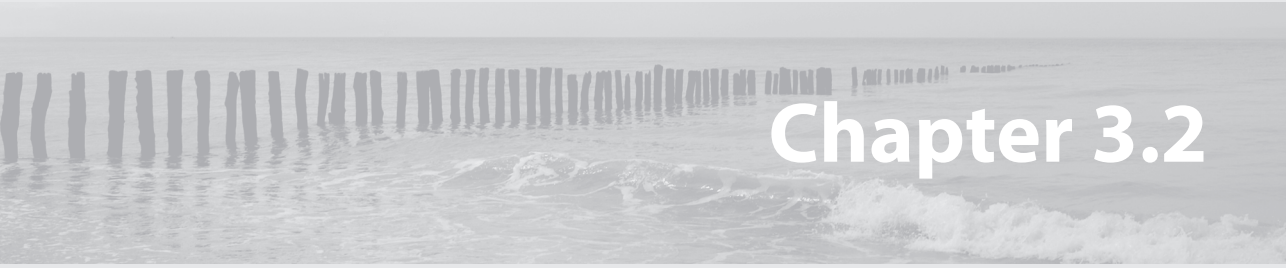

Chapter 3.2

Walking speed, rather than Expanded Disability Status Scale, relates to long-term patient-reported impact in progressive MS

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ABSTRACT

Objective: To study the relationships between 1-2 year changes in well-known physician-rated measurements (Expanded Disability Status Scale [EDSS], Timed 25-Foot Walk [T25FW], 9-Hole Peg Test [9HPT]) and the long-term (≥ 5 years) outcome in patient-reported outcome (PRO) measures (Multiple Sclerosis Impact Scale [MSIS-29], Multiple Sclerosis Walking Scale [MSWS-12]) that reflect the patient-perceived impact of disease, in progressive MS.

Methods: We selected all progressive patients having at least two complete visits within 1-2 years, from a larger cohort of prospectively-followed MS patients. These were invited for another visit, at least 5 years later, consisting of another series of similar examinations, plus 2 PRO scales: the MSIS-29 and MSWS-12. We explored associations between early changes in physician-rated measurements and the long-term outcome as per the PRO measures.

Results: In this study, 134 patients fulfilled the selection criteria. We found that early change in T25FW was the only physician-rated change that was significantly related to long-term physical impact experienced by the patient, as was assessed by MSIS-29 (Kruskal-Wallis test: χ^2=7.8, p=0.020). Early T25FW change and, to a lesser degree, early 9HPT change were significantly related to the reported long-term walking limitations, as assessed by MSWS-12 (Kruskal-Wallis test: χ^2=13.8 and p=0.001 for T25FW, χ^2=6.5 and p=0.038 for 9HPT). None of the early physician-rated changes were related to the long-term psychological impact experienced by the patient.

Conclusion: Early changes on physician-rated scales do have long-term impact in terms of potentially predictive value of outcomes for groups of patients in progressive MS, regarding walking limitations and more global physical impact. Surprisingly, early change in T25FW, rather than early change in EDSS, was significantly associated with longer-term patient-reported disease impact. Our study data support the value of using early physician-rated examinations in clinical trials in progressive MS.

INTRODUCTION

Effective treatments for progressive multiple sclerosis (MS) are eagerly awaited. When designing clinical trials for progressive MS, it is essential to understand how the short-term changes in outcome measures relate to long-term, clinically-relevant disease impact. Natural history studies in progressive MS have mainly focused on the Expanded Disability Status Scale (EDSS)[1] as an outcome measure; it is still the gold standard to rate disability levels in clinical trials in MS. Deriving from a period when psychometric knowledge was scarcely incorporated in scale construction, the EDSS has limited measurement properties and it does not incorporate the patient's perspective.[2,3] In addition, a full neurological examination must be performed, which is time consuming and requires the availability of a trained physician. The Multiple Sclerosis Functional Composite (MSFC),[4] comprised of quantitative tests of ambulation, arm function and cognition was originally proposed to address shortcomings of the EDSS; but it has not yet gained wide acceptance, mainly because it is hard to understand the clinical relevance of the change in scores. Nowadays, in a search for better clinical outcome measures, there is an increasing awareness that the examiner-driven assessments alone are not sufficient and that we cannot evaluate therapeutic effectiveness fully without incorporating the patient's perspective.[5]

