Bjørnar Kristoffersen Berli

Effects of a 4-week Inpatient Multidisciplinary Intervention on Health Status and Physical Ability in Multiple Sclerosis and Parkinson's Disease Patients

Hovedoppgave for Profesjonsstudiet i Psykologi

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Norges teknisk-naturvitenskaplige universitet
Fakultet for samfunns- og utdanningsvitenskap
Institutt for Psykologi

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Preface

This paper is based on data collected through a longstanding cooperation between Prof. Torbjørn Rundmo at the Norwegian University of Science and Technology, and Randi Dalen and Bente Oldren at Kastvollen Rehabilitation Center. Tests and surveys completed as part of rehabilitation routines from 2014 to 2017, by the professional staff at Kastvollen, has made this research possible. I was engaged in collecting data, analyzing results, and writing between March 2017 and January 2018.

The project was undertaken to fulfill graduation requirements for the Clinical Psychology degree at the Norwegian University of Science and Technology. It is written for health care professionals working in the field of rehabilitation of neurological disorders, focusing on patients' perceptions of disease impact and treatment.

I would like to thank my supervisor Prof. Torbjørn Rundmo for his superb guidance, support and patience, and for providing the opportunity to work with this project. I would also like to thank Randi Dalen, Bente Oldren and the rest of the staff at Kastvollen for enabling this research, and for their profound interest in providing the best possible care for their patients. Finally, I extend my gratitude to my wife Astrid for the support and motivation throughout the project.

Best regards,

Bjørnar Kristoffersen Berli
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Abstract

Objectives: The study has two objectives: (1) Investigate the effects of a multidisciplinary intervention (MDI) for multiple sclerosis (MS) and Parkinson's disease (PD) patients on physical ability and self-perceived health status. (2) Examine the relationship between physical ability and health status in these patient groups.

Methods: 110 patients (44 with PD, 66 with MS) were enrolled in a 4-week inpatient MDI program. Measures of health status (SF-12) and physical ability (6-minute walking, timed up-and-go test, and sit-to-stand test) were administered before and after intervention.

Results showed significant improvements on physical performance (low to moderate effect sizes) and increased physical and mental health status (moderate to strong effect sizes) in both patient groups. Physical health status (PCS) correlated significantly with all three physical tests (Pearson's r between 0,28 and 0,48). Physical test scores showed a significant predictive value on PCS, explaining 11-14% of the variance.

Conclusion: MS and PD patients seem to benefit in the short term from a multidisciplinary intervention, improving both objective and subjective perceptions of health. As expected, physical ability was closely related to perceived physical health, but not mental health, highlighting the importance of addressing psychological symptoms separately in treatment. The study supports a holistic multidisciplinary approach to treatments for PD and MS patients.

Contents

Introduction

Multiple Sclerosis (MS) and Parkinson's disease (PD) are two common chronic progressive neurodegenerative diseases in Norway, affecting 206 per 100 000 (Berg-Hansen, Moen, Harbo, & Celius, 2014) 12,6 per 100 000 (Alves et al., 2009) of the population respectively. MS is characterized by a loss of myelin in the central nervous system due to a chronic inflammatory autoimmune response. Demyelination and axonal loss disrupts communication within the nervous system resulting in a wide array of symptoms which may include various cognitive and affective impairments, tremors, clumsiness and poor balance, stiffness, bladder dysfunction, impotence, constipation, impaired vision, speech impairments, pain and fatigue (Compston & Coles, 2002). Parkinson's disease is characterized by a loss of dopamine-generating cells in the substantia nigra, although the mechanisms behind this degeneration is unknown. Cardinal symptoms of PD include bradykinesia, or slowness of movement (Berardelli, Rothwell, Thompson, & Harriet, 2001), weakness, tremor, rigidity and postural instability (Pagonabarraga, 2016). Although motor symptoms are the most recognizable symptoms of PD, especially in its early stages, various cognitive and emotional problems are also common. These include depression, constipation, pain, sleep disorders, genitourinary problems, sensory difficulties, and in later stages dementia (Chaudhuri, Healy, & Schapira, 2006).

The demographics of the two diseases differ. MS affects women more than men, with a gender ratio of 2,2:1, and has a relatively young age of onset, 40,4 years of age in Norway (Benjaminsen, Olavsen, Karlberg, & Alstadhaug, 2014). PD affects men more than women, with a 1,58:1 ratio, and generally has a much older age of onset, around 67 years of age in Norway (Alves et al., 2009). With advances in treatment, people with MS are living longer (median 40,5 years after diagnosis) and most PD patients will have a survival close to normal (a standardized mortality ratio of 1,52 in Norwegian patient population; Herlofson, Lie, Årsland, & Larsen, 2004). However, patients do become increasingly impaired as the degeneration progresses.

As the 'quantity of life' for these patient groups increases, focus is shifting towards the domain of 'quality of life' among people with MS and PD. The nature of MS and PD make the people affected susceptible to a lower QOL than the normal population. Benito-Leon, Morales, Rivera-Navarro and Mitchell (2003) identified several factors of MS which are especially taxing on patients' psychological and social well-being, including early onset of the disease, unstable properties of the condition, effects on higher cognitive functions, the relative

preservation of insight and the absence of good treatments. In people with PD, motor symptoms such as falls, restrictions in mobility and dyskinesias, as well as emotional disturbances, social embarrassment, and sleep disturbances have been indicators of reductions in QOL (Martinez-Martin, 1998). Traditional clinical evaluation has focused on objective tests and scales for cognitive and physical ability in assessing treatment, but objective disability and subjective quality of life often differ (Martinez-Martin, 1998). This highlights the importance of bringing patients' subjective experiences into focus. Quality of life measures should be an essential part of assessing symptoms and treatment for MS and PD patients.

Definition of Quality of Life

There is no consensus on a single definition of quality of life in the field. Health research commonly distinguishes between the patient-based outcomes of quality of life (QOL), health-related quality of life (HRQOL), and self-perceived health status (HS). The broad construct of QOL is defined by some researchers as a subjective global judgement of satisfaction with life (Pavot & Diener 1993; Rejeski & Mihalko, 2001), differentiating it from umbrella-terms containing multiple facets. The advantage of a simple, singular definition is in the possibility of elevating the QOL concept to a psychological construct to drive theory (Rejeski & Mihalko, 2001). The disadvantage of a global definition is not capturing nuances of people's experiences in different areas of their lives, becoming too general a concept for clinical populations (Motl & Gosney, 2008). This is captured by other definitions of QOL as an umbrella-term containing a variety of important concepts, including physical health, psychological state, social functioning, health status, levels of independence, life conditions, spirituality etc. (WHOQOL, 1995). The main issue with such an umbrella term is in the heterogeneity of domains contained under the umbrella. As a multifaceted term, QOL has no consistent definition (i.e. different instruments include different domains), but comes closer to capturing the important experiences of patients (Rejeski & Mihalko 2001).

Some researchers label the umbrella-term of QOL as HRQOL (Rejeski & Mihalko, 2001). Others define HRQOL as a narrowing of the QOL concept to those aspects of life quality which are influenced by health status or by the impact of illness (Martinez-Martin, 1998; Benito-León et al., 2003). This corresponds with the WHO's definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (1952). Although this is a highly unrealistic definition of health, especially for patients with a chronic disease, it nonetheless captures the core characteristics of the

multidimensional HRQOL construct. Adverse symptoms as well as management and treatment of chronic diseases lead to a variety of difficulties for patients, across physical, mental, social and behavioral plains. HRQOL examines how these difficulties affect the individual's life in ways that are important to the individual (Speight, Reaney, & Barnard, 2009). However, as Guyatt, Feeny and Patrick (1993) notes, when a patient is ill, almost all aspects of life can become health related. The distinction between general QOL and HRQOL can therefore become artificial, especially in patients with chronic diseases such as MS and PD, as it becomes impossible distinguish between parts of their lives influenced by their health condition and parts that are not (Anderson & Burckhardt, 1999).

Although the definitions of QOL and HRQOL are not clear, both constructs focus on subjective limitations and experiences, but also include valuations of the impact of those limitations and experiences on the subject's life (Speight et al., 2009). This second valuation is not included in the HS-construct, which is a more descriptive measure of physical and mental symptoms and limitations (Den Oudsten, Van Heck, & De Vries, 2007). HS measures subjective appraisals of a person's ability to perform various physical, emotional and social activities (De Vries, 2001). It can measure function on either a generic or disease-specific level, depending on the questionnaire used. In short, HS is a subjective measure of health. HS should be considered a determinant of QOL/HRQOL, but should not be used directly as an indicator of QOL itself (Moons, 2004; Den Oudsten et al., 2007) as it lacks judgements about the impact of well-being and individual expectations (Martinez-Martin & Kurtis, 2013). As Testa and Simonsen (1996) points out, good health does not necessarily mean high quality of life.

Although the constructs are similar, it is important to distinguish between them, especially between HS and QOL/HRQOL. A meta-analysis by Smith, Avis and Assmann (1999) concluded that HRQOL and HS are two distinct constructs which should not be used interchangeably. Other research has indicated HS to be a mediator between physical activity and QOL (McAuley et al., 2006). A major challenge and point of criticism in the field of quality-of-life research is the ambiguity of the terms and lack of uniformity in tools (Moons, 2004; Moons, Budts, & Geest, 2006; Den Oudsten et al., 2007). There are examples where QOL and HS are used interchangeably (Bradley, 2001). Also, the same questionnaire (e.g. SF-12) is sometimes labeled as measuring HRQOL (Motl, McAuley, Snook, & Gliottoni, 2008; Ware, 2000), and other times labeled as a HS-measure (McAuley et al, 2006; Speight et al., 2009), attesting to the ambiguousness of the tools used to measure QOL constructs. This makes the interpretation of results across a broad range of studies difficult. Research aiming

for progress in the field of quality of life should strive towards more precise terminology, differentiating between the more proximal HS construct capturing patients' perceived health, HRQOL capturing perceived health as well as subjective valuations, and the more distal, global QOL construct. This paper focuses on the quality of life construct most closely related to objective function; self-perceived health status. However, research on HRQOL using similar questionnaires to HS, as well as systematic reviews encompassing both constructs are still highly relevant to the current research questions.

Exercise, Disability and Quality of Life in MS and PD patients

Although MS and PD are chronic and progressive diseases with impact on QOL and widespread motor symptoms, there is broad support for the effect of exercise in improving the physical abilities of these patient groups. Systematic reviews on physical exercise for people with MS have concluded that there is high quality evidence for exercise and physical activities improving motor-function outcomes, including mobility, muscle strength and aerobic capacity (Khan & Amatya, 2017; Latimer-Cheung et al., 2013; Snook & Motl, 2009). A meta-analysis of exercise in MS patients found exercise interventions to be associated with a 10% increase in muscular fitness outcomes, and 18% increase in cardiovascular outcomes, and effect was deemed clinically meaningful (Platta, Ensari, Motl, & Pilutti, 2016). Similar positive effects of exercise interventions on physical functioning have also been found in people with PD (Goodwin, Richards, Taylor, Taylor, & Campbell, 2008; Shen, Wong-Yu, & Mak, 2016).

If exercise can limit physical deterioration, or even improve motor functions in people with MS/PD, quality of life measures may also be affected. Several previous studies have investigated changes in HS and HRQOL in people with MS. A recent meta-analysis by Latimer-Cheung et al. (2013) reviewed 21 previous studies on the effects of exercise on HS/HRQOL in MS patients. Although several of the studies reviewed showed a positive effect, Latimer-Cheung et al. found that there was insufficient evidence for a conclusion. The authors reported difficulties in drawing conclusions across studies, as a variety of disease-specific and generic instruments were used, and variations among authors in the outcomes reported (i.e. subscale scores vs composite scores). A previous meta-analysis concluded that physical exercise is associated with a significant, but small improvement in HRQOL in people with MS (Motl & Gosney, 2008).

The effect of exercise on HS/HRQOL has also been investigated in people with PD. In a systematic review, Goodwin et al. (2008) identified four previous randomized controlled

trials on the effects of exercise on HRQOL/HS (Ellis et al., 2005; Schmitz-Hubsch et al., 2005; Buruni et al., 2006; Ashburn et al., 2007), using a variety of HRQOL outcome measures including the Sickness Impact Profile (SIP-68), the Parkinson's disease questionnaire (PDQ-39) and the EuroQOL (EQ-5D). Of these, only one study (Ashburn et al., 2007) reported a significant increase in HRQL (measured by EQ-5D) due to exercise intervention. However, Goodwin et al. (2008) synthesized the relevant data from all 4 studies, with a total of 292 participants, and found a standardized mean difference of 0,27, 95% CI 0,04 – 0,51, suggesting that exercise interventions are likely to result in improvements on HRQOL/HS. Although people with MS/PD have been found to both tolerate and benefit physically from exercise, it seems the effect on HS/HRQOL is limited and poorly supported.

Even though the effect of physical exercise on HS/HRQOL is limited, the relationship between disability/physical ability and HS/HRQOL is widely supported. HS/HRQOL has been shown to decrease as disability in MS patients increases. Henriksson, Fredrikson, Masterman and Jönsson (2001) split a population of MS patients into three groups based on disability (measured by EDSS: Kurtzke Expanded Disability Status Scale), and found a significant difference in HS/HRQOL (measured by EQ-5D) between the groups. Benito-Leon, Morales and Rivera-Navarro (2002) found significant correlations between EDSS scores and all 6 dimensions of FAMS HRQOL (Functional Assessment of Multiple Sclerosis), and Pfennings et al. (1999) found that severity of MS (EDSS score), time since diagnosis, and recent MS progression had an effect on HRQOL. In PD patients, a wide array of functional ability measurements (including Timed Up-and Go test [TUG], 6 minute walking, Freezing of Gait Questionnaire [FOG-Q], and Movement Disorder Society Revision of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS]), as well as disease severity (Hoehn and Yahr stage) have been found to both correlate with, and significantly predict changes in HS/HRQOL (Josiah et al., 2012; Tu, Hwang, Hsu, & Ma 2017; Ellis et al., 2011; Nutt et al., 2014; Soh et al, 2013). The strongest relationships were found between physical ability and the mobility-related subgroups of HS/HRQOL measures, i.e. PDQ-M and SF-36 PCS (Ellis et al., 2011; Josiah et al, 2012). This is expected, as the mobility-related facets of HS rate a patient's perceptions of own physical ability. Overall, HRQOL in MS and PD patients seems to be lower the more disabling, severe, and long-lasting the disease is.

