score ranged from 18 to 62. A higher score on the RAND-12 indicated better health-related quality of life.

Fatigue

Fatigue severity was measured using the Fatigue Severity Scale (Krupp et al., 1989) (appendix 2). The fatigue severity scale has been proven to be a valid and reliable measure to determine the impact of fatigue and to detect change over time in persons with MS (Whitehead, 2009). This unidimensional fatigue questionnaire includes nine questions, scored on a scale of 1–7 (1, completely disagree; 7 completely agree). The nine items were averaged to calculate the fatigue severity total mean score that ranges from 1 (no fatigue) to 7 (very severe fatigue). The mean fatigue score ranged from 1 to 7, with a higher score indicating greater fatigue severity.

5.2.5 Statistical analysis

Descriptive statistics were calculated for demographic and personal factors, using the Statistical Package for the Social Science (IBM SPSS Statistics, version 24). Multilevel analysis was performed to determine how fatigue and activity pacing were related to the development of physical activity behaviour and health-related quality of life after rehabilitation, by using MLwiN (Charlton et al., 2017). The multilevel analysis created models of the total minutes of activity per week assessed with the adapted short questionnaire to assess health-enhancing physical activity, and models for health-related quality of life. A two-level model was used in which repeated measures within individuals (Level 1) were clustered within individuals (Level 2). The model included the covariates gender, age, and body mass index; because they are general demographic variables of interest in studies on physical activity behaviour and fatigue (Murphy and Kratz, 2012). Possible predictors for the multilevel model were fatigue, and activity pacing for both perceived risk of overactivity and engagement in activity pacing. All variables in the multilevel model were standardized. Random intercepts were considered thus allowing a unique intercept for each individual. Because we expect variation in physical activity and health-related quality of life between individuals, random slopes were entered into the model to properly account for correlations amongst repeated measures within individuals. The predicted variables were entered separately into the initial model. In model 1 fatigue was the only predictor variable. In model 2, activity pacing was the only predictor variable. In the final model, fatigue, activity pacing and interaction terms of fatigue with activity pacing were included as predictors. During each step, goodness of fit was evaluated by comparing the -2*Log Likelihood (IGLS deviance) of the previous model, with the most recent model. A p-value lower than or equal to 0.05 was regarded as statistically significant.

5.3 Results

A total of 68 adults with MS were included in this study. Descriptive statistics of the study population and outcome measures at each assessment point post rehabilitation, are presented in Table 5.1. Results indicate that the sample was on average overweight according to body mass index score, had an average age of 46 ± 11 and 33% was male.

Table 5.1 Descriptive statistics of demographic and outcome measures at post rehabilitation

Variable	Mean ± SD or N (%)					
Age in years	45.2 ± 10.9					
Body mass index (kg/m2)	26.8 ± 6.3					
Gender, Number of male (%)	29 (32.6)					
	14 weeks		33 week		1 year	
	Mean ± SD	Missing (N)	Mean ± SD	Missing (N)	Mean ± SD	Missing (N)
Physical activity	1990.32 ± 1395.06	25	2029.47 ± 1311.07	27	1650.53 ± 1335.92	40
Health-related quality of life	36.00 ± 8.61	30	37.31 ± 8.30	40	38.47 ± 7.29	46
Fatigue	5.22 ± 0.96	29	5.1 ± 1.2	37	5.1 ± 1.0	44
Engagement in pacing	3.86 ± 0.64	29	3.82 ± 0.64	38	3.84 ± 0.59	45
Perceived risk of overactivity	3.63 ± 0.80	29	3.56 ± 0.74	38	3.42 ± 0.88	45

Engagement in pacing and physical activity behaviour

Results of the multilevel analysis of activity pacing predicting the development of physical activity, while controlling demographic variables and fatigue are presented in Table 5.2. None of the variables were significant predictors of physical activity development ($p > 0.05$). Specifically, engagement in pacing was not a predictor of long-term development of physical activity ($\beta = -0.01$; $p = 0.890$).

Testing of interaction effects (table 5.2) indicated that engagement in pacing ($\beta = -0.03$; $p > 0.05$) was not significant moderators of the association between fatigue and physical activity. However, perceived risk of overactivity moderated the association between fatigue and physical activity ($\beta = -0.19$; $p = 0.021$). This indicated that for those with high perceived risk of overactivity, there is a negative association between fatigue complaints and physical activity. In other words, those who experience decreases in physical activity with increased fatigue, are more likely to be engaging in too many or prolong periods of activities.

Table 5.2 Multilevel modelling analysis predicting physical activity from activity pacing and fatigue from 14 weeks, 33 weeks and one year follow-up

Physical activity						
	Model 1		Model 2		Final model	
Fixed Factors	*p*	β (S.E.)	*p*	β (S.E.)	*p*	β (S.E.)
Constant		0.01 (0.20)		0.01 (0.21)		-0.10 (0.20)
Covariates						
Gender (female)	0.933	-0.02 (0.24)	0.9338	0.02 (0.25)	0.576	0.14 (0.24)
Age	0.968	0.01 (0.12)	0.720	-0.04 (0.12)	0.691	0.05 (0.12)
Body mass index	0.358	-0.10 (0.11)	0.329	-0.12 (0.12)	0.181	-0.15 (0.11)
Predictors						
Fatigue	0.087	-0.16 (0.09)			0.334	-0.09 (0.10)
Engagement in pacing			0.151	-0.04 (0.10)	0.890	-0.01 (0.10)
Perceived risk of overactivity			0.175	-0.01 (0.09)	0.643	0.04 (0.09)
Fatigue x engagement in pacing					0.844	0.02 (0.09))
Fatigue x perceived risk of overactivity					0.021	-0.19 (0.08
Random effects		β (S.E.)		β (S.E.)		β (S.E.)
Level 1 (within time points)						
Constant		0.41 (0.07)		0.41 (0.07)		0.40 (0.06)
Level 2 (between individuals)						
Constant		0.52 (0.13)		0.55 (0.14)		0.48 (0.12)
∆ Deviance	<0.001	116.68	<0.001	120.78	<0.001	129.01
Deviance empty model		470.54		470.54		470.54

Engagement in pacing and health-related quality of life

Results of the multilevel analysis of activity pacing predicting health-related quality of life, while controlling demographic variables and fatigue are presented in Table 5.3. Among the covariates, age was significantly related to higher health-related quality of life ($\beta = 0.27$; $p = 0.004$) and body mass index was significantly related to lower health-related quality of life ($\beta = -0.32$; $p < 0.001$) (table 3). Additionally, fatigue was negatively related to health-related quality of life ($\beta = -0.33$; $p < 0.001$). Engagement in pacing was not related to health-related quality of life ($\beta = -0.15$; $p = 0.085$). Perceived risk of overactivity moderated the association between fatigue and health-related quality of life ($\beta = -0.13$; $p = 0.040$). This indicated that for those with high perceived risk of overactivity, there is a negative association between fatigue complaints and health-related quality of life. In other words, those who experience increases in fatigue with decreased health-related quality of life, are more likely to be engaging in too many or prolong periods of activities than those who either do not experience a relation between fatigue and health-related quality of life or who experience increases in fatigue in the context of higher health-related quality of life.

Table 5.3 Multilevel modelling analysis predicting health-related quality of life from activity pacing and fatigue from 14 weeks, 3 weeks and one year follow-up

Health-related Quality of Life						
	Model 1		Model 2		Final model	
Fixed Factors	*p*	β (S.E.)	*p*	β (S.E.)	*p*	β (S.E.)
Constant		-0.21 (0.16)		-0.21 (0.19)		-0.27 (0.16)
Covariates						
Gender (female)	0.153	0.27 (0.19)	0.185	0.30 (0.23)	0.065	0.35 (0.19)
Age	0.014	0.22 (0.09)	0.177	0.15 (0.11)	0.004	0.27 (0.09)
Body mass index	0.006	-0.25 (0.09)	0.007	-0.29 (0.11)	<0.001	-0.32 (0.09)
Predictors						
Fatigue	<0.001	-0.38 (0.08)			<0.001	-0.33 (0.08)
Engagement in pacing			0.009	-0.23 (0.09)	0.085	-0.15 (0.09)
Perceived risk of overactivity			0.728	-0.03 (0.08)	0.627	0.04 (0.08)
Fatigue x engagement in pacing					0.974	0.00 (0.07)
Fatigue x perceived risk of overactivity					0.040	-0.13 (0.06)
Random effects		β (S.E.)		β (S.E.)		β (S.E.)
Level 1 (within time points)						
Constant		0.38 (0.06)		0.38 (0.05)		0.36 (0.06)
Level 2 (between individuals)						
Constant		0.26 (0.08)		0.46 (0.12)		0.24 (0.08)
Δ Deviance	<0.001	58.30	<0.001	51.89	<0.001	70.85
Deviance empty model		470.54		470.54		470.54

5.4 Discussion

In this study, we investigated the relationships between activity pacing and physical activity behaviour and health-related quality of life in a sample of adults with MS while controlling for fatigue and demographic variables. There is a paucity of research that has examined how activity pacing relates to the development of physical activity and health-related quality of life in MS, and the exploration of long-term longitudinal data in this study provides important insights. We examined the relationships between activity pacing and the development of physical activity and health-related quality of life in separate multilevel models. We found that activity pacing was not significantly related to the development of physical activity measured by the short questionnaire to assess health-enhancing physical activity. Additionally, we found that fatigue was a significant predictor of health-related quality of life. Specifically, fatigue was significantly related to low health-related quality of life. Furthermore, we found that activity pacing did not significantly moderate the relationship between physical activity and fatigue.

Testing of interaction effects in this study is important because this allows us to examine some key assumptions about activity pacing effects on a moment to moment basis. For example, it is thought that when people experience moments of high fatigue sensations, their physical activity behaviour will be affected. However, activity pacing is thought as a potential adaptive strategy to modify the expected relationship between fatigue and physical activity behaviour. In other words, activity pacing is thought to help dissociate physical activity behaviour from fatigue symptoms. This is the first known study testing whether activity pacing moderates the association between physical activity and fatigue in adults with MS. Although we expected that people who most frequently report natural use of pacing would demonstrate the weakest relationships between fatigue symptoms and physical activity, and people who most frequently report overactive behaviour would have the strongest relationships between symptoms and activity, we did not find any of these relationships.

Furthermore, we found that perceived risk of overactivity moderated the associations between fatigue and physical activity, and between fatigue and health-related quality of life. For those who frequently reported perceived risk of overactivity there were negative associations between fatigue and physical activity, and between fatigue and health-related quality of life. These findings suggest that those who experience decreases in physical activity with increased fatigue, are more likely to be engaging in too many or prolong periods of activities than those who either do not experience a relation between fatigue and physical activity or who experience increases in physical activity in the context of higher fatigue. Equally, those who experience decreases in health-related quality of life with increased fatigue, are more likely to be engaging in 'overactive' behaviour than those who either do not experience a relation between fatigue and health-related quality of life or who experience increases in health-related quality of life in the context of higher fatigue. However, it is important to note that we cannot determine from these data whether perceived risk of overactivity causes stronger associations between fatigue and physical activity, and between fatigue and health-related quality of life or whether the strong associations between fatigue and physical activity, and between fatigue and health-related quality of life evokes perceived risk of overactivity.

Taken together with the findings for the moderating effect of pacing on the fatigue-physical activity association, these findings suggest that the use of activity pacing strategies may be driven by complex coping strategies. It is likely that persons with MS engage in more complex behavioural strategies in the context of the fatigue-activity relationship. That is, they may not be only a "pacer" or an "overactive," or an avoider '' and selection of coping strategy may depend on the particular situation. For example, people may be overactive when their fatigue sensation is low and pace their activities when their fatigue sensation is high. Similarly, people may be pacing their activities when fatigue sensations are low and avoid activities when fatigue sensations are high. This points to an important fact that pacing could potentially be viewed as an adaptive or maladaptive behaviour depending upon whether or not people are using it to optimise their daily activities or as a means to avoid activities.

The findings of the present study as well as the lack of associations between activity pacing and physical activity and fatigue found in our previous cross-sectional exploratory study (Abonie et al., 2018c) indicate that there is no clear strategy among persons with MS that is successful in improving physical activity and quality of life either in short or long-term when no interventions are introduced. Thus persons with MS might benefit from guidance or advice in the form of optimal use to activity pacing to promote longitudinal engagement in physical activity. This highlights the need for the development and design of goal-directed interventions incorporating activity pacing to stimulate a physically active lifestyle in people with MS.

To help do this, more research that focuses on moment to moment dynamic associations between activity pacing, changes in fatigue, and actual physical activity behaviour is needed. This would help provide a better understanding of the relations between natural use of pacing and physical activity behaviour and help guide treatment efforts for persons with MS. Despite the feasibility and easy use of questionnaires to assess physical activity, self-reported measures are susceptible to bias. The use of a subjective measure to assess activity level in this study is a limitation and additional objective physical activity measures are recommended in future studies.

A strength of this study is the novel and long-term approach to explore the longitudinal associations between activity pacing and the development of physical activity and quality of life using multi-level modelling. This could provide important input for the development of future interventions that will impact on physical activity behaviour of persons with MS. The examination of the influence of activity pacing on the associations between fatigue and physical activity, and between fatigue and quality of life provide us novel insights in the complex interplay between fatigue and activity behaviour. This is the first known study to explore long term associations between activity pacing and the development of physical activity and quality of life in persons with MS. The unique data set spanning three measurement points of persons with MS activity pacing behaviour, physical activity, quality of life and fatigue, over a one year period is a strength of the study.

Although self-report measures are more feasible in population studies, they are susceptible to biases. Their use in this study is a limitation. The small sample size of this study limits our ability to generalize the findings. The inability of physical activity questionnaire to quantify physical activity patterns is a limitation of the study. In addition, data were skewed towards high activity pacing and fatigue. Furthermore, the lack of details on MS type / disease severity of participants limits the ability to draw firm conclusions. Future studies should include larger sample size, quantify physical activity patterns and include information on MS type and disease severity.

5.5 Conclusion

This study examined the associations between activity pacing and the development of physical activity and health-related quality of life a year after rehabilitation in a sample of adults with MS. We found no associations between pacing behaviours and development of physical activity, and between pacing behaviours and health-related quality of life. However, fatigue was related to low health-related quality of life. An examination of a potential moderating effect revealed perceived risk of overactivity moderated the associations between fatigue and physical activity, and between fatigue health-related quality of life.

Altogether, the study findings suggest that people with MS demonstrating a high perceived risk of overactivity, and decreased physical activity and health-related quality of life in the context of increased fatigue may benefit from an intervention to manage fatigue and approach activity in an effective way. Further examination that looks at dynamic moment to moment associations between activity pacing, fatigue, and physical activity behaviour would help provide a better understanding of the relations between natural use of pacing and physical activity behaviour and help guide treatment efforts for persons with MS. The inclusion of objective measures of physical activity is recommended in future studies of activity pacing effects on physical activity behaviour.

CHAPTER 6

A within daily analysis of actual physical activity behaviour and natural use of pacing and perceived risk of overactivity in adults with multiple sclerosis

Abstract

Little is known about the dynamic association between activity pacing and actual physical activity behaviour within the daily routines of persons with multiple sclerosis (MS). Understanding the association between activity pacing and actual physical activity behaviour is relevant to help optimise health promoting behaviour. The aim of this study was to explore how activity pacing relates to actual physical activity behaviours in adults with MS.

21 persons with MS (mean age= 59 ± 9 years) wore an accelerometer for 7 days to assess physical activity behaviours and filled in questionnaires on their engagement in pacing and perceived risk of overactivity (5-point Activity Pacing and Risk of Overactivity Questionnaire), fatigue (7-point Fatigue Severity Scale), and Health-related quality of life (RAND-12). Physical activity behaviours were assessed by examining activity level (7-day average activity counts per minute) and activity variability (7-day average highest activity counts per minute each day divided by activity counts per minute on that day). The relationships between the variables were examined using hierarchical regression models.

Lower activity level was related to higher engagement in pacing ($\beta = -.438$, $t = -2.66$, $p = .024$). Higher activity level was associated with higher perceived risk of overactivity ($\beta = .494$, $t = 2.84$, $p = .018$). No relations were found between activity variability and engagement in pacing ($\beta = -.225$, $t = -.96$, $p = .361$) and between activity variability and perceived risk of overactivity ($\beta = .149$, $t = .599$, $p = .562$).

The results indicate that those with lower activity levels may experience worsening symptoms with respect to physical disability, and may be more inclined and aware to pace their activities. Conversely, those with higher activity levels may experience less disruption through fatigue in daily life and may resort to the execution of too long periods of activity which may cause overactivity. Guidance on optimal use of pacing may be beneficial for persons with MS and improve their physical activity behaviour.

6.1 Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system characterized by disturbances in nerve conduction and manifested by various clinical features (Van Kessel et al., 2006; Rampello et al., 2007). Fatigue is a frequent and disabling symptom in people with MS (Bailey et al., 2007; Merkelbach et al., 2011) that has a profound impact on their activities of daily living (ADLs), ability to work, socialize, and general health (Branas et al., 2000; Bakshi, 2003; Amato et al., 2001). In addition, severity of fatigue has been found to be an independent predictor of disability and quality of life in people with MS (Khan et al., 2008; Amato et al., 2001; Johansson et al., 2007; Krause et al., 2013).

Because there is, as of yet, no clear understanding of effective modes of curing or preventing MS, increasing attention is being directed toward treating the disease and managing its symptoms (Motl et al., 2006). Physical activity might have general and unique benefits for people with MS (Simmons et al., 2004; Stuifbergen, 1992). Engagement in physical activity improves quality of life and promotes independence, improves health, mobility, participation in daily life and longevity (Moore et al., 2012), with a gain of 4.5 years of life matched to being inactive (Jones et al., 2015). Consequently, a physically active lifestyle is crucial in the management of MS (National Institute for Clinical Excellence, 2014).

However, the unpredictable illness trajectory and symptoms characteristic of MS bring challenges specific to this population and to their engagement in physical activity (Kayes et al., 2011). Invariably, there is increasing evidence that persons with MS engage in significantly lower physical activity and spend considerably more time in sedentary behaviour compared with the general population, which results in physical deconditioning and, as a consequence, perpetuate fatigue severity and reduced physical capacities that increase disability in persons with MS (van den Berg-Emons et al., 2010; Motl et al., 2005; 2006).

