

Implications of lower extremity muscle power and force for walking and fatigability in multiple sclerosis-An exploratory pilot-study

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1 **Title page**

2 **ORIGINAL ARTICLE**

3 IMPLICATIONS OF LOWER EXTREMITY MUSCLE POWER AND FORCE FOR WALKING AND

4 FATIGABILITY IN MULTIPLE SCLEROSIS – AN EXPLORATORY PILOT-STUDY

5 *Running title:* Implication of power for physical function in multiple sclerosis

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28 **Publication Ethics**

29 All participants provided informed written consent prior to involvement in the study, which was
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35 **Abstract**

36 **Background:** Limitations in physical function are common in Multiple Sclerosis (MS), yet it is neither
37 clear how muscle power implicates physical function and walking-fatigability. This pilot-study aims to
38 investigate (1) deficits in muscle power/force alongside walking in persons with MS; (2) associations
39 between muscle power/force and physical functions and (3) the impact of prolonged walking in muscle
40 power/force. **Methods:** 30 relapse-remitting persons with MS and 28 healthy controls performed chair
41 rise and plantar flexion on a force platform before and after 12-minutes of intermittent walking to
42 measure lower extremity muscle power/force. GaitRite measured walking speed. The percentage change
43 in distance walked was also calculated. Persons with MS were classified into subgroups according to
44 walking-fatigability and mobility disability status (Patient Determined Disease Steps). **Findings:** Higher
45 deficits in muscle power compared to force were observed in persons with MS vs. healthy controls
46 particularly in persons with MS having higher disability. Muscle power and force were associated with
47 walking capacity, mobility disability and subjective fatigue, but not with percentage change in distance
48 walked. Persons with MS slowed down over the course of the 12-minutes intermittent walking, whereas
49 decrements in walking speed and muscle power/force (derived from chair rise) were observed in persons
50 with MS presenting walking-fatigability only. **Interpretation:** Muscle power and force are impaired in
51 persons with MS and appear to be critical for physical function in MS. This exploratory pilot study
52 further suggests that muscle power/force from chair rise could contribute to walking-fatigability which
53 therefore offer future treatment targets.

54 **KEYWORDS:** Multiple Sclerosis; Functional Capacity; Fatigue; Muscle Function; Walking; Disability.

55 **1 Introduction**

56 A pathological hallmark of multiple sclerosis (MS) is the accumulation of demyelinating lesions
57 in the central nervous system (1). The bursts of focal inflammation, axonal loss and neurodegeneration
58 are known as predominant causes of disability (2). Common limitations in physical functions in persons
59 with MS (pwMS) include the decrement in walking speed and endurance (3-5), along with increment in
60 the time to perform stair climbing and chair rise tasks (6-8). These are partly driven by an inability of the
61 neuromuscular system to perform rapid limb movements due to insufficient volitional drive to a given
62 muscle (9, 10), along with reduced rate of force development (RFD; force or torque production within a
63 very short time window) (9). Indeed, marked deficits have been observed in the lower extremity muscle
64 strength and RFD in pwMS vs. healthy controls (HC) (11). Moreover, systematic reviews have shown
65 clear associations between lower extremity strength/RFD of different muscle groups and lower limb
66 functional capacity such as walking and sit-to-stand (6, 7, 12). While the vast majority of the studies have
67 examined lower extremity strength/RFD during isometric or dynamic muscle contractions at fixed slow-
68 to-moderate velocities, few have examined muscle power (i.e., force multiplied by velocity) (13, 14). In
69 MS, there is little information regarding muscle power, particularly when derived from functional weight-
70 bearing tasks, and more importantly how muscle power implicates physical function in pwMS (15).
71 Importantly, evidence derived from aging studies show that lower extremity muscle power is a stronger
72 predictor of physical function than muscle strength, impacting mobility (16) and the ability to avoid
73 falling during walking (17). Such a comparison between muscle power has nevertheless not been
74 examined in pwMS.

75 Fatigue is another consequence of MS and is frequently reported by pwMS (18). It can be
76 defined as perceived fatigue (subjective sensations of weariness) (19) and as motor fatigue or fatigability
77 (absolute or relative change in performance over a period of time during or after a given task) (20).
78 Importantly, fatigability is known to be associated with baseline lower extremity muscle strength (21).
79 However, no studies have so far examined whether decrement in muscle power induced by prolonged
80 walking contributes to walking-related fatigability.

81 The aims of this cross-sectional exploratory pilot-study were (1) to investigate and characterize
82 deficits in lower extremity muscle power (and force) measured during chair rise and plantar flexion on a
83 force platform alongside walking capacity in pwMS; (2) to investigate the associations between muscle
84 power (and force) and walking capacity, mobility disability status, subjective fatigue and fatigability and

85 (3) to investigate the impact of 12-minutes of intermittent walking in lower extremity muscle power (and
86 force). We hypothesized that pwMS would present substantial deficits in lower extremity muscle
87 power/force (preferentially in power) and in walking capacity, particularly in pwMS having mobility
88 disability and pwMS presenting walking-fatigability.

89 **2 Materials and methods**

90 **2.1 Participants**

91 A convenience sample of thirty-four people with MS were recruited from private neurological
92 clinics and via a MS community organization, via email and newsletter advertisements. Participants were
93 eligible if they had a confirmed diagnosis of relapse-remitting MS (RRMS) according to the revised
94 McDonald criteria (22). Participants were excluded if they had a confirmed exacerbation or relapse of MS
95 in the month prior to testing; had significant cardiac or respiratory disease, which could pose a risk when
96 performing the walking protocol; if they could not walk for two minutes without stopping. Twenty-eight
97 healthy controls (HC) matched for age (acceptable range of ± 2 y), sex, height (acceptable range of ± 5
98 cm) and weight (acceptable range of ± 5 kg) were recruited from the university staff and from friends and
99 family of the participants.

100 **2.2 Clinical evaluations**

101 Initially, participants were asked to determine their disability level according to walking function
102 using the Brazilian Patient Determined Disease Step scale (PDDS-BR)(23). PDDS is a validated patient-
103 reported measure of mobility disability. The PDDS has nine ordinal levels ranging from 0 (normal) to 8
104 (Bedridden), and presents strong correlations with the Expanded Disability Status Scale (EDSS)
105 (coefficient of correlation ranging from 0.71 to 0.78).

106 The Modified Fatigue Impact Scale (MFIS) is a self-reported assessment of fatigue assessing
107 physical, cognitive and psychosocial domains. The questionnaire contains 21-items concerning how
108 fatigue have been impacting patient's lives in the past 4 weeks (24). Given to the best previously reported
109 association between physical function and the MFIS physical subscore (25), it was a priori decided to use
110 this for the association analysis.

