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Identifying Factors to Inform the Development of Adaptive Interventions for Increasing Physical Activity Behavior Among People with Multiple Schlerosis

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IDENTIFYING FACTORS TO INFORM THE DEVELOPMENT OF ADAPTIVE INTERVENTIONS FOR INCREASING PHYSICAL ACTIVITY BEHAVIOR AMONG PEOPLE WITH MULTIPLE SCLEROSIS

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ABSTRACT

People with multiple sclerosis (MS) can benefit from physical activity, specifically exercise, for the management of disease symptoms, including walking impairments, fatigue, and depression, and improvements in quality of life. However, people with MS do not engage in adequate amounts of physical activity for the accrual of health benefits. Researchers have focused on the delivery of exercise training and behavioral interventions to improve levels of physical activity in MS. To date, there is an emerging body of research supporting the efficacy of these interventions for increasing and potentially sustaining physical activity behavior in people with MS. Yet, people with MS often have varying rates of physical activity change after completion of these programs. For example, some individuals can experience large improvements in physical activity, whereas others may demonstrate no change or even a decrease in physical activity. Reasons for these differences may include certain participant-specific characteristics, such as MS type, disease severity, knowledge, efficacy, goals, and perceived barriers to exercise. Collectively, this affirms the importance of identifying targets for tailored programs (i.e., delivery methods, intervention strategies) for people with MS.

We identified factors that influenced participants' response to the interventions using quantitative and qualitative methods. Interventions for physical activity promotion in MS should be tailored and targeted based on specific participant characteristics, perhaps theory-based constructs (e.g., goal setting), to provide differentiated levels and types of support, such as a self-directed exercise program or one-on-one behavioral coaching. Furthermore, interventions should incorporate various support methods for engagement (e.g., autonomous, one-on-one, group exercise sessions), self-regulatory strategies (e.g., reporting and monitoring progress via email, app), and long-term engagement (e.g., post-intervention resources). Overall, these findings can help clinicians and researchers in the design of optimized program and intervention strategies to increase and sustain exercise and physical activity participation in people with MS.

Keywords: exercise, physical activity, health behavior, multiple sclerosis

DEDICATION

I would like to dedicate my work to God and to my family, who supported me with endless prayers.

Do not be anxious about anything, but in everything, by prayer and petition, with thanksgiving, present your requests to God. And the peace of God, which transcends all understanding, will guard your hearts and your minds in Christ Jesus.

(Philippians 4: 6-7)

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I must thank my parents for the tremendous support that I have been provided throughout my academic career. This support allowed me to pursue a career and field of interest that I am truly passionate about. Their endless belief and prayers for me truly raised me up to be more than I otherwise could have been. My dear friends and colleagues also require special acknowledgment. I have been blessed with caring friends who are always there in times of need. They held my hands, ensuring my stable mental health throughout these stormy years. Most importantly, I would like to thank all the participants of the studies involved within this dissertation.

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LIST OF ABBREVIATIONS

CAM	Complementary and alternative medicine
GLTEQ	Godin Leisure-Time Exercise Questionnaire
MET	Metabolic equivalent of task
MVPA	Moderate to vigorous physical activity
MS	Multiple sclerosis
PDDS	Patient Determined Disease Steps
SCT	Social cognitive theory
TEAMS	Tele-Exercise and Multiple Sclerosis

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated, neurodegenerative disease of the central nervous system.[1] An estimated 1.1 million adults live with MS in the United States and 2.5 million adults live with MS worldwide.[2] MS results in heterogeneous outcomes, including mobility and cognition dysfunction and symptomatic fatigue, pain, and depression,[3] which can further compromise quality of life and participation in activities of daily living.[4, 5] In addition to traditional medical care, exercise training (as part of physical activity) has been identified as a primary therapeutic measure for long-term management of the disease progression and associated manifestations .[6-8] The common benefits from exercise participation can include improvements in walking ability,[9] disease symptoms (e.g., fatigue, depression),[10-12] and quality of life.[13]

Despite these benefits, people with MS do not engage in adequate amounts of exercise for accruing the benefits of this health behavior. This corresponds to consistent trends of lower levels of physical activity in people with MS than the general population and adults with other health conditions.[14-16] People with MS often encounter numerous barriers that prevent their exercise and physical activity participation in their community. These barriers range from the personal level (e.g., fatigue, fear, and lack of knowledge, self-regulation skills, and social support) to institutional and community levels (e.g., lack of accessible facilities/options, knowledgeable instructors, or transportation).[17] These barriers make it much more challenging for people with MS to reach the U.S. public health guideline for exercise (150 minutes/week of moderate to vigorous physical activities).

Researchers have addressed the problem of physical inactivity through the delivery of exercise training and behavioral interventions (alone and combined). To date, there is an emerging body of research supporting the efficacy of these interventions for increasing and potentially sustaining physical activity behavior in people with MS.[6, 18, 19] Programs supported by information communication technology (i.e., tele-exercise) have further enabled healthcare providers to deliver more cost-efficient and convenient options than programs offered in the community (e.g., no travel time and transportation), making it easier to reach larger groups of people with MS.[18, 20] Yet, people with MS often have varying rates of success after a standardized program (i.e., response heterogeneity).[21] In other words, some individuals can experience large improvements in physical activity after an intervention, while others may demonstrate no change or even a decrease in physical activity.[22-24] Reasons for these differences could include disease-related factors (e.g., MS type, disease severity, symptomology) and certain participant-specific characteristics, such as knowledge, efficacy, outcome expectations, goals, and perceived barriers to exercise.[22-26] Collectively, these findings affirm the importance of understanding the response heterogeneity associated with change in physical activity for optimizing the "fit" of an intervention for maximizing treatment efficacy in people with MS.

Adaptive intervention design can guide researchers to provide targeted and tailored treatments depending on participant characteristics and needs while maintaining scientific rigor.[27] An example of adaptive intervention design is presented in Figure 1. The benefit of this design is to operationalize modifications (i.e., how, when, and based on which measure to alter treatment, called *tailoring variables*) before executing the intervention so that participants are systematically allocated to the same or different intervention group based on their treatment response and adherence to the program.[28] The *tailoring variables* can be identified through (a) established theoretical framework in the field; (b) review/synthesis of evidence from prior research literature (e.g., meta-analysis when a large body of literature is available); (c) the key individual or group characteristics that influence different responses to treatment adherence and outcome in a fixed treatment (secondary data analysis); and (d) gathering information from other sources (e.g., experts' opinion, interview/focus group of population of interest).[28, 29] The design has been applied to interventions that target both physiological and behavioral responses, such as weight management,[30-32] drug abuse,[33, 34] and depression.[35, 36] To our knowledge, adaptive intervention design has not been used for research studies of people with MS.

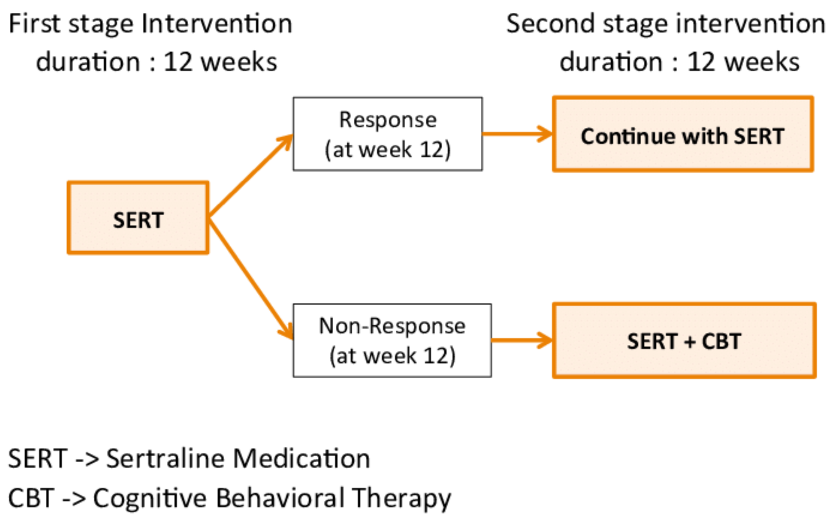

Figure 1. An example of adaptive intervention design for patients with pediatric anxiety disorder

Project Summary

This dissertation aimed to provide a quantitative synthesis of the immediate (post-intervention) and sustained effects (follow-up) of exercise training programs and behavioral interventions for changing physical activity in people with MS. We further explored factors that influenced treatment response that can help researchers optimize the program and its implementation strategies, especially for designing an *adaptive intervention*, aimed at promoting increased and sustained exercise and physical activity behavior. First, we undertook a meta-analysis of randomized controlled trials (RCTs) that targeted change in physical activity behavior and explored factors that might moderate intervention effects on physical activity behavior (e.g., intervention type and duration, type of physical activity measurement, degree of theory used in study design).

Second, we performed a secondary analysis of data from a pragmatic, cluster RCT, referred to as the Tele-Exercise and Multiple Sclerosis [TEAMS] study,[37] that targeted improvements in fatigue, pain, quality of life, and physical activity. Among the TEAMS study participants who completed a tele-exercise condition, we explored social cognitive theory (SCT) variables (i.e., self-efficacy, outcome expectations, goal setting) to predict the treatment response in physical activity level (i.e., active vs. moderately/insufficiently active) at the end of the intervention and follow-up. This can help interventionists tailor a treatment regimen based on SCT variables that can be obtained during an early stage of the intervention and provide differentiated levels of types of support (e.g., self-directed exercise program vs. intense program with behavioral coaching).

Third, we conducted a qualitative study to explore the experiences and perceptions of program components and implementation procedure among participants in the tele-exercise condition of the TEAMS study. This can inform future intervention strategies during and after the intervention period with specific implications for the tele-exercise program. To better understand response heterogeneity in people with MS, we explored potential differences in experiences and perceptions among two groups of participants, *responders* and *low-/non-responders*, based on the rate of success after the intervention (i.e., change in physical activity level).

Specific Aims

Aim 1: A meta-analysis of RCT interventions that aimed to increase physical activity behavior among people with MS.

1a. To examine the immediate (pre- to post-intervention) and sustained effects (pre-intervention to follow-up) of interventions for changing physical activity behavior (exercise training and/or behavioral interventions).

1b. To explore factors that might moderate intervention effects on physical activity behavior (e.g., intervention type and duration, type of physical activity measurement, degree of theory used in study design).

Aim 2: A secondary analysis of data from a large, cluster RCT intervention that targeted improvements in fatigue, pain, quality of life, and physical activity for people with MS.[37] This exploratory analysis included 377 people with MS who completed a 3-month tele-exercise program and three data points: baseline, 3-month follow-up (post-intervention), and 6-month follow-up.

2a. To examine the associations between SCT variables (self-efficacy, outcome expectations, goal setting) and self-reported physical activity level, using Godin Leisure-Time Exercise Questionnaire (GLTEQ).

We expected positive correlations between (a) baseline SCT variables and physical activity at 3-month follow-up (post-intervention) and (b) 3-month SCT variables and physical activity at 6-month follow-up.

2b. To explore baseline SCT variables as predictor of physical activity level at 3-month and 3-month SCT variables as predictor of physical activity at 6-month.

Aim 3: A qualitative description of the different experiences and perceptions of two groups of TEAMS participants (*responders* vs. *low-/non-responders*) who completed a 3-month TeleCAM intervention, regarding program components and implementation procedures (i.e., exercise videos, educational articles, automated communication system). *Responders* had a clinically meaningful increase in their level of physical activity after the formal intervention period. *Low- and non-responders* were people who reported no change to minimal change or a decrease in their level of physical activity.

IMMEDIATE AND SUSTAINED EFFECTS OF INTERVENTIONS FOR CHANGING PHYSICAL ACTIVITY IN PEOPLE WITH MULTIPLE SCLEROSIS: META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

by

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ABSTRACT

Objectives: To examine the immediate and sustained effects of interventions for changing physical activity behavior in people with multiple sclerosis (MS), and explore factors that might moderate intervention effects on physical activity behavior (e.g., intervention type and duration, type of physical activity measurement, intensity of theory integration [degree of theory used in study design], and study quality).

Data Sources: Systematic searches were conducted in four databases, including MEDLINE, CINAHL, PsychINFO, Google Scholar, in October 2017 and October 2018. Updated searches were conducted in September 2019 with two additional databases (Embase and Scopus) and enhanced search terms.

Study Selection: Studies were included that (1) incorporated a randomized controlled trial design of interventions that targeted change in physical activity behavior in adults with MS, namely, exercise training and behavioral intervention (alone and combined); (2) included self-reported and/or device-measured physical activity as an outcome; and (3) contained pre-post assessments.

Data Extraction: Data were extracted for immediate (pre- to post-intervention) and sustained (pre-intervention to follow-up) physical activity outcomes and study characteristics. Weighted mean effect sizes were expressed as standardized mean differences (SMD). Heterogeneity between each categorical moderator was compared using Q between statistics.

Data Synthesis: The mean SMD was 0.56 for immediate changes (*n*=24) and 0.53 for sustained changes (*n*=7) of physical activity outcomes. Self-reported physical activity measures yielded larger effects (SMD = 0.64; *n*=22) than those of device-measured physical activity (0.26; *n*=7). There appeared to be larger immediate effects of behavioral interventions (SMD = 0.71; *n*=9) than exercise training (0.53; *n*=7) and combined interventions (0.37; *n*=8).

Conclusions: Current evidence demonstrates that interventions are efficacious for increasing and potentially sustaining physical activity behavior in adults with MS. The effects appear optimized based on the delivery of behavioral interventions alone, and these interventions may be capable of supporting long-term behavior change.

Keywords: Multiple sclerosis, Rehabilitation, Physical activity, Behavior change theory, Sustainability

INTRODUCTION

Multiple sclerosis (MS) is a prevalent, immune-mediated disease of the central nervous system that results in demyelination and transection of axons in the brain, brain stem, optic nerves, and spinal cord.[1] The extent and location of damage within the central nervous system result in heterogeneous outcomes including walking and cognitive dysfunction and symptomatic fatigue, pain, and depression.[2] MS and its consequences can further compromise participation in activities of daily living and health-related quality of life.[3,4]

Participation in physical activity, including exercise training, has gained acceptance as a non-pharmaceutical, behavioral approach for managing or alleviating many consequences of MS.[5,6] This is based on meta-analyses indicating beneficial effects of physical activity on walking,[7] fatigue,[8] depression,[9,10] and indices of quality of life.[11] There may be additional benefits of physical activity for modifying the disease itself[12] as well as reducing the rate of relapses[13] and cardiovascular comorbidities.[14]

Nevertheless, persons with MS engage in less physical activity than those from the general population.[15-17] This is supported by a meta-analysis indicating a lower level of physical activity participation in people with MS than adults without conditions or disorders (mean effect size = –1.00).[17] One study has demonstrated that fewer than 20% of people with MS meet the recommended guideline for moderate-to-vigorous physical activity.[16] These data indicate that the majority of people with MS do not engage in sufficient levels of physical activity necessary for accruing benefits of this health behavior.

The persistent problem of physical inactivity in persons with MS has been addressed through the delivery of exercise training programs or behavioral interventions (alone and combined).[18] The behavioral interventions, in particular, might enhance the effects of interventions on long-term physical activity behavior (i.e., sustainability).[19-21] These interventions typically teach behavior change techniques such as self-monitoring, goal-setting, and feedback that align with thoery.[22] To date, meta-analyses have reported that behavioral interventions could increase physical activity behavior,[23,24] but the immediate and, in particular, sustained effects were estimated from a small number of carefully selected studies, and this hindered sub-analyses of potentially influential intervention characteristics. Accordingly, there are a number of unknown features regarding the effects of interventions on changes in physical activity. For example, are behavioral interventions alone sufficient to elicit immediate and sustained changes in physical activity behavior, or do behavioral interventions need to be supplemented with exercise training? Does the degree of integrating a behavioral change theory within an intervention (i.e., intensity of theory integration) moderate changes in physical activity behavior? The idea of theory integration involves the degree of theory used in the intervention design, delivery, and evaluation, and can range from sparse through extensive.[25] To that end, performing a meta-analysis with carefully selected moderators can help interventionists identify optimal strategies for increasing and sustaining physical activity behavior in people with MS.

We undertook a meta-analysis of randomized controlled trials (RCTs) that provided a quantitative synthesis of the immediate and sustained effects of exercise training programs and behavioral interventions (alone and combined) for changing physical activity in people with MS. The meta-analysis focused on two separate time-phases, namely (1) post-intervention (immediate effects) and (2) follow-up (sustained effects). We further explored factors that might moderate intervention effects on physical activity behavior, including intervention characteristics (type and duration), type of physical activity measurement, intensity of theory integration, and study quality.

METHODS

This meta-analysis followed the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[26] Using systematic review procedures, intervention studies that reported changes of physical activity behaviors in people with MS were identified, reviewed, and synthesized from six electronic databases: MEDLINE, CINAHL, PsychINFO, Embase, Scopus, and Google Scholar. The protocol registration was not performed before commencement.

Search strategy

We conducted initial searches of four electronic databases (i.e., MEDLINE, CINAHL, PsychINFO, and Google Scholar) on October 3, 2017, from the period of July 1963 (i.e., inception date) through September 2017. The searches were updated on October 31, 2018 (until September 2018). The three categories of search terms were used, namely, interventions (e.g., *exercise*, *physical activity, or behavior*), outcomes (e.g., *health behavior* or *physical activity*), and disability (*Multiple sclerosis* or *MS*). We conducted an updated search on September 19, 2019 (until September 2019) to identify papers and reports that could have potentially been published during the preparation of this paper for submission. The searches were enhanced with two additional databases (i.e., Embase and Scopus) and a broader list of searching terms: interventions (e.g., *exercise*, *physical activity, behavior therapy, or health promotion)*, outcomes (e.g., *health behavior, physical activity, or accelerometry/actigraphy*), and disability (*Multiple sclerosis* or *MS*). We provided examples of the MEDLINE searches in Appendix I.

Eligibility criteria

Studies were deemed eligible based on the following criteria: (1) included adults with MS (18 years of age or older); (2) incorporated RCT designs of interventions that targeted change in physical activity behavior (structured exercise training, behavioral intervention, or both); (3) included self-reported and/or device-measured physical activity; (4) contained a pre- and post-assessment period; and (5) published in English within peer-reviewed journals.

Studies were excluded based on the following criteria: (1) non-research publications (i.e., conference presentations, study protocol, dissertations); (2) therapeutic and/or pharmaceutical interventions that required the assistance of a licensed therapist or devices (e.g., robotic/body-weight support gait training, constrain-induced movement therapy, functional electrical stimulation); and (3) insufficient information for calculating effect size (ES) regarding physical activity outcome measures. Self-reported outcomes that included a broad aspect of health and well-being were only included when the subcategory of physical activity score was reported separately (e.g., Health-Promoting Lifestyle Profile II). Device-measured physical activity outcomes that were obtained within the intervention itself (i.e., session attendance) were not included in this meta-analysis, as we were interested in behavior change rather than compliance.

Screening process/Data extraction

The search terms were developed through interactions with a librarian and further resulted in electronic search strings per database. We refined the search criteria for generating a broader search and better representing the literature, thereby yielding a more reliable estimate of the overall effect of interventions on physical activity behavior change. The primary analyst conducted searches of the electronic databases and narrowed the search results based on the eligibility criteria of this review (e.g., human subject research, RCTs). After retrieving the studies, two analysts (primary and secondary) independently performed the screening process. This process included the following steps: (1) removed duplicate studies; (2) screened all studies at the abstract level; (3) reviewed the remaining studies in the full-text level; (4) assessed methodological quality of included studies; and (5) evaluated the intensity of theory integration of the intervention design (if applicable). Disagreements were resolved by a senior author. The senior author independently assessed a study and determined the final decision for inclusion/exclusion of the study in the meta-analysis and intensity of theory integration.

Data extraction processes were performed by the primary analyst, and the extracted data were cross-checked for accuracy by the secondary analyst. Data were organized into two spreadsheets: (1) participant and intervention characteristics using the PICOTS framework (i.e., Population, Intervention, Comparator, Outcome, Timing, Setting) and (2) physical activity outcomes. The participant characteristics included age, sex, type of MS, disease severity, and time since diagnosis. The intervention characteristics consisted of program/training prescription (frequency, intensity, time, and type), duration of the intervention (weeks from pre- to post-assessment) and follow-up (weeks from post- to follow-up assessment), and name(s) of behavior change theory applied to frame and deliver the intervention. The physical activity outcome included name and type of measure (self-reported/device-measured), sample size (pre to post/pre to follow-up), mean and standard deviation (SD) of pre-, post-, and any follow-up data for both intervention and control groups.

Moderator variables

Intervention type Intervention type was categorized into three levels: behavioral intervention, exercise training, or combined. Behavioral interventions were operationally defined as based on inclusion of behavior change techniques informed by theory for changing behavior.[22] Exercise training studies were defined as the delivery of structured and planned physical training. Studies that utilized both behavioral intervention and exercise training were categorized as *combined*. We explored the *intervention type* as a moderator of possible variability in the effect of intervention types on change in physical activity.

