THESIS

MOVEMENT FOR MOBILITY: ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY, POSTURAL CONTROL, AND GAIT IN PEOPLE WITH MULTIPLE SCLEROSIS

Submitted by

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ABSTRACT

MOVEMENT FOR MOBILITY: ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY, POSTURAL CONTROL, AND GAIT IN PEOPLE WITH MULTIPLE SCLEROSIS

Background: Approximately 80% of people with multiple sclerosis (PwMS) experience impaired balance and mobility. The optimal duration, type and intensity of physical activity (PA) to improve balance and gait is not well understood.

Purpose: Examine associations between PA duration, type and intensity with balance and gait in PwMS and neurotypical controls.

Methods: Twenty-four PwMS and twenty-one neurotypical controls reported their typical PA routine, including duration [(days/week)x(minutes/bout)], type (aerobic, resistance and/or plyometric (R/P) and yoga), and intensity (rating of perceived exertion (RPE) 6-20). Balance was assessed by the mini Balance Evaluation Systems Test (Mini-BESTest). Gait speed was measured by the two-minute walk test at a normal pace and a fast pace. Pearson's and Spearman's correlations examined associations among PA variables, balance, and gait speed. Independent t-tests and Mann-Whitney U tests examined differences in gait speeds and balance, between participants who did vs. did not perform each PA type. MANOVA and Kruskal-Wallis tests compared gait and balance performance in participants who reported ≥150 PA minutes/week, and vigorous PA (RPE ≥ 14) vs. those who did not.

Results: No significant associations were found between PA duration and any outcomes in either group. Conversely, PA intensity was significantly associated with reactive postural control,

$r_s(24) = .458$, $p < .05$, sensory orientation, r_s $(24) = .487$, $p < .05$, and dynamic gait, $r_s(24) = .429$, $\mathrm{p} < .05$, and anticipatory postural control in neurotypical controls, $r_s(21) = .476$, $p < .05$. As for PA type, self-reported habitual R/P was associated with nearly significantly superior dynamic gait performance in PwMS, $p = .07$, but significantly lower normal gait speed in neurotypical controls, $p < .05$. Participants who met and/or exceeded the 150-minute per week PA guideline did not have differences in any outcomes. Habitually vigorous PA was associated with significantly improved anticipatory postural control, $H(1) = 5.86$, $p < .05$, and nearly significantly improved Mini-BEST scores in neurotypical participants $H(1) = 3.273$, $p = 0.07$. Minimally clinically important differences in fast gait speed (> 0.10 m/s) were found in neurotypical participants habitually performing vigorous PA compared to light-to-moderate PA. Conclusions: These findings suggest PA intensity and participation in R/P and yoga are associated with better balance and gait performance. Future studies should reevaluate these associations incorporating PA intensity measured by self-report perceived intensity and objectively measured, and incorporating R/P training into PA routines to improve balance and gait outcomes in PwMS.

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Introduction

Nearly 1 million Americans live with multiple sclerosis (MS)[1], an autoimmune disease resulting in neurodegeneration of the central nervous system (CNS). Due to the varying degrees of neurodegeneration in the brain, brainstem, spinal cord and optic nerves, MS is a heterogeneous disease with a wide variety of clinical manifestations.[2] Despite the heterogeneous nature of MS, one common outcome of the disease is detriments to physical function and mobility. It is estimated that up to 90% of people with multiple sclerosis (PwMS) report mobility impairments, 50-80% report poor balance, and over 50% are predicted to fall in any three-month period.[2-6]

The mobility impairments and elevated fall risk experienced by PwMS can be linked to poorer dynamic balance strategies in part due to an impaired ability to integrate somatosensory input and/or visual information.[7,8] While research is currently investigating anatomical structures and pathophysiology responsible for balance and gait impairments, the current literature recognizes that demyelination within both white and gray matter structures of the CNS leads to slowed neuronal signaling in PwMS.[9,10] The specific location of this demyelination leads to varying disease progression[10,11] and often manifests clinically through impaired anticipatory and reactive postural adjustments, dynamic balance and mobility dysfunction in PwMS.[9]

Assessing the domains of postural adjustments is important to allow clinicians or researchers to pinpoint specific components of balance deficits in each patient and to assess fall risk. The Mini-Balance Evaluations Systems Test (Mini-BESTest) is a comprehensive test that assesses balance in four primary subdomains: anticipatory postural control, reactive postural, sensory orientation and dynamic gait. This 14-item assessment has demonstrated validity and reliability to detect balance impairments in neurological clinical disorders such as MS.[12-16] These domains were selected as they provide insight into different neurophysiological systems, each of which control various facets of balance. This is especially advantageous for clinical assessments in PwMS given the heterogeneous nature of the disease manifestation. The Mini-BESTest has been shown to be an accurate predictor of disease severity and disease-specific postural control deficits.[17] Furthermore, the Mini-BESTest has shown to be a significant predictor of falls when an individual scores below the threshold point of 22.5.[12] Additionally, poor postural control performance has been associated with slower gait speeds, a common feature of impaired mobility in PwMS, which is also associated with increased fall risk.[7,18] Therefore, the Mini-BESTest and a measurement of gait speed provide a comprehensive assessment of the complex manifestations of balance and mobility impairment in PwMS.

For PwMS, disease-related balance and mobility impairments have a significant, negative impact on quality of life, indicating a need to identify strategies to help negate balance and mobility declines among these individuals. One strategy that has demonstrated potential to improve mobility and balance outcomes in PwMS is physical activity (PA).[19-22] Several meta-analyses have concluded that PA interventions result in significant improvements in gait speed and walking endurance,[21] as well as overall balance in PwMS.[22,23,24] With this, recently published recommendations suggest that PwMS gradually increase their PA level to reach 150 minutes per week at a low-to-moderate intensity (Rating of Perceived Exertion (RPE) 11-13) to improve several facets of health.[25] Furthermore, these recommendations also encourage PwMS to participate in other modalities of PA, such as resistance training and flexibility and neuromotor PA such as yoga.[25]

