

The relationship between upper leg muscle strength and walking capacity in persons with multiple sclerosis

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BROEKMANS, Tom; GIJBELS, Domien; OP 'T EIJNDE, Bert; ALDERS, Geert; LAMERS, Ilse; ROELANTS, Machteld & FEYS, Peter (2013) The relationship between upper leg muscle strength and walking capacity in persons with multiple sclerosis. In: MULTIPLE SCLEROSIS JOURNAL, 19 (1), p. 112-119.

DOI: 10.1177/1352458512444497

Handle: <http://hdl.handle.net/1942/14599>

## ***Abstract***

**Background.** In persons with MS (PwMS), resistance training improves muscle strength, but effects on walking capacity are inconsistent.

**Objective.** The objective was to determine the relation between different types of upper leg muscle strength measurements and walking capacity in PwMS.

**Methods.** An observational cross-sectional study design was applied. Upper leg muscle strength of 52 PwMS (Expanded Disability Status Scale, EDSS range 1.5-6.5) was measured using isometric (knee extensors and flexors) and isokinetic (knee extensors) dynamometry. Walking capacity was assessed using the Timed 25-Foot Walk, Timed Up and Go and 2-Minute Walk Test. Subgroups with mild (EDSS 1.5-4.0,  $n=31$ ) and moderate (EDSS 4.5-6.5,  $n=21$ ) ambulatory dysfunction were distinguished, as results were hypothesized to differ depending on MS-related disability status. Correlation and regression analyses were performed [on the data of the most affected leg](#).

**Results.** Greatest ( $r: 0.32-0.7$ ) and ~~most~~ significant Pearson correlation coefficients were found in the moderate compared to mild MS subgroup. Within knee extensor measurements, it was found that isokinetic endurance strength related best to walking capacity. When comparing maximal isometric strength measurements, knee flexors ( $r: 0.35-0.7$ ) related better to walking capacity than knee extensors ( $r: 0.1-0.4$ ). Regression analyses confirmed that endurance knee extensor strength (~~~35-25~~ %) and isometric knee flexor strength (~~~4640~~ %) as main predictors for walking capacity.

**Conclusion.** Resistance training protocols may consider inclusion of exercises focusing on endurance knee extensor and isometric knee flexor strength when aiming to enhance walking capacity in persons with moderate ambulatory dysfunction.

## Introduction

Multiple Sclerosis (MS) is an chronic progressive inflammatory and neurodegenerative disease with a variety of motor symptoms {Noseworthy, 2000 237 /id}. Primary motor symptoms include muscle weakness, hypertonia, and coordination problems often manifesting first in the lower limb. Motor impairments may result in a reduced mobility and physical activity level, which on its turn can culminate further impairment, for example loss of muscle strength (i.e. disuse secondary to MS). Persons with MS (PwMS) perceive diminished lower limb function and walking as a major limiting disease characteristic {Heesen, 2008 436 /id} that probably contributes to a reduced quality of life {Motl, 2005 225 /id; Motl, 2009 319 /id}.

In this context ~~Therefore~~, rehabilitation in general and exercise therapy in specific was shown to poses a high ~~has the~~ potential for improving functioning and participation of PwMS {Motl, 2008 72 /id; Khan, 2007 82 /id} ~~(1;2)-, in addition to disease modifying drugs treatment because they typically prevent or slow down disease progression in a substantial number of MS patients (Muir, 2005 525 /id)-.~~

In MS rehabilitation, part of ~~the~~ studies on exercise therapy have focused on improving the function level of the International Classification of Functioning (ICF), with the aim to improve abilities at activity level such as walking. Muscular strength and fitness is certainly an important factor of walking capacity {Rantanen, 1998 680 /id; Willen, 2004 679 /id} as already documented in elderly and stroke patients {Ostchega, 2004 572 /id; Buchner, 1996 574 /id; Kim, 2004 236 /id}. To date, a number of studies in PwMS have consistently been shown that resistance training leads to increased maximal muscle strength {Gutierrez, 2005 31 /id; White, 2004 32 /id; Dalgas, 2009 257 /id; DeBolt, 2004 442 /id; Broekmans, 2011 575 /id} but not all of them reported a positive impact on walking or other functional capacity tests {DeBolt, 2004 442 /id; Broekmans, 2011 575 /id}. This can be related to factors as training intensity, duration and level of disability in patients. However, in healthy subjects it

