Title: Mapping two decades of multiple sclerosis rehabilitation trials: A systematic scoping review and call to action to advance the study of race and ethnicity in rehabilitation research.

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Abstract

Background: Multiple sclerosis (MS), is prevalent across many racial and ethnic groups, and disproportionately impacts racially minoritized populations. Rehabilitation interventions are an important component of comprehensive MS care. Yet, we do not know the extent to which MS rehabilitation trials consider race and ethnicity in defining eligibility criteria, planning recruitment strategies, selecting outcome measures, supporting intervention delivery, and designing approaches to promote adherence and retention.

Methods: We conducted a scoping review of five databases (MEDLINE, CINAHL, Cochrane Central, EMBASE, and Web of Science) to locate randomized controlled rehabilitation trials published from January 2002 to March 2022. We extracted data from relevant studies, assessed their methodological quality, and narratively summarized results. Reporting of this review is in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).

Results: Fifty-six studies of neurorehabilitation (n=3), cognitive rehabilitation (n=6), exercise training (n=9) and self-management (n=38) interventions were included in this review. The studies were predominantly from North America (n=44; 73%) or Europe (n=12; 20%) and included 4280 participants. Most participants (n=3669; 86%) were Caucasians. Less than 10% of participants were Black (n=282), Latinx/Hispanic (n=60), Asian (n=46), Indigenous (n=7), or Arab (n=2). Few studies discussed how race and/or ethnicity were considered in trial planning or execution.

Conclusions: Without consistent and systematic attention to race and ethnicity, both in terms of trial design and reporting, it is impossible to know how MS rehabilitation interventions will translate into real-world applications. This call to action – to the MS rehabilitation research community to ensure trial and intervention processes that accommodate the needs of diverse racial and ethnic groups – is an important first step in addressing inequities in rehabilitation care for persons with MS.

Keywords: Race, Ethnicity, Diversity, Multiple Sclerosis, Rehabilitation Trials, Review

1. Introduction

There is increasing awareness that multiple sclerosis (MS), long considered to primarily affect White individuals of European descent, does in fact occur in many racial and ethnic groups [1]. Epidemiological data gathered across diverse socioeconomic and ethnic groups highlight the notable prevalence and incidence of MS among Blacks and Hispanics/Latinx, and higher odds for developing MS in Black, Asian, and Minority Ethnic (BAME) groups compared to Whites [1-3]. These findings contradict previously held beliefs that these groups present as a low-risk population for MS [4, 5], and highlight the importance of considering genetic (non-modifiable) and modifiable environmental factors in rehabilitation intervention research and planning.

Racially minoritized populations with MS experience health disparities in the diagnosis and treatment of the disease. Studies report that Black persons with MS are less likely to have been treated by a specialist neurologist or to have received care at an MS clinic [6, 7]. Other researchers have reported that more Hispanics than non-Hispanics do not receive disease-modifying therapies [8]. This situation is unfortunate, as Black and Hispanic/Latinx persons with MS experience a more rapid disease progression [9-11], a greater disease burden [12-14], a lower medication adherence rate [15], and are at an increased risk for morbidity and mortality [16, 17]. These findings underscore the need for effective intervention strategies for these groups.

Ample evidence indicates that clinical research as an enterprise has often been plagued by the under-representation of racial and ethnic minority groups in randomized controlled trials (RCTs) [18-28] – the backbone of whether and how most drugs and health interventions are introduced into a health system. Indeed, in the literature specific to MS, some high-profile RCTs of drug

trials do not even report on race and ethnicity in their published manuscripts, likely concealing the low enrollment of racially minoritized populations in these otherwise pivotal studies [25, 29]. The evidence indicating differential responses and adherence to MS drugs across racial and ethnic groups [15, 30-32], further highlights the importance of considering these factors in clinical decision-making, including treatment efficacy and risk-benefit discussions [26].

In the context of comprehensive MS care, nearly three decades of scientific enquiry support the inclusion of rehabilitation interventions to reduce impairments (e.g., balance, fatigue), improve activity (e.g., walking), and enhance participation (e.g., social engagement) for persons with MS [33, 34]. Rehabilitation is broadly described as an active, client-centred, and goal-oriented process enabling recipients to maximize physical and mental functioning, and overall quality of life [35, 36]. Despite the importance of rehabilitation interventions for the well-being of all persons with MS regardless of gender, disability level, and age, there has been very little apparent consideration for race and ethnicity in the design of trials evaluating new interventions or indeed with respect to interventions in routine clinical practice.