While there is evidence that reaching this PA recommendation reduces the risk of a wide range of comorbidities for PwMS,[26] it is unclear whether this 150 minute PA duration, low-to-moderate intensity recommendation, and inclusion of resistance training and yoga is adequate to elicit any significant changes in balance and gait performance. First, the PA interventions in the current literature have varied widely in the duration, intensity and type of training, such as aerobic, resistance, and flexibility training, which makes it difficult to pinpoint the optimal type or duration of PA necessary to improve balance and gait outcomes.[22,24] Additionally, many of these studies do not report patient compliance rates for the intervention itself, making it unclear whether the prescribed PA duration was effective to achieve the favorable results.[27] Further, there are inconsistent findings on the efficacy of resistance training[28-31] and yoga to improve mobility and balance outcomes in PwMS.[31,32] However, because of the demonstrated relationship between increases in muscular function (strength, endurance, and power) observed post-resistance training and improvements in gait patterns and balance in PwMS,[30,32-36] researchers speculate that study inconsistencies such as varying intensities and frequencies that cause overall interpretation of the impact of resistance training in PwMS to be complex and difficult.[34] Finally, the measures used to assess gait, mobility and balance in the current literature fail to comprehensively assess the specific domains in which PA may influence balance or mobility, such as capturing improvements in anticipatory postural control compared to simply measuring changes in a timed task or improvements in overall balance. Rather, many of these studies focus on changes in overall balance with simple testing protocols such as single leg stands or the Berg Balance Scale, as opposed to more accurate and specific tests like the Mini-BESTest.[17,22,27]

Despite the growing evidence indicating PA may improve overall balance and mobility outcomes among PwMS to some degree, two major limitations remain in the current literature:

(1) it is still not clear whether consistently meeting the newly published PA guidelines will be adequate to produce significant improvements in mobility and balance, and (2) the specific underlying postural control systems and/or type of functional mobility that is impacted by habitual PA duration (minutes per week), intensity (RPE) or type (aerobic, yoga or resistance training) have yet to be identified.[19-22,27] The current study aimed to address these existing gaps by (1) examining associations between habitual PA duration, type and intensity, Mini-BESTest overall score and subdomain scores and gait speeds among PwMS and neurotypical controls, and (2) comparing Mini-BESTest and gait speeds between those who met the 150 minute low to moderate intensity PA guidelines to those who do not. We hypothesized that for those who reported performing aerobic, resistance training, or yoga, PA duration and intensity would be significantly and positively associated with balance and gait speed performance in both PwMS and controls. Further, we hypothesized that those who achieved PA guidelines would display improved mobility and gait speed performance compared to those who did not.

Methods

Participants

Twenty-four PwMS and twenty-one neurotypical controls were recruited from Northern Colorado. To be eligible to participate in this study, participants had to be 18-85 years of age and either have no history of MS or a neurologist confirmed diagnosis of relapsing-remitting MS, be independently ambulatory in their community, be able to stand or walk on a firm surface without shoes for 30 minutes and be able to perform a chair rise without assistance.

Disease severity is determined based on disability status which is assessed using the Expanded Disability Status Scale (EDSS). The EDSS is a subjective scale which characterizes disease progression between 0-10 with ratings ≥ 5 associated with mobility impairment. To meet the eligibility requirements for this study, participants were required to have an EDSS of 4 or less.

Eligible participants completed a questionnaire to measure PA duration, intensity, and type, the Mini-BEST and (2) two-minute walk tests (2MWT) to measure gait speeds. Colorado State University's Institutional Review Board approved this study (20-9749H), and all participants gave their informed written consent, including providing consent for their aggregated data to be reported in scientific papers and presentations, prior to all experimental procedures.

Physical Activity

Participants were asked to report their typical weekly PA duration, intensity, and type. PA duration was determined by multiplying the frequency (days per week), and average duration (minutes per exercise bout) reported. To determine intensity, participants reported the average rate of perceived exertion (RPE) during PA sessions, using the Borg 6-20 scale.[37] Finally, participants reported all types of PA, selecting from aerobic, weightlifting, plyometric, and yoga, and an option to fill-in other types of PA not listed. For analyses, participation in habitual plyometric and/or weightlifting exercises was redefined as participation in resistance training (RT).

Balance and Gait Assessments

Balance was assessed using the Mini-BESTest. The Mini-BESTest consists of 14 tasks each of which are graded from 0 (unable to complete) to 2 (performed normally) for a maximal score of 28. This test focuses on measuring four primary mobility domains: anticipatory postural adjustments, postural control, sensory orientation, and dynamic gait.[38] All Mini-BESTest assessments were video recorded to ensure proper scoring, and all test were administered and scored by the same individual within the study staff.

Following the Mini-BESTest protocol, in order to measure gait speed, participants were asked to perform two separate 2MWT down a 30-meter hallway. Participants were directed to walk at a normal, self-selected pace for one trial and a fast pace for the second trial. The 2MWT has been validated in PwMS as an appropriate test for comparable normal and fast gait speed findings when compared to the widely utilized 6-minute walk test.[39] Participants were able to have a seated rest in between each 2MWT as needed. The test was instrumented utilizing 6 wireless inertial Opal sensors (APDM Inc., USA), which contain a 3D accelerometer, 3D gyroscope and a 3D magnetometer. Gait speed data were collected and exported using Mobility Lab™ (ML, APDM, Inc., Portland, OR, USA). This software identifies and removes the gait cycles prior to, during, and following participant turns, therefore only exporting linear gait speed speeds for the current analyses.[40,41]

Prior to hypothesis testing, *t*-tests were conducted to identify significant between-leg differences in gait speed prior to hypothesis testing. Among all participants, no significant differences existed between right and left leg's gait speed for either self-selected gait speed, $t(55) = .000$, $p > .05$, and fast gait speeds, $t(55) = .256$, $p > .05$. As a result, gait speeds were averaged between both legs for the following analyses.

Additional Questionnaires

The Self Report Expanded Disability Status Scale (EDSS) was completed by participants to provide a self-reported EDSS based on the symptoms faced by the participants. This scale has demonstrated moderate to strong correlations with physician-administered disability status scores.[42] At the start of the procedures, participants completed a validated and widely-used health-related quality of life (HRQoL) questionnaire in PwMS, the Short Form-36 (SF-36).[43-45] This questionnaire consists of 36 questions regarding patient-centered feelings of health, quality of life, and overall mental health. The Multiple Sclerosis Walking Score-12 (MSWS-12), a questionnaire regarding self-perceived walking difficulty that has been validated for use in PwMS was also collected during the visit.[46] The MSWS-12 scores were transformed to a 0-100 scale by subtracting the minimum score of 12 from the overall sum and dividing the overall score by 48.[47] Additionally, the Modified Fatigue Impact Scale (MFIS) was completed by participants, a validated questionnaire used to obtain objective self-perception of fatigue.[48]

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 26.0 with statistical significance set at $p < 0.05$. To address aim 1, spearman's rank-order correlations were utilized to assess associations between PA duration and intensity with Mini-BESTest total and subdomain scores. Mann-Whitney U test was conducted to identify significant differences between Mini-BESTest scores among participants who did vs did not report habitual performance of each type of PA (aerobic, RT, and yoga). Pearson's correlation coefficients and Spearman's rank-order correlations were then conducted to identify associations among PA duration, intensity, and type, respectively, with both self-selected and fast gait speeds. The data were then assessed to identify whether an meaningful clinically important difference (MCID) was met for gait speed, which is considered to be 0.10 m/s difference or a 20% change in fast gait speed,[49-51] or the overall Mini-BESTest score, a 4 point difference, between those who did vs did not participate in each activity type.