111 **2.3 Force platform measures**

112 Measures of power (and force) during the chair rise and the plantar flexion tests were collected
113 before and after the walking protocol. Ground reaction force was measured using an AMTI force platform
114 (AMTI, Watertown, MA). Vicon Nexus software - v2.8 (Vicon, Oxford, UK) was used to acquire data on
115 kinetics at a sample rate of 1000 Hz. Data processing was performed using personalized MATLAB
116 scripts (R2015a, The Mathworks, Natick, Massachusetts, USA). Signals were filtered digitally with a 10-
117 Hz low-pass Butterworth filter (4th order) with zero phase lag (26).

118 Participants were instructed to begin the chair rise from a sitting position on a standard wooden
119 chair measuring 42 cm of height, with back support and no armrests, positioned adjacent to the force
120 platform. With their feet at a comfortable self-selected width within the boundaries of the platform, the
121 participants were instructed to cross their arms over the chest and to rise from the chair as fast but safely
122 as possible, and to sit down at a slow speed, performing sequentially five sit-to-stand without rest (26).

123 The plantar flexion consisted of five bilateral plantar flexions (heel rises) on a force platform.
124 Participants were instructed to rise to the tip of their toes with the feet at a comfortable position as fast as
125 possible, keeping the knees straight, the arms crossed on the chest and trying to keep on their tiptoe for at
126 least one second before go down (27).

127 **2.4 Walking protocol**

128 Participants were instructed to walk along a 10-meter corridor, turning 180 degrees, for 2-
129 minutes. The complete protocol was composed of six 2-minute walks with a rest period of 30 seconds
130 between bouts, adding up to a total of 12-minutes of walking. Participants were instructed to “walk as fast
131 as possible, but safely”. If necessary, the use of a walking aid was allowed. Before, during the rest periods
132 and after the last 2-minute walk, the maximal walking speed (m/s) was assessed using a 4.88-meter
133 GaitRite electronic walkway (CIR Systems Inc., Haverton, Pennsylvania, USA). Figure 1 presents the
134 experimental protocol.

135 INSERT FIGURE 1

136 **2.5 Data processing**

137 Participant’s body weight was assessed during quiet stance immediately before the trials. The
138 ground reaction force (F_z) was normalized relatively to the body weight. The chair rise movement began
139 with a relief phase and ended when F_z was equal to 1 - when the subject was standing (26, 28). We have
140 not included the preparation phase in the analysis and we chose to analyse the chair rise from the first
141 moment when the body weight was reached ($F_z \sim 1$, before the peak force) until the standing position
142 (figure 2, A) (28). For the plantar flexion, the F_z was equal to 1 at the beginning of the movement, followed
143 by an increase on F_z - reaching the peak force, and a rebound force event following the peak force. The end
144 of the plantar flexion was defined when the F_z was around 1 after the rebound force event (figure 2, B).

145 INSERT FIGURE 2

146 Regarding to the F_z parameters, figure 2 presents the interval from the force-time curve chosen
147 to extract force and calculate power. The peak force normalized per body weight (N/bw - Newton per

148 body weight) was used in the analysis. To calculate power, the velocity-time curve was obtained by
149 dividing the resultant force-time curve by the participant's body weight to find the acceleration-time
150 curve. The acceleration was then numerically integrated with respect to time using the trapezoid rule, and
151 the instantaneous power was calculated as the product of the force and velocity (29). The normalized peak
152 power (Watts per body weight - W/bw) was used in the analysis.

153 In order to investigate fatigability during walking, the Distance Walk Index (DWI%) (30) was
154 calculated based on the total distance walked during the first and in the last 2-minute walks. Adopting a
155 cut-off of 10% of slowing down, DWI $[\leq -10]$ (31), pwMS were allocated into two groups: MS
156 fatigability and MS non-fatigability. In addition, another subgroup classification was also adopted for
157 pwMS according to their mobility disability status, based on the PDDS score. Those with PDDS equal to
158 zero were included in the PDDS Low group, while the remaining participants with PDDS ≥ 1 were
159 included in the PDDS High group.

160 **2.6 Statistical analysis**

161 Statistical analyses were performed using linear mixed model in Stata version 14.2 (StataCorp
162 LP, Texas, USA). Distribution of data was visually checked by box-plots, q-q-plots, histograms and dot-
163 plots, showing that all the data were normally distributed, except for the plantar flexion force which was
164 subsequently transformed prior to analysis: $(1/\text{plantar flexion})^{\wedge 2}$. All baseline data were analysed with
165 Group (HC and MS All; HC, MS non-fatigability and MS fatigability; HC, PDDS Low and PDDS High)
166 as a fixed effect and Participant ID as a random effect. Deficit scores were also calculated as the mean
167 (95% confidence interval, CI 95%) percentage difference for pwMS in relation to the mean value from
168 HC. To investigate the changes in the distance walked (m) and in the walking speed (m/s) over the 12-
169 minutes of intermittent walking, analysis was performed with repeated measures for each group.

170 Simple linear regression analysis and multivariate regression analysis adjusting for age and sex
171 were carried out to examine potential associations between muscle power and force with walking speed
172 (walking speed at baseline, m/s), distance (total distance from the 12-minutes walking, m), DWI (%),
173 PDDS (score) and MFIS physical (physical subscore) in the total sample of pwMS. Associations are
174 presented as r^2 -values (i.e., the square of the correlation coefficient), with $r^2 > 0.81$ ($r > 0.90$) interpreted
175 as very strong, $r^2 = 0.49-0.80$ ($r = 0.70-0.89$) as strong, $r^2 = 0.25-0.48$ ($r = 0.50-0.69$) as moderate, $r^2 =$
176 $0.09-0.24$ ($r = 0.30-0.49$) as weak, and $r^2 < 0.08$ ($r < 0.29$) as negligible (32). Data are presented as mean
177 (CI 95%) unless otherwise stated. The effects of the walking protocol on muscle power/force and walking

178 speed were analysed with Group (HC and MS All; HC, MS non-fatigability and MS fatigability; HC,
179 PDDS Low and PDDS High) and Time (Pre and Post) as fixed effects and Participant ID as a random
180 effect. Changes in force, power and walking speed were also calculated as the mean (CI 95%) percentage
181 difference between pre and post (delta, $\Delta\%$) the 12-minutes of intermittent walking. Graphs were made
182 using GraphPad Prism version 7.03 (GraphPad Software, California, USA). Level of statistical
183 significance was set at $p < 0.05$.