Intervention duration Intervention duration was categorized into two levels: interventions equal or less than 12 weeks (≤ 12 weeks) or more than 12 weeks (> 12 weeks). The levels were determined based on moderator analyses of a previous meta-analysis.[24]

Type of physical activity measurement Type of physical activity measurement was categorized into two levels: self-reported (questionnaire) and device-measured physical activity (e.g., accelerometry). We explored the *type of physical activity measurement* as a moderator to see whether or not the magnitude of physical activity behavior change differs based on the presumption of larger effects with self-reported than device-measured physical activity.

Intensity of theory integration Theory integration informs the degree of theory included in the study design, delivery, and evaluation (i.e., sparse through extensive). The intensity of theory integration was evaluated using a modified version of the Theory Coding Scheme.[25,27] The modified version differs from the original in that it emphasizes the identification of theory, constructs, and specific methods related to theory measurement and evaluation in the intervention design, and excludes nonrelevant items (e.g., evaluation of how the study results might be used for refining theories). The coding scheme was previously applied to evaluate the magnitude of the theory application of physical activity interventions among breast cancer survivors.[25] The coding consisted of eight items, rated as present or absent of application, with a range of scores between 0 and 8. The intensity of theory application was classified and interpreted as followings: Level 1 (sparse) if 3 or fewer items were satisfied, Level 2 (moderate) if 4 to 5 items were satisfied, or Level 3 (extensive) if 6 or more items were satisfied.[25] Higher scores reflect greater inclusion of theory in the design, delivery, and evaluation of a study and its effects on physical activity behavior change. We explored the *intensity of theory integration* as a moderator based on the presumption that more intense inclusion of theory in informing the intervention would yield larger changes in physical activity.

Study Quality The methodological quality of each study was assessed using the Physiotherapy Evidence Database (PEDro) scale.[28] The PEDro scale has a maximum possible score of 10 points. Two items (blinding of therapists/trainers and blinding of subjects) were considered as not applicable in rehabilitation research when comparing an intervention group with a non-training control group. Therefore, these two items of each study were credited.[29,30] A higher score indicates better methodological quality. The methodological quality of each study was then categorized into two levels using the Spinal Cord Injury Rehabilitation Evidence system.[31] This is a 5-level system that distinguishes between studies of differing quality and incorporates the types of research designs commonly used in rehabilitation research (Appendix II). This system has been applied in several systematic reviews and meta-analyses in the field of MS research.[30,32-34] The level of the evidence within RCTs was interpreted as Level 1 if the PEDro score is > 6 and Level 2 when the score is ≤ 6.[31] We added *study quality* as a moderator to explore whether or not the quality of studies influence the effects of the interventions. For example, low-quality studies may yield larger effects with high chances of bias than high-quality studies.

Data analysis

The mean ES was computed using a random effect model based on the assumption that the samples of the selected studies represent the population and that the true effects differ between studies[35] and adjusted by sample size using the Comprehensive meta-analysis software.[a] The weighted mean ESs were expressed as standardized mean differences (SMD), which is often referred to as Cohen's *d*. SMD was calculated based on the mean change of physical activity outcomes from before and after the intervention minus the mean change of the control group. The mean changes between the two groups were then divided by pooled change score SD of intervention and control groups. A positive SMD indicated an improvement in physical activity behavior after intervention (favors intervention), whereas a negative SMD represented a worsening of physical activity behavior in the intervention group compared to controls (favors control). The ES was interpreted according to Cohen's benchmarks[36]: small, SMD of 0.20; medium, SMD of 0.50; and large, SMD of 0.80. We further computed a 95% confidence interval (CI) around the mean ES. CI excluding zero were considered statistically significant. The interpretation of analyses accounted for statistical significance as well as clinical meaningfulness based on the guideline of ½ SD (i.e., Cohen's *d* of 0.5); this guideline of ½ SD has been deemed as a universal threshold for judging effects as clinically meaningful.[37]

When a study used two intervention groups (two different types of exercise) and one control group, we created a mean ES in that study by averaging the ESs estimated from these groups. This process included the following steps: (1) assign subgroups (i.e., Exercise 1 and Exercise 2) within the study; (2) compute data (i.e., sample size, mean, and SD) of each subgroup; (3) compute data of control group more than once; (4) create two ESs estimated from each subgroup (i.e., the mean ESs of Exercise 1 vs. Control and of Exercise B vs. Control); (5) average the ESs estimated from these groups and then create a mean ES in that study. The variance of the averaged ESs was corrected by the software[a] to account doubled sample size of the control group.[35,38] When a study had multiple physical activity outcomes within a study, based on the same participants, we created a mean ES per study by averaging the ESs estimated from these outcomes. This process included the following steps: (1) compute data of each outcome; (2) create multiple ESs estimated from each outcome (e.g., accelerometry, GLTEQ); (3) average the ESs estimated from these outcomes and then create a mean ES in that study. The multiple ESs from the same study are assumed to be not independent among the different groups and outcomes.[35,38]

The analyses were conducted separately for the two-time phases: (1) immediate (pre-post) and (2) sustained (pre-follow-up) physical activity outcomes. We further performed moderator analyses of each time phase for the physical activity outcomes. The moderators were the intervention type (behavioral intervention vs. exercise training vs. combined), the intervention duration (≤ 12 weeks vs. > 12 weeks), the type of physical activity measurement (self-reported vs. device-measured), the intensity of theory integration (Level 1 vs. Level 2 vs. Level 3), and study quality (Level 1 vs. Level 2).

To estimate heterogeneity in ESs, we used an I^2 statistic. We report the Q statistic as a test of heterogeneity with the caveat that it may have low power to detect heterogeneity and is dependent on the number of studies.[39] I^2 represents the percentage of variability in observed results caused by heterogeneity rather than sampling error.[39] I^2 values of 25%, 50%, and 75% represent low, medium, and high heterogeneity, respectively.[40] When substantial heterogeneity was observed (determined by I^2 value >50%), we further explored the reasons for heterogeneity using the visual inspection forest plots and study characteristics. To estimate heterogeneity in ESs between each categoric moderator, we used the Q between statistic (Q_B). Statistically significant Q_B indicates that we can reject the null hypothesis of no moderating effect in physical activity outcome (i.e., effect size variability can be explained by the categoric moderator variables).[35]

RESULTS

Study description

The results of the study selection process are provided in a PRISMA flowchart in Figure 1. The search strategy returned 2,851 studies from the electronic databases. After removing duplicates, 2,479 studies were screened at the abstract level based on the eligibility criteria, and 229 studies were retained. The remaining studies were then reviewed at the full-text level. This yielded a total of 24 studies[41-64] that met the eligibility criteria and provided sufficient data on physical activity to compute an ES (i.e., sample size, means, and SDs). Of those, nine studies were located through additional searches: four from the external searches (October 2017) and five from the updated searches (September 2019).

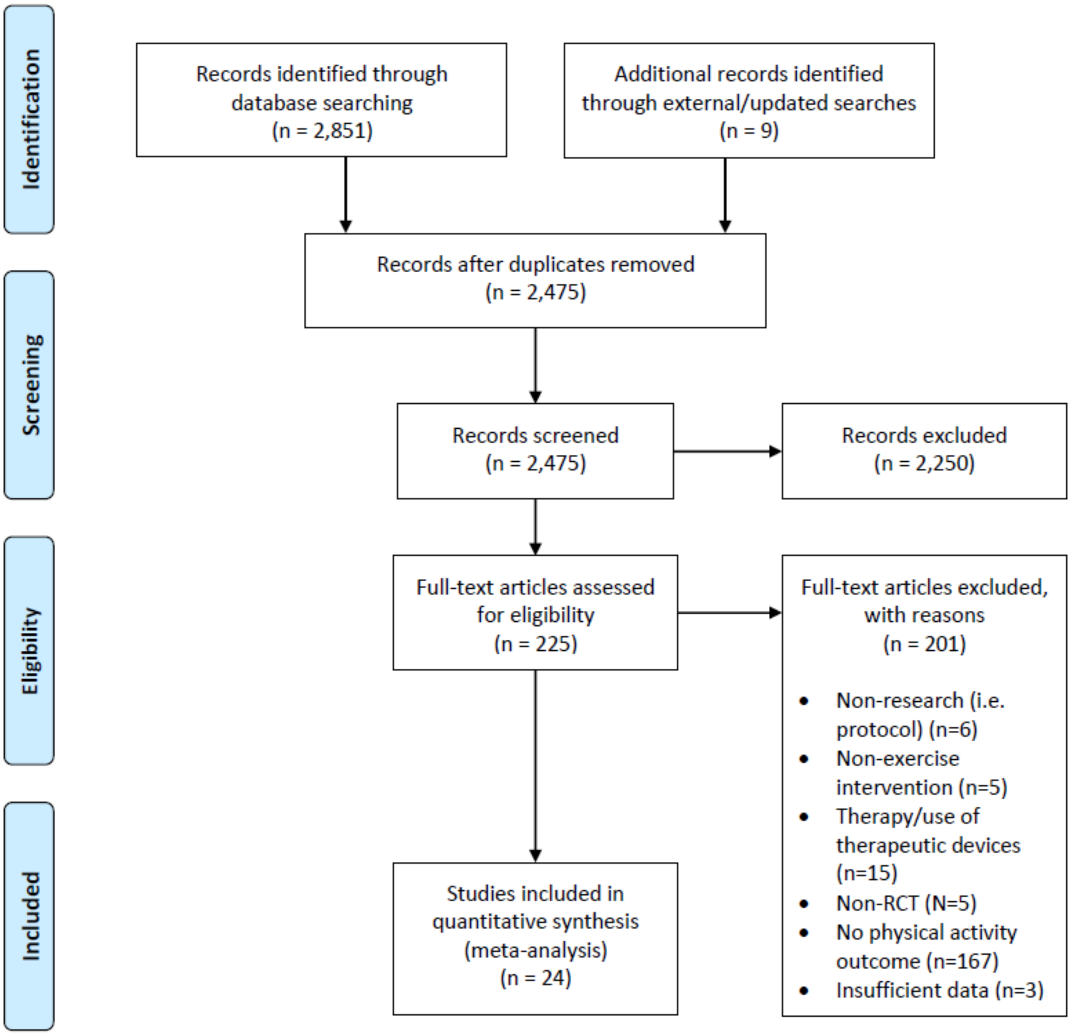

Figure 1. Preferred Items for Systematic Reviews and Meta-analysis flowchart

Among the 24 studies in the immediate analyses, nine studies (38%) included at least one follow-up point. Of those, two studies[61,62] did not provide follow-up data of control groups since the waitlist controls received intervention upon the completion of the post-intervention measures. Therefore, only seven studies[42-44,54,56,59,63] were included in the sustained analyses. The detailed characteristics of the studies included in the quantitative synthesis are presented in Table 1 using the PICOTS framework.

Table 1. Characteristics of the studies included in the quantitative synthesis (n=24) reported using the Population, Intervention, Comparator, Outcome, Timing, Setting framework

Study	Group	Population	Intervention & Comparator	Physical Activity Outcome	Timing	
		Sample size: n Age (y): Mean (SD) Sex (M, F): n MS type (RR) n (%) Disability Level (EDSS or PDDS): Mean (SD) MS duration (y): Mean (SD)			Length of INT (week)	Length of Follow-up (week)
Bombardier et al., 2013	INT	n=44 Age: 47.1 (8.9) Sex: 5, 39 RR: 32 (76) EDSS: 5.5 or less MS duration: 9.4 (7.1)	Behavioral coaching using MI • 1x initial face-to-face session at a clinic (60 min) • 7x scheduled telephone calls (30 min/session) • 1x final face-to-face session at a clinic (60 min)	7-day Physical Activity Recall	12	-
	COM	n=48 Age: 49.7 (7.9) Sex: 8, 40 RR: 36 (75) EDSS: 5.5 or less MS duration: 11.7 (7.9)	Waitlist Control			

Carter et al., 2013	INT	n=16 Age: 39.5 (6.5) Sex: 2, 14 RR: *ns* EDSS: 3.0 (1.1) MS duration: *ns*	Exercise training (flexibility, aerobic, strengthening, balance) Incorporating behavioral techniques into the exercise sessions using the TTM • 2x/week 1-on-1, supervised training (60 min/session) • Aerobic exercise targeted 50-69% of APMHR & RPE 11-13 • 1x/week unsupervised, home exercise	GLTEQ	10	12
	COM	n=14 Age: 40.9 (8.7) Sex: 2, 12 RR: *ns* EDSS: 3.1 (1.7) MS duration: *ns*	Usual care			
Coote et al., 2017	INT	n=33 Age: 43.3 (9.9) Sex: 4, 29 RR: 27 (82) EDSS: 3.3 (0.7) MS duration: 6.7 (5.7)	Exercise training (aerobic, strengthening) • 6x supervised, group exercise and coaching sessions (75 to 90 min/session) • Aerobic exercise targeted moderate intensity • Strengthening exercise targeted 1x of 10-15 reps and then progressed to 2x of 8-12 reps Behavioral coaching based on SCT • 4x via telephone	GLTEQ & Sense wear armband	10	12, 24
	COM	n=32 Age: 41.9 (9.3) Sex: 6, 26 RR: 27 (84) EDSS: 3.3 (0.7) MS duration: 7.0 (6.1)	Attention control Exercise training (aerobic, strengthening) Education sessions unrelated to PA behavior (e.g., diet, sleep, temperature and hydration, immunizations)			

Dlugonski et al., 2012	INT	n=22 Age: 48.5 (10.1) Sex: 4, 18 RR: 22 (100) PDDS: 1.0 (0-6) (Mdn, range) MS duration: 10.3 (9.2)	Behavioral intervention; Contents (text-based and video files) are developed based on SCT • New contents and video coaching calls (5 to 10 min) were available 4x for first month, 2x for second month, and 1x for third month • Participants were encouraged to wear a pedometer for recording daily steps and self-monitoring purpose • Home; Internet	GLTEQ	12	12
	COM	n=23 Age: 44.8 (9.1) Sex: 2, 21 RR: 23 (100) PDDS: 1.0 (0-6) (Mdn, range) MS duration: 8.5 (6.2)	Waitlist control			
Duff et al., 2018	INT	n=15 Age: 45.7 (9.4) Sex: 3, 12 RR: 14 (93) PDDS: 2.1 (1.8) PDDS MS duration: *ns*	Exercise training (Pilates) & massage after each Pilates session • Pilates: 50 min, 2x/week • Massage: 60 min, 2x/week • Clinic, Group exercise	Accelerometer	12	-
	COM	n=15 Age: 45.1 (7.4) Sex: 4, 11 RR: 11 (73) PDDS: 2.3 (2.3) MS duration: *ns*	Massage: 60 min, 2x/week			

Ennis et al., 2006	INT	n=31 Age: 45 (9) Sex: 11, 20 RR: 16 (50) EDDS: 0-3 (22%); 3.5-6 (69%); 6.5-7 (9%) MS duration: 7 (5)	Multidisciplinary health promotion education based on Self-efficacy belief (exercise and physical activity, fatigue and stress management, nutritional awareness) • 180 min, 1 time/week • Hospital; Group	HPLP II (Physical activity subscale)	8	-
	COM	n=30 Age: 46 (8) Sex: 11, 19 RR: 12 (40) EDDS: 0-3 (23%); 3.5-6 (74%); 6.5-7 (3%) MS duration: 8 (6)	Waitlist control			
Hayes et al., 2017	INT	n=33 Age: 43.3 (9.9) Sex: 4, 29 RR: 27 (82) EDDS: 3.3 (0.7) MS duration: 6.7 (5.7)	Same as Coote et al., 2017	GLTEQ	10	-
	COM	n=32 Age: 41.9 (9.3) Sex: 6, 26 RR: 27 (84) EDDS: 3.3 (0.7) MS duration: 7.0 (6.1)	Same as Coote et al., 2017			

Learmonth et al., 2012	INT	n=20 Age: 51.4 (8.06) Sex: 5, 15 RR: *ns* EDDS: 6.14 (0.36) MS duration: 13.4 (6.4)	Exercise training (aerobic, strengthening, balance) using a circuit training approach • 60 min, 2x/week • Leisure center; supervised, group	Phone FITT	12	-
	COM	n=12 Age: 51.8 (8.0) Sex: 4, 8 RR: *ns* EDDS: 5.82 (0.51) MS duration: 12.6 (8.1)	Usual care			
Learmonth et al., 2017	INT	n=29 Age: 48.7 (10.4) Sex: 1, 28 RR: 26 (90) EDDS: 1.25 (2.5) (Mdn, IQR) MS duration: 14.8 (13.0)	Exercise training (aerobic and strengthening) • Aerobic exercise (walking) targeted moderator intensity, 10-30 min, 2x/week • Pedometer for monitoring and tracking • Strengthening exercise targeted 1-2 sets of 10-15 repetitions for 10 exercises, 2x/week • Home; DVD Behavioral coaching to monitor progression and discuss newsletter contents, which is developed based on SCT • 6x for 12 weeks • Internet; 1-on-1 coaching	GLTEQ & Accelerometer	16	-
	COM	n=28 Age: 48.2 (9.1) Sex: 1, 27 RR: 25 (90) EDDS: 2 (3) (Mdn, IQR) MS duration: 13.0 (7.7)	Waitlist control			

McAuley et al., 2015	INT	n=24 Age: 59.62 (1.43) Sex: 6, 18 RR: 16 (66.7) EDDS: *ns* MS duration: 18.10 (9.42)	Exercise training (flexibility, strengthening, balance) • 3x/week • Strengthening training targeted 1-2 sets of 8 to 10 repetitions (RPE 10-12) and then progress to 2 sets of 10 to 12 repetitions (RPE 13-15) • Home; DVD	GLTEQ	24	-
	COM	n=24 Age: 59.78 (1.50) Sex: 6, 18 RR: 16 (66.7) EDDS: *ns* MS duration: 59.78 (1.50)	Attention control • Watching *Healthy Aging* documentary (85 min) • DVD, Home			
Mostert & Kesselring, 2002	INT	n=13 Age: 45.23 (8.66) Sex: 3, 10 RR: 4 (30.8) EDDS: 4.6 (1.2) MS duration: 11.2 (8.5)	Exercise training (aerobic) • 30 min, 5x per 2 weeks using a bicycle ergometer • Rehab center; Supervised	BAECEK (Work, Sport, Leisure)	4	-
	COM	n=13 Age: 43.92 (13.90) Sex: 2, 11 RR: 5 (38.5) EDDS: 4.5 (1.9) MS duration: 12.6 (8.1)	Usual care			
Motl et al., 2011	INT	n=23 Age: 46.1 (10.4) Sex: 2, 21 RR: 23 (100) PDDS: 2.0 (1.8) MS duration: 8.1 (6.5)	Same as Dlugonski et al., 2012	GLTEQ	12	-

	COM	n=25 Age: 45.6 (9.2) Sex: 2, 22 RR: 25 (100) PDDS: 2.1 (1.9); PDDS MS duration: 7.3 (6.2)	Waitlist control			
Motl et al., 2017	INT	n=23 Age: 52.3 (10.3) Sex: 2, 21 RR: 20 (87.0) EDSS: 3.5 (1.5) (Mdn, IQR) MS duration: 14.4 (10.4)	Behavioral intervention; Contents (text-based and video files) are developed based on SCT • New contents and video coaching calls were available 7x for first 2-month, 4x for second 2-month, and 2x for third 2-month • Graphical goal tracking • Home; Internet	GLTEQ & Accelerometer	24	-
	COM	n=24 Age: 51.4 (7.4) Sex: 5, 19 RR: 21 (87.5) EDSS: 3.5 (2.0) (Mdn, IQR) MS duration: 21.1 (8.7)	Waitlist control			
Paul et al., 2019	INT	n=45 Age: 55.6 (10.2) Sex: 13, 32 RR: 15 (33) EDSS: 6.0 (Mdn) MS duration: 10 (12) (Mdn, IQR)	Exercise training (aerobic, strengthening, balance) • 2x/week • Exercise (videos, text, and audio descriptions) and educational contents (disease-specific advice) were delivered via a website. Alterations of exercise based on level and comments • Home, Internet	Accelerometer	24	12

	COM	n=45 Age: 56.5 (9.1) Sex: 8, 37 RR: 15 (33) EDSS: 6.0 (Mdn) MS duration: 15 (13) (Mdn, IQR)	Attention control • Printed sheet of exercise program • 2x/week, Home			
Pilutti et al., 2014	INT	n=41 Age: 48.4 (9.1) Sex: 11, 30 RR: 31 (75.6) EDSS: 2.0 (4.0) (Mdn, IQR) MS duration: 10.6 (7.1)	Same as Motl et al., 2017	GLTEQ & Accelerometer	24	-
	COM	n=41 Age: 49.5 (9.2) Sex: 9, 32 RR: 34 (82.9) EDSS: 3.0 (3.0) (Mdn, IQR) MS duration: 13.0 (9.1)	Waitlist control			
Plow et al., 2014	INT	n=14 Age: 47 (9) Sex: 0, 14 RR: 14 (100) PDDS: 1.79 (1.72) MS duration: 8 (7)	Behavioral intervention; Contents (customized pamphlets) were developed based on SCT and TTM • 1x pamphlet for every three weeks • Home; Mailout Exercise training • 2x in-person, to prescribe an individualized home exercise program	GLTEQ & PADS	12	12
	COM	n=16 Age: 48 (10) Sex: 0, 16 RR: 16 (100)	Waitlist control			