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**Opmerking [PF3]:** If you have to delete refs, you could delete some older ones)

was reported that knee extensor muscle strength is best related with walking speed {Ostchega, 2004 572 /id}, while Thoumie et al. {Thoumie, 2005 30 /id} reported in MS patients that ~~the correlation between~~especially isokinetic (60°/s) ~~muscle~~ strength of knee flexors was most related to and gait velocity ~~was actually highest for knee flexors~~.

An improved understanding of ~~different isometric and isokinetic muscle performance variables, as well as~~which muscle groups ~~that~~ predict ambulatory walking capacity in MS, as well as the importance of different isometric and isokinetic muscle performance variables may assist optimization of future resistance training programs. ~~Therefore,~~ the present study aimed to determine the relationship between muscle strength and walking capacity in PwMS.

A first objective was to investigate the relationship between various knee extensor strength outcomes with walking capacity. From clinical point of view, one could think that isometric muscle strength is most related to abilities to stand up from a chair to a stable standing position and accelerate towards comfortable or maximal walking while isokinetic muscle strength and especially endurance variables may relate better to sustained walking. Therefore, both short and long walking tests were included as well as a measure including sit-to-stance mobility. A second objective was to investigate whether isometric knee extensor or flexor isometric strength related best with walking capacity. Based on findings of Thoumie et al (2005), we hypothesize hamstrings muscle strength to best most related to walking velocity.

**Opmerking [PF4]:** Reference van Thoumie toevoegen

MS subgroups with different ambulatory dysfunction were distinguished as size of relationships were hypothesized to ~~differ~~be greatest in persons with more pronounced ambulatory dysfunction, depending on the individual's mobility status.

## ***Methods***

### ***Subjects***

The data of the present study ~~was a part of~~ were collected at baseline of a larger ~~research project~~ intervention study (see [www.controlled-trials.com/ISRCTN60122826](http://www.controlled-trials.com/ISRCTN60122826)) that examined the effects of resistance and whole body vibration training on muscle strength and functional capacity in PwMS {Broekmans, 2010 443 /id; Broekmans, 2011 575 /id}. Fifty-three ambulatory persons with MS residing in the Hasselt region were assessed for eligibility and Fifty-two ambulatory MS subjects (Table 1) were recruited with the inclusion criteria: a definite MS diagnosis according to the McDonald criteria {McDonald, 2001 224 /id} and EDSS score between 1.5 and 6.5. Patients were excluded if they experienced a relapse or were under relapse related corticoid treatment, one month prior to the start of the study or had any other orthopedic problem(s) interfering with walking.

Subject were subdivided in subgroups with mild ( $EDSS \leq 4.0$ ) and moderate ( $EDSS > 4.0$  and  $\leq 6.5$ ) ambulatory dysfunction. This EDSS cut-off score of 4.5 (able to walk without aid or rest some 300 metres) was previously successfully used to discriminate patients with relatively mild versus moderate to severe ambulatory dysfunction {Gijbels, 2010 304 /id}. All participants signed the informed consent, which was approved by the Hasselt University Ethics Committee according to the Helsinki declaration.

### ***Experimental Design & Outcome measures***

The present study reports baseline values of muscle strength and walking capacity tests of above-mentioned research project, using a cross-sectional study design. Muscle strength and

walking tests were applied on two different days interspersed with at least 48 hours rest interval to avoid mutual interference.

### *Muscle Strength*

Maximal voluntary unilateral strength of the right and left leg was evaluated on an isokinetic dynamometer (Biodex Medical Systems®, system 3, Inc, Shirley, New York) at a sampling rate of 100Hz. After a 5-min standardized warm-up on a quadriceps bench, strength tests were performed in a seated position on a backward inclined (5°) chair. The rotational axis of the dynamometer was aligned with the transverse knee-joint axis and connected to the distal end of tibia by means of a length adjustable lever arm. The upper leg, hips and shoulders were stabilized with safety belts. ~~Here, muscle strength is expressed as average of both legs.~~

*Maximal isometric torque.* Following one sub maximal trial contraction, two maximal isometric contractions were performed by knee extensors and flexors at knee angles of 45° and 90°. Maximal contractions (during 3s) were interspersed by 90-s rest intervals.

