

A wearable sensor identifies alterations in community ambulation in multiple sclerosis: contributors to real-world gait quality and physical activity

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ABSTRACT

People with multiple sclerosis (pwMS) often suffer from gait impairments. These changes in gait have been well-studied in laboratory and clinical settings. A thorough investigation of gait alterations during community ambulation and their contributing factors, however, is lacking. The aim of the present study was to evaluate community ambulation and physical activity in pwMS and healthy controls and to compare in-lab gait to community ambulation. To this end, 104 subjects were studied: 44 pwMS and 60 healthy controls (whose age was similar to the controls). The subjects wore a tri-axial, lower-back accelerometer during usual-walking and dual-task walking in the lab and during community ambulation (1 week) to evaluate the amount, type, and quality of activity. The results showed that during community ambulation, pwMS took fewer steps and walked more slowly, with greater asymmetry, and larger stride-to-stride variability, compared to the healthy controls ($p < 0.001$). Gait speed during most of community ambulation was significantly lower than the in-lab usual-walking value and similar to the in-lab dual-tasking value. Significant group (pwMS /controls) by walking condition (in-lab/community ambulation) interactions were observed (e.g., gait speed). Greater disability was associated with fewer steps and reduced gait speed during community ambulation. In contrast, physical fatigue was correlated with sedentary activity but was not related to any of the measures of community ambulation gait quality including gait speed. This disparity suggests that more than one mechanism contributes to community ambulation and physical activity in pwMS. Together, these findings demonstrate that during community ambulation, pwMS have marked gait alterations in multiple gait features, reminiscent of dual-task walking measured in the laboratory. Disease-related factors associated with these changes might be targets of rehabilitation.

INTRODUCTION

Impairments of gait and mobility frequently affect people with multiple sclerosis (pwMS) [1] and are often considered among the most important functions that are affected by MS [2-4]. Given its importance, the assessment of walking in MS has been a focus of much scientific inquiry. Traditionally, gait impairments have been quantified using performance-based measures [5], lab-based motion analyses [6], and self-report [7]. Laboratory-based gait assessments indicate that pwMS walk more slowly and with a lower cadence than healthy individuals [1]. In addition, pwMS have greater stride-to-stride variability [1, 8], reflective of an unstable gait and a higher fall risk compared to healthy controls [1, 9, 10].

These conventional approaches have provided considerable insight into MS. Nonetheless, they present only a static snapshot of walking ability, may have limited ecological relevance, and may suffer from issues related to recall and self-report bias. Measuring walking in the real-world may provide a better estimate of actual walking, not just a snapshot picture of how a person walks in the lab, but gait quality and its changes during the day and week. Indeed, accumulating evidence reveals significant differences between multiple aspects of in-lab, as compared to real-world walking (both quantity and quality), among people with an impaired gait like older adults and patients with Parkinson's disease [11-13]. These differences suggest that the two assessment environments reflect different aspects of behavior, perhaps what a person can do versus how the subject actually performs in free-living, real-world conditions [12]. To address these gaps, there has been growing interest in objectively quantifying physical activity [14, 15, 15, 16] and walking in the “real-world” in pwMS [14, 17, 18]. Initial studies utilizing wearable technology reported that daily-living movement was associated with disability level, that quantity of walking (e.g. step counts and time spent walking) are lower in pwMS than in controls and may be a sensitive measure of disease progression [17-20]. The ability to measure the quality of walking (e.g. spatiotemporal parameters of gait) during real-world, community ambulation has the potential to inform interventions aimed at increasing mobility and quality of life [11, 15]. However, to date, the gait quality of pwMS during real-world, community ambulation has largely not been studied.

To evaluate how real-world, community ambulation differs in pwMS and healthy individuals, we used a wearable device to assess the gait and physical activity of pwMS and healthy controls in the lab as well as during community ambulation. Our main goals were: (1) to examine gait quality and activity patterns during real-world, community

ambulation in pwMS as compared to a group of healthy subjects of a similar age, (2) to compare gait measured in the lab to real-world, community ambulation walking in pwMS and in healthy controls, and (3) to explore the association between clinical features of MS (e.g., fatigue, level of disability, cognitive dysfunction) and real-world gait quality and activity in pwMS.

MATERIALS AND METHODS

Participants

The findings presented here are based on the post-hoc analysis of data collected for different purposes in two different studies. Participants with relapsing-remitting MS (n=44) were recruited as part of a multi-center intervention study aimed at ameliorating motor-cognitive interactions in MS patients using virtual-reality (NCT02427997). Inclusion criteria for the MS patients were: relapsing-remitting type of MS according to McDonald criteria 2010, ages 18-65 years, free of relapse in the past 30 days, mild to moderate disability (i.e., Expanded Disability Status Scales (EDSS) score of 2 to 6) and a grade of ≥ 2 in at least one of the functional scales due to pyramidal, cerebellar, or proprioceptive disorder in the lower limbs. A convenient sample of healthy controls was included in a study designed to evaluate Parkinson's disease; they were included if they had no neurological, orthopedic or psychiatric disorders that may affect gait and no substantial cognitive impairment (Montreal Cognitive Assessment score > 21); their data were collected from February 2017 through October 2018. The data collection for gait and community ambulation was identical, except as noted below, for the dual-task walk. Subjects who wore the long-term monitoring device (see below) for less than 5 days were excluded. All participants provided written informed consent prior to participation. Study protocols were approved by the local ethical review boards and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

In-lab procedures

Demographic (e.g., age, sex, height, education level) and MS-related subject characteristics (e.g., disease duration, EDSS) were obtained. All subjects walked at a self-selected pace for 1 minute (i.e., usual-walk) and again while performing a concurrent cognitive, dual-task [21]. Because of the post hoc nature of the present analyses, different dual tasks were used, although have been widely applied in previous dual-task studies of gait. The patients with MS performed a word-list generating task; this task has been used previously used to study dual-task walking in MS [22-

26]. The healthy control group performed serial subtractions of 7 from a 3-digit number; a task has previously been used in multiple studies in MS and other cohorts [22, 27, 28]. As described below, gait quality was measured with a tri-axial accelerometer (Opal, APDM) worn on the lower back [12, 13, 29]. In addition, participants in the MS group performed the timed-25 foot walk (T25FW) to assess walking disability [5] and the symbol-digit modalities test (SDMT) to assess cognitive function, processing speed [30]. Finally, the MS patients completed the modified fatigue impact scale (MFIS), a self-report measure of perceived physical, cognitive, and psychosocial fatigue [31].