In summary, exercise interventions have been found effective in improving physical ability (reducing disability) in MS and PD patients. Disability has also shown to be significantly related to patient reported HS and HRQOL, especially to the physical sub-scores of the HS/HRQOL-measures. Even so, interventions focusing on exercise and physical

therapy have shown weak results in improving patient-perceived health. This suggests that relying on physical therapy alone is insufficient for achieving improvements that are meaningful to the patients. A broader, multidisciplinary approach to treatment may be necessary to positively influence quality of life in MS and PD patients, targeting social and psychological difficulties in addition to motor symptoms. A holistic treatment ideology is relevant in this approach as it emphasizes the patients' own assessment and contribution in treatment. However, effects of multidisciplinary interventions on quality of life have yet to be established (Khan, Turner-Stokes, Ng, Kilpatrick, & Amatya, 2007; Kahn, Pallant, Brand, & Kilpatrick, 2008; Van der Marck et al., 2009; Van der Marck et al., 2013a; Van der Marck et al., 2013b), few interventions employ holistic methods, and studies on the impact of inpatient rehabilitating programs on quality of life are sorely lacking.

Expanding upon previous research, the current study has two primary objectives: First, it assesses the treatment effects of a holistic 4-week inpatient multidisciplinary intervention on physical ability and health status in patients with Parkinson's disease and patients with Multiple Sclerosis. Secondly, it explores the relationship between physical ability and self-perceived health status in these patient groups. Based on previous studies, the physical component of health status is expected to correlate with tests of physical performance. Physical test scores are expected to be of predictive value for patient-perceived physical health status, while the mental component of health status is expected to show a weaker relation to measures of physical performance.

Methods

Participants

The participant group consisted of 44 patients with Parkinson's disease and 66 patients with Multiple Sclerosis admitted to an extensive 4-week rehabilitation program in Norway. The patients were chosen by the rehabilitating institution based on need of treatment and motivation. The participant group included 62 women and 48 men. Their age ranged from 36 to 84 years old, with a mean of 61,21. PD comprised the oldest patient group with a mean age of 68,16, while the MS patients had a mean age of 56,58.

Additionally, data from 27 patients who responded to McGill's Quality of Life Questionnaire before SF-12 was introduced to the program are included. 9 of these were diagnosed with Parkinson's disease, while 18 had Multiple Sclerosis; 13 were female, 14 males, and age varied between 32 and 82 years of age with a mean of 59,12.

Intervention

Each participant stayed at the treatment institution for 4 weeks, receiving multidisciplinary rehabilitation. The team consisted of physical therapists, occupational therapists, nurses, social workers, psychologists, and doctors. The intervention emphasizes a holistic approach to treatment encouraging patients to be active agents, not passive receivers, of treatment. Accordingly, the intervention was not standardized but tailored for each individual according to goals and needs identified in collaboration with the patient. Treatment included physical- and occupational therapy, weight and balance training, as well as outdoor activities. The program also emphasizes mental health with both individual and group interventions focusing on psychoeducation, strategies for self-care and coping with the diseases, health promotion advice etc. It targeted symptoms of sleep disturbances, pain, and malnutrition. Social aspects were included, involving activities such as restaurant visits, horseback riding, hikes, board games etc. Data collection was conducted at admission and at program completion.

Physical tests

The patients carried out three different physical tests aimed to measure motor function:

6-Minute-Walk Test (6MW). The 6MW is a measure of the maximum distance a person is able to walk in 6 minutes. Originally a 12-minute walk-run test of maximal oxygen uptake (Cooper, 1968), the 6MW was later modified to measure sub-maximal aerobic capacity. The test has been used extensively in research, and has shown good test-retest reliability in elderly

people (Rikli & Jones, 1998; Harada, Chiu, & Stewart; 1999; Steffen, Hacker, & Mollinger, 2002) and patients with cardiovascular disease (Guyatt et al., 1985). Construct validity has been supported through correlations with activity level in elderly people (Rikli & Jones, 1998), and maximal oxygen consumption in a variety of patient groups (Solway, Brooks, Lacasse, & Thomas, 2001). In MS patients, limitations in ADL-functions, subjective fatigue and resting heart rate have been found as significant determinants for 6MW (Savci et al., 2005). The 6MW was deemed the walk test of choice in a 2001 review (Solway et al.) because of its ease of administration, correlations with ADL functions, and tolerance in patient groups with impaired motor functions.

Timed Up-and-Go Test (TUG). The TUG test is a timed test of a subject's speed in standing up from an armchair, walking a distance of three meters, turning, walking back to the chair again, and sitting down. It was originally used for clinical observations of balance in elderly people, assessing risk of falling (Matthias, Nayak, & Isaacs, 1986). Later modified by Podsiadlo and Richardson (1991), it is now a timed test used to evaluate basic mobility skills. The validity of the test has been found satisfactory through correlation of TUG scores with measurements on the Berg Balance Scale, Dynamic Gait Index, Hauser Deambulation Index, Dizziness Handicap Inventory, and Activities-specific Balance Confidence in people with MS (Cattaneo, Regola, & Meotti, 2006). TUG has also been deemed valid for use in people with PD, and the interrater and test-retest reliability of TUG was found to be high in this patient population (Morris, Morris, & Iansek, 2011). The TUG test has been found to discriminate well between fallers and non-fallers in elderly subjects (Steffen et al., 2002; Chiu, Au.Yeung, & Lo, 2003).

Sit-To-Stand Test (STS). The STS test is administered by measuring the number of times a person is able to stand and sit on a chair in the span of 30 seconds. It is used as a test of functional lower body strength (Bohannon, 1995), and has been shown to be a significant predictor of falls and ADL-functions in elderly people (Zhang et al., 2013; Buatois et al., 2008). It has also shown significant predictive effect on mobility disability status (measured by 800m walking and climbing a flight of stairs) in elderly people (Wang, Yeh, & Hu, 2009). The 5-repetition STS test has shown good test-retest reliability across numerous studies on older adults (Bohannon, 2011), and also been validated and found reliable amongst both PD and MS patients (Duncan, Leddy, & Earhart, 2011; Møller et al., 2012).

Quality of Life Questionnaires

12-item Short-Form Health Survey (SF-12) translated to Norwegian was used to measure patient-perceived health status. The SF-12 is a self-report questionnaire measuring generic health status. The choice of health status questionnaire had to be generic because of the inclusion of two different diagnostic groups. Ware, Kosinski, Dewey, and Gandek (1993) originally developed a 36-item questionnaire (SF-36) to capture health outcomes and disease burden from the patient point of view. It was designed to measure the eight most central concepts related to health, disease and treatment derived from the Medical Outcomes Study (Ware et al., 1993), and has become a widely used tool for measuring health status (Ware, Kosinski, Turner-Bowker, & Gandek, 2002). The development of SF-12 stems from the need of an even shorter questionnaire, being easier to administer, and less taxing for a patient to complete. Ware, Kosinski, and Keller (1996) derived 12 items from the SF-36 using regression methods, with the intent to reproduce two of the original eight constructs: the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. The SF-12 has been shown to accurately reproduce the two summary scores PCS and MCS in the general population (Ware et al., 1996) and among various patient groups, including PD, congestive heart failure, sleep apnea, and benign prostatic hypertrophy (Jenkinson et al., 1997). Substantial correlations between the SF-36 and SF-12 outcomes has also been found specifically in the Norwegian population (correlations of 0,95 [PCS] and 0,97 [MCS]) (Gandek et al., 1998). Based on symptoms cognitive impairments and fatigue being common in people with PD or MS, the SF-12 was chosen for its briefness and ease of administration. The PCS and MCS summary scores were calculated using the published algorithm (Ware et al., 2002).

McGill's Quality of Life Questionnaire (MQOL). Developed by Cohen, Mount, Strobel and Bui (1995) the MQOL is a generic measure of quality of life designed for people with life-threatening diseases. It includes six facets: Overall quality of life, physical well-being, physical symptoms, psychological symptoms, existential well-being, and support. The questionnaire has mostly been used in palliative care, and has shown adequate internal consistency and reliability (Cohen et al., 1997). The MQOL was initially used for this study, but observations and qualitative assessments during administration indicated reduced validity for the patient group. Cognitive symptoms are prevalent among MS and PD patients and the participants showed difficulties completing the questionnaire, resulting in many incomplete responses in the data set. Many of the questions in the MQOL explore concepts related to

global quality of life. SF-12 was subsequently selected as it measures health status, a less abstract construct more closely related to the patients' disabilities. The SF-12 is also shorter than the MQOL, further easing the strain of completing the questionnaire.

Analyses

To test treatment effect on physical ability, paired samples t-tests were conducted, independently comparing the results of three physical tests, 6-minutes walking (Walk), Timed up-and-go test (TUG), and stand-sit test (Stand), before and after the intervention. Treatment effects were tested for the total patient population, and for each patient group separately. The data was also split among people with low-, intermediate- and high pretest physical scores, and treatment effect was tested for each group separately. Similarly, paired samples t-tests were conducted to test the treatment effect on the SF-12 outcomes on the Physical Composite Scale (PCS) and Mental Composite Scale (MCS). T-tests were also used to analyze the difference in SF-12 HS between the treatment group and the general population.

A Cox proportional hazard model was used to examine factors associated with program success. Cox regression is an analysis measuring the effect of different variables upon the time of a specified event. In this study it was used to examine the effect of various categorical covariates on the level of improvement on physical ability and health status. The categorical covariates used was pretest physical ability (patient data grouped into three groups of low-, intermediate- or high-scorers on each of the physical tests), posttest physical ability (low-, intermediate- or high-scorers) or diagnostic group (MS or PD). The dependent variables were either posttest physical ability (on 6MW, STS and TUG separately), posttest HS (PCS or MCS) or changes in these variables (i.e. improvement from pretest to posttest scores). The time variable of the analysis was continuous. The effects of covariates are interpreted through hazard ratios (HR) and β-values, where a HR of 1 indicates no difference between the groups. With a significant HR, the β-value shows the direction and magnitude of the difference. Usually utilized for survival analyses (i.e. the specified event is death), the cox regression used in this study analyzes the chance of "surviving" each increment of further improvement.

To test differences in improvements on physical tests and SF-12 outcomes due to various demographics (diagnosis, age, gender), a multivariate analysis of variance (MANOVA) was used. Significant group effects found by MANOVA was further investigated by subsequent univariate F-tests.

Bivariate correlations were analyzed examining the strength of the associations between the two SF-12 outcomes (PCS and MCS) and the three physical outcome measures (6MW, TUG, STS). Multiple hierarchical regression analyses were conducted, testing the predictive value of various variables on SF-12 outcome measures. The independent variables were entered systematically as two different blocks. Block 1 consisted of static variables not modifiable through intervention (i.e. demographic variables: diagnosis, gender, and age). Block 2 comprised the three physical variables responsive to treatment (6MW, TUG, STS). The analysis was conducted four times, with different dependent variables: Pretest PCS and MCS scores of SF-12, and posttest PCS and MCS scores. The physical test scores of block 2 were in accordance with the time of measurement of the dependent variable (i.e. when analyzing regression for pretest PCS, the independent variables used were pretest 6MW, TUG and STS). All data was analyzed using the IBM SPSS 23 software.

Results

1.1 Treatment effect on Physical Performance

Table 1: Differences in physical performance before and after treatment:

	Parkinson's disease					Multiple Sclerosis				
	Before	SD	After	SD	t	Before	SD	After	SD	t
6MW	494,72	139,35	548,58	152,08	-7,35*	319,76	178,23	378,42	186,73	-8,03*
TUG	7,95	5,09	6,56	4,27	3,64*	14,24	9,88	12,10	8,46	3,54*
STS	14,33	5,87	17,21	6,35	-7,71*	9,69	4,03	12,51	5,21	-8,00*

N=43-103; *p<0,01
Note: 6MW = 6-minute walk test; TUG = Timed up-and-go test; STS = Sit-to-stand test

Table 1 shows the results of paired samples t-tests analyzing differences in physical performance before and after treatment intervention. There were significant improvements in performance on all three tests across the two patient groups ($p < 0,01$). Both the patient group with Parkinson's disease and the patient group with Multiple Sclerosis walked further on the 6MW test after treatment than before treatment, improving by 53,86 meters ($t = -7,35$, $p < 0,01$) and 58,66 meters ($t = -8,03$, $p < 0,01$) respectively, showing low to moderate effect sizes (Cohen's $d = 0,37$ and $d = 0,32$). The PD group reduced test-time on the TUG test by 1,39 seconds ($t = 3,64$, $p < 0,01$) and the MS group reduced time by 2,14 seconds ($t = 3,54$, $p < 0,01$), but the effect sizes here were low (Cohen's $d = 0,29$ and $d = 0,23$). Both patient groups also improved on the STS test increasing the amount of times they were able to stand and sit by 2,88 (PD, $t = -7,71$, $p < 0,01$) and 2,82 (MS, $t = -8,00$, $p < 0,01$). This improvement was of moderate effect size (Cohen's $d = 0,47$ and $d = 0,60$). These results show that the treatment intervention was successful in improving the physical ability of the patients, although modest effect sizes indicate that these improvements may be somewhat limited.

Table 2: Differences in physical performance before and after treatment according to pre-treatment physical ability.

	Low pretest score			Medium pretest score			High pretest score		
	Before	After	t	Before	After	t	Before	After	t
6MW	184,12	224,45	-4,19**	418,45	500,48	-8,72**	582,71	631,76	-7,73**
TUG	20,63	17,07	3,46**	8,24	6,94	6,33**	5,33	4,84	5,42**
STS	6,23	8,81	-6,91**	10,39	13,3	-9,51**	17,15	20,16	-5,34**

N = 31-38; **p < 0,01
Note: 6MW = 6-minute walk test; TUG = Timed up-and-go test; STS = Sit-to-stand test

For analytical purposes, the data was split into three groups according to performance on each of the physical tests before treatment. The low-performance group consisted of the patients scoring in the lower third of the population on each of the three tests separately (i.e. walked shortest on the 6MW test, completed the TUG test slowest, performed fewest repetitions on the STS test), the intermediate group placing in the middle third, and the high pretest group scoring in the upper third of the participant population. Analysis of treatment effects show significant improvements in all three groups, on all three physical tests ($p < 0,01$) (see table 2). On the 6MW test, the patients in the low- and high-performance groups showed a moderate improvement (Cohen's $d = 0,44$ and Cohen's $d = 0,56$ respectively), while the intermediate group showed a strong improvement (Cohen's $d = 1,56$). Similarly, the groups of low- and high-scorers on the TUG-test pretreatment showed an improvement with moderate effect sizes (Cohen's $d = 0,39$ and Cohen's $d = 0,58$ respectively), and the intermediate group showed a stronger improvement (Cohen's $d = 1,00$). The strongest increase on the STS test was shown in the intermediate group as well as well (Cohen's $d = 1,82$), but here the low-scoring group showed an increase with strong effect size (Cohen's $d = 1,16$) and the high-scorers improved moderately/strongly (Cohen's $d = 0,60$).