For aim 2, we performed a Multivariate Analysis of Variance (MANOVA), to compare the normal and fast gait speeds in participants who did vs did not meet PA guidelines of 150 minutes per week, and those who reported meeting light to moderate (RPE $\leq$ 13) vs vigorous (RPE $\geq$14) intensities. Additionally, Kruskal-Wallis tests were performed to assess balance performance differences in PwMS and neurotypical control participants who did vs did not meet PA guidelines of 150 minutes per week and those who reported light-to-moderate vs vigorous PA. Differences between fast gait speeds and Mini-BESTest scores were then assessed to identify whether the MCID were met between participants who met PA guidelines for duration or intensity and those who did not.

Results

Participants

Twenty-four PwMS (49 ± 12 years, 25.2 $\pm$ 3.9 $kg \cdot m^{-2}$) with a median expanded disability status score (EDSS) of 3.75 (0-4.0), and twenty-one neurotypical controls (47 $\pm$ 17 years, 24.6 $\pm$ 3.1 $kg \cdot m^{-2}$) completed the study protocol. Participant demographics can be found in Table 1. PwMS reported a mean of 277 $\pm$ 229 minutes of habitual PA per week, whereas neurotypical controls reported 221 $\pm$ 108 minutes of habitual PA per week. The PA intensity (RPE) reported was 13 $\pm$ 3 and 13 ± 2 for PwMS and neurotypical controls, respectively. All of the PwMS and all but one neurotypical control participant reported some form of aerobic PA. Therefore, participants were stratified into those who performed aerobic activity alone and those who additionally reported either RT or yoga. With this, participants reported participation in habitual aerobic activity + RT (50%), and aerobic + yoga (33%) activity. Similarly, the neurotypical controls reported participation in aerobic + RT (65%) and aerobic + yoga (25%) activity. Furthermore, 18 PwMS (78%) and 16 neurotypical controls (76%) reported meeting the 150 minute per week PA guidelines. In regards to intensity, 9 PwMS (38%) and 9 neurotypical controls (43%) reported habitual PA at or above an RPE of 14. Overall, PwMS had slower gait speeds across both conditions and greater balance impairments, as indicated by lower overall Mini-BESTest total scores and all subdomain scores, when compared to neurotypical controls (Table 2). Mann-Whitney U tests identified significantly lower Mini-BESTest scores aside from anticipatory postural control, $p = 0.07$, and sensory orientation, $p = 0.050$, for PwMS relative to neurotypical controls. Similarly, when compared to neurotypical controls, independent t-tests identified that both normal, $t = 3.19$, $p < 0.05$, and fast, $t = 4.63$, $p < 0.05$, gait speeds were significantly slower in PwMS.

Aim 1: Associations Among PA Variables, Gait and Balance

In PwMS and neurotypical controls, PA duration was not significantly associated with any of the Mini-BESTest scores or subdomains. One-way Spearman's rank-order correlations found positive, trending significant associations among PA intensity and overall Mini-BESTest scores, in PwMS $r_s(24) = .373$, $p = 0.07$. Additionally, PwMS exhibited significant, medium-sized associations between PA intensity and reactive postural control, $r_s(24) = .458$, $p < 0.05$, sensory orientation, $r_s(24) = .487$, $p < 0.05$, and dynamic gait, $r_s(24) = .429$, $p < 0.05$ (Figure 1). Similarly, PA intensity of neurotypical participants was significantly associated with better anticipatory postural control scores, $r_s(21) = .476$, $p < 0.05$, and trended towards a significant association with a superior overall Mini-BESTest score, $r_s(21) = .347$, $p = 0.06$.

As for PA type, Mann-Whitney Tests revealed that PwMS that performed aerobic + RT had superior median dynamic gait scores, *Mdn* = 8, then those who reported only aerobic PA, *Mdn* = 7, nearly reaching statistical significance, $U = 40.50$, $p = 0.07$. Similarly, the overall

Mini-BESTest score in participants reported habitual aerobic + yoga, 24, nearly met the MCID in the difference from participants who only performed aerobic activity, 20.5 (Figure 2).

For both PwMS, neither self-selected nor fast gait speeds displayed significant associations with any of the PA variables. In contrast, habitual aerobic + RT was significantly associated with slower self-selected gait speeds, $r_{pb}(21) = -.512$, $p < 0.05$ in neurotypical controls. While not statistically significant, the difference in the mean fast gait speed in participants who reported participation in aerobic + yoga activity, 1.8 $\pm$ 0.2 m/s, met the MCID for fast gait speeds ($\geq$ 0.10 m/s), when compared to participants who only performed aerobic activity, 1.7 $\pm$ 0.2 m/s. Associations among PA duration, intensity, and performing habitual aerobic + yoga PA were not statistically significant with either self-selected or fast gait speed in PwMS.

Aim 2: Meeting vs Not Meeting PA Guidelines

Kruskal-Wallis tests were conducted to identify significant differences in Mini-BESTest rankings between participants who did or did not report 150 minutes per week of PA. For both neurotypical controls and PwMS, the Kruskal-Wallis test did not find any significant differences in Mini-BESTest outcomes between participants who did vs did not meet the PA duration recommendation. Thus, the difference in the median Mini-BESTest score in both neurotypical participants and PwMS who reported meeting the 150-minute guideline compared to the score of those who did not meet the guideline did not meet the MCID for the Mini-BESTest, a 4 point difference.

Kruskal-Wallis tests were then conducted to assess Mini-BESTest ranking differences in those who reported light to moderate (RPE $\leq$ 13) vs vigorous (RPE $\geq$14) PA. For PwMS, these analyses found that reporting meeting the intensity guidelines did not find significant differences in participant scores in any of the Mini-BESTest variables. Similarly, the MCID for the Mini-BESTest was not met when comparing the median scores in PwMS or neurotypical controls who reported light-to-moderate PA compared to those who reported vigorous PA. Neurotypical participants who reported performing vigorous intensity PA scored higher on the overall Mini-BESTest, *Mdn* = 27, relative to those who performed moderate or less intense activity *Mdn* = 24, $H(1) = 3.273$, $p = 0.07$. Further, neurotypical participants who reported vigorous activity, ranked significantly higher on the anticipatory postural control subdomain, *Mdn* = 6, $H(1) = 5.86$, $p < .05$, compared to those who did not, *Mdn* = 5. No additional subdomains presented with significant differences in PwMS or neurotypical adults.

