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Walking endurance in multiple sclerosis: Meta-analysis of six-minute walk test performance

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ABSTRACT

Background: The 6-minute walk (6 MW) is the most commonly applied measure of endurance walking capacity in persons with multiple sclerosis (MS); however, we are not aware of a quantitative synthesis of 6 MW performance in MS.

Research question: We undertook a meta-analysis quantifying the overall magnitude of difference in 6 MW performance between MS and healthy controls (HCs), and then within MS as a function of disability status. We further examined possible moderator variables of 6 MW performance.

Methods: The systematic search was conducted for articles that included the 6 MW in persons with MS and involved comparison groups (i.e., HCs or MS disability subgroups (i.e., mild vs moderate-to-severe disability status)). The mean and standard deviation of the distance traveled during the 6 MW as well as sample sizes were entered into Comprehensive Meta-Analysis software and we estimated the overall effect size (Cohen's *d*) using a random effects model and examined categorical variables as possible moderators (e.g., instruction protocol, provision of encouragement, method of distance measurement, and course description).

Results: Thirty-four studies met inclusion criteria with a total sample size of 3204 persons (MS: 2683; HC: 521) yielding 42 total comparisons. Persons with MS walked a shorter distance than HCs (mean difference = –177.2 ± 19.1 m) with a large effect size (d = – 1.87). Persons with mild disability walked further than those with moderate-to-severe disability (mean difference = 185.19 ± 9.2 m) with a large effect (d = 1.83). The categorical variables of provision of encouragement and course layout moderated the effect of MS and course layout moderated the effect of disability status on 6 MW performance.

Significance: This meta-analysis of 6 MW performance defines mean difference in 6 MW performance in MS compared with HCs and provides an estimate of the disease-related effect of MS on endurance walking capacity for application within clinical research and practice.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system that often results in compromised endurance walking capacity [1]. The 6-minute walk (6 MW) [2] has been the most commonly applied performance-based measure of endurance walking capacity in MS [3]. Importantly, the 6 MW was originally applied for evaluating pulmonary function [4] and has since been adopted for other purposes in neurological conditions, including MS (e.g., endurance walking capacity) [5]. The 6 MW is further included in a core set of outcome measures for adults with neurological conditions [5]. To date, we are not aware of a meta-analysis that has provided a quantitative synthesis of endurance walking capacity in MS based on 6 MW performance. One study completed a systematic review of 36 different protocols used for administering the 6 MW in adults post-stroke [6]; however, this information is not known for persons with MS. Such a meta-analysis is important for synthesizing the difference in 6 MW performance in MS compared with healthy controls (HCs) and providing an estimate of the disease-related effect of MS on endurance walking capacity. The provision of a meta-analysis can further identify categorical variables such as the 6 MW instructions or course set-up that might moderate the overall effects of MS and disability status on endurance walking capacity. This is important as different types of instructions and/or approaches used during administration of the 6 MW test may influence overall performance.

The current paper describes a meta-analysis of 6 MW performance in persons with MS by comparing the difference in 6 MW scores between MS and HCs and then within MS as a function of disability status.

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This paper further provides summary values for 6 MW performance across included samples for expected values when interpreting future research on endurance walking capacity in MS within clinical research and practice. The paper lastly examines categorical variables (e.g., instruction protocol, provision of encouragement, method of distance measurement, and course description) as potential moderators that could be significantly associated with 6 MW performance, and this analysis will identify possible conditions of 6 MW administration that yield larger differences between groups when examining endurance walking performance.

2. Methods

2.1. Search strategy

The procedure for this search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) and Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines. One member of the research team (KLC) performed a systematic search in January 2019 using four databases including PubMed, CINAHL, SCOPUS, and EMBASE and the search terms ("6-Minute Walk Test" OR "6 min Walk Test" OR "6-Minute Walk" OR "6 min Walk" OR "6 MW" OR "Six minute walk" OR "6 MWT") AND ("multiple sclerosis" OR "MS"). No date range was utilized during this search and search filters included (1) "humans"; (2) English; and (3) full-text. Articles were first searched at the title and abstract level and duplicates were removed. Articles were then screened at the full-text level for eligibility criteria. Reference lists of included articles were further searched for identification of relevant articles meeting the inclusion criteria not located in the database search.