Real-world, community ambulation data collection

After completing the in-lab assessment, subjects were asked to wear a small, body-fixed sensor (Axivity AX3, York, UK; dimensions: 23.0×32.5×7.6 mm; weight: 11 grams; 100 Hz sampling rate) taped to their lower back (lumbar vertebrae 4-5) to capture physical activity and real-world, community ambulation during the subsequent 7-day period [12, 13]. The participants were instructed to leave the device on throughout the week and to continue their daily activities as usual, without changing their routine. Upon completion of the recording, participants removed and returned the device to one of the study sites for data processing.

Community ambulation and in-lab gait metrics and data processing

An algorithm automatically identified the different types of activities (i.e., walking, lying, standing or sitting quietly) and each period of walking throughout the week-long recording [12, 32]. We then extracted three types of activity measures that reflect (1) the amount of physical activity (regardless of its source or type), (2) type of activity, and (3) the quality of walking [12, 32] (see Table 1). To compare measurements between the lab and real-world settings, we applied a similar analysis to the accelerometer data of the first 30 seconds of each walk during usual and dual-task walking trials in the lab and each walking bout during community ambulation. We extracted metrics of gait speed, cadence, stride regularity (higher values indicated greater regularity and lower stride-to-stride variability), step regularity (higher values indicated greater symmetry), and gait complexity (sample entropy, higher values indicate greater complexity) [12, 13, 29]. Based on all walking bouts of each subject's 7-day recording, the typical (median), best (90%), and worst (10%) values of each parameter were extracted [12, 13].

Statistical analyses

Statistical analyses were performed using SPSS (version 25, IBM, Armonk, NY, USA) and SAS (version 9.4). The Shapiro-Wilk test and visual inspection of box-plots assessed normality. To examine between-group differences in subject characteristics and real-world, community ambulation measures, we used independent t-tests, the Mann-Whitney U tests (also referred to as Wilcoxon rank-sum tests), or Pearson's chi-square tests, as appropriate. To address our second aim, we conducted nonparametric repeated-measures analysis to compare representative gait metrics (e.g., gait speed, cadence) obtained in the lab to real-world walking values. Outliers were observed in some variables and not all variables passed the normality test. To be consistent across all measures, nonparametric analysis was thus applied to both parametric and nonparametric data. Nonparametric method was rank-based and it was robust to outliers. We applied a rank-based method using mixed models [33, 34] to examine any group (pwMS vs. controls) by type of walk (in-lab vs. community ambulation) interaction effects, as well group and type of walk effects, adjusting for age and gender (similar results were obtained using the parametric RM ANOVA). If the significant group by type was significant, post-hoc test was thus performed to examine the relationship between each subject's typical (median), best (90%), and worst (10%) real-world, daily-living walking, on the one hand, and each subject's in-lab usual walking and dual-task walking, on the other hand [12]. To minimize the effects of multiple comparisons, only p-values ≤ 0.01 were considered as significantly different for these group comparisons. Correlation analyses among the patients with pwMS quantified the associations between the quantity and quality of real-world, community ambulation and the activity domains (i.e., type, quantity, and quality) and MS-related characteristics (e.g., disease duration, EDSS). Spearman's partial correlation coefficients were estimated after adjusting for age and sex effects.

RESULTS

Subject characteristics

The two groups were similar with respect to age, height and education level (all p's > 0.112, see Table 2). The percentage of female participants tended to be larger among the pwMS (73%) than in the controls (51%, p=0.065). The average disease duration of the pwMS was 13.3±9.3 years and scores on the EDSS ranged between 2 and 6 with a median score of 3.5 (interquartile range: 2.5-5.0). As anticipated, when tested in the lab, pwMS walked slower under usual- and dual-task walking conditions as compared to the healthy controls (p<0.001). As expected, subjects in both groups

showed a significant effect of the dual-task on gait (e.g., gait speed was significantly lower during dual-tasking than during usual walking, $p < 0.001$). The % change in gait speed during dual-tasking was 11.7 ± 15.3 % in the pwMS and 15.3 ± 7.8 % in the control subjects ($p = 0.175$, unadjusted).

Between-group differences in real-world, community ambulation

PwMS wore the accelerometer for 6.3 ± 1.1 days and controls for 5.7 ± 1.6 days ($p = 0.741$). Compared to the controls, pwMS were significantly less active (see Table 3). PwMS took fewer steps per day ($p < 0.001$), engaged in significantly fewer walking periods longer than 30 seconds, ($p < 0.001$), and their overall physical activity during the day was lower. In addition, patients with MS spent significantly less time (1.20 ± 0.54 hours) walking than the controls (1.90 ± 0.72 hours) during the day ($p < 0.001$). The duration of other types of activities during the day did not differ between the two groups ($p > 0.05$; see Table 3).

When comparing the quality of real-world gait (i.e., each subject's "typical" values) between the two groups (see Table 3), pwMS walked significantly slower with a lower cadence than the controls ($p < 0.001$). Moreover, during community ambulation, patients with MS walked with a less consistent gait pattern compared to the controls, as evidenced by a lower stride regularity, and with greater asymmetry (i.e., lower step regularity) ($p < 0.001$). The pwMS also walked with a lower sample entropy (i.e., decreased complexity of real-world gait acceleration) than the healthy individuals ($p < 0.001$). The significant differences between the two groups in real-world, daily-living activity and gait measures persisted after adjusting for gender.