The current study found that neither PwMS nor neurotypical participants who reported habitually meeting the 150-minute threshold for weekly PA had clinically or statistically significant differences in either self-selected or fast gait speed. Similarly, no clinically or statistically significant gait speed differences were seen in PwMS when stratified into those who reported light to moderate (RPE $\geq$ 13) vs vigorous (RPE >14) habitual PA. However, when stratifying the neurotypical controls by habitual intensity, there was a clinically significant difference in fast gait speed (> 0.10 m/s) between those who reported habitual light-to-moderate PA, 1.6 ± 0.1 m/s, and those who reported vigorous PA, 1.7 ± 0.2 m/s. All remaining gait-related differences in the neurotypical controls, were not statistically or clinically significant.

Discussion

This study is the first to investigate how habitual participation in various PA durations, intensities and types is associated with changes in gait speed and balance performance within domains including anticipatory postural control, reactive postural control, sensory orientation and dynamic gait in both PwMS and neurotypical adults. While PA duration was not associated with balance performance in PwMS and neurotypical adults, greater PA intensity was associated with significantly better reactive postural control, sensory orientation and dynamic gait scores in PwMS, and trended towards significantly greater anticipatory postural control performance in neurotypical controls. Additionally, aerobic + RT, was associated with significantly better dynamic gait in PwMS, and significantly worse self-selected gait speeds in the neurotypical participants. PwMS and neurotypical controls who reported habitual aerobic + yoga activity performed better in balance and gait, respectively. Moreover, neurotypical control participants who reported habitual participation in vigorous PA displayed faster gait speeds that met the threshold of meaningful clinical differences (0.10 m/s). While these findings fail to support all of the components of the initial hypotheses, they underscore the potential importance of PA intensity, and a possible utility of RT and yoga in the context of improving gait and balance in both PwMS and neurotypical adults. Additionally, these findings suggest some components of the current PA recommendations for PwMS and neurotypical adults may be beneficial to improve balance and gait outcomes in these populations.

PA Intensity

The current study suggests that PA intensity may be a more important metric than PA duration in the context of improving gait and balance outcomes in both neurotypical adults and PwMS. While the newly released exercise recommendations state that PwMS should reach moderate to vigorous PA (MVPA) intensity levels, they generally recommend maintaining an RPE of 11-13, which constitutes light to moderate intensity, and for those with greater fitness levels exercising at upwards of an RPE of 15, which is the lowest degree of vigorous activity.[25,37]

Our study found a significant association with PA intensity and several facets of postural control, including reactive postural control, sensory orientation and dynamic gait in PwMS and anticipatory postural control in neurotypical controls, as well as a trend indicating those who reported vigorous (RPE $\geq$ 14) habitual PA performed better across all functional outcomes than those who performed moderate and less intense PA (Figure 1 and 2). These findings are suggestive that vigorous PA may elicit a more powerful stimulus to better improve functional outcomes and are in agreement with the general consensus seen in the high intensity PA literature.

High Intensity PA in PwMS

The current findings align with those seen in the vigorous or high intensity PA literature in PwMS. Within the past decade, there has been a rapidly accumulating body of evidence suggesting that incorporation of higher intensity activity likely provides a more potent stimulus to better promote beneficial physiological changes associated with exercise, relative to lower intensities, for PwMS. Similar to studies in the neurotypical population,[52,53] as well as several chronic disease types,[54,55] PwMS have displayed significantly improved cardiometabolic markers, muscular strength and endurance, health-related quality of life, cardiorespiratory fitness and performance in functional assessments (2MWT, and timed up and go test) following a HIIT protocol.[56] One particularly relevant finding reported in a study by Orban et al., was improved mitochondrial function in the tibialis anterior, a muscle critical for postural control and proper gait mechanics.[57-60] This finding is especially clinically relevant as PwMS often display dysfunctional muscle activity of the TA, which often displays clinically as drop foot and slower gait speeds in PwMS.[61,62] While this particular study did not find improvements in functional outcomes (6 minute walk test and the timed up and go), the authors attributed this to ceiling effects of this test and being underpowered.[58] It is possible that in the current study, higher habitual PA intensity leading to improved fitness of critical postural control and gait musculature could have led to the better performance in these outcomes.

While no studies have investigated the association between long-term habitual vigorous intensity PA with gait speed and balance outcomes, maintenance of improvements in functional outcomes in high intensity groups has been previously investigated. Specifically, the only HIIT study that included a follow-up assessment found that though participants in the HIIT group displayed greater improvements in the 2MWT distance and leg power compared to continuous low-intensity PA, after the termination of exercise, many of these improvements reversed.[63] This is suggestive that continuing vigorous exercise may be necessary to maintain the benefits associated with it. This, as well as the neurophysiological benefits previously described, may provide insight as to how regular participation in higher intensity PA was associated with better postural control, even without a formal intervention.

Interestingly, while research has identified a significant negative association between EDSS and time spent in MVPA,[64] our post-hoc analyses found almost no association between EDSS and the self-reported intensity of PA in the current study, $r_s(24) = -.022$, $p = .919$. This is suggestive of either a greater perception of intensity within daily activities in some, but not all, more severely disabled participants, an unusual degree of higher intensity PA reported in more severely disabled PwMS, some degree of neuroprotection associated with this more vigorous PA that may have attenuated disability progression, or some combination of these factors. This last suggestion is plausible given the findings regarding neuroregeneration associated with MVPA in PwMS.[65]

Potential Mechanisms for Vigorous PA to Improve Balance and Gait

Mechanisms behind the functional improvements seen in the literature and those seen in the current study likely stem from the underlying neuroprotective and neuroregenerative role MVPA serves in both neurotypical adults and PwMS.[65] Research has found that PA as measured through accelerometery and self-report methods is an independent, significant predictor of cardiorespiratory fitness even after controlling for EDSS.[66] With this, aerobic fitness has been positively associated with neuroprotection, specifically through negative associations with lesion load volume, and positive associations with grey matter volume in midline cortical structures, as well as white matter preservation.[67] Similarly, accelerometer-measured PA has been associated with improved functional connectivity between the left and right hippocampus and the posteromedial cortex.[68] Several of the brain structures and improved functional connectivity that are positively associated with aerobic fitness, including the hippocampus, basal ganglia, and frontal gyrus which have been deemed fundamental for balance and gait performance.[68-72] Another hypothesis that may be responsible for these effects is improved neuronal mitochondrial function. A recent pilot study that investigated potential neurophysiological mechanisms that may be responsible for some of the benefits associated with high intensity aerobic activity in PwMS and found that following this protocol, PwMS demonstrated improved mitochondrial function in the tibialis anterior.[57-60] The authors speculated that if this bioenergetic improvement occurs in the CNS, it may be responsible for the neuroplasticity seen following aerobic activity.[58] However, additional research needs to investigate these hypotheses further with larger sample sizes than those seen in this, or the current study.

