Clinical Importance of Steps Taken per Day among Persons with Multiple Sclerosis

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Abstract

Background: The number of steps taken per day (steps/day) provides a reliable and valid outcome of free-living walking behavior in persons with multiple sclerosis (MS).

Objective: This study examined the clinical meaningfulness of steps/day using the minimal clinically important difference (MCID) value across stages representing the developing impact of MS.

Methods: This study was a secondary analysis of de-identified data from 15 investigations totaling 786 persons with MS and 157 healthy controls. All participants provided demographic information and wore an accelerometer or pedometer during the waking hours of a 7-day period. Those with MS further provided real-life, health, and clinical information and completed the Multiple Sclerosis Walking Scale-12 (MSWS-12) and Patient Determined Disease Steps (PDDS) scale. MCID estimates were based on regression analyses and analysis of variance for between group differences.

Results: The mean MCID from self-report scales that capture subtle changes in ambulation (1-point change in PDSS scores and 10-point change in MSWS-12 scores) was 779 steps/day (14% of mean score for MS sample); the mean MCID for clinical/health outcomes (MS type, duration, weight status) was 1,455 steps/day (26% of mean score for MS sample); real-life anchors (unemployment, divorce, assistive device use) resulted in a mean MCID of 2,580 steps/day (45% of mean score for MS sample); and the MCID for the cumulative impact of MS (MS vs. control) was 2,747 steps/day (48% of mean score for MS sample).

Conclusion: The change in motion sensor output of ~800 steps/day appears to represent a lower-bound estimate of clinically meaningful change in free-living walking behavior in interventions of MS.

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Introduction

There has been an ongoing debate regarding outcome measures in clinical research involving persons with multiple sclerosis (MS) [1], with increasing interest in approaches for objectively monitoring patients under real-world conditions [2]. This interest has highlighted the potential for the objective monitoring of free-living walking behavior using motion sensors such as accelerometers and pedometers in clinical research involving persons with neurologic diseases [3] including MS [2]. Such devices are worn around the waist or ankle during the waking hours of the day and over a representative sampling period (e.g., seven days). The motion sensors capture the total amount of walking undertaken in free-living conditions based on metrics such as steps taken per day (steps/day). The number of steps/day reflects a straightforward metric of the overall amount of walking undertaken during one’s everyday life, representing free-living walking behavior [2,3].

Accumulating data demonstrates that the number of steps/day provides a reliable and valid measure of free-living walking behavior in MS [4–7]. Steps/day has demonstrated acceptable test-retest reliability over a two-week time period in persons with MS [4], and as few as three days of data with an appropriate amount of wear time (i.e., 10 or more hours/day) yields a reliable estimate of usual ambulatory-based behavior [5]. Regarding validity, steps/day has correlated strongly with clinical (e.g., Expanded Disability Status Scale scores), performance (e.g., timed 25-foot walk and 6-minute walk), and patient-reported (e.g., 12-Item Multiple Sclerosis Walking Scale or MSWS-12 scores) measures of ambulation in persons with MS [6,7]. To date, there are no published data evaluating the clinical importance of differences in steps/day among those with MS (i.e., amount of difference in steps/day that actually reflects a difference) on a group level. Such minimal clinically important difference (MCID) values are necessary for designing and interpreting clinical trials.
clinical importance wherein steps/day is an outcome measure of free-living walking behavior.

There are many possible approaches for establishing MCID values. We a priori propose an approach wherein MCID values are generated based on stages corresponding with the developing impact of MS. This would involve, for example, stages of MCID values based on smaller changes through to large changes in the impact of MS, progressively indicated by (a) scales that capture subtle, perceived changes in ambulation (e.g., MSWS-12 and Patient Determined Disease Steps or PDDS scale); (b) clinical and health outcomes including MS type, disease duration, and overweight/obesity status based on body mass index (BMI); (c) real-life anchors including unemployment, divorce, and assistive device requirements (e.g., cane for ambulation); and (d) cumulative impact of MS based on a comparison with healthy controls. Such an approach could provide several vantage points of the MCID, including stages and ranges of MCIDs, and afford researchers options for MCID selection that are appropriate for specific populations and circumstances (e.g., overall disease activity vs. symptomatic changes) in MS interventions.