2.2. Eligibility criteria and study selection

Original articles were included in the analysis that: (a) administered the 6 MW in persons with MS; (b) reported sample sizes, means, and standard deviations (SDs) of the distance traveled during the 6 MW (or provided sufficient information to calculate the outcomes); (c) involved comparison of 6 MW performance between MS and HCs or MS disability subgroups (i.e., mild vs moderate-to-severe disability); (d) were reported in the English language; and (e) were full-text accessible. We contacted corresponding authors in the event that articles did not report sufficient data to calculate these outcomes. Any outcome measurements reported in feet were converted into meters. Abstracts, book chapters, reviews, presentations, and protocol papers were excluded from this analysis.

2.3. Data extraction

Two members of the research team (KLC and EMS) extracted relevant information from papers meeting eligibility criteria, including sample sizes, demographic and clinical characteristics (i.e., sex, age, MS sub-type, disease duration, clinical disability), 6 MW administration details (e.g., purpose of the 6 MW, instruction protocol, method of distance measurement, and course description), as well as means and SDs of the distance traveled during the 6 MW. If articles included more than one measure of 6 MW performance (e.g., pre- and post-intervention assessment), the baseline or initial 6 MW distance was extracted for the current analysis. We grouped articles by disability status subgroups based on the definitions provided within each paper (e.g., mild, moderate, severe, or moderate-to-severe); this was necessary as there was no universally applied guideline for classifying disability status. Of note, groups classified as having moderate-to-severe, moderate, or severe MS-related disability were consolidated into one group (i.e., "moderate-to-severe") based on the lack of standardized definitions of score ranges across papers and varied methods of classifying disability status (i.e., Expanded Disability Status Scale (EDSS) and Patient Determined Disease Steps (PDDS)).

2.4. Statistical analysis

All analyses were conducted using Excel and Comprehensive Meta-Analysis (CMA) version 3 software (Biostat, Inc.) and descriptive data are presented as means and SDs, unless otherwise specified. Means and SDs of the distance traveled during the 6 MW as well as sample sizes were entered into CMA software to estimate effect sizes (ESs; Cohen's *d*) and ESs of 0.2, 0.5, and 0.8 were interpreted as small, moderate, and large respectively [7]. Positive ESs for 6 MW were interpreted as better performance (more distance traveled) and negative were interpreted as worse performance (less distance traveled) when comparing the MS and HCs as well as the disability subgroups. We assessed heterogeneity among included articles with Cochran's Q and the I^2 statistic. Significance was based on an *a priori p*-value of 0.01 as a more stringent criterion to ensure the analysis was accurately capturing a meaningful difference despite the natural variability in 6 MW performance. A significant Cochran's Q statistic prompted the use of a random effects model for computing weighted mean ESs. The mean difference in 6 MW distance between groups was reported in meters and calculated by subtracting group means. Publication bias was assessed graphically with funnel plots and statistically with Egger's test whereby a 2-sided significant *p*-value of less than 0.05 was suggestive of significant publication bias. The fail-safe N was calculated to indicate the number of additional studies that would be required to nullify the results of these analyses.

We conducted secondary, fixed effects analyses in CMA wherein we estimated the effect of potential moderators of 6 MW performance. Potential moderators were identified as: (1) walking pace instruction (i.e., "as fast and as far as possible" [2] vs. "at your own pace" [8]); (2) whether or not participants received encouragement or feedback during the 6 MW; (3) 6 MW course layout (i.e., continuous pathway vs. straight pathway with 180° turns at each end); and (4) the method of measuring distance traveled during the 6 MW (i.e., objective vs. estimated). The determination of walking pace instructions was based on the specific pacing instructions reported in the article or citing the protocol associated with "as fast and as far as possible" [2] or "at your own pace" [8]. Whether participants received encouragement and/or feedback was based on author reporting (e.g., "feedback provided every minute" or "standardized encouraging comments") and these were converged into a single category (i.e., encouragement/feedback). The moderators were coded for input into CMA as categorical variables. The included studies were grouped by the moderator of interest and the effect was analyzed between and within levels of the respective moderator variable. Of note, articles that did not report on the moderator of interest were excluded from the secondary analysis with the respective moderator variable. The effect of categorical moderators was based on the significance of ESs at an *a priori p*-value of 0.05.