Upon further inspection, a significant difference in improvement on the 6MW test between the three groups arranged by pretest 6MW score was found, as determined by one-way ANOVA ($F(2,95) = 6,48$, $p < 0,01$). A Tukey post hoc test revealed that the improvements in 6MW distance was significantly lower among the high-scoring group ($49,06 \pm 37,0$, $p < 0,05$) and the low-scoring group ($40,33 \pm 55,3$, $p < 0,01$) compared to the intermediate group ($82,03 \pm 52,4$). No significant differences were found in STS improvements among the low-, medium- and high-scoring pretest STS groups ($F(2,99) = 0,25$, $p = NS$). However, a one-way ANOVA revealed a statistically significant difference in TUG improvements between the three groups arranged by pretest TUG results ($F(2,100) = 6,40$, $p < 0,01$). Here, a Tukey post hoc test revealed that the group with the poorest TUG performance before treatment improved more ($3,56 \pm 6,2$) than both the high-functioning ($0,49 \pm 0,5$, $p < 0,01$) and medium-functioning groups ($1,30 \pm .1,2$, $p < 0,05$). No significant difference was observed between the medium- and high-scoring groups. These results indicate that both high-, moderate- and low-functioning patients benefit from the treatment program, but the magnitude of the improvements seem to differ among the various groups and tests.

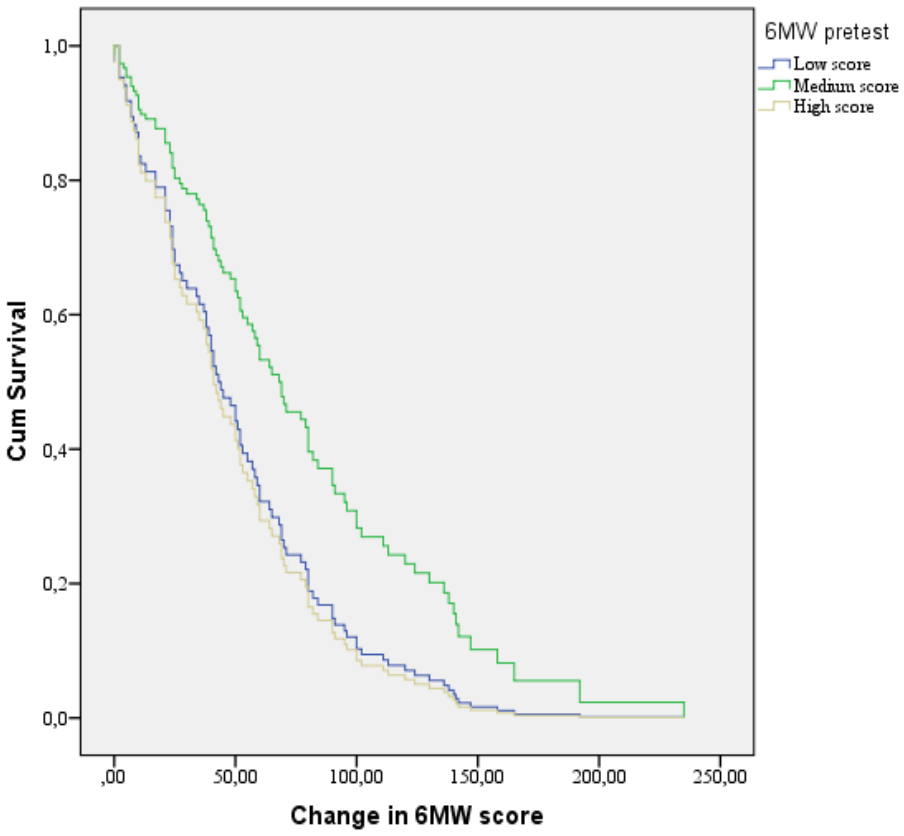
Table 3: Covariates related to change in physical performance

	Pretest score	N	B	Hazard ratio	95,0% CI for Exp(B)	
					Lower	Upper
Change in 6MW	Low	30	-0,08	0,93	0,50	1,71
	Medium	31	-0,66	0,51*	0,31	0,86
	High'	34				
Change in STS	Low	31	0,19	1,20	0,70	2,08
	Medium	33	0,12	1,12	0,67	1,88
	High'	36				
Change in TUG	Low	27	-3,25	0,04**	0,02	0,09
	Medium	31	-1,39	0,25**	0,13	0,46
	High'	28				

*p < 0,05, **p < 0,01
Note: The high scoring groups were used as reference groups for the analysis.
6MW = 6-minute walk test; TUG = Timed up-and-go test; STS = Sit-to-stand test

Table 3 shows associations between physical ability pretreatment and changes in physical performance during treatment, analyzed by Cox regression. These Cox regression analyses measure the chance of "surviving" each increment of posttest performance (i.e. the chance of achieving a high posttest result). Significant differences in treatment effects on the 6MW test

Figure 1: Survival function for change in 6MW according to 6MW pretest ability



between the groups was found. The patients with moderate pretest scores showed a higher probability of still improving on 6MW at time x [P(X>x)] than the patients with a better pretreatment test score (HR = 0,51, p < 0,05). This difference is illustrated in figure 1. The survival function shows how large a fraction of the treatment population (y-axis) was able to achieve a certain treatment effect (x-axis).

No difference was found between the patient groups on change in STS score, but analysis of change in TUG yielded significant results. The patients with poorest pretest ability had a greater chance of still improving at time x [P(X>x)] than the high-performance group (HR = 0,04, p < 0,01). The intermediate group also showed greater chance of improvement than the best pretest performers (HR = 0,25, p < 0,01) (see figure 2).

Figure 2: Survival function for change in TUG according to pretest TUG ability

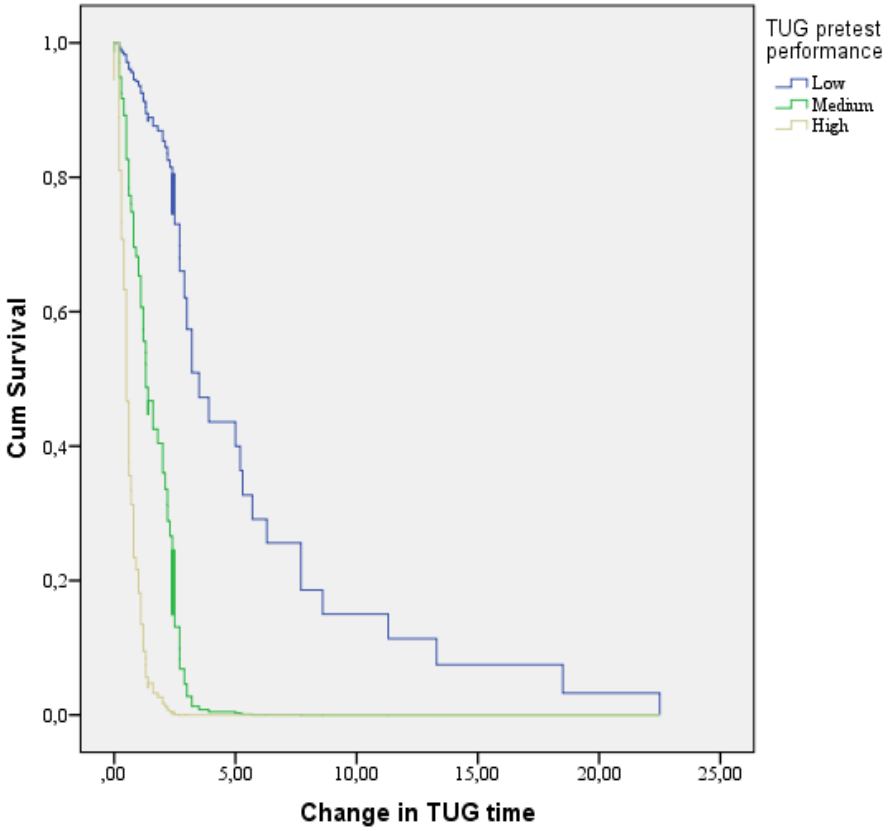


Table 4: Covariates related to posttest physical performance

	Pretest score	N	B	Hazard ratio	95,0% CI for Exp(B)	
					Lower	Upper
Posttest 6MW	Low	33	6,20	476,14**	93,37	2428,08
	Medium	31	1,74	5,69**	3,10	10,42
	High'	34				
Posttest STS	Low	31	3,29	26,80**	12,36	58,10
	Medium	33	1,78	5,93**	3,06	11,50
	High'	38				
Posttest TUG	Low	36	-4,89	0,01**	0,00	0,02
	Medium	33	-2,07	0,13**	0,06	0,25
	High'	34				

*p < 0,05, **p < 0,01
Note: The high scoring groups were used as reference groups for the analysis.
6MW = 6-minute walk test; TUG = Timed up-and-go test; STS = Sit-to-stand test

Associations between physical performance after treatment and patient group arranged according to pretest scores was also analyzed (see table 4). The results show that the high pretest-performance group had a greater chance of achieving a good posttest result than both the moderate-scorers and the low-scoring group, and this probability was significantly higher across all three physical tests (p < 0,01) (see figures 3, 4 and 5). Note that a higher score on the 6MW and STS indicates better physical ability, while a short time on TUG indicates better function.

Figure 3: Survival function for posttest 6MW distance according to pretest 6MW ability

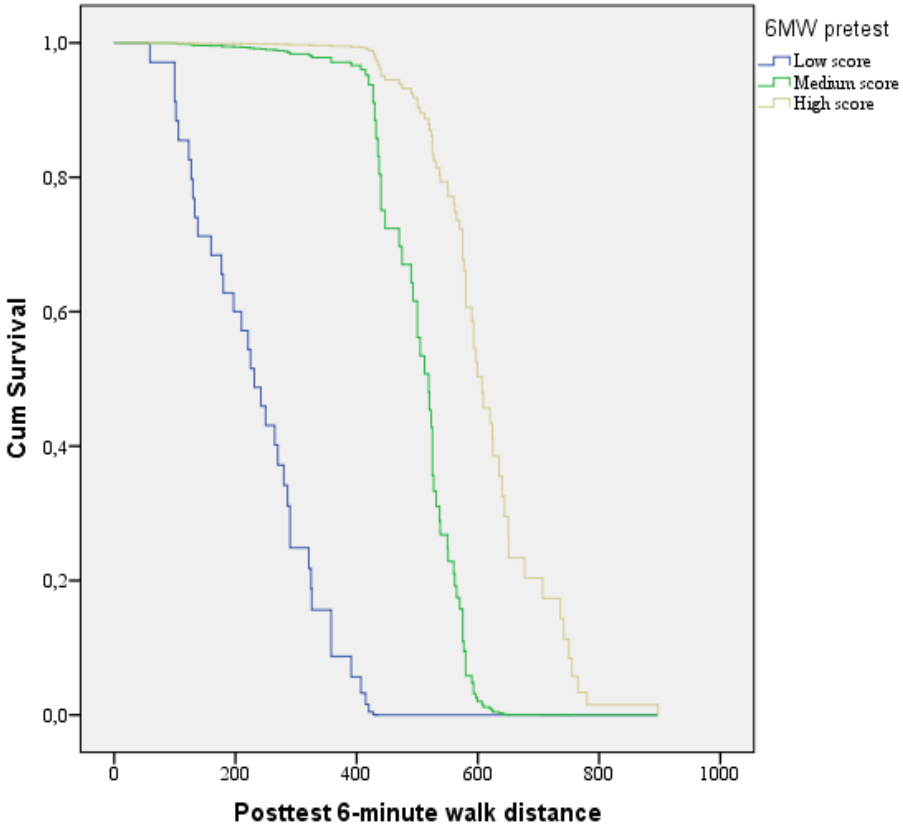


Figure 4: Survival function for posttest STS score according to pretest STS ability

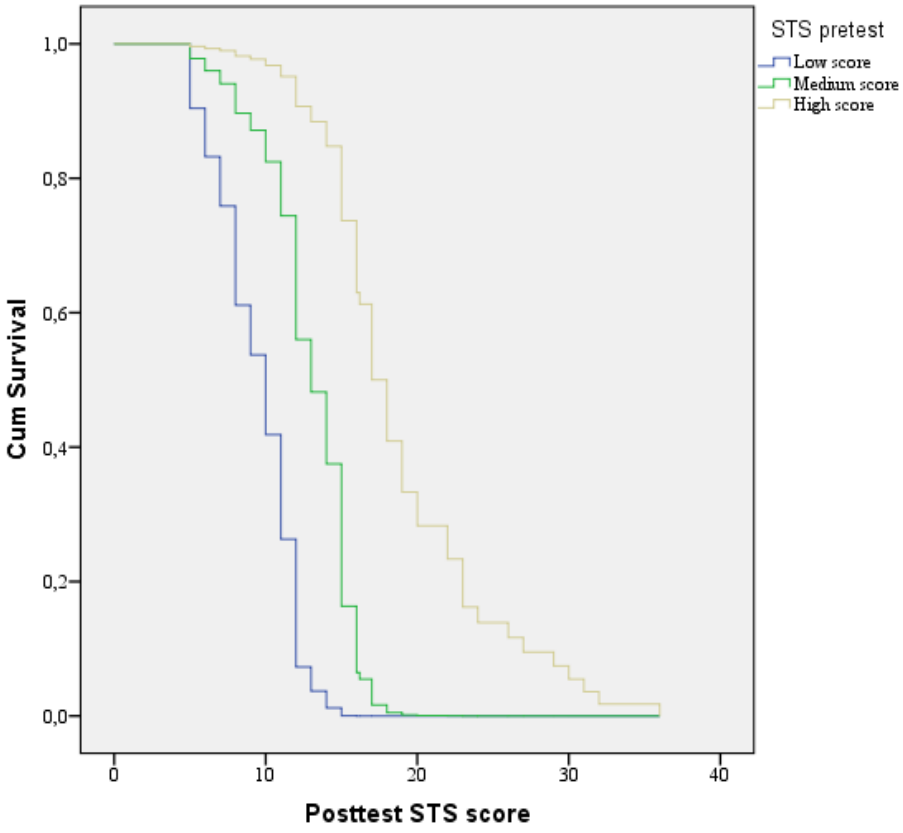
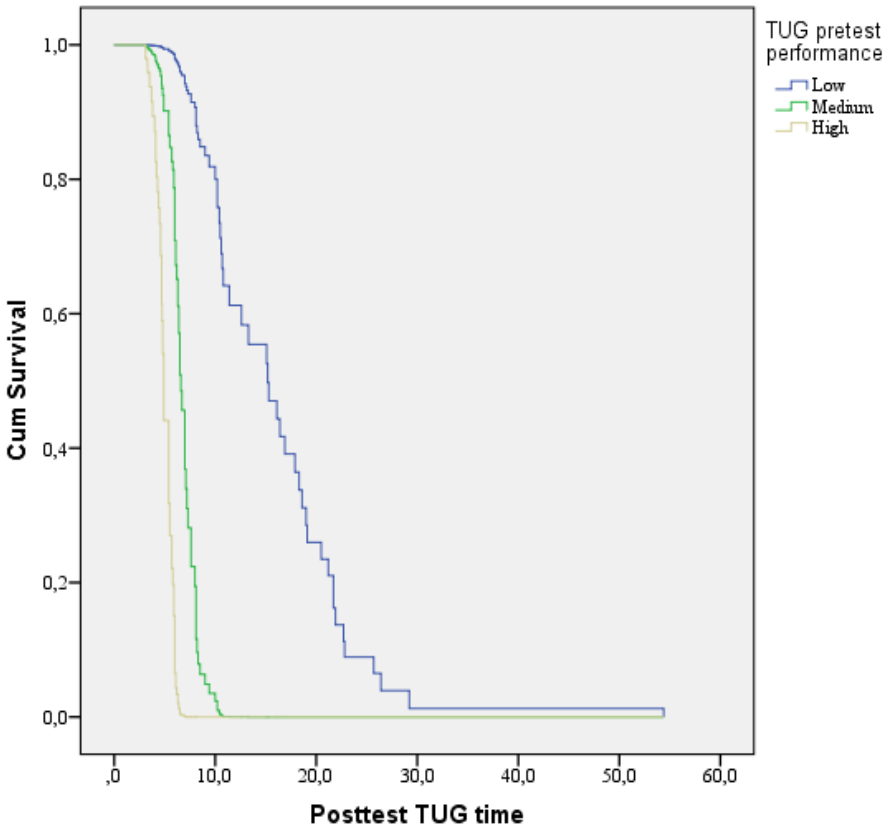