*Maximal isokinetic torque.* Subjects performed four maximal consecutive isokinetic knee-extensions at a velocity of 60°/s after three sub-maximal trial contractions. Knee extensions were initiated at a joint angle of 90° towards an angle of 160°. Following each extension, the leg was returned passively to the starting position from which the next contraction was immediately initiated. The highest of four-isokinetic extension torques (Nm) was selected as maximal dynamic torque.

*Maximal isokinetic muscle endurance.* Finally and following three sub-maximal trial contractions, subjects performed twenty maximal isokinetic knee extensions at a velocity of 180°/s to assess muscle strength endurance. The knee extensions were initiated at a joint angle of 90° towards an angle of 160°. Following each extension the leg was returned passively to

the starting position from which the next contraction was immediately initiated. Muscle strength endurance was expressed as the percentual decrease in average work (J) of the first three and last three contractions.

### *Walking capacity*

Assistive devices were permitted if necessary during all walking tests, which were performed in random order.

~~Timed 25 Foot Walk test (T25FW; {Nilsagard, 2007 109 /id}. Subjects were instructed to walk 25 foot as quickly but safely as possible.~~

*Timed Get Up and Go (TUG; {Podsiadlo, 1991 114 /id}. Time (s) was recorded while subjects get up of a chair, walk 3 meter, turn around, walk back and sit down again. Although not a traditional measure of walking, this test was included given the role of quadriceps strength for getting in and out of the chair.*

~~Timed 25 Foot Walk test (T25FW; {Nilsagard, 2007 109 /id}. Subjects were instructed to walk 25 foot as quickly but safely as possible.~~

*Two Minute Walk Test (2MWT; {Butland, 1982 117 /id}. Subjects were instructed to walk as much distance within the two minutes period. Outcome on the 2MWT was shown in PwMS, to be strongly related to that on the 6MWT {Gijbels, 2011 694 /id}.*

### *Statistical analyses*

The normal distribution of all variables was investigated using the Shapiro-Wilk test. Student's t-test for independent samples or Mann-Whitney tests was applied to examine differences between subgroups. Further analyses were applied on the total sample as well as on subgroups separately.

For data analysis, the most paretic leg of each subject was taken. Pearson correlation coefficients were calculated to examine the relationship between maximal knee muscle strength and functional mobility tests and were interpreted as poor ( $r < 0.30$ ); low ( $r: 0.30-0.50$ ); moderate ( $r: 0.50-0.70$ ); high ( $r: 0.70-0.90$ ) or very high ( $r: > 0.90$ ). To investigate which knee extensor strength variable contributed most importantly to walking capacity, multiple regression models with a backward selection procedure were performed for the maximal isometric, isokinetic knee extensor peak torque and maximal dynamic knee extensor endurance of the most affectedweakest leg as independent variables while each walking test served as dependent variable. To investigate whether knee extensor or flexor isometric strength of the weakesmost affectedt leg contributed most importantly to walking capacity, multiple regression models with a backward selection procedure were performed for the maximal isometric knee extensor and flexor peak torque as independent variables while each walking test served as dependent variable. Multicollinearity was checked for all models. The level of statistical significance was set at  $p < 0.05$  and data are presented as mean  $\pm$  SE. Statistical analyses were performed using SAS<sup>®</sup> software (Version 9.2; SAS Institute, Inc., Cary, NC). Post hoc power calculations were performed using G power 3 software {Faul, 2007 377 /id}.



## Results

### Description of the MS subgroups

Table 1 presents the clinical characteristics and experimental outcome measures of the total MS group and both subgroups. Age and disease duration were not significantly different between subgroups with different EDSS scores. All muscle strength variables and walking capacity tests were significantly ( $p < 0.05$ ) worse in the subgroup with moderate compared to mild ambulatory dysfunction ~~with exception of isokinetic knee extensor endurance strength,~~ justifying the use of the EDSS 4.5 cut-off score for differentiation among MS subgroups.