3. Results

3.1. Paper identification

The PRISMA diagram of the aforementioned systematic search is presented in Fig. 1. The initial search of the four databases identified 683 articles screened by title and abstract resulting in 145 relevant articles. After removing duplicates and excluding 2 articles for not meeting inclusion criteria, 59 articles were screened at the full text level. Twenty-five articles were then excluded for not meeting inclusion criteria (e.g., no data reported for the 6 MW). Overall, 34 articles were included in the meta-analysis [2,9–41].

3.2. Paper and participant characteristics

Among the 34 articles included in the meta-analysis, there was a

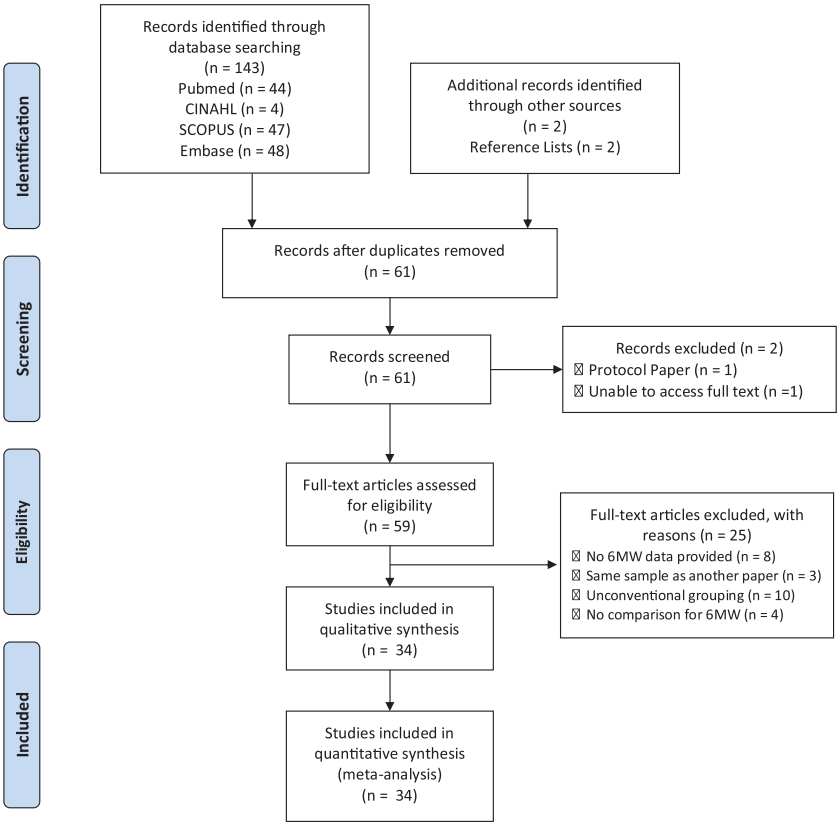

Fig. 1. PRISMA Diagram.

total of 42 comparisons (i.e., 21 comparisons between MS vs. HCs and 21 comparisons between mild vs moderate-to-severe) with sufficient data to calculate ESs. Of note, 27 articles reported disability status based on the EDSS and 5 based on the PDDS with 12 articles comparing "mild" vs. "moderate;" 6 comparing "mild" vs. "moderate" vs. "severe;" and 2 comparing "mild" vs. "moderate-to-severe"; the other 12 papers did not compare 6 MW between disability groups. With regard to potential moderators, 33 articles reported walking pace instruction (25 "as fast and as far" vs. 8 "at your own pace"); 12 reported the provision of encouragement/feedback (6 yes vs. 6 no); 30 reported course layout (6 continuous vs. 24 straight with 180° turns), and 20 reported distance measurement method (14 objective by measuring wheel or accelerometer vs. 6 estimated by markers placed on the ground or wall).

Demographic and clinical characteristics of included participants per article are presented in Supplementary Table 1. There was a total of 3204 participants across included studies; 2683 participants with MS and 521 HCs. The average sample size per study was 94 participants with an average of 79 persons with MS and 25 HCs. Participants with MS were mostly female (n = 1978; 71.4%) with an average age was 46.2 ± 9.6 years and HCs were of comparable age and sex (i.e., 42.0 ± 10.2 years and 71.0% female [n = 333]).

