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Randomized Controlled Trial of the Behavioral Intervention for Increasing Physical Activity in Multiple Sclerosis Project: Secondary, Patient-reported Outcomes

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Abstract
Background
We undertook a randomized controlled trial (RCT) that investigated the effectiveness of a theory-based, Internet-delivered, behavioral intervention focusing on physical activity promotion for immediate and sustained improvements in secondary, patient-reported outcomes (PROs) of function, symptoms, and quality of life (QOL) in multiple sclerosis (MS).

Method
Persons with MS (N = 318) were recruited from throughout the United States and randomized into behavioral intervention (n = 159) or attention/social contact control (n = 159) conditions. The conditions were administered over a 6-month period by persons who were uninvolved in screening, recruitment, random assignment, and outcome assessment. There was a 6-month follow-up period without intervention access/content. We collected PROs data every 6 months over the 12-month period. The PROs included validated measures of walking and cognitive function, symptoms of fatigue, depression, anxiety, pain, and sleep quality, and QOL. The data analysis involved a modified intent-to-treat approach using a linear mixed model in JMP Pro 16.0.

Results
There was a significant group by time interaction on Fatigue Severity Scale scores (p < .01) and physical subscale scores of the Modified Fatigue Impact Scale (p < .05). Scores on both measures decreased immediately after the 6-month period in the behavioral intervention compared with no change in the control condition, and this differential pattern of change was sustained over the 6-month follow-up. There were no group by time interactions on the other PROs.

Discussion
This study provides evidence for the effectiveness of a novel, widely scalable approach for physical activity promotion and fatigue management in persons with MS, yet this must be contextualized with the absence of improvements in the other PROs.

Keywords
Multiple sclerosis, Physical activity, Behavior change, Theory, E-learning

1. Introduction
There has been recent interest in the promotion of lifestyle physical activity (LPA) as a second-line approach for managing manifestations of neurological diseases including multiple sclerosis (MS). LPA involves the accumulation of physical activity through planned or unplanned leisure, occupational, or household activities as part of everyday life, and represents a public-health approach for managing manifestations of MS.

One avenue for promoting LPA involves the provision of behavioral interventions that teach skills, strategies, and techniques for behavior change based on a theory. We have developed, refined, and tested a behavioral intervention based on Social Cognitive Theory (SCT) and delivered through an Internet website for increasing LPA and improving secondary outcomes in persons with MS. Of note, one recently completed phase-II, randomized controlled trial (RCT) examined the efficacy of an Internet website that delivered a SCT-based behavioral intervention using e-learning approaches for increasing LPA and improving secondary, patient-
reported outcomes (PROs) over a 6-month period in persons with MS. There were positive intervention effects on self-reported and device-measured LPA as well as PROs measuring fatigue, depression and anxiety symptoms, walking mobility, and disability status. Such outcomes provided proof-of-principle evidence for designing a large, phase-III RCT testing the effectiveness of the same approach compared with an active control condition for immediate and sustained improvements in LPA and secondary effects on PROs and mediator variables based on SCT.

We undertook a phase-III, RCT that investigated the effectiveness of the aforementioned behavioral intervention for increasing LPA and improving secondary PROs among a large sample of people with MS residing throughout the United States. We reported in a separate, primary outcomes paper that this behavioral intervention yielded immediate and sustained improvements in device-measured and self-reported physical activity compared with a social-contact and attention control condition. The current paper focuses on secondary results regarding immediate and sustained effects on scores from validated PROs of walking and cognitive function, symptoms of fatigue, depression, anxiety, pain, sleep quality, and QOL. The focus on sustained effects on PROs was based on the theory-based, behavioral intervention yielding immediate improvements in LPA that were sustained over a six-month follow-up period. As reported in the protocol paper, we included PROs, rather than objective outcomes, as these measures account for change based on the perspective of persons with MS and further align with the nation-wide recruitment of the sample and collection of data without in-person laboratory visits.