Figure 5: Survival function for posttest TUG time according to pretest TUG ability



1.2 Treatment effect on Health Status (SF-12)

Table 5: Differences in SF-12 health status before and after treatment:

	Total (N=72)			**PD (N=33)**			**MS (N=39)**		
	Before	After	t	Before	After	t	Before	After	t
PCS	36,56	42,49	-6,55**	40,42	44,15	-3,20**	33,30	41,09	-6,05**
MCS	46,55	55,38	-7,46**	47,92	54,51	-3,93**	45,39	56,12	-6,62**

**p<0,01
Note: PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score

Table 5 shows changes in SF-12 scores between pre-treatment and post-treatment measurements. There were significant improvements on both the mental and physical composite scores of SF-12 (MCS and PCS) across patient groups. The total participant group showed improvement on PCS from 36,56 to 42,49, $t(71) = 6,55$ $p < 0,05$, with a moderate effect size (Cohen's $d = 0,68$). There were improvements on MCS from 46,55 to 55,38; $t(71) = 7,46$ $p < 0,05$, with a strong effect size (Cohen's $d = 0,88$). The patient group diagnosed with PD improved on both reported PCS; $t(32) = 3,20$ $p < 0,05$, and MCS; $t(32) = 3,93$ $p < 0,05$, with moderate effect sizes (Cohen's $d = 0,47$ and $0,74$ respectively). The MS group

improved on both facets of SF-12 HS; t(38) = 6,05 p < 0,05 (PCS), and t(38) = 6,62 p < 0,05 (MCS) with strong effect sizes (Cohen's d = 0,89 and 0,99).

When divided into two age groups, 35-59 and 60-85 years of age, significant improvements in SF-12 HS were observed in both groups. The younger patients showed improvements on both PCS (t(40) = -5,10, p < 0,01) and MCS (t(40) = -6,33, p < 0,01) and these improvements were strong (Cohen's d = 0,87 and Cohen's d = 0,89 respectively). Older patients improved moderately on PCS (t(30) = -2,95, p < 0,01, Cohen's d = 0,43) and strongly on the MCS facet of SF-12 QOL (t(30) = -4,35, p < 0,01, Cohen's d = 0,86). These results show that both diagnostic groups and age groups reported improved HS measured by SF-12, with moderate to strong effect sizes.

2.1 Group differences in Physical Performance

Table 6 shows differences in physical performance between different patient groups, age groups and gender, comparing test results for the different demographic groups both before- and after treatment. An overall difference on physical scores was found between patients with Parkinson's disease and Multiple Sclerosis (Wilks λ = 0,740, p < 0,01). More specifically, PD patients walked further on the 6-minute walk test, achieved faster times on the Timed Up-and-Go test and managed more repetitions of standing and sitting on the Stand-to-Sit than MS patients both before treatment and after treatment (p < 0,01).

Table 6: Differences in physical performance among demographic groups

	Diagnosis			**Age**			**Gender**		
	PD	MS	F-value	35-59	60-85	F-value	Female	Male	F-value
Pre 6MW	494,72	323,70	26,98**	372,51	421,02	1,30	372,57	433,35	0,35
Pre TUG	7,95	12,99	13,87**	10,85	10,68	1,40	11,01	10,43	0,12
Pre STS	14,33	9,96	20,64**	11,92	11,87	8,50**	10,17	14,06	10,23**
Post 6MW	548,58	382,46	25,55**	440,42	468,59	2,58	433,02	485,09	0,17
Post TUG	6,56	11,49	13,55**	9,07	9,49	2,19	9,89	8,57	0,01
Post STS	17,21	12,82	16,36**	14,98	14,59	6,90**	13,11	16,84	7,22**

*p<0,05 **p<0,01 Wilks λ = 0,740** Wilks λ = 0,879 Wilks λ =0,825*
N=43-54; Note: PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score

No significant difference was found between age groups on physical ability, but there was an overall difference between the two genders (Wilks λ =0,825, p < 0,05). Male participants performed significantly better than female participants on the STS test both before and after treatment (F(1,89) = 10,23, p < 0,01 and F(1,89) = 7,22, p < 0,05 respectively). However, no

such gender difference was observed on the 6MW or the TUG test. No statistically significant interaction effects was observed between any combinations of the independent variable.

Table 7: Associations between diagnostic group and physical performance

		N	B	Hazard ratio	95,0% CI for Exp(B)	
					Lower	Upper
Post 6MW	Parkinson	43	-0,85	0,42**	0,26	0,70
	MS	55				
Post STS	Parkinson	43	-0,80	0,45**	0,28	0,73
	MS	60				
Post TUG	Parkinson	43	1,37	3,92**	2,23	6,92
	MS	60				

*p<0,05, **p<0,01
Note: PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score

Table 7 shows associations between diagnostic group and performance on the three physical measures after treatment. The probability of achieving a high posttest score was significantly greater for the Parkinson's patients compared to MS patients on all three physical tests; 6MW test (HR = 0,42, $p < 0,01$, see appendix figure A1), STS test (HR = 0,45, $p < 0,01$, see appendix figure A2) and TUG test (HR = 3,92, $p < 0,01$, see appendix figure A3).

2.2 Group differences in Health status

Table 8: Differences in SF-12 health status between Parkinson's and MS patients

	Parkinson	MS	F-value
Pretest PCS	40,42	33,30	12,30**
Pretest MCS	47,92	45,39	0,67
Posttest PCS	44,15	41,10	5,54*
Posttest MCS	54,51	56,12	1,22

N=33-39; * $p < 0,05$, **$p < 0,01$**;** Wilks $\lambda = 0,791$**
Note: PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score

Table 8 shows differences in measures of SF-12 quality of life between PD and MS patients. There was an overall significant difference between the patients with PD and patients with MS in SF-12 HS (Wilks $\lambda = 0,791$ $p < 0,01$). PD patients received significantly higher Physical Composite Scores than the MS group before treatment, with a score of 40,42 compared to 33,30 ($F(4,65) = 12,30$ $p < 0,01$), a difference of 7,12 points on a scale from 1-100. A significant difference in PCS is maintained post treatment with PD patients scoring

44,15 and MS patients scoring 41,10 ($F(4,65) = 5,54$ $p < 0,05$), a difference of 3,05 points. For the Mental Composite Score, no significant difference was found between the two patient groups. Further analyses by Cox regression showed significant differences between the two diagnostic groups in both facets of post-test HS (see table 9). Patients with PD showed a greater chance of still "improving" post-treatment PCS at time x [P(X>x)] than MS patients (HR = 0,61, $p < 0,05$, see appendix figure A4). For post-treatment MCS, however, MS patients showed a significantly greater chance of reporting a high score than PD patients (HR = 2,17, $p < 0,01$, see appendix figure A5).

Table 9: Associations between diagnostic group and SF-12 health status after treatment

		N	B	Hazard Ratio	95,0% CI for Exp(B)	
					Lower	Upper
Posttest PCS	Parkinson	42	-0,50	0,61*	0,38	0,98
	MS	56				
Posttest MCS	Parkinson	42	0,78	2,17**	1,30	3,62
	MS	56				

*p<0,05, **p<0,01
Note: PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score

Exploring gender differences, male participants was found to report significantly higher PCS before treatment than female participants (Wilks $\lambda = 0,804$, $p < 0.01$; $F(1, 70) = 8,56$ $p < 0,05$), but this difference did not persist post treatment. No differences in HS was found between the younger patients and the older patients (Wilks $\lambda = 0,949$, NS), and no interaction effect was observed between diagnosis, age group and gender.

McGill's QOL Questionnaire Treatment effects

The quality of life data from the patients completing McGill's QOL questionnaire shows an increase in QOL (measured by averaging all questionnaire items) from before treatment to after treatment. The total group of 27 patients completing the questionnaire showed a significant improvement from 4,74 to 5,05 on the scale from 1-10 ($t(26) = -3,95$, $p < 0,01$) with a large effect size (Cohens d = 0,84). When analyzing the two different diagnostic groups individually, no significant improvement in QOL was found among the 9 Parkinson patients who completed the questionnaire, but the MS group improved significantly from 4,71 to 5,13 ($t(16) = -3,91$, $p < 0,01$) with a large effect size (Cohens d = 1,13). Exploring differences in McGill's QOL among the two patient groups, age groups or genders, no overall significant difference was found. Although limited in number of participants, the data from

the McGill-responders indicate that the treatment may have a positive effect on overall quality of life.

3.1 Comparing Physical Ability to Health Status

Table 10: Relationships between physical performance and health status

	PrePCS	PreMCS		PostPCS	PostMCS
Pre 6MW	0,48**	0,03	**Post 6MW**	0,44**	-0,24*
Pre TUG	-0,43**	0,04	**Post TUG**	-0,32**	0,29**
Pre STS	0,40**	0,24*	**PostSTS**	0,28**	-0,03

N= 75-103; *p<0,05 **p<0,01
Note: Reported values are Pearson's r. 6MW = 6-minute Walking Test; TUG = Timed Up-and-Go Test; STS = Stand-to-Sit Test; PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score.

Correlation analyses (table 10) show that the Physical Composite Score of SF-12 (PCS) correlated significantly with all three measures of physical performance both before and after treatment. Individuals scoring higher on PCS walked further in the 6MW test ($r = 0,48$, $p < 0,01$ before, and $r = 0,44$, $p < 0,01$ after), achieved a faster time on the TUG test ($r = -0,43$, $p < 0,01$ before and $r = -0,44$, $p < 0,01$ after), and performed better on the STS test ($r = 0,40$, $p < 0,01$ before, and $r = 0,28$, $p < 0,01$ after). The correlations of the Mental Composite Score of SF-12 (MCS) were less clear-cut. Before treatment, individuals scoring higher on MCS performed significantly better in the STS ($r = 0,24$, $p < 0,05$), but the pretest MCS score showed no relationship with the other two physical tests. After treatment, no correlation was found between MCS and the STS, but higher MCS was significantly related to worse performance on both the 6MW ($r = -0,24$, $p < 0,05$) and a slower TUG time (0,29, $p < 0,01$).

Regression analyses (see table 11) were conducted testing the predictive value of demographic variables and measures of physical performance on patient perceived health status. In model one, diagnosis, gender and age group was found to contribute significantly to the regression model for PCS before treatment ($F (3,70) = 4,36$, $p<0,05$), and accounted for 16% of the variation in PCS. According to the regression analysis only diagnostic group had a significant unique predictive effect ($\beta = -0,35$, $p<0,05$). Adding physical test scores increased the predictive value of model 2, explaining an additional 11% of the variance in physical HS and this change in R^2 was significant ($F(3,67) = 3,30$, $p<0,05$).

Table 11: Regression models predicting health status with demographic variables and physical performance

	Pretest PCS		**Pretest MCS**		**Posttest PCS**		**Posttest MCS**	
Model 1	β	t	β	t	β	t	β	t
Diagnosis	-0,31	-2,33*	-0,24	-1,70	-0,30	-2,27*	0,28	2,10*
Gender	0,19	1,58	0,04	0,33	-0,05	-0,38	0,14	1,16
Age	-0,04	-0,34	-0,10	-0,73	-0,20	-1,64	0,12	0,98
R^2	0,16		0,05		0,06		0,05	
F	4,36**		1,20		1,91		1,57	
Model 2								
Diagnosis	-0,10	-0,68	-0,24	-1,55	-0,03	-0,24	0,17	1,15
Gender	0,19	1,49	-0,11	-0,78	-0,02	-0,18	0,05	0,41
Age	-0,02	-0,14	-0,04	-0,26	-0,11	-0,87	0,12	0,94
Pretest 6MW	0,29	1,45	-0,28	-1,27				
Posttest 6MW					0,48	2,61	-0,34	-1,76
Pretest TUG	-0,11	-0,67	0,11	0,59				
Posttest TUG					0,01	0,08	0,16	1,03
Pretest STS	-0,01	-0,04	0,47	2,50				
Posttest STS					-0,06	-0,38	0,38	2,47*
R^2	0,27		0,13		0,21		0,15	
R^2 change	0,11		0,08		0,14		0,10	
F change	3,30*		2,17		4,79**		3,21*	

Pretest N= 74, posttest N=88; **p<0,01, *p<0,05
Note: 6MW = 6-minute Walking Test; TUG = Timed-Up-and-Go Test; STS = Stand-Sit Test; PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score.