We need to understand the extent to which MS rehabilitation researchers recruit and include racially and ethnically diverse representative samples, and report on race and ethnicity in their trials. In addition, we need to explore whether MS rehabilitation researchers pay attention to examining race and ethnicity as possible mediators/moderators of intervention outcomes, or consider how these factors may influence intervention adherence.

Examining the effectiveness of interventions in general, without attention to effectiveness and adherence across racial and ethnic groups, can disguise inequities (e.g., reduced sense of

belongingness among participants) in these interventions [27]. Researchers may inadvertently perpetuate the assumption that research findings apply to all persons with MS when they do not explicitly test this assumption. We contend that this presents a significant opportunity to examine the extent to which persons from different racial and ethnic backgrounds respond and/or adhere to rehabilitation interventions that are considered to be effective. Addressing these knowledge gaps is a critical first step to advancing MS rehabilitation care. We must know whether and how race and ethnicity are considered in MS rehabilitation trials to be able to set priorities, correct inequalities, and ultimately ensure that rehabilitation interventions are fit for the "whole person", and for diverse MS communities.

We note upfront that "race" and "ethnicity" are each socially constructed terms that are not rooted in biology [37]. In fact, a biological basis for race has been definitively debunked in the scientific literature [38-40]. In contrast to, but not totally independent of, biological ancestry and genetic admixture, "race" and "ethnicity" are flexible, unstable, and contested concepts, often driven by power (political, financial, etc.). Ethnicity, the state of belonging to a social group that has a common national religious or cultural tradition [41], can include people of all races.

1.1. Review Question

Following a Population Concept Context (PCC) format, we sought to answer the following research question: To what extent do MS rehabilitation trials consider race and ethnicity in defining eligibility criteria, planning recruitment strategies, selecting outcome measures, supporting intervention delivery, and designing approaches to promote adherence and retention?

2. Methods

We used the methodological framework proposed by Arksey and O'Malley in 2005 [42], and further refined by Levac et al., in 2010 [43] and the Joanna Briggs Institute [44] to inform the methodology of this scoping review. We registered our scoping review protocol in Open Science Framework on 14 February 2022 (https://osf.io/m9qug). Reporting of this review is in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [45].

2.1. Eligibility criteria

Participants: We included studies that focused on individuals diagnosed with MS regardless of age, phenotype, or level of disability. Studies that did not report data from people with MS separately from populations with other chronic neurological conditions (e.g., Parkinson's disease) were excluded.

Concept: We included studies describing any type of rehabilitation intervention, including but not limited to, exercise interventions, cognitive rehabilitation, self-management etc. Studies with interventions that were <3 weeks in duration were excluded [46].

Context: We included studies published from January 2002 to March 2022. This 20-year period was chosen to encompass the earliest studies that first described racial and ethnic differences in MS (e.g., Marrie et al., [13]). Studies that were not published in English or that did not mention race and/or ethnicity considerations in eligibility, recruitment, outcome measurement, adherence or retention were excluded.

Types of studies: We included peer-reviewed RCTs i.e., feasibility (including pilots), efficacy, and effectiveness trials, as well as protocols of RCTs. We chose to focus on RCTs because they are considered the gold standard for evaluating the efficacy and effectiveness of interventions [47]. Conference abstracts, observational studies, systematic and non-systematic literature reviews, case studies, opinion pieces, and letters to the editor were excluded.

2.2. Search strategy

We searched five commonly used databases in the health sciences – OVID MEDLINE, EMBASE, CINAHL, Cochrane Central, and Web of Science – to locate relevant articles on MS rehabilitation trials. A peer-reviewed search strategy [48] was developed in collaboration with a health sciences librarian with expertise in systematic reviews (AP). The preliminary search through CINAHL was screened by the first author to refine the search terms and inclusion/exclusion criteria. Finally, an update of the original search strategy was completed by the librarian (AP) on 08 March 2022. The final search strategy as applied to OVID MEDLINE is provided in Supplementary Material 1.

2.3. Study selection

Search results were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) and duplicates were removed. A two-stage screening process was used to select the final papers to include in this review. Studies were first screened by title/abstract by two independent reviewers and eligible studies proceeded to the second stage of review. In the second stage, full-text records were screened again using

the eligibility criteria. Full texts that were not available from the reviewers' university library were requested as interlibrary loans and added if they were found. Disagreements that arose between the reviewers at each stage of the study selection process were resolved through discussion.