Differences between gait measured in-lab versus real-world walking

As summarized in Figure 1, the significant differences in gait quality between the two groups were maintained across all types of walking conditions (in-lab usual and dual-task walking, and real-world, community ambulation typical, best, and worst values) with the pwMS walking slower and with a lower cadence, stride regularity, step regularity, and sample entropy (group main effect p -values < 0.001). A significant main effect of walk type was found for all metrics, suggesting there were differences between in-lab gait and real-world settings (main effect p -values < 0.001). Group x walking condition interaction effects were observed for gait speed, cadence and sample entropy, indicating that the

impact of the walking condition was not similar in both groups for these aspects of walking. Trends for group x walking condition interaction effects were also observed for step regularity and stride regularity.

For the pwMS and the controls, the typical value (each subject's median of all walking bouts) during real-world, community ambulation was similar to the dual-task in-lab value of gait speed and cadence (and different from the in-lab usual-walking values). The best (90%) values of gait speed during community ambulation were significantly higher than the values of usual-walking in the lab among the controls. In contrast, among the pwMS, the best values of community ambulation gait speed were similar ($p=0.298$) to the usual-walking values in the lab. For the pwMS (but not for the controls), community living typical values of step regularity and stride regularity were also similar to the dual-task in-lab values.

Correlations between MS-related characteristics and real-world, community ambulation

The associations between real-world gait, physical activity, and MS symptoms are summarized in Table 4. Among the MS patients, higher daily-living step counts and increased engagement in relatively long walking bouts (i.e., ≥ 30 seconds) were associated with shorter disease duration, lower disability level, higher (i.e., better) walking speed, and cognitive processing speed. Similar correlations were also observed between time spent walking during the day and disability level, motor and cognitive function. As expected, better gait quality (e.g., gait speed, cadence, step and stride regularity, and sample entropy) measured in the community was associated with lower disability levels and faster walking in the lab.

Interestingly, better cognitive function as measured with the SDMT was related to faster walking speed, greater cadence, higher stride regularity, and higher sample entropy during community ambulation (Table 4). In addition, subjects who reported higher levels of physical fatigue had fewer long walking bouts, spent less time sitting or standing, and significantly more time lying down during the day. In contrast, both physical and cognitive fatigue were unrelated to any of the gait-quality measures during community ambulation.

Wear time compliance

Among the people with MS, 5 subjects were excluded from the analysis due to low wear time days (as compared with the 44 subjects who had more than 5 days of wear time). The subjects who were excluded and those who were not excluded were similar ($p>0.28$) with respect to age, sex, EDSS, disease duration and years of education. In other words, the device was acceptable and correctly worn in about 90% of the pwMS. Among the control subjects, twenty subjects were excluded from analysis due to low wear time days (vs 60 subjects with more than 5 days of wear time). The control subjects who were excluded and those controls who were not excluded were similar ($p>0.23$) with respect to age, sex and years of education.

DISCUSSION

This investigation provides some of the first results that demonstrate gait alterations in multiple domains during real-world, community ambulation in pwMS. Specifically, the results confirm that pwMS are significantly less active than their healthy peers [16] and that daily-living step counts are sensitive to MS [19], while also showing that MS gait is impaired in natural, unconstrained walking. Interestingly, for multiple aspects of gait among patients with MS, the typical daily-gait performance was similar to dual-task walking values in the lab, whereas usual in-lab gait values more closely resembled walking periods that captured the "best" performance in the community setting (recall Figure 1). This observation suggests that to assess the gait of an MS patient in a clinic so that it reflects what happens outside of the lab during community ambulation, it is advisable to include a dual-task walking condition. We can also speculate that enhancing dual-tasking gait in the lab should be a therapeutic goal [35] since this walking condition more closely resembles much of the values of gait observed during community ambulation (recall Figure 1).

Previous studies using wearable sensors in pwMS reported the sum or the intensity of the activity [16, 36, 37], while others examined a single domain of gait in the home setting [15, 20]. Our findings extend that work by describing free-living, community ambulation gait across multiple domains. We found group and walking condition differences in all five measures of community ambulation gait quality, with significant or trends for group X walking condition interactions for all five measures as well. This suggests that the differences between in-lab gait and community ambulation are not parallel in MS and controls. For example, the controls were able to increase their gait speed during community ambulation best (90%) walking, compared to in-lab usual walking. In contrast, for the pwMS, these best

values were not higher than the in-lab usual walking values. (recall Figure 1). Furthermore, pwMS had lower values of sample entropy measured during community ambulation compared to the controls, which may also reflect a less complex gait pattern during daily-living and suggest less adaptive gait [38]. Indeed, lower values of the complexity of gait have been associated with aging [39], a higher risk of falls [38], and lower levels of activity [40] among older adults. The limited ability of pwMS to change their pattern of walking during everyday life may restrict their capability to successfully navigate through complex environments, perhaps impinging on functional independence, and social participation. Given the importance of gait adaptability to safe ambulation, this may serve as a potential target of interventions.

The group by walking condition interactions that were observed for gait speed, cadence, and sample entropy (complexity) demonstrate that community ambulation gait measures are not just a simple mirror-image of in-lab values in pwMS; this discrepancy is reminiscent of what has been seen in other cohorts [12, 13]. This idea is supported by the mild-moderate correlations between the in-lab measure of gait speed and community ambulation gait quality measures in pwMS (recall Table 4). For most gait quality measures, more than 50% of the variance (ρ^2) is not explained by the in-lab value of gait speed. These findings have important implications for clinical trials and research, as they open the door to additional, largely independent ways of quantifying gait impairments and daily functioning in pwMS and perhaps may allow for smaller sample sizes or shorter longitudinal studies.