INSERT TABLE 1 HERE

*Different types of maximal knee extensor strength in relation to walking capacity.*

Table 2 displays the correlations coefficients between upper leg strength and walking tests. First, the relationships between isometric, isokinetic and endurance knee extensor strength and the walking tests are described. In the total MS sample, all strength measures were significantly, ranging from poor to moderate, related to the walking tests. ~~When analyzing results of the~~ For the subgroup with mild ambulatory dysfunction separately, ~~no~~ any significant correlations between knee extensor strength and walking capacity tests ~~were~~ found except for a low correlation between isometric knee extensor strength at 45° and the 2MWT. In ~~contrast, in~~ the subgroup with moderate ambulatory dysfunction, ~~all~~ correlation coefficients (0.60-0.47 up to 0.62-0.55) between muscle endurance and ~~all~~ walking tests were all significant. ~~Besides, added with~~ a significant correlation between isokinetic strength and the 2MWT was found.

Secondly, the relationships between knee extensor versus knee flexor isometric strength and the walking tests ~~was investigated~~ are discussed. For the total MS group as well as both

**Opmerking [PF5]:** Weet niet of dit nog zo is, als ik nu tabel 1 beschouw. Zou durven stellen dat het wel verschillend is gezien de lage SD tov het gemiddelde. In dat geval moet de tweede helft van de zin hier geschrapt worden.

subgroups, correlations between isometric strength of knee flexors and walking capacity was systematically greater than ~~better related to walking capacity tests compared to~~ that of knee extensors. In the subgroup with mild ambulatory dysfunction, isometric muscle strength of knee extensors (at 45° only) ~~and knee flexors~~ were significantly correlated with the 2MWT, while correlations with any of the shorter walking tests were smaller and not significant. Isometric muscle strength of the knee flexors was significantly correlated with the 2MWT (both 45 and 90°), as well as with the shorter walking tests (45°). In the subgroup with moderate ambulatory dysfunction, isometric knee extensor strength was not significantly related with any of the walking capacity tests, while moderate to high correlations were found for the isometric strength of knee flexors.

INSERT TABLE 2 HERE

*-Predictive value of various knee strength variables for walking capacity*

Given the fact that the highest correlation coefficients were found in the moderate subgroup, multiple regression models to predict walking capacity with different knee strength variables were only applied in this subgroup (see Table 3). Power of all regression analyses were above 0.80 (Range 0.93-0.96). First, various knee extensor strength variables were used as independent variables, to predict walking capacity. The only significant predictor (range 3318-3527%) was endurance strength. Second, isometric knee extensor and flexor strength variables were used as independent variables, to predict walking capacity. For all walking tests, isometric knee flexor strength at 90° was the only significant predictor with a ~~consistent~~ predictive value of 34-46%.

INSERT TABLE 3 HERE

## ***Discussion***

To our knowledge, only a few studies have extensively investigated the relationship between muscle strength and walking capacity in neurological conditions, taking different types of strength measures as well as different muscle groups into account. The present study in persons with MS, also taking severity of ambulatory dysfunction into account, revealed muscle endurance strength to be the most predictive knee extensor variable for walking in persons with moderate ambulatory dysfunction only, while isometric muscle strength of knee flexors is more predictive for walking compared to the knee extensors.

### *Relationships between various knee extensor strength measures and walking capacity*

The first objective was to investigate the clinical relevance of different muscle strength measures and walking capacity. Isometric and isokinetic strength of the knee extensors, as well as a measure for muscle endurance, were significantly related to short (T25FW and TUG) and longer (2MWT) walking tests in the total group. In line with a previous study {Gijbels, 2010 304 /id}, the EDSS cut-off score of 4.5 validly distinguished subgroups with mild and moderate ambulatory dysfunction, given significant differences in walking capacity.

As well, muscle strength was different between subgroups ~~except for the endurance measure~~.