Analyzing the post-test data, only model two contributed significantly to the regression equation, and it was predictive of both PCS ($F(6,81) = 3,47$, $p<0,01$) and the mental component of HS (MCS) ($F(6,81) = 2,45$, $p<0,05$), explaining 21% (physical test scores contributing to 14%) of the variance in PCS and 15% (physical test scores contributing 10%) of the variance in MCS. Diagnosis had a significant unique predictive effect on both PCS ($\beta = -0,30$, $p<0,05$) and MCS ($\beta = -0,38$, $p<0,05$), but the performance on the STS also had a unique predictive effect on MCS ($\beta = -0,38$, $p<0,05$). In summary, the physical test scores included in model two seem to be important predictors of SF-12 HS, with greater contributions towards predicting PCS than MCS.

Table 12: Pretest physical covariates related to posttest SF-12 health status

		N	B	Hazard ratio	95,0% CI for Exp(B)	
					Lower	Upper
	Pretest 6MW score					
Posttest PCS	Low	30	1,26	3,54**	1,84	6,80
	Medium	30	0,44	1,56	0,92	2,64
	High'	29				
Posttest MCS	Low	30	-0,59	0,55	0,28	1,11
	Medium	30	0,36	1,43	0,81	2,54
	High'	29				
	Pretest TUG score					
Posttest PCS	Low	32	1,00	2,72**	1,50	4,93
	Medium	31	0,32	1,38	0,79	2,41
	High'	30				
Posttest MCS	Low	32	-0,45	0,64	0,31	1,30
	Medium	31	0,24	1,27	0,72	2,25
	High'	30				
	Pretest STS score					
Posttest PCS	Low	28	0,97	2,63**	1,43	4,83
	Medium	29	-0,19	0,83	0,47	1,46
	High'	35				
Posttest MCS	Low	28	-0,28	0,76	0,39	1,49
	Medium	29	0,43	1,54	0,88	2,70
	High'	35				

*p < 0,05, **p < 0,01
Note: The high scoring groups were used as reference groups for the analysis. 6MW = 6-minute Walking Test; TUG = Timed-Up-and-Go Test; STS = Stand-Sit Test; PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score.

Table 12 shows the effects of pretest physical covariates on posttest SF-12 HS scores. The patients were arranged into three groups based on physical ability on each of the three physical tests before treatment. Differences in HS between the groups was then analyzed. The results show significant differences in post-test PCS between the groups on all three physical tests. The probability of still improving posttest PCS at time x [P(X>x)] was significantly lower among those with low pre-test 6MW performance than the group scoring high on the 6MW test before treatment (HR = 3,54, p < 0,01, see appendix figure A6). The low-scoring TUG-test group also showed a lower chance of still improving posttest PCS at time x [P(X>x)] then the high-scoring group (HR = 2,72, p < 0,01, see appendix figure A7). Similar results were found on the groups based on pretest STS score. Low-performers showed

significantly lower probability of scoring high on PCS after treatment, than the high-performing STS group (HR = 2,63, p < 0,01, see appendix figure A8).

No associations between pretest physical performance and posttest MCS was found. However, survival analyses of MCS difference scores (i.e. change from pretest to posttest MCS) showed that the patients in the lower half of pretest physical performance displayed a greater chance of improving MCS at time x [P(X>x)] than the upper half of physical performers. This difference was significant for the TUG test group (HR = 0,36, p < 0,05, appendix figure A9) and the STS group (HR = 0,30, p < 0,01, appendix figure A10), but not for the groups based on pretest 6MW-performance.

Table 13: Posttest physical covariates related to posttest health status

		N	B	Hazard ratio	95,0% CI for Exp(B)	
					Lower	Upper
	Posttest 6MW score					
Posttest PCS	Low	29	1,28	3,60**	1,80	7,19
	Medium	31	0,55	1,73	0,99	3,05
	High'	28				
Posttest MCS	Low	29	-0,31	0,73	0,37	1,47
	Medium	31	0,37	1,44	0,82	2,53
	High'	28				
	Posttest TUG score					
Posttest PCS	Low	29	0,70	2,02*	1,06	3,87
	Medium	31	0,32	1,38	0,81	2,33
	High'	32				
Posttest MCS	Low	29	-0,56	0,57	0,30	1,11
	Medium	31	0,14	1,15	0,65	2,02
	High'	32				
	Posttest STS score					
Posttest PCS	Low	39	0,72	2,06*	1,16	3,65
	Medium	27	-0,17	0,84	0,47	1,51
	High'	26				
Posttest MCS	Low	39	0,19	1,21	0,62	2,36
	Medium	27	0,37	1,44	0,80	2,60
	High'	26				

*p < 0,05, **p < 0,01
Note: The high scoring groups were used as reference groups for the analysis. 6MW = 6-minute Walking Test; TUG = Timed-Up-and-Go Test; STS = Stand-Sit Test; PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score.

In table 13, associations between posttest physical performance and health status after treatment are displayed. As in the previous analysis, the patients were arranged into groups

based on physical ability, but this time posttest score was the deciding factor for the groups. These results also showed that the low-scoring groups had a lower probability of still improving posttest PCS at time x [P(X>x)] than the high-performance groups for all three tests; 6MW (HR = 3,60, p < 0,01, appendix figure A11), TUG (HR = 2,02, p < 0,05, appendix figure A12), and STS (HR = 2,06, p < 0,05, appendix figure A13). No significant associations were found between posttest physical group and posttest MCS score. When compared to change in MCS, however, the lower half of STS scorers after treatment displayed a larger improvement of MCS (HR = 0,32, p < 0,01, appendix figure A14). This association was not found in the 6MW and TUG groups.

4.1 Comparing PD and MS patients to US norms

Table 14: Differences in health status between patient group post treatment and US norms

		Treatment population			**US Norms**					
Age		Mean	SD	N	Mean	SD	N	diff	t	Cohen's *d*
35-44	PCS	43,24	8,04	6	52,18	7,30	487	-8,94	2,98**	1,16
	MCS	46,11	13,44		50,10	8,62		-3,99	1,12	
45-54	PCS	42,95	8,73	23	49,71	9,50	324	-6,76	3,31**	0,74
	MCS	54,62	9,61		50,45	9,55		4,17	2,02*	0,43
55-64	PCS	42,63	8,00	28	46,55	10,63	250	-3,92	1,89	
	MCS	58,23	7,71		50,57	9,82		7,66	3,99**	0,87
65-74	PCS	43,49	8,46	29	43,65	11,02	408	-0,16	0,08	
	MCS	55,46	9,21		52,10	9,53		3,36	1,84	
75-95	PCS	37,30	6,83	12	38,68	11,04	217	-1,38	0,43	
	MCS	55,21	9,43		50,06	10,94		5,15	1,60	
Total	PCS	42,34	8,25	98	50,12	9,45	2329	-7,78	8,02**	0,88
	MCS	55,45	9,44		50,04	9,59		5,41	5,47**	0,57

*p<0,05, **p<0,01
Note: PCS = SF-12 Physical Composite Score; MCS = SF-12 Mental Composite Score.

Table 14 shows differences in health status, measured by the SF-12 facets PCS and MCS, between treatment population after intervention and US norms. Examining the data including all age groups, the treatment population showed significantly lower PCS than the US norm (t(2328) = -7,78, p < 0,01) and this difference was large (Cohen's *d* = 0,88). There was also a significant difference in MCS between the two groups, but surprisingly this difference favored the treatment group. They showed higher MCS post treatment than the US norm (t(2328) = 5,47, p < 0,01) with a moderate effect size (Cohen's *d* = 0,57).

Distinguishing between age groups the data shows a more nuanced picture. PCS is only significantly different among the two youngest age groups from 35 – 45 and 45 - 54

years old. This part of the patient population showed lower PCS than US norms ($p < 0,01$), with strong effect sizes (Cohen's $d = 1,16$ and $d = 0,74$ respectively). No such difference was found for the population over 55 years of age. For the MCS data only the patients of age between 45 – 54 and 55 – 64 showed significantly higher scores than US norms ($p < 0,05$; $p < 0,01$). Effect sizes here were moderate for ages 45 – 54 (Cohen's $d = 0,43$) and strong for ages 55 – 64 (Cohen's $d = 0,87$). Overall these results indicate that older patients with PD or MS experience similar perceived health status to the US norm population, while younger patients experience lower physical HS than norms, but may experience better mental HS.

Discussion

Treatment effect

Positive changes in both physical and mental health status indicate that patient-perceived health status is changeable through treatment intervention. Previous studies examining the effects of general interventions on health status and health-related quality of life among these patient groups are inconclusive, or indicate only small improvements (Goodwin et al., 2008; Latimer-Cheung et al., 2013; Van der Marck et al., 2009; Khan et al., 2007; Storr, Sørensen, & Ravnborg, 2006). Moderate PCS- and large MCS improvements in this study were therefore not expected. These improvements show that patients perceive their own health as better after treatment, both physically and psychologically. The limited data from McGill QOL questionnaire indicate a positive improvement in global QOL, further supporting the effect of the treatment intervention.

Few previous studies have explored the effects of short, intensive, inpatient treatment programs on quality of life measures in these patient groups. Results of the current study suggests that the short intensive inpatient rehabilitation is effective in producing short term improvements. The MDI programs studied in the literature vary in focus, duration, frequency, intensity etc. Knowing the heterogeneity of MS and PD patients regarding symptoms and disability, finding an 'ideal' intervention across patients is nearly impossible. This variation within the patient groups makes studying mechanisms of change, or pathways leading to improvements in quality of life, difficult. Two plausible mechanisms are proposed: First, improvements on the level of physical function may influence HS positively. Secondly, the holistic, multidisciplinary approach to treatment may target non-motor factors important to patient-perceived HS.

Supporting the first mechanism, physical ability/disability was found to be significant related to physical health status, and this is supported by previous research (Ellis et al., 2011; Henriksson et al., 2011; Josiah et al., 2012; Schrag, Jahanshahi, & Quinn, 2000; Tu et al., 2017). The regression- and correlational results were similar in magnitude to the findings of previous studies (Ellis et al., 2011; Nutt et al., 2014), supporting the growing body of evidence for the relationship between objective physical ability and self-perceived physical health. Mobility and motor functions play an important role in perceived physical health status for MS and PD patients. However, the modest magnitude of these relations indicate that other factors are important to perceived health. There is considerable discrepancy between subjective and objective measurements of health. Theoretically, physical health status is the most proximal patient-reported outcome measure to physical ability. Both health-related

quality of life, and global quality of life are more distal constructs. Even so, most of the variance in perceived physical health was explained by other factors than physical test scores, showing the importance of non-motor factors. This is further highlighted by the divergent, inconclusive results for the relationship between mental health status and physical ability, supporting the model of mental health as a construct more distant from physical function. Although physical ability affects HS, the increase in both physical and mental components of HS seen in the current study must also be affected by changes in factors not related to physical disability.

The observation of HS changes exceeding the improvements in physical ability gives credence to the second proposed mechanism of critical non-motor factors being affected by the intervention. A multidisciplinary treatment involves a variety of health care professionals, such as occupational therapists, social workers, nurses, neurologists, psychologists and doctors. Each background provides a different view of the patient and the patient's disability. Involving different health care professions in treatment ensures that a broad spectrum of social, psychological, affective and cognitive symptoms are targeted. It is likely that improvements across a variety of symptoms affects the patients' quality of life positively. Numerous previous studies have explored the effects of individual symptoms on quality of life in MS and PD patients, identifying depressive symptoms as one of the strongest links to decreases in HS/HRQOL (Benito-Leon et al., 2003; Soh, Morris, & McGinley, 2011; Den Oudsten et al., 2007; Tu et al., 2017). Other variables related to HS/HRQOL in these patient groups are psychosocial functioning (Van Uem et al., 2016), fatigue (Motl, McAuley, Snook, & Gliottoni, 2009), and emotional adjustment to illness (Benito-Leon et al., 2003). There is support for some effect of exercise improving depressive symptoms in the general population (Cooney, Dwan, & Mead, 2014), and the effect has found specifically in MS patients (Herring, Fleming, Hayes, Motl, & Coote, 2017). The effects of exercise on fatigue is limited but may indicate a small improvement (Latimer-Cheung et al., 2013; Khan & Amatya, 2017). Knowing the high incidence and large impact of depression and fatigue in these patient groups, and the central role of psychosocial functioning and emotional adjustment in quality of life outcomes, targeting these symptoms specifically through multidisciplinary treatments is crucial.

The holistic approach to rehabilitation, emphasizing the patients' own experiences, values and goals, may be important in improving quality of life. Storr et al.'s (2007) randomized controlled trial assessed an inpatient intervention of similar duration (3-5 weeks) to the current study but found no difference in QOL measures between treatment group and

controls. Although the studies differ in research design, one unique trait of the current intervention compared to the intervention of Storr et al.'s (2007) study is the holistic ideology. An explicit focus on patient-driven treatment is a differentiating factor that could be important in producing effects at the level of patient reported outcomes.

Corresponding with previous research, both patient groups showed improvements in physical ability. However, the effects of the current intervention were low- to moderate in size. The characteristics of the physical therapy provided in treatment corresponded well to those identified as important for short interventions in Latimer-Chang et al.'s (2013) systematic review; a high frequency (3 times per week or more) and supervision during training. This indicates that other factors may have contributed to the modest results. Primarily, the short duration of 4-weeks for an intervention aimed at improved motor function is thought to be a factor. Also, the large variance in physical function within the patient groups is a statistical factor yielding lower effect sizes. High standard deviation is expected in patient groups of progressive neurodegenerative diseases where the severity of the motor symptoms vary greatly from early- to late stages of the diseases.

The short-term gains found are uplifting, but due to the lack of follow-up data long-term effects are unknown. Fraszzita et al.'s (2012) study on a 4-week intensive rehabilitation for PD patients suggests good effects countering loss of ADL-functions and physical ability up to one year after intervention. However, further research is needed to explore the stability of improvements in physical function and quality of life over time. Also, inpatient rehabilitation is an expensive intervention. Analyses of the cost-effectiveness of such programs are needed for a discussion on treatment choices for MS and PD patients.

Group Differences

Some differences among the two patient groups of the study were found, both in health and treatment response. PD patients performed better physically, and reported better physical health status than MS patients, both before and after treatment, despite the fact that MS patients on average were younger. MS patients showed a larger improvement in mental health over the course of the treatment. These findings are in accordance with a previous study, where people with MS generally reported poorer physical health, but better mental health than people with PD (Riazi et al., 2003). The disparity in physical ability between the patient groups is likely due to the different nature of the diseases' impact on motor function. The difference in mental health benefits of the program may need further study.