It is therefore essential to explore ways to keep people with MS physically active. Activity pacing is a strategy to divide one's daily activities into smaller, more manageable portions, in a way that should not exacerbate their symptoms, which then allows gradual progressive increases in activity (Nijs et al., 2009; Murphy and Kratz, 2014). However, the potential of activity pacing to stimulate efficient engagement in physical activity has not been fully explored (Abonie et al., 2018a).

More recently, we explored relations between self-reported activity levels, fatigue, health-related quality of life and engagement in pacing and perceived risk of overactivity in persons' with MS using the data collected in the ReSpAct study (Alingh et al., 2015) and found fatigue was associated with low quality of life (Abonie et al., 2018c; 2018d). Conversely, we found no association between activity pacing and physical activity. However, self-report measures are susceptible to biases and this makes it difficult to accurately quantify physical activity outcomes, such as activity level and activity variability (amount of fluctuation in physical activity level or prevalence of peaks and valleys in physical activity patterns).

Methods that use an objective approach such as accelerometry to examine moment-to moment dynamic association between physical activity behaviour and activity pacing allow for more firm conclusions regarding physical activity behaviour, and are advantageous compared to self-report measures, which involve recall (over days, weeks, or months) that could lead to underreporting (Gignac et al., 2000). Thus, such methods could provide a better understanding of how activity pacing affects the way people actually engage in physical activity, such as physical activity variability.

No studies could be found that examined how persons with MS natural use of activity pacing in daily life influenced their actual physical activity behaviour measured with accelerometer. Thus, the purpose of this study was to explore relationships between objective physical activity level and physical activity variability, and engagement in pacing behaviour within the daily routines of adults with multiple sclerosis. Based on our expectation that activity pacing could be a positive strategy to maintain a steady pace and progressively increase activity levels (Abonie et al., 2018a), we hypothesized that engagement in pacing would be related to objective physical activity levels and physical activity variability.

6.2 Method

6.2.1 Design

This was a cross sectional design based on baseline measurement of engagement in pacing and perceived risk of overactivity in naturalistic pacing behaviour, physical activity behaviour, fatigue severity and health-related quality of life. All study procedures were approved by the Ethics Committee at the University of Essex.

6.2.2 Participants

Participants were recruited from MS-UK (a national charity, based in Colchester, which supports people with MS and who regularly run exercise classes for people with MS) and MS Society local group in Colchester (a local group providing friendship, support and information for people with MS) through public advertisements (online and e-posters). Recruitment was conducted by contacting facilitators of local self-help groups. Those interested in participation were contacted by the researchers who explained the study rationale, potential benefits, procedures, answered all questions, and, in the event of meeting inclusion criteria and voluntarily agreeing to participate, a written informed consent was obtained. Criteria for inclusion in this study were; persons 18 years and older, living with MS, been relapse free during the last 30 days, not currently or recently (in the previous 12 months) received activity management or behavioural therapy that included activity pacing instruction, ambulatory (with or without assistive device) and were English-speaking.

6.2.3 Procedure

Enrolled participants were assessed through standardised baseline measurements obtained from two clinic visits and at home. During the first visit, demographic and health status information were collected. Background demographics included age, gender, MS diagnosis, self-reported duration of illness (years since diagnosis), body mass index; calculated from measured weight (kg)/ height $(m)]^2$ and physical disability, assessed using the Patient Determined Disease Steps (PDDS) (Marrie and Goldman, 2007). The PDDS is a valid patient-reported outcome of disability in multiple sclerosis and is strongly correlated with expanded disability status scale (Learmonth et al., 2013). Participants were then instructed on wearing an accelerometer. Participants wore the accelerometer for seven days during the home monitoring period. They were asked to keep it on at all times except on occasions when it could become wet (e.g., showering or swimming). After the home monitoring period, participants returned the accelerometer and completed the final part of the measurement. This consisted of filling out a set of questionnaires. First, participants filled out a self-report questionnaire on their engagement in pacing and risk of overactivity (as detailed in Align et al., 2015). Second, participants completed short questionnaires on their fatigue and health-related quality of life (Selim et al., 2009; Krupp et al., 1989). Details of the measurements are given in next section.

6.2.4 Measures

Physical activity behaviour

Waist-worn accelerometers (ActiGraph GT3X+, LLC, Fort Walton Beach, FL) were used for real-time monitoring of physical activity behaviour. The used waist-worn accelerometers can accurately measure activity counts between subjects of various ages (Focht et al., 2003). De Vries (2006) reported that the ActiGraph series was the most studied activity monitor, and many studies have validated its reliability and performance. The GT3X+ uses a triaxial accelerometer for more accurate physical activity monitoring. Changes in acceleration were recorded into the accelerometer as activity counts, saved every 10 s, and then averaged each minute. The resulting unit of measurement is activity counts per minute. Activity counts were computed based on a pre-defined algorithm cut points; Freedson Adults VM3, 1998 (Sasaki et al., 2011). Total physical activity was calculated by averaging the cumulative activity counts per minute over 7 days.

Besides the activity counts per minute, the pure, untransformed data generated by the accelerometer were used to calculate the peak ratio which indicates physical activity variability and corresponds to the fluctuating nature of the physical activity pattern throughout the week. The peak ratio for each day was calculated as the amount of physical activity during the peak activity hour for each day (identified as the hour with the highest number of activity counts), divided by the mean amount of physical activity on that day, and averaged over 7 days. A high activity variability indicated a stronger concentration of physical activity, while a low activity variability suggested that the participant spread his/her physical activity throughout the day more equally (Nijs et al., 2009).

Engagement in pacing

Engagement in pacing was assessed with the active engagement in pacing decisions subscale of Activity Pacing and Risk of Overactivity Questionnaire (as detailed in Alingh et al., 2015) (Appendix 1). The questionnaire was developed for use in the multicentre Dutch longitudinal cohort study ‘Rehabilitation, Sport and Active lifestyle’ and provides insight into how and based on what aspects persons modify their physical activity behaviour over the day. Participants were asked to score each of the 7 items of the complete questionnaire on a scale of 1–5 (1, never; 2, rarely; 3, sometimes; 4, often; 5, very often). This generated two subscale scores: the active engagement in pacing decisions score indicating person’s engagement in pacing (which was a primary outcome of the current study), and the perceived difficulty in preventing overactivity score relating to person's perceived risk of overactivity (which a secondary outcome of the current study). The scores of both subscales ranged from 1-5.

Fatigue

Fatigue severity was measured using the Fatigue Severity Scale (appendix 2) (Krupp et al., 1989). This unidimensional fatigue questionnaire includes nine questions, scored on a scale of 1–7 (1, completely disagree; 7 completely agree). The nine items were averaged to calculate the fatigue severity total mean score that ranged from 1 (no fatigue) to 7 (very severe fatigue). The fatigue severity scale has been proven to be a reliable and valid measurement tool to get insight into the impact of fatigue (Whitehead, 2009; Krupp et al., 1989).

Health-Related Quality of Life

Health-related quality of life was assessed by the RAND 12–Item Short-Form Health Survey (Version 1.0) Questionnaire (Selim et al., 2009) (appendix 4). The RAND–12 is a self-reported questionnaire that assesses health and well-being as rated by the respondent(s). The RAND-12 is a multidimensional health-related quality of life questionnaire that includes questions on general health, physical functioning, role limitations due to physical health problem, role limitations due to emotional problems, vitality/mental health and social functioning. The RAND-12 was scored using the recommended scoring algorithm for estimating global health (Hays, 1998). This method of scoring is based on a principle component factor analysis with orthogonal factor rotations (Ware et al., 1996). The RAND scoring approach better discriminates between known groups and appears more responsive to change in persons with MS (Nortvedt et al., 2000).

6.2.5 Data Analysis

All statistical analyses were performed using version 25.0 of the IBM Statistical Package for the Social Sciences (SPSS) software (IBM co., 2017). The statistical significance was set at alpha level (α) ≤ 0.05. All values are reported using descriptive statistics of means (M) ± standard deviation (SD) to summarise characteristics of participants.

Data were checked for normality using Shapiro-Wilk test and visually inspecting Q-Q plots. The data were generally normally distributed. Where they were not, the median and interquartile range was presented.

The relations between engagement in pacing and perceived risk of overactivity in naturalistic pacing behaviour and physical activity behaviour over the 7-day period assessed at baseline were examined using two hierarchical linear regression models with physical activity counts per minute or peak ratio as the dependent variables. This statistical approach was optimal for adjustment for covariates. In both models, at the first step, age, gender, body mass index, MS type and disease duration were entered. At the second step, fatigue and health-related quality of life were entered. At the third step, risk of overactivity was entered. At the fourth step, engagement in pacing was entered. The variance inflation factors (VIFs) of both models were examined for multicollinearity.

These variables were included in the models based on the fact that they are general demographic variables of interest in studies on physical activity behaviour and fatigue experience and on known associations between pacing, fatigue symptoms, and physical activity behaviour (Murphy et al., 2012). We chose to analyse our data using these models based on the literature and our expectation that activity pacing may be a positive strategy to manage fatigue and optimise daily activities (Abonie et al., 2018a; 2018b).

6.3 Results

Characteristics of the sample (n = 21) are shown in Table 6.1. Of the sample, 71% were male and the mean age was 59 ± 9 years. Results indicated that the sample reported severe levels of fatigue and moderate disability. Body mass index values indicated that the sample was, on average, slightly overweight according the World Health Organization standards (e.g., Body mass index ≥ 25.0).

Table 6.1 | Demographics of Participants

Variable		Range
Number of participants	21	
Age, years (M ± SD)	59.33 ± 8.67	41.00 – 71.00
Body mass index, kg/m^2 (median, IQR)	25.20 (3.40)	21.50 – 35.90
Gender, No. of men (%)	15 (71.42)	
MS type, No. of RRMS (%)	11 (52.38)	
No. of PPMS (%)	9 (42.86)	
No. of SPMS (%)	1 (4.76)	
Disease duration, year (M ± SD)	14.57 ± 11.84	1 – 38.00
Patient determined disease step (M ± SD)	3.10 ± 1.26	1 – 6
Engagement in pacing (M ± SD)	3.25 ± .74	1.60 – 4.60
Perceived risk of overactivty (M ± SD)	3.38 ± 1.02	1.00 – 5.00
Fatigue severity (M ± SD)	4.75 ± 1.61	1.00 – 7.00
Physical activity counts (median, IQR)	241.07 (144.68)	71.86 – 636.33
Physical activity variability (M ± SD)	3.96 ± .72	2.87 – 5.93
Health-related quality of life (M ± SD)	42.66 ± 8.13	31.17 – 57.07

M = Mean; PPMS = Primary Progressive MS; SPMS = Secondary Progressive MS; RRMS = Relapsing Remitting MS; SD = Standard Deviation; IQR = Interquartile range

Prior to conducting the analyses to address the primary study aims, we examined the correlations of all the variables to be included in the hierarchical linear regression model (Table 6.2). The variables were not generally very strongly correlated ($r < .8$) with each other. The highest correlation was between fatigue and health-related quality of life ($r = -.726$). Disease duration and physical disability had the second highest correlation ($r = .703$). The next highest correlations were between age and MS type ($r = -.583$), between perceived risk of overactivty and physical activity level ($r = .519$) and between MS type and disease duration ($r = -.519$). Followed by the correlations between physical activity level and physical disability ($r = -.493$), between fatigue and physical activity level ($r = -.482$), between physical activity level and physical activity variability ($r = .467$), between gender and physical disability ($r = .465$) and between age and physical disability ($r = .459$). All other correlations were of modest magnitude ($r \leq \pm.445$).

Table 6.2 | Bivariate Pearson Correlations of all variables in the hierarchical linear regression models

	2	3	4	5	6	7	8	9	10	11	12
1. Engagement in pacing	080	.075	-.381	-.418	-.101	.094	.163	-.326	-.422	.325	.166
2. Perceived risk of overactivity		-069	.519*	.041	-.132	.002	-.241	-.406	.143	.123	-.204
3. Fatigue			-.482*	-.389	-.726**	-.133	.167	.201	-.108	-.007	.181
4. Physical activity level				.467*	.235	-.223	-.137	-.342	.298	-.290	-.493*
5. Physical activity variability					.529*	-.253	-.382	.213	.304	-.434*	-.445*
6. Health-related quality of life						.146	-.134	.188	.077	-.094	-.187
7. Age							.125	-.030	-.583**	.433	.459*
8. Gender								.062	-.208	.169	.465*
9. Body mass index									-.115	-.100	.171
10. Multiple Sclerosis type										-.300	-.519*
11. Disease duration											.703**
12 Physical disability											1

* Correlation is significant at the 0.05 level ** Correlation is significant at the 0.01 level

Relationship between engagement in pacing and physical activity level

The relationship between physical activity counts per minute and engagement in pacing was examined, controlling for demographic variables, perceived risk of overactivity, fatigue and quality of life in a hierarchical linear regression model (Table 6.3).

Table 6.3 | Hierarchical multiple regression analysis with physical activity level as the dependent variable.

Step	Predictor	β^a	β^b	β^c	β	ΔR^2
1						.323
	Age	-.017	-.060	-.160	-.200	
	Gender	.124	.183	.170	.213	
	Body mass index	-.253	-.114	-.043	-.239	
	MS type	.017	.082	-.085	-.129	
	Disease duration	.047	.015	-.238	-.087	
	Physical disability	-.526	-.438	-.181	-.213	
2						.161
	Fatigue		-.561	-.503	-.351	
	Health-related quality of life		-.193	-.069	.049	
3						.175*
	Perceived risk of overactivity			.515*	.494*	
4						.141*
	Engagement in pacing				-.438*	

[a] Standardised regression coefficients are from the complete regression model not accounting for fatigue and health-related quality of life.

[b] Standardised regression coefficients are from the complete regression model not accounting for perceived risk of overactivity.

[c] Standardised regression coefficients are from the complete regression model not accounting for engagement in pacing.

*$p < .05$ two-tailed.

At step 1, the demographic variables did not explain a significant amount of variance in physical activity, R^2 = .323, F (6, 14) = 1.113, p =.403. At step 2, fatigue and health-related quality of life did not explain a significant amount of variance in physical activity, ΔR^2= .161, ∆F (2, 12) = 1.871, ∆p = .196. At step 3, perceived risk of overactivity explained a significant amount of variance in physical activity, ΔR^2 = .175, ∆F (1, 11) = 5.642, ∆p= .037. In the final model with all variables entered, engagement in pacing explained 14.1% of the variability in physical activity above and beyond perceived risk of overactivity, ΔR^2 = .141, ∆F (1, 10) = 7.084, ∆p= .024. A negative relationship between engagement in pacing and physical activity was found. Higher engagement in pacing was associated with lower physical activity (β = -.438, *t* [10] = -2.662, *p* = .024). Also, a higher perceived risk of overactivity was associated with increased physical activity (β = .494, *t* [10] = 2.837, *p* = .018).

Relationship between engagement in pacing and physical activity variability

The relationship between physical activity variability and engagement in pacing assessed was examined, controlling for demographic variables, perceived risk of overactivity, fatigue and quality of life in a hierarchical linear regression model (Table 6.4).

Table 6.4 | Hierarchical multiple regression analysis with physical activity variability as the dependent variable.

Step	Predictor	β[a]	β[b]	β[c]	β	ΔR^2
1						.343
	Age	-.002	-.145	-.176	-.196	
	Gender	-.237	-.225	-.229	-.208	
	Body mass index	.258	.173	.195	.095	
	MS type	.066	.083	.030	-.008	
	Disease duration	-.187	-.252	-.330	-.253	
	Physical disability	-.215	.007	.087	.070	
2						.197
	Fatigue		-.148	-.130	-.052	
	Health-related quality of life		.362	.410	.461	
3						.017
	Perceived risk of overactivity			.159	.149	
4						.037
	Engagement in pacing				-.225	

[a] Standardised regression coefficients are from the complete regression model not accounting for fatigue and health-related quality of life.

[b] Standardised regression coefficients are from the complete regression model not accounting for perceived risk of overactivity.

[c] Standardised regression coefficients are from the complete regression model not accounting for engagement in pacing.

At step 1, the demographic variables did not explain a significant amount of variance in the in physical activity variability, $R^2 = .343$, $F(6, 14) = 1.221$, $p = .353$. At step 2, fatigue and health-related quality of life did not explain a significant amount of variance in physical activity variability, $\Delta R^2 = .197$, $\Delta F(2, 12) = 2.576$, $\Delta p = .117$. At step 3, perceived risk of overactivity did not explain a significant amount of variance in physical activity variability, ΔR^2 = .017, ΔF (1, 11) = .417, Δp= .532. In the final model with all variables entered, engagement in pacing did not explain a significant amount of variance in physical activity variability, ΔR^2= .037, ΔF (1, 10) = .918, Δp = .361. Despite not reaching statistical significance, higher engagement in pacing tended to be associated with lower physical activity variability (β = -.225, t [10] = -.958, p = .361).

For all analyses, the variance inflation factors (VIFs) were low showing that there was no problem of multicollinearity (range: 1.28–3.79)

6.4 Discussion

This study is the first to explore the relationship between self-reported engagement in pacing and perceived risk of overactivity in naturalistic pacing behaviour and physical activity behaviour objectively measured using accelerometry in adults with multiple sclerosis. Bivariate correlation analysis to test for multicollinearity conducted prior to testing the study hypotheses revealed there was strong negative association between fatigue and health-related quality of life, and strong positive associations between disease duration and physical disability.

There were also moderate positive associations between perceived risk of overactivity and physical activity level, between physical activity level and physical activity variability, between age and physical disability, and between gender and physical disability. Furthermore, there were moderate negative associations between physical activity level and fatigue, between physical activity level and physical disability, between physical activity variability and physical disability, between physical activity variability and disease duration, between age and MS type, and between MS type and physical disability.

With regard to the main analysis to test the study hypotheses, results showed that lower physical activity levels were associated with higher engagement in pacing and higher physical activity levels were related to higher perceived risk of overactivity.

These relationships remained after controlling for other factors such as perceived risk of overactivity in daily life, level of disability and fatigue experience.