The associations observed between physical activity and MS-related features are consistent with previous reports linking lower physical activity levels in MS with greater disability and poorer performance in walking speed and cognitive function [41-43]. In addition, moderate to strong correlations were found between disability and in-lab walking speed and worse gait quality in the community, extending preliminary observations [18]. Furthermore, we found interesting associations between fatigue and daily-living physical activity. Physical and cognitive fatigue were unrelated to daily step count, daily walking time, or any of the gait quality measures. In contrast, worse physical fatigue was significantly correlated with a lower number of long walking events, less time sitting or standing, and more time resting (i.e., lying down) during the day. These disparate findings suggest that two distinct factors may contribute to daily-living walking and physical activity in pwMS. Other research groups observed only weak associations between the physical perceived fatigue and the amount, intensity and pattern of activity [44, 45]. Moreover, factors such as age,

type of MS, anxiety, and depression have moderated this association [45]. The present findings reveal a stronger association between fatigue and rest, suggesting that fatigue may not impact the quality of the activity but perhaps impacts the behavioral *response* to the activity, in the form of daytime rest. Future steps should explore whether fatiguing actions during the day are followed by periods of rest and whether resting benefits the quality of subsequent walking. The results also suggest that interventions that target fatigue should assess a broader range of behavior and not focus solely on gait or other dynamic activities, as these may be less sensitive markers of fatigue. To optimally augment daily-living mobility and function among pwMS, factors that contribute to gait, fatigue, and rest should be considered.

Limitations and Conclusions

The present study has several limitations. For example, because we used a convenient sample of healthy controls, the two groups were not perfectly matched with respect to gender distribution. However, even after adjusting for gender, the group differences persisted. In addition, because this study was essentially a post-hoc analysis of data collected for two different purposes, two different secondary, cognitive dual-tasks were used during the in-lab testing of dual-task walking. This might explain the trend toward a larger mean value in the controls. Still, it is important to keep in mind that both groups elucidated the well-known dual-task effects on gait (i.e., gait speed was significantly lower during dual-task walking in both groups) and that the focus of this study was on comparing in-lab gait to walking during community ambulation in both groups. Nonetheless, because different cognitive tasks were used, we cannot directly compare the impact of the dual-task walking in the lab setting across groups, as has been done previously [22]. Another consideration is that we did not evaluate the impact of the dual-task walking in the lab setting on the cognitive task. To obtain a more complete picture of the dual-task costs, it is best to evaluate dual-task changes in the performance of both the walking and the cognitive task [22, 27, 46]. In addition, we did not explicitly ask the subjects to prioritize one task over the other when dual-tasking. In the future, it would be informative to study different types of dual-tasks in pwMS [22] and controls and the role of prioritization [23, 47, 48] when comparing in-lab walking performance to community ambulation. Perhaps specific dual-task and prioritization paradigms more closely reflect what happens during community ambulation than others. Nonetheless, the results shown in Figure 1 do provide an important comparison of dual-task walking in a lab-based setting to community ambulation.

Extending previous work that has shown the potential of using wearables in MS [14-16, 19, 21, 37, 41, 42], the results of the present study demonstrate marked changes in multiple domains of community ambulation gait quality, physical activity, and step counts in pwMS and potentially modifiable factors that are associated with these changes. The results show how important it is to evaluate walking characteristics in the real-world and not only in the clinic. Measurements based on a wearable device worn for multiple days also make it possible to understand the extent to which different types of tests in the clinic correlate with actual functioning, going beyond a single snapshot and toward metrics that are more relevant to the patient and more ecologically valid. They also suggest that multiple mechanisms affect different aspects of community ambulation and every-day physical activity in pwMS, potentially pointing the way towards multi-modal interventions. Nonetheless, prospective and intervention studies are needed to further evaluate the utility of these real-world measures and their responsiveness to therapy. The present findings set the stage for the future development, refinement, and evaluation of the utility of wearable-based methods to enhance the tracking of gait impairments, disease progression, and the effects of interventions in pwMS.

FIGURE CAPTION

Figure 1. Comparison between in-lab and real-world, community ambulation among patients with multiple sclerosis (pwMS) and healthy controls. The gait metrics were extracted from the 30-second walking bouts of usual and dual-task walking trials in the lab, as well as from each subject's worst (i.e., 10th percentile), typical (i.e., median) and best (i.e., 90th percentile) real-world walking. "A" denotes a significant difference (i.e., $p < 0.01$) from in-lab usual walking and "B" indicates a significant difference ($p < 0.01$) from in-lab dual-task walking. The nonparametric repeated measures ANOVA and the post-hoc, pairwise comparisons between in-lab and daily-living walking events within each group were adjusted for age and sex. Note that during real-world walking, pwMS did not walk faster than the speed measured during usual-walking in the lab, as reflected in the "best" values, while controls were able to walk faster during their "best" real-world values compared to the lab.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Gait speed [cm/sec]