The present study involved a secondary analysis of a combined data set from multiple investigations for establishing the clinical importance of steps/day in persons with MS based on stages that correspond with the developing impact of MS. We hypothesized that the MCID values would increase as a function of expressing the degree of impact of MS, moving from subtle, perceived differences in ambulation through to a comparison with healthy controls that represents the cumulative disease impact. The primary end result of the secondary analysis of data involved establishing stages and ranges of MCID estimates for interpreting changes in steps/day among persons with MS.

**Methods**

**Ethics statement**

The studies and associated procedures were all approved by the Institutional Review Board on the University of Illinois at Urbana-Champaign campus, and all participants provided written informed consent. The informed consent across all studies was broadly for examinations of ambulatory physical activity behavior and its determinants and consequences in persons with MS and/or healthy controls.

**Participants**

This secondary analysis was performed on a combined dataset of persons with MS and healthy controls from a series of previous investigations of physical activity and its associations with symptomatic, social cognitive, or quality of life outcomes. The data from each investigation had been de-identified before amalgamation and analysis as a combined dataset in this paper; this precluded examination of seasonal effects as there was no link between data and identifications, but the data were collected across all seasons over a multi-year period. Participants with MS were recruited from throughout the United States using print and email flyers and an online advertisement on the National Multiple Sclerosis Society website. Healthy controls were recruited via public e-mail postings delivered across a University community and “word-of-mouth.” The common inclusion criteria across the investigations for persons with MS were (a) diagnosis of MS (both self-reported and neurologist confirmed), (b) relapse free in the previous 30 days, (c) ambulatory with or without assistive devices, (d) age between 18 and 64 years, and (e) willingness to wear a motion sensor for 7 days. The same inclusion criteria were applied for the healthy controls, with the exception of diagnosis of MS and relapse free over the past 30 days. The final combined samples included 786 persons with MS and 157 healthy controls, and all persons satisfied inclusion criteria and provided usable steps/day data for analyses (i.e., 3 or more days of data with sufficient wear time for generating a reliable estimate of usual behavior) [5].

**Devices**

Steps/day were measured with Yamax SW-200 (NEWlifestyles) pedometers or ActiGraph accelerometers (models 7164 or GT3X; ActiGraph), as there is evidence for the accuracy of these devices during normal walking speeds in persons with MS and controls [9,9].

**Walking impairment**

The MSWS-12 is a 12-item patient-rated measure of the impact of MS on walking-related activities (including walking, running, standing, climbing stairs) [10]. The items are rated on a 5-point scale of 1 (Not at all) to 5 (Extremely), and the items represent limitations of walking during the past 2 weeks. The MSWS-12 was scored as recommended [10] and resulted in a total score that ranged between 0 and 100. The MSWS-12 has good evidence for its reliability and validity of scores as a measure of walking...
impairment in MS [10]. We examined values of steps/day across 10-point increments of MSWS-12 scores as this value reflects equivalent incremental changes across the entire range of MSWS-12 scores.

Disability status

The Patient-Determined Disease Steps (PDDS) scale is a single item for measuring self-reported disability status on an ordinal scale ranging from 0 (Normal) through 8 (Bedridden) [11]. This scale was developed as an alternate for the physician-rated Expanded Disability Status Scale (EDSS), and scores from the PDDS have been linearly and strongly related with EDSS scores derived from a neurological examination [12]. Persons were categorized into no device, cane use, and bilateral support for ambulation based on PDDS scale scores of 1–3, 4–5, and 6, respectively, for analyses. We examined steps/day across 1-point incremental increases in PDDS scores and this is consistent with 1-point changes in EDSS considered as reflecting worsening MS disability.