3.3. Multiple sclerosis vs. healthy controls

Cochran's Q and the I^2 statistic indicated significant heterogeneity among effect sizes (Q: 130.73; I^2: 84.70; $p < 0.001$) and a random effects model was applied in the comparison between MS and HCs. Participants with MS walked a shorter distance than HCs such that the mean (SD) distance walked by those with MS was 448.0 (100.9) meters compared with 628.9 (72.1) meters for HC's (mean (SD) difference: –177.2 (19.1) meters). The summary of the ESs between MS and HCs is presented in Fig. 2 and there was a significant, large weighted mean (SD) ES: –1.87 (0.17) ($p < 0.001$). Combined, Egger's test ($p = 0.034$) and graphical inspection of the funnel plot (Fig. 3) indicated a potential for publication bias wherein the funnel plot is skewed suggesting a relationship between the treatment effect and precision. The fail-safe N determined 3689 articles with contradictory results would be required to nullify these findings.

Regarding the analysis of potential moderator variables, there were larger effects between MS and HCs for encouragement/feedback (ES: –2.67; 95% CI: –2.736, –2.119; mean difference: –243.1 (39.1) meters) than no encouragement/feedback (ES: –1.39; 95% CI: –1.819, –0.956; mean difference: –86.2 (12.3) meters) during the 6 MW (Q: 14.794; df (Q): 1; $p < 0.001$). There further were larger effects between MS and HCs for a continuous course (ES: –2.62; 95% CI: –2.592, –1.937; mean difference: –249.0 (39.8) meters) than a straight course with 180° turns at either end (ES: –1.55; 95% CI: –1.626, –1.333; mean difference: –148.6 (19.9) meters) during the 6MW (Q: 18.397; df(Q): 1; $p < 0.001$). There was no effect on the magnitude of ES between MS and HCs when considering instructions for walking speed or measurement method as moderators of 6MW performance. The summary of the ESs between MS and HCs for each moderator variable are presented in Supplementary Figs. 1 through 4.

3.4. Multiple sclerosis: mild vs. moderate-to-severe disability

Cochran's Q and I^2 statistic indicated significant heterogeneity among effect sizes (Q: 60.909; I^2: 67.164; $p < 0.001$) and a random effects model was applied in the comparison within MS between mild and moderate-to-severe disability levels. Persons with mild disability walked significantly further than those with moderate-to-severe disability (515.9 (91.0) meters and 329.2 (107.2) meters, respectively; mean difference: 185.19 (9.2) meters). The summary of ESs between those with mild disability and moderate-to-severe disability is presented in Fig. 4. Disability status had a large effect on 6 MW performance with a weighted mean ES of 1.83 (0.10) ($p < 0.001$). Graphical