The lower physical activity levels associated with engagement in pacing found in this study can be interpreted in two ways. First, this suggests persons with lower physical activity levels may be to too careful in their engagement in pacing and may be using pacing as alternative avoidance behaviour towards physical activity to prevent exacerbation of symptoms. On the other hand, they may be experiencing more disruption from fatigue in their daily life and may have resorted to pace activities to prevent symptoms from further worsening. This is in line with the notion that self-reported natural use of pacing may be a reactionary response to increased symptoms and associated with lower physical activity level (Murphy et al., 2008; 2012; Murphy and Kratz, 2014).

However, higher physical activity levels were related to higher perceived risk of overactivity in daily life. Studies have shown that persons with high physical activity levels experience less fatigue (Andersson et al., 2015; Rongen-van Dartel et al., 2014; Husson et al., 2015). Since these persons experience less disruption through fatigue in daily life they may consequently resort to the execution of too many or too long periods of activity which may cause overactivity. With overactivity evident to lead to disability and poor health outcomes (Andrews et al., 2012), there is a need to encourage and counsel individuals with MS who exhibit overactive behaviours to approach activity in an effective way.

With regards to physical activity variability, no significant associations were found between engagement in pacing and physical activity variability, or between perceived risk of overactivity and physical activity variability. The finding that natural levels of pacing are not significantly related to daily variability in activity was similar to that reported by Murphy et al., (2012) in their study of the association between activity pacing and activity variability in a sample of adults with hip or knee osteoarthritis. The lack of associations between physical activity variability and engagement in pacing and perceived risk of overactivity indicates the complexity of the behaviour and the need for further exploratory studies.

Exploring engagement in pacing and perceived risk of overactivity in the daily life of persons with MS may be one way to identify the target group who would most benefit from intervention to approach physical activity efficiently, and accordingly adapt interventions for successful outcomes. The findings of this study indicate that people with MS may either be too careful in their pacing behaviour or use pacing as a maladaptive reactionary response to increased fatigue-related symptoms. Consequently, persons with MS may require guidance on the anticipatory use of pacing to prevent overactive and avoidance behaviours towards physical activity, and to manage symptoms and promote physical activity important for health.

Our findings can be generalized only to adults with MS; the chronic condition sampled is likely an important distinction as physical activity behaviour may vary by condition (Kayes et al., 2011). Secondly, because this sample was primarily English, findings are limited in their generalizability to a more diverse population. In addition, the small sample size, atypical high percentage of men and older persons with MS are limitations of the study, as MS affect almost three times as many women as men, and most people diagnosed between the ages 20 and 40 years. The lack of significant association between engagement in pacing and physical activity variability, and between perceived risk of overactivity and physical activity variability found in the test for multicollinearity prior to the main analysis may have accounted for the lack of associations in the main analysis, and is a limitation of this study.

Strengths of the study include the novel approach to explore the association between engagement in pacing during their daily routines and actual physical activity behaviour during daily routines measured by accelerometry, using hierarchical regression modelling. To our knowledge, this is the first known study to explore how activity pacing affect how adults with MS actually engage in physical activity. This could provide valuable insights to help find the target group who may benefit from interventions to engage in an active lifestyle, as well as offering timely advice and guidance tailored to their specific physical activity behaviour, engagement in pacing or perceived risk of overactivity. The findings of this study consequently provide the basis to develop and design interventions to keep people with MS physically active while their experience and expectation of fatigue in relation to engagement in physical activity is adequately managed. Incorporating such interventions in physical activity promotion and comparable programmes aimed to optimally advice persons with MS to engage in active lifestyle could lead to better treatment outcomes.

6.5 Conclusion

In summary, this study examined physical activity behaviour using accelerometry, and engagement in pacing and perceived risk of overactivity in the daily routines of adults with multiple sclerosis. Lower physical activity levels were found to be associated with higher engagement in pacing behaviour, and higher physical activity levels were found to be associated with a higher perceived risk of overactivity in persons with MS. From these findings, we surmise that the natural use of pacing may be a complex behaviour that may be directed by factors such as need to cope with problematic symptoms. This suggests that persons may either be too careful in their pacing behaviour or resort to the execution of too many activity. Persons with lower physical activity levels and higher perceived risk of overactivity may benefit from targeted interventions to improve their physical activity behaviour. On the basis of this study, we suggest that individualised guidance on optimal use of pacing as an anticipatory strategy to promote physical activity important for health needs to be incorporated in physical activity promotion programmes for persons with MS. More research is needed to determine how the use of pacing (both use of pacing naturally and after pacing instruction) affects physical activity variability over longer periods of time.

CHAPTER 7

Effect of a tailored activity pacing intervention on fatigue, physical activity and health-related quality of life in adults with multiple sclerosis: A pilot study

Abstract

Our previous exploratory studies support a tailored approach to activity pacing to manage fatigue and to improve physical activity. However, there is a gap in literature on how to tailor activity pacing for people with fatigue complaints, such as people with MS. The aim of this study was to evaluate the effectiveness of a tailored activity pacing intervention based on attitudes towards pacing, physical activity and fatigue, in improving fatigue, physical activity and health-related quality of life in adults with MS.

21 adults with MS (age 59 ± 9 yrs.) were randomly allocated to a tailored activity pacing (n = 11) or a control group (n = 10). All participants wore an ActiGraph accelerometer for 7 days that measured activity level and variability, and reported their engagement of pacing and perceived risk of overactivity, leisure time activity, health-related quality of life and fatigue severity and expectation, using the Activity Pacing and Risk of Overactivity Questionnaire, adapted SQUASH, RAND-12 Item Health Survey, Fatigue Severity Scale and a 1-Item Survey respectively at baseline and 4-week follow-up.

Compared to the control group, the tailored activity pacing group demonstrated increased activity levels (22.79 ± 44.70 vs. -18.11 ± 36.07; p =.03) and decreased activity variability (-.10 ± .53 vs. .53 ± .80; p =.04). No group differences in fatigue severity (-.10 ± .75 vs. .26 ± .70; p =.27), fatigue expectation (-.36 ± .81 vs. .00 ± .47; p =.23), health-related quality of life (2.76 ± 6.12 vs. -.93 ± 3.8; p =.12), self-reported activity (346.55 ± 498.48 vs. 600.00 ± 1128.78; p =.51), engagement in pacing (-.25 ± .42 vs. .10 ± .65; p =.15) and perceived risk of overactivity (-.09 ± 1.09 vs. .35 ± 1.00; p = .35) were found.

Tailoring activity pacing based on attitudes towards pacing, physical activity and fatigue experience was effective in improving activity levels and reducing activity variability without exacerbating fatigue in adults with MS. This provides the basis to incorporate activity pacing interventions in health promotion programmes for people with MS to better manage fatigue and optimise their engagement in physical activity important for health, mobility and participation.

7.1 Introduction

A physically active lifestyle is considered an important health promoting behaviour for all populations and has the potential to preserve and improve physical and mental health, as well as quality of life. Equally, a physically active lifestyle is associated with a gain of 4.5 years of life matched to being inactive (Jones et al., 2015), even in previously sedentary and chronically diseased persons, including persons with MS (Simmons et al., 2004; Stuifbergen, 1992; Moore et al., 2012).

However, engagement in physical activity is difficult for people with MS as fatigue worsens throughout the course of the day and has a profound impact on activities of daily living, which subsequently perpetuate fatigue severity and physical disability (van den Berg-Emons et al., 2010; Motl et al., 2005; 2006). This highlights the need to develop effective interventions for enabling physically active lifestyles in persons with MS.

In this context, activity pacing has the potential to play a role in stimulating an active lifestyle in people with MS over time; such that their experience and expectations of fatigue in relation to their engagement in physical activity are well-managed, and physical functioning maintained to enable continued participation in daily activities. Activity pacing is defined as a strategy to divide one's daily activities into smaller, more manageable, portions, in a way that should not exacerbate their symptoms, which then allows gradual progressive increases in activity (Andrews et al., 2012).

The rationale for activity pacing intervention can be found in several strategies observed in persons with MS such as reduced activity levels resulting from and in anticipation of fatigue (Van Kessel et al., 2006; Skerrett & Moss-Morris, 2006). Similarly, people with MS exhibit unevenly distributed activity patterns: activity peaks are followed by very long rest periods (Sutherland et al., 2001), and an ability to perform short periods of light to moderate activity without exacerbating symptoms (Dodd et al., 2006; Smith et al., 2009).

The premise that both underactivity and overactivity are linked to physical activity decline and its further negative consequences, gives further basis towards the introduction of activity pacing as a potential positive strategy to prevent major symptoms of fatigue to occur while maintaining sufficient physical activity levels (Andrew et al., 2012; Butler et al., 2003). Thus activity pacing has the potential to alter inefficient activity patterns such as the underactivity-overactivity cycles found in persons with MS.

Our previous exploratory studies showed that fatigue was related to quality of life in the short and long term, and perceived risk of overactivity moderated the relationship between fatigue and quality of life at the long-term in persons with MS (Abonie et al., 2018c; 2018d). More importantly, we found engagement in pacing and perceived risk of overactivity were related to lower activity level and higher activity level respectively (Abonie et al., 2018e). These findings suggest that guidance on optimal use of pacing may be beneficial for persons with MS to improve their fatigue symptoms and physical activity behaviour.

However, evidence on formal instructions or guidance in activity pacing is limited (Antcliff et al., 2013; 2015). Furthermore, studies examining the effect of activity pacing interventions were done in populations with a range of chronic disabling conditions, other than MS (Murphy et al., 2012; 2008; 2010 Murphy and Kratz, 2014; Nijs et al., 2009), with most interventions targeting problematic symptoms that arise from overactivity (White et al., 2011; Kos et al., 2015; Murphy et al., 2008; 2012; Nijs et al 2009). This however represent a pitfall in literature as also underactivity has been evident to link to functional impairment (Birkholtz et al., 2004).

It is possible that previous interventional study designs that reported poor outcomes may have been sampled from persons with prior underactive behaviour for whom instructions regarding prevention of overactivity is likely to be non-beneficial, while positive outcomes may have been obtained in an overactive sample of the population. Thus interventions modelled on the assumption that overactivity needs to be prevented are less likely to be effective in underactive persons. Accordingly, it is imperative to consider the physical behaviour and attitudes towards physical activity of individuals when delivering activity pacing interventions.

This, together with the valuable insights provided by our meta-analysis and exploratory studies exploring relations between attitudes towards activity pacing, fatigue, physical activity and quality of life (Abonie et al., 2018b; 2018c; 2018d; 2018e), point to the fact that an individually tailored activity pacing approach based not only on a person's symptoms profile but also on their physical behaviour and attitudes towards physical activity assessed at baseline is needed to improve the success of activity pacing intervention. To our knowledge, no work has explored the effect of a tailored activity pacing approach based on attitudes and behaviour towards physical activity in promoting an active lifestyle and managing fatigue in people with MS.

The purpose of this study was thus to examine the effectiveness of a tailored activity pacing intervention based on providing information about individual's engagement in pacing, perceived risk of overactivity, fatigue experience and physical activity patterns, and targeting activity spread throughout the day in lowering fatigue and perceived risk of overactivity and improving physical activity level, physical activity variability and health-related quality of life in adults with MS.

We based our hypotheses on the findings of our previous meta-analysis and exploratory studies (Abonie et al., 2018b; 2018c; 2018d). We hypothesized that tailoring activity pacing to the individual's attitude towards physical activity will lead to decreased fatigue, increased physical activity level, decreased physical activity variability, better quality of life and lower perceived risk of overactivity in people with MS.

7.2 Method

7.2.1 Participants

Community-dwelling adult participants were recruited from MS-UK centre and MS Society focus group through public advertisements (online and e-posters) in Colchester, Essex. Recruitment was conducted by contacting facilitators of local self-help groups. Those interested in participation were contacted by the researchers who explained the study rationale, potential benefits, procedures, answered all questions, conducted a brief screening, and, in the event of meeting inclusion criteria and voluntarily agreeing to participate, a written informed consent was obtained. The study protocols were approved by the Ethics Board at the University of Essex. Participants were asked to inform the researcher of change or initiation of any medical or conservative treatment during the study period. We did not record the types of medication used but did monitor changes in medication use in the study period.

Participants were included if they were age 18 years or older, had an established definite diagnosis of MS, been relapse free during the last 30 days, and ambulatory (with or without an assistive device), could reliably wear the ActiGraph accelerometer used in the study, and were English-speaking. People were excluded if non-ambulatory (unable to walk with or without an assistive device), if they had experienced a relapse in the past month, if they had changed medications within the past 2 weeks that could interfere with symptom ratings or accelerometer data, or if they had currently or recently (in the previous 12 months) received activity management or behavioural therapy that included activity pacing instruction.

7.2.2 Procedure

Recruitment for this study began in July 2017 and ended in October 2017. The main data collection periods were at baseline and at 4 week follow-up. We thought that application of the techniques and advice from the intervention session targeting an even spread of physical activity through the day could be adequately integrated into daily routines within that follow up period. At the baseline visit, demographic and health status information was collected. Background demographics included age, gender, MS diagnosis, self-reported duration of illness (years since diagnosis), body mass index; calculated from measured weight (kg) / height $(m)]^2$ and physical disability, assessed using the Patient Determined Disease Steps (PDDS) (Marrie and Goldman, 2007). All participants were then instructed on wearing an accelerometer on their waist and use the accompanying log book to record fatigue experience, activity pacing behaviours and daily activities during the seven days home monitoring period. The accelerometer measured physical activity and participants were also asked to keep it at all times except on occasions when it could become wet (e.g., showering or swimming). Participants recorded their fatigue experience, activity pacing behaviours and daily activities three times per day (morning, afternoon and 30 minutes before bed) in addition to wake-up and bed times each day in the logbook. After the home monitoring period, participants returned the accelerometer and logbook and completed questionnaires. Participants were then stratified by age and gender and randomized into the intervention group or the control group. Participants were asked to blindly pick a folded paper marked with “intervention” or “control” out of a box. The intervention began within the week after the baseline assessment. At 4 week follow-up, all participants wore the accelerometer for a seven day home monitoring period and completed the same set questionnaires as at baseline. To prevent test order and administration bias, participants completed the questionnaires in random order and alone without input from the researcher.

7.2.3 Tailored Activity Pacing Intervention

Activity pacing was tailored based on a personalised report that summarised and depicted each person's physical activity pattern, fatigue experience, engagement in pacing and perceived risk of overactivity assessed at baseline. Specifically, the waist-worn accelerometer and fill in logbook during the home monitoring period were used to collect data on person's fatigue experience, physical activity patterns and attitudes and behaviour towards physical activity. The data were used to generate personalised reports that summarised and visually depicted each person's symptom-activity relationship based on their physical activity and fatigue, physical activity patterns and attitudes and behaviour towards physical activity. This gave a representation of person's attitudes and behaviour towards physical activity such as avoidance behaviour and all-or-nothing behaviour. In the tailored group, this information was used to formulate individual activity pacing goals.

For those whose summarised personalised report gave a picture of avoiding physical activity in response to fatigue or limiting their activities in the fear of a relapse, they were provided with information on perceptions and expectations with respect to activity related symptoms and strategies to develop graded consistent physical activity to increase their physical activity level and fitness, as well as given information on strategies to help change their beliefs that "I should do less if I am tired" or "symptoms are always a sign that I am damaging myself."

Similarly, those whose summarised personalised report exemplified an all-or-nothing behaviour style (overdoing activities when feeling better, resulting in worsen fatigue and then needing to rest for prolong periods to recover were provided with information on developing a consistent pattern of paced activity and rest and gradual increase in physical activity. The principles of this intervention were chosen for their potential to impact the overactivity–underactivity cycle in MS. The intervention was to provide information on developing an even spread of daily activities. The intervention session was approximately 30–60min long – this depended on the participant.

7.2.4 Outcome Measures

Engagement in pacing and perceived risk of overactivity

Engagement in pacing and perceived risk of overactivity were assessed with the Activity Pacing and Risk of Overactivity Questionnaire (as detailed in Alingh et al., 2015) (Appendix 1). This new questionnaire was developed for use in an ongoing multicentre longitudinal cohort study (Rehabilitation, Sport and Active lifestyle) and has provided more insight into the different components of the concept of activity pacing, giving a better understanding of the nature of activity pacing (Abonie et al,. 2018c; 2018d, 2018e). The items of the questionnaire were based on previous research about activity pacing, indicating the importance of engagement in pacing behaviour as well as perceived risks of overactivity. Participants were asked to score each of the 7 items of the questionnaire on a scale of 1–5 (1, never; 2, rarely; 3, sometimes; 4, often; 5, very often). This generates two subscale scores that ranged from 1 to 5: the engagement in pacing score indicates person's active engagement in pacing decisions and the perceived risk of overactivity score corresponds to person's perceived difficulty in preventing overactivity within their daily routines.

Fatigue

Fatigue severity was measured using the Fatigue Severity Scale (appendix 2) (Krupp et al., 1989). This unidimensional fatigue questionnaire includes nine questions, scored on a scale of 1–7 (1, completely disagree; 7 completely agree). The nine items were averaged to calculate the fatigue severity total mean score that ranges from 1 (no fatigue) to 7 (very severe fatigue). The fatigue severity scale has been proven to be a reliable and valid measurement tool to determine the impact of fatigue and to detect change over time (Whitehead, 2009; Krupp et al., 1989).

Fatigue expectation in relation to physical activity was a secondary outcome measure. Since no generic questionnaire was available yet, fatigue expectation in relation to physical activity was assessed with a single Item Questionnaire scored on a scale of 1–5 (1, not at all; 5, extremely) (appendix 5). The item read, “Do you expect to be fatigued from physical activities?”

Health-Related Quality of Life

Health-related quality of life was assessed by the RAND 12–Item Short-Form Health Survey (Version 1.0) Questionnaire (Selim et al., 2009) (appendix 4). The RAND–12 is a self-reported questionnaire that assesses health and well-being as rated by the respondent(s). The RAND-12 is a multidimensional health-related quality of life questionnaire that includes questions on general health, physical functioning, role limitations due to physical health problem, and role limitations due to emotional problems, vitality /mental health and social functioning. The RAND-12 was scored using the recommended scoring algorithm for calculating global health (Hays, 1998). The score ranged from 18 to 62. This method of scoring is based on principle component factor analysis with orthogonal factor rotations (Ware et al., 1996). The RAND scoring approach better discriminates between known groups and appears more responsive to change in persons with MS (Nortvedt et al., 2000).