Additionally, the current study found that habitual PA intensity was associated with improvements in anticipatory postural control in neurotypical participants, and reactive postural control, sensory orientation and dynamic gait in PwMS. This is in agreement with the current literature, which suggests that in neurotypical older adults, habitual PA may attenuate declines in anticipatory postural control. A study by Carvalho et al., recruited individuals for three groups: habitual joggers, beginner (average of 3 years) exercisers, and sedentary inactive individuals.[73] This study found that the sedentary group exhibited significantly greater antagonist muscular coactivation to maintain postural control.[73] This disproportionate antagonist muscle coactivation is the same strategy utilized by older adults to stabilize the joint and attempt to compensate for reduced strength as well as neuromuscular and sensorimotor decline, all of which are positively influenced by PA in neurotypical and MS populations.[74-76] Therefore, the authors concluded that habitual exercise may delay age-related declines to anticipatory postural control. In the context of the participants with MS, there is evidence to suggest the use of excessive coactivation is also utilized during gait and balance exercises in PwMS.[77] Further, researchers have identified that this abnormal coactivation may lead to reduced gait speeds and decreases in metabolic efficiency.[77] Therefore, despite the fact that anticipatory postural control was not associated with PA duration in PwMS, it is possible that this coactivation compensatory strategy may have led to the reduced scores in dynamic gait and sensory orientation. While muscular electromyography (EMG) was not measured in the current study, it is possible that the attenuation of excessive coactivation was a mechanism for which habitual PA was associated with improved anticipatory postural control scores in neurotypical controls and may have played a role in the significant association with superior dynamic gait scores in PwMS in the current study. It is not yet clear in the literature as to whether light PA is able to elicit the same neuroplasticity as moderate and vigorous intensity PA, which may further indicate why greater PA intensity and not PA duration was positively associated with balance and gait in the current study.

Safety of High Intensity PA in PwMS

Given the clear benefits associated with participation of PwMS, as well as the general population, it is critical to address the factor of safety in the participation in these exercise protocols. Although the safety of high intensity exercise programs in neurotypical and several chronically diseased populations has been demonstrated,[78-80] increasing PA intensity to more vigorous levels beyond the standard MVPA recommendation remains a relatively novel feature in exercise interventions in PwMS. The safety concern revolving around high intensity exercise programs in PwMS stems from the fear of an exacerbation of symptoms that is commonly seen with increased core temperature, previously hypothesized to occur during bouts of intense PA.[81] However, a study comparing HIIT and steady state exercise found no significant difference in core temperature throughout the exercise session.[82] Additionally, in a systematic review by Campbell et al., of the 11 studies and 249 participants that performed high-intensity interval training (HIIT) in PwMS, only 4 participants from one of the studies investigated experienced an adverse event attributed to the intervention.[56] This supports the use of a vigorous PA intervention when performed with caution and patient-oriented exercise prescriptions in most, but not all, PwMS.[56,58,81-83] As more high intensity PA studies emerge, it is critical that the literature identify the characteristics of PwMS who are and are not appropriate to participate in higher intensity PA. By understanding those appropriate for this approach, HIIT or other high intensity protocols may become a more widely used technique by clinicians to improve a variety of outcomes for PwMS, including mobility and balance, more rapidly and to a greater degree than more traditional strategies.

PA Type

The current study found that habitual participation in R/P coincided with improved dynamic gait scores in PwMS, but slower self-selected gait speeds in neurotypical individuals. The association with greater dynamic gait parallels other findings in the literature. For example, a study by Sandroff et al., reported that knee-extensor strength asymmetry was associated significantly with gait performance measured on the 25-foot walk and the six-minute walk test in PwMS.[84] Additionally, these strength asymmetries explained variance within gait kinetics in the participant group.[84] The authors of this paper encouraged the use of strength training as an intervention to improve mobility in PwMS, which support the overall findings and recommendation of the current study.[84] Studies on other modalities of PA, such as a swimming intervention, have found no significant change in gait parameters even when the intervention was performed at a moderate-to-vigorous intensity (60-75% of heart rate max).[85] In addition to RT, reporting habitual participation in yoga was associated with improved overall Mini-BESTest balance in PwMS, and better fast gait speeds in neurotypical participants. The current body of literature does not strongly support the use of yoga to improve mobility, but given the low degree of adverse events and safety concerns, in addition to the multitude of potential benefits, it is still recommended in the general guidelines for PwMS.[86,87] In the neurotypical older population, there has been evidence to suggest an improvement in mobility, balance, and strength utilizing yoga as an intervention.[88] The wide range of findings of the impact of yoga on PwMS is unsurprising given the heterogeneity of yoga as a form of PA. If an individual's yoga practice incorporates balance and muscle strengthening exercises, it is likely they will see differing benefits from another individual prioritizing meditation. Given the current study did not ask in-depth questions regarding the specific type of yoga practiced, it is not possible to address questions surrounding this. However, this may explain the differing findings between PwMS and neurotypical individuals, given it may be possible participants in either group performed an extremely different variety of yoga.

Additionally, the findings of the current study are in line with the basic exercise principal of specificity, which suggests the kind of activity performed should be related mechanistically to the desired outcome to improve. Therefore, it understandable that a non-weight bearing activity like swimming[85] would not have the same physiological responses to improve mobility as a RT protocol that strengthens the lower extremity muscles responsible for successful locomotion, or a yoga intervention to improve postural control.[89] Therefore, it is possible that these additional physiological stimuli may have provided additional benefits on top of a regularly performed walking routine.