160
140
120
100
80

walk $p < 0.001$, group $p < 0.001$
group x walk $p < 0.001$

HC

pwMS

Lab - Usual

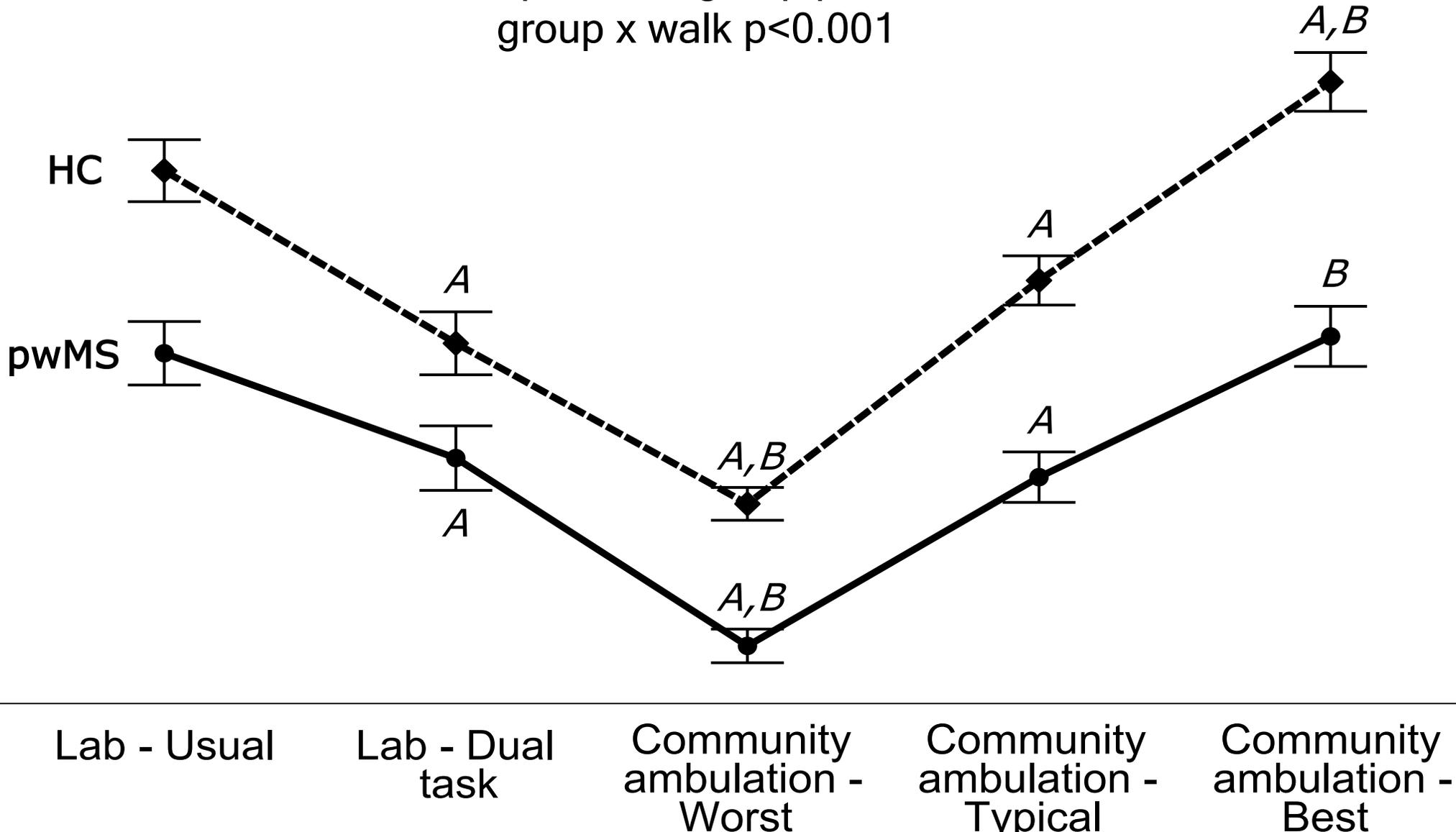
Lab - Dual
task

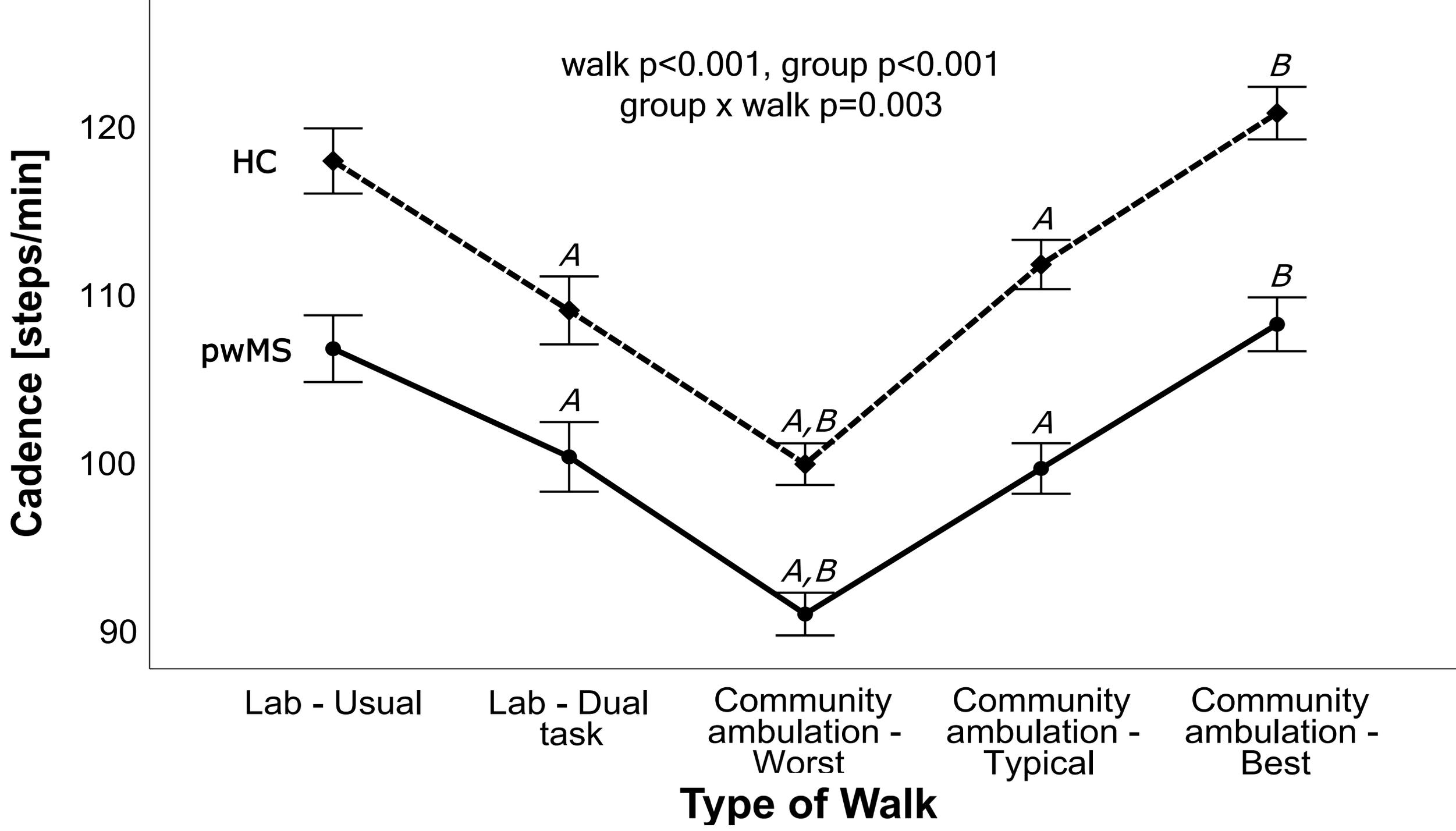
Community
ambulation -
Worst

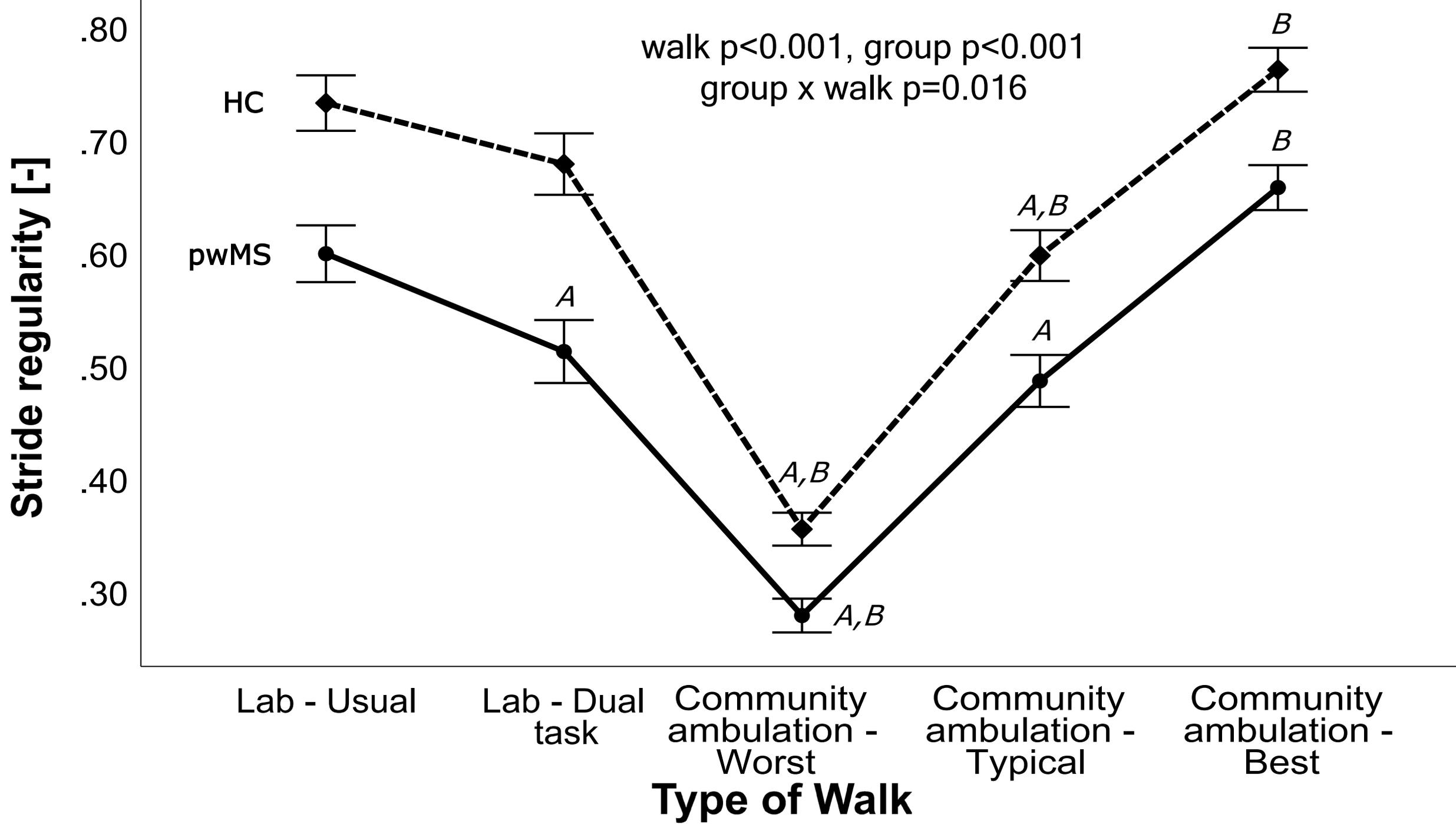
Community
ambulation -