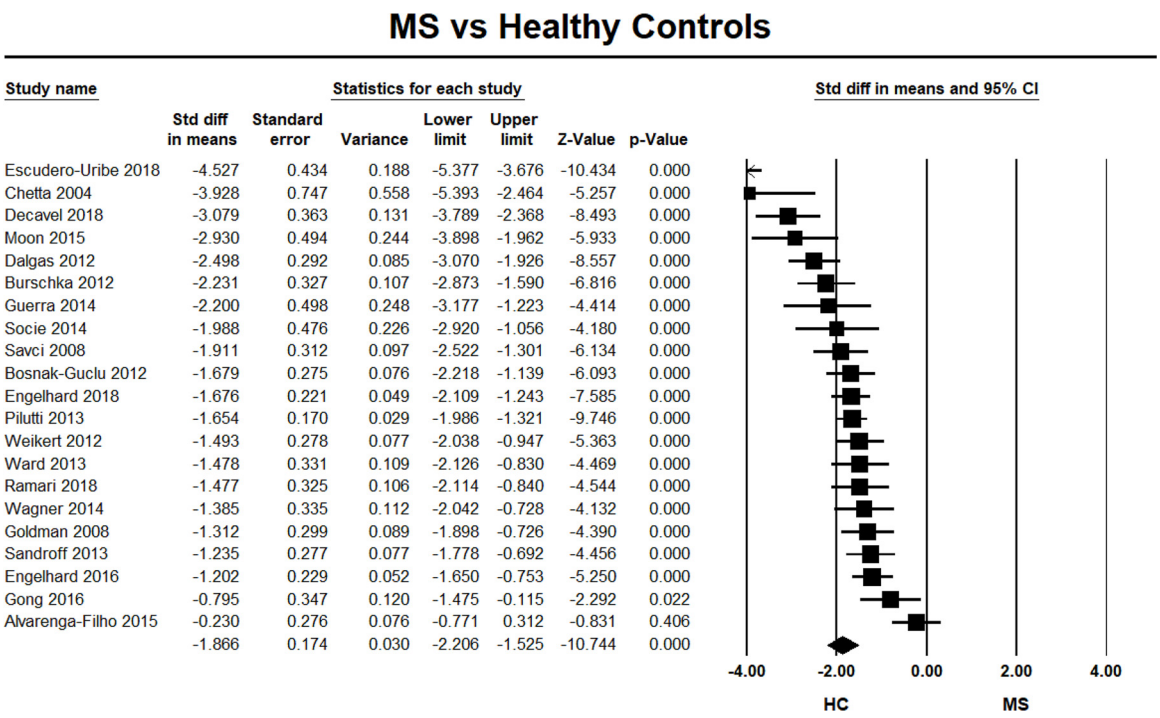

Fig. 2. Summary statistics for the comparison of distance traveled during the 6-minute walk test between people with multiple sclerosis and healthy controls.

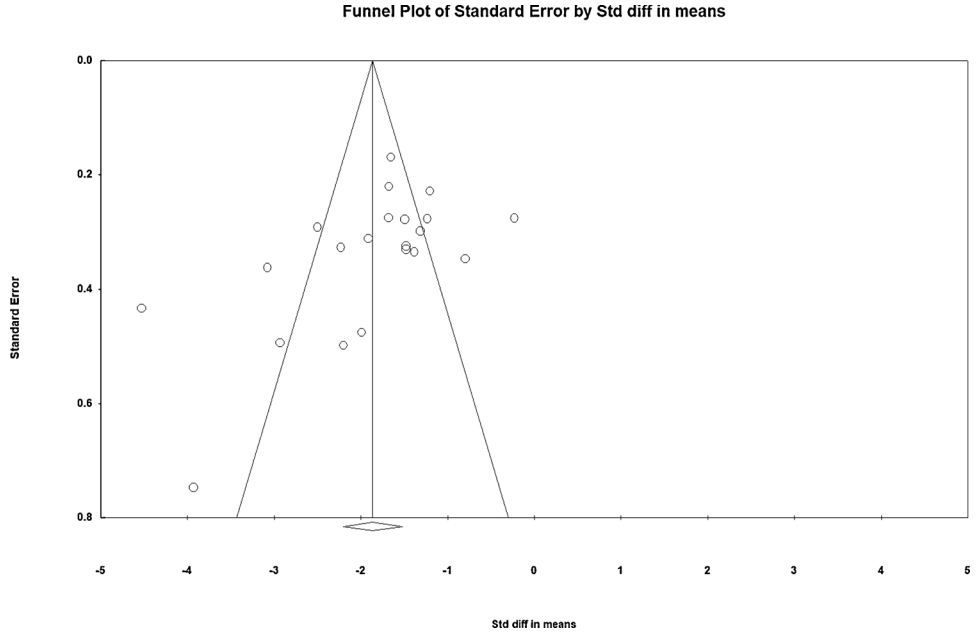

Fig. 3. Funnel plot of papers (n = 20) with comparisons between people with multiple sclerosis and healthy controls for distance traveled during the 6-minute walk test.

inspection of the funnel plot (Fig. 5) indicated a low likelihood of publication bias that was confirmed with Egger's test ($p = 0.4369$). The fail-safe N indicated 5303 contradictory results would be required to nullify these findings.

Regarding the analysis of potential moderator variables, there were larger effects between mild and moderate-to-severe disability status for continuous course (ES: 2.54; 95% CI: 1.963, 2.716; mean difference: 189.1 (20.6) meters) than a straight course with 180° turns at either end (ES: 1.68; 95% CI: 1.584, 1.816; mean difference: 178.6 (11.6) meters) during the 6 MW (Q: 10.117; df(Q): 1; $p < 0.001$). There were no differences in the magnitude of ES between mild and moderate-to-severe disability status when considering instructions for walking speed, provision of encouragement, or measurement method as moderators of 6MW performance. The summary of the ESs between mild and moderate-to-severe disability status for each moderator variable are presented in Supplementary Figs. 5 through 8.