		PDDS: 2.69 (2.06) MS duration: 10 (7)				
Rice et al., 2015	INT	n=9 Age: 53.3 (11.1) Sex: 3, 6 RR: 3 (33.3) EDSS/PDDS: *ns* MS duration: 13.2 (8.9)	1x wheelchair skill/technique training using multimedia Behavior coaching based on SCT (Home; Telephone; 1 time/week)	Accelerometer	12	
	COM	n=5 Age: 54 (0.4) Sex: 1, 4 RR: 2 (40) EDSS/PDDS: *ns* MS duration: 17.6 (8.5)	Waitlist control			
Sandroff et al., 2014	INT	n=37 Age: 48.8 (8.3) Sex: 10, 27 RR: 28 (75.7) EDSS: 0-2 (48.6%); 3-6 (51.4%); 10.7 (6.8) MS duration: *ns*	Same as Motl et al., 2017	IPAQ	24	
	COM	n=39 Age: 50.3 (8.4) Sex: 9, 30 RR: 32 (82.1) EDSS: 0-2 (46.2%); 3-6 (53.8%); 13.4 (9.4) MS duration: *ns*	Waitlist control			
Stuifbergen et al., 2003	INT & COM	n=56 (INT) n=57 (CON) Age: 45.79 (10.9) Sex: 0,113	Multidisciplinary health promotion education (90 min one time) • 90 min, 1x/week (clinic, group)	HPLP II PA subscale	8	12 & 24

		RR: 62 (55) EDSS/PDDS: *ns* MS duration: 10.76 (6.92)	• Bimonthly phone calls during follow-up period (Home, telephone) Usual care control group			
Suh et al., 2015	INT	n=34 Age: 50.1 (8.1) Sex: *ns* RR: 33 (97.1) PDDS: 2.0 (1.8) MS duration: 11.6 (7.1)	Behavior coaching based on SCT • Printed newsletters (Mail out & email) • 1x/week, 1-on-1 telephone coaching • Pedometer and log book for self-monitoring and motivation purpose	GLTEQ	6	-
	COM	n=34 Age: 48.0 (9.4) Sex: *ns* RR: 33 (97.1) PDDS: 2.2 (1.8) MS duration: 12.7 (8.8)	Attention control • Received educational materials unrelated to physical activity (stress management, nutrition, allergies) • 1x/week telephone call to check up whether or not the participant received newsletters			
Tallner et al., 2016	INT	n=59 Age: 40.9 (10.4) Sex: 15, 44 RR: 52 (88.1) EDSS: 2.8 (0.8) MS duration: 9.8 (9.2)	Exercise training (aerobic, strengthening) • Moderate to high intensity (RPE 11-16) • Home-based, supervised via internet Aerobic training (walking, cycling, jogging, swimming) • 10-60 min, 1x/week Strengthening training • 2x/week, 2-3 sets per exercise	BAECEK (Sport)	12	12
	COM	n=67 Age: 40.7 (9.5) Sex: 17, 50 RR: 57 (85.1) EDSS: 2.7 (0.8) MS duration: 9.2 (7.2)	Waitlist control			
Thomas et al., 2017	INT	n=15 Age: 50.9 (8.08)	Gaming intervention using Nintendo Wii	GLTEQ	24	24

		Sex: 1, 14 RR: 12 (80) EDSS/PDDS: *ns* MS duration: *ns*	• 2x supervised, face-to-face session for familiarization at a hospital (week 1 & 2) • 3x Home visit to set the equipment and risk assessment (week 3, 7, & 16) • 3x Telephone/email for monitoring and ongoing support (week 5, 12, 20) Incorporating behavioral techniques throughout intervention using MI			
	COM	n=15 Age: 47.6 (9.26) Sex: 2, 13 RR: 9 (60) EDSS/PDDS: *ns* MS duration: *ns*	Waitlist control			
Turner et al., 2016	INT	n=31 Age: 52.7 (11.6) Sex: *ns* RR: 19 (65.5) EDSS/PDDS: *ns* MS duration: 11.33 (9.00)	Behavioral coaching using MI • 1x/week (90 min for first session, 30-60 min for remaining sessions) • Home, Telephone Exercise training using DVD • Encouraged to perform 45 min or more of high-intensity exercise, 1-2 times/week	GLTEQ	12	12
	COM	n=33 Age: 53.6 (13.1) Sex: *ns* RR: 23 (69.7) EDSS/PDDS: *ns* MS duration: 11.85 (10.41)	Attention control • Self-directed education using DVD information (facilitating motivation, ability to matched peer model to promote self-efficacy, examples) • Home, mail out			

Wens et al., 2015	INT	n=11 Age: 47 (9.9) Sex: 5, 6 RR: 8 (72.7) EDSS: 2.7 (1.0) MS duration: *ns*	Exercise training (aerobic, strengthening), 5x per 2 weeks High intensity continuous aerobic training (cycle ergometer) • 5x1 min interval (week 1 – 5) with 80-90% MHR • 5x2 min interval (week 6-12) with 90-100% MHR Moderate to high-intensity resistance training • Progressed from 1 set of 10 repetitions to 2 set of 20 repetitions for 5 exercises	PASIPD	12	
	INT	n=12 Age: 43 (10.4) Sex: 5, 7 RR: 10 (83.3) EDSS: 2.3 (1.0) MS duration: *ns*	Exercise training (aerobic, strengthening), 5x per 2 weeks High-intensity interval training (cycle & treadmill walking/running) • 1x6 min interval (week 1 – 5) with 80-90% MHR • 2x10 min interval (week 6-12) with 80-90% MHR Moderate to high-intensity resistance training • Same as high-intensity continuous training group			
	COM	n=11 Age: 47 (9.9) Sex: 2, 9 RR: 8 (72.7) EDSS: 2.5 (1.0) MS duration: *ns*	Usual care			

Note. PA, physical activity, APHMR, age-predicted maximum heart rate; BAECKE, Baecke Physical Activity Questionnaire; COM, comparator; EDSS, Expanded Disability Status Scale; FITT, frequency, intensity, time, and type; GLTEQ, Godin Leisure-Time Exercise Questionnaire; HPLP II, Health-Promoting Lifestyle Profile II; INT, intervention; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range (Q3-Q1); MHR, maximum heart rate; MI, motivational interviewing; ns, not specified; PADS, Physical Activity and Disability Survey; PASIPD, Physical Activity Scale for Individuals with Physical Disabilities; PDDS, Patient Determined Disease Steps; PICOTS, Population, Intervention, Comparator, Outcome, Timing, Setting; RPE, ratings of perceived exertion; RR, relapsing-remitting; SCI, spinal cord injury; SCT, social cognitive theory; TTM, transtheoretical model.

Participant characteristics Summary characteristics of all studies included in the quantitative synthesis are provided in Table 2. Overall, 1,373 people with MS were included in the studies with a mean age of 48 ± 2 years. The samples predominately consisted of women (*n*=1,018/1,245, 82%) and relapsing-remitting MS (*n*=985/1,321, 75%); two studies did not clarify either sex[60,63] or type of MS.[42,48] Studies reported disease severity using the Expanded Disability Status Scale (EDSS) or Patient Determined Disease Steps (PDDS). The study participants generally presented with mild-to-moderate disability (e.g., EDSS scores between 0 and 6.5). Only one study included individuals with MS who used a wheelchair.[57] The mean duration of MS among the participants was 12 ± 2 years. Several studies did not report either disease severity of participants,[50,59,62,63] or MS duration.[42,45,62,64]

Table 2. Summary characteristic of all studies (*n*=24) and studies with a follow-up period (*n*=7) included in the quantitative synthesis

	All studies (*n*=24)		Studies with a follow-up (*n*=7)	
	n	%	n	%
Total number of participants				
Intervention	901	50	279	49
Control	901	50	286	51
Average number of participants (Mean ± SD)				
Intervention	24 (11)		21 (12)	
Control	24 (13)		22 (13)	
Type of Intervention				
Exercise training	7	29	1	14
Behavioral intervention	9	38	2	29
Combined	8	33	4	57
Length of intervention, week				
Median (Range)	12 (4-24)		-	
Length of follow-up, week				
Median (Range)	-		12 (12-24)	
Physical activity outcome				
Self-reported	22	67	7	70
Device-measured	7	21	2	20
Both	4	12	1	10
Study quality				
PEDro score, Median (Range)	9 (6-10)		9 (7-10)	
Level 1 (> 6)	22	84	7	100
Level 2 (≤ 6)	2	16	0	0
Intensity of theory integration				
Median (Range)	4 (3-7)		4.5 (3-6)	
Level 1 (≥ 3)	5	29	2	33
Level 2 (4-5)	6	35	2	33
Level 3 (≤ 6)	6	35	2	33

Intervention characteristics & Settings The interventions consisted of exercise training (*n*=7/24, 29%),[45,48,50,51,54,61,64] behavioral interventions (*n*=9/24, 38%),[41,44,46,52,53,55,58-60] and combined (*n*=8/24, 33%).[42,43,47,49,56,57,62,63] Exercise modality mainly included aerobic (e.g., walking, cycling), strengthening (e.g., weight lifting), and/or balance training (e.g., standing still, walking with objects). Exercise training was either supervised and delivered in a laboratory, clinic, or community center (*n*=4, 57%) or unsupervised and delivered via DVD or internet in participant's homes (*n*=3, 43%). Behavioral and combined interventions were generally framed and delivered based on one or more behavior change theories. The behavior change theories that were predominantly used included social cognitive theory (n=12/17, 76%),[43,44,47,49,52,53,55-58,60,62] motivational interviewing (n=3, 18%),[41,62,63] transtheoretical model (n=2, 12%),[42,56] and self-efficacy theory (n=2, 12%).[46,59] Three studies (18%) applied more than one theory.[56,59,62]

Comparator Interventions typically included non-active comparison groups (i.e., usual care, waitlist control). Only four studies included active comparison groups (i.e., attention control), and delivered either education sessions or materials unrelated to physical activity behavior.[43,47,50,54,60,63]

Physical activity outcomes The studies included a variety of physical activity measures. The device-measurement of physical activity included either a waist-worn accelerometer or sense wear armband (*n*=7/21, 33%).[43,45,49,53-55,57] The self-report measures of physical activity include: Godin Leisure-Time Exercise Questionnaire (*n*=13/21, 70%);[42-44,47,49,50,52,53,55,56,60,62,63] Baecke Physical Activity Questionnaire (*n*=2,10%);[51,61] Health-Promoting Lifestyle Profile II (*n*=2, 10%);[46,59] International Physical Activity Questionnaire (*n*=1, 5%);[58] Physical Activity and Disability Survey (*n*=1, 5%);[56] 7-day Physical Activity Recall (*n*=1, 5%);[41] Phone-FITT Questionnaire (*n*=1, 5%);[48] Physical Activity Scale for Individuals with Physical Disabilities (*n*=1, 5%).[64] Five studies included more than one measure of physical activity.[43,49,53,55,56]

Timing The average duration of interventions was 12.4 ± 5.8 weeks (Median = 12 weeks) with a range between 4 and 24 weeks. The average duration of follow-up was 15.4 ± 5.9 weeks (Median = 12 weeks) with a range between 12 and 24 weeks. All seven studies included a 12-week follow-up of physical activity outcomes; two studies included an additional 24-week follow-up assessment.

Intensity of Theory Integration Both behavioral (*n*=9) and combined interventions (*n*=8) were framed and delivered based on one or more behavior change theories. Using the modified version of the Theory Coding Scheme,[25,27] five studies were classified as Level I (Sparse),[42,53,55,58,63] six as Level 2 (Moderate),[41,44,47,56,57,62] and six as Level 3 (Extensive).[43,46,49,52,59,60] Studies with exercise training alone did not apply a behavior change theory, and these studies were excluded from the moderator analyses. The intensity of theory integration of studies that applied behavior change theory included in the quantitative synthesis is provided in Figure 2 and Table 3.

Study Quality The methodological quality assessment of all studies included in the quantitative synthesis is provided in Table 3 and Appendix III. The overall methodological quality was good (median 9, range 6-10) based on the PEDro scale. Using the Spinal Cord Injury Rehabilitation Evidence system, 22 studies were classified as Level I[41-50,52-56,58-64] and two studies were classified as Level II.[51,57]

		Bombardier et al., 2013	Carter et al., 2013	Coote et al., 2017	Dlugonski et al., 2012	Duff et al., 2018	Ennis et al., 2006	Hayes et al., 2017	Learmonth et al., 2012	Learmonth et al., 2017	McAuley et al., 2015	Mostert & Kesselring et al., 2002	Motl et al., 2011	Motl et al., 2017	Paul et al., 2019	Pilutti et al., 2014	Plow et al., 2014	Rice et al., 2015	Sandroff et al., 2014	Stuifbergen et al., 2003	Suh et al., 2015	Tallner et al., 2015	Thomas et al., 2017	Turner et al., 2016	Wens et al., 2015
1	Theory mentioned	■	■	■	■		■	■		■			■	■		■	■	■	■	■	■		■	■	
2	Relevant constructs targeted	■	■	■	■		■	■		■			■	■		■	■	■	■	■	■		■	■	
3	Change method linked to at least one construct	■	■	■	■		■	■		■			■	■		■	■	■	■	■	■		■	■	
4	Participants selected based on a score of a theory-related construct																				■				
5	Interventions tailored to different subgroups																■								
6	At least one construct or theory measured post-intervention			■			■			■			■							■	■		■		
7	All theory measures presented some evidence of reliability			■			■			■			■							■	■		■		
8	Results discussed in relation to theory	■		■	■		■	■		■			■				■	■		■	■				
	Summed score	4	3	6	4	n/a	6	4		6	n/a	n/a	6	3	n/a	3	5	4	3	6	7	n/a	5	3	n/a

Figure 2. Intensity of theory integration. Abbreviation: n/a, not applicable.

Table 3. Moderators of all studies included in the quantitative analyses (*n*=24)

Study	***Study Quality** (Level)	**Theory**	***Theory Intensity** (Level)	***Training Type**	***Intervention length** (Week)	***Follow-up length** (Week)	***Instrument Type** (Device-measured/ Subjective)	**Physical Activity Outcome**
Bombardier et al., 2013	1	MI	Moderate	Behavior	12	-	Subjective	7-Day PAR
Carter et al., 2013	1	TTM	Sparse	Combined	10	12	Subjective	GLTEQ
Coote et al., 2017	1	SCT	Extensive	Combined	10	12	Subjective	GLTEQ
							Device-measured	SenseWear armband
Dlugonski et al., 2012	1	SCT	Moderate	Behavior	12	12	Subjective	GLTEQ
Duff et al., 2018	1	-	-	Exercise	12	-	Device-measured	Accelerometer
Ennis et al., 2006	1	Self-efficacy	Extensive	Behavior	8	-	Subjective	HPLP II
Hayes et al., 2017	1	SCT	Moderate	Combined	10	-	Subjective	GLTEQ
Learmonth et al., 2012	1	-	-	Exercise	12	-	Subjective	Phone FITT
Learmonth et al., 2017	1	SCT	Extensive	Combined	16	-	Subjective	GLTEQ
							Device-measured	Accelerometer
McAuley et al., 2015	1	-	-	Exercise	24	-	Subjective	GLTEQ
Mostert & Kesselring, 2002	2	-	-	Exercise	4	-	Subjective	BAECKE
Motl et al., 2011	1	SCT	Extensive	Behavior	12	-	Subjective	GLTEQ
Motl et al., 2017	1	SCT	Sparse	Behavior	24	-	Subjective	GLTEQ
							Device-measured	Accelerometer
Paul et al., 2019	1	-	-	Exercise	24	12	Device-measured	Accelerometer
Pilutti et al., 2014	1	SCT	Sparse	Behavior	24		Subjective	GLTEQ
						-	Device-measured	Accelerometer
Plow et al., 2014	1	SCT & TTM	Moderate	Combined	12	12	Subjective	GLTEQ
								PADS

Rice et al., 2015	2	SCT	Moderate	Combined	12	-	Device-measured	Accelerometer
Sandroff et al., 2014	1	SCT	Sparse	Behavior	24	-	Subjective	IPAQ
Stuifbergen et al., 2003	1	HBM, Self-efficacy, Pender's model of health promotion	Extensive	Behavior	8	12	Subjective	HPLP II
Suh et al., 2015	1	SCT	Extensive	Behavior	6	-	Subjective	GLTEQ
Tallner et al., 2016	1	-	-	Exercise	12	-	Subjective	BAECKE
Thomas et al., 2017	1	MI, SCT, Cognitive Behavioral, Self-Determination	Moderate	Combined	24	-	Subjective	GLTEQ
Turner et al., 2016	1	MI	Sparse	Combined	12	12	Subjective	GLTEQ
Wens et al., 2015	1	-	-	Exercise	12	-	Subjective	PASIPD

Note. MI = Motivational Interviewing; TTM = Transtheoretical Model ; SCT = Social Cognitive Theory; HBM = Health Belief Model; BAECEK = Baecke Physical Activity Questionnaire; Phone FITT = a brief physical activity interview for older adults; PASIPD = Physical Activity Scale for Individuals with Physical Disabilities; HPLP II = Health-Promoting Lifestyle Profile II; GLTEQ = Godin Leisure-Time Exercise Questionnaire; IPAQ = International Physical Activity Questionnaire; PADS = Physical Activity and Disability Survey

Immediate effect of interventions on physical activity behavior

The immediate effects of interventions on physical activity behavior from the 24 studies are illustrated in Figure 3 and Table 4. Overall, there was a statistically significant increase in physical activity levels favoring intervention compared with control ($P < 0.001$); the SMD was moderate (0.56) in magnitude and surpassed the threshold for clinical meaningfulness. The test of heterogeneity was significant (Q = 35.69, $df = 23$, $P = 0.044$, $I^2 = 36\%$) and supported examination of moderator variables.

Among the studies included in the analysis of sustainability (*n*=7/24, 29%), there was a statistically significant immediate increase in physical activity levels favoring the intervention conditions compared with control conditions ($P = 0.005$); the SMD was small (0.40) in magnitude and did not surpass the threshold for clinical significance. The level of heterogeneity was not significant (Q = 10.74, $df = 6$, $P = 0.095$, $I^2 = 44\%$).

Sustained effect of interventions on physical activity behavior

Seven studies[42-44,54,56,59,63] were included in the sustainability analyses with 12-week follow-up points. Only two studies provided 24-week follow-up points, which were omitted from the analysis. Four studies with follow-up periods included combined interventions,[42,43,56,63] two studies included behavioral intervention only,[44,59] and one provided only exercise training.[54]

The sustained effects on overall physical activity levels are provided in Figure 4 and Table 4. There was a statistically significant increase in physical activity levels favoring intervention compared with control ($P < 0.001$); the SMD was moderate (0.53) and surpassed the threshold for clinical significance. The level of heterogeneity was not significant (Q = 8.83, *df* = 6, *P* = 0.183, I^2 = 32%).

Moderator effects of interventions on physical activity behavior

The moderator variables for understanding variability in the average ES are provided in Table 3. The immediate effects of interventions on physical activity behavior by moderators (i.e., intervention type and duration, measurement type of physical activity, intensity of theory integration, and study quality) are presented in Table 4.

The Q_B statistic indicated that the immediate effects of the intervention on physical activity outcomes significantly differed based on the *type of physical activity measurement* (self-reported vs. device-measured) (Q_B = 6.21, *df* = 2, *P* = 0.013). The interventions with self-reported outcomes yielded a moderate effect (SMD = 0.62), whereas there was a small effect (SMD = 0.26) for studies that included device-measured physical activity. Other Q_B values were not significant for the study or intervention characteristic moderators.