In subjects with mild ambulatory dysfunction, no significant correlations were found except for isometric knee extensor strength measured at 45° with the longer 2MWT. The lack of robust relationships between maximal muscle strength and walking capacity tests may be related to the fact that the mild subgroup almost performed as good as healthy subjects {Fritz, 2009 569 /id}, possibly inducing floor effects on short walking tests as already reported in other patient populations {English, 2006 616 /id; Erdmann, 2005 617 /id}. In addition, levels

of knee extensor strength in this subgroup was likely greater than what is strictly required for walking, as well as getting up from a chair {Rantanen, 1998 680 /id;Willen, 2004 679 /id}. In contrast, patients with moderate ambulatory dysfunction showed greater albeit not always significant correlations between walking capacity and knee extensor strength measures. Specifically, knee extensor endurance strength was systematically significantly related to walking capacity in contrast to~~instead of~~ maximal isometric and isokinetic strength~~was revealed as an important variable related to walking rather than maximal muscle strength,~~ which was also ~~unambiguously~~ confirmed by the regression analyses. This muscle endurance strength variable can be considered as a measure of muscle fatigability during repeated contractions, which is also required during walking. An exploratory study in MS by Schwid et al. {Schwid, 1999 437 /id} indicated that fatigability, defined as reduced strength as routine exercise of muscle groups proceeds {Dobkin, 2008 399 /id}, was associated with maximal walking distance and time needed to walk 5 feet {Schwid, 1999 437 /id}. Intriguingly, muscle endurance, ~~which was not different between subgroups,~~ did not significantly relate with walking capacity in PwMS with mild ambulatory impairment. The latter may indicate that muscle strength during gait remained above a certain threshold in this subgroup, even after repeated contractions.

#### *Relationships between knee extensor and flexor isometric muscle strength and walking capacity*

The second objective was to investigate whether relationships between knee extensor and flexor isometric strength with walking capacity differed. Strikingly, maximal isometric knee flexor strength showed systematically greater correlations coefficients compared to isometric knee extensor strength across subgroups. More particular, the greatest correlations were found in the subgroup with moderate ambulatory dysfunction, while in the mild subgroup, correlations of isometric muscle strength and walking tests were low and generally not

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significant except for the longer 2MWT. —

A better association between isokinetic knee flexor compared to knee extensor strength, and walking capacity, ~~has already been~~ was previously reported before in stroke {Kim, 2003 390 /id; Nasciutti-Prudente, 2009 392 /id} and in MS {Thoumie, 2005 30 /id}. In the walking pattern of healthy subjects, knee flexors act concentrically at mid-swing to augment knee flexion for foot clearance and thus unimpeded limb progression, and eccentrically at terminal swing to decelerate the lower limb in preparation of initial contact while avoiding knee hyperextension {Perry J, 1992 640 /id}. These activations influence the gait pattern and related variables as step length {Perry J, 1992 640 /id}. MS patients of the moderate subgroup might have importantly shown poor knee flexion during the swing phase, similarly as suggested in stroke patients with a paretic lower limb {Nasciutti-Prudente, 2009 392 /id}, as isometric muscle strength at 90° knee flexion showed greater correlations and was most predictive for diminished walking capacity in the regression analysis compared to strength at 45°. In support of this view, Olney et al. {Olney, 1994 636 /id} identified, in patients with hemiplegia, a positive relationship between maximal flexor moments of knee, hip and ankle during swing phase and gait speed. Unfortunately, an important limitation of the present study was that it did not include kinematic analysis or recordings of spatio-temporal characteristics {Sacco, 2011 695 /id}, making it difficult to ~~define-be conclude on the mechanism of the contribution-of~~ knee flexor weakness impacting on the gait ~~pattern-and~~ speed with certainty. In this regard, future research should also include strength measurements of hip and ankle muscles in the investigation of the relationship between muscle strength and gait velocity, as this would provide information whether distal rather than proximal muscle weakness may have impacted the swing phase (drop foot, hip flexion) or stance phase (hip extension and stability) had likely influenced gait speed. Also, the impact of other muscle weakness, such as calf muscles or hip extensors, should be taken in account in future research. One may also