In summary, currently clinical trials mainly focus on relatively short-term changes in physician-rated scales, e.g. EDSS and MSFC, whereas patients are mainly interested in the long-term changes in disease that impact their health and functionality. Therefore, in this study we investigated the relationship between 1-2 year changes seen by well-known physician-based measures (EDSS, MSFC) and the long-term (≥ 5 years) outcome, as assessed by two disease-specific patient-reported outcome (PRO) scales that have been validated to adequately reflect patient-perceived impact of their disease: the Multiple Sclerosis Impact Scale (MSIS-29)[6] and also the Multiple Sclerosis Walking Scale (MSWS-12),[7] given that walking disability is a pronounced feature of progressive MS.[8,9]

METHODS

Patients and outcomes

A large cohort of MS patients was prospectively followed up by serial clinical assessments, as part of a health status program designed to improve individual patient care at the MS Center of the VU University Medical Center. From this cohort, we selected all progressive patients,

whether primary progressive (PP) or secondary progressive (SP),[10] who had repeated clinical examinations available within a time interval of 1-2 years (± 2 months) within the years 2000-2005, having recorded *short-term* or *early* change, a change during the *first time interval* (**Figure 3.2.1**). Patients were diagnosed as having MS, as ascertained by either Poser et al.[11] or revised McDonald criteria,[12] and their treating neurologist determined that the disease course was progressive. No criteria for age, gender or disability level were applied during selection of qualifying patient data for the present analyses. Data about short-term changes in various widely-used physician-rated scales in MS were available from the following tests: the Expanded Disability Status Scale (EDSS), the Timed 25-Foot Walk (T25FW) and the 9-Hole Peg Test (9HPT). The EDSS assesses neurological impairment and disability, leading to a score varying between 0-10.[1] T25FW and 9HPT are both components of the MSFC. The T25FW measures the time needed to walk 25 feet, a measure of ambulatory function. The 9HPT measures the time needed to insert and remove 9 pegs, a measure of arm function.[4] For the present study, both tests were considered separately instead of combined into a total MSFC score (the third component was left out: a cognitive component called the Paced Auditory Serial Addition Test (PASAT)).

All patients who fulfilled our selection criteria of two visits within the years 2000-2005 were invited back for a third visit after a time interval of at least five years, for another series of examinations (in order to look at the *long-term* outcome, after the *second time interval*, **Figure 3.2.1**), in which we included the PRO scales. The MSIS-29, measuring disease impact on daily life, can be divided into two subscales: a 20-item physical scale (MSIS Physical) and a 9-item psychological scale (MSIS Psychological). The range of scores is 1 (no impact on daily life) to 5 (extremely influencing daily life). Two separate scores for the subscales were calculated.[6] The MSWS-12, measuring disease-related impact on walking ability, is a 12-item scale, ranging from 1-5 (no problems with walking at all to extremely difficult, respectively).[7]

All assessments of EDSS, T25FW and 9HPT were obtained as part of outpatient care during regular visits and were held under standardized conditions (by well trained examiners). In the

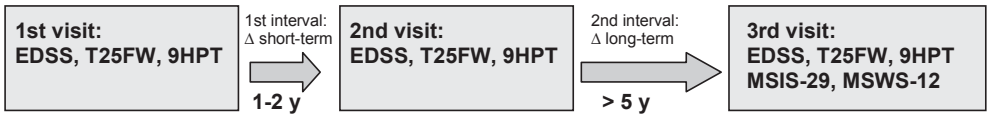


Figure 3.2.1 Patient visit scheme.
EDSS: Expanded Disability Status Scale, 9HPT: 9-Hole Peg Test, MSIS-29: Multiple Sclerosis Impact Scale, MSWS-12: Multiple Sclerosis Walking Scale, T25FW: Timed 25-Foot Walk, y: years, Δ: delta (change).