Typical

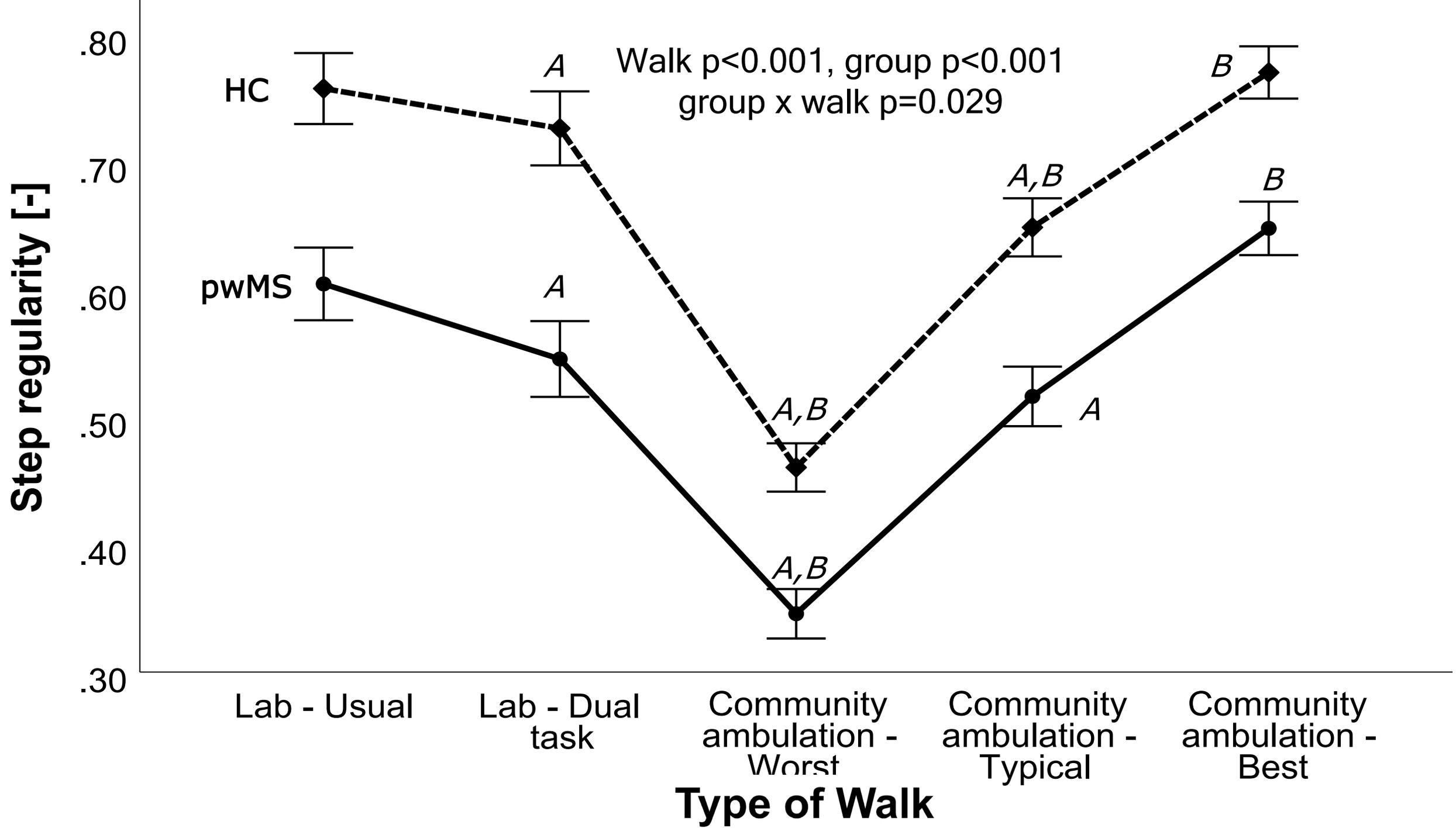
Community
ambulation -
Best

Type of Walk









Sample Entropy [-]

.54
.44
.34
.24
.14

Walk $p < 0.001$, group $p < 0.001$
group x walk $p = 0.010$

Lab - Usual Lab - Dual task Community ambulation - Worst Community ambulation - Typical Community ambulation - Best