Socio-demographic, real-life, and health variables

We included a standard scale to measure all sociodemographic, health, and real-life variables. The sociodemographic variables included sex, age, race, and education for descriptive purposes. The scale further included marital status (coded as married vs. divorced for analyses with all other categories excluded), height and weight for generation of body mass index (BMI; coded as normal weight, overweight, and obese based on recommended guidelines of 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m², respectively, for analyses) [13], and employment (coded as employed vs. unemployed for analyses) for analyses.

Clinical variables

We included a standard scale for measuring clinical variables in those with MS. Clinical course of MS was recorded based on descriptions provided in Lublin and Reingold [14] and coded for analyses as relapsing-remitting or progressive forms of MS. Disease duration was recorded based on time since the date of confirmed MS diagnosis and coded for analyses as early (<10 years), middle (10–20 years), or later (>20 years) stage of MS.

Procedure

The studies and associated procedures were all approved by the same University institutional review board, and all participants provided written informed consent. The studies were conducted during all seasons of the year over a three-year period. After telephone screening for inclusion and provision of a signed informed consent document, all participants received a pedometer or accelerometer, a log sheet, instructions for wearing the device, and the scale for measuring sociodemographic, real-life, and health outcomes; those with MS further received the PDDS scale, MSWS-12, and the scale for measuring sociodemographic, real-life, and mental status of the patients in this sample, and the PDDS has not have data for characterizing the current treatment regimens with 95% CI. We adopted an alpha value of .01 when judging statistical significance to control the study-wise error rate. The standardized effect size (Cohen’s d) was estimated as the difference in means between groups divided by the pooled standard deviation [15]. The data are available from the first author upon formal written request and approval of the University of Illinois.

Results

Demographic and clinical characteristics of samples

The demographic characteristics along with identified differences between the samples of persons with MS and healthy controls are provided in Table 1. The table further contains the clinical characteristics of the persons with MS. The median PDDS score was 2.0 (range = 0–6). This indicated that the sample overall was characterized by moderate disability (i.e., no limitations in walking but significant problems due to MS that limit daily activity in other ways) with a range between normal and two-point assistance (e.g., rollator or frame). The average duration of MS was 9.9 years with nearly 90% (n = 710) of the sample reporting a diagnosis of relapsing-remitting multiple sclerosis (RRMS). We do not have data for characterizing the current treatment regimens and mental status of the patients in this sample, and the PDDS has not been validated for capturing the Multiple Sclerosis Severity Score as a marker of disease severity.

Regression analyses

Steps/day Based on Perceived Changes in Ambulation of Persons with MS

We regressed steps/day on MSWS-12 scores and the association was presented as a scatter plot in Figure 1. The regression model was statistically significant (F₁,₁₁₁ = 241.68,
Table 1. Demographic and clinical characteristics of the samples of multiple sclerosis and healthy controls.

| Variable                  | MS (N=786) | Controls (N=157) | p-value |
|---------------------------|------------|------------------|---------|
| Age (years)               | 47.3 (10.5) | 43.4 (9.8)       | .0001   |
| Height (cm)               | 167.8 (9.3) | 167.8 (8.2)      | .959    |
| Weight (kg)               | 78.6 (20.4) | 73.8 (16.0)      | .006    |
| BMI (kg/m²)               | 27.9 (7.6)  | 26.2 (5.7)       | .007    |
| Sex (% female/male)       | 84.9/15.1   | 91.1/8.9         | .035    |
| Education ( % college graduate) | 21.7       | 51.2             | .0001   |
| Income (% >$40,000/year)  | 68.3        | 80.7             | .001    |
| Employment (% employed)   | 62.3        | 94.6             | .0001   |
| Race (% Caucasian)        | 92.0        | 79.5             | .0001   |
| MS Type (% RRMS)          | 89.7        | –                |         |
| Disease duration (years)  | 9.9 (8.0)   | –                |         |
| PDDS score (mdn, IQR)     | 2.0 (2.0)   | –                |         |
| MSWS-12                   | 40.3        | 29.1             |         |

Note: Values are mean (standard deviation), unless otherwise noted. MS = multiple sclerosis. BMI = body mass index. RRMS = relapsing-remitting multiple sclerosis. PDDS = Patient Determined Disease Steps scale; MSWS-12 = Multiple Sclerosis Walking Scale-12.