SPMS patients, no assessment was obtained during a relapse, nor within 3 months of one. If patients were unable or unwilling to come to the hospital for the third visit, the assessment was performed by telephone for the EDSS[13] and the PRO scales were completed at home. In these cases, T25FW and 9HPT were missing. If patients were unable to perform either the T25FW or 9HPT due to MS-related symptoms, the maximum allowed time for this test was assigned (180 seconds for T25FW and 300 seconds for 9HPT).[14,15] If patients could not walk at all due to MS, this was stated on the MSWS-12 questionnaire, which was not completed in these cases. MSIS Physical, MSIS Psychological and MSWS-12 scores were converted to a 0-100 scale.[16] Our study was performed with the approval of the medical ethics committee of the VU University Medical Center. Informed consent was obtained from all participants.

Statistical analysis

The short-term changes, which were observed during selection as differences in test scores between the first and second visit, were calculated and annualized to account for differences in duration of the first interval. This way, *annualized early changes* on EDSS, T25FW and 9HPT were calculated. The MSIS Physical, MSIS Psychological and MSWS-12 results were used as outcome variables. Patients were divided into three groups (group 1, 2 and 3, respectively) based on outcome scores, as follows:

- **MSIS Physical:** based on tertiles of the scores (low – moderate – high physical impact).
- **MSIS Psychological:** based on tertiles of the scores (low – moderate – high psychological impact).
- **MSWS-12:** based on a median split of the scores of those patients still able to walk and one group 'not walking' (minimal walking limitations – moderate limitations – extreme limitations).

For all outcomes, we investigated whether the three groups differed significantly in annualized early change on the physician-rated scales; in other words, the relation between the extent of early change and subsequently-experienced long-term disease-impact. We used non-parametric tests (Kruskal-Wallis and Mann-Whitney) to compare the different groups, because not all variables were normally distributed. Analyses were repeated for the PPMS and SPMS subgroups separately, to test whether relationships were different in both subgroups. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 15.0 (SPSS, Inc., Chicago, Ill., USA).

Table 3.2.1 Clinical characteristics at baseline (the first patient visit; n=134)

Type MS	
PP	61 (46%)
SP	73 (54%)
Gender	
Female	74 (55%)
Male	60 (45%)
Disease duration, mean (SD), y	10 (7.4)
Age, mean (SD), y	49 (9.4)

MS: multiple sclerosis, PP: primary progressive, SP: secondary progressive, y: years.

RESULTS

Descriptives of the study population

A total of 134 patients fulfilled our selection criteria, of which 46% was primary progressive and 54% secondary progressive. The mean durations of the first and second intervals were 1.2 years (SD=0.35) and 7.2 (SD=1.0) years (mean total follow-up duration 8.4 years, SD=1.0). At the time of the first visit, the mean disease duration was 10 years and mean age was 49 years (**Table 3.2.1**). Of those 134 patients fulfilling the selection criteria, 94 were willing and able to come to the hospital for a face-to-face third visit (70%). The remaining 40 patients were unable or unwilling to return to the hospital for a third visit, but they were assessed by telephone (30%). A subset of 43 patients (32%) stated they 'cannot walk at all' on the MSWS-12, which was therefore not completed (for all patients, this was in accordance with their EDSS score). These non-mobile patients were included in the outcome MSWS-12 as a separate group, as we explained previously.

Missing data

Because patients were selected on the basis of having two complete examinations available for EDSS, T25FW and 9HPT, there were no missing data from the first two visits. During the third visit, the MSIS-29 was missing for three patients.

Disease Modifying Therapy (DMT)

Only 11 patients (8%) were exposed to a DMT during the third visit: 8 patients were treated with interferon beta, two were treated with methotrexate and one with glatiramer acetate. Forty-seven patients (35%) had ever used DMT (interferon beta, glatiramer acetate or methotrexate).

Given the lack of proven effective therapies for progressive MS, and the relatively small number of patients exposed during the last visit, we did not explore the influence of treatment.