Regarding the *intervention type* as a moderator, the studies that delivered behavioral intervention alone produced a moderate effect (SMD = 0.71) with a medium level of heterogeneity (I^2 = 54%). The SMDs of the studies with exercise training alone and combined interventions were 0.53 and 0.38, respectively, with low levels of heterogeneity. Regarding *intervention duration* as a moderator, both levels (≤ 12 weeks and > 12 weeks) produced moderate effects with low levels of heterogeneity. Regarding the *intensity of theory integration* as a moderator, all levels produced medium effects, but the studies with extensive use of theory had a high level of heterogeneity (I^2 = 63%). Regarding the *study quality*, Level 1 studies yielded a moderate effect (SMD = 0.57) with a low level of heterogeneity, whereas Level 2 studies had a small effect (SMD=0.31) with a confidence interval, including zero.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Statistics for each study						
Bombardier et al., 2013	0.37	0.21	0.04	-0.05	0.78	1.74	0.08
Carter et al., 2013	0.03	0.39	0.15	-0.74	0.80	0.07	0.94
Coote et al., 2017	0.20	0.27	0.07	-0.33	0.74	0.75	0.45
Dlugonski et al., 2012	1.09	0.32	0.10	0.46	1.72	3.41	0.00
Duff et al., 2018	0.34	0.40	0.16	-0.44	1.11	0.84	0.40
Ennis et al., 2006	1.42	0.29	0.08	0.85	1.98	4.94	0.00
Hayes et al., 2017	0.33	0.27	0.08	-0.21	0.86	1.19	0.23
Learmonth et al., 2012	0.88	0.38	0.15	0.13	1.63	2.30	0.02
Learmonth et al., 2017	0.32	0.27	0.07	-0.21	0.84	1.19	0.23
McAuley et al., 2015	0.60	0.30	0.09	0.02	1.17	2.02	0.04
Mostert & Kesselring, 2002	0.39	0.41	0.17	-0.41	1.18	0.95	0.34
Motl et al., 2011	0.63	0.30	0.09	0.05	1.21	2.11	0.03
Motl et al., 2017	1.08	0.33	0.11	0.43	1.72	3.29	0.00
Paul et al., 2019	0.05	0.24	0.06	-0.43	0.52	0.20	0.84
Pilutti et al., 2013	0.57	0.24	0.06	0.11	1.03	2.43	0.02
Plow et al., 2014	0.99	0.39	0.15	0.23	1.75	2.55	0.01
Rice et al., 2015	0.14	0.61	0.38	-1.06	1.34	0.22	0.82
Sandroff et al., 2013	0.81	0.24	0.06	0.34	1.28	3.40	0.00
Stuifbergen et al., 2003	0.27	0.19	0.04	-0.10	0.65	1.45	0.15
Suh et al., 2015	0.55	0.25	0.06	0.06	1.03	2.21	0.03
Tallner et al., 2016	0.46	0.20	0.04	0.07	0.84	2.33	0.02
Thomas et al., 2017	0.63	0.39	0.16	-0.14	1.41	1.60	0.11
Turner et al., 2016	0.42	0.26	0.07	-0.08	0.92	1.65	0.10
Wens et al., 2015 5	1.24	0.33	0.11	0.60	1.88	3.80	0.00
	0.56	0.07	0.01	0.42	0.70	7.63	0.00

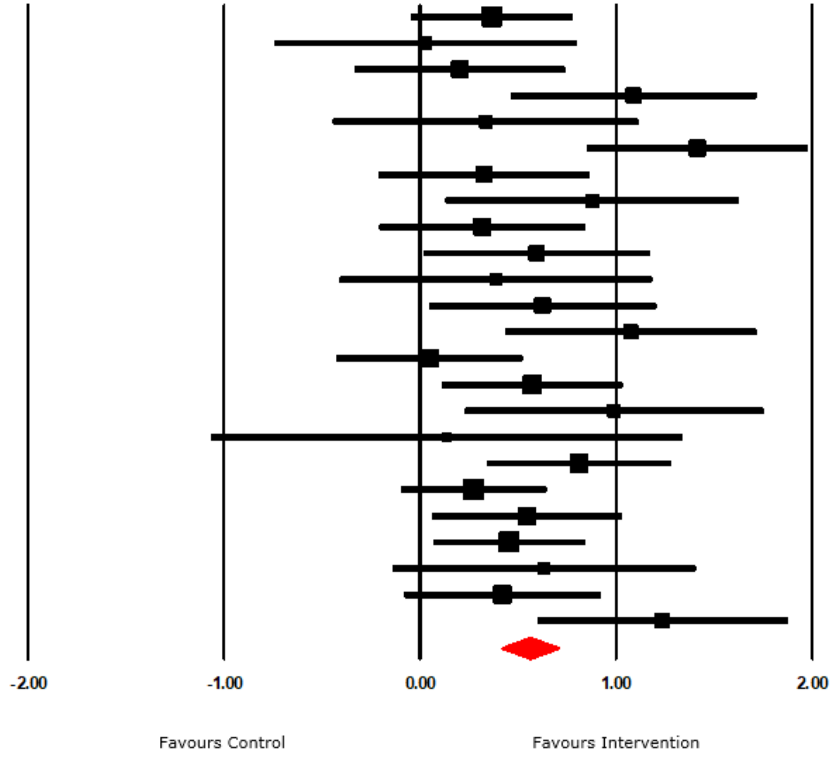

Figure 3. Immediate, post-intervention effect on overall physical activity levels.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Carter et al., 2013	0.37	0.41	0.17	-0.43	1.18	0.91	0.36
Coote et al., 2017	0.17	0.31	0.10	-0.44	0.78	0.55	0.58
Dlugonski et al., 2012	1.08	0.32	0.10	0.46	1.71	3.39	0.00
Paul et al., 2019	0.12	0.25	0.06	-0.38	0.62	0.47	0.64
Plow et al., 2014	0.87	0.38	0.15	0.12	1.62	2.26	0.02
Stuifbergen et al., 2003	0.52	0.19	0.04	0.14	0.89	2.71	0.01
Turner et al., 2016	0.76	0.26	0.07	0.25	1.27	2.91	0.00
	0.54	0.13	0.02	0.28	0.79	4.10	0.00

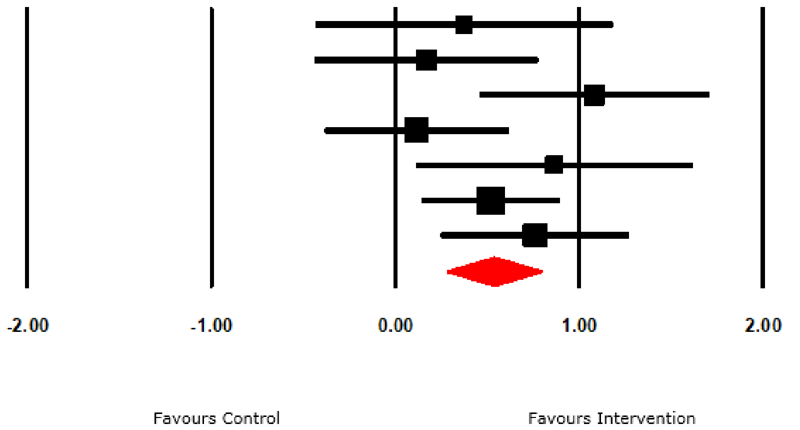

Figure 4. Sustained, 12-week follow-up effect on overall physical activity levels.

Table 4. Moderators of the effects of the interventions on physical activity behavior

Categoric Moderator	Q_B	*P*	Level of Moderator	Study n	SMD	SE	Lower CI	Upper CI	I^2
Immediate Effects									
Overall	35.69 (Q)*	0.04		24	0.56	0.07	0.42	0.70	36
Intervention type	3.89	0.14	Exercise	7	0.53	0.15	0.24	0.82	40
			Behavioral	9	0.71	0.12	0.46	0.95	54
			Combined	8	0.38	0.11	0.15	0.60	0
Intervention duration	0.01	0.93	≥ 12 weeks	17	0.57	0.09	0.38	0.75	40
			< 12 weeks	7	0.55	0.13	0.30	0.80	32
Measurement type	6.21*	0.01	Device-measured	7	0.26	0.12	0.04	0.49	8
			Self-reported	17	0.62	0.09	0.45	0.79	37
Intensity of theory integration	0.09	0.96	Level 1 (Sparse)	5	0.61	0.15	0.33	0.90	27
			Level 2 (Moderate)	6	0.58	0.15	0.29	0.86	17
			Level 3 (Extensive)	6	0.55	0.17	0.21	0.88	63
Study quality	0.56	0.45	Level 1	22	0.57	0.08	0.42	0.72	40
			Level 2	2	0.31	0.34	-0.35	0.98	0
Immediate Effects									
Studies included follow-ups	10.74 (Q)	0.10		7	0.40	0.14	0.12	0.67	44
Intervention type			Exercise	1	0.05	0.24	-0.43	0.52	0
			Behavioral	2	0.64	0.41	-0.15	1.44	79

			Combined	4	0.39	0.17	0.05	0.73	19
Intervention duration			≥ 12 weeks	6	0.47	0.16	0.16	0.77	42
			< 12 weeks	1	0.05	0.24	-0.43	0.52	0
Measurement type			Device-measured	2	0.13	0.18	-0.22	0.49	0
			Self-reported	5	0.53	0.19	0.17	0.89	49
Intensity of theory integration			Level 1 (Sparse)	2	0.30	0.21	-0.12	0.72	0
			Level 2 (Moderate)	2	1.05	0.25	0.57	1.53	0
			Level 3 (Extensive)	2	0.25	0.16	-0.05	0.56	0
Study quality			Level 1	7	0.40	0.14	0.12	0.67	44
			Level 2	0					
Sustained Effects									
Overall	8.83 (Q)	0.18		7	0.53	0.13	0.27	0.79	32
Intervention type			Exercise	1	0.12	0.26	-0.38	0.62	0
			Behavioral	2	0.74	0.28	0.20	1.29	56
			Combined	4	0.56	0.16	0.24	0.88	0
Intervention duration			≥ 12 weeks	1	0.12	0.26	-0.38	0.62	0
			< 12 weeks	6	0.62	0.12	0.37	0.86	10
Measurement type			Device-measured	2	0.16	0.20	-0.23	0.54	0
			Self-reported	5	0.68	0.13	0.44	0.93	0

Intensity of theory integration	Level 1 (Sparse)	2	0.65	0.22	0.22	1.08	0
	Level 2 (Moderate)	2	0.96	0.25	0.51	1.48	0
	Level 3 (Extensive)	2	0.42	0.16	0.10	0.74	0
Study quality	Level 1	7	0.53	0.13	0.27	0.79	32
	Level 2	0					

Note. n = number of studies; Q = Test for heterogeneity in study effect sizes; Q_B = Test for heterogeneity within categorial moderators; I^2 = Degree of inconsistency; *$p < 0.05$

DISCUSSION

This paper provided a comprehensive meta-analysis that quantified the immediate and sustained effects of interventions to increase physical activity behavior among people with MS. The cumulative evidence demonstrated that the interventions had moderate effects on both immediate and sustained changes in physical activity behavior; those effects exceeded ½ SD as a threshold for clinical meaningfulness. The moderator analyses identified study features associated with the trend for larger physical activity changes, and these included self-reported physical activity measurement (vs. device-measured physical activity) and behavioral interventions (vs. exercise training/combined interventions), but not study quality, intervention duration, and intensity of theory integration. Such findings have important implications for designing and developing future RCTs that target physical activity behavior for people with MS.

When examining immediate changes in physical activity, the interventions (*n*=24) had moderate effects on physical activity behavior (SMD = 0.56). The magnitude of the effect is consistent with previous meta-analyses of behavioral interventions in people with MS (ES = 0.64)[24] and other neurological disorders, including MS (ES = 0.53).[65] The findings are further comparable with those reported by a previous meta-analysis of interventions that were delivered through technology in people with MS (ES = 0.59).[66] However, we note that the previous meta-analyses have focused on small, specific interventions, such as behavioral interventions or technology-based interventions. Overall, our findings indicate that people with MS who participate in an intervention can increase physical activity levels upon completing the intervention.

When examining sustained changes in physical activity, the interventions (*n*=7) had moderate effects on physical activity behavior (SMD = 0.53) that were comparable with a previous meta-analysis (SMD = 0.60).[23] The resultant sustained effects appeared slightly higher than those identified from pre- to post-intervention (i.e., immediate effects) (*n*=7; SMD=0.40). This indicates that participants increased physical activity behavior pre-post intervention and sustained, and perhaps, built upon these changes throughout follow-up. Only one of the seven studies did not report the application of behavioral change strategies.[54] Collectively, the findings emphasize the importance of incorporating behavioral change techniques aligned with theory within interventions that target sustainable changes in physical activity behavior; such findings regarding sustainability should be confirmed by RCTs.

Regarding moderator analyses of the immediate intervention effects, we identified moderate effects when studies included self-reported measures of physical activity (SMD = 0.62), and small effects in studies that used device-measured physical activity (SMD = 0.26). This observation is comparable with previous research[23,24] that demonstrated the differences between self-reported and device-measured physical activity. Such findings should be interpreted with caution as the studies in the present meta-analysis primarily included self-reported measures of physical activity.

Moderator analyses of *intervention type* demonstrated that the behavioral interventions alone yielded the largest effect (SMD = 0.71), followed by the exercise training studies and the combined interventions. There was a medium level of heterogeneity among the behavioral interventions (I^2 = 54%). This appeared to be influenced by two studies with multidisciplinary health promotion education (i.e., wellness interventions) that produced small effects. This is consistent with a previous meta-analysis of physical activity interventions in healthy adults that reported larger effects with interventions that used behavioral strategies (ES = 0.25) compared with other interventions that targetted general health education (ES = 0.17).[67] Overall, these findings indicate that behavioral interventions alone may be capable of addressing the long-standing problem of physical inactivity in MS.

Interestingly, interventions that provided both exercise training and behavioral coaching resulted in a smaller effect (SMD = 0.38) than the behavioral interventions alone on immediate changes in physical activity behavior (SMD = 0.71). One likely explanation for this difference could be the dose of the behavioral coaching. The combined interventions consisted of 185 total sessions, and only 57 sessions (31%) focused solely on behavioral coaching. Exercise training accounted for 103 sessions (56%) and the other 25 sessions (13%) embedded behavioral coaching during exercise training. The behavioral interventions delivered only behavioral coaching content (84 sessions), and the combined interventions may have had a lower volume or dose of behavioral coaching. Of note, due to inadequate reporting, we were unable to discern the precise amount of time spent on behavioral coaching. Further research may explore optimal doses of behavioral coaching for physical activity change in MS.

Regarding the *intensity of theory integration*, we anticipated that a higher intensity would yield larger immediate changes in physical activity. However, we observed moderate and meaningful effects of interventions across all levels of theory integration. One explanation is that the classification method (a modified version of a behavior theory coding framework) may not have been sensitive to detect such differences, with the sparse amount of reported details concerning behavioral coaching. One previous meta-analysis encountered a similar issue when attempting to classify and analyze behavioral interventions based on the original Theory Coding Scheme.[23]

Future directions

The findings of this meta-analysis are encouraging, but several knowledge gaps require further investigation. The most common follow-up duration was rather short (three months), and this is critical since the impetus for designing physical activity interventions is that people will adopt and maintain an active lifestyle over a prolonged period for improving and managing health and function. The analysts observed that interventions often did not provide enough detail regarding behavior change techniques to allow replication of study procedures or identification of mechanisms that resulted in the observed changes in behavior. Of note, our findings indicated that few studies examined sustainable changes in physical activity behavior. Sustainability is a critical area that warrants further investigation, considering that people with MS experience numerous barriers (i.e., personal and environmental) for sustained behavior change.

Study limitations

This meta-analysis had limitations. The study participants had mostly mild-to-moderate mobility disability, which is not surprising since walking was the most commonly prescribed type of physical activity. However, this finding indicates a need for programs that are inclusive of a wider variety of movement capabilities, such as for people who use wheelchairs. Only one study included people with MS who used wheelchairs as a primary mobility aid.[57] This limits the generalizability of our findings among people with mild-to-moderate disabilities. The findings of the sustainability analyses were statistically significant but should be interpreted with caution given the relatively small number of studies that had follow-ups; this further hindered the statistical comparisons among the categorical moderators. Ideally, the findings of moderator analyses should be compared and interpreted in the context of associations with other moderators.

CONCLUSIONS

This meta-analysis demonstrated that behavioral interventions alone are efficacious for increasing and perhaps sustaining physical activity behavior in adults with MS. These findings are encouraging and provide an initial foundation for future research exploring sustainability. We further identified several knowledge gaps that require additional research, including longer follow-up durations and the moderating effects of the intervention and/or participant characteristics.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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SOCIAL COGNITIVE THEORY CONSTRUCTS AS CORRELATES OF PHYSICAL ACTIVITY IN PEOPLE WITH MULTIPLE SCLEROSIS: SECONDARY DATA ANALYSIS OF A TELE-EXERCISE INTERVENTION

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ABSTRACT

Objectives: This is a secondary analysis of data focused on examination of social cognitive theory (SCT) variables as correlates of self-reported physical activity level in people with multiple sclerosis (MS) after a tele-exercise intervention. This study further focused on estimation of cut-off points of SCT variables that could be applied as tailoring variables for designing an adaptive intervention that aimed at increasing and sustaining physical activity behavior.

Methods: The analysis included 377 persons with MS who completed a 3-month tele-exercise intervention and received SCT-based educational materials/automated calls over a 1-year period. Outcomes included self-reported moderate-to-vigorous physical activity using the Godin Leisure-Time Exercise Questionnaire (GLTEQ), and SCT variables of exercise self-efficacy, outcome expectations, and goal setting. The associations were examined using Spearman and partial Spearman correlations (r), adjusted for age, sex, MS type, disease severity, clinic allocation, and baseline GLTEQ scores. The cut-off points were estimated using multiple logistic regression and a receiver operating characteristic (ROC) curve. Binary anchor groups were defined using the GLTEQ < 24 vs. ≥ 24 (i.e., *active* vs. *moderately/insufficiently active*) at 3-month and 6-month follow-up.

Results: The partial Spearman correlation indicated that the 3-month goal setting variable has moderate and statistically significant correlation with physical activity level at 6-month follow-up ($r = 0.24$) ($p < 0.001$). The goal setting variable was then entered into the multiple logistic regression model with the binary physical activity anchor group, and the area under the curve of ROC was calculated. The results indicated that a baseline goal setting had 0.863 AUC (81% sensitivity, 31% specificity) with an estimated cut-off point of 33.

Conclusions: This study identified 3-month goal setting as the strongest predictor for physical activity level 6 months after an intervention. This might inform the design and delivery of future interventions for optimizing program levels and types of support based on SCT for maximizing treatment efficacy for people with MS.

Keywords: multiple sclerosis, exercise, physical activity, health, behavior

INTRODUCTION

Substantial evidence supports the beneficial effects of exercise training (as part of physical activity) for improving health and functional outcomes and managing many consequences of multiple sclerosis (MS).[1-3] Despite the benefits, people with MS engage in considerably lower levels of physical activity than the general population or adults with other health conditions.[4-6] Further evidence has shown that only 20% of people with MS meet the recommended U.S. public health guideline for accruing health benefits through exercise (150 minutes/week of moderate to vigorous physical activities [MVPA]).[5] The low level of physical activity may result from multiple levels of barriers that people with MS experience with exercise and physical activity participation in community settings (e.g., a lack of accessible facilities/options, knowledgeable instructors, transportation, or social support).[7]

To date, an emerging body of research supports the efficacy of exercise training programs and behavioral interventions (alone and combined) for increasing and potentially sustaining physical activity behavior in people with MS.[1, 8, 9] Yet, people with MS often have varying rates of success with a standardized program; this is referred to as response heterogeneity.[10] A few studies have identified that the efficacy of interventions (i.e., change in physical activity outcomes) depends on disease-related factors (e.g., MS type, disease severity) and participant-specific characteristics, such as motivation, efficacy, outcome expectations, goal-setting skills, and perceived barriers to exercise.[10-13] Collectively, these findings suggest that examining response heterogeneity may help to develop more targeted and tailored exercise interventions for people with MS.

One approach for informing the development of future interventions for improving physical activity involves examining the key individual or group characteristics that influence different responses to treatment adherence and outcome in a fixed treatment. Using the principles of adaptive intervention design, a treatment regimen can be tailored and titrated based on the data for individual or group participants that are obtained during the early intervention stage.[14] The benefit of this design is to operationalize modifications (i.e., how, when, and based on which measure to alter treatment; this is referred to as tailoring variables) before executing the intervention so that participants are systematically allocated to the same or different group based on their needs.[15] This design has been applied to health behavior interventions that target weight management,[16-18] substance abuse,[19, 20] and depression.[21, 22] To our knowledge, no other researchers have applied adaptive intervention design to studies for people with MS.

There has been a proliferation of research describing significant associations between physical activity behavior and the core sets of social cognitive theory (SCT) constructs (i.e., self-efficacy, outcome expectations, goal setting and planning, and perceived facilitators/barriers to exercise).[1, 9, 23] SCT further informs *a stepwise implementation model*,[24] which suggests that healthcare providers offer individually tailored programs with differentiated levels and types of support based on participants' motivational readiness (i.e., level of self-efficacy and outcome expectations when initiating a physical activity behavior change). We are aware of only one study that specifically designed a behavioral intervention for moderate levels of efficacy in people with MS (i.e., between 50 and 70).[25] A cross-sectional study has further demonstrated that participants with higher baseline levels of self-efficacy, outcome expectations, and goal setting/planning had larger increases in physical activity after completing an internet-based behavioral intervention.[13] A recent qualitative study indicated that people with MS demonstrated knowledge of health risks and benefits, confidence, outcome expectations, goals, and perceived barriers to exercise in different ways that were aligned with the classifications of the stepwise implementation model.[25]

One area that needs further study is identifying the precise, quantitative levels of SCT variables using questionnaires with measurable responses that can predict future physical activity behavior (i.e., what is the score of SCT variable(s) to determine intervention allocation into either a self-directed program or an intense program with face-to-face, behavioral coaching?). Such research would be advantageous for providing stronger tailoring variables for designing adaptive interventions among people with MS.