Type of Walk

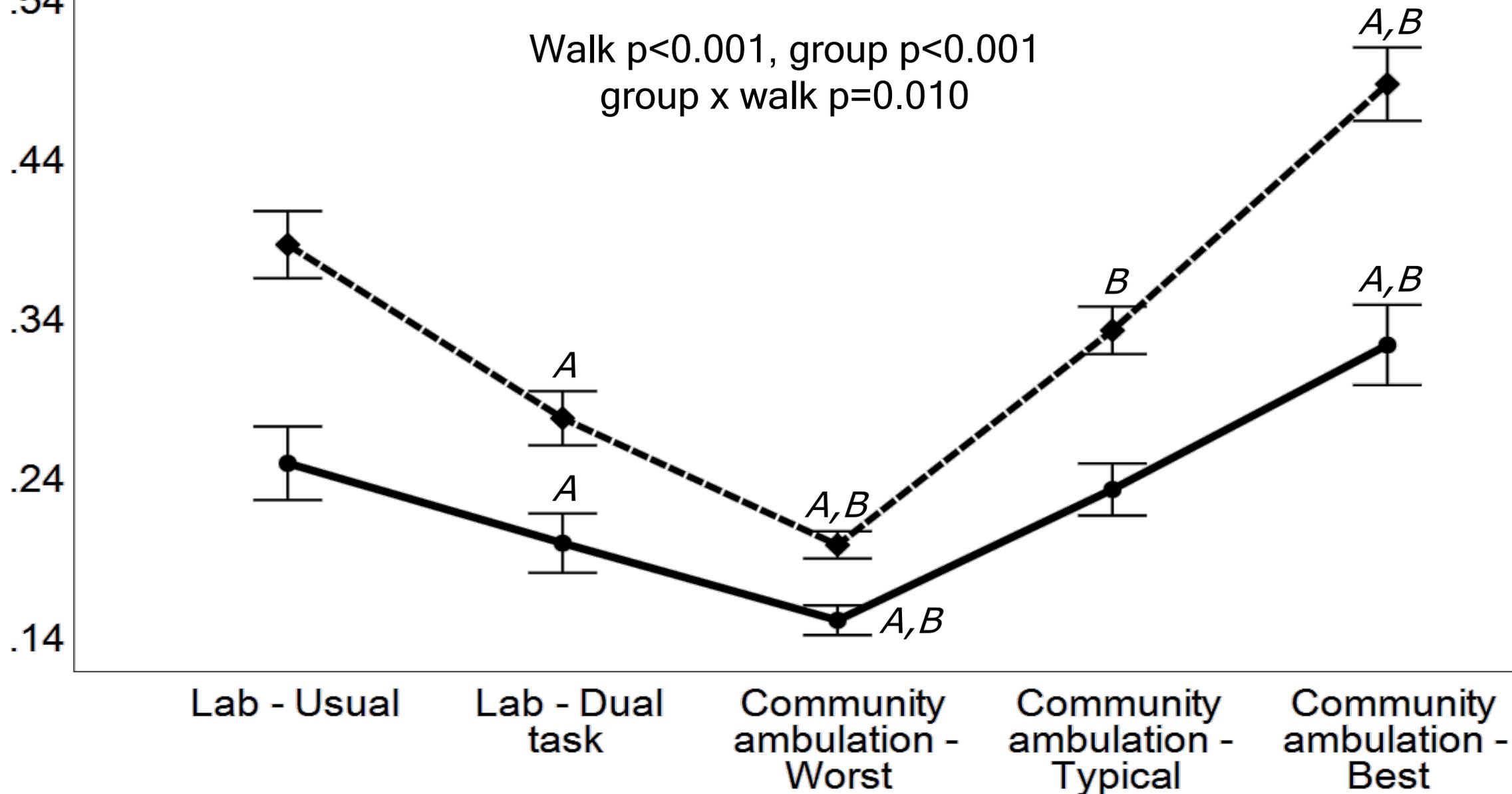


Table 1. Summary of the physical activity, type of physical activity, and quality of walking measures that were extracted from a body-fixed sensor worn on the lower back during community ambulation for one week.