Physical Activity

Self-reported level of daily physical activity was assessed with an adapted version of the Short Questionnaire to Assess Health-Enhancing Physical Activity (Wendel-Vos et al., 2003) (appendix 3). The Short Questionnaire to Assess Health-Enhancing Physical Activity is a self-reported recall questionnaire to assess daily physical activity of healthy adults based on an average week in the past month. The Short Questionnaire to Assess Health-Enhancing Physical Activity was adapted to make it applicable for people with a physical disability. The self-reported intensity was categorised as ‘light’, ‘moderate’ and ‘vigorous’, instead of ‘slow’, ‘moderate’ and ‘fast’ and scored on a scale of 1–9. Total minutes of physical activity per week was calculated by multiplying frequency (days/week), duration (minutes/day) and intensity score. The original Short Questionnaire to Assess Health-Enhancing Physical Activity has demonstrated good test-retest reliability and internal consistency and moderate concurrent validity in ordering participants according to their level of physical activity in an adult population (Wendel-Vos et al., 2003) and in several patient groups (Arends et al., 2013; Wagenmakers et al., 2008).

Waist-worn accelerometers (ActiGraph GT3X+, LLC, Fort Walton Beach, FL) were used for real-time monitoring of physical activity behaviour. These devices can accurately measure activity counts between subjects of various ages (Focht et al., 2003). De Vries (2006) reported that the ActiGraph series was the most studied activity monitor, and many studies have validated its reliability and performance. The GT3X+ uses a triaxial accelerometer for more accurate physical activity monitoring. Changes in acceleration were recorded into the accelerometer as activity counts, saved every 10 s, and then averaged each minute. The resulting unit of measurement is activity counts per minute. Activity counts were computed based on a pre-defined algorithm cut points; Freedson Adults VM3, 1998 (Sasaki et al., 2011). Total physical activity was calculated by averaging the cumulative activity counts per minute over 7 days.

Besides the activity counts per minute, the pure, untransformed data generated by the accelerometer were used to calculate peak ratio which indicates variability in physical activity patterns. The peak ratio for each day was calculated as the amount of physical activity during the peak activity hour for each day (identified as the hour with the highest number of activity counts) divided by mean amount of physical activity on that day, and averaged over 7 days. A high peak ratio indicated high activity variability and a stronger concentration of physical activity, while a low peak ratio activity suggested low variability and that the participant spread his/her physical activity throughout the day more equally (Nijs et al., 2009).

Participants also kept a logbook during the home monitoring periods (appendix 6). The logbook contained a 0-4 VAS scale used to rate activities (0, no activities; 1, little activities; 2, moderate activities; 3, several activities; 4, extreme number of activities), fatigue (0 = no fatigue, 1= mild fatigue, 2 = moderate fatigue, 3 = severe fatigue, 4 = extremely severe fatigue) and activity pacing (0 = not at all, 1= very little, 2 = sometimes, 3 = most of the time, 4 = always). Participants were asked to fill out the VAS scales three times a day; in the morning, at noon (immediately after lunch) and in the evening (before going to bed). Data and information generated from the logbook were used to tailor the intervention and were not used in further analysis.

7.2.4 Data Analysis

All statistical analyses were performed using version 25.0 of the IBM Statistical Package for the Social Sciences (SPSS) software (IBM co., 2017). The statistical significance was set at alpha level (α) ≤ 0.05. All values were reported using descriptive statistics of means ± standard deviation (SD) to summarise characteristics of participants.

A mean fatigue severity scale score greater or equal to 4 has been used by others as the cut off indicating clinically significant fatigue in MS (Smedal et al., 2011), and was adopted as the cut-offs in the present study. Higher scores indicate a greater effect of fatigue on daily activities. A reduction in mean score of 0.5 points was considered to be clinically significant.

For intention-to-treat analyses, all eligible participants were included, and missing data were carried forward from earlier results (notionally designating conservative outcomes of non-improvement over time). Independent-sample two-tailed t-tests were conducted to compare variables between groups. Data were checked for normality using Shapiro-Wilk test and visually inspecting Q-Q plots. The data were generally normally distributed. Where they were not, the t-test outcome was verified with a non-parametric test.

Outcomes were analysed by univariate analysis of variance (ANOVA) two-tailed tests of change scores from baseline to follow up. Level of significance for all statistical analyses was set at the .05 α-level. Because the small sample size likely affects the power to detect small to moderate effects, the effect size d is also presented for these analyses (Cohen, 1988). Effect sizes were calculated as t score divided by the square root of n (Borenstein, 2009) and interpreted according to Cohen's d (Cohen, 1988). Effect sizes of 0.20 are considered small, 0.50 moderate, and 0.80 large.

7.3 Results

Participant Flow and Participant characteristics

Among the 30 individuals who were identified as eligible to participate and who were informed about the study, 24 individuals were randomly assigned to either the tailored information or the control condition and 21 recruited into the study with adequate baseline measures completed (intervention condition: n = 11; control condition: n = 10). The flow of participants through the study and reasons for exclusions and withdrawals are displayed in Figure 7.1. Demographics and baseline measures of participants are presented in Table 7.1.

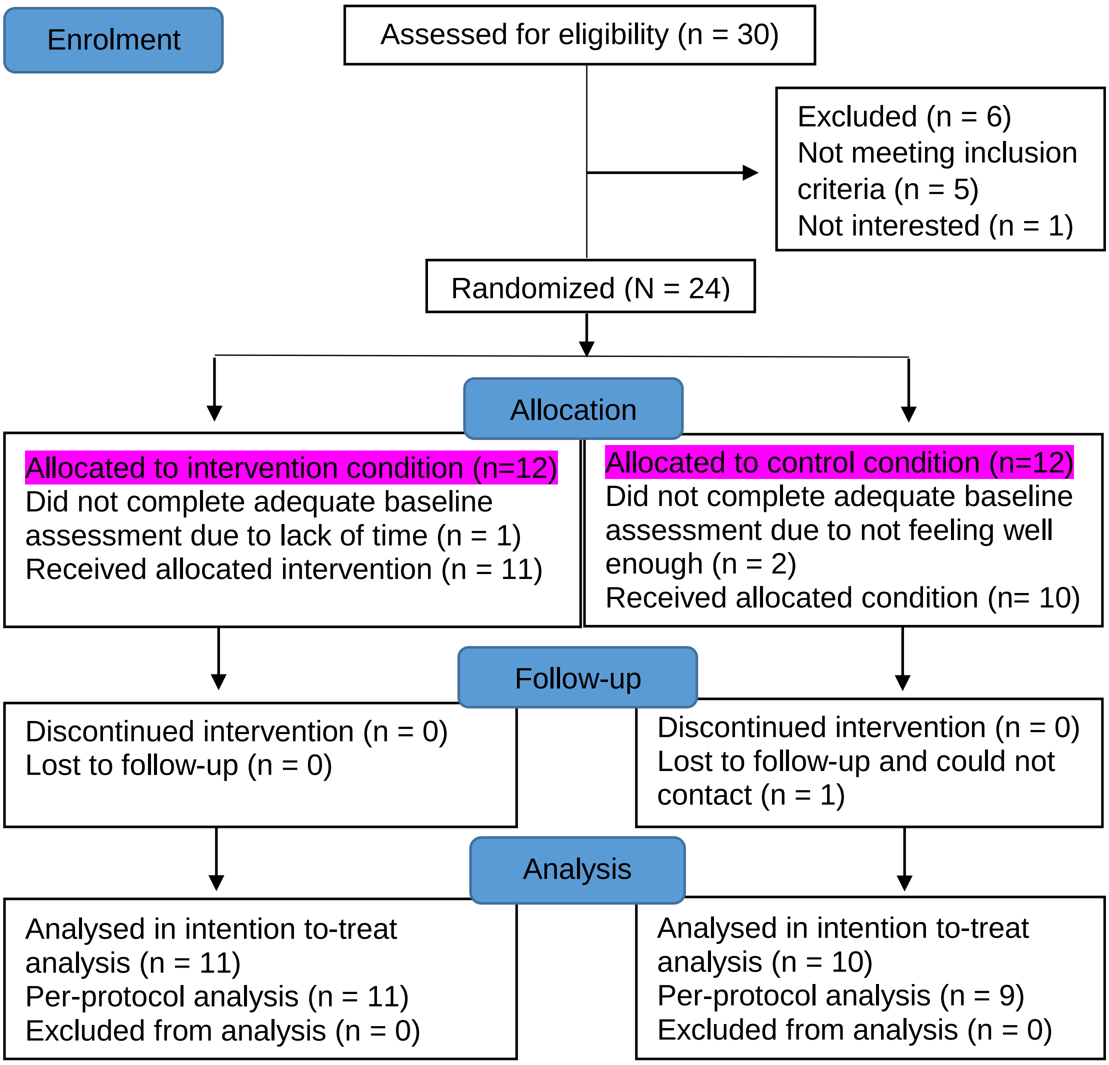


Figure 7.1 Flow diagram of participants through the intervention

Table 7.1 Descriptive Characteristics of Participant

Variable	Tailored Information Group	Control Group	p
Number of participants	11	10	
Age, year (M ± SD)	57.91 ± 7.98	60.90 ± 9.55	.444
Body mass index, kg/m^2 (median, IQR)	25.20 (3.90)	25.10 (7.65)	.310
Gender, No. of males (%)	8 (73)	7 (70)	.897
MS type, No. of RRMS (%)	6 (60)	4 (40)	.610
No. of PPMS (%)	1 (50)	1 (50)	
No. of SPMS (%)	4 (55)	5 (50)	
Disease duration, year (median, IQR)	12.00 (24.00)	9.50 (19.50)	.551
PDDS disability scale (median, IQR)	2.00 (2.00)	3.50 (2.00)	.727
Fatigue severity (M ± SD)	4.70 ± 1.96	4.81 ± 1.23	.876
Expectation of fatigue (median, IQR)	4.00 (1.00)	3.50 (1.25)	.466
Activity level, cpm (median, IQR)	296.46 (149.24)	195.19 (131.66)	.063
Activity variability (M ± SD)	3.99 ± 0.87	3.93 ± 0.55	.869
Self-reported PA, min/wk (median, IQR)	720 (1320.00)	2175.00 (3213.75)	.091
Health-related quality of life (M ± SD)	43.01 ± 8.59	42.27 ± 8.04	.840
Engagement in Pacing (M ± SD)	3.25 ± 0.76	3.24 ± .75	.965
Perceived risk of overactivity (M ±SD)	3.55 ± 1.27	3.20 ± .67	.454

cpm = counts per minutes; IQR = interquartile range; M = mean; min/wk = minutes per week; PA = Physical activity; PDDS = Patient Determined Disease Steps; PPMS = Primary Progressive MS; RRMS = Relapsing Remitting MS; SD = standard deviation; SPMS = Secondary Progressive MS.

The sample (n = 21) was 71% male, and the mean age was 59.33 ± 1.89 years. 76% of the sample had clinically significant fatigue (A mean fatigue severity scale score greater or equal to 4). There were no statistically significant differences between the groups at baseline. However, compared with the control group, participants in the tailored information group were slightly younger (57.91 ± 7.98 vs. 60.90 ± 9.55 years, p =.44) and had less reported fatigue on the fatigue severity scale at baseline (4.70 ± 1.96 vs. 4.81 ± 1.23, p =.88). Compared to the intervention group, participants in the control group had higher expectation of fatigue (3.37 ± .67 vs. 3.80 ± .79, p =.19).

Physical activity levels were similar across groups at baseline. Specifically, the way physical activity was spread through the day by group was very similar (intervention: 3.99 ± 0.87 versus control: 3.93 ± 0.55, p=.87). Two participants discontinued due to illness, work or family commitments. One participant completed baseline self-report questionnaires allowing an intention-to-treat analysis to be conducted.

7.3.1 Influence of tailored activity pacing intervention

The descriptive data of the tailored activity pacing intervention effect at 4–weeks follow-up are presented in appendix 7.

A clinically-significant improvement in fatigue was observed in 2 of 11 participants in the tailored activity pacing intervention group compared to 1 of 10 in the control group (p = 0.10, X^2) at 4–weeks follow-up. In support of this response designation, these participants had a more significant mean reduction in expectation of fatigue in relation to engagement in physical activity of M=-1.00, SD=1.00 compared to participants who had no clinically significant improvement in fatigue (M=-.056, SD=.54; t(19)= 2.50, p=0.02). From the control group, two participants deteriorated (increase in mean fatigue severity scale score by 0.5 points) at 4–weeks follow-up. Only one participant from the tailored activity pacing intervention group reported deterioration.

Physical Activity

For physical activity-related variables, there was a significant increase in the physical activity level (counts per minute) from baseline to follow-up (mean difference [M_{diff}] = 40.91, 95% CI: 3.84 – 77.96, p =.03). Activity level increased in the intervention group (M = +22.79, SD = 44.70) and decreased in the control group (M = -18.11, SD = 36.07). This indicated an effect size of d = 1.06 (Table 7.2).

Furthermore, there was a significant group difference in physical activity variability (the way physical activity was spread throughout the day) between baseline and follow-up (M_{diff} = -.63, 95% CI: -1.25 – .00, p = .04). Participants in the intervention group had a more even spread of activities throughout the day (M = -.10, SD = .53) compared to the control group (M = .53, SD = .80). This indicated an effect size of d = .99 (Table 7.2).

There was no significant difference in self-reported physical activity (minutes per week) from baseline to follow-up measured with the Short Questionnaire to Assess Health-Enhancing Physical Activity between the intervention and the control group (M_{diff} = -253.5, 95% CI: -10337.12 – 530.21, p = .51) (Table 7.2).

Fatigue

There was no significant group difference in fatigue severity score (M_{diff} = -.36, 95% CI: -1.02 – .30, p = 0.27) between baseline and 4-weeks follow-up. However, participants in the intervention group appear to have lower fatigue severity (M = -.10, SD = .75) in comparison to the control arm (M = .26, SD = .70) (Table 7.2).

For expectation of fatigue in relation to activity, participants in the intervention group seem to have decreased expectation of fatigue from baseline to follow-up (M = -.36, SD = .81) in comparison to the control arm (M = .00, SD = .47). However, the difference in change score was not statistically significant (M_{diff} = -.36, 95% CI: -.97 – .24, p = .23) (Table 7.2).

Table 7.2 Changes in outcomes between baseline and follow up

Outcome	Group	Change Score	Mean Difference (95%CI)	F	p	d
Fatigue severity	Int	-.10 ± .75	-.36 (-1.02 – .30)	1.273	.273	.52
	Con	.26 ± .70				
Fatigue expectation	Int	-.36 ± .81	-.36 (-.97 – .24)	1.540	.230	.57
	Con	.00 ± .47				
Activity level (cpm)	Int	22.79 ± 44.70	40.91 (3.84 – 77.96)	5.338	.032	1.06
	Con	-18.11 ± 36.07				
Activity variability	Int	-.10 ± .53	-.63 (-1.25 – .02)	4.661	.044	.99
	Con	.53 ± .80				
Self-reported PA	Int	346.55 ± 498.48	-253.5 (-10337.12–530.21)	.458	.507	.31
(minutes/week)	Con	600.00 ± 1128.78				
Health-related	Int	2.76 ± 6.12	3.70 (-1.03 – 8.42)	2.678	.118	.75
quality of life	Con	-.93 ± 3.85				
Engagement in	Int	-.25 ± .42	-.35 (-.85 – .14)	2.255	.150	.69
pacing	Con	.10 ± .65				
Perceived risk of	Int	-.09 ± 1.09	-.44 (-1.40 – .51)	.924	.348	.44
of overactivity	Con	.35 ± 1.00				

Values are presented as mean ± standard deviation; con = control; cpm = counts per minute; d = Cohen's d effect size; Int = intervention; PA = physical activity

Health Related Quality of Life

There was no significant group difference in health related quality of life change score from baseline to follow-up (M_{diff} = 3.70, 95% CI: -1.03 – 8.42, p = .12). Taking a closer inspection of the groups change scores, participants in the intervention group appear to have improved health related quality of life (M = +2.76, SD = 6.12), compared to those in the control group (M = -.93, SD = 3.85) (Table 7.2).

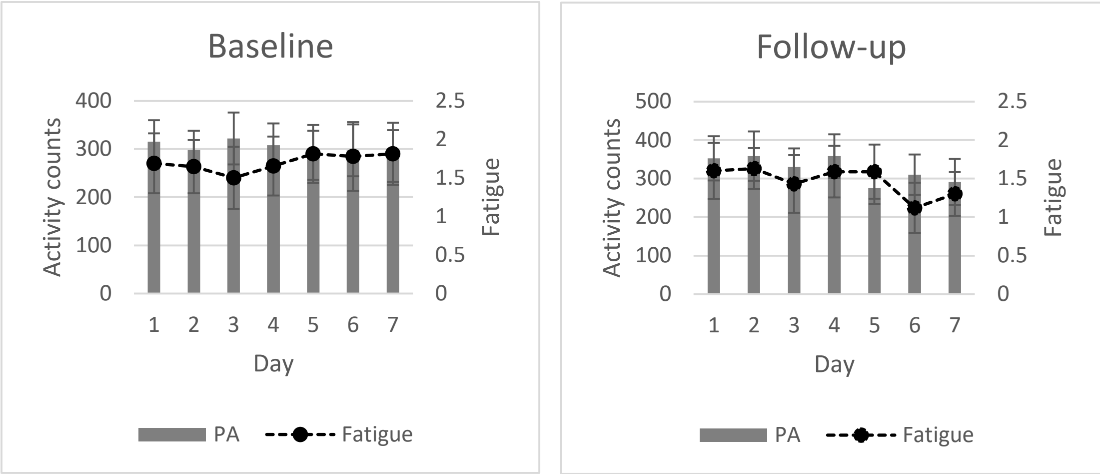
Engagement in pacing and perceived risk of overactivity

There was no significant group difference in self-reported engagement in pacing score (i.e. reports of planning several moments to recover, performing activity at slow pace, taking fatigue in account, alternating intensive activities with less intensive activities and dividing activities over the day) from baseline to follow-up (M_{diff} = -.35, 95% CI: -.85 – .14, p = .15). Taking a closer inspection of the groups score, participants in the intervention group appear to have decreased perceived engagement in pacing (M=-.25, SD = .42) while those in the control arm seem to have increased perceived engagement in pacing (M = .10, SD = .65) (Table 7.2). This points towards to less consciousness of energy management in the intervention group compared to the control group.