To build a data-driven adaptive intervention, we undertook a secondary analysis of data[26] from a large pragmatic, cluster randomized controlled trial (referred to as the Tele-Exercise and Multiple Sclerosis [TEAMS] study) that targeted improvements in fatigue, pain, quality of life, and physical activity. First, we examined associations between SCT variables (i.e., self-efficacy, outcome expectations, and goal setting) and self-reported physical activity level among people with MS who completed the tele-exercise condition of the TEAMS study. We included four pairs of analyses and expected positive correlations between (a) baseline SCT variables and absolute physical activity at 3-month follow-up (post-intervention); (b) baseline SCT variables and 3-month change in physical activity (from baseline to 3-month follow-up); (c) 3-month SCT variables and absolute physical activity at 6-month follow-up; and (d) 3-month SCT variables and 3-month change in physical activity (from 3- to 6-month follow-up). Second, we estimated cut-off points of baseline and 3-month SCT variables relative to absolute physical activity level and change in physical activity level. For absolute physical activity level, we used a well-established classification of MVPA scores in the self-reported physical activity questionnaire among persons with MS[27] and defined two binary anchor groups, *active* (≥ 24 units; substantial benefits) vs. *moderately/insufficiently active* (< 24 units; some/low benefits). For change in physical activity level, we used the clinically meaningful change based on the guideline of 0.5 standard deviation change.

METHODS

Participants

There were 837 people with MS who were enrolled in the TEAMS study between 2016 and 2021 and randomized into two conditions: complementary and alternative medicine (CAM) intervention at a clinic by a therapist or at home through use of a tablet (TeleCAM). The present study included the 377 participants who completed the TeleCAM condition of the TEAMS intervention.

The inclusion criteria of the TEAMS study were: (1) 18-70 years of age; (2) ability to ambulate with or without assistive device (i.e., Patient Determined Disease Steps [PDDS] scale between 0 and 7);[28] (3) ability to use arms and legs for exercise while standing or seated; and (4) physician permission to participate in the study. Exclusion criteria were: (1) already meeting physical activity guidelines (Total score of the Godin Leisure-Time Exercise Questionnaire [GLTEQ] $\geq$ 24);[29] (2) visual acuity that prevents seeing exercise videos on a tablet screen; (3) cardiovascular disease event within the past 6 months, severe pulmonary disease, or renal failure; (4) active pressure ulcer; (5) currently pregnant; and (6) participation in a rehabilitation session within 30 days.

Outcomes

The present study included physical activity outcomes for baseline, 3-month follow-up, and 6-month follow-up assessments as well as SCT variables for baseline and 3-month follow-up assessments.

Physical activity The physical activity outcomes consisted of a self-reported measure of physical activity using the GLTEQ.[29] The GLTEQ is a valid measure of physical activity that has been commonly applied in the general population of adults and for more targeted populations, including cancer survivors[30] and people with MS.[31] In MS research, the GLTEQ is the most commonly applied self-reported physical activity measure for describing rates, patterns, correlates, consequences, and interventions.[9, 32] The GLTEQ includes three items that measure the frequency of physical activity engagement in 15 or more minutes of strenuous (vigorous), moderate, or mild activity in the previous week. The GLTEQ provides the descriptions and examples of strenuous, moderate, or mild physical activity. The GLTEQ total activity leisure score is calculated by multiplying frequency of strenuous, moderate, and mild physical activity by nine, five, and three metabolic equivalents of task (METs), respectively, and then summing the weighted scores (ranging from 0 to 119 METs). The GLTEQ health contribution score (HCS) is a sum of the weighted strenuous and moderate physical activity scores (ranging from 0 to 98 METs). Higher scores reflect participation in a greater volume of physical activity. The HCS corresponds with public health guidelines for levels of MVPA in the general population[33] and people with MS[27] and reflects categories of *active* (≥ 24 units; substantial benefits), *moderately active* (14–23 units; some benefits), or *insufficiently active* (< 14; low benefits). We only included the GLTEQ HCS in the statistical analysis. The CAM intervention involved exercise training through yoga, which is explicitly listed as an example of a mild activity in the GLTEQ. The present study examined physical activity behavior change through the intervention rather than the intervention compliance (e.g., session attendance).

SCT variables The SCT variables included self-reported measures of (1) Exercise Self-efficacy Scale (EXSE),[34, 35] (2) Multidimensional Outcome Expectations for Exercise Scale (MOEES),[36] and (3) Exercise Goal-setting Scale (EGS).[37] The EXSE[34, 35] assesses an individual's belief in their ability to engage in more than 40 minutes of moderate physical activity 3 times per week, in 1-month increments, across the next 8 months. This measure contains 8 items and is rated on a scale from 0 (Not at all confident) to 100 (Completely confident). The scores are averaged into a composite score that ranges between 0 and 100. Higher scores represent greater confidence in engaging in exercise regularly. The scale has good internal consistency and evidence of score validity in adults.[38] The scale has been used in previous research on physical activity in MS.[39-42] The MOEES[36] assesses three domains of physical, social, and self-evaluative outcome expectations for exercise. This measure, containing 15 items, is rated on a 5-point scale from 1 (Strongly disagree) to 5 (Strongly agree). The scores are summed into an overall score that ranges between 15 and 75. Higher scores indicate greater perceptions on outcome expectations. There is evidence that supports internal consistency and validity of scores in older adults[43] as well as persons with MS.[44] The EGS[37] assesses a tendency for setting goals for exercise. This measure contains 10 items and is rated on a 5-point scale from 1 (Does not describe) to 5 (Describes completely). The scores are summed into an overall score that ranges between 10 and 50. Higher scores reflect a stronger tendency for setting exercise goals. There is evidence that supports reliability and validity of scores in young adults,[37] and it has been used in previous research on physical activity in MS.[40, 41]

Demographics/Clinical characteristics Participants self-reported age, sex, MS type, residential location, clinic allocation, and disease severity. Disease severity was measured using the PDDS scale, which contains a single item for measuring mobility disability using an ordinal scale from 0 (Normal) through 8 (Bedridden). The PDDS scale is linearly and strongly related with the physician-administered Expanded Disability Status Scale.[28]

Tele-Exercise and Multiple Sclerosis [TEAMS] Study

The TEAMS study was delivered over a 1-year period (3-month CAM intervention and 9-month follow-up) and primarily aimed at improving fatigue, pain, quality of life, and physical activity level. The CAM intervention consisted of yoga, Pilates and neurorehabilitation exercises (dual-tasking, functional movements). In addition, TeleCAM participants received SCT-based information using educational articles and an automated communications system. The system provided individually tailored feedback and encouragement (verbal persuasion), targeting self-regulation, self-efficacy, and social supports. Further details about this program are provided elsewhere.[26]

Data Analysis

All analyses were performed using Stata 16.1. Descriptive characteristics are presented as mean ± standard deviation (SD), unless otherwise noted (e.g., median, interquartile range [IQR], frequency [*n*], and percentage [%]). Data were examined for outliers who reported GLTEQ HCS > 98 for physical activity outcomes at baseline, 3-month follow-up, and 6-month follow-up and excluded from the analysis.

We conducted Spearman rank-order correlations and partial Spearman correlations for examining the associations due to non-normal distribution of the main outcome variables and less sensitivity to outliers. The partial Spearman correlation was adjusted for the following covariates: age (year), sex (male vs. female), MS type (relapse-remitting vs. others [progressive, unknown]), disease severity [PDDS ≤ 2 vs. > 2], and clinic allocation (22 sites). Following examination of the associations between SCT variables and absolute physical activity, the partial Spearman correlation was further adjusted for baseline and 3-month physical activity. Correlation coefficients (r) of 0.1, 0.3, and 0.5 were interpreted as small, moderate, and large, respectively.[45]

SCT variables showing significant associations with physical activity level in partial Spearman correlation analyses were entered into multiple logistic regression models, and a covariate-adjusted ROC analysis was used to determine the optimal cut-off points for each predictor. Covariates included were age, sex, MS type, and PDDS, and clinic allocation was also included as a random factor. The absolute physical activity at 3- and 6-month follow-up was categorized into two binary anchor groups (0 = *active group* [≥ 24 units]; 1 = *moderately/ insufficiently active* [< 24 units]), respectively. The change in physical activity was categorized into two binary anchor groups (0 = responders [Δz score ≥ 0.5]; 1 = low-/non-responders [Δz score < 0.5].

We determined the optimal threshold (i.e., cut-off value) of SCT variables by maximizing the Youden Index (sensitivity + specificity -1). The Youden Index measures the effectiveness of a diagnostic marker (e.g., diseased vs. healthy individuals) and permits the selection of an optimal cut-off point for the biomarker of interest.[46] In our case, the biomarker of interest was the binary physical activity anchor group (i.e., being physically active vs. moderately/insufficiently active). The accuracy of a diagnostic test is often summarized by the area under the curve (AUC)[47] and interpreted using the following categories: 0.5– 0.6 is fail, 0.6–0.7 is poor, 0.7–0.8 is fair, 0.8–0.9 is good, and 0.9–1.0 is very good.[48]

RESULTS

Participants

A total of 377 records were initially retrieved from the TEAMS database, and 326 records of individuals who reported at least one physical activity outcome measure were included in the final analyses. The sample was middle-aged (50 ± 11 years) and primarily female, Caucasian, metropolitan residents, and relapsing-remitting course of disease with moderate mobility disability based on a median (IQR) PDDS score of 2, with a range of 1 to 4. The detailed characteristics of participants are provided in Table 1.

Table 1. Participant demographics and clinical characteristics (*n* = 326)

Variable	All
Age, year; mean ± SD [range]	50 ± 11 [20, 71]
Sex, female/male *n* (%)	291 (91) / 35 (11)
MS type, RRMS/others *n* (%)	261 (80) / 65 (20)
Race, Caucasian/others *n* (%)	239 (74) / 86 (26)
Residential Area, metropolitan/others *n* (%)	245 (75) / 81 (25)
PDDS Median (IQR)	2 (1-4)

Note. SD = standard deviation; RRMS = relapse-remitting multiple sclerosis; Others in MS type includes progressive MS and unknown diagnosis; Others in race includes African American and others; Others in residential area includes micropolitan, small town, and rural area; IQR = Interquartile range; PDDS = Patient Determined Disease Steps.

Physical Activity and SCT Outcomes

The mean of 3-month change in the GLTEQ HCS (baseline to 3-month follow-up) was 4.32 ± 14.79 arbitrary units (n = 273), ranging from -55 to 62. The mean of 3-month change in the GLTEQ HCS (3- to 6-month follow-up) was 5.88 ± 17.16 arbitrary units (n = 241), ranging from -60 to 70. The mean of the GLTEQ HCS at 3-month follow-up was 12.95 ± 16.53 arbitrary units (n = 298), ranging from 0 to 80. The mean of the GLTEQ HCS at 6-month follow-up was 14.64 ± 17.90 arbitrary units (n = 278), ranging from 0 to 98. The median of GLTEQ HCS at 3-month and 6-month was 0 arbitrary units (IQR 0 – 10).

There were decreases in the mean value of self-efficacy (-11.23 ± 24.30, ranging from -100 to 68.7) and outcome expectations (-1.48 ± 8.18, ranging from -56 to 23) from baseline to 3-month follow-up. The mean value of goal setting was increased (4.53 ± 8.82, ranging from -26 to 40) from baseline to 3-month follow-up.

Correlations Among SCT Variables and Physical Activity

The correlations between SCT variables and physical activity are presented in Table 2. The partial Spearman correlation indicated goal setting was the strongest and most statistically significant variable with physical activity level. Among the overall sample, there were small correlations between 3-month goal setting and physical activity at 6-month follow-up (0.24); this was statistically significant ($p < 0.001$).

Table 2. Spearman and partial Spearman correlation coefficients

	GLTEQ HCS at 3-month (n=273)	Change in GLTEQ HCS (baseline to 3mo) (n=273)
Baseline EXES	0.03	0.02
Baseline MOEES	0.12	0.08
Physical	0.08	0.07
Social	0.17†	0.13*
Self-evaluative	0.04	0.00
Baseline EGS	0.18†	0.07
	GLTEQ HCS at 6-month (n=234)	Change in GLTEQ HCS (3- to 6-month) (n=231)
3-month EXES	0.08	0.09
3-month MOEES	-0.08	-0.06
Physical	-0.02	-0.06
Social	-0.13	-0.12
Self-evaluative	-0.02	-0.02
3-month EGS	0.24†	0.19†

Notes. EXES = Exercise Self-efficacy scale; MOEES = Multidimensional Outcome Expectations for Exercise Scale; EGS = Exercise Goal-setting Scale; GLTEQ HCS = Godin Leisure-Time Exercise Questionnaire health contribution score. *$p < 0.05$; †$p < 0.01$

Estimation of Cut-Off Points

The results of multiple logistic regression models are presented in Table 3, predicting binary physical activity anchor groups were significant with baseline goal setting, baseline outcome expectations - social, and 3-month goal setting, after accounting for covariates (age, sex, MS type, PDDS, and clinic allocation). The cut-off values of baseline goal setting, baseline outcome expectations, and 3-month goal setting were calculated by ROC (Table 3). The cut-off value of 3-month goal setting was chosen at 33 units, with an AUC of 0.863 (good), whereas the cut-off value of 3-month goal setting was 32 units with an AUC of 0.734 (fair). The cut-off value of baseline outcome expectations was chosen at 12 units, with an AUC of 0.695 (poor).

Table 3. Results from multivariable logistic regression model, estimated AUC, and cut-off values in the physical activity level

Physical activity anchor (DV)	SCT Predictor (IV)	F-value	*p*-value	AUC	Cut-off value	Sensitivity	1-Specificity
Absolute GLTEQ HCS vs. SCT predictor							
3-month GLTEQ HCS [<24 vs. ≥24]	Baseline MOEES Social	6.67	0.010*	0.630	12	50%	25%
3-month GLTEQ HCS [<24 vs. ≥24]	Baseline EGS	3.88	0..050	-	-	-	-
6-month GLTEQ HCS [<24 vs. ≥24]	3-month EGS	6.87	0.009†	0.863	33	81%	31%
Change in GLTEQ HCS vs. SCT predictor							
Baseline to 3-month GLTEQ HCS change [<6 vs. ≥6]	Baseline MOEES Social	3.11	0.079	-	-	-	-
3- to 6-month GLTEQ HCS change [<29 vs. ≥29]	3-month EGS	14.99	<0.001†	0.734	32	69%	31%

Notes. DV = dependent variable; IV = independent variable; GLTEQ HCS = Godin Leisure-Time Exercise Questionnaire health contribution score; EXES = Exercise Self-efficacy scale; MOEES = Multidimensional Outcome Expectations for Exercise Scale; EGS = Exercise Goal-setting Scale; AUC = area under the curve. *$p < 0.05$; †$p < 0.01$

DISCUSSION

This study involved examination of SCT variables as correlates of self-reported physical activity behavior among people with MS who completed a tele-exercise intervention of the TEAMS study. Further, this study involved examination of SCT as predictors of MVPA level after the TEAMS intervention (i.e., *active* vs. *moderately/insufficiently active*). To our knowledge, this is the first known examination that has used SCT variables to gauge future success of physical activity level. Our results may have practical implications for developing future adaptive interventions for changing physical activity behavior for people with MS.

The present study identified positive, moderate associations between baseline goal setting and outcome expectations and physical activity level at 3-month follow-up, and between 3-month goal setting and self-efficacy and physical activity level at 6-month follow-up. Our results are similar to previous studies in the sense that goal setting was the strongest predictor of physical activity level among SCT variables, yet the findings are not directly comparable.[13, 49] The previous studies focused on correlations between changes in physical activity level after behavioral interventions and SCT variables (e.g., baseline SCT variables with 3-month changes in physical activity; 3-month changes of SCT variables with 3-month changes in physical activity).[13, 49] We were not able to replicate the previous findings in our data set.

Possible explanations for why we found no relationships between SCT variables and changes in physical activity after the intervention might be the observed ceiling effects of SCT instruments, the lack of variability, and measurement error issues in estimating physical activity using the GLTEQ in pragmatic settings. For example, we observed that half of the participants (53%, n = 399/753) reached the ceiling of self-efficacy scale at baseline, whereas 38% of participants reported the maximum score in this scale at 3-month follow-up. The trend of reduction in self-efficacy scores after an intervention is similar to previous studies.[49] This might be a result of participants' "misunderstanding" their capacity to perform physical activity at true baseline, and participation in the intervention helps them to know how much they can do and then build a stronger understanding of their abilities to perform physical activity. This observation might support adjusting the timing of psychometric measures upon completion of a brief intervention period (e.g., 2-week pre-session) and then determining participants' remaining intervention regimen (e.g., needs of one-on-one support, behavioral coaching, progression of exercise minutes). Further, researchers may consider modifying the current SCT instruments and developing a comprehensive, more targeted SCT-based instrument to predict physical activity, which has been implemented in the field of spinal cord injury research.[50]

This present study identified two ideal cut-off points (22 in baseline goal-setting scale and 33 in 3-month goal setting scale) as candidate scores to differentiate levels and types of support. Based on the notion of a stepwise implementation approach, individuals with higher levels of goal setting (e.g., ≥ 22 in baseline) might have the easiest path for successfully increasing physical activity with self-directed programs and minimal support for behavioral change. In comparison, people with lower levels of goal setting (e.g., < 22 in baseline) may require a more intense approach for initiating behavioral change through face-to-face behavioral coaching to develop self-regulatory strategies, a sense of efficacy, positive outcome expectations, and knowledge. Such findings have implications for designing and developing future interventions that tailor group allocation based on participant characteristics that are obtained during an early stage of the intervention. Of note, we observed similar baseline mean and distribution (SD) of goal-setting scores among the TEAMS participants (23.47 ± 9.45) compared to those in previous studies (intervention and cross-sectional studies).[41, 51] The baseline mean and SD of physical activity scores (i.e., 20.48 ± 18.55 of GLTEQ total leisure score) were also similar between the TEAMS participants and those in previous studies.

This study includes limitations. First, this study involved an exploratory analysis of data from a CAM intervention that targeted both exercise and neurorehabilitation with relatively low intensity of behavioral change strategies delivery (no involvement of in-person coaching or counseling). Although the TEAMS study aimed to increase physical activity, this may have created a disconnection between the type of intervention and changes in outcome interest (SCT variables, physical activity). Second, the current study primarily focused on a relatively narrow set of SCT variables, and there is a range of other important constructs (e.g., goal planning, knowledge, facilitators/impediments, social support) that might operate independently and interactively with SCT variables to explain the relationship with physical activity in the TEAMS intervention. Last, the identified cut-off points of goal setting in this study (identification step) have not yet been tested. Future studies are warranted to consider validating these cut-off points in a second independent population (i.e., validation step).

CONCLUSIONS

This study identified goal setting within SCT variables as the strongest factor for achieving an active level of physical activity. The findings of this study support the importance of personalized, tailored program content to participants' baseline level of goal-setting ability with differentiated levels and types of support (e.g., self-directed programs vs. intense programs with behavioral coaching). The findings of this study also suggest goal setting as a strong candidate for a tailoring variable when researchers are designing future adaptive interventions. Thus, this study strengthens the growing body of work on this topic and informs future intervention design, especially adaptive intervention, aimed at promoting physical activity behavior.

Conflict of interest

The authors declare no conflict of interest.

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A QUALITATIVE EXPLORATION OF A TELE-EXERCISE PROGRAM TO INFORM THE DESIGN OF ADAPTIVE INTERVENTION STRATEGIES FOR ADULTS WITH MULTIPLE SCLEROSIS

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ABSTRACT

Purpose: We examined the experiences, perceptions, and suggestions of people with multiple sclerosis (MS) who completed a 3-month tele-exercise program regarding program components and implementation procedures (i.e., exercise videos, educational articles, automated communication system). This study sought to identify modifiable factors that could be used to develop an adaptive tele-exercise intervention from two groups of participants (people who increased their physical activity level after the intervention vs. no change/decreased their physical activity level) and two time points (during and after the 3-month formal intervention period).

Methods: Twenty-two people with MS were interviewed using a semi-structured interview guide on the exercise program and its delivery. Participants were recruited from a tele-exercise program which was grounded in the social cognitive theory (self-efficacy, outcome expectations, barriers, facilitators, self-regulatory strategy). Using interpretive thematic analysis, we identified desired components of tele-exercise programs and their delivery.

Results: Our analysis indicated the importance of individualized, ongoing modification of exercise program difficulty to accommodate changes in participants' functional abilities and health status. Participants reported an ideal time point of human support, preferably every 3 weeks via phone and/or videoconference calls to make the intervention modifications (e.g., variation of exercise position, difficulty, clarification of movements). We further identified desirable components for behavioral modifications, such as inclusion of an exercise companion, exercise reminder text/email, and self-monitoring tool to gauge their progression during the formal intervention period, and post-intervention resources for sustained participation after completion of the formal intervention component.

Conclusions: The findings of this study offer insights to researchers for tailoring and targeting future adaptive tele-exercise intervention designs aimed at promoting engaged and sustained exercise participation in people with MS.