Clinical Importance

Steps/day Based on Clinical Characteristics and Health Outcomes in Persons with MS. There were statistically significant differences in steps/day among persons with MS when considering MS type (F₁,766 = 37.67, p = .0001), disease duration (F₁,773 = 12.60, p = .0001), and weight status (F₁,521 = 10.95, p = .0001); the mean scores are provided in Table 2 and displayed in Figure 3. When comparing clinical course of MS (i.e., relapsing-remitting vs. progressive MS), the difference was 2,233 steps/day (95% CI = 1,719–2,580) and moderate-to-large in magnitude (d = 0.73). When consider disease duration, the difference between short (i.e., <10 years) and long disease duration was 788 steps/day (95% CI = 166–1,411) and small in magnitude (d = 0.25), whilst between middle and long disease duration the difference was 1,621 steps/day (95% CI = 763–2,476) and moderate in magnitude (d = 0.52). There was no significant difference in steps/day between middle (i.e., 10–20 years) and longer (i.e., >20 years) disease duration. Regarding weight status, there was no significant difference in steps/day between normal and overweight groups. By comparison, there were statistically significant differences of 1,436 steps/day (95% CI = 676–2,196) and 1,196 steps/day (95% CI = 356–2,096) that were moderate in magnitude when comparing normal vs. obese (d = 0.49) and overweight vs. obese (d = 0.43) persons with MS, respectively. Overall, the mean MCID across clinical characteristics and health outcomes that demonstrated statistically significant differences between groups was ~1,455 steps/day (range = 788–2,239) or 26% of the mean steps/day for the MS sample.

Steps/day Based on Real-life Anchors in Persons with MS. There were statistically significant differences among persons with MS as a function of employment (F₁,772 = 95.90, p = .0001), marital (F₁,223 = 11.67, p = .0001), and device type (F₁,307 = 95.49, p = .0001); the mean scores are provided in Table 2 and displayed in Figure 3. When considering the employment status of persons with MS (i.e., employed vs. unemployed), the mean difference was 2,150 steps/day (95% CI = 1,719–2,580) and moderate-to-large in magnitude (d = 0.75). Analysis of marital status (married vs. divorced) indicated a difference of 1,557 steps/day (95% CI = 659–2,456) that was moderate in magnitude (d = 0.46). The differences were 3,029 steps/day (95% CI = 2,373–3,681) and 4,596 steps/day (95% CI = 3,440–5,752) and large in magnitude when considering device type as no device (none; PDDS score = 1–3) vs. cane (PDDS score = 4–5; d = 1.10) and no device (none) vs. walker (PDDS score = 6; d = 1.64), respectively, among persons with MS. Comparing device type categorized as cane vs. walker, the difference was 1,567 steps/day (95% CI = 316–2,817) and moderate in magnitude (d = 0.79).

Overall, the mean MCID across real-life anchors that demonstrated statistically significant differences between groups was ~2,580 steps/day (range = 1557–4596) or 45% of the mean steps/day for the MS sample.

Steps/day between MS and Controls. There was a statistically significant and large (F₁,941 = 167.87, p = .0001, d = 1.13) difference of 3,640 steps/day (95% CI = 3,088–4,191) between persons with MS and controls (i.e., 64% of the mean steps/day for the MS sample). The mean for the controls (N = 157) was 9,342 steps/day (SD = 5,588, 95% CI = 8,838–9,845), whereas the mean for the persons with MS (N = 786) was 5,702 steps/day (SD = 3,134, 95% CI = 5,477–5,927). This difference was 2,747 steps/day (95% CI = 2,151–3,344), after controlling for age, BMI, sex, employment, education, income, and race as covariates (p = .0001, d = 0.88), or 48% of the mean steps/day for the MS sample. There further was a statistically significant (F₁,741 = 121.69, p = .0001) difference in steps/day between PDSS groups (1–3, 4–5, and 6) and healthy controls. The mean for the controls (N = 157) again was 9,342 steps/day (SD = 5,588, 95% CI = 8,838–9,845), whereas the means for the persons with MS were 6,568 steps/day (SD = 2,920, 95% CI = 6,311–6,825), 3,539 steps/day (SD = 2,170, 95% CI = 3,071–4,006), and 1,972 steps/day (SD = 1,260, 95% CI = 1,062–2,382) per PDSS group (1–3, 4–5, and 6, respectively).