184 **3 Results**

185 **3.1 Baseline characteristics**

186 Table 1 presents the characteristics of the participants along with clinical results. No differences
187 were found regarding sex proportions, age, height, and weight between HC and pwMS. Subjective
188 (perceived) fatigue measured using the MFIS were higher in pwMS compared to HC. The MS fatigability
189 group presented a lower score for the MFIS total and a higher score for the MFIS physical, when compared
190 to the MS non-fatigability group. MFIS total and all subscores were ~~all~~ higher for the PDDS High group
191 compared to the PDDS Low and to the HC group. As a measure of physical function, the total distance (m)
192 travelled during the 12-minutes of intermittent walking was shorter for pwMS vs. HC. Comparisons of
193 subgroups revealed shorter distances walked in MS fatigability when compared to MS non-fatigability as
194 well as in PDDS High compared to PDDS Low. In general, pwMS showed higher DWI (%) compared to
195 HC suggesting the presence of walking-related fatigability. Moreover, DWI (%) was higher in MS
196 fatigability group compared to the MS non-fatigability group. In addition, DWI (%) was not impacted by
197 PDDS, and no differences could be found between PDDS Low and PDDS High groups.

198 INSERT TABLE 1

199 Figure 3 presents the course of the distance walked and the walking speed over the 12-minutes of
200 intermittent walking for each group. Changes were predominantly observed in the MS fatigability group.

201 INSERT FIGURE 3

202 **3.2 Deficit in lower extremity muscle power/force and walking capacity - comparisons of subgroups**

203 As shown in figures 3 and 4, pwMS presented greater limitations in walking endurance and
204 speed compared to HC. In addition, lower extremity muscle force and preferentially muscle power were
205 substantially lower in pwMS compared to HC (corresponding to deficits of 5% in force and 15 to 20% in
206 power). MS fatigability and MS non-fatigability groups presented deficits in total distance walked, in
207 walking speed, and in plantar flexion muscle power when compared to the HC. Deficits in total distance

208 walked were found for MS fatigability group compared to the MS non-fatigability group. Deficits in
209 plantar flexion muscle force and power as well as chair rise muscle power were only present in non-
210 fatigability pwMS (figure 4b). PDDS High group showed deficits in walking capacity and in muscle
211 power (and force) when compared to HC and PDDS Low groups (Figure 4c). Although the PDDS Low
212 group showed deficits in walking capacity when compared to HC, measures of power (and force) were
213 not different from HC.

214 INSERT FIGURE 4

215 **3.3 Baseline associations between muscle power/force and walking capacity, mobility disability** 216 **status and physical subjective fatigue in pwMS**

217 Muscle power and force were significantly associated with walking speed (walking speed at
218 baseline), distance (total distance from the 12-minutes walking) and mobility disability status (PDDS)
219 (Table 2). No associations were found between muscle power/force and the reduced walking distance and
220 speed over the 12-minutes of intermittent walking (i.e., DWI %). Associations between chair rise force
221 and walking speed, total distance walked in the 12-minutes walking, disease steps (PDDS) as well as
222 physical subjective fatigue (MFIS physical), were stronger compared to the associations found for plantar
223 flexion force. In addition, age and sex did not impact the results as presented in table 3 for the multiple
224 regression analysis.

225 INSERT TABLE 2

226 INSERT TABLE 3

227 **3.4 Pre-post changes induced by the 12-minutes of intermittent walking - comparisons between** 228 **subgroups**

229 MS fatigability group presented trends towards delta changes (%) in power (and force) from
230 chair rise compared to HC and to MS non-fatigability (see Table 3). No pre-post changes were found for
231 the PDDS subgroups.

232 Regarding walking speed, pre-post change was only significant for the MS fatigability group, with
233 reduced walking speed after the 12-minutes of intermittent walking. In addition, a trend for significance
234 was found for delta (%) between MS fatigability group and non-fatigability group.

235 INSERT TABLE 4

236

237 **4 Discussion**

238 The main findings of this exploratory pilot-study: (1) a more pronounced deficit in lower
239 extremity muscle power vs. muscle force was observed in pwMS, particularly in pwMS having higher
240 mobility disability (PDDS score ≥ 1); (2) lower extremity muscle power and force were (to a comparable
241 extent) associated with walking capacity, PDDS score and MFIS physical (power $r^2=0.11 - 0.39$ / force
242 $r^2=0.11 - 0.43$), but not with walking-related fatigability (i.e. DWI%); (3) pwMS significantly decreased
243 walking speed over the 12-minutes of intermittent walking (preferentially in pwMS presenting walking-
244 related fatigability = MS fatigability group); (4) the absence of any apparent walking-induced decrements
245 in absolute values of lower extremity muscle power and force suggest that walking fatigability was not
246 dependent of such factors in our sample.

247 **4.1 Deficit in lower extremity muscle power/force and walking capacity - comparisons of subgroups**

248 In general, pwMS presented approximately 20% of deficit in walking capacity in relation to HC,
249 and our results thus corroborate with previous findings (5), both for short distance (15, 33) and long-
250 distance walking (4).

251 For all pwMS, deficit in muscle power (15-20%) were shown to be more prominent than deficit
252 in muscle force (5%). According to a review by Jørgensen et al. (11), a deficit of approximately 25% in
253 pwMS compared to HC has been reported for lower extremity muscle strength (isokinetic dynamometer
254 assessment) and for knee extensor muscle power (despite the absence of any deficit dorsiflexor muscle
255 power) (13). Moreover, in a cross-sectional study by Stagsted et al. (15), a deficit in chair rise power as
256 well as leg press power (assessed by use of position transducer) in pwMS compared to HC corresponded
257 to 26% and 23%, respectively. The markedly lower deficit in force in the present study is probably partly
258 due to the tasks performed, to the method applied to extract power/force (i.e. GRF), and to the enrolment
259 of predominantly mildly impaired pwMS. Cruz et. al. (34) also found deficits in rapid muscle force (i.e.
260 Rate of Force Development – RFD; derived from chair rise on a force platform) in pwMS vs. HC, known
261 to be a pre-requisite of producing muscle power – as examined in the present study.