Keywords: Multiple sclerosis, exercise, telehealth, adaptive intervention, qualitative evaluation

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated, neurodegenerative disease of the central nervous system[1] that results in mobility and cognition dysfunction and symptomatic fatigue, pain, and depression.[2] Such consequences can further reduce participation in activities of daily living and compromise quality of life.[3, 4] MS requires long-term rehabilitation for managing the progression of the disease and associated manifestations over time. In addition to traditional medical treatment, participation in physical activity, including exercise training, has been identified as a primary therapeutic measure for improving and maintaining health and function. There is a substantial evidence base that exercise training can improve health, symptomatic, and functional outcomes in people with MS,[5-7] including maintaining walking ability,[8] reducing fatigue[9] and depression,[10, 11] and improving overall quality of life.[12] Further evidence suggests that exercise is associated with a reduced rate of relapse and disease progression in MS.[13, 14]

Despite these benefits, few people with MS engage in adequate amounts of exercise for accruing health benefits. This corresponds to a consistent trend of low levels of physical activity in persons with MS compared to the general population and adults with other health conditions.[15-17] People with MS often encounter a myriad of unique, perceived barriers that restrict their exercise and physical activity participation in society. These barriers can range from personal level (e.g., fatigue, fear, lack of knowledge, self-regulation skills, social support) to environmental level within the community (e.g., lack of accessible facilities/options, knowledgeable instructors, or transportation).[18] These barriers make it much more challenging for people with MS to achieve the U.S. public health guideline of 150 minutes/week of moderate to vigorous physical activities (MVPA).

One area that needs further study is designing and delivering more targeted and tailored exercise programs for people with MS. Exercise responses often have varying rates of success at the individual level.[19] These factors are referred to as response heterogeneity. Some individuals can experience large improvements in physical activity after an exercise trial while others may demonstrate no change or even a decrease in physical activity.[20-22] Reasons for these differences could include certain participant-specific characteristics, such as MS type, disability severity, knowledge, self-efficacy, outcome expectations, goal setting, and facilitators/barriers to exercise.[20-24] Collectively, these findings suggest that examining response heterogeneity may help to develop more targeted and tailored exercise interventions for people with MS.

A few qualitative studies have suggested that people with MS want exercise programs with meaningful benefits, tools for initiating and maintaining exercise behaviors, and various ways that they can do the exercise (e.g., different locations between home and community; support methods through autonomous, one-on-one, and group exercise).[25-27] Exercise programs supported by information communication technology (i.e., tele-exercise) have gained in popularity over the last decade and may help to address the needs of participants with MS.[28] Tele-exercise programs support people at home, which is convenient for many people with disabilities. Tele-exercise is also more cost efficient and convenient (i.e., do not require transportation or large travel times) than programs offered in the community, making it easier to reach larger groups of people with MS.[29] To date, studies have not specifically identified needs and preferences for participation in a tele-exercise program in people with MS.

To better understand response heterogeneity in people with MS, we conducted a qualitative study to describe the experiences and perceptions of program components and implementation processes (i.e., exercise videos, educational articles, automated communications system) during and after a 3-month tele-exercise program. The study was nested within a pragmatic, cluster randomized controlled trial referred to as the Tele-Exercise and Multiple Sclerosis [TEAMS] study.[30] The TEAMS study compared the effectiveness of a tele-exercise program to the same intervention delivered in a clinic by a therapist on fatigue, pain, quality of life, and physical activity. The design of the TEAMS study was supplemented by behavioral change strategies for increasing exercise at home and adherence to physical activity both during and after the intervention. The primary purpose of this qualitative study was to examine two groups of TEAMS participants, *responders* vs. *Low-/non-responders*. Responders had a clinically meaningful increase in their level of physical activity after the formal intervention period. Low-/non-responders were people who reported minimal to none change or a decrease in their level of physical activity. Accordingly, this qualitative research study sought to answer the following central research question: What are the different experiences, perceptions, and suggestions between responders and low-/non-responders regarding program components and implementation procedures during and after participation in a tele-exercise program?

METHODS

Philosophical Assumptions and Design

A narrative inquiry was chosen in this qualitative study underpinned by an interpretivism paradigm. The narrative inquiry focuses on the storied experiences of individuals (i.e., narrators) based on their lives within the social worlds and particular perspectives to do certain things (e.g., exercise participation with MS) and layout the meaning of those experiences in chronological order.[31] This inquiry has been commonly used to learn more about the historical experiences and lifestyle of individuals.[32] Thus, we used the specific inquiry to understand the details of situations, experiences, and perceptions not elsewhere recorded during program participation. The interpretivism paradigm is characterized by two philosophical assumptions. First, ontological relativism asserts that reality is subjective, multiple, and socially constructed.[33] Second, epistemological constructivism asserts that knowledge is constructed through interactions between individuals and social and cultural environments.[34] Accordingly, both participants and researchers were actively involved in recalling and crafting the narratives that resulted from participation in the program.

Sampling Procedure and Participants

We utilized purposeful sampling strategies, including convenience, maximum variation, and criterion-based sampling techniques. The participants were a convenience sample recruited from the tele-exercise arm (TeleCAM) of the TEAMS study.[30] Individuals, who had expressed interest in completing a post-intervention interview and/or being contacted for future studies, were screened based on completion of the (1) 3-month intervention, (2) physical activity questionnaire for both baseline and 3-month follow-up assessments, and (3) completion of the (1-year) TEAMS program no more than 6 months before the interview.

The maximum variation sampling method facilitates matched characteristics between the two groups of participants, including age, sex, race, location (metropolitan vs. micropolitan/small town), type of MS, and disease severity. Disease severity was reported using the Patient Determined Disease Steps (PDDS) scale, which is linear and strongly related to the physician-administered Expanded Disability Status Scale scores.[35] The scale mainly measures mobility limitation using an ordinal scale from 0 (normal) through 8 (bedridden).

The criterion-based strategy was used to recruit individuals who possess different knowledge and experience with the phenomenon of interest and to seek detailed, in-depth, and rich information.[36] We sought to include two groups of participants (*responders* and *low-/non-responders*) based on the response to treatment outcome, physical activity. The level of physical activity was measured using health contribution scores from the Godin Leisure-Time Exercise Questionnaire (GLTEQ).[37] The GLTEQ is a valid measure of physical activity in the general population of adults and people with MS.[38] The health contribution scores from the GLTEQ reflect public health guidelines for levels of MVPA in people with MS.[39]

From the initial dataset ($n = 230$), we created z scores for the baseline and 3-month follow-up physical activity measures. The z score was calculated based on the observation minus mean of the entire sample divided by standard deviation (SD) of the entire sample using SPSS Statistics 25 (IBM, Inc., Armonk, NY). We then created

Δz (i.e., change in z scores) between baseline and follow-up (follow-up minus baseline z scores). This Δz can be directly interpreted as change in SD units and accounted for clinical meaningfulness based on the guideline of 0.5 SD (i.e., Cohen's *d* of 0.5); this guideline of 0.5 SD has been deemed as a universal threshold for judging effects as clinically meaningful.[40] Therefore, participants who demonstrated a clinically meaningful increase in physical activity (i.e., a Δz of ≥ 0.5 SD) were categorized as *responders* (i.e., ≥ 9 changes in the GLTEQ *health contribution scores*), whereas participants who reported minimal to none change or decrease in physical activity were categorized as low-/*non-responders* (i.e., < 9 changes in the GLTEQ *health contribution score*).

A total of 110 people initially consented to either a formal program evaluation interview or contact for future studies. Of those, we excluded 51 due to incompletion of physical activity questionnaire for baseline and/or 3-month follow-up assessments, completion of the 1-year program longer than 6 months before the interview, and participation in a formal program evaluation interview prior to this study. We identified 59 potential participants for this qualitative study. Of those, 19 were responders and 40 were low-/non-responders based on the criterion-based sampling strategy. The first author (YK) emailed an initial invitation among 59 potential participants. 25 expressed interests, and seven were lost to follow-up or did not attend the interview. This yielded a sample of 22 (8 responders, 10 low-/non-responders). Then, the first author emailed a follow-up invitation to recruit matched characteristics of participants between groups (age, sex, resident location) and reach theoretical saturation for each group. This yielded a final sample of 22, including *responders* (*n* = 10) and *non-responders* (*n* = 12).

Tele-Exercise and Multiple Sclerosis [TEAMS] Intervention

The TEAMS study is a multicenter, cluster randomized, effectiveness-controlled trial that was delivered through 41 rehabilitation clinics in Alabama, Mississippi, and Tennessee among 837 people with MS between 2016 and 2021. The study primarily aims at improving pain, fatigue, quality of life, and physical activity behavior through the delivery of a 3-month complementary and alternative medicine (CAM) exercise intervention into two delivery modes: home through the use of a tablet or at a clinic by a therapist. The TEAMS study is a 1-year study that includes the 3-month intervention (20-session) and a 9-month follow-up period.

The CAM intervention involves elements of yoga[41-48] and Pilates exercises,[49-53] and neurorehabilitation activities (dual-tasking and functional movements).[54, 55] The yoga and Pilates exercise routine features a series of movements aimed at addressing flexibility, strength, balance/proprioception, balance, and relaxation through breathing practices. The routine of dual-tasking and functional movements involves performing vision, cognition, and gross/fine motor tasks aimed at improving the ability to perform more than one task at a time successfully without compromising balance and increasing fall risk (e.g., multidirectional reach while carrying on a conversation; ball bouncing while tracking the ball with head and eye movements). The first 8-week component (weeks 1-8) includes yoga, Pilates, and neurorehabilitation activities (20 minutes each) that are prescribed twice a week. The second 4-week component (weeks 9-12) contains only yoga and Pilates and the frequency is reduced to once a week. The intervention is adapted and tailored to each participant's mobility level using the Timed 25-Foot Walk score as a proxy for functional mobility.

The design of the TEAMS study was grounded in social cognitive theory (SCT). SCT has been a commonly applied theoretical framework in MS research when designing and testing health promotion interventions, including physical activity.[5, 56, 57] The participants in the tele-exercise program, who were also included in this qualitative study, received a tablet with preloaded videos and articles that contained educational information aligned with the key constructs of SCT (self-efficacy, outcome expectation, knowledge, self-regulatory strategies, facilitators/barriers). In addition, tele-exercise program participants received weekly phone calls through an automated communication system (i.e., Interactive Voice Response system). The system further provided individually tailored feedback and encouragement (verbal persuasion), targeting self-regulation, self-efficacy, and social supports. Further details about this program are provided elsewhere.[30]

Data Collection

Prior to the interview, we provided a full description of study and obtained verbal consent. The data collection method included a semi-structured, a single one-on-one interview. The interview was conducted via telephone or Zoom conference call based on the participant's preferences. The interview was guided based on preplanned questions (i.e., interview guide) presented in Appendix IV. The interview questions were framed around the key SCT constructs and further refined from previous literature and our experiences in the field of MS research. Each interview lasted up to one hour and was audio-recorded. The audio-recorded interviews were then transcribed *verbatim*, using an external transcription service (Samedaytranscription.com). The participant's response was clarified when needed using probes (e.g., Is this what you mean? Am I hearing this correctly?). Upon completing the interview, each participant received a $25 gift card.

Data Analysis

All participants were assigned an identification number. The transcripts were analyzed using thematic analysis. This method focuses on describing patterns across an entire data set (i.e., themes) by highlighting similarities and differences and summarizing key features.[58] The flexibility of thematic analysis allows researchers to choose a theoretical framework that facilitates rich, detailed and complex descriptions of the collected data.

The analysis technique involved the following steps performed independently for the *responder* and *non-responder* groups. The first step was to *generate initial codes* (*general themes*) across the entire data set in a systematic fashion (i.e., segment by segment). We identified initial codes by looking for common threads in the transcripts using specific words or phrases within passages and organized them into 5 categories (i.e., barriers, facilitators, likes, dislikes, and suggestions). Two analysts (YK, BL) performed independent, segment-by-segment coding. The second step was to *categorize the initial codes into focused codes* (*general description of each initial code*). The analysts discussed grouping the initial codes into logical categories by assembling descriptions and interpretations of the initial codes. The first analyst (YK) then revisited the data to enhance the initial and focused codes with a detailed description. The third step was to *organize the focused codes into higher-level categories* (*themes*) that can provide a rich description of the phenomenon. The fourth step was to *categorize the themes into two time-period categories:* (1) during the 3-month intervention period and (2) after completing the formal intervention component (i.e., during the 9-month follow-up period). The final step was to *synthesize the results of the coding process into a bullet list of modifications* (e.g., how, when, and based on which measure to alter treatment) by noting the needs and recommendations that were described across participants, thereby providing further context for adaptive intervention components for people with MS.

Ensuring Rigor

Three approaches were implemented to maintain the transparency and trustworthiness of this study: audit trail, coding triangulation, and critical friend. The audit trail was used to disclose a detailed, trackable document that accounts for the methods, procedures, and decision points while analyzing the qualitative data. Two analysts performed independent, segment-by-segment coding and then discussed the themes and final coding scheme jointly. The iterative data analysis and discussion processes contributed to achieving trustworthiness between the two analysts.[59] In addition, the "critical friend" was involved to ensure the appropriate research process and weight on the interpretation of relevance and importance of themes.[33] The critical friend in this study (EB) has been prolific in the field of rehabilitation research with her qualitative expertise.

RESULTS

The summary characteristics of all participants are provided in Table 1. The overall samples predominantly consisted of women (*n* = 19/22, 86%), Caucasian (*n* = 16/22, 73%), relapsing-remitting MS (*n* = 15/22, 68%), and urban residents (i.e., metropolitan) (*n* = 16/22, 82%). The two groups of participants were matched by age, gender, MS type, and resident location. However, the groups differed on race and disease severity. We had a smaller number of African Americans in the low-/non-responder group (*n* = 2/12, 17%) vs. the responder group (*n* = 4/10, 40%). While study participants represented a broad range of disease severity (PDDS from 0 [normal] to 7 [use of wheelchair/scooter as main form of mobility]), the low-/non-responder group had a higher number of people with mobility disability (PDDS score below 3; *n* = 7/12, 58%) compared to responder group (*n* = 3/10, 30%).

The resultant themes and sub-themes are described below. Four themes related to program component and its delivery during the 3-month formal intervention period (Themes 1 – 4), and two themes related to study participation during the 9-month follow-up period (Themes 5 – 6).

Table 1. Participant characteristics (*n* = 22)

ID	Age	Sex	Race	Location	MS Type	PDDS	Change HCS
1	31	F	AA	Metro	RR	1	60
6	46	F	AA	Metro	RR	0	10
8	41	F	C	Metro	Unknown	1	15
12	24	F	C	Metro	Unknown	2	15
13	46	F	C	Micro	RR	3	10
14	25	F	C	Metro	Unknown	3	19
15	51	M	C	Micro	RR	6	30
19	55	F	AA	Metro	RR	2	10
20	67	F	C	Metro	RR	0	15
23	41	F	C	Micro	RR	1	39
Responders (*n* = 10)	43 (13)	9 F / 1 M	6 C / 4 AA	7 Metro / 3 Micro	7 RR / 3 Unknown	2 (1 – 3)	
3	58	F	C	Metro	RR	4	4
4	49	F	C	Metro	RR	4	0
5	33	F	C	Micro	Progressive	3	-10
7	61	F	C	Metro	RR	1	4
9	41	F	C	Micro	RR	3	5
10	56	F	C	Metro	Unknown	4	0
11	53	M	C	Metro	Unknown	4	0
16	26	F	AA	Small Town	RR	0	-10
17	34	F	AA	Metro	RR	1	5
18	60	F	C	Metro	RR	1	-5
21	48	M	C	Metro	Progressive	7	-20
22	58	F	C	Metro	RR	2	-15
Non-responders (*n* = 12)	48 (12)	10F / 2M	10 C / 2 AA	9 Metro / 2 Micro / 1 Small Town	8 RR / 2 Progressive / 2 Unknown	3 (1 – 4)	

Note. Age is reported as mean (standard deviation) and disease severity (i.e., PDDS) was reported as median (IQR). F: female; M: male; C: Caucasian; AA: African American; Metro: metropolitan; Micro: micropolitan; RR: relapsing-remitting; PDDS: Patient Determined Disease Steps; GLTEQ: Godin leisure-time exercise questionnaire

Theme 1. Desired appropriate level of challenges over time to facilitate positive perception

The first theme highlights the importance of providing participants with an appropriate level of challenges for maintaining positive views and attitudes toward exercise. Participants liked the variations of the movements and progression of the exercise program. Many participants commented that the exercises were appropriate for their ability throughout the intervention period, which created feelings of confidence, achievement, and self-improvement. In contrast, when content was perceived as not relevant to their stage of post-diagnosis or functional ability, participants discussed negative perceptions regarding program content that could potentially be modified to optimize program participation. Two sub-themes were identified: (a) non-challenging exercises caused boredom or lack of interest; and (b) overly challenging exercises created feelings of frustration, anxiety, and loss of confidence during performance. These experiences and perceptions were observed across responder and non-responder groups.

(a) Non-challenging exercises caused boredom or lack of interest.

Participants reported that too easy/slow exercises were not perceived as "exercise" and created feelings of boredom and lack of interest. Some participants reported that their expectations of program intensity were not adequately met throughout the intervention period. Participant 8 remarked on previous experiences with Pilates and commented,

> "I thought that the program was going to be more challenging as far as the exercises went. I thought it would be something that was going to make me push myself a little harder. My normal exercises were Pilates so I was used to doing that, that's why I said I was expecting something just a little bit more."

There were participants who felt that exercise was no longer beneficial with their progression during the middle to end of the program. Across participants, the timing ranged from 8 to 10 weeks (average of 9 weeks). These feelings of disinterest and no longer receiving benefits from the program were shared by participant 3, who stated,

> "There were times [*moving toward 8 – 9 weeks of the program*] that I felt like that I could do more. And I didn't necessarily want to do the initial visit and assessment over again. I would've liked to have had the option to maybe try a more difficult level. And if I couldn't do it, then I couldn't do it. But at least I could try because I felt like at a certain point I wasn't getting anything out of it. I wanted to see if I could do something a little bit tougher and you don't have that option. You're locked into your level."

(b) Overly challenging exercises created feelings of frustration, anxiety, and loss of confidence.

In contrast, participants reported that when the program was perceived as too difficult, it created feelings of frustration, anxiety, and loss of confidence during performance. Some participants completely skipped the movements, whereas others did their best to match the movements (e.g., pause/start the video repeatedly, use a chair for balance support). However, when they performed the movement unsuccessfully, it created a feeling of frustration. Participants commented that their starting levels of fitness and balance made some movements difficult to perform, which created anxiety and deteriorated confidence over time. The loss of confidence when the exercise was perceived as too challenging was noted by participant 9, who stated,

> "When I started I was confident and as they got slightly harder I got less confident if that makes sense. There was a lot of balance and that is my weak spot so I think I started to feel less confident the more it pushed you to do

more. My physical balance is bad so whenever there were more challenging balance exercises I became less confident. More anxious, that's the word."

Theme 2. Preference for personalized content and communication channels to support exercise behavior change

The second theme identified that participants desired multiple communication channels that can facilitate program participation and exercise behavior change. Two sub-themes were identified: (a) general, irrelevant content created feelings of disinterest and disconnection; and (b) participants wanted multiple communication channels to support exercise behavior modification. These experiences and perceptions were described from both responders and non-responders.

(a) General, irrelevant content created feelings of disinterest and disconnection. Related to the educational articles that aligned with the key constructs of the SCT, participants reported that articles contained important information about MS. However, many participants felt that the content was too general and irrelevant to themselves, which created feelings of disinterest. Participants wanted more personalized, targeted information for their topics of interest (e.g., specific barriers to the individual, exercise and cognition). Similarly, related to the automated communication system, participants reported feelings of disconnection when the questions, response options, and feedback were not matched to the person's situation, goal, and achievement. The feeling of frustration was remarked on by participant 8 when the system did not allow the person to report accurate numbers of exercises.

> "The automated calls I liked at first but then when I was exceeding the number of times of doing the exercises, it wouldn't allow me to input that information,

> so it was like okay then nobody really cares that I did it five times this week, they just wanted to make sure I did it two or three."

(b) Multiple communication channels to support exercise behavior modification. Related to the educational articles, many participants reported that they were unaware of the articles being included in the exercise app. Participants suggested multiple ways of increasing their attention to the app and the visibility of the articles (e.g., reminder text, notification within the exercise app). One way of facilitating the use of resources is to add a reminder at the end of the exercise video. Participant 11 commented,

> "My only suggestion is maybe if you have an article that's related to each week, put it at the end of the video. Because if you remember going to a gym, there's always a cool-down time; once the class ends, they want you to kind of just walk around so your muscles don't tighten up. Maybe if you add the article at the end of the video as a cool-down period, it might get more attention. The lady can say, "As you cool down, remember or think about this, and then they could throw that slide up for that article that they want to--that would relate to that week's workout."