4. Discussion

We undertook a meta-analysis for providing a synthesis of endurance walking capacity based on 6 MW performance in adults with MS compared with HCs and as a function of disability status. The results indicated that persons with MS had substantially worse 6 MW performance compared with HCs (mean difference (SD): –173.6 (19.3)

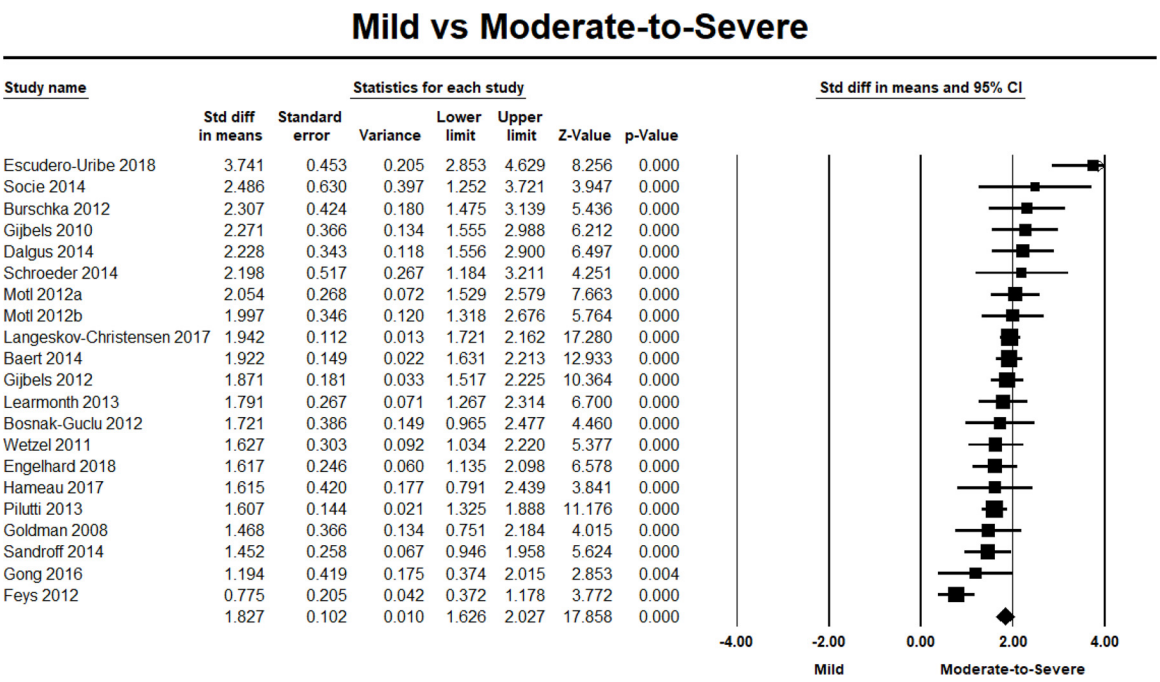

Fig. 4. Summary statistics for the comparison of distance traveled during the 6-minute walk test in people with multiple sclerosis with mild or moderate-to-severe disability.