262 Analysis of subgroups revealed a substantial difference in the total distance walked during the
263 12-minutes of intermittent walking in MS fatigability compared to MS non-fatigability group, whereas
264 baseline walking speed did not differ between groups. This emphasizes that assessment of walking-
265 fatigability should be prioritized when assessing pwMS suffering from fatigue. Regarding the deficits in
266 muscle power/force, our results showed no differences between MS fatigability and MS non-fatigability
267 group. These results suggest that the decrements over time (i.e. DWI%) was not affected by the baseline

268 values of lower extremity muscle power/force in our sample (at least not in the way we have assessed it
269 by performing the tasks with a fast yet safe speed). Subjective fatigue (i.e. MFIS) has been reported to be
270 weakly associated with walking capacity (25) as well as muscle strength (35). Yet no studies have, to our
271 knowledge, previously reported differences in walking speed and in lower extremity muscle power/force
272 in resting conditions and after a 12-minutes of intermittent walking in pwMS (especially not in
273 fatigability subgroups) and compared to HC have been proposed.

274 Concerning the subgroup's classification according to fatigability status and mobility disability
275 status, disparate findings were observed. Whilst higher mobility disability status was accompanied by
276 decrements in baseline outcomes, higher fatigability status was accompanied by higher decrement in
277 walking speed. Since differences in muscle power/force between the PDDS Low and High groups were
278 substantial during the chair rise task but not during the plantar flexion, this indicate that more complex
279 dynamic tasks such as chair rise may require a more optimal motor control in order to synchronise
280 different muscular groups (36) and might be more sensitive in terms of detecting motor deficiency across
281 disability status in pwMS.

282 **4.2 Baseline associations between muscle power/force and walking capacity, mobility disability** 283 **status, and physical subjective fatigue in pwMS**

284 Although associations between plantar flexion muscle power/force during and walking capacity,
285 mobility disability status as well as subjective fatigue were observed (corresponding to weak
286 associations), chair rise muscle power/force (i.e. a more complex motor task) presented better
287 associations with walking capacity, mobility disability and subjective fatigue (corresponding to weak-to-
288 moderate associations). Our findings corroborate with a review from our research group (12), where
289 lower-limb muscle strength was associated with a number of lower-limb functional capacity tests (r^2 -
290 values ranging from 0.20 to 0.30). Despite the small sample size ($n=30$) presented in the current
291 exploratory pilot-study, more pronounced deficits in muscle power vs. muscle force was found in pwMS,
292 even so, muscle force presented higher associations with walking capacity.

293 **4.3 Changes induced by the 12-minutes of intermittent walking - comparisons between subgroups**

294 No apparent differences in absolute lower extremity muscle power/force were found between pre
295 and post the 12-minutes of intermittent walking in pwMS and HC. In a study by McLoughlin et al. (37), a
296 walking-induced (6-minutes walking) decrement in both knee extensor and dorsiflexor muscle strength
297 assessed during isolated muscle contractions was reported in pwMS. However, the current exploratory

298 pilot study is the first to evaluate lower extremity muscle power/force using functional tasks before and
299 after an intermittent walking in pwMS. The lack of decrements in muscle power/force that was
300 hypothesised to occur, may be due to the time period (about 4 min) taken to perform the post evaluation.
301 Future studies should consider to evaluate real-time lower extremity muscle power/force (i.e., during
302 walking) and, to include a larger sample size of pwMS presenting walking-fatigability in order to identify
303 potential mechanisms related to fatigability in MS.

304 Concerning the course of distance walked over the 12-minutes, pwMS slowed down over time.
305 However, when analysis of subgroups was carried out, differences over time could no longer be found for
306 the MS non-fatigability group. Interestingly, decrement in distance walked was found in the PDDS Low
307 group but not in the PDDS High group, suggesting a more conservative strategy from the more disable
308 patients. Analysis of walking speed over time revealed significant decline only for the MS fatigability
309 group. Previous studies investigating the impact of two- and six-minutes walking on spatiotemporal gait
310 parameters in pwMS did not found decrement in walking speed (38, 39). In addition, it has been shown
311 that six-minutes walking induced an increment in walking speed (at a comfortable pace) and there was no
312 effect on fast walking speed in pwMS (40). Corroborating with the findings from the literature, no change
313 in walking speed was found in our study when the analysis was carried out for the entire sample of
314 pwMS.

315 **4.4 Clinical implications**

316 The present exploratory pilot study highlights the importance of including objective methods to
317 identify pwMS presenting walking-fatigability. From our MS sample, 30% slowed down during the 12-
318 minutes of intermittent walking. In this context, it is important to perform analysis of subgroups with
319 larger sample size including pwMS presenting and not presenting walking-fatigability. PwMS presenting
320 walking-fatigability may alter biomechanical gait parameters (i.e., spatiotemporal, kinematics and
321 kinetics) and muscle functions during prolonged walking, and, the real-time assessment of these
322 parameters could elucidate potential factors related to fatigue in MS. In addition, muscle power/force are
323 modifiable factors that can be trained and improved with physical exercise, more precisely with resistance
324 training. Improvements in muscle functions such as power, should be considered in clinical practice
325 during rehabilitation and exercise interventions in order to improve physical functions in pwMS.

326 **4.5 Limitations of the study**

327 The current study is the first to investigate the effects of 6 x 2 minutes (12-minutes in total) of
328 intermittent walking on walking speed and on muscle power/force and the associations with walking-
329 related fatigability in pwMS. A number of limitations nevertheless deserve mentioning: (1) characterized
330 as an exploratory pilot-study (and thus not powered a priori to examine the selected outcomes), the results
331 must be interpreted as such, hence without drawing strong conclusions regarding the impact of prolonged
332 walking on the decrement of muscle power/force in pwMS; (2) the sample size may have been too small,
333 especially across the subgroups (e.g. MS fatigability and MS non-fatigability); (3) pwMS enrolled in this
334 study had mostly mild MS; (4) the time taken to perform the muscle power/force evaluation after the 12-
335 minutes walking may have allowed partial recovery of muscle function and thus hampering the detection
336 of the effects of the prolonged walking; (5) the chair rise task was performed at a fast and safe speed, but
337 perhaps not maximal, which affected the absolute values of power and, possibly, diminishing the
338 associations of muscle power with physical functions; (6) the cross-sectional design do not allow
339 inference related to causality from impairments in the lower extremity muscle power/force and walking-
340 fatigability; (7) as pwMS in general usually present impairments in balance control and coordination,
341 these motor capacities were not evaluated in our study and their potential interference with the
342 performance of motor tasks should also be taken into consideration.

343 **5 Conclusions**

344 The present exploratory pilot-study revealed greater deficits (pwMS vs. HC) in muscle power
345 compared to force, particularly in pwMS having higher mobility disability (PDDS \geq 1). Muscle power
346 and force were associated with walking capacity, mobility disability status and subjective fatigue, but not
347 with slowing down over time (i.e., DWI %). PwMS slowed down over the course of the 12-minutes
348 intermittent walking, whereas decrements in walking speed and muscle power/force delta (derived from
349 chair rise) were observed in pwMS presenting walking-fatigability only.