Related to the automated communication system, participants reported that the weekly calls provided reminders and positive verbal encouragement to perform the exercises. Yet, some participants desired additional cues or prompts for their behavior modification using email or text reminders before the scheduled exercise date and time. Participant 6 stated,

> "I had [*IVR*] calls on Wednesdays and on Saturdays. And I would see the call from the TEAMS study and would be like, "Oh, my God, I forgot to exercise again." You know, so, I mean, I can take ownership and say that I could've

> done better at reminding myself. But maybe just a reminder call to say, "Hey, you know, don't forget to exercise this week," probably would've been nice."

In addition, participants desired multiple ways to report and monitor their progressions through the program. Participants commented that the IVR system did not support logging of performance at their convenience and monitoring what they reported. The reporting could be done through the app that was used for the exercise videos, emails, or callbacks to the IVR system. To gauge their progression, they wanted to see what they had reported using a graph, summary report, or reward through the app or email. The feeling of motivation through monitoring their progression was noted by participant 12, who said,

> "I know a lot of those apps, like the exercise apps, they have like a little animated sticker or something, something to track your progress. […] or just even a progress report kind of thing on TEAMS app maybe, showing you what week you're on and what you've done in the past maybe could help motivate someone who is not feeling very well that week."

Theme 3. Desired human interaction to increase participation through accountability

The third theme identified the importance of optimal human interaction and support to increase participation through a sense of accountability. Two sub-themes were identified: (a) human connection enhances feelings of support; and (b) exercise companionship enhances motivation. Both responder and non-responder groups reported similar experiences, perceptions, and suggestions.

(a) Human connection enhances feelings of support.

Participants wanted human support from research staff for an occasional check-up as a supplement or replacement to IVR, preferably every 3 to 4 weeks. Many participants reported that one-way communication created feelings of frustration because IVR calls left participants with no options to reschedule the call, call back, or provide elaborate responses beyond simple yes, no, or number. They described that potential check-up calls from a research staff member can resolve technology usability issues (e.g., unable to open videos/articles, errors of IVR calls, loss of ID/password) and answer frequent questions for exercise programs (e.g., variation/adaptation of exercise position, difficulty, clarification of exercise movements). The need for and potential uses of human support were discussed by participant 11, who remarked:

> "I know it would be a lot of phone calls, but Week 3, this group could be called, and Week 2, this week could be called. Once a month would probably been, "How's your equipment going? Is it challenging enough?" And maybe at that point, if I would have been asked so many weeks out, "Is it challenging enough?" "Well, I'm still doing that--I'm still doing the exercises, but could I have a little bit more?" And that person could say, "Okay, let's look at what you're doing. You're in Group B. Group A is a little bit more challenging, would you be interested in that?" and then see they could."

(b) Exercise companionship enhances motivation.

Participants reported that exercise support enhanced their motivation to participate. Many participants had a companion (spouse, children, grandchildren, members in a support group) that provided physical assistance or social support through verbal encouragement and accountability. The options of support could include a companion or group class that could be done in-person or through a videoconference call. The potential benefit of having an exercise companion was remarked on by participant 21, who said,

> “To have somebody or group, you know, that is going through the exercise that, you know, working on going through the exercise together, that would probably actually be helpful, as well, to be able to motivate each other.”

Theme 4. Perceived barriers to program participation

Participants discussed a multitude of complications that caused lapses in participation. Participants in both responder and non-responder groups reported similar barriers to program participation. Three sub-themes were identified: (a) daily variation of MS symptoms, (b) life stressors and responsibilities, and (c) unexpected injury and health issues.

(a) Daily variation of MS symptoms.

A variety of MS symptoms, such as severe fatigue, heat sensitivity, or spasticity, were reported as barriers. The severity of the symptoms fluctuated on sometimes a daily or seasonal basis. When the symptoms were severe, they directly prevented participation, as participants wanted to avoid exacerbating their condition. The challenge associated with MS symptoms during the summer was shared by participant 1, who remarked,

> “My MS is super affected in the summertime. So, during the summer months it was—oh my gosh—hit or miss. Maybe once a week I was doing something successful. But even on a week-to-week basis there would be times where I wouldn’t do the exercises at all because literally all I could do was get out of my bed, and like get to my couch in the living room.”

(b) Life stressors and responsibilities.

Participants reported multiple roles and responsibilities in their daily living. The responsibilities include parental duties, house chores, caregiving for a family member with an illness, and work life. These responsibilities were understandably placed at a higher priority over exercise within their daily routine. The fatigue after long hours of work was shared as a barrier to exercise by participant 18, who pointed out,

> "It became a little more difficult to get to exercise after working. As I've gotten older, I'm more fatigued; when I get off work after being there ten hours--ten hours is the shift I work now--so, I know that exercise is supposed to give you more energy, but I sometimes shoot myself in the foot by when I'm fatigued, instead of going to exercise to get more energy."

(c) Unexpected injury or health issues.

Participants reported several unexpected health issues and non-study related injuries that occurred during the intervention period, such as MS relapse, broken bone, biopsy, rotator cuff injury, and bulging disc. These incidents stopped them from participating in the program. Participant 17 said,

> "When we got towards between the middle towards the end, because it was more intense and holding them longer and stuff like that. I found out that I had a bulging disc that I didn't know I had. So, we may have to pause you on doing the end of it and I think at that point may have had four or five more weeks left to do. I don't even think I had that much left to do. I was really close to the end but I couldn't finish it out."

Theme 5. Post-intervention resources may reengage participants in exercise

Both groups of participants reported that the intervention videos are good resources to continue exercise during the follow-up period. However, participants reported that they could be reengaged by supplementary materials that can be given to them after the program. Additionally, some participants had recommendations that could potentially increase their motivation to achieve higher volumes of exercise during the follow-up period. The supplementary materials could include videos with fewer movement instructions or new challenging movements, as well as reminder summary sheets of the exercises. Together, these materials could comprise quick and easy access resources. The feeling of boredom and lack of interest toward the end of the program was shared by participant 11, who commented,

> "After Week 12, it stopped as far as new stuff. And I--for repetitive stuff, it became very mundane. So, in my opinion, if the study could have said, "Well, Week 12 is what we're aiming at getting people; but if there's anybody that would be interested in extending past that Week 12, then that's what I would have liked is more combination of exercise that would extend me past the Week 12. […] There were three different groups based on, I guess, our flexibility because when we had our evaluations done, you're a Group A, Group B, or Group C. If we completed it in B and the therapist signed off and said, "Yeah, you're doing everything great; it looks like you've improved your flexibility. Do you want to go to the next level?" Maybe they could have offered us Group A--and it doesn't have to be supervised, but it would probably--we don't know if that would have given us more exercises or variations to the exercises."

Theme 6. Experiencing benefits facilitates the sustainability of exercise behavior Participants in both responder and non-responder groups reported that they continued the program throughout the follow-up period (i.e., after the completion of the primary 3-month program component) because of the benefits that they received from the intervention. Benefits included improved flexibility, balance, and coordination, as well as reduced muscle stiffness. Also, participants reported increased energy, which eased the performance of daily activities, such as shopping more and walking longer periods of time. Participants reported that the program helped their MS-related symptoms, including increased sleep quality and decreased pain. In addition, participants reported that exercise was used as a coping mechanism (stress relief, relaxation, centering themselves, emotional control) for life stressors, such as parental duties or loss of family. The multiple areas of improvement on physical and psychosocial aspects were shared by participant 16, who said,

> "When I first started the program, I was walking anywhere from 15 to 20, 25 minutes a day. I got to do that five times a week taking my breaks and walking. And now, it's almost... I can walk a while. So, it helped, all of it; it really worked hand in hand. That program, it changes everything; not just physically, but it makes you change how you schedule, and you notice that you improve outside of yoga--through the program--your mental space, everything is better because you're taking that time--that yoga was part of me taking time for me."

DISCUSSION

This qualitative study investigated the experiences, perceptions, and suggestions of participants who undertook a tele-exercise intervention study regarding the program content and implementation procedures during and after the 3-month formal intervention period. To our knowledge, this is the first qualitative study that aimed to explore different experiences, perceptions, and suggestions of people with MS after undertaking program participation based on level of success (i.e., response to treatment outcome). We sought to compare and contrast different experiences and perceptions of people who increased their level of physical activity after the intervention with those who reported minimal to none change or decreased their activity level. We had anticipated that the non-responders would present more challenges to adhering to the exercise regimen but that was not the case. Our findings demonstrated that the two groups of participants reported similar positive and negative perceptions, experienced similar barriers and facilitators to program participation, and described similar preferences for future intervention design. Therefore, we presented the findings jointly. Based upon the findings, we established potential areas to improve the design and delivery of both the formal program components and the post-intervention period that could be used to develop an adaptive tele-exercise intervention for people with MS.

The lack of differences between the two groups may be a result of the classification method using the "snapshot" of physical activity before and after the intervention and measurement error issues in estimating physical activity using the

GLTEQ in pragmatic settings. Further, all participants were interviewed after the completion of the 1-year TEAMS study, ranging from 371 to 540 days from the baseline assessment date. This may influence their responses and reflect the discordance between the qualitative responses and responder status. An alternative method of classification for criterion-based sampling could be done through the automated communication system, which includes weekly adherence questions regarding whether individuals performed exercises with the videos (yes/no), and if yes, how many times they did exercise.

Another reason that we found no differences between groups may have been that all of the participants had similar issues with their health (e.g., fatigue) and common barriers associated with motivation, self-regulation skills, and social support (found in various populations). In related fields of research, when the experiences, perceptions, and suggestions have been directly compared and contrasted, studies often included distinct samples (e.g., healthcare providers vs. people with disabilities, healthcare providers with different professions).[60, 61]

Many participants believed that exercise would be a beneficial and important approach as a non-invasive, non-pharmaceutical MS treatment. Related to the exercise program components, our results indicated that the exercise type (yoga and Pilates) and frequency were acceptable to the participants. The participants also valued the structured, MS-specific exercise program with variations of movements and progression. Some participants indicated that an appropriate level of challenges over time would optimize their exercise participation (Theme 1). Negative feelings and perceptions toward the exercise program were observed when the level of difficulty in the program did not match their functional ability. They suggested occasional human interaction with study staff (phone calls or conference calls) to ask questions about exercise programs (e.g., variation/adaptation to make it more challenging and/or different positions to stimulate the same muscle group with different movements, how to engage core better, and clarification of exercise movements) (Theme 3). Based on the responses across participants, an ideal time point for human contact could be every 3 weeks of the program, ranging from 2 to 4 weeks. This observation is comparable with a few weight loss studies that suggested session 3 and 7 as candidate time points for intervening with participants to assess needs and difficulties and make necessary changes to maximize the treatment response.[62-65]

Participants desired flexibility to modify ongoing programs toward their functional ability when progressing through the exercise program (Theme 1) and accommodate participants' needs and difficulties from their health status change (Theme 4). The participants reported various circumstances that were related to health status changes and temporarily prevented exercise participation (e.g., MS relapse and intensified symptoms, unexpected injury and health issues). This finding aligns with a previous review identifying that the common reasons for dropping out of exercise interventions included health issues and accidents, injury, or adverse event.[66] Considering common medical conditions in people with MS, researchers may need to be prepared to accommodate individuals who present with one or more of these events, especially in long-term studies where the risk of an event occurring is greater. These findings support the idea that the initial assessment should not be the only one that determines their 3-month exercise regimen. Modifications should be made at varying time points across the intervention.

As interventionists adapt exercises throughout ongoing exercise programs on a case-by-case basis, there is a need to ensure that scientific rigor is maintained when making such modifications, which can be done through development of an adaptive intervention design. The design has been commonly applied to health-enhancing behavior interventions targeting weight management,[67-69] drug abuse,[70, 71] and depression.[72, 73] We are unaware of intervention applied adaptive design for people with MS. The benefit of this design is to operationalize modifications (i.e., how, when, and based on which measure to alter treatment) before executing the intervention so that participants are systematically allocated to the same or different group based on their needs.[74] The identification of the key individual or group characteristics that influence different responses to treatment adherence and outcome in a fixed treatment can serve as tailoring variables (i.e., information to make a decision).[75] Thus, modifications could be made by conducting a needs assessment periodically throughout the intervention while setting a threshold such as their response to the treatment outcome or level of adherence (e.g., video watching minutes). The human support (i.e., check-up at every 3-week period) can be also used as a tailoring variable to make the intervention modifications when designing a future adaptive tele-exercise intervention.

The participants included in this study received asynchronous exercise training with no direct human involvement. While this was suitable for some people, asynchronous training was not preferable for all. Some participants desired human interaction through an expert-led program. These findings are consistent with the previous observation, as persons with MS were interested in one-on-one and group-based exercise programs guided by fitness professionals or healthcare providers.[25, 26] Some participants wanted human interaction through exercising with other participants without an expert's involvement. An adaptive intervention could accommodate people who need human connectedness by separating them into a different group that receives additional support (group and/or one-on-one exercise sessions or online support groups via videoconference calls). Doing this will provide a sense of accountability and motivate them to exercise, which is consistent with findings of previous studies.[76, 77]

Related to behavioral change components (educational articles and automated communication system), participants indicated their preference for multiple communication channels to optimize their exercise behavior change (Theme 2). Participants indicated the importance of easily accessible reporting and monitoring strategies to boost their feelings of success and achievement. This observation is comparable with previous research that demonstrated self-monitoring is an important correlate of physical activity behavior among people with MS.[78] It was interesting that participants desired personalized choices of reporting and monitoring options through multiple communication channels, such as the app, email, and/or call back. These findings emphasize that future intervention curricula should aim to provide/incorporate multiple ways of reporting and monitoring mechanisms, which can help participants to identify the best self-monitoring methods and enhance the improvements of self-regulation strategies. In the application of adaptive intervention design, the reports from participants could be used as a tailoring variable (information to make a decision) to assess program adherence in addition to video watching minutes.

Although program benefits were not within our study aims, it is important to note that participants reported diverse benefits to their health and function from the program (Theme 6). The reported improvements in physical function and emotional well-being were consistent with previous studies that delivered the same exercise modality, such as yoga[41-48], Pilates[49-53], and neurorehabilitation activities (dual-tasking, functional tasks).[54, 55] In addition to positive changes in physical aspects, participants often noted that the program was beneficial for their mental and emotional well-being (e.g., relaxation, stress management, increased self-efficacy). Further investigation is needed to quantitatively confirm these benefits from the participants who will complete the TEAMS study.

This study had limitations. First, people from rural locations were underrepresented; a majority of our interview participants lived in urban areas with relatively stable internet access. Thus, the findings related to real-time exercise sessions (i.e., exercise companionship) via conference call may not be transferable to the subgroup (i.e., people who live in a rural area with unstable or lack of internet access). Future studies are warranted that consider providing tailored exercise programs based on individual-specific characteristics, such as functional ability and preferences, as well as the optimal level of human support. Second, this study was conducted during the lockdown at the height of the COVID-19 pandemic, which may have influenced participants' responses. Third, it is possible that participants recruited for this interview were generally more motivated to engage in exercise than people with MS from the broader population, as they had all volunteered for the TEAMS parent study.

CONCLUSIONS

This study identified modifiable factors to improve a tele-exercise program for people with MS. The findings of this study support the importance of personalized, ongoing modification of program content to participants' functional abilities and health status (i.e., accommodation of individuals experiencing discontinuation of the program). The study findings also suggest researchers prioritize better tailoring and targeting of future intervention design (i.e., adaptive designs) with optimal human interaction, behavioral modification strategies, and long-term engagement by providing post-intervention resources. Thus, this study strengthens the growing body of work on this topic, helping us better understand the therapeutic potential of exercise in MS management and informing future intervention strategies, especially for designing an adaptive intervention aimed at promoting sustained exercise participation.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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CONCLUSIONS

Current evidence demonstrates that interventions are efficacious for increasing and potentially sustaining physical activity behavior (Study 1); yet treatment responses often have varying rates of success at the individual level. This dissertation identified factors that influenced participants' response to intervention that can be used to optimize future intervention design (i.e., adaptive intervention), targeting an increase in physical activity behavior for people with MS. We also identified intervention strategies, with a specific implication of home-based, self-directed exercise program delivery, that may help in improving adherence to the program and treatment response. This provided a foundation for designing a pilot Sequential Multiple Assignment Randomized Trial (SMART) to test the identified factors and further optimize the design of adaptive intervention for people with MS.

The meta-analysis demonstrated that the effects appear to be optimized based on the delivery of behavioral intervention alone, and these interventions may be capable of supporting greater chance and long-term maintenance of physical activity behavior (Study 1). Combining with previous research, we identified goal setting within SCT as a primary *tailoring variable* that can be accomplished during early intervention stages and used to tailor future intervention strategies (Study 2). Based on the level of baseline goal setting, participants may be starting a self-directed program with minimal support for behavioral change or receiving one-on-one behavioral coaching for developing a sense of efficacy, positive outcome expectations, and self-regulatory strategies. Yet, the observations of ceiling effects and lack of variability of other important SCT variables (i.e., self-efficacy and outcome expectations) potentially imply a future need to adjust the timing of these measures upon completion of a brief intervention period (e.g., 2-week pre-session). Future studies are warranted that consider investigating an optimized true baseline for implementing these SCT-based measures for people with MS; this will give participants a stronger understanding of their ability to perform physical activity, and it will help researchers to better determine the remaining intervention regimen.

In addition, we provided modifiable factors to improve the design and delivery of both the formal program components and the post-intervention period that could be used to develop an adaptive intervention for people with MS, a specific implication of the tele-exercise program (Study 3). The findings from the qualitative study support the importance of personalized, ongoing modification of program content to participants' functional abilities and changes in health status. The candidate time point of human contact from study staff was identified as every 3 weeks to assess needs and difficulties and make necessary changes (e.g., switch to an intense program). This qualitative approach can enhance a needs assessment in addition to monitoring participants' response to the treatment outcome or adherence rate to program (e.g., video watching minutes) with a preset threshold. The study findings also suggest the needs of various support methods for exercise (e.g., autonomous, one-on-one, and group exercise); self-regulatory strategies (e.g., multiple ways of reporting and monitoring mechanisms through email, app, call back to automated communication system); and long-term engagement by providing post-intervention resources. Overall, this project strengthens the growing body of work on this topic, helping us better understand the therapeutic potential of exercise and physical activity behavior in MS management and informing future intervention strategies, especially for designing an adaptive intervention, aimed at promoting increased and sustained exercise and physical activity participation.

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APPENDIX I

EXAMPLES OF THE MEDLINE SEARCHES

EXAMPLES OF THE MEDLINE SEARCHES

<table>
<tr><th>Date of Search</th><th>Search Terms</th></tr>
<tr><td>9/19/2019 (Updated)</td><td>(((((((((((exercise[mesh]) OR exercis*) OR health behavior[mesh]) OR behavior therapy[mesh]) OR behavior*) OR behaviour*) OR physical activity) OR health promotion[mesh]) OR accelerometry[mesh]) OR actigraphy[mesh])) AND multiple sclerosis[mesh]</td></tr>
<tr><td>10/31/2018 (Updated)</td><td rowspan="2">((((((((((("Counseling"[Mesh]) OR "Health Education"[Mesh]) OR "Health Promotion"[Mesh]) OR "Exercise"[Mesh]) OR "Physical activity"[Mesh]) OR "Exercise Therapy"[Mesh]) OR "Primary Prevention"[Mesh]) OR "Telemedicine"[Mesh]) OR "Telerehabilitation"[Mesh]) OR "Self-Help Devices"[Mesh])) AND ((((((((((((((("Quality of Life"[Mesh] OR "Activities of Daily Living"[Mesh]) OR "Health Behavior"[Mesh]) OR "Health Status"[Mesh]) OR "Comorbidity"[Mesh]) OR "Outcome and Process Assessment (Health Care)"[Mesh]) OR "Attitude to Health"[Mesh]) OR "Risk"[Mesh]) OR "Risk Reduction Behavior"[Mesh]) OR "Pilot Projects"[Mesh]) OR "Disability Evaluation"[Mesh]) OR "Cohort Studies"[Mesh]) OR "Program Evaluation"[Mesh])) AND ((("Multiple Sclerosis"[Mesh]) OR “MS”[Title/Abstract]))</td></tr>
<tr><td>10/3/2017 (Initial)</td></tr>
</table>

APPENDIX II

LEVEL OF EVIDENCE AND CRITERIA APPLIED TO THE STUDIES INCLUDED IN THE QUANTITATIVE SYNTHESIS BASED ON THE SPINAL CORD INJURY REHABILITATION EVIDENCE SYSTEM

LEVEL OF EVIDENCE AND CRITERIA APPLIED TO THE STUDIES INCLUDED IN THE QUANTITATIVE SYNTHESIS BASED ON THE SPINAL CORD INJURY REHABILITATION EVIDENCE SYSTEM

Level of evidence	Criteria
Level 1	• **RCT**: PEDro Score > 6. Includes cross over design with randomized experimental conditions and within-subjects comparison.
Level 2	• **RCT**: PEDro Score ≤ 6. • **Prospective controlled trial**: Non-randomized. • **Cohort**: Longitudinal study using two (minimal) similar groups with one group being exposed to a condition.
Level 3	• **Case-control**: Retrospective study comparing controls conditions.
Level 4	• **Pre-post**: Trial with a baseline measure, intervention and a post-test using a single group of subjects. • **Post-test**: Post-test with two or more groups using a single group (intervention followed by a post-test with no retest or baseline assessment).
Level 5	• **Observational**: Study using cross sectional analysis to interpret relations.