Contrary to the chronic progressive degenerative nature of the diseases, age was not found to be a significant factor for either physical ability or HS. This was surprising. Previous studies have identified time since diagnosis as a significant predictor for disability and HS/HRQOL in both PD and MS patients (Soh et al., 2013; Pfennings et al, 1999; Benito-Leon et al., 2002). The lack of difference found in the current study could be explained the differences between the diagnostic groups. The PD patients were on average older than MS patients, but the PD patients generally performed better physically and rated their physical health higher. This may have created a canceling effect, where physical function likely decreases with age in the study population, but the effect being cancelled due to the group with highest physical function (PD patients) comprising a higher percentage of the older patients. Factors differentiating the treatment response between the two patient groups should be investigated in future research.

The best predictor of physical ability and health at program completion was physical ability and health before the intervention, and this was expected. Differences in treatment responses among low-, intermediate- and high functioning patients showed ambiguous results. For some tests, the group with the largest physical disabilities showed the greatest improvements (TUG, SF-12 MCS-score), for another the intermediate scorers showed the best improvements (6MW). The mechanisms behind these discrepancies are unclear and the results may be skewed by a difference in function and treatment effects between the two diagnostic groups. Smaller improvements among patients with good pretest function could be explained by a ceiling effect, where improvements stagnate when approaching an upper bound of function and health in these diagnostic groups. The high-functioning patients could also have been having a healthier lifestyle, more closely resembling that of the rehabilitation conditions, before the intervention. The program and staff could have been better suited for, or spend more resources on, the more disabled patients leading to larger effects for this group. Possible advantages for the intermediate pre-treatment group on 6MW improvements may be good enough function to participate in activities and recover from exercise, while still having room for improvement. Differences in improvements among the tests may indicate a difference in the tests ability to distinguish between function as results deviate from the norm. This shows the necessity of including multiple tests of physical ability in a study. The ability to profit from treatment depending on diagnosis or disability is difficult to discern in a study with multiple interaction effects between disease, motor function, HS and individualized treatment. Randomized, controlled studies exploring fewer variables are needed to identify specific factors leading to positive changes.

Compared to general population

The treatment population rated their physical health status much lower than US norms. This result was expected and supports earlier findings on the impact of these diseases on physical health status (Riazi et al, 2003; Schrag et al., 2000). However, the mental health status reported by patients after treatment was significantly better than US-norms. This was unexpected. When interpreting this result, Nortvedt et al.'s (2000) study on MS patients' responses on SF-12 is relevant. They found that the SF-12 questionnaire tended to overestimate mental health (MCS) in MS patients. The authors attributed this overestimation to the orthogonal factor rotation used to calculate the PCS and MCS factors (i.e. to differentiate between the two components, some factors loading positively on PCS load negatively on MCS, and vica versa). Poor ratings on the PCS facet (seen in treatment population) may therefore affect the MCS measurement positively. This must be considered when reviewing the positive results on perceived mental health. Indications that the treatment population perceive their disease's impact on physical health as greater than mental health are interpreted with caution.

Examining specific age groups, PCS was only significantly worse among the younger patients. Again, this may be due to MS patients comprising a large percentage of the younger participants, as this diagnostic groups showed the lowest PCS. The middle age groups (45-64) showed highest MCS compared to norms. A young age of onset may have higher impact on HS, being especially taxing as it is chronic, progressive, without good treatments (Benito-Leon et al., 2003). Differences in HS were not found in patients older than 65 years of age. This may be due to PCS decreasing with increasing age in the norm population, indicating an increase in physical limitations among older people.

Methodological challenges

The current study is not without methodological limitations. It uses a pretest – posttest design, and the lack of a control condition makes the results susceptible to confounding placebo effects or patient/caregiver expectations. Even though MS and PD are progressive diseases with expected increase in disability over time, QOL outcomes may be over-estimated in non-experimental conditions. A meta-analysis by Motl and Gosney (2008) found no significant differences in effect sizes of HS/HRQOL improvements between experimental and non-experimental designs, but results showed a tendency of overestimation when no control condition was included. Considering the strong treatment effects of the current study, a possible overestimation does not alter the positive conclusion.

No follow-up data was included in this study. Conclusions can therefore only be drawn for effects in the short-term. Also, selection bias needs to be considered in this study. Patients participating in program were motivated for treatment, and a doctor's referral was needed to attend the program, attesting to a need for rehabilitation. There was no "blindness" among staff or patients regarding data collection or goals of the intervention. The collection of data was a part of rehabilitation routines at the institution, and both caregivers and patients knew that posttest results would be compared to results at entry.

The inclusion of two different diagnostic groups in the study necessitated the use of a generic QOL measure. Comparing generic and specific measures, a meta-analysis by Motl and Gosney (2008) found that MS-specific measures of QOL were generally associated with larger effects. Disease-specific instruments have also been recommended for PD patients (Martínez-Martín 1998). A cross-sectional study has contradicted this, finding no difference between generic and disease-specific measures in same group of MS patients (Motl et al., 2008). The use of a generic tool may have contributed to underestimations of effects. The inclusion of disease-specific measures as an addition to the generic measure would have given the results increased validity. Also, health status measures (including SF-12) focus on limitations/negative experiences, bringing adverse symptoms to the foreground. Quality of life questionnaires focusing on positive experiences, personal resources and protective factors could expose important favorable traits in the patient population. A combination of generic and specific instruments, as well as both proximal and distal QOL-measures would provide a broader foundation for conclusion but would be more taxing for the patients to complete, and it would increase the scope of the study considerably.

As previously noted, the orthogonal factor rotation used in differentiating between the physical and mental composite scores of the SF-12 is a methodological issue, especially for patients showing large discrepancies between physical and mental health. Caution is therefore advised in accentuating the high MCS seen in this patient group. The overestimation is expected to be lower for PD patients as this group reported better physical health status.

Despite methodological challenges there is still a solid foundation for conclusion. The study analyzes changes of the measured variables from beginning to the end of the 4 week rehabilitation. Due to the progressive nature of PD and MS, spontaneous improvement in disability and QOL is not expected as time progresses. Although the study does not control for placebo effects, the treatment effect found is of such magnitude that a positive conclusion should be reported. Due to the lack of follow-up data, conclusion is limited to short term effects.

Conclusion

Short, inpatient, multidisciplinary treatment was found to be an effective intervention for multiple sclerosis and Parkinson's disease patients, improving both physical and mental health in the short term. Physical ability seems to be an important factor for patient-perceived physical health, but not for mental health status. Quality of life outcomes for these patients rely on both motor and non-motor factors, implying a need for broad interventions. The results of the current study support a holistic, multidisciplinary approach to treatment of MS and PD, but follow-up data is needed to support long-term effect.

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Appendix A

Figure A1: Survival function for posttest 6MW score according to diagnostic group

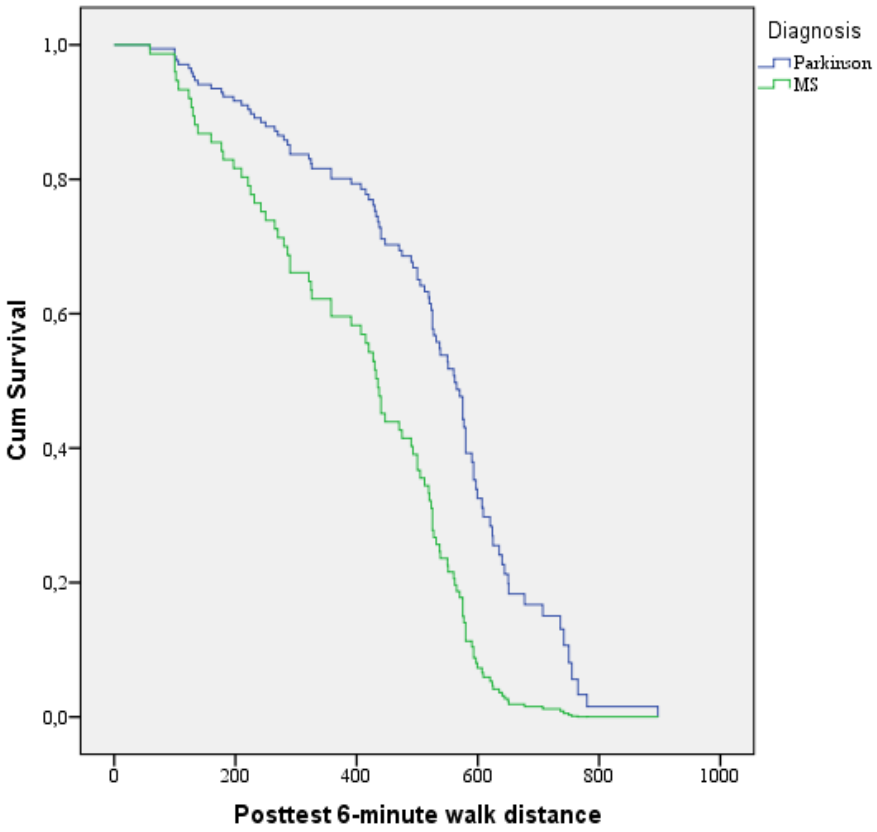


Figure A2: Survival function for posttest STS score according to diagnostic group

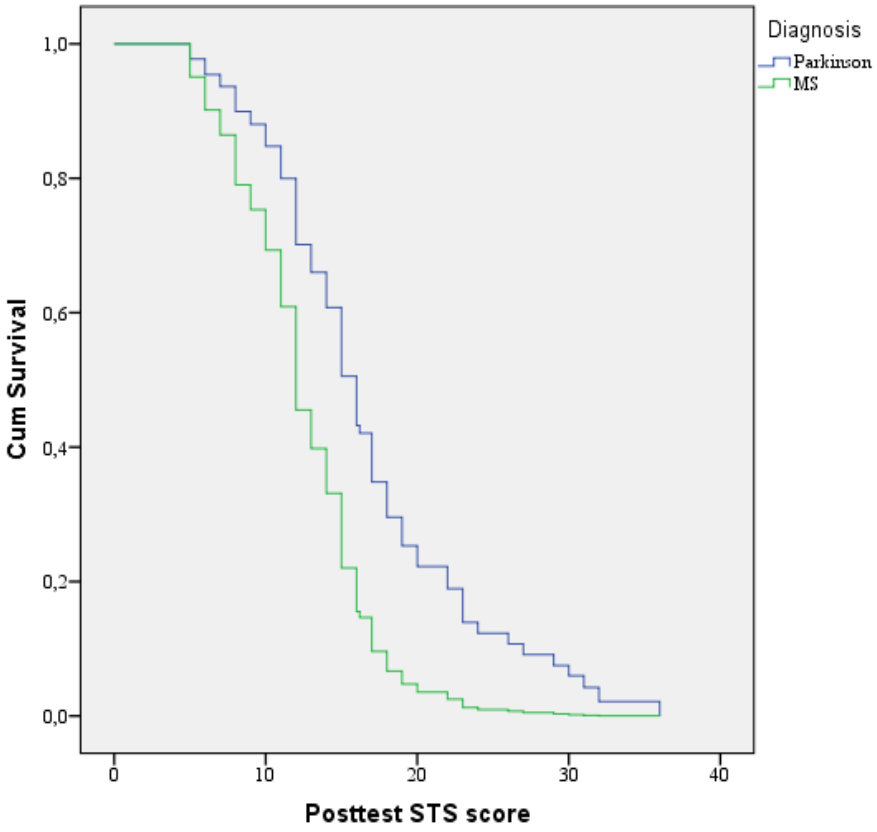


Figure A3: Survival function for posttest TUG time according to diagnostic group

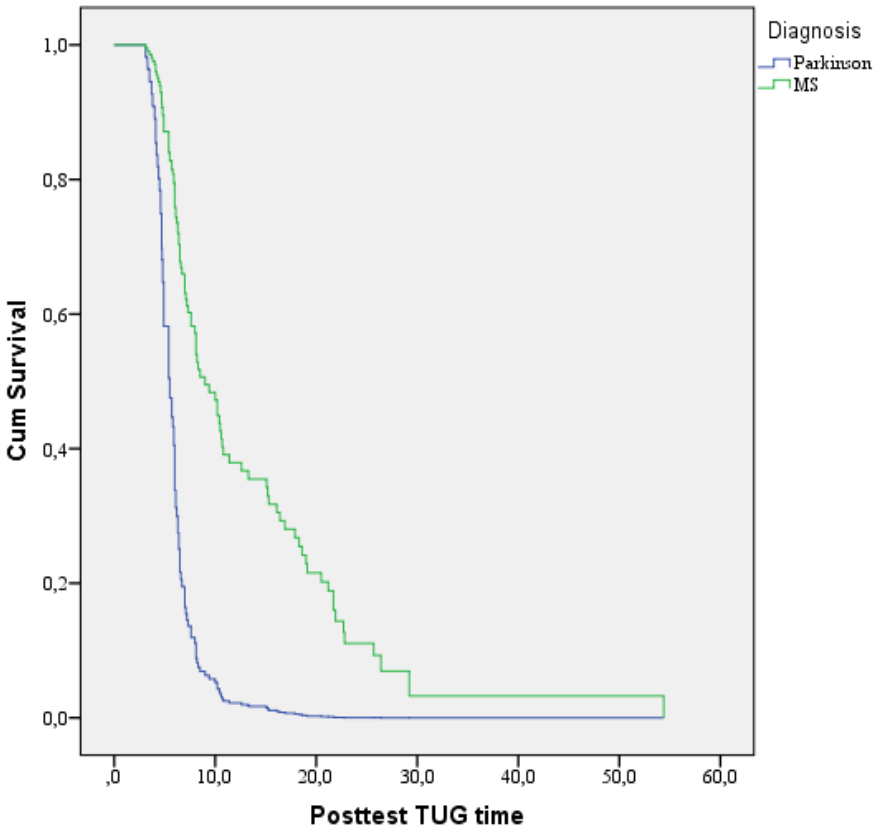


Figure A4: Survival function for posttest PCS score according to diagnostic group