2.4. Data extraction

We used a data-charting form adapted from the Joanna Briggs Institute guidance for the conduct of systematic reviews [49] for data extraction. This form was pilot tested by the first author and a co-reviewer to ensure the data extraction was both comprehensive and feasible. Data extraction was carried out by two independent reviewers. Disagreements that arose between the reviewers during the data extraction process were resolved through discussion. We extracted the following information from each article:

- Citation (author, year, journal);
- Country in which the study was conducted;
- Study design and methods;
- Guidelines used in reporting study details (e.g., CONSORT);
- Inclusion/Exclusion criteria (list) and if race and ethnicity were considered (yes/no);
- Recruitment strategies (list) and if race and ethnicity were considered (yes/no);
- Participant characteristics (age, race, ethnicity, gender, MS phenotype). We did not extract this information from a subset of articles that were protocols of yet-to-be-completed/unpublished interventions;
- Outcome measures used in data collection (list);

- Intervention characteristics (focus, duration, number of sessions, delivery format);
- Adherence strategies (list) and if race and ethnicity were considered (yes/no); and
- Retention strategies (list) and if race and ethnicity were considered (yes/no)

2.5. Quality Assessment

A quality assessment of the included articles was performed following the guidelines outlined in the Mixed Methods Appraisal Tool (MMAT) [50]. The MMAT is a five-item appraisal tool designed to review the methodological quality of quantitative, qualitative, and mixed methods studies. Consistent with previous scoping reviews [51], we rated quality based on the percentage of item criteria met by the studies that were appraised: very low (20%), low (40%), moderate (60%), moderate-high (80%), and high (100%). Protocol papers were not assigned a score, as these study types are not accounted for in the MMAT. Two independent reviewers conducted quality assessments. Disagreements that arose between the reviewers during the quality assessment process were resolved through discussion.

2.6. Data analysis

Data analysis involved a descriptive summary and narrative synthesis of the extracted information. The narrative synthesis was undertaken by collating, summarizing, and reporting on findings based on our initial research question [42, 43]. As recommended by Levac et al. [43], we concluded narrative synthesis with consideration of the implications of the study within the broader context of research and practice, by providing recommendations to advance the field of MS rehabilitation.

3. Results

After deduplication, we screened (titles and abstracts) 3101 citations and excluded 2230 irrelevant citations. We further excluded 803 articles (for 519, the lack of consideration of race and ethnicity was the reason) at full-text review. Articles reporting data from the same intervention at different time points were considered together. Consequently, 56 distinct intervention studies reported in 68 articles were included in the review. The PRISMA-ScR flow diagram in Figure 1 outlines the study selection process.

[Insert figure 1 here]

3.1 Description of included studies

The characteristics of the included studies are summarized in Table 1. The studies were predominantly carried out in North America (n=40; 71%) [52-91] or Europe (n=12; 21%) [92-103], and published between 2014-2019 (n=31; 55%) [55-57, 59, 60, 62, 69, 70, 72, 74-76, 79-84, 86, 89-91, 93, 94, 96, 100-102, 104-106]. Most of the studies were effectiveness or efficacy trials (n=36; 64%) [52-76, 90-92, 95-99, 103, 105, 106]. About a third of the studies utilized waitlist (n=18; 32%) [52, 53, 58, 63, 68, 73, 76, 78, 80-82, 84, 85, 88, 92, 93, 101, 105] or active control (n=18; 32%) [57, 60, 65-67, 69-72, 75, 87, 91, 94, 95, 97, 99, 104, 106] groups. Most of the studies included a CONSORT flow diagram (n=40; 71%) [52, 53, 57-60, 62-65, 67, 68, 70, 73-77, 79, 80, 82, 84-90, 92-96, 98-100, 104-107], but only six (11%) studies [55, 56, 78, 91, 101, 103] explicitly stated the use of CONSORT reporting guidelines. Study quality ranged from moderate to high, with the majority of studies appraised as high (n=27;48%), followed by moderate-high (n=11; 20%), and moderate (n=8; 14%).