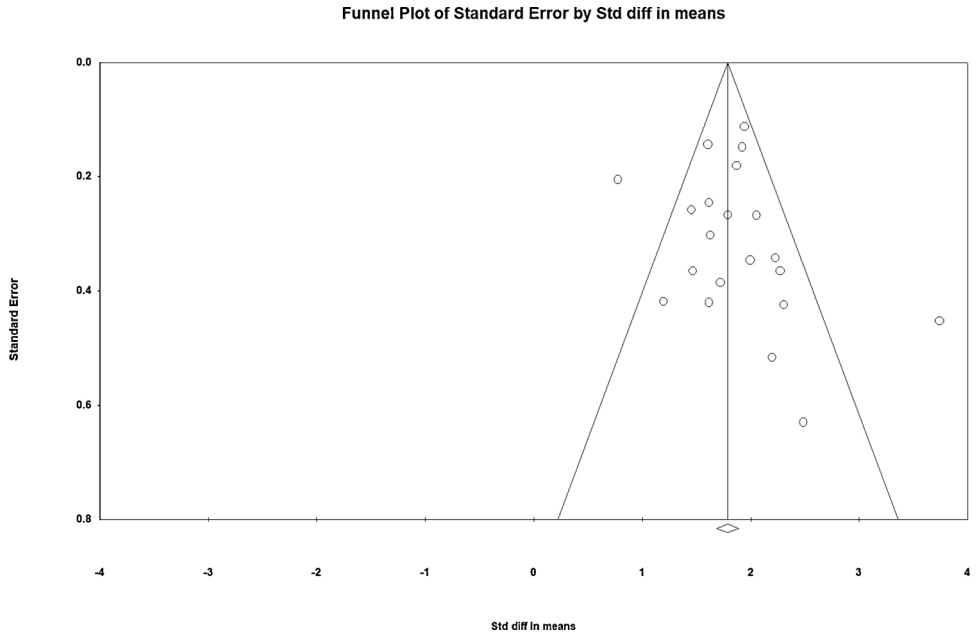

Fig. 5. Funnel plot of papers (n = 20) with comparisons between mild and moderate-to-severe disability for distance traveled during the 6-minute walk test for people with multiple sclerosis.

meters) and those with moderate-to-severe disability demonstrated worse 6 MW performance than those with mild disability (mean difference (SD): –185.19 (9.2) meters). This substantial magnitude of difference in walking endurance capacity likely has an effect on community participation and quality of life (QOL) metrics. One study indicated that 6 MW performance accounted for 45% of the variance in mean steps/day and a decrease of 10 m on the 6 MW was associated with a decrease of 130 steps/day in persons with MS [42]; this would translate into a reduction of nearly 2250 steps per/day and represents a substantial decline in community-based ambulation. 6 MW performance was further associated with participation outcomes, specifically autonomy and family role subscales [42]. Accordingly, worse 6 MW performance in persons with MS as well as with increasing disability status is likely substantial enough that it may have a negative impact on activities of daily living, participation in community activities, and functional independence in persons with MS.

The current meta-analysis indicated a large difference in endurance walking capacity based on 6 MW between persons with MS and HCs with a weighted mean ES of –1.73 whereby persons with MS walked a shorter distance during the 6 MW than HCs. Additionally, our results indicated a large difference in endurance walking capacity between persons with mild disability compared with moderate-to-severe disability status with a weighted mean ES of 1.83 whereby persons with worse disability walked a shorter distance during the 6 MW than

persons with mild disability. These large ESs likely reflect clinically meaningful deficits in endurance walking capacity as ESs that exceed 0.5 SDs often translate into distinguishable effects on health-related QOL [43]. This suggests that there may be tremendous value in remediating the declines in endurance walking capacity through a variety of disease modifying and rehabilitation approaches for improving QOL in MS.

We identified course layout as a moderator for the effect of both MS and disability status on walking endurance during the 6 MW whereby there was a greater difference in mean 6 MW distance when a continuous course was utilized than with a straight course with 180° turns at either end. The continuous course provides participants the opportunity to maintain a constant pace throughout the 6 MW, whereas a straight course with 180° turns requires that participants reduce walking pace at either end of the course in order to maintain stability and continue walking. This idea may be supported by previous literature using the Timed Up and Go (TUG) as a measure of walking mobility, wherein higher disability status was associated with a longer amount of time required to complete the TUG [44]. The TUG requires participants to stand from a chair, walk 3 m, make a 180° turn, and return to the chair to finish in a seated position. Perhaps those with moderate-to-severe disability present with greater instability when making sharp turns, thereby requiring a greater length of time to make 180° turns during the 6 MW. Accordingly, our results suggest that a continuous course may provide a more accurate estimation of endurance walking capacity as this condition of 6 MW administration further highlighted the differences between groups. The type of course utilized for administering the 6 MW in adults with MS is important to consider in clinical practice and research as a continuous course may maximize the understanding of walking endurance in persons with MS and those with greater mobility impairment compared with HCs and persons with less mobility impairment, respectively.