Clinical scores at all visits

Table 3.2.2 shows the median scores obtained on all clinical scales administered during the three visits (EDSS and MSFC data from the third visit are listed, but were not used in our analyses). Concerning the PRO scales: At the third visit, median scores were 55.0 (interquartile range (IQR)=46.3-72.5) for the physical and 30.6 (IQR=13.9-47.2) for the psychological impact score of the MSIS-29, and 75.0 (IQR=54.2-91.7) for the MSWS-12 (**Table 3.2.2**). A moderate to good correlation was found between the physical and psychological impact scores of the MSIS-29 ($r=0.63$, $p<0.001$). Correlation between the MSWS-12 and MSIS Physical was also moderate to good ($r=0.68$, $p<0.001$), but between MSWS-12 and MSIS Psychological the correlation was weak ($r=0.30$, $p=0.004$; data not shown). **Figure 3.2.2** gives an overview of the distribution of disability levels throughout all three visits. As expected in progressive MS, patient disability levels clearly move up with each visit.

Table 3.2.2 Median scores on all scales throughout the three visits (total n=134)

	Visit 1	Visit 2	Visit 3	
EDSS				
median (IQR)	4.5 (3.5-6.0)	5.0 (4.0-6.1)	6.5 (5.9-7.5)	
range	1.5-7.0	2.0-7.5	3.0-9.5	
T25FW				
median (IQR), s	6.9 (5.3-10.2)	8.0 (6.0-13.8)	15.5 (7.6-180.0)	*n=92*
range, s	3.2-111.9	3.5-180.0	3.6-180.0	
9HPT				
median (IQR), s	24.7 (21.1-29.8)	25.0 (21.5-32.9)	27.4 (23.2-42.4)	*n=94*
range, s	14.5-82.7	16.5-163.9	16.5-300.0	
MSIS Physical				
median (IQR)			55.0 (46.3-72.5)	*n=131*
range			1.3-100.0	
MSIS Psychological				
median (IQR)			30.6 (13.9-47.2)	*n=131*
range			0-97.2	
MSWS-12				
median (IQR)			75.0 (54.2-91.7)	*n=91*
range			8.0-100.0	

EDSS: Expanded Disability Status Scale, 9HPT: 9-Hole Peg Test, IQR: inter quartile range, MSIS: Multiple Sclerosis Impact Scale, MSWS-12: Multiple Sclerosis Walking Scale, s: seconds, T25FW: Timed 25-Foot Walk.

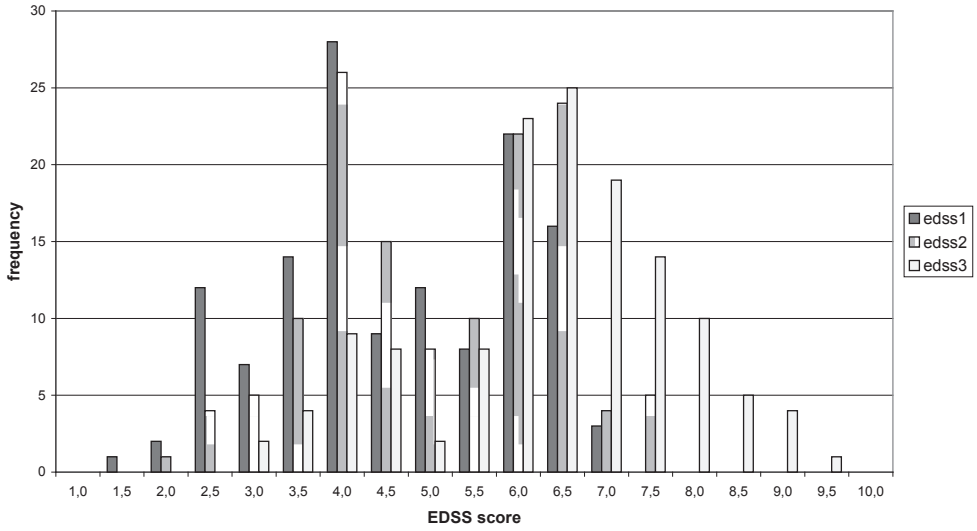


Figure 3.2.2 Disability levels during the three visits.
EDSS: Expanded Disability Status Scale.