350 Muscle power as well as force are impaired in pwMS and appear to be critical for physical
351 function in MS. This exploratory pilot study further suggest that muscle power/force could contribute to
352 walking-fatigability which therefore offer future treatment targets.

353

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361

362 **Author contribution:**

- 363 • Conception or design of the work: CR, LGH, ACD, FG
- 364 • Data collection: CR, ARG, FG
- 365 • Data-analysis: CR, UD, LGH
- 366 • Interpretation of data: All
- 367 • Drafting the work: CR, LGH
- 368 • Revising the work: All
- 369 • Final approval of the version to be published: All
- 370 • Agreement to be accountable for all aspects of the work: All

371

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Tables

Table 1. Characteristics and clinical results of the participants.

	HC	MS All	MS non-fatigability	MS fatigability	PDDS Low	PDDS High
n (females)	28 (22)	30 (24)	21 (18)	9 (6)	13 (11)	17 (13)
Age (y)	40.3 (35.9 : 44.6)	41.9 (37.7 : 46.1)	40.6 (36 : 45.2)	45 (34.6 : 55.4)	39.8 (32.8 : 46.9)	43.5 (37.9 : 49.1)
Height (m)	1.66 (1.62 : 1.70)	1.65 (1.61 : 1.69)	1.63 (1.59 : 1.67)	1.70 (1.61 : 1.78) <i>b</i>	1.64 (1.59 : 1.69)	1.66 (1.60 : 1.71)
Weight (kg)	67.6 (62.05 : 73.31)	68.37 (62.5 : 74.2)	63.9 (58.4 : 69.5)	78.6 (64.4 : 92.9) a,b	66.8 (57.2 : 76.4)	69.5 (61.3 : 77.6)
PDDS (0 - 8)	---	1.23 (0.6 : 1.81)	1 (0.42 : 1.57)	1.77 (0.20 : 3.35)	0	2.1 (1.42 : 2.93) c
Walking aid (n)		5	2	3	0	5
Time since diagnosis (yrs)	---	7.7 (5.3 : 10.1)	6.5 (4.2 : 8.8)	10.6 (4.05 : 17.2) <i>b</i>	6.8 (3.0 : 10.6)	8.4 (4.8 : 11.9)
MFIS total (0 - 84)	24.6 (19.3 : 29.8)	39.1 (31.7 : 46.5) a	39.7 (30 : 49.4) a	37.7 (24.8 : 50.7) a,b	29.4 (18.1 : 40.8)	46.6 (37.5 : 55.6) a,c
MFIS cognitive (0 - 40)	12.3 (9.3 : 15.2)	17.3 (13.6 : 20.9) a	18 (13.1 : 22.9) a	15.5 (9.6 : 21.4)	13.3 (7.2 : 19.4)	20.2 (15.7 : 24.8) a,c
MFIS physical (0 - 36)	10.5 (7.9 : 13.1)	18.2 (14.9 : 21.4) a	17.9 (13.9 : 22) a	18.8 (12.1 : 25.6) a,b	13.5 (8.9 : 18.0)	21.8 (17.7 : 25.9) a,c
MFIS psychosocial (0 - 8)	2.0 (1.3 : 2.7)	3.6 (2.7 : 4.5) a	3.7 (2.5 : 4.9) a	3.3 (1.5 : 5.1)	2.5 (1.2 : 3.8)	4.4 (3.2 : 5.7) a,c
Distance total, 12 min (m)	1156 (1102 : 1210)	898.3 (808.4 : 988.3) a	955.9 (867.1 : 1045) a	764.1 (538.3 : 989.9) a,b	1051 (985.5 : 1117) <i>a</i>	781.4 (652.6 : 910.1) a,c
DWI (%)	-1 (-3 : 1)	-7 (-10 : -3) a	-1 (-3 : 1)	-19 (-25 : -13) a,b	-6 (-11 : -2) <i>a</i>	-7 (-13 : -1) a

Results are presented as mean and 95% confidence interval (CI). PDDS, patient determined disease steps. MFIS, modified fatigue impact scale. Walking aid to perform the walking protocol. DWI, distance walked index. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by **a**: different from healthy controls (HC), **b**: different from Non-Fatigable persons with MS, and **c**: different from PDDS Low.

Table 2. Associations between muscle power/force and walking capacity, fatigability, perception of fatigue and mobility disability status in persons with MS.

	Plantar Flexion				Chair Rise			
	Power (W/bw)		Force (N/bw)		Power (W/bw)		Force (N/bw)	
	r ²	p-Value	r ²	p-Value	r ²	p-Value	r ²	p-Value
Walking speed (m/s)	0.18	0.019 ^d	0.25	0.005 ^d	0.15	0.038 ^d	0.33	0.001 ^d
Distance total (m) - 12 min	0.20	0.013 ^d	0.19	0.014 ^d	0.27	0.003 ^d	0.43	0.000 ^d
DWI (%)	0.05	0.197	0.00	0.865	0.00	0.866	0.01	0.557
MFIS phys., score	0.13	0.048 ^d	0.14	0.035 ^d	0.39	0.000 ^d	0.35	0.001 ^d
PDDS, score	0.21	0.010 ^d	0.11	0.068 ^d	0.18	0.022 ^d	0.25	0.005 ^d

DWI, distance walked index. PDDS, patient determined disease step. MFIS, modified fatigue impact scale. N/bw, Newton/body weight. W/bw, Watts/body weight. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in *italic*) are denoted by *d*.

Table 3. Multivariate regression analysis adjusting for age and sex between muscle power/force and walking capacity, fatigability, perception of fatigue and mobility disability status in persons with MS.