Steps/day Based on Motion Sensor Type in Persons with MS. There was not a statistically significant difference in steps/day among persons with MS when considering the type of motion sensor (F₁,734 = 3.97, p > .01). The mean for the pedometer (N = 273) was 6,007 steps/day (SD = 3,277, 95% CI = 5,635–6,379), whereas the mean for the accelerometer (N = 513) was 5,540 steps/day (SD = 3,045, 95% CI = 5,269–5,811). The difference between motion sensors was 467 steps/day (95% CI = 7–927; 9% of the mean steps/day for the MS sample) and small in
Figure 1. Scatter plot of the association between Multiple Sclerosis Walking Scale-12 (MSWS-12) scores and steps/day in persons with multiple sclerosis.
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Figure 2. Bar graph of the association between Patient Determined Disease Steps (PDDS) scale scores and steps/day in persons with multiple sclerosis. The number within the bars represents the mean score for steps/day per level of the PDDS.
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magnitude \(d = 0.15\). This indicated that the MCID estimates did not depend on the type of motion sensor as there was no difference in steps/day between motion sensors. Such a conclusion was confirmed in additional analyses generating MCID estimates using only accelerometer derived steps/day as such estimates differed marginally from those reporting using both pedometers and accelerometers.

**Discussion**

This study estimated values for the clinical importance (i.e., MCID) of steps/day as a measure of free-living walking behavior in persons with MS. To that end, the MCID for steps/day ranged between 779 and 2,747 steps/day on the basis of expressing the developing impact of MS with the smallest value reflecting subtle, perceived differences in ambulation by the patient and the largest value reflecting the cumulative impact of MS compared with healthy controls. These MCIDs translate into a range of difference between 14% and 48% of the mean steps/day for the entire MS sample. Such a conclusion suggests that a value of 800 steps/day \(\pm 15\%\) would reflect the smallest clinically important change in community-based walking behavior in persons with MS (corresponding with incremental, unit changes in perceived walking impairment or disability identified by the patient), whereas a value of \(~2,750\) steps/day \(~50\%\) would reflect the largest clinically important change in community-based walking behavior (corresponding with global burden of MS compared against controls without the disease). We do not have data regarding the MCID values associated with a relapse. Nevertheless, these MCID estimates for steps/day could be applied in isolation or in combination with those developed for the MSIS-29 physical subscale (i.e., 8 point change) [16] and the MSWS-12 (i.e., 4–6 point change) [17] in therapeutic interventions among persons with MS. The combined approach might provide a comprehensive assessment of clinically important change among persons with MS, and likely depends on the focus and intended outcomes of a clinical trial.

An important consideration is the attainability of the MCID values of 800 to 2,750 steps/day in clinical research involving persons with MS. This might be addressed based on physical activity interventions for increasing daily ambulatory activity in persons with MS; no interventions of disease modifying agents have examined steps/day as an outcome. To that end, physical activity interventions lasting 12 weeks have reported changes of