PPMS vs SPMS

For PPMS patients the mean age at the first visit was higher than for SPMS patients: 51 years (SD=9.4) vs 47 years old (SD=9.0). Mean disease duration at the time of the first visit was shorter for PPMS (8 yrs, SD=6.7) than for SPMS (12 yrs, SD=7.5). Gender frequencies and baseline EDSS were not significantly different. Between PPMS and SPMS patients, there were no significant differences in annualized early EDSS, T25FW or 9HPT changes recorded, nor were there significant differences in MSIS Physical, MSIS Psychological or MSWS-12 scores at the third visit.

Relationships between early changes and long-term outcomes

The division of each patient-reported outcome into the different groups of variable impact is shown in **Table 3.2.3**. All groups were of approximately equal size. There were no significant differences between the groups within each PRO, concerning duration of follow-up.

The relationship between the different physician-rated early changes and long-term impact as measured with the PRO scales is shown in **Table 3.2.4**. The Kruskal-Wallis test on the left shows the results of the comparison of all three groups within each PRO (as were shown in

Table 3.2.3 Long-term patient-rated outcomes divided into groups, with percent distribution of patients

MSIS Physical		MSIS Psychological		MSWS-12	
1. low physical impact	(35%)	1. low psychological impact	(30%)	1. minimal walking limitations	(34%)
2. moderate physical impact	(35%)	2. moderate psychological impact	(38%)	2. moderate walking limitations	(34%)
3. high physical impact	(30%)	3. high psychological impact	(32%)	3. extreme walking limitations	(32%)

MSIS: Multiple Sclerosis Impact Scale, MSWS-12: Multiple Sclerosis Walking Scale.

Table 3.2.3), concurrently. The Mann-Whitney test on the right shows a one-to-one comparison of the groups. The different outcomes for MSIS Physical, MSIS Psychological and MSWS-12 are listed vertically, with the physician-rated scales below each outcome, and corresponding statistical values expressing the strength of the relationship between physician-rated change and the outcome. In this way **Table 3.2.4** shows which short-term physician-rated changes were most related to the subsequently experienced, longer-term impact.

Looking at the experienced *physical impact as outcome*, as assessed by MSIS Physical, **Table 3.2.4** shows that early T25FW change was significantly related to subsequently experienced physical impact (Kruskal-Wallis test: χ^2=7.8, p=0.020): When all 3 groups of variable physical impact were compared at the same time, they were significantly different in their distribution of early T25FW change scores, which was mainly driven by differences in early T25FW change between patients experiencing low or high physical impact of their MS on daily living, in the long-term (Mann-Whitney test: U=579.5, p=0.005). Interestingly, the other early physician-rated changes were not significantly related to long-term patient-experienced physical impact.

As concerns the *self-reported walking limitations as outcome* (assessed by MSWS-12), early T25FW changes, and to a lesser degree 9HPT changes, were found to be significantly related to the amount of later patient-reported walking limitations (Kruskal-Wallis test: χ^2=13.8 and p=0.001 for T25FW, χ^2=6.5 and p=0.038 for 9HPT). More specifically, patients experiencing extreme walking limitations at the long-term assessment were distinct from those with either minimal or moderate walking limitations, with respect to the early T25FW changes (Mann-Whitney test: U=557.0 and p<0.001; and U=662.0, p=0.011 respectively). In addition, with respect to early 9HPT changes, the patients experiencing extreme walking limitations at the long-term assessment were distinct from those with minimal walking limitations (Mann-Whitney test: U=690.0 and p=0.014). Lastly, there was a modest relationship between early EDSS

Table 3.2.4 Relationship between physician-rated early changes (by EDSS, T25FW and 9HPT) and long-term disease impact of MS as measured with the patient-opinion based tests MSIS Physical, MSIS Psychological and MSWS-12. Statistical significance as assessed by two statistical methods.