2. Methods
2.1. Brief study overview
The study was funded by the National MS Society (RG 5144A6/1), registered on clinicaltrials.gov (NCT03490240), approved by an Institutional Review Board (IRB#170609001), and described completely in a protocol paper. The study involved a parallel group RCT design and enrolled 318 physically-inactive participants with MS who were randomly assigned into either behavioral intervention (n = 159) or attention/social contact control (n = 159) conditions using a computer-generated sequence with concealed allocation. The conditions were administered over six months and supported by behavioral coaches who were uninvolved in screening, recruitment, random assignment, and outcome assessments using a fidelity monitoring protocol. There was a six-month follow-up period wherein participants did not access the study website nor engage with the behavioral coaches. We collected outcomes every six months over the 12-month period (i.e., baseline, immediate follow-up, and 6-month follow-up). The outcomes of interest for this paper were validated PROs of walking and cognitive function, symptoms of fatigue, depression, anxiety, pain, and sleep quality, and physical and mental QOL, and these were administered in paper-pencil format with instructions consistent with the original validation research. The data analyses followed modified intent-to-treat principles using a linear mixed model in JMP Pro 16.0.

2.2. Participants
The sample was recruited from across the United States through electronic advertisements disseminated by the National MS Society. The advertisements described the study as comparing two approaches delivered through the Internet for managing consequences of MS. Those interested in participation contacted the project coordinator who described the study and its procedures, answered questions, and conducted a scripted screening for inclusion/exclusion criteria. The inclusion criteria were: (a) self-reported diagnosis of MS; (b) relapse free and no steroids in the past 30 days; (c) Internet and email access; (d) willingness to complete the questionnaires, wear the accelerometer, and undergo randomization; (e) not meeting current physical activity guidelines for MS (i.e., self-reported not engaging in regular physical activity on more than two days of the week during the previous six months); (f) ability to ambulate with or without a cane or walker; (g) age between 18 and
64 years; and (h) English as the primary language. The sole exclusion criterion was moderate or high risk for contraindications of strenuous or maximal exercise based on the Physical Activity Readiness Questionnaire\textsuperscript{15}. The participants meeting these inclusion criteria might represent a highly selective rather than representative sample of persons with MS.

Sample Size.

We conducted a power analysis for estimating the sample size for detecting a Condition (2 levels of between-subjects factor: Intervention vs. Control) × Time (3 levels of within-subjects factor: 0, 6, & 12 months) interaction on the primary study outcome of device-measured MVPA, but not the secondary PROs\textsuperscript{12}. The power analysis indicated that the minimum total sample size for testing the Time × Condition interaction on device-measured MVPA should be 240 participants. This supported our initial goal of recruiting 280 participants as yielding adequate power, based on an estimated retention of 85\% of the participants\textsuperscript{12}. Our actual recruitment yielded a sample of 318 persons with MS, exceeding this goal by 13.5\%; the oversampling was based on overcoming any possible effects of COVID-19 on study retention and outcomes.

2.3. Patient-reported outcomes

Demographic and Clinical Information. We captured demographic and clinical information from the participants using our standard laboratory questionnaire. The Patient Determined Disease Steps (PDDS) scale characterized the disability status of the sample\textsuperscript{16}.

Walking and Cognitive Function. Walking mobility was measured by the Multiple Sclerosis Walking Scale-12 (MSWS-12; \textsuperscript{17}). The MSWS-12 provides a 12-item, patient-reported outcome of walking impairment over the past two weeks. Cognitive function was assessed using the Perceived Deficits Questionnaire (PDQ; \textsuperscript{18}) and MS Neuropsychological Questionnaire (MSNQ; \textsuperscript{19}). The PDQ provides a self-report of cognitive dysfunction in MS and contains 20 items that measure perceived problems with memory, attention, and concentration over the past four weeks. The MSNQ is a self-administered questionnaire that contains 15 items and measures the frequency of experiencing problems with attention, processing speed, memory, and other cognitive functions during the past three months; we did not administer the informant report version of the MSNQ.