For perceived risk of overactivity, there was no significant difference in self-reported risk of overactivity score (i.e. reports of difficulty to limit and stop activities timely) between intervention group and control group from baseline to follow-up (M_{diff} = -.44, 95% CI: -1.40 – .51, p = .35). Taking a closer inspection of the groups score, participants in the intervention group seem to have decreased perceived risk of overactivity (M = -.09, SD = 1.09) while those in the control group appear to have increased risk of overactivity (M = .35, SD = 1.00) (Table 7.2). This points towards a more balanced activity and rest throughout the day in the intervention group compared to the control group.

Plotting of the mean fatigue severity score and activity counts of all participants together for each day during the baseline and follow-up home monitoring periods (Figure 7.2), revealed positive changes in fatigue severity and activity levels in favour of the tailored activity pacing group compared to the control which were in line with the results of the analysis of change scores from baseline to follow-up (Table 7.2).

Tailored pacing group



Control group

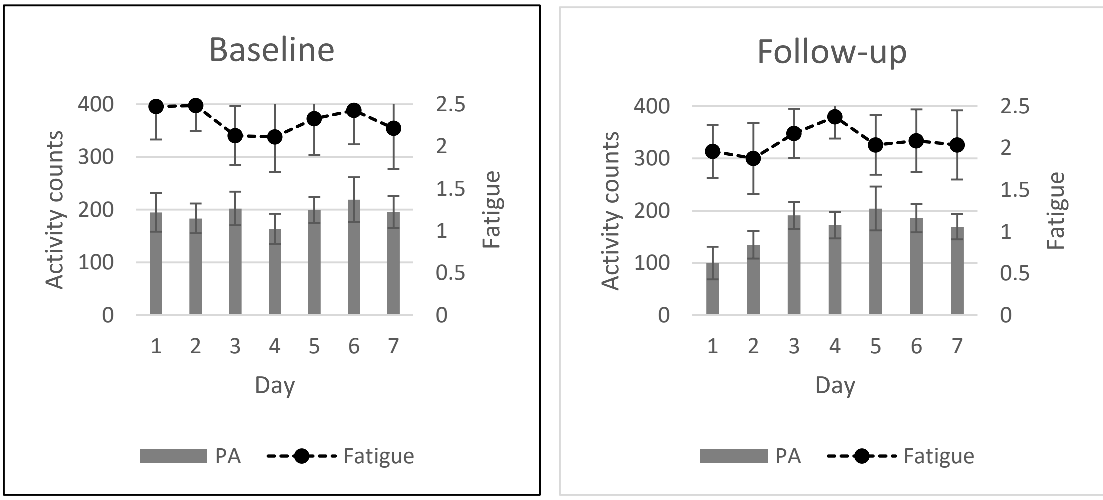


Figure 7.2. Changes in fatigue (dashed line) and activity counts per minute (grey bar) between baseline and follow-up over a 7-day period.

7.4 Discussion

This study examined the effectiveness of tailored activity pacing based on personalised reports that summarised and depicted a person's physical activity behaviour, fatigue experience, natural use of pacing and risk of overactivity in improving fatigue severity, physical activity and health-related quality of life in adults with MS. We found that tailored activity pacing was effective in improving physical activity level and spread of physical activity throughout. In addition, the study results suggest that tailored activity pacing is effective in improving fatigue expectation and experience, and health related quality of life. The study findings were unlikely to be biased by the fluctuating nature of the health status of people with MS. Indeed, the outcome of the comparison of the data generated during the first and final home monitoring was confirmed by the analysis (Table 7.2) and plotting (Figure 7.2) of fatigue and physical activity of all participants at baseline and 4 week follow-up.

For objective physical activity measured with accelerometry, a significant change and a large effect size was observed in physical activity counts per minute. We observed an increase in the physical activity counts per minute in the intervention group (+22.79 ± 44.70) compared to a decrease in the activity counts per minute in the control group (-18.11 ± 36.07). Other studies did not find these beneficial effects on physical activity (Murphy et al., 2012; Nijs et al., 2009). Most of these studies tailored activity pacing to prevent overactivity and fatigue symptom exacerbation, and measured physical activity with wrist-worn accelerometers. Placement of the device (wrist versus waist for example) has been reported to affect measurement of specific activities (Gironda et al., 2007). The large effect size obtained in this study points at the important role of tailoring activity pacing to a persons' characteristics for beneficial health outcome.

In addition, there was a significant decrease in physical activity variability throughout the week in the intervention group. This study is the first to show that tailored activity pacing was effective in improving activity levels and variability in persons with MS.

Previous works in adults with osteoarthritis found beneficial effect on activity variability but not activity levels (Murphy et al., 2012). Our tailored activity pacing intervention specifically targeted a behavioural change by attempting to spread the amount of physical activity throughout the day and stabilize the fluctuating nature of the physical activity pattern throughout the week. Given that the tailored intervention was designed to target inefficient activity patterns from the home monitoring period, it is not surprising and worth mentioning that physical activity levels and physical activity variability were most greatly impacted in the tailored activity pacing intervention as shown in figure 2 and the large significant beneficial effect sizes for activity levels (1.06) and activity variability (.99).

The large beneficial effect sizes coupled with the statistically significant finding for physical activity counts per minute and physical activity variability throughout the week provided valuable insights. This indicated the effectiveness of a tailored activity pacing intervention to stimulate an active lifestyle in persons with MS and suggests that tailored activity pacing may need to be incorporated in activity stimulation programme for people with MS to help them remain or become active which may be an important in promoting health behaviour in people with MS.

For self-reported physical activity measured with the Short Questionnaire to Assess Health-Enhancing Physical Activity, the intervention had no beneficial effect. This finding was similar to that reported in the study by Sandler et al., (2017) but contrary to the findings of Wallman et al., (2004) and Marques et al., (2014) both of which reported beneficial effects. However, in these studies activity pacing was integrated into a cognitive behaviour therapy and or graded exercise programme. The lack of a beneficial effect on self-reported activity despite the beneficial effects on objective physical activity level and physical activity variability found in this study may be indicative of the susceptibility of self-reported recall measures to biases such as under and over reporting of engagement in physical activity.

Although not statistically significant, the decrease in self-reported engagement in pacing and perceived risk of overactivity in daily life following the intervention in the tailored activity pacing group found in this study provides some valuable insights. The very fact that the intervention had a large beneficial effect on physical activity levels and physical activity variability suggests persons with MS may be to too careful in their self-reported engagement in pacing behaviour in an attempt to prevent exacerbation of their symptoms. Additionally, persons with MS may be experiencing more disruption through fatigue in daily life and may consequently resort to self-reported pacing as a reactionary response to increased fatigue, to prevent further worsening of symptom.

This suggests that previous activity pacing interventions that had negative outcome effects may have re-enforced this maladaptive self-reported use of pacing by focusing largely on preventing overactivity and symptom exacerbation in a sample that may largely be exhibiting avoidance behaviour towards physical activity. Although most of these interventions target problematic symptoms that arise from overactivity, none evaluated perceived risk of overactivity in daily life and the subsequent influence of the intervention on perceived risk of overactivity. Exploring this is necessary to identify and characterize the target population and help adapt interventions for successful outcomes.

As an improvement, the current study tailored activity pacing to the person's self-reported use of pacing and physical activity behaviour in addition to their perceived risk of overactivity and fatigue experience assessed at baseline, to dissociate symptoms from activity. The increase in physical activity levels and decrease in activity variability without exacerbation of fatigue found in this study support the need to disassociate symptoms from activity when tailoring pacing so that behaviours are not reactionary response to increased symptoms but rather anticipatory strategy (Nielson et al., 2014). This suggests that pacing could potentially be viewed as an adaptive or maladaptive behaviour depending upon whether or not people received guidance on how to pace (Murphy and Clauw, 2010).

Regarding fatigue, despite the results not reaching statistical significance, decreases in fatigue severity and expectation of fatigue in relation to activity were observed in the tailored pacing group. The observed decrease in fatigue severity was similar to that in adults with chronic fatigue syndrome (Nijs et al., 2009; Marques et al., 2014) and osteoarthritis (Murphy et al., 2012).

Participants in the tailored activity pacing group also showed a trend towards improvement in health-related quality of life but failed to reach significance. This result is in line with previous studies (Goudsmit et al., 2009; Nijs et al., 2009). The effect found in this study was similar to the average effect size for health-related quality of life found in earlier trials (Marques et al., 2014) and point at the psychological deterioration and increasing disability resulting from the burden of a prolonged chronic condition.

7.5 Limitations and recommendations for future research

The small sample size which likely affects statistical power (the ability to detect small to moderate effects) is a limitation of this pilot study. The atypical high proportion of males and older people with MS in this pilot study limits our ability to generalize the findings.

Participants may have been unusually motivated to participate in the study; they were regular attendants at an exercise clinic and consequently had already made initial steps toward behaviour change. Thus, conclusions may not be extended to the entire MS population.

Additionally, to be able to participate in the intervention, participants had to be ambulatory. This inclusion criterion may have excluded people who were severely affected by MS (i.e., mostly wheel chair dependent or bedridden) from participating. Including these people should be part of future research.

Furthermore, a longer follow-up assessment was not included in the present study, which means that participants' long-term response was not evaluated. Further treatment sessions would be required to provide a comprehensive programme and, a longer follow up will provide more insight into the potential benefits of tailored activity pacing for those with MS. Replicating the study in a larger sample is warranted to examine subject variables that may moderate the effects of the tailored activity pacing intervention and allow firm conclusions.

7.6 Conclusion

In summary, this study shows that tailoring activity pacing to individuals' attitudes towards pacing, risk of overactivity, fatigue experience and physical activity behaviour, targeting an even spread of daily physical activity has significant large beneficial effect upon physical activity levels and physical activity variability through the day in adults with MS. The study results suggest the approach was effective in improving physical activity behaviour without exacerbating fatigue symptoms.

These findings are very promising and point to short term benefits of tailored activity pacing for people with MS and call for a larger study with a longer follow-up assessment to evaluate the medium term effects of the tailored activity pacing intervention for people with MS. This low-resource intervention looks promising for the management of fatigue and stimulation of an active lifestyle. The study findings provide the basis to incorporate tailored activity pacing in physical activity promotion programme to help people with MS remain or become active.

CHAPTER 8

Conclusion and Summary

8.1 Summary

This thesis explored possibilities of activity pacing to stimulate an active lifestyle, and obtained insight into the relations between activity pacing, fatigue, quality of life and physical activity behaviour, firstly using self-report measures and then accelerometry. The insight gained from the exploratory studies was subsequently used to adapt, tailor and optimise activity pacing in people with MS to manage their fatigue and improve their physical activity behaviour and quality of life. Because, little remains known about the relationships between activity pacing, fatigue, physical activity and health-related quality of life, a review of literature and a meta-analysis of the current literature taking into account the concept and context of the pacing behaviour were conducted to determine the overall effect of activity pacing interventions on fatigue and physical behaviour, and to examine factors that moderate the effect. We found small-to-moderate effect for fatigue and inconsequential effects for physical activity and physical functioning. However, there were considerable variations in effects, which could not be accounted for due to the limited number of eligible and included studies.

An interesting feature that has not been studied is whether the level of naturalistic pacing of a person might influence the efficiency of a programmatic pacing programme. To gain a better understanding of this, the first important step is to obtain more information about the concept of naturalistic activity pacing. Subsequently, we examined within-person associations of naturalistic pacing behaviour, symptoms of fatigue, quality of life and physical activity, firstly using self-report measures and found that fatigue was related to low health-related quality at both short-term and long-term. Next we examined the relationships between naturalistic pacing behaviour, symptoms of fatigue and physical activity behaviour using accelerometry and found that engagement in pacing and perceived risk of overactivity varied in persons with MS and were related to activity levels assessed with accelerometers. Specifically, natural use of pacing was related to low activity level and perceived risk of overactivity was related

to high activity level. This suggest that those with worsening symptoms with respect to physical disability may be inclined and aware to pace their activities and those who experience less disruption through fatigue in daily life may consequently resort to the execution of too long periods of activity which may cause overactivity. Together, these findings points to the fact that there is no clear strategy for using physical activity to ameliorate fatigue symptoms amongst people with MS.

Accordingly, we used these insights to develop and examine the effect of a tailored activity pacing information based on combined personalised self-reported attitudes to pacing, perceived risk of overactivity, fatigue experience and physical activity patterns assessed at baseline. We found that the approach was effective in improving activity level, and spread activity through the day more equally, as measured by accelerometry. Furthermore, persons' fatigue severity and expectation of fatigue in relation to engagement in activity appears to decrease through the intervention.

Based on the results presented in this work, it can be concluded that adequate management of fatigue is crucial for health and wellbeing and that activity pacing could potentially be viewed as an adaptive or maladaptive behaviour depending upon whether or not persons receive guidance on how to pace their activities. In the context of current work as described in Table 8.1 guidance in the form of a tailored approach to activity pacing based on persons attitudes towards engagement in physical activity and fatigue experience, and aimed at distributing activity evenly throughout the day could potentially stimulate activity pacing as an adaptive behaviour to lessen fatigue and promote efficient engagement in physical activity in persons with MS. The results of this work support a tailored approach as a framework for physical activity stimulation and exercise prescription, but on the basis that persons attitudes towards physical activity is given the same priority as their fatigue experience.

Evaluating person's attitudes towards physical activity such as engagement in pacing and perceived risk of overactivity, in addition to fatigue experience in daily life is relevant to identify target population who might benefit from targeted interventions to manage symptoms and promote physical activity. As demonstrated in this thesis, programmes that incorporate this design feature may help to reveal the effectiveness of activity pacing as a useful adaptive behaviour that promote physical activity in persons with MS in order to underpin optimal health and wellbeing, particularly in the interests of offsetting the negative outcomes associated with physical inactivity. In general this thesis provides the basis to adapt a tailored approach to activity pacing in current clinical practice and to incorporate this design into physical activity stimulation programmes for persons with MS. Based on works in this thesis, it can be advocated that activity pacing is a goal-directed behavioural process of decision making and planning of how and where to distribute available energy over daily activities with the aim to distribute activities evenly throughout the day whilst steadily increasing overall activity.

Table 8.1 Summary of most significant results from each study

Study	Results
Activity pacing intervention effects: Meta-analysis	Medium (SMD = 0.50) and marginal (SMD = 0.34) effects for fatigue at post-treatment and follow-up. Trivial effects (SMD = 0.08 to 0.30) for physical functioning and physical activity at post-treatment and follow-up.
Cross-sectional naturalistic pacing relations	Fatigue was related to low health-related quality of life (β = -.34; p = .01). No associations between activity pacing and fatigue (β = .20; p = .16), and between activity pacing and physical activity (β = -.24; p = .12).
Longitudinal naturalistic pacing relations	Fatigue was related to low health-related quality of life (β = -.33; p < .001). Perceived risk of overactivity moderated the relationships between fatigue and physical activity (β = -0.19; p = .02), and between health-related quality of life (β = -0.13; p = .04). No associations between activity pacing and physical activity (β = -0.01; p = .89), and between activity pacing and health-related quality of life (β = -0.15; p = .09) over time.
Within daily naturalistic pacing relations	Engagement in pacing was related to low activity levels (β = -.44; p = .02). Perceived risk of overactivity was related to high activity level (β = .49; p =.01).
Tailored pacing intervention effects	Tailored pacing group had increased activity level (+19.28 ± 42.98 vs. -4.05 ± 48.26; p= .03) and decreased activity variability (-.01 ± .02 vs. +.03 ± .06; p = .04) compared to the control group.

8.2 Implications for practice affect effect

As evidenced by the review of the literature, meta-analysis and across the observational and interventional studies in this work, it can be suggested that the pacing behaviour persons enact in daily life without formal instructions could potentially be maladaptive, while their pacing behaviour after guidance on how to optimally pace activities could potentially be adaptive. However, the extent to which this is the case is likely to be dependent on current physical activity behaviour and attitudes towards physical activity of the adult with MS, with some for example, likely to be overactive whilst others may be underactive and still others approaching activities at their optimum. This has implication for the way in which a person with MS physical activities goals should be programmed and that baseline attitudes towards physical activity is an equally important factor to consider along fatigue symptoms when designing an activity pacing intervention. Clinicians must consider the persons perceived risk of overactivity and engagement in pacing when providing guidance on engagement in physical activity to optimise health and wellbeing.

As a direct extension from the potential of pacing been viewed as adaptive or maladaptive behaviour considered in the preceding paragraph, and the positive results of the tailored activity pacing intervention on physical activity behaviour as evidenced by the intervention study in this thesis, activity pacing can, and should, be individualised based on the attitudes towards physical activity and fatigue experience of a given person. For example, if a person avoid or limit physical activity in response to fatigue, it would be beneficial to provide guidance on engaging in consistent physical activity and such individuals could be provided with a graded consistent programme of physical activity, as well as be given information and strategies to help change beliefs that “I should do less if I am tired” or “symptoms are always a sign that I am damaging myself.” Similarly, if a person’s lifestyle is often characterized by periods of extreme fluctuations such as overactivity (when feeling good) and as a consequence of that, feeling overtly fatigued afterwards, followed by long extensive rest periods to recover from residual symptoms or prevent any symptoms re-occurring, it would be useful to provide them with advice on optimal use of pacing to develop a consistent pattern of paced activity and rest, with the aim of spreading activity evenly throughout the day. With an individualised approach to activity pacing, people with MS could be able to engage in physical activity at a level needed to maintain health without exacerbating their symptoms.