		Plantar Flexion						Chair Rise					
		Power	Age	Sex	Force	Age	Sex	Power	Age	Sex	Force	Age	Sex
WS, m/s	β	0.38	-0.14	-0.15	0.47	-0.17	-0.15	0.42	-0.06	-0.32	0.60	-0.01	-0.31
	p-value	<i>0.05^d</i>	0.42	0.40	0.01^d	0.32	0.38	0.02^d	0.71	0.08	0.00^d	0.92	<i>0.05^d</i>
	Model	<i>R² = 0.13</i>			<i>R² = 0.21</i>			<i>R² = 0.16</i>			<i>R² = 0.36</i>		
Dist.-12m, m	β	0.43	-0.34	-0.03	0.42	-0.33	-0.15	0.53	-0.22	-0.28	0.67	-0.17	-0.28
	p-value	0.01^d	0.04^d	0.85	0.01^d	<i>0.05^d</i>	0.35	0.004^d	0.17	0.09	0.00^d	0.22	<i>0.05^d</i>
	Model	<i>R² = 0.23</i>			<i>R² = 0.23</i>			<i>R² = 0.31</i>			<i>R² = 0.47</i>		
DWI, %	β	0.18	-0.14	-0.21	0.02	-0.15	-0.26	0.01	-0.16	-0.34	0.16	-0.12	-0.37
	p-value	0.35	0.44	0.27	0.90	0.42	0.16	0.94	0.40	0.08	0.41	0.52	<i>0.05^d</i>
	Model	<i>R² = -0.01</i>			<i>R² = -0.02</i>			<i>R² = 0.02</i>			<i>R² = 0.05</i>		
MFIS phys., score	β	-0.39	0.03	-0.11	-0.38	0.02	-0.00	-0.70	-0.12	0.16	-0.67	-0.13	0.13
	p-value	0.04^d	0.86	0.54	0.04^d	0.90	0.97	0.000^d	0.42	0.29	0.000^d	0.42	0.42
	Model	<i>R² = 0.04</i>			<i>R² = -0.05</i>			<i>R² = 0.36</i>			<i>R² = 0.31</i>		
PDDS, score	β	-0.40	0.13	0.21	-0.33	0.12	0.33	-0.55	0.01	0.47	-0.62	-0.01	0.46
	p-value	0.03^d	0.44	0.23	0.06	0.47	0.06	0.003^d	0.92	0.008^d	0.001^d	0.91	0.005^d
	Model	<i>R² = 0.18</i>			<i>R² = 0.13</i>			<i>R² = 0.31</i>			<i>R² = 0.39</i>		

WS, walking speed. DWI, distance walked index. PDDS, patient determined disease step. MFIS, modified fatigue impact scale. N/bw, Newton/body weight. W/bw, Watts/body weight. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in *italic*) are denoted by *d*.

Table 4. Lower extremity force/power and walking speed pre and post the walking-fatigability protocol.

		HC	MS All	MS non-fatigability	MS fatigability	PDDS Low	PDDS High
<i>Plantar Flexion</i>							
Force (N/bw)	pre	1.40 (1.35 : 1.45)	1.33 (1.28 : 1.39) a	1.33 (1.27 : 1.39) a	1.34 (1.19 : 1.50)	1.38 (1.27 : 1.48)	1.30 (1.24 : 1.36) a
	post	1.39 (1.34 : 1.45)	1.35 (1.29 : 1.42)	1.34 (1.28 : 1.41)	1.37 (1.18 : 1.56)	1.42 (1.28 : 1.55)	1.31 (1.24 : 1.37)
	Δ %	0 (-3 : 2)	1 (-1 : 3)	0 (-2 : 4)	2 (-3 : 7)	2 (-1 : 5)	0 (-3 : 4)
Power (W/bw)	pre	5.06 (4.48 : 5.65)	3.94 (3.40 : 4.47) a	4.02 (3.33 : 4.72) a	3.73 (2.82 : 4.65) a	4.43 (3.53 : 5.34)	3.55 (2.90 : 4.21) a, c
	post	5.31 (4.63 : 5.99)	4.15 (3.63 : 4.67)	4.19 (3.55 : 4.83)	4.03 (2.91 : 5.16)	4.66 (4.09 : 5.22)	3.79 (3.01 : 4.58)
	Δ %	5 (-3 : 13)	15 (-4 : 33)	15 (-11 : 41)	14 (-2 : 31)	22 (-20 : 65)	9 (-8 : 27)
<i>Chair Rise</i>							
Force (N/bw)	pre	1.33 (1.29 : 1.37)	1.27 (1.22 : 1.32) a	1.27 (1.21 : 1.33) a	1.26 (1.13 : 1.39)	1.33 (1.26 : 1.40)	1.22 (1.15 : 1.28) a, c
	post	1.36 (1.32 : 1.40)	1.28 (1.22 : 1.33)	1.29 (1.23 : 1.35)	1.24 (1.09 : 1.40)	1.34 (1.27 : 1.41)	1.23 (1.16 : 1.31)
	Δ %	2 (0 : 4)	1 (-0 : 2)	2 (1 : 3)	-2 (-5 : 2) a, b	1 (-2 : 3)	1 (-0 : 3)
Power (W/bw)	pre	5.47 (4.52 : 6.43)	4.58 (3.75 : 5.41)	4.44 (3.46 : 5.41)	4.94 (2.92 : 6.96)	5.64 (4.44 : 6.85)	3.71 (2.65 : 4.77) a, c
	post	5.60 (4.80 : 6.41)	4.89 (3.92 : 5.86)	4.89 (3.78 : 5.99)	4.35 (1.69 : 7.0)	5.96 (4.40 : 7.53)	3.84 (2.68 : 5.01)
	Δ %	11 (-4 : 26)	14 (-12 : 41)	27 (-5 : 60)	-15 (-49 : 19) b	6 (-9 : 22)	21 (-28 : 70)
<i>Gait Parameter</i>							
Walking speed (m/s)	pre	1.90 (1.81 : 2.00)	1.52 (1.37 : 1.68) a	1.55 (1.37 : 1.73) a	1.45 (1.05 : 1.86) a	1.71 (1.56 : 1.86) a	1.39 (1.15 : 1.63) a, c
	post	1.83 (1.71 : 1.94)	1.42 (1.25 : 1.60)	1.52 (1.30 : 1.74)	1.20 (0.88 : 1.52) d	1.58 (1.36 : 1.80)	1.30 (1.03 : 1.57)
	Δ %	-4 (-8 : 1)	-4 (-17 : 10)	2 (-16 : 21)	-20 (-27 : -12) b	-6 (-20 : 8)	-2 (-24 : 20)

Results are presented as mean and 95% confidence interval (CI). Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by **a**: different from healthy controls (HC), **b**: different from MS Non-Fatigable, **c**: different from PDDS Low, and **d**: different from Pre (within same group).