Symptoms. The symptoms of fatigue, depression, anxiety, pain, and sleep quality were measured by the Fatigue Severity Scale (FSS; \textsuperscript{20}), subscales of the Modified Fatigue Impact Scale (MFIS; \textsuperscript{21}), Hospital Anxiety and Depression Scale (HADS; \textsuperscript{22}), short-form McGill Pain Questionnaire (SF-MPQ; \textsuperscript{23}), and Pittsburgh Sleep Quality Index (PSQI; \textsuperscript{24}), respectively. We deliberately selected the FSS as an overall measure of fatigue based on its unidimensionality\textsuperscript{20}, whereas we purposefully selected the MFIS for examining domains of fatigue based on its multidimensionality\textsuperscript{21}. Indeed, the FSS is a nine-item unidimensional measure of overall fatigue severity during the past week in MS. The MFIS is a 21-item multidimensional measure of fatigue, including the three subcomponents of physical, cognitive, and psychosocial fatigue during the past four weeks. The HADS contains 14 items that measure the frequency of anxiety and depressive symptoms over the past week. The SF-MPQ has a 15-item adjective checklist that captures sensory and affective dimensions of pain experienced over the past week. The PSQI is a 19-item, self-rated questionnaire that yields a global score of sleep quality over the past month.

QOL. QOL was measured by the 36-item Short Form Health Survey (SF-36; \textsuperscript{25}) and the 29-item Multiple Sclerosis Impact Scale-29 (MSIS-29; \textsuperscript{26}). The SF-36 is a generic, 36-item measure of physical and mental components of health-related QOL over the past four weeks. The MSIS-29 is a disease-specific, 29-item measure of mental and physical domains of QOL over the past four weeks.
2.4. Procedures
The study procedures and conditions were described fully in protocol and fidelity monitoring papers\textsuperscript{12,14}. After initial screening, the project coordinator distributed the informed consent document through email or postal mail among participants who satisfied inclusion/exclusion criteria. This was followed by a phone call for ensuring participants received the document, understood the study and associated procedures, and signed the informed consent. Participants completed enrollment by returning a signed copy of this document.

Once enrolled, the project coordinator contacted participants and scheduled baseline data collection. The project coordinator sent a packet containing PROs and an accelerometer along with instructions via certified United States Postal Service (USPS) delivery. The project coordinator sent brief e-mails for reminding participants about completing the PROs and wearing the accelerometer in the middle of the seven-day period. This was followed by a phone call making sure that the participants completed the PROs and wore the accelerometer daily during the seven-day period and then returned the materials through the USPS using a pre-stamped and pre-addressed envelope.

After completion of the baseline assessment, participants were randomized into either an intervention (Behavioral Intervention for Physical Activity in MS; BIPAMS) or control (Wellness for MS; WellMS) condition using a computerized random-numbers generator with concealed allocation (i.e., opaque sealed envelopes) by a member of the research team uninvolved in delivering the intervention. The intervention/control conditions were delivered across a 6-month period in six waves of approximately 50 participants per wave. The participants completed the same measurement procedures immediately (i.e., immediate follow-up) and six-months (i.e., six-month follow-up) after the six-month intervention/control conditions, and there was no website access or chats during the six-month follow-up period. Participants received $50 USD remuneration per measurement period.

2.5. Data analysis
The data were entered into IBM SPSS Statistics 24 by trained laboratory personnel. The data were manually checked for accuracy and then examined for errors (e.g., out of range values) using frequency analyses in IBM SPSS Statistics 24.

We completed basic descriptive statistics when starting the data analysis process in IBM SPSS Statistics 24. We then undertook comparisons of participants in the two conditions using independent samples \( t \)-tests and chi-square analyses to identify any potential imbalances that may be considered for adjustment in subsequent analyses (i.e., covariates).

The main data analysis involved a modified intent-to-treat (ITT) approach with a linear mixed model in JMP Pro 16.0. The modified ITT involved using available data from only those who received the allocated conditions. The linear mixed model included condition and time as fixed effects, and subject nested within condition as a random effect using unbounded variance components and the REML method (https://www.jmp.com/content/dam/jmp/documents/en/academic/learning-library/08-repeated-measures-analysis-(mixed-model).pdf). The condition by time interaction was decomposed using least square means and Student's \( t \)-tests.