Kruskal-Wallis test			Mann-Whitney test		
Annualized early change on:	Chi-Square (χ^2)	Significance (p)		Mann-Whitney U	Significance (p)
Outcome MSIS Physical					
EDSS	3.8	0.150	group 1 vs 2	1022.0	0.771
			group 1 vs 3	702.0	0.074
			group 2 vs 3	722.5	0.112
T25FW	7.8	***0.020***	group 1 vs 2	886.5	0.180
			group 1 vs 3	579.5	***0.005***
			group 2 vs 3	726.5	0.133
9HPT	2.9	0.239	group 1 vs 2	947.5	0.388
			group 1 vs 3	706.0	0.092
			group 2 vs 3	799.0	0.387
Outcome MSIS Psychological					
EDSS	2.0	0.362	group 1 vs 2	945.0	0.797
			group 1 vs 3	709.0	0.280
			group 2 vs 3	885.0	0.181
T25FW	3.7	0.160	group 1 vs 2	845.0	0.282
			group 1 vs 3	635.5	0.083
			group 2 vs 3	893.5	0.220
9HPT	2.2	0.328	group 1 vs 2	835.5	0.249
			group 1 vs 3	803.0	0.880
			group 2 vs 3	876.0	0.173
Outcome MSWS-12					
EDSS	5.3	0.070	group 1 vs 2	880.5	0.200
			group 1 vs 3	718.0	***0.021***
			group 2 vs 3	851.5	0.320
T25FW	13.8	***0.001***	group 1 vs 2	870.5	0.192
			group 1 vs 3	557.0	***<0.001***
			group 2 vs 3	662.0	***0.011***
9HPT	6.5	***0.038***	group 1 vs 2	910.5	0.323
			group 1 vs 3	690.0	***0.014***
			group 2 vs 3	767.0	0.094

EDSS: Expanded Disability Status Scale, 9HPT: 9-Hole Peg Test, MS: multiple sclerosis, MSIS: Multiple Sclerosis Impact Scale, MSWS-12: Multiple Sclerosis Walking Scale, T25FW: Timed 25-Foot Walk, vs: versus.

changes and the amount of long-term reported walking limitations: those patients experiencing extreme walking limitations at the long-term assessment point were distinct from those with minimal walking limitations (Mann-Whitney test: U=718.0 and p=0.021).

When we looked at the *psychological impact as outcome*, as assessed by MSIS Psychological, there were no significant differences between the three groups in the amount of early physician-rated change. None of the early physician-rated changes was significantly related to the amount of long-term psychological impact experienced by the patient.

Figure 3.2.3 shows *mean* annualized early changes seen in EDSS, T25FW and 9HPT for the three impact groups within all outcome groups.

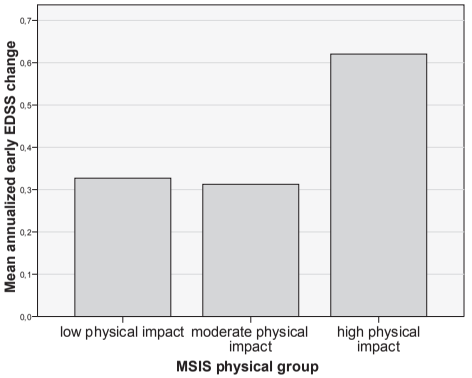
DISCUSSION

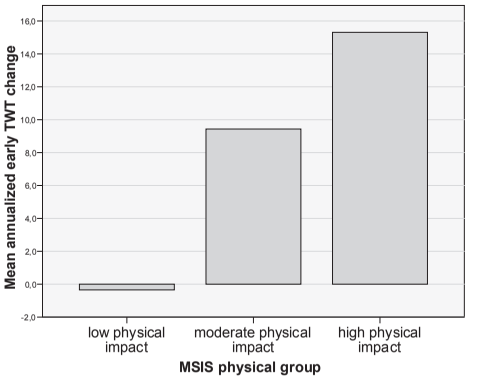
This study focused on clinical changes in primary and secondary progressive MS, a phase of the disease characterized by accumulation of unremitting disability. We studied whether and how changes that were assessed between 1-2 year points in testing using different standard physician-rated measurements were related in any way to longer-term, patient-reported outcomes, which were measured with different PRO-scales that focused on the overall disease impact and on walking ability, as that is frequently impaired in progressive MS. This study's results showed that early changes using physician-rated scales like EDSS and the components of MSFC, were related to patient-perceived long-term disease impact. In particular, early changes on the T25FW test were found to be associated with long-term reported impact of progressive MS, not only regarding walking limitations, but also regarding more global physical impact. Furthermore, early change in 9HPT was also significantly associated with subsequently-experienced walking limitations at least five years later. Also, early change on the EDSS was associated with long-term reported walking limitations, although in a less pronounced way than the long-term effects seen following early changes in T25FW (and 9HPT) assessments.