Figures and Captions

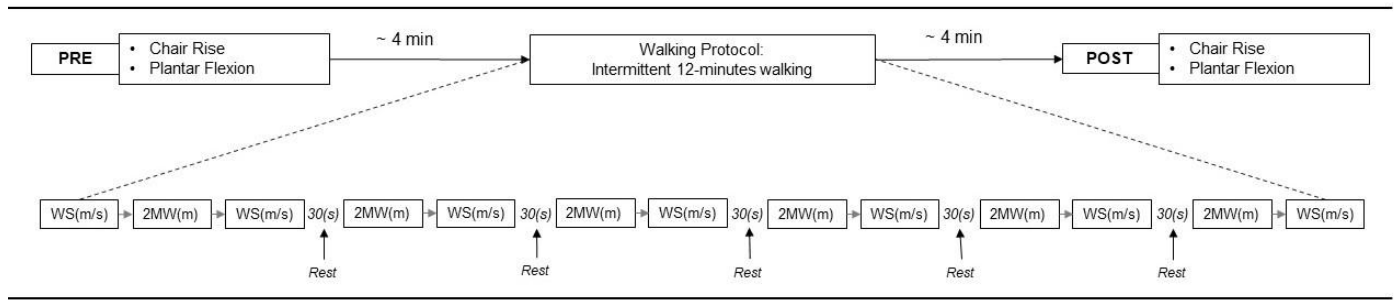


Figure 1. Experimental protocol. WS, maximal walking speed (meters/second). 2MW, 2-minute walk (distance in meters). Rest (30 seconds).

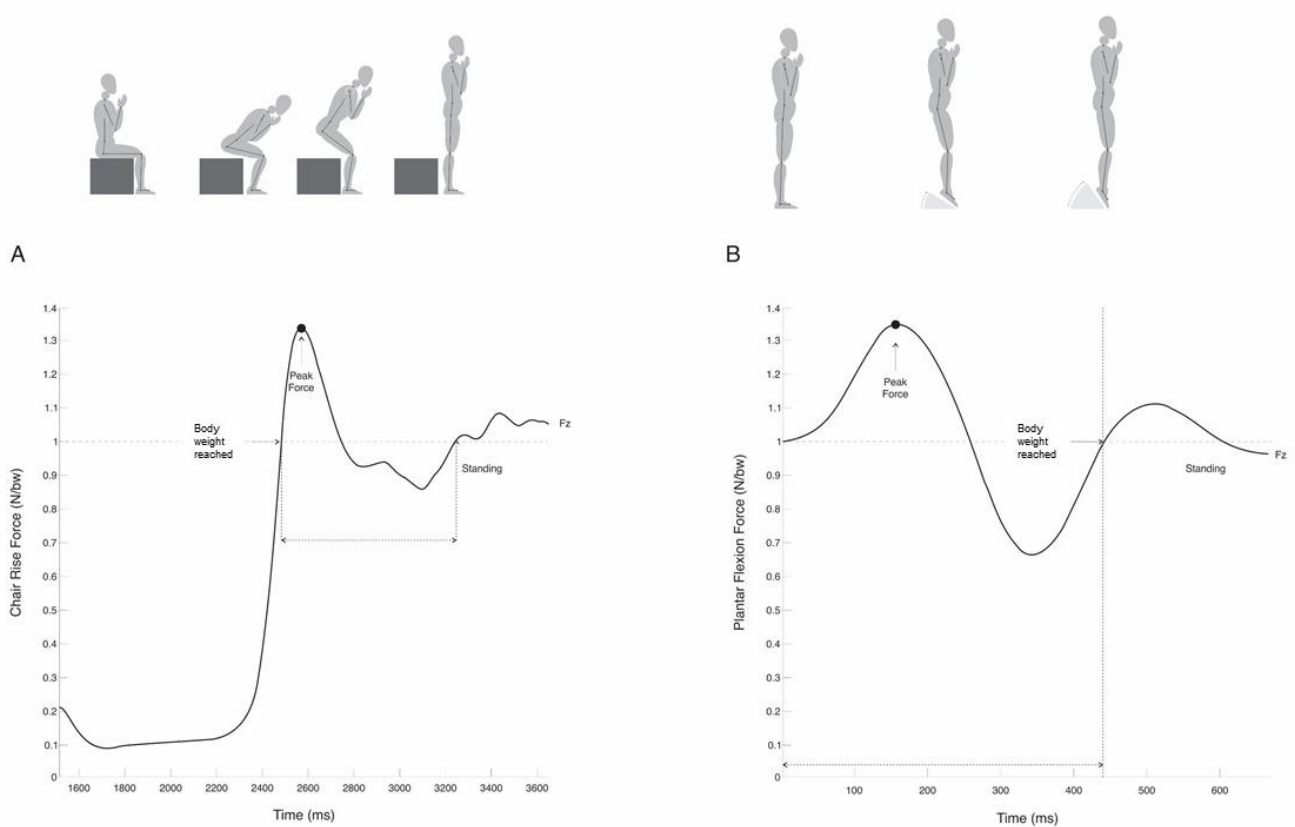


Figure 2. Individual data from a MS participant with mild disability (PDDS = 0) during the chair rise (A) and the plantar flexion (B) performance. The grey dotted line indicates the normalized body weight (=1). Non-dotted arrows indicate the events when the body weight and the peak force were reached. The black dotted two-sides arrows and the black dotted lines indicate the force-time curve interval used to extract force and power parameters.