3. Results
3.1. Sample characteristics
The flow of participants through the study is reported in the CONSORT diagram in Fig. 1. The exact number of persons who received information about the study is unknown based on the electronic distribution of advertisements for recruitment. We screened 510 persons for eligibility, and 192 of them were excluded based on not meeting eligibility criteria or declining participation. The remaining 318 persons were randomly assigned
into BIPAMS \((n = 159)\) or WellMS \((n = 159)\), and 135 and 134 persons in BIPAMS (85% of those randomized) and WellMS (84% of those randomized), respectively, received the allocated intervention (i.e., modified ITT cohort). There were 128 persons in BIPAMS (5% dropout among those who received allocated intervention) and 129 in WellMS (4% dropout among those who received allocated intervention) who completed immediate follow-up testing. There were 124 participants in both BIPAMS and WellMS who completed 6-month follow-up testing (>96% retention).

Fig. 1. CONSORT diagram of participant flow through the randomized controlled trial.

The baseline sociodemographic and clinical characteristics of the overall sample \((N = 269)\) and subsamples per condition are documented in Table 1. There were no significant differences between conditions in age \((p = .97)\), sex \((p = .32)\), race \((p = .82)\), employment \((p = .59)\), marital status \((p = .83)\), or years of education \((p = .35)\). There further were no significant differences between conditions in disease duration \((p = .22)\), disability status \((p = .24)\), disease course \((p = .69)\), or disease-modifying therapy use \((p = .18)\). The median PDDS score, average duration of disease, and primarily RRMS disease course indicated that the sample largely consisted of relative early-stage MS with mild disability/disease status.

Table 1. Characteristics of participants overall and within BIPAMS and WellMS conditions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>BIPAMS</th>
<th>WellMS</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>48.8 (9.4)</td>
<td>48.8 (9.4)</td>
<td>48.8 (9.5)</td>
<td>(p = .97)</td>
</tr>
<tr>
<td>Sex, n/% female</td>
<td>237/87.8</td>
<td>122/90.4%</td>
<td>115/86.5%</td>
<td>(p = .32)</td>
</tr>
<tr>
<td>Race, n/% white</td>
<td>229/85.1%</td>
<td>117/86.7%</td>
<td>112/84.2%</td>
<td>(p = .82)</td>
</tr>
<tr>
<td>Employment status, n/% employed</td>
<td>172/63.9%</td>
<td>82/61.2%</td>
<td>90/67.2%</td>
<td>(p = .59)</td>
</tr>
<tr>
<td>Marital status, n/% married</td>
<td>168/62.4%</td>
<td>82/60.1%</td>
<td>86/64.2%</td>
<td>(p = .83)</td>
</tr>
<tr>
<td>Education, years</td>
<td>17.2 (1.9)</td>
<td>17.3 (2.0)</td>
<td>17.0 (1.9)</td>
<td>(p = .35)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>12.6 (8.8)</td>
<td>13.9 (8.7)</td>
<td>11.4 (8.8)</td>
<td>(p = .22)</td>
</tr>
<tr>
<td>PDDS, mdn (IQR)</td>
<td>2.0 (4.0)</td>
<td>2.0 (3.0)</td>
<td>2.0 (4.0)</td>
<td>(p = .24)</td>
</tr>
<tr>
<td>Disease course, n/% RRMS</td>
<td>226/84.0%</td>
<td>116/85.9%</td>
<td>110/82.1%</td>
<td>(p = .69)</td>
</tr>
<tr>
<td>DMT use, n/% using DMTs</td>
<td>240/89.2%</td>
<td>117/86.7%</td>
<td>123/91.8%</td>
<td>(p = .18)</td>
</tr>
</tbody>
</table>

Note: Values are mean scores (standard deviations) unless otherwise noted. There were no statistically significant differences in baseline scores between the conditions. BIPAMS, Behavioral Intervention for Physical Activity in Multiple Sclerosis. WellMS, Wellness for Multiple Sclerosis. DMT, disease-modifying therapy; PDDS, Patient-determined Disease Steps; RRMS, relapsing-remitting multiple sclerosis.
### 3.2. Patient-reported outcomes

The mean scores and standard errors for the PROs per condition over time are provided in Table 2. The baseline mean scores for the FSS and MFIS exceeded threshold values indicating significant or elevated symptom status in MS\textsuperscript{20,21,27}, whereas this was not the case for baselines scores on the other PROs whereby the mean scores were either below thresholds and/or within the lower portion of the range of scores for the scale\textsuperscript{18,19,22,23,24,25,26,28,29,30}.