Key points

- ❖ Without an intervention, there is no clear strategy for using physical activity to ameliorate fatigue symptoms amongst people with MS.
- ❖ People with MS could benefit from goal-directed interventions to adequately manage fatigue symptoms and improve their health and wellbeing.
- ❖ Evaluating person’s attitudes towards physical activity such as natural use of pacing and perceived risk of overactivity in daily life is essential to identify target population, and to develop and adapt interventions that could be beneficial to their specific needs.
- ❖ Activity pacing could potentially be viewed as an adaptive or maladaptive behaviour depending upon whether or not persons received guidance on how to optimally pace their activities.
- ❖ People with MS could benefit from individualised guidance on optimal use of pacing, aimed at evenly spreading activity throughout the day, to help approach physical activity efficiently.
- ❖ People with MS, particularly those demonstrating a high perceived risk of overactivity and decreased physical activity and health-related quality of life in the context of increased fatigue may benefit from a tailored activity intervention to manage fatigue and approach activity in an effective way.

- ❖ Tailoring activity pacing based on attitudes towards pacing, physical activity and fatigue experience was effective in improving activity levels and reducing activity variability without exacerbating fatigue in people with MS.
- ❖ Incorporating this design in standard care for persons with MS could help manage fatigue and promote longitudinal engagement in physical activity important for health and wellbeing.

8.3 Limitations

This research has a number of limitations that could be addressed by researchers in the future:

- In the meta-analyses, a lack of uniformity in how activity pacing programmes were defined, described or implemented could contribute to high heterogeneity and, therefore, the accuracy of the results.
- In addition to the above, in half of the included studies in the meta-analysis, the intervention of interest (activity pacing) was usually carried out alongside complementary interventions which could also affect the result. This means that an isolation of the effect of activity pacing alone is not possible.
- In the meta-analysis, because the number of eligible and included studies were small, the categorization of subgroups were based on intervention characteristics of the included studies and so limited the evaluation effects of potential moderators.
- There are very few studies which outline the effects of activity pacing on physical activity in the sample population, meaning knowledge in this area is currently scarce.
- Across all studies, number of participants was relatively low, potentially limiting the findings' applicability to a wider population.

- Though the utilised measure of activity pacing used in the observational and interventional studies was novel, findings are limited in their comparison to studies that used different measures.
- Findings can be mostly generalized to adults with MS; the chronic condition sampled in the observational and interventional studies is likely an important distinction as symptoms characteristic and physical activity behaviour may vary by condition.
- Due to difficulties in logistics and participant recruitment, the randomisation of participants to tailored pacing and control groups was sometimes not performed. Participants were initially randomised into control and intervention groups. However, recruitments of participants become difficult in the course of the study and to ensure that both groups had close to equal number of participants and gender type, participants were purposely allocated to either group in the latter stage of' allocation to groups.
- Additionally, in the intervention study, participants had to be ambulatory with or without a cane. This inclusion criterion may have excluded people who were severely affected by MS (i.e., mostly wheel chair dependent or bedridden).
- Most of studies were correlational in approach, thus causation cannot be implied.
- The atypical high proportion of men and older persons with MS in some of the studies are limitations, as MS affect almost three times as many women as men, and most people diagnosed between the ages 20 and 40 years.
- The findings that the sample reported activity pacing and risk of overactivity scores near the possible upper limits may be more of a reflection of the parameters the Activity Pacing and Risk of Overactivity Questionnaire is able to measure than of how the individuals may be ultimately functioning. This is a limitation of the current study and further demonstrate the complexity of naturalistic pacing behaviour in the context of fatigue and physical activity. In

addition, data were skewed towards high engagement in pacing, perceived risk of overactivity and fatigue.

- The inability of the self-reported physical activity questionnaire to quantify physical activity patterns is a limitation of the study.

8.4 Future directions

The underpinning factors for an individualised approach to activity pacing have been discussed extensively throughout the preceding chapters and it seems that a natural progression of this work would be to investigate how a tailored approach to activity pacing affects physical activity behaviour, fatigue symptoms and health-related quality of life over an extensive period of time. Such research would be enhanced by the provision and evaluation of booster sessions in a cohort of adults with MS over an extensive period of time, contrasting with the relatively short-term intervention undertaken in the current work. The provision of booster sessions might help alleviate the possible effect of symptoms replase periods and help reinforce the adaptive behaviour in the long term. Additionally, replicating the study design in a larger cohort sample of adults with MS is warranted to enhance the examination of subject variables (such as type of MS and duration of illness) that may moderate the effects of the tailored activity pacing intervention, and allow firm conclusions.

However, there are a number of other issues that could be addressed by researchers in the future. Future studies employing the study design should include the typical MS population of more women compared to men, and individuals aged between 20 and 40 years. A further development of the research design of the intervention in this study would be to replicate the design in a different sample population such as adults with osteoarthritis to help evaluate if condition characteristics could be a factor in the magnitude of the observed effects. This would help in adopting the study design to different population with somewhat similar illness trajectory and symptoms characteristics. Furthermore, there is the need to standardize activity pacing based on a clear theoretical concept and consideration of the context in which the behaviour occurs in future studies. In addition, further validity studies of measures of activity pacing are needed to help streamline the construct. Future studies are needed to provide more support for adherence to programmatic pacing as evidence suggests persons did not change naturalistic pacing behaviour.

REFERENCES

Abonie, U. S., Edwards M., Hettinga, F. J. (2018a). Optimising activity pacing to promote a physically active lifestyle in persons with a disability or chronic disease: a review.

Abonie, U. S., Hettinga, F. J. (2018c). Activity pacing, fatigue, physical activity and quality of life in adults with multiple sclerosis: A ReSpAct cross sectional study.

Abonie, U. S., Hettinga F. J. (2018d). A longitudinal study of associations between activity pacing, fatigue, physical activity and quality of life in adults with multiple sclerosis: A l study.

Abonie, U. S., Hettinga F. J. (2018e). Within daily analysis of physical activity behaviour in adults with multiple sclerosis.

Abonie, U. S., Sandercook, G. R. H., Hettinga F. J. (2018b). Effects of Activity Pacing in patients with chronic conditions associated with fatigue complaints: A meta-Analysis. Disability and Rehabilitation, 1-10. doi: 10.1080/09638288.2018.1504994.

Afari, N., & Buchwald, D. (2003). Chronic fatigue syndrome: a review. *American Journal of Psychiatry*, **160**(2), 221-236.

Alingh, R. A., Hoekstra, F., van der Schans, C. P., Hettinga, F. J., Dekker, R., & van der Woude, L. H. (2015). Protocol of a longitudinal cohort study on physical activity behaviour in physically disabled patients participating in a rehabilitation counselling programme: ReSpAct. *BMJ open*, ***5***(1), e007591.

Amato, M. P., Ponziani, G., Rossi, F., Liedl, C. L., Stefanile, C., & Rossi, L. (2001). Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Multiple Sclerosis Journal*, **7**(5), 340-344.

Ament, W., & Verkerke, G. J. (2009). Exercise and fatigue. *Sports Medicine*, **39**(5), 389-422.

Anderson, V. R., Jason, L. A., Hlavaty, L. E., Porter, N., & Cudia, J. (2012). A review and meta-synthesis of qualitative studies on myalgic encephalomyelitis/chronic fatigue syndrome. *Patient education and counseling*, **86**(2), 147-155.

Andersson, M., Stridsman, C., Rönmark, E., Lindberg, A., & Emtner, M. (2015). Physical activity and fatigue in chronic obstructive pulmonary disease–a population based study. *Respiratory medicine*, **109**(8), 1048-1057.

Andrews, N. E., Strong, J., & Meredith, P. J. (2012). Activity pacing, avoidance, endurance, and associations with patient functioning in chronic pain: a systematic review and meta-analysis. *Archives of physical medicine and rehabilitation*, **93**(11), 2109-2121.

Antcliff, D., Campbell, M., Woby, S., & Keeley, P. (2015). Assessing the psychometric properties of an activity pacing questionnaire for chronic pain and fatigue. *Physical therapy*, **95**(9), 1274-1286.

Arends, S., Hofman, M., Kamsma, Y. P., van der Veer, E., Houtman, P. M., Kallenberg, C. G., Spoorenberg, A. & Brouwer, E. (2013). Daily physical activity in ankylosing spondylitis: validity and reliability of the IPAQ and SQUASH and the relation with clinical assessments. *Arthritis research & therapy*, **15**(4), p.R99.

Avlund, K., Rantanen, T., & Schroll, M. (2006). Tiredness and subsequent disability in older adults: The role of walking limitations. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, **61**(11), 1201-1205.

Bailey, A., Channon, S., & Beaumont, J. G. (2007). The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. *Multiple Sclerosis Journal*, **13**(1), 73-80.

Bakkum, A. J., de Groot, S., van der Woude, L. H., & Janssen, T. W. (2013). The effects of hybrid cycle training in inactive people with long-term spinal cord injury: Design of a multicenter randomized controlled trial. *Disability and rehabilitation*, **35**(13), 1127-1132.

Bakshi, R. (2003). Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Multiple Sclerosis Journal*, **9**(3), 219-227.

Bakshi, R., Shaikh, Z. A., Miletich, R. S., Czarnecki, D., Dmochowski, J., Henschel, K., ... & Kinkel, P. R. (2000). Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Multiple Sclerosis Journal*, ***6***(3), 181-185.

Barnett, K., Mercer, S. W., Norbury, M., Watt, G., Wyke, S., & Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*, **380**(9836), 37-43.

Birkholtz, M., Aylwin, L., & Harman, R. M. (2004). Activity pacing in chronic pain management: one aim, but which method? Part one: introduction and literature review. *British journal of occupational therapy*, **67**(10), 447-452.

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Calhoun, S. L., Vela-Bueno, A., & Kales, A. (2005). Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *The Journal of Clinical Endocrinology & Metabolism*, **90**(8), 4510-4515.

Blair, S. N., Cheng, Y., & Holder, J. S. (2001). Is physical activity or physical fitness more important in defining health benefits? *Medicine & Science in Sports & Exercise*, **33**(6), S379-S399.

Bol, Y., Duits, A. A., Hupperts, R. M., Vlaeyen, J. W., & Verhey, F. R. (2009). The psychology of fatigue in patients with multiple sclerosis: a review. Journal of psychosomatic research, **66**(1), 3-11.

Borenstein, M. (2009). Effect sizes for continuous data. In: *The handbook of research synthesis and meta analysis* (eds Cooper H., Hedges, L. V., & Valentine J. C.) pp. 221-237. New York: Russell Sage Foundation.

Borenstein, M., Hedges, L. V., Higgins, J., Rothstein, H. R. (2009). *Introduction to meta-analysis*. Chichester (UK). Wiley & Sons, Ltd.

Boutron, I., Rannou, F., JardinaudLopez, M., Meric, G., Revel, M., and Poiraudeau, S. (2008). Disability and quality of life of patients with knee or hip osteoarthritis in the primary care setting and factors associated with general practitioners' indication for prosthetic replacement within 1 year. *Osteoarthritis Cartilage*, **16**(9):1024-31

Brañas, P., Jordan, R., Fry-Smith, A., Burls, A., & Hyde, C. (2000). Treatments for fatigue in multiple sclerosis: a rapid and systematic review. *Health technology assessment*, **4**(27), 1-61.

Brick, N. E., MacIntyre, T. E., & Campbell, M. J. (2016). Thinking and action: a cognitive perspective on self-regulation during endurance performance. *Frontiers in physiology*, **7**, 159.

Brurberg, K. G., Odgaard-Jensen, J., Price, J. R., & Larun, L. (2017). Exercise therapy for chronic fatigue syndrome. *The Cochrane Database of Systematic Reviews,* 2017(4).

Butler, D. S., & Moseley, G. L. (2003). *Explain pain*. Adelaide (Australia). Noigroup Publications.

Castell, B. D., Kazantzis, N., & Moss-Morris, R. E. (2011). Cognitive behavioral therapy and graded exercise for chronic fatigue syndrome: A meta-analysis. *Clinical Psychology: Science and Practice*, **18**(4), 311-324.

Cesari, M., Onder, G., Zamboni, V., Manini, T., Shorr, R. I., Russo, A., ... & Landi, F. (2008). Physical function and self-rated health status as predictors of mortality: results from longitudinal analysis in the ilSIRENTE study. *BMC geriatrics*, **8**(1), 34.

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., & Wallace, E. P. (1993). Development of a fatigue scale. *Journal of psychosomatic research*, **37**(2), 147-153.

Chalder, T., Goldsmith, K. A., White, P. D., Sharpe, M., & Pickles, A. R. (2015). Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial. *The Lancet Psychiatry*, **2**(2), 141-152.

Charlton, C., Rasbash, J., Browne, W.J., Healy, M. and Cameron, B. (2017). *MLwiN Version **3.00***. Centre for Multilevel Modelling, University of Bristol.

Chou, P. H., Huang, Y. P., Lou, S. Z., Tseng, W. Z., Wang, R. T., & Chou, Y. L. (2012). Effects of fatigue on stability of upper extremity during bench-press exercise. *Journal of Medical and Biological Engineering*, **32**(6), 437-441.

Clark, L. V., & White, P. D. (2005). The role of deconditioning and therapeutic exercise in chronic fatigue syndrome (CFS). *Journal of mental health*, **14**(3), 237-252.

Cohen, J. (1988). Statistical Power Analysis for the Behavioural Sciences, 2nd edition. New Jersey. Erlbaum, Hillsdale.

Cohen, J. (1992). A power primer. *Psychological bulletin*, **112**(1), 155-159.

Compston A, Coles A. (2002). Multiple sclerosis. *Lancet*, **359**, 1221–31.

Cook, D. B., Nagelkirk, P. R., Peckerman, A., Poluri, A., Mores, J., & Natelson, B. H. (2005). Exercise and cognitive performance in chronic fatigue syndrome. *Medicine & Science in Sports & Exercise*, **37**(9), 1460-1467.

Craig, C. L., Marshall, A. L., Sjorstrom, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., ... & Oja, P. (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise*, **35**(8), 1381-1395.

de Vries, S. I., Bakker, I., Hopman-Rock, M., Hirasing, R. A., & van Mechelen, W. (2006). Clinimetric review of motion sensors in children and adolescents. *Journal of clinical epidemiology*, **59**(7), 670-680.

Deale, A., Chalder, T., Marks, I., & Wessely, S. (1997). Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. *The American journal of psychiatry*, **154**(3), 408-414.

DeLuca, J. (Ed.). (2005). Fatigue as a Window to the Brain. MIT press.

Dodd, K. J., Taylor, N. F., Denisenko, S., & Prasad, D. (2006). A qualitative analysis of a progressive resistance exercise programme for people with multiple sclerosis. *Disability and rehabilitation*, **28**(18), 1127-1134.

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology & Community Health*, **52**(6), 377-384.

Durstine, J. L., Painter, P., Franklin, B. A., Morgan, D., Pitetti, K. H., & Roberts, S. O. (2000). Physical activity for the chronically ill and disabled. *Sports Medicine*, **30**(3), 207-219.

Edwards, A. M., & Noakes, T. D. (2009). Dehydration: cause of fatigue or sign of pacing in elite soccer?. *Sports Medicine*, **39**(1), 1-13.

Edwards, A. M., Bentley, M. B., Mann, M. E., & Seaholme, T. S. (2011). Self-pacing in interval training: A teleoanticipatory approach. *Psychophysiology*, **48**(1), 136-141.

Edwards, A., & Polman, R. (2012). *Pacing in sport and exercise: a psychophysiological perspective*. Nova Science Publishers.

Eldadah, B. A. (2010). Fatigue and fatigability in older adults. *PM&R*, **2**(5), 406-413.

Elferink-Gemser, M. T., & Hettinga, F. J. (2017). Pacing and Self-regulation: Important Skills for Talent Development in Endurance Sports. *International journal of sports physiology and performance*, **12**(6), 831-835.

Enoka, R. M., & Duchateau, J. (2016). Translating fatigue to human performance. *Medicine and science in sports and exercise*, **48**(11), 2228.

Evers, A. W., Taal, E., Kraaimaat, F. W., Jacobs, J. W., Abdel-Nasser, A., Rasker, J. J., & Bijlsma, J. W. (1998). A comparison of two recently developed health status instruments for patients with arthritis: Dutch-AIMS2 and IRGL. Arthritis Impact Measurement Scales. Impact of Rheumatic diseases on General health and Lifestyle. *British journal of rheumatology*, **37**(2), 157-164.

Fisk, J. D. P. A., Ritvo P. G., Archibald C. J., Murray T. J. (1994). The impact of fatigue on patients with multiple sclerosis. *Canadian Journal of Neurological Science*, **21**, 9–14

Focht, B. C., Sanders, W. M., Brubaker, P. H., & Rejeski, W. J. (2003). Initial validation of the CSA activity monitor during rehabilitative exercise among older adults with chronic disease. *Journal of Aging and Physical Activity*, **11**(3), 293-304.

Foster, C., Hendrickson, K., Peyer, K., Reiner, B., Lucia, A., Battista, R., ... & Wright, G. (2009). Pattern of developing the performance template. *British Journal of Sports Medicine*, **43**(10), 765-769.

Fordyce, W. E. (1976). Behavioural methods for chronic pain and illness. St. Louis. Mosby.

Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., & Komaroff, A. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of internal medicine*, **121**(12), 953-959.

Galea, M. P. (2012). Spinal cord injury and physical activity: preservation of the body. *Spinal Cord*, **50**(5), 344-351.

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., ... & Swain, D. P. (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise*, **43**(7), 1334-1359.

Gignac, M. A., Cott, C., & Badley, E. M. (2000). Adaptation to chronic illness and disability and its relationship to perceptions of independence and dependence. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, **55**(6), P362-P372.

Gill, T. M., Desai, M. M., Gahbauer, E. A., Holford, T. R., & Williams, C. S. (2001). Restricted activity among community-living older persons: incidence, precipitants, and health care utilization. *Annals of internal medicine*, **135**(5), 313-321.

Ginis, K. A. M., Jörgensen, S., & Stapleton, J. (2012). Exercise and sport for persons with spinal cord injury. *PM&R*, **4**(11), 894-900.

Gironda, R. J., Lloyd, J., Clark, M. E., & Walker, R. L. (2007). Preliminary evaluation of reliability and criterion validity of Actiwatch-Score. *Journal of rehabilitation research and development*, **44**(2), 223-230

Goggins, J., Baker, K., & Felson, D. (2005). What WOMAC pain score should make a patient eligible for a trial in knee osteoarthritis? *The Journal of rheumatology*, **32**(3), 540-542.