APPENDIX III

METHODOLOGICAL QUALITY ASSESSMENT OF ALL STUDIES INCLUDED IN THE QUANTITATIVE SYNTHESIS

METHODOLOGICAL QUALITY ASSESSMENT OF ALL STUDIES INCLUDED IN THE QUANTITATIVE SYNTHESIS

	Criterion										
Author/Year	1	2	3	4	5	6	7	8	9	10	Total Scores
Bombardier et al., 2013	1	1	0	1	1	1	1	1	1	1	9
Carter et al., 2013	1	1	1	1	1	1	1	1	1	1	10
Coote et al., 2017	1	1	1	1	1	1	0	0	1	1	8
Dlugonski et al., 2012	1	1	1	1	1	0	1	1	1	1	9
Duff et al., 2018	1	1	1	1	1	1	1	1	1	1	10
Ennis et al., 2006	1	0	1	1	1	0	1	0	1	1	7
Hayes et al., 2017	1	1	1	1	1	1	0	1	1	1	9
Learmonth et al., 2012	1	1	1	1	1	1	1	1	1	1	10
Learmonth et al., 2017	1	1	1	1	1	1	1	1	1	1	10
McAuley et al., 2015	1	0	1	1	1	1	1	1	1	1	9
Mostert & Kesselring, 2002	1	0	1	1	1	0	0	0	1	1	6
Motl et al., 2011	1	0	1	1	1	0	1	1	1	1	8
Motl et al., 2017	1	1	1	1	1	1	1	1	1	1	10
Paul et al., 2018	1	1	1	1	1	0	1	1	1	1	9
Pilutti et al., 2013	1	0	1	1	1	1	1	0	1	1	8
Plow et al., 2014	1	1	1	1	1	0	1	1	1	1	9
Rice et al., 2015	1	0	0	1	1	0	1	0	1	1	6
Sandroff et al., 2013	1	0	1	1	1	0	1	0	1	1	7
Stuifbergen et al., 2003	1	0	1	1	1	1	0	0	1	1	7
Suh et al., 2015	1	1	1	1	1	1	1	1	1	1	10
Tallner et al., 2016	1	1	1	1	1	0	0	0	1	1	7
Thomas et al., 2017	1	1	0	1	1	1	1	0	0	1	7
Turner et al., 2016	1	1	1	1	1	1	1	1	1	1	10
Wens et al., 2015	1	0	1	1	1	0	1	1	1	1	8

*Note*s. The methodological quality was assessed with PEDro score including 10 items (1-10) raged as “Yes” (1) or “No” (0).

Criterion 1 = Randomization method adequate; 2 = Treatment allocation concealed; 3 = Group similarity at the baseline; 4 = Blinding of all subjects; 5 = Blinding of all therapists; 6 = Blinding of all outcome assessors; 7 = Drop-outs acceptable; 8 = "Intention to treat" analysis; 9 = Between-group statistical comparison; 10 = Inclusion of a point measure and measure of variability

APPENDIX IV

INTERVIEW QUESTIONS GUIDE

INTERVIEW QUESTIONS GUIDE

1. What made you to join/sign up in this program?

2. At the start of the program, what were you expecting to get from the program?

    2a. Did this change up to the mid of the program?

    2b. Did this change from the mid to the end of the program?

3. (Considering this program was 100% online, no personal coaching or interaction) At the start of the program, how confident were you that you could do, stick to, or maintain the program?

    3a. Did this change in the middle of the program? If yes, how different? If no, why not?

    3b. Did this change after the program? If yes, how different? If no, why not?

4. Tell me about your overall perceptions of the program you participated in.

    4a. Can you describe the positive experiences that you have had from the program?

    4b. Can you describe the negative experiences that you have had from the program?

I would love to talk about the detailed program components. What you liked and disliked, how would you like to change.

5. Tell me about how you felt about the *exercise videos/regimen* at the start of the program.

    5a. Did this change in the middle of the program? If yes, how different? If no, why not?

    5b. Did this change after the program? If yes, how different? If no, why not?

6. Tell me about what factors (some things) that prevented you from the exercise. (barriers)

7. Tell me about what factors (some things) that helped you with the exercise. (facilitators)

8. What would you like to add or how would you like to change this program and its delivery?

9. Tell me about how you felt about the *newsletters*?

    9a. Did this change in the middle of the program? If yes, how different? If no, why not?

    9b. Did this change after the program? If yes, how different? If no, why not?

    9c. Were you able to apply what you learned from the *newsletters* to your activities of daily living? Why/Why not?

10. Tell me about how you felt about the *automated calls (i.e., IVR)* to monitor your progress and keep up with the program? Why/Why not?

    10a. Did this change in the middle of the program? If yes, how different? If no, why not?

    10b. Did this change after the program? If yes, how different? If no, why not?

11. Tell me how you felt about the technology that was used to deliver the program (app, tablet)

12. Tell me about your exercise or activity routine.

    12a. Do you think your physical activity level has changed (more active vs. less active vs. same) compared to before?

13. Do you have anything else that you would like to add?

APPENDIX V

CODING FOR RESPONDERS

CODING FOR RESPONDERS

	Themes	Focused codes & Initial codes
Before	***Factors that influence their decision to join a teleexercise program***	**<u>Potential benefits to their and others' health motivated them to *participate* in the program</u>** -Some people anticipated benefits of exercise (i.e., outcome expectations) to their physical fitness (muscle strength, reflexes, auditory function, daily activity performance, such as walking longer, faster, safer), psychosocial strain (dealing with life stress, such as work, house chores), MS symptoms, being physically active, and maintain quality of life. (06, 08, 12, 19, 20) -Some people desired to learn (knowledge) how to improve health and function through exercise. (12, 14, 15) -Some people wanted to contribute research knowledge to help others with MS. (12, 19) **<u>Previous exercise experiences positively affect their level of confidence to be able to *join* the study</u>** -Previous exercise experience of Yoga/Pilates, general exercise behavior (considered themselves as an active person, exerciser, runner), exercises with other videos, and successful completion/positive physical outcomes from previous exercise challenges helped them join the program. (06, 08, 12, 20) **<u>Some people wanted to *join* the program because they felt the home program safer than the community program</u>** -The benefits of the home program are to have control over/adaptation compared to the community-based exercise programs/facility (e.g., Programs are specifically designed for MS, stopped exercising at community gym with disease progression, unable to do Yoga class due to high room temperature) (12, 20) -Some people see the benefits of home program for avoiding negative perceptions of community-based exercise program, such as being afraid to make a mistake and being embarrassed/staired when making a mistake/stumble. (12, 13, 14) -Remotely delivered, home exercise eliminates travel time to a physical exercise location, convenient for scheduling (13, 14, 20) -Some people see the benefits of the home-based program to avoid exposure to COVID (20)
During	***Content that was perceived as not-relevant to their***	**<u>Non-challenging exercises caused lack of interest and boredom</u>** -The exercise type/focus was not matched with their interest (e.g., no sweat/ lack of emphasis on one's weakness – core area). (01, 08)

	stage of post-diagnosis, functional ability, or interest affect their participation.	-The program was perceived to be less challenging ('lacking stimulation') with their previous experience with Yoga/Pilates as well as current level of fitness. (08, 20) -Some people felt that the exercise pace was too slow due to the repeated instruction of the video. (01, 08, 12, 19) **<u>Some people felt an appropriate level of challenge, which affects participation with a feeling of achievement and improvement</u>** (06, 08, 12, 19, 23) **<u>Overly challenging exercises caused frustration and anxiety</u>** -due to their physical limitations (hip replacement surgery, big belly with pregnancy) or the position being on the floor – hard to get up, sudden position change with dizziness, back pain. (06, 12, 13, 14, 15, 23) **<u>Not specific or personalized contents (newsletters, IVRs) caused a lack of interest and a feeling of disconnection</u>** -Some people were not aware of the newsletters and/or interested due to the general contents (irrelevant to the person or their specific barriers). (01, 06, 08, 13, 15, 19, 20, 23) -Some people felt that the newsletter (general info) was helpful for people who are newly diagnosed with MS. (12, 13, 14) -IVR calls were perceived as monotonous, burdensome, and extra work due to impersonal content (questions) and feedback on their goal and achievement. (01, 06, 08, 13, 14, 15, 19)
	Human interaction is need for a sense of accountability to increase participation.	**<u>Human connection/support enhance the feeling of support</u>** <u>('somebody is behind me! Have my back')</u> -Some people wanted human supports from research staff for an occasional check-up (replacement of IVR calls; an average of 3 wks) and exercise FAQ (e.g., variation/adaptation to make it more challenging and/or different position to stimulate the same muscle group with different movement, how to engage core better, and clarification of exercise movements). (08, 13, 15, 20, 23) -One-way communication created frustration (Unable to refer people to the study, IVRs had no option to reschedule the call, call back, clarify/explain/correct their response – e.g., They did not exercise because of hospitalization but with other factors; They did not have support, but they just do not need it.) (01, 08, 12, 13, 15, 20, 23)

		-Some people wanted in-person exercise training or exercise companionship in a small group (‘exercise buddy/virtual partner’) with or without a mediator (study staff) (06, 13, 15, 20) **<u>Technology usability issue</u>** (couldn’t find ID/PW, disappeared videos, no articles available, app opening takes time, tablet battery life, measurement equipment, errors of IVR calls) (06, 12, 13, 15)
	A program designed for behavioral change strategies (self-regulatory strategies) enhances their participation.	**<u>Personalized goal-setting, self-monitoring, and positive feedback can encourage their feeling of success, achievement</u>** -The questions from the IVR calls were impersonal, irrelevant to them (01, 06, 08, 13, 14, 15, 19, 20) and to their goal (e.g., limited input setting did not allow them to report more than x number of exercises even though they did more.) (08) -Some people wanted to report their post-workout results (how many, what they did) directly through the app (right after the exercise session) and be able to monitor/track their progression and improvement (through the app, badges/stickers) (01, 08, 12, 13, 19, 20) -The negative feedback from the IVR calls (“you did not meet that exercise goal”) discouraged them (14) -IVR calls provided goal-setting/scheduling and informative feedback (positive and encouragement) (06, 12, 23) -Some people wanted additional reminder (call/text) before the exercise schedule (01, 06)
	Exercise programs need to accommodate an individual.	**<u>Daily variation of MS symptoms directly and indirectly prevent participation</u>** (fatigue, heat sensitivity, pain, perceived low level of energy). – When symptoms are intensified (‘down, bad days’), it lowers confidence, motivation, and interest to participate. (01, 06, 08, 19, 20) **<u>Life stressors and responsibilities *take priority over exercise* and prevent participation</u>** (Everyday chores/family and child care demand much of their energy, couldn’t find tablet/charger due to house moving, lack of time with busy work). (01, 12, 14) **<u>Unexpected/non-study-related injury or health issues caused short lapses in participation</u>** (car accident, MS relapse).
After	**Experiencing benefits increases**	**<u>Continuing the TEAMS video to maintain the benefits that they’ve experienced</u>** (01, 06, 08, 12, 13, 14)**, and <u>it became a valuable routine for them to be more active with extra exercise</u>** <u>(08, 12, 19)</u>

	the sustainability of exercise behavior.	-Exercise improved *physical health* (ROM, joint/muscle stiffness, pain), more energy/stamina, being more physically active, daily living activities (e.g., shopping, walk longer), sleep better, and MS related symptoms (burning sensation, pain management) as well as *emotional well-being* (stress relief, relaxation, center themselves, emotional control). **Alternative modes of the study materials would facilitate quick/better access** (videos without instructions, paper-based summary exercises, when facing tech issues, etc.) (08, 12, 19)

APPENDIX VI

CODING FOR LOW-/NON-RESPONDERS

CODING FOR LOW-/NON-RESPONDERS

	Themes	Focused codes & Initial codes
Before	***Factors that influence their decision to join a teleexercise program***	**<u>Potential benefits to health motivated them to *participate* in the program</u>** -Some people anticipated benefits (i.e., outcome expectations) to their physical fitness (flexibility, muscle strength/endurance, balance/fall prevention, mobility, weight management), cognition (memory, focus), psychosocial strain (dealing with life stress, such as family care, personal healthcare), MS symptoms (pain), being physically active, and being physically independent. (03, 04, 05, 07, 09, 10, 11, 17, 21, 22) -Some people desired to learn (i.e., knowledge) how to improve/maintain health and function and achieve an active lifestyle through exercise. (07, 18) -Some people perceived exercise as a non-invasive, non-pharmaceutical MS treatment. (03, 11) **<u>Previous exercise experiences positively or negatively affect their level of confidence to be able to *join* the program</u>** -Previous exercise experience of Yoga, exercise videos (e.g., YouTube), general exercise behavior (considered themselves as an active person) helped them join/keep up with the program with minimal assistance. (09, 16, 18, 22) -Program that is specifically designed for MS increased their confidence to join the program considering their negative exercise experiences with community-based programs (i.e., programs were not adaptive for wheelchair users, their functional level). (16, 21, 22) -Some people worried about using technology (exercise with videos, tablet). (07, 10) **<u>Some people wanted to *join* the program because they felt the home program safer than the community program</u>** -The benefits of the home program are to have control over/adaptation (i.e., Exercises at a comfortable "my own" pace) compared to the community-based group exercise programs (e.g., lack of structural/pace adaptations for their functional limitation, wheelchair users). (03, 09, 11, 16, 21, 22) -Some people wanted to avoid negative perceptions of exercise in a public place (feeling of embarrassment when making a mistake and taking extra breaks (not being able to keep up with others/group). (04, 05, 11) -Some people see the benefits of the home-based program to avoid exposure to COVID-19 (03, 07, 16)

During	***Content that was perceived as not relevant to their stage of post-diagnosis and functional ability***	**<u>Non-challenging exercises caused boredom or lack of interest</u>** -Beginning of the program was too "slow" or too easy, not perceived as "exercise" (22) -Exercises perceived as non-challenging/non-beneficial during the middle-to-end of the program (avg at wk 8) (03, 04) -Some people felt that the instruction of the video was lengthy and slow down the exercise pace. (09, 22) **<u>Some people felt that the three level modifications of the program provided an appropriate level of challenge, which was positively influenced their confidence with feelings of achievement and improvement.</u>** (03, 04, 05, 04, 09, 10, 11, 16, 18) **<u>Overly challenging exercises created feelings of frustration, anxiety, and loss of confidence during performance</u>** -The beginning was challenging due to the participants' starting level of fitness, balance issues (created a feeling of unsafety, increased anxiety), which lowered the high level of confidence. (03, 04, 09) -Some exercises were challenging (with the position being on the floor, back and forth/fast position change from ground to standing, coordination) – prevented them from participating in all exercises in the video, so they did their best, skipped the moves, needed to stop the video, extra support to get up, etc. (05, 09, 10, 22) -Some people wanted diversity to understand exercise poses better (an actor with overweight, with limited ROM) (05, 17) **<u>Not specific or personalized contents (newsletters, IVRs) caused a lack of interest and a feeling of disconnection</u>** -Some people were not aware of the newsletters and/or did not grab their attention because the contents were general, considered irrelevant to the person and/or nothing new to learn. (04, 05, 07, 09, 11, 16, 17, 21) -IVR calls were perceived as monotonous, irritating with impersonal/confusing content and feedback (e.g., you were not able to do exercise?). (03, 07, 10, 16)
	Human interaction is need for a sense	**<u>Human connection/support enhance the feeling of support</u>**

	of accountability to increase participation.	-Some people wanted human supports from research staff for an occasional check-up (replacement of IVR calls; an average of 3 wks) and exercise FAQ (e.g., confirmation of exercise poses, technique). (03, 04, 05, 07, 10, 11, 17, 18, 21, 22) -One-way communication created frustration and a feeling of disconnection (IVRs had no option to reschedule the call, call back, clarify/explain/correct their response, leave questions/comments) (04, 07, 11, 16, 18) -Some people wanted virtual group exercise sessions and/or voluntary group social networking facilitated with or without a mediator (study staff, exercise instructor, mentor who completed the program) (04, 05, 21) -Some people actively searched for their social support, verbal encouragement, exercise companion outside of the study to have a sense of accountability (spouse, children, grandchildren, members in the support group) (04, 05, 07, 09, 11, 16, 17) **<u>Technology usability issues created a feeling of frustration</u>** (faulty tablet, navigating the app, IVR calls with errors, missing/extra calls, lack of an option to see the video on a bigger screen) (03, 09, 17, 16, 18, 22)
	A program designed for behavioral change strategies (self-regulatory strategies) enhances their participation.	**<u>Providing tools for self-monitoring can encourage them to stick to the program</u>** -Some people wanted to report their workout status (how many, what did) through the app, call back, or email and be able to monitor/track their progression and improvement (through the app). (04, 07, 11, 16, 17, 21) -Some people created own logbook, weekly planner, and/or calendar reminder to set up day to day goal, keep up with exercise, and motivate themselves with completion and progression (07, 16, 21) -Some people felt that the IVR served as a reminder of schedule, check-in, and verbal encouragement. (04, 05, 11, 16, 18) -Some people wanted additional verbal encouragement through text, email, the app, and/or exercise video. (17)
	Exercise programs need to accommodate an individual.	**<u>Daily variation of MS symptoms cause short lapses in participation</u>** (fatigue, heat sensitivity, spasticity). – intensified symptoms influenced decreases in confidence, motivation, and interest to participate. (03, 04, 09, 10) **<u>Life stressors and responsibilities take priority over exercise and prevent participation</u>** (illness, work, family responsibilities, daily chores, home/farm care) (09, 11, 18)

		Unexpected/non-study-related injury and/or health issues caused short lapses in participation (break a bone, biopsy, rotator cuff injury, bulging disc). (03, 09, 16, 17, 21)
After	**Experiencing benefits increases the sustainability of exercise behavior.**	**Continuing the TEAMS video to maintain the benefits that they've experienced.** (10, 11, 16, 18) **Post-intervention materials would be valuable for further challenges** (i.e., videos from another functional group) (11, 16)

APPENDIX VII

INSTITUTIONAL REVIEW BOARD APPROVAL

INSTITUTIONAL REVIEW BOARD APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 | irb@uab.edu

APPROVAL LETTER

TO: Rimmer, James

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 14-Nov-2020

RE: IRB-161017003
Comparative Effectiveness Trial Between a Clinic- and Home-Based Complementary and Alternative Medicine Telerehabilitation Intervention for Adults with Multiple Sclerosis (MS)

The IRB reviewed and approved the Revision/Amendment submitted on 10-Nov-2020 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Expedited
Expedited Categories: b2,
Determination: Approved
Approval Date: 14-Nov-2020
Expiration Date: 11-Feb-2021

The following apply to this project related to informed consent and/or assent:

- Waiver (Partial) of HIPAA

Please note: The Waiver of Informed Consent Documentation is approved only for Ms. Kim's sub-study that involves a single interview.

Documents Included in Review:

- phonescript.201110
- praf.201110
- waiverdocumentation.201110

To access stamped consent/assent forms (full and expedited protocols only) and/or other approved documents:
1. Open your protocol in IRAP.
2. On the Submissions page, open the submission corresponding to this approval letter. NOTE: The Determination for the submission will be "Approved."
3. In the list of documents, select and download the desired approved documents. The stamped consent/assent form(s) will be listed with a category of Consent/Assent Document (CF, AF, Info Sheet, Phone Script, etc.)

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FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 08-Nov-2020

RE: IRB-161017003
Comparative Effectiveness Trial Between a Clinic- and Home-Based Complementary and Alternative Medicine Telerehabilitation Intervention for Adults with Multiple Sclerosis (MS)

The IRB reviewed and approved the Revision/Amendment submitted on 03-Nov-2020 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Expedited
Expedited Categories: b2,
Determination: Approved
Approval Date: 08-Nov-2020
Expiration Date: 11-Feb-2021

The following apply to this project related to informed consent and/or assent:

- Waiver (Partial) of HIPAA

Documents Included in Review:

- consent.clean.201102
- praf.201102

To access stamped consent/assent forms (full and expedited protocols only) and/or other approved documents:
1. Open your protocol in IRAP.

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TO: Rimmer, James

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

IORG Registration # IRB00012550 (IRB 03)

DATE: 24-Aug-2020

RE: IRB-161017003
Comparative Effectiveness Trial Between a Clinic- and Home-Based Complementary and Alternative Medicine Telerehabilitation Intervention for Adults with Multiple Sclerosis (MS)

The IRB reviewed and approved the Revision/Amendment submitted on 18-Aug-2020 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Expedited
Expedited Categories: b2,
Determination: Approved
Approval Date: 24-Aug-2020
Expiration Date: 11-Feb-2021

The following apply to this project related to informed consent and/or assent:

- Waiver (Partial) of HIPAA

Documents Included in Review:

- consent.200817
- praf.200817
- interview.200817