Walking and Cognitive Function PROs. The linear mixed model did not identify statistically significant interactions between condition and time on MSWS-12 ($p = .83$), PDQ ($p = .45$), or MSNQ ($p = .89$) scores.

Symptoms PROs. The linear mixed model identified a statistically significant interaction between condition and time on overall FSS scores ($p < .01$) and physical subscale scores from the MFIS ($p < .05$), but not cognitive ($p = .39$) or psychosocial ($p = .46$) subscale scores from the MFIS. There was a statistically significant decrease in overall FSS score between baseline and the immediate follow-up ($\Delta-0.4$ [95% CI: $-0.2, -0.6$]) and baseline and the 6-month follow-up ($\Delta-0.3$ [95% CI: $-0.1, -0.5$]) for the BIPAMS conditions; there were no statistically significant changes over time for WellMS. The change in FSS scores for BIPAMS approached, but did not exceed, the minimally important difference (MID) value (i.e., 0.45 points on FSS) for a clinically relevant change in fatigue in MS\textsuperscript{31}. There further was a statistically significant decrease in physical subscale scores from the MFIS between baseline and the immediate follow-up ($\Delta-2.5$ [95% CI: $-1.4, -3.6$]) and baseline and the 6-month follow-up ($\Delta-1.4$ [95% CI: $-0.3, -2.5$]) for the BIPAMS conditions; there were no statistically significant changes over time for WellMS. This indicated immediate and sustained reductions in overall fatigue severity (Fig. 2a) and the physical impact of fatigue (Fig. 2b) in the BIPAMS condition, but not in the WellMS condition.
Table 2. Patient-reported outcome data for condition by time interaction tested using linear mixed model.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BIPAMS</th>
<th>WellMS</th>
<th>p-value for Condition by Time interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Immediate Follow-up</td>
<td>6-month Follow-up</td>
</tr>
<tr>
<td>Empty Cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSWS-12 (0–100)</td>
<td>38.1 (2.7)</td>
<td>39.3 (2.7)</td>
<td>39.4 (2.7)</td>
</tr>
<tr>
<td>PDQ (0–80)</td>
<td>29.2 (1.3)</td>
<td>30.0 (1.4)</td>
<td>29.7 (1.4)</td>
</tr>
<tr>
<td>MSNQ (0–60)</td>
<td>21.8 (1.0)</td>
<td>22.6 (1.0)</td>
<td>22.2 (1.0)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSS (1–7)</td>
<td>5.0 (0.1)</td>
<td>4.6 (0.1)</td>
<td>4.7 (0.1)</td>
</tr>
<tr>
<td>MFIS-Physical (0–36)</td>
<td>19.8 (0.8)</td>
<td>17.3 (0.8)</td>
<td>18.4 (0.8)</td>
</tr>
<tr>
<td>MFIS-Psychosocial (0–8)</td>
<td>3.7 (0.2)</td>
<td>3.2 (0.2)</td>
<td>3.5 (0.2)</td>
</tr>
<tr>
<td>MFIS-Cognitive (0–40)</td>
<td>17.2 (0.8)</td>
<td>15.6 (0.8)</td>
<td>15.3 (0.9)</td>
</tr>
<tr>
<td>HADS-Depression (0–21)</td>
<td>6.7 (0.4)</td>
<td>6.0 (0.4)</td>
<td>6.0 (0.4)</td>
</tr>
<tr>
<td>HADS-Anxiety (0–21)</td>
<td>5.9 (0.3)</td>
<td>5.4 (0.3)</td>
<td>5.2 (0.3)</td>
</tr>
<tr>
<td>MPQ-Short Form (0–45)</td>
<td>9.2 (0.7)</td>
<td>8.6 (0.7)</td>
<td>9.2 (0.7)</td>
</tr>
<tr>
<td>PSQI (0–21)</td>
<td>8.4 (0.3)</td>
<td>7.8 (0.4)</td>
<td>8.1 (0.4)</td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36, physical (0–100)</td>
<td>39.5 (1.0)</td>
<td>40.1 (1.0)</td>
<td>39.9 (1.0)</td>
</tr>
<tr>
<td>SF-36, mental (0–100)</td>
<td>46.3 (1.0)</td>
<td>47.0 (1.0)</td>
<td>47.0 (1.0)</td>
</tr>
<tr>
<td>MSIS-29, physical (0–100)</td>
<td>31.6 (1.9)</td>
<td>28.8 (2.0)</td>
<td>31.8 (2.0)</td>
</tr>
<tr>
<td>MSIS-29, mental (0–100)</td>
<td>32.4 (1.8)</td>
<td>28.5 (1.8)</td>
<td>28.4 (1.9)</td>
</tr>
</tbody>
</table>