Another notable clinical finding was that the median Mini-BESTest scores of PwMS who performed aerobic + RT and aerobic + yoga had scores above a 22.5 threshold identified as a cutoff of high fall risk in PwMS by Ross and colleagues (2016), whereas participants who did not report each type of PA had a median Mini-BESTest score below this threshold, indicating these participants have higher fall risk (Figure 2).[12] This potential protective influence on falling has been seen following yoga interventions in individuals with neuromuscular diseases including MS,[90] and resistance training interventions in neurotypical frail older adults.[91] Qualitative work with PwMS has also found that individuals with the condition reported wanting both strength and balance exercises to help prevent a fall.[92] While the current study did not compare each type independently to a combination of the PA types, it is likely that a combination of resistance training and yoga (balance) activity would be the most effective at preventing falls compared to performing only one type.

As for the seemingly negative association between aerobic + RT, exploratory analyses between groups found that the neurotypical individuals who reported performing aerobic + RT were an average of 52 $\pm$ 16 years of age, which was approximately 12 years older than the participants who did not perform RT as well, 30 $\pm$ 15 years. However, even when accounting for age as a covariate, the mean self-selected gait speed is significantly lower in the neurotypical participants who reported habitual aerobic + RT, $F(1, 17) = 7.61$, $p < .05$. These findings are in contrast to those seen in the literature.

PA Duration

There is a lack of studies investing the duration of PA performed as an independent predictor of mobility in PwMS, limiting the ability to compare the current study's findings to others seen in the literature. Currently, greater durations of MVPA have been associated with significant reductions in perceived functional limitations and MS-related symptoms.[93,94] However, this may be more indicative of the importance of intensity rather than duration. As of recent, researchers in the field suggested future work systematically test the impact of varying PA durations on mobility, which was discovered to be unassociated with mobility in the current study.[94]

The lack of association in the current study may have been influenced by several variables. First, the degree of PA duration found in the current study is in contrast to those typically reported in the literature. It should first be noted that data from the Behavioral Risk Factor Surveillance System (BRFSS) have identified Colorado as one of the most active states in the United States, and therefore the activity level of this cohort is likely not representative of the general population, both the neurotypical population and PwMS.[95] For example, other studies have found that approximately 19.5% of PwMS and 47.4% of control participants met the 150 minute per week guidelines of MVPA, which our study far exceeded in regards to minutes per week.[96] However, this duration may also be inflated given the possibility that participants may have reported minutes of light PA as part of their daily exercise whereas others may have strictly reported MVPA. Previous work has found that increased EDSS is associated with greater time spent in light PA, and that PwMS in the current study's age range (40-50 years) average 287.7 ± 85.2 minutes per day of light PA a day.[97,98] While this is far exceeding the current study's 277 ± 229 and 221 ± 108 minutes of habitual PA per week reported in PwMS and neurotypical controls, respectively.

Another potential influence limiting the associations found in the current study was that the current sample may have met a PA duration threshold in which activity duration beyond this point did not elicit additional benefits. The concept of diminishing returns of PA has been studied in the context of various chronic diseases, including breast cancer, type 2 diabetes, ischemic heart disease and chronic obstructive pulmonary disease.[99] In each of these chronic conditions, prospective observational data have found a curvilinear relationship between metabolic equivalent hours per week (MET-H/week) and hazard ratios for all-cause mortality.[99] However, this concept of diminished returns with PA has not been investigated in PwMS in regards to mobility outcomes. As a result, it is not possible to identify whether the lack of associations in the current study were due to the current sample surpassing this theoretical point of diminished mobility improvement.

Post-Hoc Testing: Stratifying PA Duration by Intensity

While the use of self-report questionnaires has been validated against objectively measured PA in this population,[64] many self-report questionnaires traditionally stratify between light, moderate and vigorous PA. Therefore, some of the discrepancies seen between the PA reported in the literature relative to those in the current study may have been the result of the current self-report questionnaire not stratifying by intensity. While the questionnaire asked participants to record the duration of an exercise bout, they were not able to define the category of intensity of the PA reported (i.e., 30 minutes in moderate to vigorous PA and 60 minutes in light PA), making it difficult to compare current participants to others reported in the existing literature. Given the potential importance for intensity to elicit significant changes to balance and gait performance, we performed a post-hoc correlational analysis with PA duration and balance and gait outcomes without the participants who reported performing low-intensity (RPE $\leq$ 11). By excluding these participants, specifically 5 PwMS and 2 neurotypical controls, the reported PA duration may be more indicative of the minutes per week of MVPA performed, which is more comparable to the current literature.

After removing the participant who reported primarily performing light PA, the mean PA duration reported were 285 $\pm$ 253 minutes per week and 223 $\pm$ 114 minutes per week in PwMS and neurotypical controls, respectively. However, the Spearman's and Pearson's correlational analyses did not find significant associations between PA duration and Mini-BESTest variables, and gait speeds in either group. While unexpected, these findings indicate that there may have been additional factors influencing the accuracy PA duration, or other factors influencing gait and balance measures for certain participants. In general, given the data suggesting PA duration, both light PA and MVPA, having some association with positive functional outcomes in PwMS[100-102] and neurotypical adults,[103,104] these findings should not be interpreted as PA duration being unimportant entirely for the given gait and balance outcomes. More likely, these findings suggest another unknown factor confounded the findings significantly.

Post-Hoc Multiple Regression Analysis

To further attempt to explain the unusual lack of association between PA duration and any balance or gait outcome in PwMS, post-hoc analyses were performed. First, the association between PA duration and EDSS was explored using Spearman's rank-order correlations. PA duration had a small, positive, but non-significant association with EDSS, $r_s(24) = .228$, $p = .296$. This supports the previous theory that there may have been discrepancy among participants as to whether light PA or strictly MVPA was reported, given there has traditionally been either a strong negative relationship between EDSS and MVPA, or a strong positive association with EDSS and light PA.[97] Additionally, the weak associations between EDSS and balance variables reactive postural control, $r_s(24) = -.371$, $p = .074$, sensory orientation, $r_s(24) = -.289$, $p = .170$, dynamic gait, $r_s(24) = -.377$, $p = .074$ as well as self-selected gait speed, $r_s(24) = -..257$, $p = .226$ were discovered in post-hoc testing. This is unlike associations seen in other cohorts, such as EDSS being significantly associated with static posturography variables.[105] Conversely, in the neurotypical participants, age was a factor negatively and significantly associated with several outcomes, including fast gait speed, and all Mini-BESTest balance variables, but shared a non-significant, negative association with PA duration, $r(21) = -.331$, $p = .143$. This negative association between age, postural control[106] and PA duration[107] is similar to levels seen in the literature.