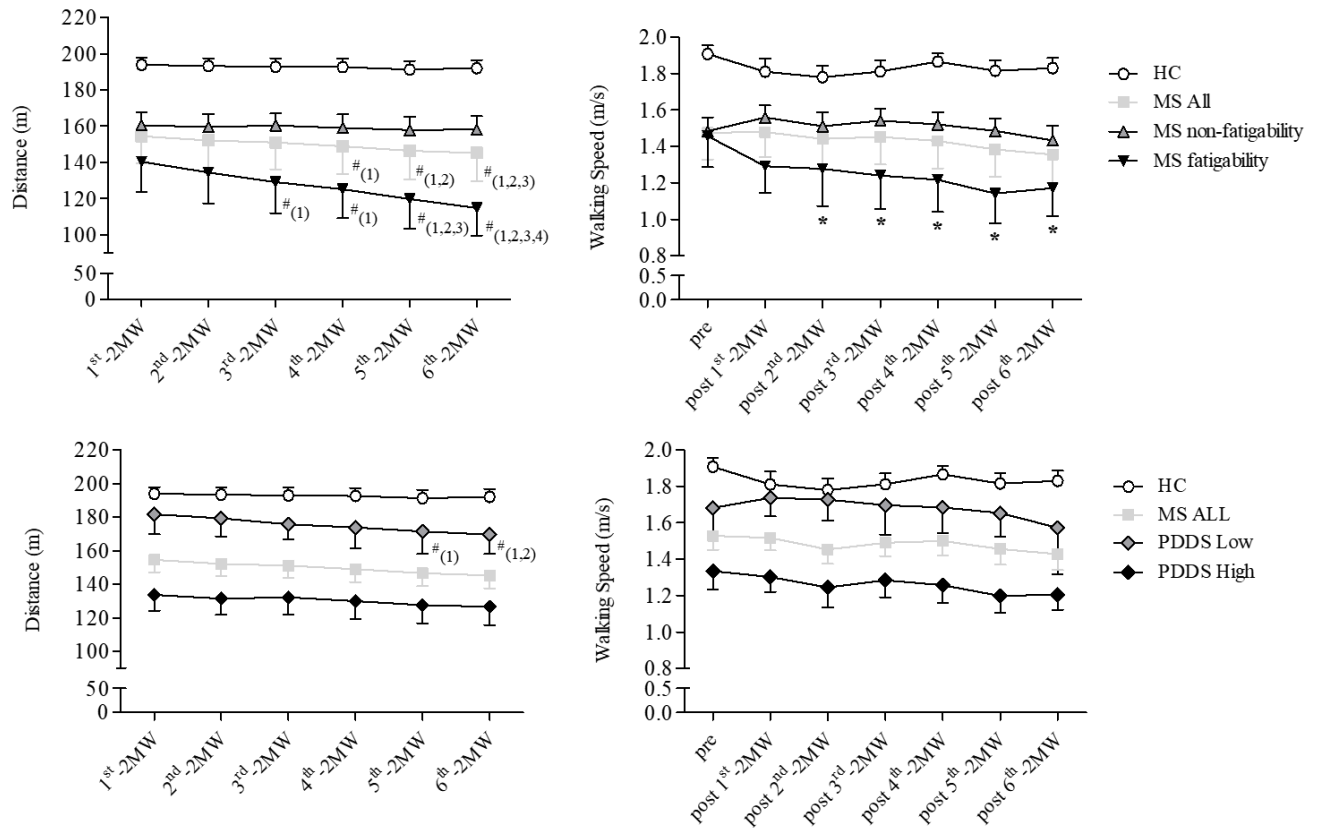


Figure 3. Course of the distance walked and the walking speed over the 12-minutes intermittent walking. HC, healthy controls. MS All, total sample of multiple sclerosis (MS) participants. MS non-fatigability, MS participants not presenting walking-fatigability. MS fatigability, MS participants presenting walking-fatigability. PDDS Low, MS participants with a score equal to zero in the Patient Determined Disease Step. PDDS High, MS participants with a score equal or higher than 1 in the Patient Determined Disease Step. Results are presented as mean and standard error. Statistical significances ($p \leq 0.05$) are denoted by #(1): different from the first 2-minute walk (1st-2MW); #(1,2): different from the 1st- and the 2nd-2MW; #(1,2,3): different from 1st-, 2nd- and 3rd-2MW; #(1,2,3,4): different from 1st-, 2nd-, 3rd and 4th-2MW. *, denotes statistical significance from the moment pre (walking speed performed before the entire 12-minutes walking).

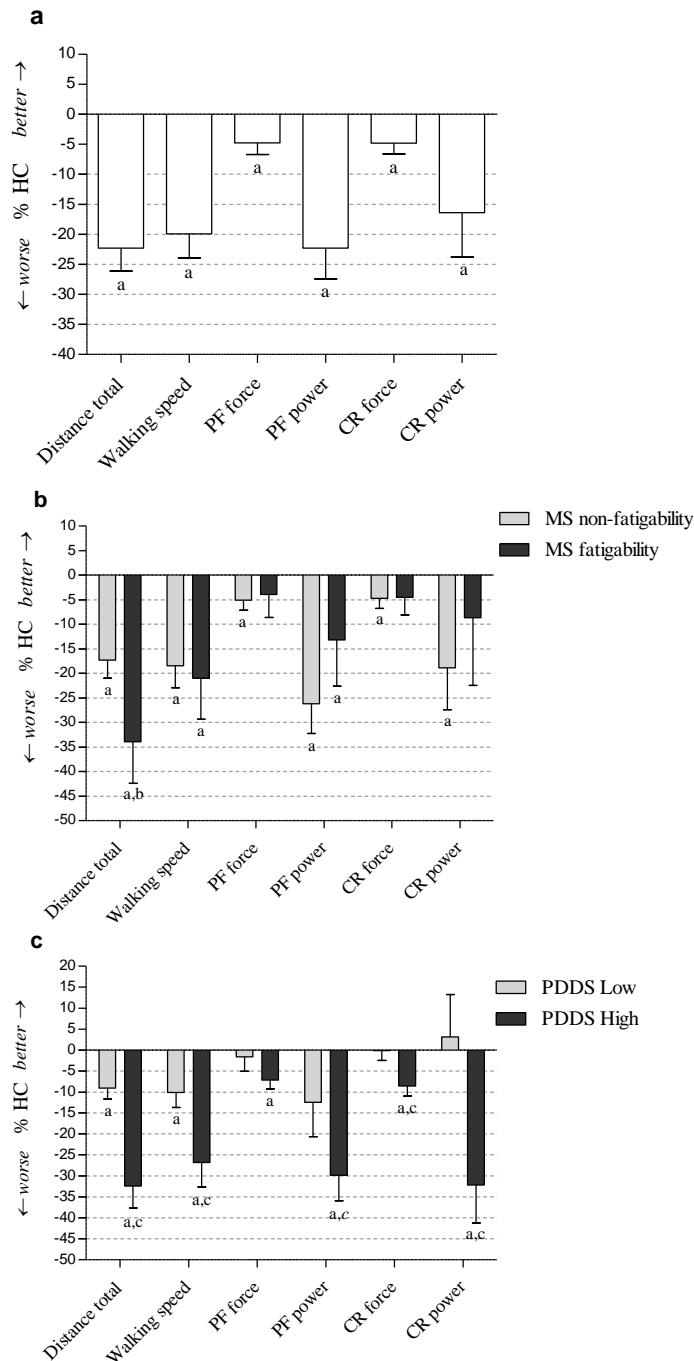


Figure 4. Deficits in physical functions regarding to walking capacity and lower extremity muscle power/force calculated as the percentage of the mean values from the healthy control (HC) group. Results are presented as mean and standard error. **a**, deficits are presented for the entire sample of persons with multiple sclerosis (MS). **b**, deficits presented for the MS non-fatigability group and MS fatigability group. **c**, deficits presented according to the PDDS (Patient Determined Disease Step) score, Low (= 0) or High (≥ 1). PF, plantar flexion. CR, chair rise. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by “a”: different from healthy controls (HC), “b”: different from Non-Fatigable persons with MS, and “c”: different from PDDS Low.