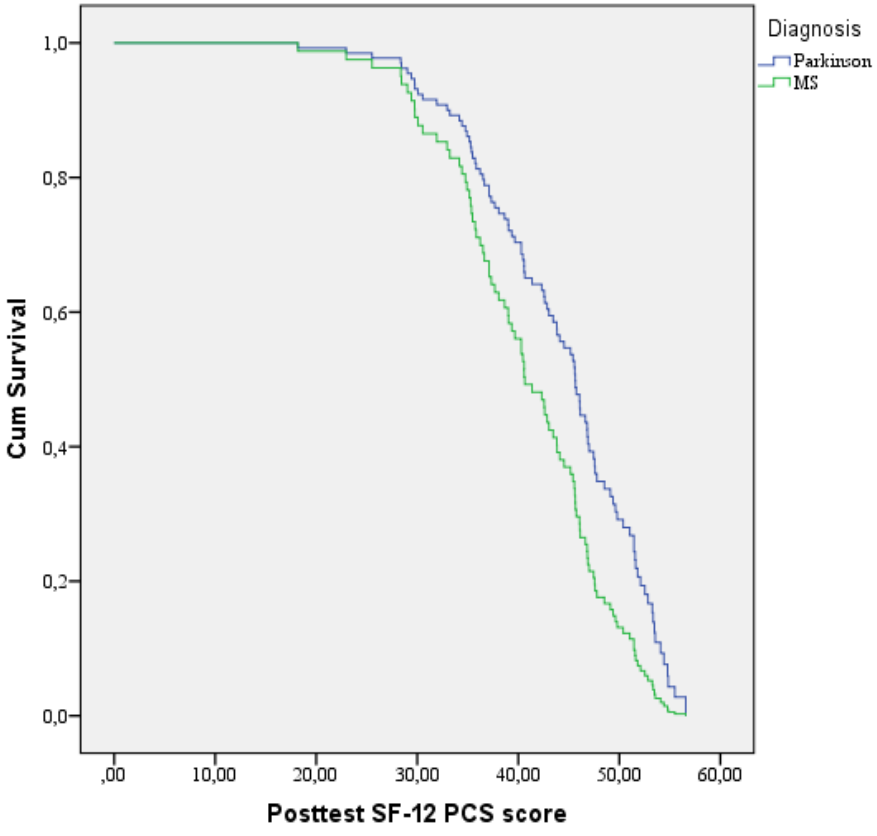


Figure A5: Survival function for posttest MCS score according to diagnostic group

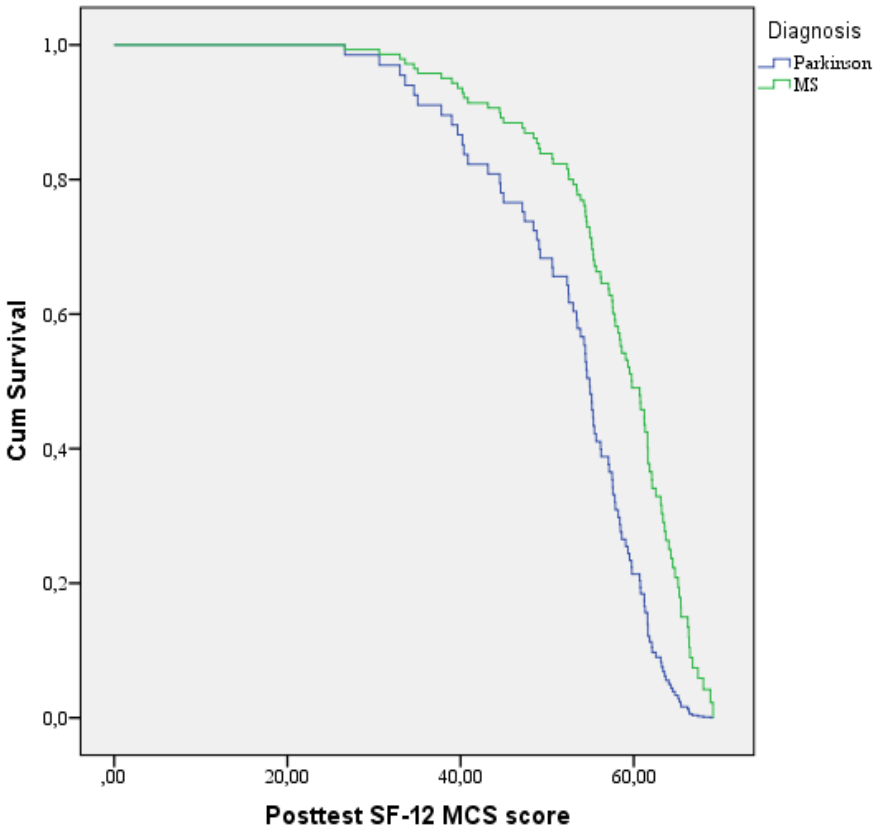


Figure A6: Survival function for posttest PCS score according to pretest 6MW ability