Note. Values are least square means (standard error). BIPAMS, Behavioral Intervention for Physical Activity in Multiple Sclerosis. WellMS, Wellness for Multiple Sclerosis; MSWS-12, 12-items Multiple Sclerosis Walking Scale; PDQ, Perceived Deficits Questionnaire; MSNQ, Multiple Sclerosis Neuropsychological Questionnaire; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; HADS, Hospital Anxiety and Depression Scale; MPQ, McGill Pain Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SF-36, 36-item Short Form Survey; MSIS-29, 29-item Multiple Sclerosis Impact Scale.
4. Discussion

We undertook a RCT that examined the effectiveness of a behavioral intervention based on SCT and delivered through the Internet using e-learning approaches for immediate and sustained increases in LPA and secondary improvements in PROs of function, symptoms, and QOL among physically inactive persons with MS residing throughout the United States. Our primary outcomes paper reported immediate and sustained increases in a comprehensive battery of physical activity outcomes, including minutes/day of MVPA and steps/day measured using accelerometry. There further was high compliance with the conditions, low dropout, and few adverse events. The current paper examined secondary intervention effects on PROs of function, symptoms, and QOL, and we observed immediate and sustained reductions in overall fatigue severity and the physical impact of fatigue for the behavioral intervention compared with minimal changes in those outcomes for the social contact/attention control condition. The change in fatigue scores were not considered clinically meaningful based on only approaching, but not exceeding MID value for FSS; we could not locate a MID for MFIS subscale.
scores in MS. Importantly, there were no statistically significant changes in the other PROs, and this might suggest a negative study and the need for other interventions that target self-reported function, symptoms of depression, anxiety, and sleep, and QOL in MS. Overall, our results provided evidence for the effectiveness of a novel, widely scalable approach for immediate and sustained increases in LPA and secondary improvements in perceived fatigue among persons with MS, but this should be balanced by the lack of changes in the other PROs.