Goudsmit, E. M., Nijs, J., Jason, L. A., & Wallman, K. E. (2012). Pacing as a strategy to improve energy management in myalgic encephalomyelitis/chronic fatigue syndrome: a consensus document. *Disability and rehabilitation*, **34**(13), 1140-1147.

Grotle, M., Hagen, K. B., Natvig, B., Dahl, F. A., & Kvien, T. K. (2008). Prevalence and burden of osteoarthritis: results from a population survey in Norway. *The Journal of rheumatology*, **35**(4), 677-684.

Hanson, R. W., & Gerber, K. E. (1990). *Coping with chronic pain: A guide to patient self-management*. New York. Guilford Press.

Hardy, S. E., & Studenski, S. A. (2008). Fatigue and function over 3 years among older adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, **63**(12), 1389-1392.

Hartung HP, Gonsette R, Konig N, et al for the Mitoxantrone in Multiple Sclerosis Study Group (MIMS). (2002). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet*, **360**, 2018–25.

Hasenbring, M. I., & Verbunt, J. A. (2010). Fear-avoidance and endurance-related responses to pain: new models of behavior and their consequences for clinical practice. *The Clinical journal of pain*, **26**(9), 747-753.

Haskell, W. L., Lee, I. M., Pate, R. R., Powell, K. E., Blair, S. N., Franklin, B. A., ... & Bauman, A. (2007). Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*, **116**(9), 1081.

Hays, R. D. (1998). *RAND 36 health status inventory*. New York. Harcourt Brace & Company.

Hedges, L. V. (1981). Distribution theory for Glass's estimator of effect size and related estimators. *Journal of Educational Statistics*, **6**(2), 107-128.

Heine, M., van den Akker, L. E., Blikman, L., Hoekstra, T., Van Munster, E., Verschuren, O., ... & Malekzadeh, A. (2016). Real-time assessment of fatigue in patients with multiple sclerosis: how does it relate to commonly used self-report fatigue questionnaires?. *Archives of physical medicine and rehabilitation*, **97**(11), 1887-1894.

Hettinga, F. J., Renfree, A., Pageaux, B., Jones, H. S., Corbett, J., Micklewright, D., & Mauger, A. R. (2017). Regulation of endurance performance: new frontiers. *Frontiers in physiology*, **8**, 727.

Hickie, I., Hadzi-Pavlovic, D., Scott, E., Davenport, T., Koschera, A., & Naismith, S. (1998). SPHERE: a national depression project. *Australasian Psychiatry*, **6**(5), 248-250.

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*, ***343***, d5928.

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ: British Medical Journal*, **327**(7414), 557.

Hollmann, W., Strüder, H. K., Tagarakis, C. V., & King, G. (2007). Physical activity and the elderly. *European Journal of Cardiovascular Prevention & Rehabilitation*, **14**(6), 730-739.

Hooper K. (2011). Managing Progressive MS. New York, NY: National Multiple Sclerosis Society.

Husson, O., Oerlemans, S., Mols, F., Schep, G., & Van De Poll-Franse, L. V. (2015). High levels of physical activity are associated with lower levels of fatigue among lymphoma patients: Results from the longitudinal PROFILES registry. *Acta Oncologica*, **54**(5), 678-684.

IBM Corp. (2015). IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

IBM Corp. (2016). IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

IBM Corp. (2017). IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Janardhan, V., & Bakshi, R. (2002). Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *Journal of the neurological sciences*, **205**(1), 51-58.

Jensen, L. D., Maribo, T., Schiøttz-Christensen, B., Madsen, F. H., Gonge, B., Christensen, M., & Frost, P. (2011). Counselling low-back-pain patients in secondary healthcare: a randomised trial addressing experienced workplace barriers and physical activity. *Occupational and environmental medicine*, **69**, 21–28.

Jo Nijs PhD, P. T., Inge van Eupen, O. T., Vandecauter, J., Augustinus, E., Greta Moorkens PhD, M. D., & Mira Meeus PhD, P. T. (2009). Can pacing self-management alter physical behavior and symptom severity in chronic fatigue syndrome? A case series. *Journal of rehabilitation research and development*, **46**(7), 985.

Johansson, S., Ytterberg, C., Claesson, I. M., Lindberg, J., Hillert, J., Andersson, M., ... & von Koch, L. (2007). High concurrent presence of disability in multiple sclerosis. *Journal of neurology*, **254**(6), 767.

Kappos, L., Polman, C. H., Freedman, M. S., et al. (2006). Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology*, **67**, 1242-1249

Kayes, N. M., McPherson, K. M., Taylor, D., Schlüter, P. J., & Kolt, G. S. (2011). Facilitators and barriers to engagement in physical activity for people with multiple sclerosis: a qualitative investigation. *Disability and rehabilitation*, **33**(8), 625-642.

Khan, F., Pallant, J. F., Brand, C., & Kilpatrick, T. J. (2008). Effectiveness of rehabilitation intervention in persons with multiple sclerosis: a randomised controlled trial. *Journal of Neurology, Neurosurgery & Psychiatry*, **79**(11), 1230-1235.

Kindermans, H. P., Roelofs, J., Goossens, M. E., Huijnen, I. P., Verbunt, J. A., & Vlaeyen, J. W. (2011). Activity patterns in chronic pain: underlying dimensions and associations with disability and depressed mood. *The Journal of Pain*, **12**(10), 1049-1058.

Konings, M. J., & Hettinga, F. J. (2018). Pacing decision making in sport and the effects of interpersonal competition: A critical review. *Sports Medicine*, 1-15.

Kos, D., Van Eupen, I., Meirte, J., Van Cauwenbergh, D., Moorkens, G., Meeus, M., & Nijs, J. (2015). Activity pacing self-management in chronic fatigue syndrome: a randomized controlled trial. *American Journal of Occupational Therapy*, **69**(5), 1-11.

Kotte, EMG, Alingh RA, Hettinga FJ, van der Woude LHV. (2015). Understanding Activity Pacing in the context of rehabilitation: Analysis of a newly developed Activity Pacing Questionnaire and associations with fatigue and perceived activity. Master Graduation Project. Center for Human Movement Sciences University of Groningen.

Krause, I., Kern, S., Horntrich, A., & Ziemssen, T. (2013). Employment status in multiple sclerosis: impact of disease-specific and non-disease-specific factors. *Multiple Sclerosis Journal*, **19**(13), 1792-1799.

Kuhlmann, T., Lingfeld, G., Bitsch, A., Schuchardt, J., & Brück, W. (2002). Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. *Brain*, **125**(10), 2202-2212.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of neurology*, **46**(10), 1121-1123.

Lander, P. J., Butterly, R. J., & Edwards, A. M. (2009). Self-paced exercise is less physically challenging than enforced constant pace exercise of the same intensity: influence of complex central metabolic control. *British Journal of Sports Medicine*, **43**(10), 789-795.

Learmonth, Y. C., Motl, R. W., Sandroff, B. M., Pula, J. H., & Cadavid, D. (2013). Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. BMC neurology, **13**(1), 37.

Lee, I. M., & Skerrett, P. J. (2001). Physical activity and all-cause mortality: what is the dose-response relation? *Medicine & Science in Sports & Exercise*, **33**(6), S459-S471.

Le Page, E., Leray, E., Taurin, G., Coustans, M., Chaperon, J., Morrissey, S. P., & Edan, G. (2008). Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. *Journal of Neurology, Neurosurgery & Psychiatry*, **79**(1), 52-56.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., ... & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of Internal Medicine, **151**(4):65–94.

Malouff, J. M., Thorsteinsson, E. B., Rooke, S. E., Bhullar, N., & Schutte, N. S. (2008). Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: a meta-analysis. *Clinical psychology review*, **28**(5), 736-745.

Marcora, S. M. (2008). Do we really need a central governor to explain brain regulation of exercise performance? *European journal of applied physiology*, **104**(5), 929.

Marques, M. M., De Gucht, V., Gouveia, M. J., Leal, I., & Maes, S. (2015). Differential effects of behavioral interventions with a graded physical activity component in patients suffering from Chronic Fatigue (Syndrome): An updated systematic review and meta-analysis. *Clinical psychology review*, ***40***, 123-137.

Marques, M., De Gucht, V., Leal, I., & Maes, S. (2015). Effects of a self-regulation based physical activity program (the "4-STEPS") for unexplained chronic fatigue: a randomized controlled trial. *International journal of behavioral medicine*, **22**(2), 187-196.

Marino, F. E. (2014). If only I were paramecium too! A case for the complex, intelligent system of anticipatory regulation in fatigue. *Fatigue: Biomedicine, Health & Behavior,* **2**(4), 185-201.

Marrie, R. A., & Goldman, M. (2007). Validity of performance scales for disability assessment in multiple sclerosis. *Multiple Sclerosis Journal*, **13**(9), 1176-1182.

McCracken, L. M., & Samuel, V. M. (2007). The role of avoidance, pacing, and other activity patterns in chronic pain. *Pain*, **130**(1-2), 119-125.

Mendoza, T., Wang, X. S., Cleeland, C. S., Morrissey, M., Johnson, B. A., Wendt, J. K., & Huber, S. L. (1999). Brief Fatigue Inventory. *Cancer*, **85**,1186-1196

Merkelbach, S., Schulz, H., Kölmel, H. W., Gora, G., Klingelhöfer, J., Dachsel, R., ... & Polzer, U. (2011). Fatigue, sleepiness, and physical activity in patients with multiple sclerosis. *Journal of neurology*, **258**(1), 74-79.

Merkelbach S, Sittinger H, Koenig J (2002). Is there a differential impact of fatigue and physical disability on quality of life in multiple sclerosis? *The Journal of nervous and mental disease*, **190**(6), 388-393.

Miles, L. (2007). Physical activity and health. *Nutrition bulletin*, **32**(4), 314-363.

Mitchell, S. A. (2010). Cancer-related fatigue: state of the science. *PM&R*, **2**(5), 364-383.

Mohr DC, Cox D. (2001). Multiple sclerosis: empirical literature for the clinical health psychologist. *Journal of Clinical Psychology*, **57**(4), 479–949

Moore, S. C., Patel, A. V., Matthews, C. E., Berrington de Gonzalez, A., Park, Y., Katki, H. A., ... Lee, I. M. (2012). Leisure Time Physical Activity of Moderate to Vigorous Intensity and Mortality: A Large Pooled Cohort Analysis. *PLoS Medicine*, **9**(11), 1-14.

Motl, R. W., McAuley, E., & Snook, E. M. (2005). Physical activity and multiple sclerosis: a meta-analysis. *Multiple Sclerosis Journal*, **11**(4), 459-463.

Motl, R. W., McAuley, E., Snook, E. M., & Scott, J. A. (2006). Validity of physical activity measures in ambulatory individuals with multiple sclerosis. *Disability and rehabilitation*, **28**(18), 1151-1156.

Motl, R. W., Snook, E. M., McAuley, E., Scott, J. A., & Douglass, M. L. (2006). Correlates of physical activity among individuals with multiple sclerosis. *Annals of behavioural medicine*, **32**(2), 154-161.

Multiple Sclerosis Trust. (2018). URL http:// www.mstrust.org.uk/a-z/prevalence-and-incidence-multiple-sclerosis. Last retrieved on 30 Jan 2018.

Murphy, S. L., & Clauw, D. J. (2010). Activity pacing: what are we measuring and how does that relate to intervention? *Pain*, **149**(3), 582-583.

Murphy, S. L., & Kratz, A. L. (2014). Activity pacing in daily life: A within-day analysis. *PAIN®*, **155**(12), 2630-2637.

Murphy, S. L., Kratz, A. L., Williams, D. A., & Geisser, M. E. (2012). The association between symptoms, pain coping strategies, and physical activity among people with symptomatic knee and hip osteoarthritis. *Frontiers in psychology*, **3**, 326.

Murphy, S. L., Lyden, A. K., Smith, D. M., Dong, Q., & Koliba, J. F. (2010). Effects of a tailored activity pacing intervention on pain and fatigue for adults with osteoarthritis. *American Journal of Occupational Therapy*, **64**(6), 869-876.

Murphy, S. L., Smith, D. M., & Alexander, N. B. (2008). Measuring activity pacing in women with lower-extremity osteoarthritis: a pilot study. *American Journal of Occupational Therapy*, **62**(3), 329-334.

Murphy, S. L., Smith, D. M., & Lyden, A. K. (2012). Type of activity pacing instruction affects physical activity variability in adults with symptomatic knee or hip osteoarthritis. *Journal of Physical Activity and Health*, **9**(3), 360-366.

Murphy, S. L., Smith, D. M., Clauw, D. J., & Alexander, N. B. (2008). The impact of momentary pain and fatigue on physical activity in women with osteoarthritis. *Arthritis Care & Research*, **59**(6), 849-856.

Murphy, S. L., Strasburg, D. M., Lyden, A. K., Smith, D. M., Koliba, J. F., Dadabhoy, D. P., & Wallis, S. M. (2008). Effects of activity strategy training on pain and physical activity in older adults with knee or hip osteoarthritis: a pilot study. *Arthritis Care & Research*, **59**(10), 1480-1487.

Murray, C. J., & Lopez, A. D. (1997). Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *The Lancet*, **349**(9064), 1498-1504.

National Institute for Clinical Excellence (NICE). (2014). Multiple sclerosis in adults: management. Clinical Guidelines 186. London: National Institute for Clinical Excellence. URL https://www.nice.org.uk/guidance/cg186. Last retrieved on 19.05.18.

National Institute for Health and Clinical Excellence. Clinical guideline CG53. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management. London: NICE; 2007. URL http://guidance.nice.org.uk/CG53. Last retrieved on 20.11.18

Nicholas, M., Molloy, A., Beeston, L., & Tonkin L. (2011). *Manage your pain. Practical and positive ways of adapting to chronic pain*. 2nd edition. pp. Sydney. ABC Books.

Nielson, W. R., & Jensen, M. P. (2004). Relationship between changes in coping and treatment outcome in patients with Fibromyalgia Syndrome. *Pain*, **109**(3), 233-241.

Nielson, W. R., Jensen, M. P., & Hill, M. L. (2001). An activity pacing scale for the chronic pain coping inventory: development in a sample of patients with fibromyalgia syndrome. *Pain*, **89**(2-3), 111-115.

Nielson, W. R., Jensen, M. P., Karsdorp, P. A., & Vlaeyen, J. W. (2013). Activity pacing in chronic pain: concepts, evidence, and future directions. *The Clinical journal of pain*, **29**(5), 461-468.

Nielson, W. R., Jensen, M. P., Karsdorp, P. A., & Vlaeyen, J. W. (2014). A content analysis of activity pacing in chronic pain: What are we measuring and why? *The Clinical journal of pain*, **30**(7), 639-645.

Nijs, J., & Thielemans, A. (2008). Kinesiophobia and symptomatology in chronic fatigue syndrome: a psychometric study of two questionnaires. *Psychology and Psychotherapy: Theory, Research and Practice*, **81**(3), 273-283.

Nijs, J., Inge van Eupen, Vandecauter, J., Augustinus, E., Greta Moorkens, & Mira Meeus. (2009). Can pacing self-management alter physical behavior and symptom severity in chronic fatigue syndrome? A case series. *Journal of rehabilitation research and development*, **46**(7), 985.

Nijs, J., Paul, L., & Wallman, K. (2008). Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. *Journal of rehabilitation medicine*, **40**(4), 241-247.

Nijs, J., Roussel, N., Van Oosterwijck, J., De Kooning, M., Ickmans, K., Struyf, F., ... & Lundberg, M. (2013). Fear of movement and avoidance behaviour toward physical activity in chronic-fatigue syndrome and fibromyalgia: state of the art and implications for clinical practice. *Clinical rheumatology*, **32**(8), 1121-1129.

Nijs, J., Wallman, K, Paul L. (2011). Chronic fatigue syndrome. In *Exercise and chronic disease: an evidence-based approach* (ed Saxton, J.) pp. 322–338. New York. Taylor & Francis.

Noakes, T. D., Gibson, A. S. C., & Lambert, E. V. (2005). From catastrophe to complexity: a novel model of integrative central neural regulation of effort and fatigue during exercise in humans: summary and conclusions. *British Journal of Sports Medicine*, **39**(2), 120-124.

Nortvedt, M. W., Riise, T., Myhr, K. M., & Nyland, H. I. (2000). Performance of the SF-36, SF-12, and RAND-36 summary scales in a multiple sclerosis population. *Medical care*, **38**(10), 1022-1028.

O'Brien-Cousins, S. (1996). An older adult exercise status inventory: reliability and validity. *Journal of Sport Behavior*, **19**(4), 288-302.

Paterson, D. H., Jones, G. R., & Rice, C. L. (2007). Ageing and physical activity: evidence to develop exercise recommendations for older adults. *Applied Physiology, Nutrition, and Metabolism*, **32**(S2E), S69-S108.

Pinto, B. M., Papandonatos, G. D., & Goldstein, M. G. (2013). A randomized trial to promote physical activity among breast cancer patients. *Health Psychology*, **32**(6), 616-626.

Pisters, M. F., Veenhof, C., de Bakker, D. H., Schellevis, F. G., & Dekker, J. (2010). Behavioural graded activity results in better exercise adherence and more physical activity than usual care in people with osteoarthritis: a cluster-randomised trial. *Journal of physiotherapy*, **56**(1), 41-47.

Plotnikoff, R. C., Karunamuni, N., Courneya, K. S., Sigal, R. J., Johnson, J. A., & Johnson, S. T. (2012). The Alberta Diabetes and Physical Activity Trial (ADAPT): a randomized trial evaluating theory-based interventions to increase physical activity in adults with type 2 diabetes. *Annals of Behavioral Medicine*, **45**(1), 45-56.

Power, J. D., Badley, E. M., French, M. R., Wall, A. J., & Hawker, G. A. (2008). Fatigue in osteoarthritis: a qualitative study. *BMC musculoskeletal disorders*, **9(**1), 63.

Puetz, T. W. (2006). Physical activity and feelings of energy and fatigue. *Sports medicine*, **36**(9), 767-780.

Rampello, A., Franceschini, M., Piepoli, M., Antenucci, R., Lenti, G., Olivieri, D., & Chetta, A. (2007). Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomized crossover controlled study. *Physical therapy*, **87**(5), 545-555.