Following this, post-hoc multiple regression analyses were performed to examine the degree to which PA duration, when paired with EDSS, acted as a predictor of Mini-BESTest variables and gait speed. The regression equation was significant for Mini-BESTest total score, $F(2, 20) = 3.99$, $p < .05$, anticipatory postural control, $F(2, 20) = 4.83$, $p < .05$, fast gait speed, $F(2, 20) = 3.80$, $p < .05$. All other regression equations were not significant. The total variance accounted for by the three regression equations were 28.5%, 32.6%, and 27.5%, for the Mini-

BESTest total score, anticipatory postural control and fast gait speed, respectively. According to Cohen (1988) these are considered medium effect sizes.[108] However, these effect sizes were driven primarily by the significant predictive ability of EDSS on the three dependent variables, given PA duration was a non-significant predictor in the Mini-BESTest, anticipatory postural control, and fast gait speed, $\beta = .084, .235, -.265$. Similar findings were seen with neurotypical controls, with the incorporation of age instead of EDSS into the regression model. While the Mini-BESTest score, $F(2, 18) = 15.78$, $p < .05$, anticipatory postural control, $F(2, 18) = 18.15$, $p < .05$, dynamic gait, $F(2, 18) = 6.41$, $p < .05$, and fast gait speed, $F(2, 18) = 3.92$, $p < .05$, with 63.7%, 66.9%, 41.6%, and 22.6% of the variance accounted for by each respective model. However, similarly to PwMS, PA duration was not a significant predictor in any of these models. These data further support that in the current study, the overall duration of self-reported PA shared no association with any of the balance and gait outcomes measured.

Interestingly, across various models, the literature consistently suggests that PA is a mechanism that can improve mobility and balance outcomes in PwMS. The degree to which PA interventions improve outcomes has varied widely, leading to Snook et al., concluding that the effect size for PA to improve walking mobility is relatively small.[27] However, this small effect size is comparable to that of disease-modifying drugs, underscoring the overall utility of PA to improve mobility in PwMS, even if to a small degree.[27] Therefore, in agreement with their study, the findings in the current study suggest there may be a small, but significant, degree of functional benefits associated with habitually performing PA, particularly when done at a particular intensity threshold, and by incorporating RT.

Limitations

The current study's measurement of PA duration may have allowed for a misrepresentation of the true PA, both duration and potentially the intensity, of both participant groups. However, this method should not be discounted entirely. Notably, PA intensity is a multidimensional construct that may be interpreted as either subjective perceived intensity (i.e., RPE) or more objective metrics such as accelerometry or heart rate. By using a self-report method, we collected perceived intensity in a population that often exhibits extreme perceived fatigue and fatigability,[109,110] in which objective measures of intensity likely do not accurately represent the construct of intensity. Additionally, using only objective measurements may result in a bias known as the Hawthorne effect,[111] or the altering of a normal behavior (i.e., PA) when aware that it is being measured. There is currently limited research as to how the Hawthorne may play a role in PA measurements in PwMS, further underscoring the utility of self-report measures alongside objective measures.[112]

The small sample size of the current study also limited the ability to compare groups further (i.e., investigating the differences in participants who reported habitually aerobic + R/P, aerobic + yoga vs participation in all three PA types). Other limitations included only studying PwMS with relapsing-remitting MS with low-to-moderate severity, and a low degree of overall representation of the general population given all participants were from the Northern Colorado area were additional limitations. With this, given the high degree of reported PA in the current cohort, no statements can be made regarding sedentary individuals in either population. This may be preventing revealing certain associations that may exist in either population (i.e., MCIDs being met when comparing highly sedentary individuals compared to the habitually vigorously active individuals) from being revealed given the homogeneity of the sample.

Additionally, research has consistently found acceptable levels of validity with self-reported PA measures. A study by Shook et al., reported that the discrepancy between objective and subjective measures of MVPA was greater in unfit compared to fit neurotypical individuals, as the unfit participants overestimated their MVPA by 36%.[113] However, when compared to neurotypical controls, PwMS have both performed and reported reduced MVPA, correlating significantly and with a medium effect size with objectively measured PA, providing additional evidence to suggest this is a valid measure in this population.[64] Though these findings were not found in the current study, as PwMS and neurotypical controls reported a similar degree of PA duration. Ultimately, while previous work has validated the use of self-report measures in PwMS[114] and the neurotypical population,[113] the current study's inability to differentiate PA duration into concrete intensities reduces the ability to make generalizable statements regarding the impact of PA duration on mobility and balance. This is especially true given the clear importance of PA intensity on these variables.

Future Research

The current study found associations between perceived intensity and superior postural control and gait performance; however, causation cannot be determined from the current findings. With this, previous research has found significant associations between interventions utilizing objective metrics of physical activity, such as accelerometry, VO_{2max}, and heart rate, and some, but not all, found improvements in functional outcomes.[83] These interventions were hypothesized to not provide enough time to elicit adequate induce neuroregeneration given the slowly evolving nature of nervous tissue.[115] Therefore, future work in this field should incorporate methodology from both the current project and previous work in a longitudinal randomized clinical trial to randomly assign participants singular and combinations of components from the current study (i.e., the addition of resistance training, yoga, and higher intensity PA). This activity should be measured using an objective measure of PA duration and intensity, such as using heart rate in conjunction with accelerometry, as well as incorporating a perceived self-report intensity metric to provide additional information on the resistance training, yoga and aerobic activity. Incorporating both methods (subjective and objective) of measuring PA intensity could also indicate which should be used in clinical settings based on whether one is more strongly linked to mobility in PwMS.

This work would provide insight into potential causation in regard to the associations found in the current study, with adequate study duration to elicit changes that are hypothesized to be seen with habitual performance of the activities. Additionally, this work would investigate whether combining these forms of PA, as recommended in PA guidelines,[25] would provide additional benefit relative to performing each type independently. Ultimately, a high-quality randomized control trial of this nature is necessary to identify optimal levels of PA necessary to provide long-term preservation of mobility, and to identify whether there is a point of diminished returns of PA to improve these outcomes in PwMS.

Despite the current evidence supporting the utility of performing high intensity PA to improve physical function in PwMS and neurotypical adults, emerging data continue to suggest that sedentary behavior is independently associated with several poorer outcomes, including poorer mobility in PwMS.[116,117] Therefore, the benefits of light PA should not be underestimated, particularly in a highly sedentary population like PwMS,[117,118] and an increasingly sedentary neurotypical population.[116] Instead, a clinical trial should strategically assign groups to higher intensity PA, either aerobic + RT and/or aerobic + yoga, alongside light PA to break up sedentary behaviors may provide the most optimal intervention to preserve mobility.