consider inclusion of the Motricity Index as a comprehensive clinical measure of strength in hip, knee and foot muscles. However, ordinal scoring on separate items is less suited for advanced statistical processing and regression analyses. Furthermore, it is acknowledged that the current study performed an unidimensional measurement of muscle strength, while while it is also acknowledged that walking capacity in MS is also influenced by factors such as impaired postural control, sensory dysfunction and increased muscle tone, similar as previously documented in stroke {Kligyte, 2003 643 /id;Nadeau, 1999 642 /id;Hsu, 2003 641 /id;Kim, 2003 390 /id}. ~~In future research, it may be worthwhile to also take into account the impact of potential muscle weakness at ankle and hips joints, and other impairments on walking capacity of PwMS. However, it is noted that the findings of the present study regarding the importance of the knee flexors for non-assisted gait are similar to those of Thoumie et al {Thoumie, 2005 30 /id} who included patients with different types of impairment (sensory, cerebellar, pyramidal).~~

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Relationships between muscle strength and walking capacity appeared to be different in the subgroups of different ambulatory dysfunction. In contrast to the present study, Thoumie et al. concluded that knee extensor strength is more related with walking than knee flexors when disability level increased {Thoumie, 2005 30 /id}. However, the latter study differentiated subgroups without (n=65) and with (n=35) cane assisted-walking importantly documenting that the use of a cane likely alters the relationships between muscle strength and gait speed. In our study, only six subjects in the subgroup with moderate ambulatory dysfunction made use of a cane, which did statistically not allow the formation of a separate subgroup of patients with severe ambulatory dysfunction to verify above-mentioned findings. One may also comment that we compare results of isometric muscle strength in the present study with that of isokinetic muscle strength in the study of Thoumie et al {Thoumie, 2005 30 /id}. However, it is noted that, despite this methodological bias, knee flexor maximal strength explained

~~similarly about~~approximately 45% of the variance of walking capacity in both studies.

~~Furthermore, the present study only focused on motor impairment caused by muscle weakness, while Thoumie et al (Thoumie, 2005 30 /id) included patients with different types of impairment (sensory, cerebellar, pyramidal) still coming to similar conclusions regarding the importance of the knee flexors for non-assisted gait.~~

### *Clinical Implementations*

The findings of the present study seem relevant to improve clinical evidence-based practice. ~~So far, It is indicated that, in patients with only mild ambulatory dysfunction, no major a few studies showed significant~~ carry-over effects of increased muscle strength after resistance training on walking capacity tests, ~~in patients with relative mild disability,~~ (3) ~~while other studies showed no functional benefits should be expected.~~ However, it is not excluded that other activities such as stair climbing, requiring higher levels of muscle strength, may improve after resistance training. In PwMS with moderate ambulatory dysfunction, however, training of especially knee extensor endurance strength and maximal isometric knee flexor strength seems advocated given strong associations with walking capacity. So far, most resistance training programs in healthy individuals {2009 227 /id; Kraemer, 2002 240 /id; Liu, 2009 362 /id}, stroke {Engardt, 1995 598 /id; Teixeira-Salmela, 1999 599 /id; Ada, 2006 600 /id}, and MS patients {Dalgas, 2009 257 /id; Gutierrez, 2005 31 /id; White, 2004 32 /id; DeBolt, 2004 442 /id; Broekmans, 2011 575 /id} seem to focus on increasing maximal peak strength of commonly the knee extensors. The content of standardized exercise therapy programs in previous studies may explain to some extent the limited effects of resistance training on walking capacity. While effects of resistance training on maximal knee flexor strength has been shown before {Broekmans, 2011 575 /id; Dalgas, 2009 257 /id}, it is rather unclear whether muscle endurance can be improved after specifically designed training

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protocols. Besides, future research should also investigate whether endurance of knee flexors is equally important as that of knee extensors.

Findings of the present study indicate that knee extensor endurance strength, as well as isometric knee flexor strength are important predictors for walking capacity in PwMS with moderate ambulatory dysfunction.

### **Acknowledgments**

This study was partly supported by IWT tetra grant #50078, Flanders, Belgium.



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**Opmerking [PF7]:** Deze refs moet je dan not zelf invoegen