**Table 2.** Steps/day in persons with multiple sclerosis by clinical, health, and real-life characteristics.

| Category      | Groups            | N  | Mean  | SD   | 95% CI       |
|---------------|-------------------|----|-------|------|--------------|
| MS type       |                   |    |       |      |              |
|               | Relapsing-remitting MS | 689| 5951  | 3131 | 5722, 6180   |
|               | Progressive MS     | 79 | 3718  | 2382 | 3042, 4395   |
| Disease duration | ≤ 10 years        | 490| 6093  | 3227 | 5820, 6366   |
|               | 10–20 years        | 198| 5305  | 2932 | 4875, 5734   |
|               | ≥ 20 years         | 88 | 4472  | 2519 | 3827, 5117   |
| Weight status | Normal             | 226| 6264  | 3267 | 5870, 6659   |
|               | Overweight         | 146| 6024  | 3121 | 5533, 6515   |
|               | Obese              | 152| 4828  | 2483 | 4347, 5309   |
| Employment status | Employed          | 485| 6510  | 3176 | 6247, 6774   |
|               | Unemployed         | 289| 4361  | 2536 | 4020, 4702   |
| Marital status | Married            | 121| 6797  | 3842 | 6187, 7408   |
|               | Divorced           | 104| 5240  | 2822 | 4581, 5899   |
| Device type   | No device          | 427| 6568  | 2920 | 6311, 6825   |
|               | Cane               | 129| 3539  | 2170 | 3071, 4006   |
|               | Walker             | 34 | 1972  | 1260 | 1062, 2882   |

Note. SD = standard deviation. CI = confidence interval represented as upper and lower boundaries. MS = multiple sclerosis. The sample sizes per characteristic in the MS sample differ because of missing data or focus on specific levels of a variable. doi:10.1371/journal.pone.0073247.t002
between ~1,400 and ~1,800 steps/day [18,19]. Such changes are larger than the smallest MCID of ~900 steps/day identified in the current analysis and fall in the middle of the range of MCID values. This would support the idea that such MCID values for steps/day are attainable in clinical research involving persons with MS who take part in a physical activity intervention, and perhaps other therapeutic interventions. Importantly, we are aware of one study that reported a change of ~600 steps/day one month after treatment for a relapse using intravenous methylprednisolone therapy in 49 consecutive patients with RRMS [20].

This study provides information on the clinical importance of steps/day in persons with MS. Such a contribution extends the research on validity of motion sensor output, particularly steps/day, as a measure of free-living walking behavior in MS [2]. These results might set the stage for inclusion of motion sensors in interventional trials measuring ambulation. The inclusion of motion sensors might provide information about changes in free-living walking behavior (i.e., improvement and worsening). To date, we are unaware of research that has adopted motion sensors and capitalized on such an opportunity for clinical trials in MS.

There are limitations of this study that should be considered when interpreting the results. One limitation is that the sample primarily consisted of women with relapsing-remitting MS and this might limit generalizability and applicability among men and those with a progressive course of MS. Consequently, the MCID may differ for another MS cohort with different demographics, including level of disability. The methods for identifying clinical importance of steps/day involved the reliance upon self-reported scales and data, rather than a physician-based rating or performance outcomes. This reliance upon self-report for classification of clinical and health variables could introduce error that biases the estimates of the MCIDs. The third limitation is that we did not compare differences in steps/day between demographic or health variables across the group factor of MS and controls (i.e., an interaction of the characteristic by MS vs. control groups), as there were not sufficient numbers of cases per level of the variables in the healthy controls (e.g., there were only nine unemployed controls).

This does not permit an examination of the generalizability or specificity of the differences in steps/day per real-life (e.g., unemployment) and health (e.g., overweight and obese weight status) variables. This further does not permit an understanding of variables such as weight status as antecedents or consequences of reductions in steps/day. Lastly, the MS and control groups differed in sociodemographic variables, and we controlled for such differences in the analysis, but there may be other variables besides MS and its manifestations that account for differences between MS and healthy controls.

Overall, this secondary analysis established MCID estimates for understanding the clinical importance of steps/day as a measure of free-living walking behavior in MS. These data along with existing evidence for reliability and validity will be important for designing clinical trials involving motion sensors and steps/day as an outcome measure of free-living walking behavior in MS. Such results will guide and inform researchers and clinicians on the clinical importance of steps/day in persons with MS.

Author Contributions
Conceived and designed the experiments: RWM MDG TB. Performed the experiments: RWM LAP YCL MDG TB. Analyzed the data: RWM LAP YCL. Contributed reagents/materials/analysis tools: RWM. Wrote the paper: RWM LAP YCL MDG TB.

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