We further identified the provision of encouragement/feedback as a moderator for the effect of MS on 6 MW performance when compared with HCs whereby there was a greater difference in mean 6 MW distance between MS and HCs when encouragement/feedback was provided than when no encouragement/feedback was provided. Encouragement/feedback throughout the 6 MW provides participants awareness regarding the time elapsed and time remaining throughout the test; thus, participants may be more inclined to monitor pace in an effort to minimize fatigue over time. Another potential explanation for the greater difference between MS and HC groups lies within the nature of the 6 MW wherein, for persons without disability, the 6 MW may be more of a submaximal test whereas in persons with mobility disability (i.e., persons with MS), the 6 MW may often be a maximal effort test. Accordingly, encouragement or feedback throughout the 6 MW may elicit participants with greater disability to perform a more maximal 6 MW test (i.e., a greater distance covered during the 6 MW). Conversely, when there was no encouragement or feedback provided throughout the test participants may demonstrate a self-initiated pace that reflects daily life events during the 6 MW. Thus, a test environment that does not include feedback or encouragement may elicit a more representative endurance walking capacity as measured by the 6 MW that may maximize the understanding of walking endurance in persons with MS when compared to HCs. Based on these results, perhaps encouragement and/or feedback should be provided during the 6 MW if the intended purpose of the test is to capture a representative measure of maximal walking endurance (i.e., prolonged, walking capacity) and that no encouragement or feedback be provided if the intention is to measure more daily activity mobility (i.e., prolonged, self-paced walking) in persons with MS.

Based on all MS participants from the included articles, the mean (SD) distance traveled during the 6 MW was 452.1 (103.2) meters; those with mild disability walked a distance of 516.6 (91.8) meters and moderate-to-severe walked 331.8 (110.2) meters. To our knowledge, there are no reported clinical normative or calculated benchmark values established for persons with MS; however, one cross-sectional study provided reference values for the 6 MW in a sample of 474 participants with MS (200 with mild disability and 274 with moderate disability) [24]. The total sample walked 353 (159) meters and those with mild disability walked 482 (116) meters and those with moderate disability walked 259 (114) meters; this was a shorter distance compared to the overall distance traveled and per each group reported in this meta-analysis. These values, along with the mean values reported in this meta-analysis, are important to consider when assessing walking performance and change in performance based on the 6 MW in clinical research and practice.

There are limitations and sources of bias that should be considered when interpreting the results of this meta-analysis. The lack of normative and benchmark values precludes any opportunity to translate the estimated mean differences from this study into a functional measure or outcome. When defining disability subgroups, articles that classified participants as moderate or severe were collapsed into a single group (i.e., moderate-to-severe) based on the lack of a standardized definition of disability subgroups. Additionally, articles included in this analysis reported and classified participants into a disability status (i.e., mild, moderate, and/or severe) based on scores from the EDSS or the PDDS. We recommend that a standardized and accepted classification of disability subgroups, based on both EDSS and PDDS, be adopted to minimize this potential source of bias. Additionally, there was inconsistent delivery of protocol instructions for the 6 MW, wherein participants were instructed to complete the 6 MW “as fast” as possible [2] or at their “own pace” [4]. There were differences in methodology among articles including the aforementioned moderator variables (i.e., provision of encouragement/feedback, course layout, and the method of measuring distance traveled during the test). We recommend that a standardized method of administering the 6 MW be adopted in adults with MS to reduce this source of bias.

This meta-analysis provides a mean expected difference in 6 MW performance for MS compared with HCs, and provides an estimate of the disease-related effect of MS on endurance walking capacity for comparison within clinical research and practice. The mean values reported in this meta-analysis for 6 MW performance are important for clinicians and researchers as these indicate expected values for those with MS and can provide a basis for predicting walking endurance capacity among those who are newly diagnosed with MS or for those who are transitioning into a more severe disability status or a progressive disease course.

Author contributions

Katie L.J. Cederberg: Data curation, formal analysis, interpretation of data, investigation, methodology, project administration, original draft, review and editing.

E. Morghen Sikes: Investigation, methodology, interpretation of data, validation, reviewing and editing.

Alfred A. Bartolucci: Methodology, supervision, validation, reviewing and editing.

Robert W. Motl: Conceptualizing, investigation, methodology, resources, software, supervision, validation, reviewing and editing.

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Declaration of Competing Interest

The authors have no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.gaitpost.2019.07.125.

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