Conclusion

The literature continuously supports the use of PA as a method to improve a wide variety of outcomes for PwMS. This study investigated associations between specific variables of PA, as well as the impact of meeting the PA recommendations for the general population and PwMS, with gait and balance variables. This study found significant associations between PA intensity and type (RT) and balance and gait outcomes. These findings also suggest that while the 150 minute PA threshold may not be adequate to elicit a meaningful change in balance or gait speed, the intensity recommendations, as well as the inclusion of additional PA modalities like RT and yoga, may provide some benefit. The results of the current study are aligned with the emerging body of evidence suggesting that intensity of PA may be an important factor to improve balance and gait in PwMS and neurotypical adults, and that PA type, both RT and yoga, may be particularly impactful to improve functional outcomes in PwMS and neurotypical adults.

Overall, these associations should be revisited to identify causality utilizing both subjective and objective measures of PA duration, intensity, and more specific information regarding the modalities performed habitually. Additionally, research should shift focus away from general safety of high intensity PA interventions in PwMS, to identifying those who are not appropriate for these interventions, and how to properly administer these protocols safely to those who are. By incorporating these methods to clinical practice, both PwMS and neurotypical adults may have an improvement in balance and mobility outcomes.

FIGURES

Table 1. Participant demographics. Scores are mean ± SD and median (range).

	People with MS	Neurotypical Controls
N	24	21
Gender (M:F)	6:18	7:14
Age (years)	49 ± 12	47 ± 17
Height (cm)	165 ± 7	170 ± 8
Mass (kg)	68.2 ± 9.4	71.6 ± 12.8
BMI (kg·m^{-2})	25.2 ± 3.9	24.6 ± 3.1
EDSS	3.75 (0-4)	
Type of MS	Relapsing-Remitting (100%)	
MFIS	36.5 (0-59)	
MSWS-12	28.2 ± 24.8	

Table 2. Postural control and gait variables in participant groups. Values are mean + SD or median (range).

	People with MS	Controls
Mini-BESTest Total Score	22.5 (14-27)	26 (22-28)
Anticipatory Postural Control	5 (3-6)	6 (4-6)
Reactive Postural Control	4 (2-6)	6 (4-6)
Sensory Orientation	6 (4-6)	6 (5-6)
Dynamic Gait	7.5 (5-10)	9 (7-10)
Normal Gait Speed (m/s)	1.1 ± 0.2	1.3 ± 0.1
Fast Gait Speed (m/s)	1.4 ± 0.3	1.7 ± 0.2

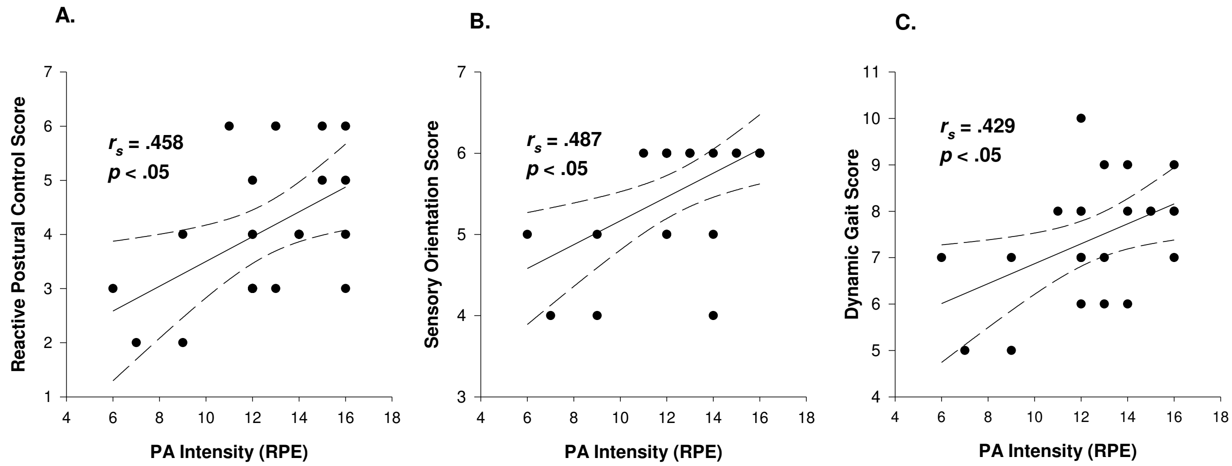

Figure 1. Associations between self-reported habitual PA intensity and A) reactive postural control, B) sensory orientation, and C) dynamic gait in PwMS. Spearman's correlation coefficient and significance displayed. Black points are PwMS scores.

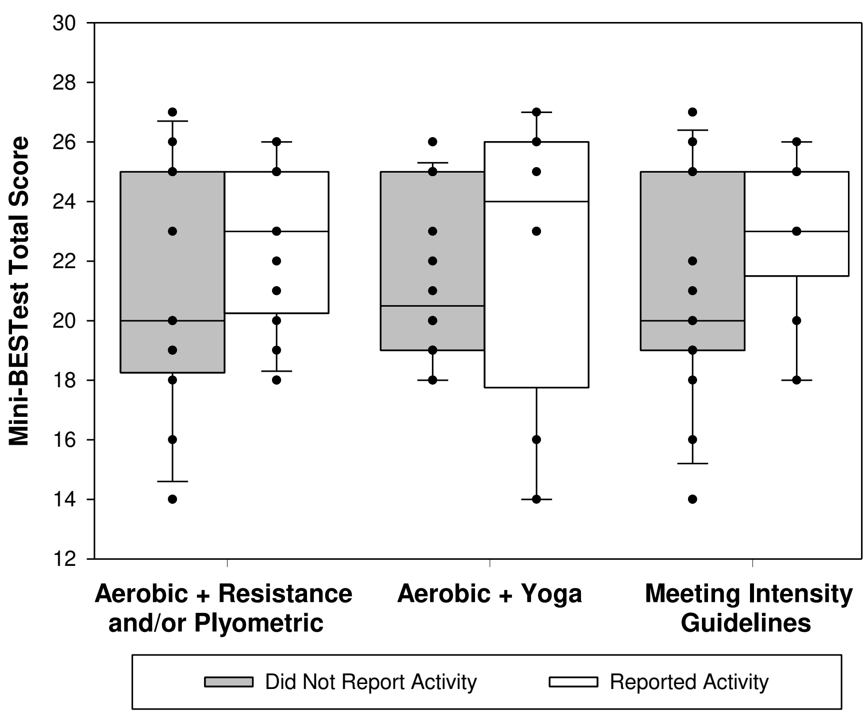

Figure 2. Box and whisker plots stratifying PwMS between participation in aerobic + R/P, aerobic + yoga, and higher intensity PA. Black points are participant scores.

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