Renfree, A., Mytton, G. J., Skorski, S., & Gibson, A. S. C. (2014). Tactical considerations in the middle-distance running events at the 2012 olympic games: a case study. *International Journal of Sports Physiology and Performance*, **9**(2), 362-364.

Review Manager (RevMan). (2014). [Computer program]. Version 5.3. The Nordic Cochrane Centre. Copenhagen (Denmark).

Richardson, C. A., Glynn, N. W., Ferrucci, L. G., & Mackey, D. C. (2014). Walking energetics, fatigability, and fatigue in older adults: the study of energy and aging pilot. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, **70**(4), 487-494.

Rimer, B. K., & Kreuter, M. W. (2006). Advancing tailored health communication: A persuasion and message effects perspective. Journal of communication, **56**(s1): S184-S201.

Rimmer, J. H., Marques, A. C. (2012). Physical activity for people with disabilities. *The Lancet*, **21**(380**)**:193–195.

Rockwood, K., Davis, H. S., Merry, H. R., MacKnight, C., & McDowell, I. (2001). Sleep disturbances and mortality: results from the Canadian Study of Health and Aging. *Journal of the American Geriatrics Society*, **49**(5), 639-641.

Roehrs, T. G., & Karst, G. M. (2004). Effects of an aquatics exercise program on quality of life measures for individuals with progressive multiple sclerosis. *Journal of Neurologic Physical Therapy*, **28**(2), 63-71.

Rongen-van Dartel, S. A. A., Repping-Wuts, H., Hoogmoed, D. V., Knoop, H., Bleijenberg, G., Riel, P. L. C. M., & Fransen, J. (2014). Relationship between objectively assessed physical activity and fatigue in patients with rheumatoid arthritis: inverse correlation of activity and fatigue. *Arthritis care & research*, **66**(6), 852-860.

Sandler, C. X., Goldstein, D., Horsfield, S., Bennett, B. K., Friedlander, M., Bastick, P. A., ... & Webber, K. (2017). Randomized evaluation of cognitive-behavioral therapy and graded exercise therapy for post-cancer fatigue. *Journal of pain and symptom management*, **54**(1), 74-84.

Sasaki, J. E., John, D., & Freedson, P. S. (2011). Validation and comparison of ActiGraph activity monitors. *Journal of Science and Medicine in Sport*, **14**(5), 411-416.

Schapiro, R. T. (2003). *Managing the Symptoms of Multiple Sclerosis,* 4th Edition. New York. Demos Medical.

Schultz-Larsen, K., & Avlund, K. (2007). Tiredness in daily activities: a subjective measure for the identification of frailty among non-disabled community-living older adults. *Archives of Gerontology and Geriatrics*, **44**(1), 83-93.

Seves BL, van der Woude LHV, Hettinga FJ. (2018). Fatigability in people with disabilities and the impact on an active lifestyle and quality of life: a narrative review. Sports Med (under review)

Selim, A. J., Rogers, W., Fleishman, J. A., Qian, S. X., Fincke, B. G., Rothendler, J. A., & Kazis, L. E. (2009). Updated US population standard for the Veterans RAND 12-item Health Survey (VR-12). *Quality of Life Research*, **18**(1), 43-52.

Seves, B. L., Hoekstra F., Schoenmakers J. W.A., Hoekstra T., Hettinga F. J., Dekker R., van der Woude L. H.V., van der Schans C. P. Test-retest reliability and concurrent validity of the Adapted Short Questionnaire to Assess Health-enhancing physical activity (Adapted-SQUASH) in adults with disabilities. (Under review).

Sharpe, M. C., Archard, L. C., Banatvala, J. E., Borysiewicz, L. K., Clare, A. W., David, A., ... & Lane, R. J. (1991). A report--chronic fatigue syndrome: guidelines for research. *Journal of the Royal Society of Medicine*, **84**(2), 118.

Simmons, R. D., Ponsonby, A. L., Van Der Mei, I. A., & Sheridan, P. (2004). What affects your MS? Responses to an anonymous, Internet-based epidemiological survey. *Multiple Sclerosis Journal*, **10**(2), 202-211.

Simonsick, E. M., Schrack, J. A., Glynn, N. W., & Ferrucci, L. (2014). Assessing fatigability in mobility-intact older adults. *Journal of the American Geriatrics Society*, **62**(2), 347-351.

Singer, J. D. (1998). Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. *Journal of educational and behavioral statistics*, **23**(4), 323-355.

Skerrett, T. N., & Moss-Morris, R. (2006). Fatigue and social impairment in multiple sclerosis: the role of patients' cognitive and behavioral responses to their symptoms. *Journal of psychosomatic research*, **61**(5), 587-593.

Smedal, T., Beiske, A. G., Glad, S. B., Myhr, K. M., Aarseth, J. H., Svensson, E., ... & Strand, L. I. (2011). Fatigue in multiple sclerosis: associations with health-related quality of life and physical performance. *European journal of neurology*, **18**(1), 114-120.

Smith, C., Hale, L., Olson, K., & Schneiders, A. G. (2009). How does exercise influence fatigue in people with multiple sclerosis?. *Disability and rehabilitation*, **31**(9), 685-692.

Smits, B. L., Pepping, G. J., & Hettinga, F. J. (2014). Pacing and decision making in sport and exercise: the roles of perception and action in the regulation of exercise intensity. *Sports Medicine*, **44**(6), 763-775.

St Clair Gibson, A., Swart, J., & Tucker, R. (2018). The interaction of psychological and physiological homeostatic drives and role of general control principles in the regulation of physiological systems, exercise and the fatigue process–The Integrative Governor theory. *European Journal of Sport Science*, **18**(1), 25-36.

Stuifbergen, A. (1992). Meeting the demands of illness: Types and sources of support for individuals with MS and their partners. *Rehabilitation and Nursing Research*, **1**, 14-23.

Sutbeyaz, S. T., Sezer, N., Koseoglu, B. F., Ibrahimoglu, F., & Tekin, D. (2007). Influence of knee osteoarthritis on exercise capacity and quality of life in obese adults. *Obesity*, **15**(8), 2071-2076.

Sutherland, G. M. B. A., & Andersen, M. B. (2001). Exercise and multiple sclerosis: physiological, psychological, and quality of life issues. *Journal of Sports Medicine and Physical Fitness*, **41**(4), 421.

Theis, K. A., Murphy, L., Hootman, J. M., Helmick, C. G., & Yelin, E. (2007). Prevalence and correlates of arthritis-attributable work limitation in the US population among persons ages 18–64: 2002 National Health Interview Survey Data. *Arthritis Care & Research*, **57**(3), 355-363.

Thombs, B. D., Ziegelstein, R. C., Stewart, D. E., Abbey, S. E., Parakh, K., & Grace, S. L. (2008). Physical health status assessed during hospitalization for acute coronary syndrome predicts mortality 12 months later. *Journal of psychosomatic research*, **65**(6), 587-593.

Tucker, R. (2009). The anticipatory regulation of performance: the physiological basis for pacing strategies and the development of a perception-based model for exercise performance. *British Journal of Sports Medicine,* **43**(6), 392-*400*.

Ulmer, H. V. (1996). Concept of an extracellular regulation of muscular metabolic rate during heavy exercise in humans by psychophysiological feedback. *Experientia,* **52**(5), 416-420

van den Berg-Emons, R. J., Bussmann, J. B., & Stam, H. J. (2010). Accelerometry-based activity spectrum in persons with chronic physical conditions. *Archives of physical medicine and rehabilitation*, **91**(12), 1856-1861.

van den Berg-Emons, R. J., Bussmann, J. B., Haisma, J. A., Sluis, T. A., van der Woude, L. H., Bergen, M. P., & Stam, H. J. (2008). A prospective study on physical activity levels after spinal cord injury during inpatient rehabilitation and the year after discharge. *Archives of physical medicine and rehabilitation*, **89**(11), 2094-2101.

Van der Ploeg, H. P., Streppel, K. R., Van der Beek, A. J., Van der Woude, L. H., Vollenbroek-Hutten, M. M., Van Harten, W. H., & Van Mechelen, W. (2007). Successfully improving physical activity behavior after rehabilitation. *American Journal of Health Promotion*, **21**(3), 153-159.

van der Werf, S. P., Prins, J. B., Vercoulen, J. H., van der Meer, J. W., & Bleijenberg, G. (2000). Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. *Journal of psychosomatic research*, **49**(5), 373-379.

Van Kessel, K., & Moss-Morris, R. (2006). Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *Journal of psychosomatic research*, **61**(5), 583-585.

van Koulil, S., van Lankveld, W., Kraaimaat, F. W., van Helmond, T., Vedder, A., van Hoorn, H., ... & van Riel, P. L. (2010). Tailored cognitive–behavioral therapy and exercise training for high-risk patients with fibromyalgia. *Arthritis care & research*, **62**(10), 1377-1385.

Venhorst, A., Micklewright, D., & Noakes, T. D. (2018). Towards a three-dimensional framework of centrally regulated and goal-directed exercise behaviour: a narrative review. *British Journal of Sports Medicine*, **52**(15), 957-966.

Vercoulen, J. H. M. M., Alberts, M., Bleijenberg, G. (1999). The checklist individual strength (CIS). *Gedragstherapie*, **32**(131), 6.

Vestergaard, S., Nayfield, S. G., Patel, K. V., Eldadah, B., Cesari, M., Ferrucci, L., ... & Guralnik, J. M. (2009). Fatigue in a representative population of older persons and its association with functional impairment, functional limitation, and disability. Journals of Gerontology Series A: *Biomedical Sciences and Medical Sciences*, **64**(1), 76-82.

Wagenmakers, R., van den Akker-Scheek, I., Groothoff, J. W., Zijlstra, W., Bulstra, S. K., Kootstra, J. W., ... & Stevens, M. (2008). Reliability and validity of the short questionnaire to assess health-enhancing physical activity (SQUASH) in patients after total hip arthroplasty. *BMC Musculoskeletal Disorders*, **9**(1), 141.

Wallman, K. E., Morton, A. R., Goodman, C., Grove, R., & Guilfoyle, A. M. (2004). Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Medical Journal of Australia*, **180**(9), 444.

Ward BW, Schiller JS, Goodman RA. (2014). Multiple chronic conditions among US adults: a 2012 update. Preventing Chronic Disease,**11**, E62.

Ware Jr, J. E., Kosinski, M., & Keller, S. D. (1996). A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical care*, **34**(3), 220-233.

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical care*, ***30***(6), 473-483.

Wendel-Vos, G. W., Schuit, A. J., Saris, W. H., & Kromhout, D. (2003). Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *Journal of clinical epidemiology*, **56**(12), 1163-1169.

White, P. D., Goldsmith, K. A., Johnson, A. L., Potts, L., Walwyn, R., DeCesare, J. C., ... & Bavinton, J. (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *The Lancet*, **377**(9768), 823-836.

Whitehead, L. (2009). The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. *Journal of pain and symptom management*, **37**(1), 107-128.

Wiborg, J. F., Knoop, H., Stulemeijer, M., Prins, J. B., & Bleijenberg, G. (2010). How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. *Psychological medicine*, **40**(8), 1281-1287.

Wolfe, F. (1999). Determinants of WOMAC function, pain and stiffness scores: evidence for the role of low back pain, symptom counts, fatigue and depression in osteoarthritis, rheumatoid arthritis and fibromyalgia. *Rheumatology* (Oxford, England), **38**(4), 355-361.

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., ... & Fam, A. G. (1990). The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis & Rheumatology*, **33**(2), 160-172.

World Health Organization. (2001). International Classification of Functioning, Disability, and Health (ICF). ICF full version. Geneva, Switzerland. URL http://www.who.int/classifications/drafticfpracticalmanual2.pdf?ua=1. Last retrieved on 18.05.18

World Health Organization. (2002). Physical activity. URL http://www.who.int/en/news-room/fact-sheets/detail/physical-activity. Last retrieved on 20.12.17.

World Health Organization. (2002). The world health report 2002: reducing risks, promoting healthy life. Geneva. URL http://www.who.int/whr/2002/en/whr02_en.pdf?ua=1. Last retrieved on 11.05.16

World Health Organization. (2004a). Global Burden of Disease. URL http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Last retrieved on 19.05.18.

World Health Organization. (2004b). Atlas: Country Resources for Neurological Disorders. Results of a collaborative study of World Health Organization and World Federation of Neurology. Geneva. URL http://www.who.int/iris/handle/10665/43075. Last retrieved on 1.01.17

World Health Organization. (2010). Global recommendations on physical activity for health. URL http://whqlibdoc.who.int/publications/2010/9789241599979_eng.pdf. Last retrieved on 2.09.15.

APPENDICES

Appendix 1

Activity Pacing and Risk of Overactivity Questionnaire (APQ)

Instructions: Circle the number that applies to you.

.	Never	Rarely	Sometimes	Often	Very Often
A. During the day I plan several moments to recover	1	2	3	4	5
B. I perform my activities at a slow pace.	1	2	3	4	5
C. When performing my activities, I take my fatigue into account.	1	2	3	4	5
D. When I'm engaged in an activity, I find it difficult to stop timely.	1	2	3	4	5
E. I alternate intensive activities with less intensive activities.	1	2	3	4	5
F. I divide my activities over the day	1	2	3	4	5
G. I find it hard to limit my activities	1	2	3	4	5

Appendix 2

Fatigue Severity Scale (FSS)

Instructions: Circle the number that best represents your response to each question.

Scoring range: 1=strongly disagree with the statement to 7=strongly agree with the statement.

During the past week, I have found that:	Score						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Appendix 3

Short Questionnaire to assess Health Enhancing Physical Activity (SQUASH)

Think about an average week in the past months. Please indicate how many days per week you performed the following activities, how much time on average you were engaged in this, and (if applicable) how strenuous this activity was for you?

Commuting Activities | days per week | average time per day | Effort (circle)
(round trip)

Walking to/from work or school	days	hour	minutes	slow /moderate /fast
Cycling to/from work or school	days	hour	minutes	slow /moderate /fast

Not applicable

Leisure Time Activities

Hiking	days	hour	minutes	slow /moderate /fast
Cycling	days	hour	minutes	slow /moderate /fast
Gardening	days	hour	minutes	light/moderate/intense
DIY jobs	days	hour	minutes	light/moderate/intense

Sports (please write down yourself) e.g., tennis, fitness, skating, swimming, dancing

1.	days	hour	minutes	light/moderate/intense
2.	days	hour	minutes	light/moderate/intense
3.	days	hour	minutes	light/moderate/intense
4.	days	hour	minutes	light/moderate/intense

Household Activities

Light household work (cooking, washing dishes, ironing, child care)	days	hour	minutes
Intense household work (scrubbing floor, walking with heavy shopping bags)	days	hour	minutes

Activity at Work and School

Light work (sitting/standing with some walking, e.g., a desk job)	hour	minutes
Intense work (regularly lifting heavy objects at work)	hour	minutes

Not applicable

Appendix 4

RAND 12-Item Health Survey

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
3. Climbing a few flights of stairs	[1]	[2]	[3]

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Circle One Number on Each Line)

	Yes	No
4. Accomplished less than you would like	1	2
5. Were limited in the kind of work or other activities I do	1	2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Circle One Number on Each Line)

	Yes	No
6. Accomplished less than you would like	1	2
7. Didn't do work or other activities as carefully as usual	1	2

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Circle One Number)	
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks (Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9. Have you felt calm and peaceful?						
10. Did you feel very energetic?						
11. Have you felt downhearted and blue?						

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (Circle One Number)	
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

Appendix 5

Expectation of Fatigue in relation to physical activity

Do you expect to be fatigued from physical activities? Circle the number that best represents your response.

Not at all	A little bit	Moderately	Quite a bit	Extremely
1	2	3	4	5

Appendix 6

Logbook

Please score your activity patterns since the last time by rating each of the question on a scale of 0 – 4 (0 = not at all, 1= very little, 2 = sometimes, 3 = most of the time, 4 = always).

1) How often have you gone slowly to do your activities?

2) How often have you taken your fatigue into account to do your activities?

3) How often did you alternate intensive activities with less intensive activities; and

4) How often did you break activities into manageable pieces to do them?

Please score your experience of fatigue since the last time on a scale of 0 – 4 (0 = no fatigue, 1= mild fatigue, 2 = moderate fatigue, 3 = severe fatigue, 4 = extremely severe fatigue).

Please score how many activities you performed since the last time on a scale of 0 – 4 (0=no activities, 1= minimal activities, 2 = moderate activities, 3 = several activities, 4 = extreme number of activities).

Please also enter your wake up time and bedtime for each day.

Time / Day	Wake up time	Morning (before 11am)						Afternoon (by 3pm)						Evening (by 7pm)						Bed time
		Activity Patterns				Fatigue	Activity	Activity Patterns				Fatigue	Activity	Activity Patterns				Fatigue	Activity	
		1	2	3	4			1	2	3	4			1	2	3	4			
Monday																				
Tuesday																				
Wednesday																				
Thursday																				
Friday																				
Saturday																				
Sunday																				

Appendix 7

Descriptive data of tailored activity pacing intervention effect at 4-weeks follow-up

Variable	Group	Mean ± Standard deviation
Fatigue severity	Tailored activity pacing (n=11)	4.33 ± 1.51
	Control (n=10)	5.36 ± 1.52
Expectation of fatigue	Tailored activity pacing (n=11)	3.00 ± .77
	Control (n=10)	3.80 ± .92
Activity counts	Tailored activity pacing (n=11)	295.85 ± 161.63
	Control (n=10)	208.10 ± 99.80
Activity variability	Tailored activity pacing (n=11)	.16 ± .04
	Control (n=10)	.20 ± .07
Perceived activity	Tailored activity pacing (n=11)	4026.36 ± 2564.47
	Control (n=10)	6075.00 ± 4746.99
Health-related quality of life	Tailored activity pacing (n=11)	65.45 ± 13.94
	Control (n=10)	52.44 ± 22.18
Engagement in pacing	Tailored activity pacing (n=11)	3.11 ± .60
	Control (n=10)	3.22 ± .85
Perceived risk of overactivity	Tailored activity pacing (n=11)	3.59 ± 1.02
	Control (n=10)	3.40 ± 1.05