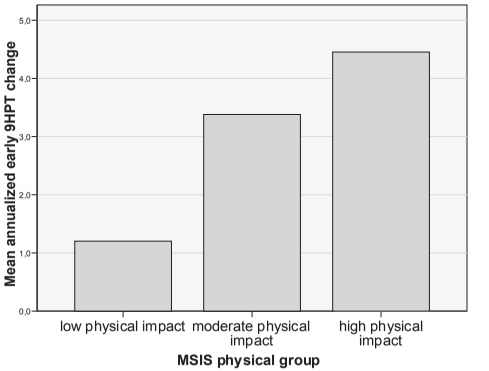
In terms of the long-term psychological impact of progressive MS, any associations with short-term changes on commonly-used physician-rated scales turned out to be absent. This is not an unexpected finding, since we know that the psychological impact score of the MSIS-29 has only weak correlations with both EDSS and MSFC, because it is mainly determined by mood, fatigue and cognition,[14] which are domains not captured in the older EDSS, T25FW and 9HPT tests.

It is important to recognize that the associations we observed are at the group level. This is relevant and helpful knowledge in a trial design for progressive MS. Although clear associations were observed, our observations cannot be directly translated into clear predictive values on an

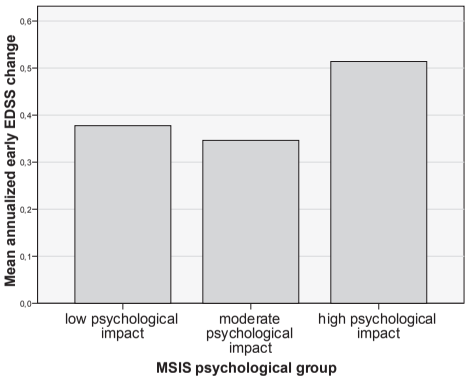
MSIS Physical:

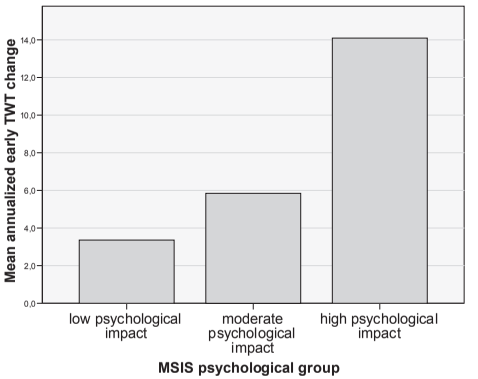


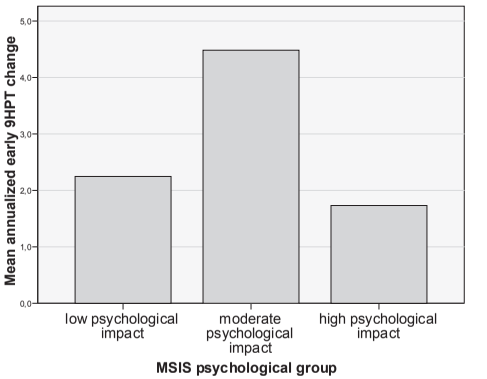




MSIS Psychological:







MSWS-12:

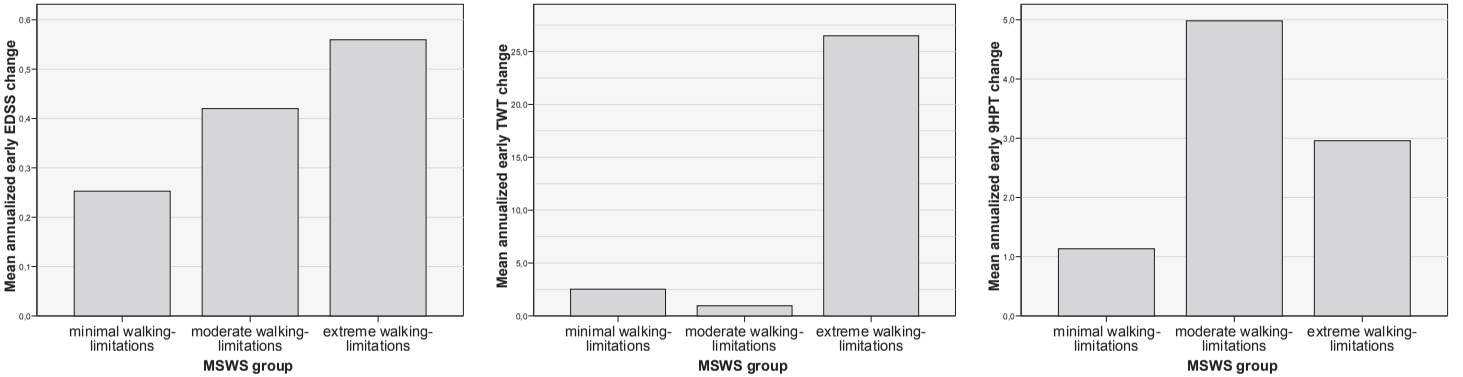


Figure 3.2.3 Mean annualized early changes for separate impact groups of all outcomes.
EDSS: Expanded Disability Status Scale, 9HPT: 9-Hole Peg Test, MSIS: Multiple Sclerosis Impact Scale, MSWS-12: Multiple Sclerosis Walking Scale, TWT: Timed 25-Foot Walk.

individual basis. The large variability in short-term changes and the overlap between patients eventually experiencing minimal, moderate or extreme impact of the disease, precludes the use of these short-term changes to predict disease impact in *individual* patients with sufficient reliability. Predicting disease impact at the individual level remains a major future challenge.

In addition we want to address some other possible limitations of our study. The second (long-term) time interval was defined as at least 5 years. It has a certain variability (IQR=6.8-8.0 yrs), as a result of which the duration of this second time interval could have some influence on the amount of reported impact. We could not easily correct for differences in duration of the second interval as we did for the first interval, by annualizing all changes, because we looked at the subsequent impact, not the *change* in impact. However, at the group level there were no significant differences in the mean follow-up duration between the subgroups that we used for comparison. Another point of potential criticism could be that the changes on the physician-rated scales were based on single testing, i.e. they were not confirmed by repeated measurements after a few months. A final possible limitation of our study is the lack of information on the impact of the early change at the end of the first time interval: at this point the impact was not assessed, which leaves us without a frame of reference concerning the baseline impact. Despite these limitations, this study is unique in that it did for the first time provide longitudinal data on a cohort of progressive MS patients, which showed that 1-2 year changes in physician-rated outcomes, especially T25FW and to a lesser extent 9HPT and EDSS, were associated with long-term (more than 7 years on average) patient-perceived walking ability and global disease impact, as assessed by MSWS-12 and MSIS-29.

We can only speculate why, in this study, the associations for the T25FW were more apparent than for the EDSS. Maybe this is related to the fact that the measurement of T25FW is much more standardized and precise compared to EDSS, so that changes have a better signal-to-noise ratio. Another possible explanation could be that in progressive MS patients (within a certain range of disability levels), the T25FW is more responsive to physical changes than the EDSS, due to the ordinal and non-linear nature of the EDSS and relatively long 'staying times' at the higher levels.[17-19] When the early change scores are higher, there is obviously a greater chance to detect an association with the long-term patient-perceived impact of disease.

Our study data support the value of early, objective, physician-rated examinations in clinical trials, by demonstrating that changes on these scales are indeed later associated with long-term disease impact at a group level. In this respect, of all the physician-rated scales, the T25FW turned out to be the most promising scale in terms of general group predictive value, in our study of progressive MS.

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