Amount of Physical Activity	Type of Activity	Quality of Walking	
<ul style="list-style-type: none"> • Number of steps • Number of walking bouts (stratified by bout length) • Intensity (average of signal vector magnitude over 15-second epochs and sum of total physical activity) 	<ul style="list-style-type: none"> • Time spent walking • Time spent sitting/standing quality • Time spent lying down during day 	<i>Domain</i>	<i>Metric</i>
		Pace	Gait speed
		Rhythm	Cadence
		Variability	Stride regularity
		Symmetry	Step regularity
		Complexity	Sample entropy

Table 2. Subject characteristics

	People with		p-value
	multiple sclerosis N=44	Healthy controls N=60	
Age [yrs]	49.2±10.7	52.1±7.1	0.112
Gender [% Female]	73%	51%	0.065 ^a
Height [m]	1.68±0.09	1.70±0.08	0.157
Education [% high school / % undergrad degree / % graduate degree]	9% / 48% / 43%	7% / 38% / 55%	0.239 ^b
Usual gait speed [cm/sec]	107±31	129±17	<0.001
Dual-task gait speed [cm/sec]	96±32	110±14	<0.001
MS-related characteristics			
Disease duration [yrs]	13.3±9.3		
EDSS [median (interquartile range)]	3.5 (2.5-5.0)		
Timed-25 foot walking speed [m/sec]	1.32±0.51		
Symbol-digit modalities test score	47.6±14.4		
Modified fatigue impact scale			
Total score	40.4±16.5		
Physical fatigue score	20.1±7.8		
Cognitive fatigue score	16.9±8.7		
Psycho-social fatigue score	3.4±2.0		

Entries present mean ± SD unless otherwise stated. EDSS- Expanded disability status scale.

^ap-value is based on Pearson's chi-square. ^bp-value is based on Mann-Whitney U tests.

Table 3. Differences in real-world, community ambulation between people with multiple sclerosis and healthy controls

	Multiple sclerosis (n=44)	Healthy controls (n=60)	p-value	
Amount of activity	Step count [#]	5979.3±2855.1	10062.5±3958.7	<0.001^b
	Total activity during the day [g]	142.5±42.9	179.8±49.2	<0.001^a
	Number of walking events ≥30 sec [#]	215.0±128.4	465.88±321.2	<0.001^b
Type of activity	Daily walking [hours]	1.20±0.54	1.90±0.72	<0.001^b
	Daily lying supine [hours]	2.78±2.63	2.38±1.25	0.459 ^b
	Daily standing or sitting [hours]	5.37±2.67	5.42±1.44	0.459 ^b
Quality of gait*	Gait speed [cm/sec]	94±24	115±15	<0.001^b
	Cadence [steps/minute]	99.3±11.8	109.5±7.2	<0.001^a
	Stride regularity [arbitrary units]	0.48±0.18	0.58±0.12	0.001^b
	Step regularity [arbitrary units]	0.52±0.18	0.63±0.13	<0.001^b
	Sample entropy [arbitrary units]	0.24±0.11	0.32±0.09	<0.001^a

*Quality of gait was calculated based on all walking bouts of 30 seconds or more for each subject. Quality of walking here refers to each subject's "typical" median value among all walking bouts throughout the week. All significant differences persisted when adjusted for sex. Entries present mean ± SD of the real-world, daily activity. Physical activity is reported in units of g (gravity). ^a p-value is based on independent t-tests. ^bp-value is based on Mann-Whitney U tests.

Table 4. Spearman correlations between community ambulation metrics and disease-related characteristics among the patients with multiple sclerosis, adjusted for age and sex.

		Disease duration	Disability level (EDSS)	Fast walking speed (T25FW)	Cognitive processing speed (SDMT)	Physical fatigue	Cognitive fatigue
Amount of activity	Daily step count [#]	-0.432**	-0.530**	0.483**	0.451**	-0.334	-0.269
	Total activity during the day [g]	-0.324*	-0.337*	0.303	0.324*	-0.083	-0.121
	Number of walking bouts \geq 30 seconds [#]	-0.340*	-0.400**	0.355*	0.426**	-0.400*	-0.145
Type of activity	Walking during the day [hours]	-0.380*	-0.492**	0.377*	0.410**	-0.305	-0.354*
	Lying during the day [hours]	0.235	0.199	-0.179	-0.146	0.551**	0.255
	Sitting/standing during the day [hours]	-0.315*	-0.297	0.291	0.199	-0.484*	-0.192
Quality of gait	Gait speed [cm/sec]	-0.111	-0.502**	0.740**	0.398**	-0.277	-0.028
	Cadence [steps/minute]	-0.100	-0.445**	0.691**	0.331*	-0.264	0.133
	Stride regularity [arbitrary units]	-0.110	-0.367*	0.578**	0.353*	-0.197	-0.047
	Step regularity [arbitrary units]	-0.256	-0.406**	0.627**	0.297	-0.296	-0.007
	Sample entropy [arbitrary units]	-0.167	-0.400**	0.687**	0.328*	-0.257	0.008

*p-value<0.05; **p-value<0.01 (entries with p-values <0.01 are bolded). Please note that psycho-social fatigue was not correlated with any of the community ambulation measures. Table entries are the Spearman correlation coefficient Rho.