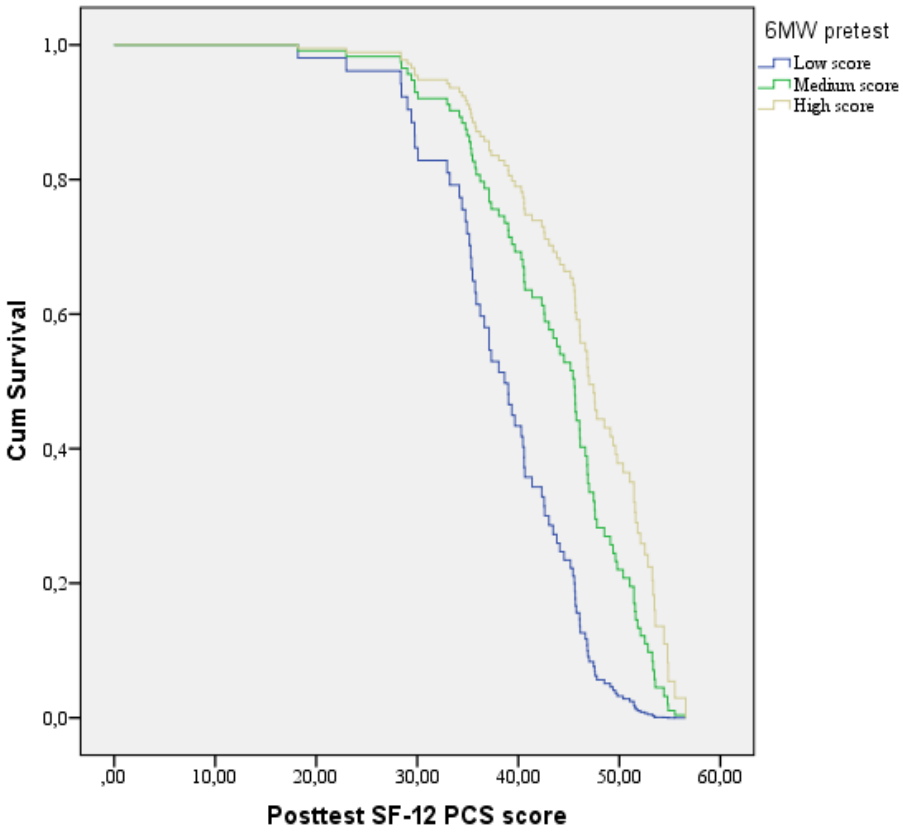


Figure A7: Survival function for posttest PCS according to pretest TUG ability

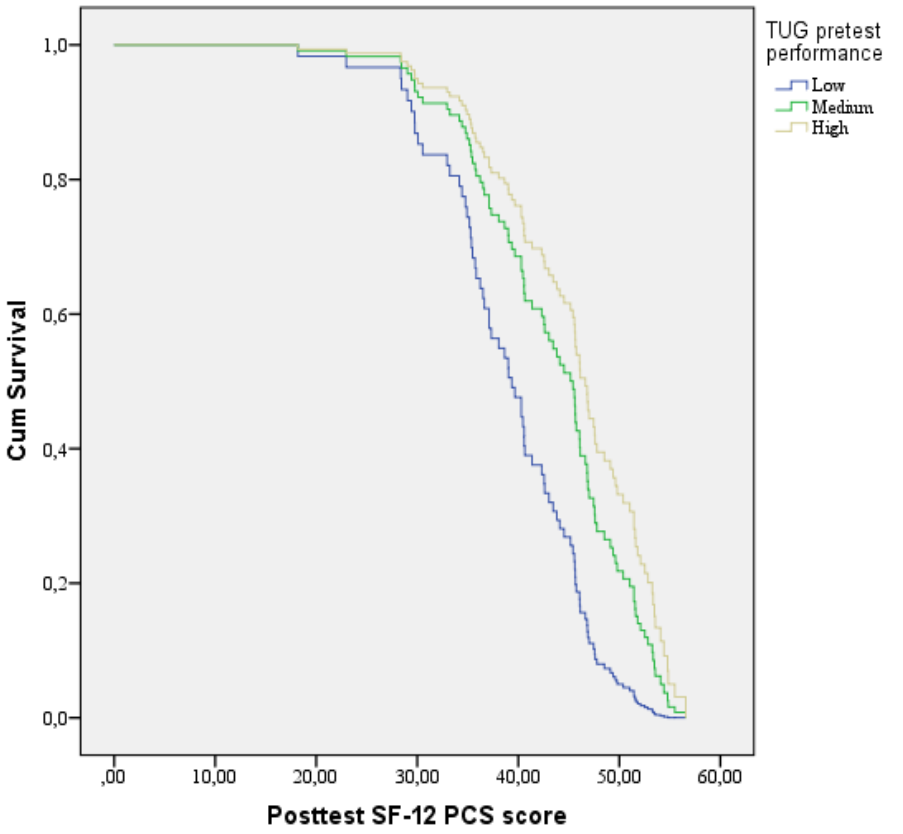


Figure A8: Survival function for posttest PCS according to pretest STS score

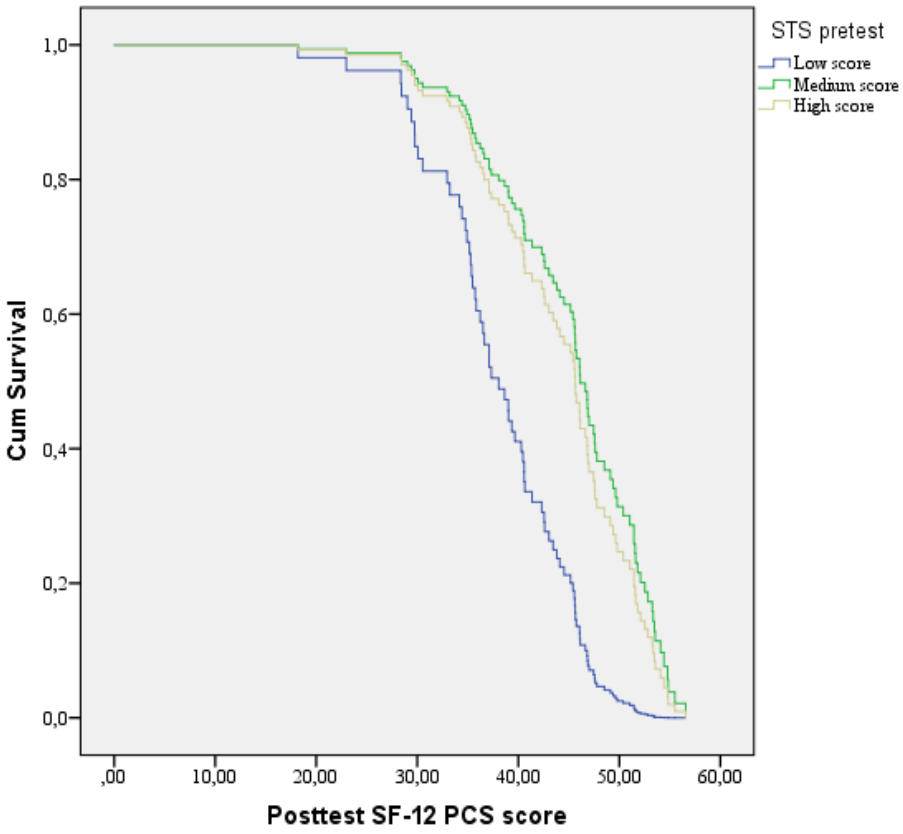


Figure A9: Survival function for change in MCS according to pretest TUG ability

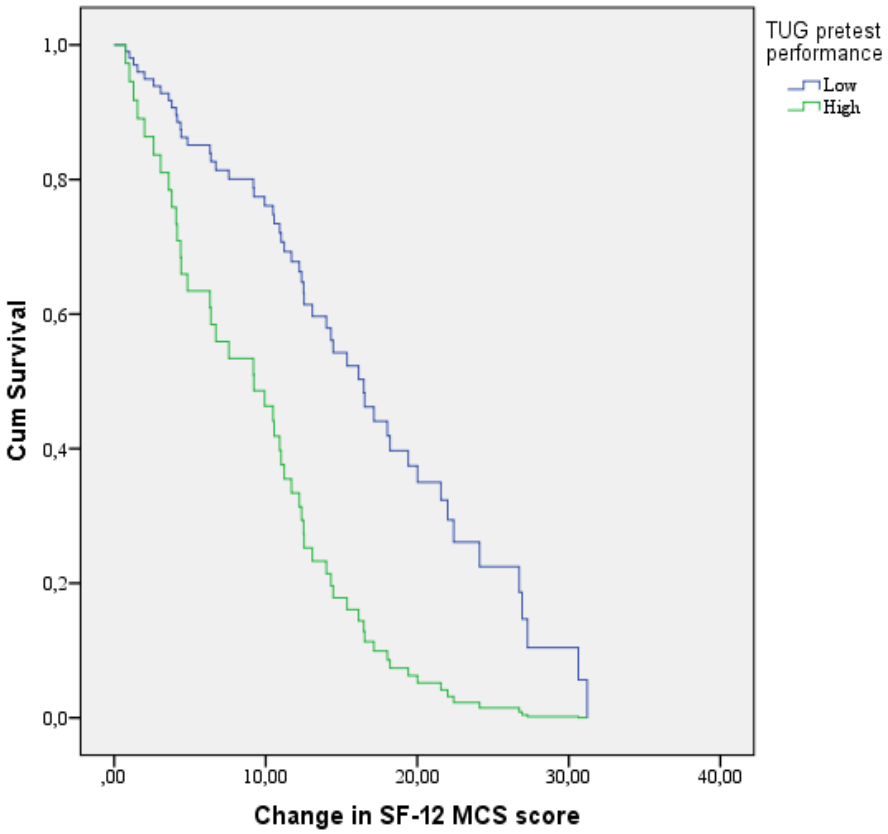


Figure A10: Survival function for change in MCS according to pretest STS score

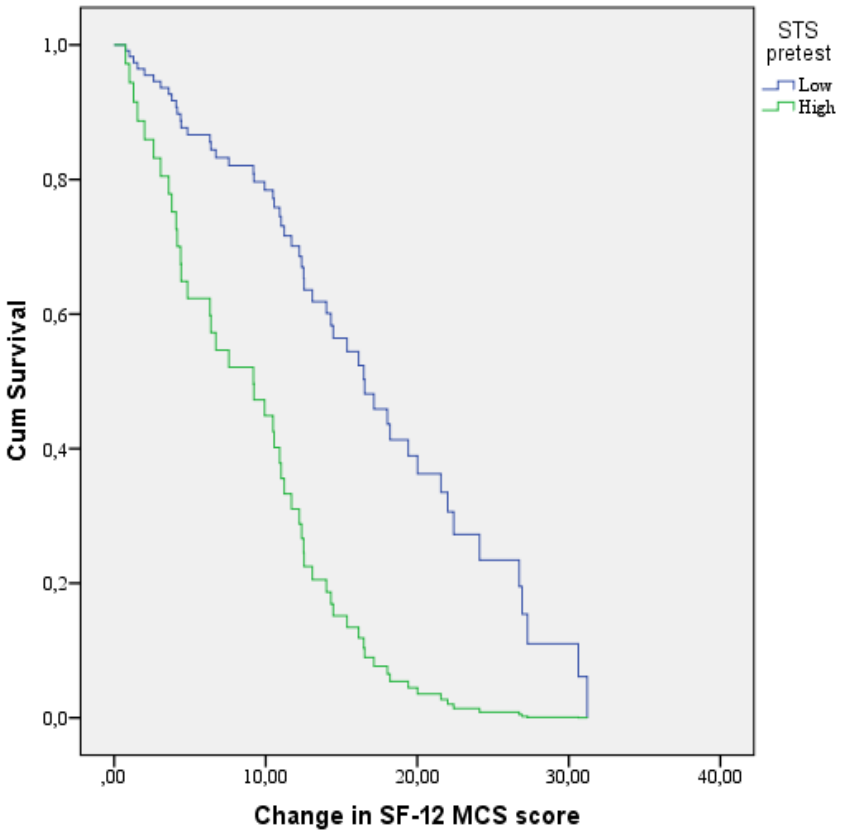


Figure A11: Survival function for posttest PCS score according to posttest 6MW performance

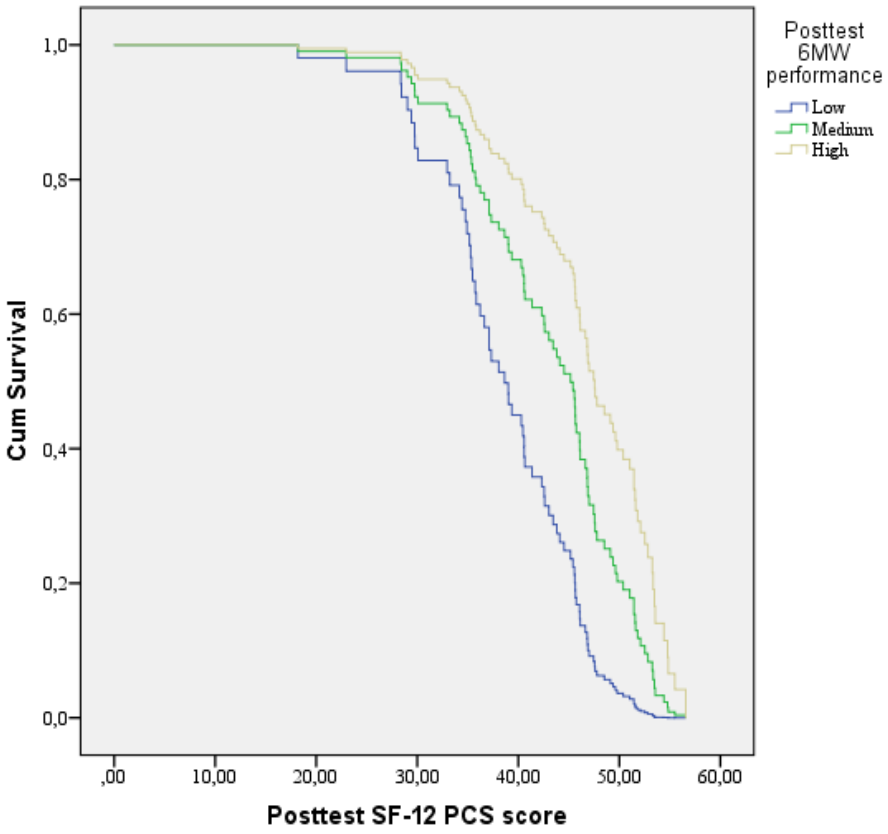


Figure A12: Survival function for posttest PCS according to posttest TUG ability

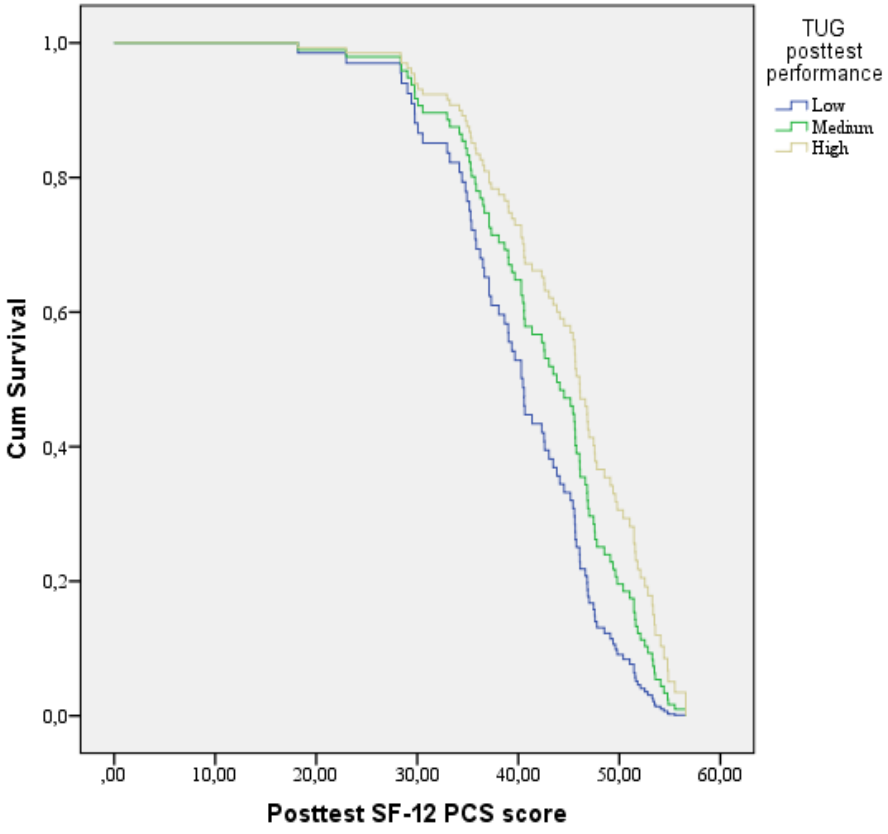


Figure A13: Survival function for posttest PCS score according to posttest STS performance

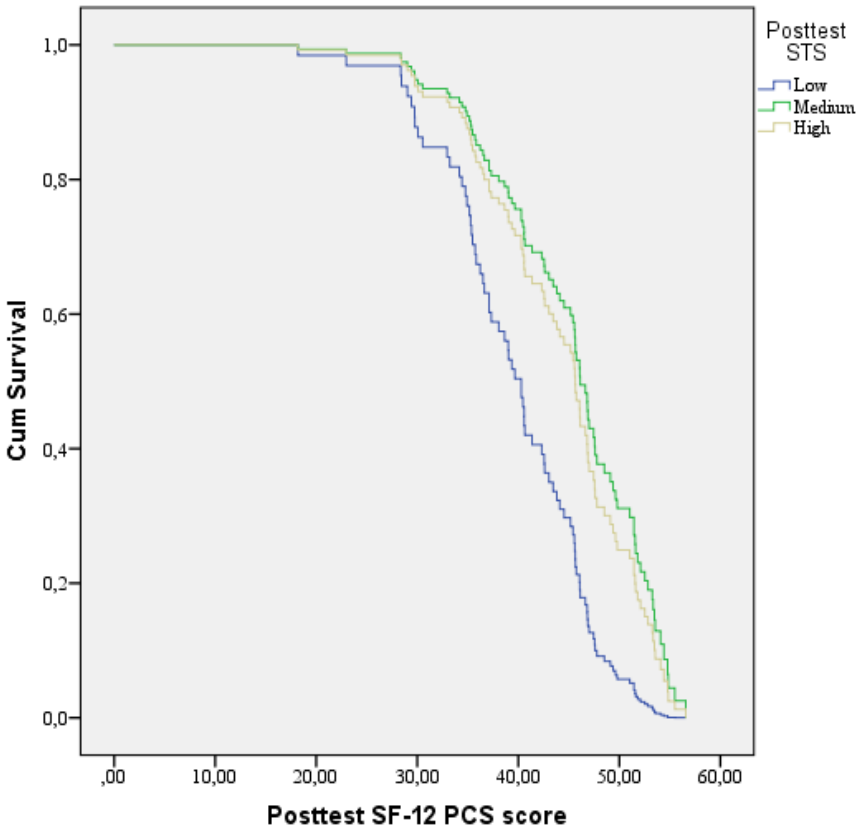
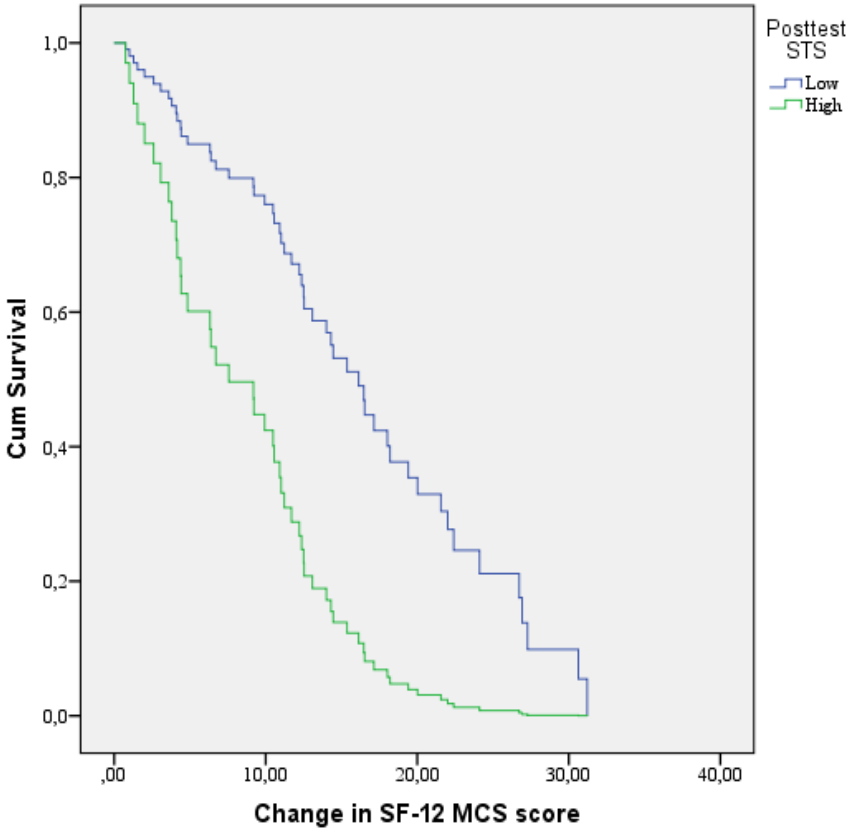


Figure A14: Survival function for change in MCS score according to posttest STS



Appendix B

SF-12

Spørsmålene under handler om hvordan du oppfatter helsen din. Disse opplysningene vil hjelpe oss til å forstå hvordan du føler deg og hvor godt du er i stand til å utføre dine vanlige aktiviteter.
Hvert spørsmål skal besvares ved å sette et kryss (X) i den boksen som passer best for deg.

1. Stort sett, vil du si at helsen din er:

Utmerket	Veldig god	God	Nokså god	Dårlig
☐	☐	☐	☐	☐

2. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er helsen din slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye? [Kryss (X) en boks på hver linje.]

		Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke
a	**Moderate aktiviteter** som å flytte et bord, støvsuge, gå en spasertur eller drive med hagearbeid	☐	☐	☐
b	Gå opp trappen **flere** etasjer	☐	☐	☐

3. I løpet av de siste fire ukene, har du hatt noen av de følgende problemene i arbeidet ditt eller i andre daglige aktiviteter på grunn av din fysiske helse?

		Ja	Nei
		Ja	Nei
a	**Fått gjort mindre** enn du ønsket	☐	☐
b	Vært begrenset i type **arbeidsoppgaver** eller andre aktiviteter	☐	☐

4. I løpet av de siste fire ukene, har du hatt noen av de følgende problemene i arbeidet ditt eller i andre daglige aktiviteter på grunn av følelsesmessige problemer (som å føle seg engstelig eller deprimert)?

		Ja	Nei
		Ja	Nei
a	**Fått gjort mindre** enn du ønsket	☐	☐
b	Utført arbeid eller andre aktiviteter **mindre grundig** enn vanlig	☐	☐

5. I løpet av de siste fire ukene, hvor mye har smerter påvirket det vanlige arbeidet ditt (gjelder både arbeid utenfor hjemmet og husarbeid)?

Ikke i det hele tatt	Litt	Moderat	Ganske mye	Ekstremt mye
☐	☐	☐	☐	☐

6. De neste spørsmålene handler om hvordan du føler deg og hvordan du har hatt det i løpet av de siste fire ukene. For hvert spørsmål, ber vi deg velge det svaret som best beskriver hvordan du har følt deg.

Hvor ofte i løpet av de siste fire ukene:

		Hele tiden	Mesteparten av tiden	En god del av tiden	Noe av tiden	Litt av tiden	Aldri
a	Har du følt deg rolig og avslappet?	☐	☐	☐	☐	☐	☐
b	Har du hatt mye overskudd?	☐	☐	☐	☐	☐	☐
c	Har du følt deg nedfor og deprimert?	☐	☐	☐	☐	☐	☐

7. I løpet av de siste fire ukene, hvor mye av tiden har den fysiske helsen din eller følelsesmessige problemer påvirket dine sosiale aktiviteter (som å besøke venner, slektninger osv.)?

Hele tiden	Mesteparten av tiden	En del av tiden	Litt av tiden	Aldri
☐	☐	☐	☐	☐