The primary novel finding in this paper was that of immediate reductions in overall fatigue severity and the physical impact of fatigue that were sustained over time for the behavioral intervention. Importantly, the immediate reduction in those measures of fatigue was consistent with the efficacy data provided in our initial Phase II RCT. We note, however, that the lack of change in PROs of depression, anxiety, and walking mobility was inconsistent with the efficacy data provided through our initial Phase II RCT. There are several likely explanations for the observed pattern of results regarding the PROs. The first explanation is that reductions in fatigue represent a consistent, robust and clinically meaningful outcome reported in the existing research examining benefits of exercise training and physical activity in MS. The second explanation involves baseline scores whereby only scores for fatigue outcomes were elevated in the baseline data, and perhaps there were floor effects for the other PROs. The third explanation is that fatigue was not targeted in the content of the social contact/attention control condition (WellMS), and therefore we were able to detect a significant condition by time interaction on this outcome and demonstrate reductions in fatigue with the behavior intervention. The fourth explanation is that the current study was powered for detecting a change in the primary outcome of minutes/day of device-measured MVPA, and therefore underpowered for detecting changes in other PROs of function, symptoms, and QOL. The final explanation is that the PROs of walking and cognitive function, symptoms of depression, anxiety, pain, sleep quality, and QOL require other, focal interventions for yielding improvements in scores. Nevertheless, the increase in LPA combined with the reduction in fatigue that were maintained over time may provide a basis for the future application of behavioral interventions for managing outcomes, particularly fatigue, in samples with MS who have elevated symptom expression. This is important considering that fatigue is prevalent and burdensome in MS, and currently incompletely managed through pharmacological interventions, whereas psychological interventions do have effects on fatigue, but often involve energy conservation as an approach for fatigue management that may be counter-productive for increasing LPA and yielding its health benefits.

We included a large, comprehensive set of PROs for capturing perceived changes in function, symptoms, and QOL with the behavioral intervention targeting LPA. We did so as the current RCT included an active control condition that accounted for social contact and attention as well as receipt of meaningful content. This control condition therefore permitted a strong, RCT design for examination of changes in LPA and scores from a comprehensive battery of secondary PROs. Nevertheless, this design and the large number of PROs might have resulted in a null intervention effect for many of the PROs. The logic is based on the inclusion of too many PROs obscuring the capture of intervention effects based on survey fatigue. Such an observation combined with lower scores on baseline PROs measures indicates that future research might directly examine the effectiveness of this behavioral intervention for improving focal outcomes within a sample that is recruited and prescreened for a problem of interest. We note that this has been undertaken in a RCT of LPA for improving restless leg syndrome (RLS) and sleep outcomes using the same behavioral intervention. That RCT reported behavioral intervention effects on RLS severity and self-reported sleep quality compared with control in a sample of persons with MS who had a diagnosis of RLS and moderate-to-severe RLS symptomology. On the other hand, such focal research may be complicated by the heterogeneous nature of MS and its manifestations, and this perspective would imply that future research focus on a population of interest with a focal problem and examine secondary effects on other symptomatic outcomes.
There are notable limitations of this research. The intervention content was only available in English and therefore is not currently transferable into non-English speaking persons with MS or countries. We only collected follow-up data for 6-month post-intervention cessation, and this might be considered a medium-term rather than long-term outcome for examining changes in PROs of function, symptoms, and QOL\textsuperscript{11}. We only included PROs of secondary outcomes, and perhaps these measures were not as sensitive for capturing behavioral intervention effects compared with objective, neuro-performance measures. The time-frame for reporting further varied across the PROs. We did not capture information on the exact medications taken by participants, and therefore could not control for medications in the analysis of study outcomes; the same limitation exists for rehabilitation approaches that can influence study outcomes. The sample was recruited broadly from across the United States, and some persons lived in warmer, or cooler, environments that might have influenced the study outcomes. We lastly did not power the study a priori for capturing changes in PROs, but rather for detecting change in minutes/day of device-measured MVPA.

This RCT tested the effectiveness of a behavioral intervention\textsuperscript{12,13,14} for increasing LPA and secondarily improving scores on PROs that align with common manifestations of this disease among a large sample of people with MS residing throughout the United States. The primary result indicated an immediate and sustained effect of the behavioral intervention on overall fatigue severity and the physical impact of fatigue, yet there were no changes in other PROs. Such research presents a significant and substantial advancement in the study and management of fatigue through the promotion of LPA behavior change for persons with MS. Subsequent research might further evaluate intervention effects on other outcomes by enrolling samples with elevated baseline scores and/or including a smaller, focal battery of PROs along with objective assessments. There may be further value in directly examining the effects of the WellMS condition as credible treatment for outcomes in MS, as this condition aligns with an electronic delivery of wellness-related content for MS.

**Declaration of Competing Interest**

We report no financial conflicts of interest with the research reported in this paper.

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**Data availability**

Data will be made available on request.

**References**