[Insert Table 1 here]

3.2. Description of participant eligibility criteria and recruitment strategies

Table 2 summarizes eligibility criteria and recruitment strategies utilized across the included studies. The eligibility criteria were widely diverse across the studies. Potential participants were considered eligible based on several factors that reflect social determinants of health, including age (e.g., 18-60 years old); geographical location (e.g., residing near a large MS clinical center for receipt of intervention), language (e.g., reads, speaks, and understand English), or absence of comorbidity (e.g., depressive symptoms). Two protocol studies [72, 106] reported race and ethnicity considerations in defining eligibility criteria. No studies reported the race and/or ethnicity of excluded individuals. Most studies (n=39; 70%) used a combination of two or more recruitment strategies. The most used combined strategies were recruiting through MS clinics and MS organizations (n=12; 21%) [67, 68, 72, 74, 88, 94, 95, 97, 100, 102-104]. Of the remaining 17 studies that used a single recruitment strategy, the most common strategy was recruiting through MS clinics (n=11; 20%) [54, 56, 60, 62, 65, 77, 79, 80, 90, 91, 99].

[Insert Table 2 here]

3.3. Description of enrolled participants

The characteristics of the enrolled participants are summarized in Table 3. Across the studies (excluding nine protocols [55, 56, 69, 71, 72, 97, 100, 106, 107]), the total number of participants was 4280, with a sample size ranging between 14 [78] and 449 [98]. The mean/median age of participants ranged between 37 [105] and 65 [86] years. The participants predominantly were

females (n=3240; 76%) with relapsing-remitting MS (n=2239; 52%). More than half of the participants (n=3669; 86%) were White or Caucasians, included in 45 studies. A small number of participants were Black (n=282; 7%), included in 24 studies [52, 54, 57-64, 66, 67, 73, 74, 76-78, 82, 83, 85, 88, 90, 98, 108] . About 1% of the participants were Latinx/Hispanic (n=60) or Asian (n=47), included in 15 [52, 57, 59, 61, 63, 66, 67, 73, 74, 77, 82, 83, 90, 91, 109] and nine [52, 61, 66, 67, 73, 77, 90, 98, 105] studies, respectively. Less than 1% of the participants were Indigenous (n=7), included in three studies [53, 67, 82], or Arab (n=2), included in one study [52].

[Insert Table 3 here]

3.4. Description of interventions, outcome measures, and approaches to promote adherence and retention

As shown in Table 1, interventions focused mostly on self-management/behaviour change (n=38; 68%) and involved the use of individual (n=35; 63%), face-to-face (n=22; 39%) delivery format. Interventions were typically delivered over a period of 6-12 weeks (n=38; 68%) with session length ranging between 30-60 minutes per session (n=25; 45%). One protocol study [72] included a plan to analyze the heterogeneity of intervention effects in a racially diverse sample.

Five broad categories of outcome measures were reported across the 56 studies including those at the level of impairment (e.g., fatigue, pain, balance, cognition etc.; n=42); activity (e.g., walking speed, transfers; n=13); participation (e.g., personal goals, household activities; n=17); health service utilization (e.g., use and cost of health care services, homecare use;

n=5); and personal factors (e.g., self-efficacy, motivation; n=25). Most of the studies (n=30; 54%) included ≥2 outcome categories. No studies *explicitly* reported whether race and/or ethnicity were considered in selecting outcome measures (e.g., by reporting psychometric properties among racially or ethnically diverse groups).

More than half of the studies did not report approaches to promote adherence (n=33; 60%) or retention (n=38; 68%). Of the 22 studies that reported approaches to promote adherence, eight studies used logbooks/diaries [55, 64, 70, 79, 84, 85, 90, 97], six studies used follow-up calls [57, 58, 78, 89, 108, 109], and four studies used reminder calls/text messages [65, 77, 104, 107]. Five studies used a combination of strategies including logbooks and review of practice activities [56, 110]; follow-up calls and logbooks [111]; reminders, logbooks, and follow-up calls [112]; and follow-up calls, education, reminders, and logbooks[72]. Of the 18 studies that reported approaches for promoting retention, financial incentive was used in 13 (23%) studies [55, 56, 60, 67, 69, 72, 73, 81, 85, 86, 88, 89, 98]. No studies *explicitly* reported considering race and ethnicity in selecting approaches for promoting adherence and/or retention.

4. Discussion

We undertook this scoping review to better understand the current state of knowledge relative to the representation of racially and ethnically diverse groups in trials of MS rehabilitation interventions. Only 56 out of 871 (6%) full text studies reviewed provided information about race and/or ethnicity over a 20-year period, reflecting limited consideration of this important topic within the domain of MS rehabilitation interventions. Across the studies, data relating to racial and ethnic minorities were significantly under-reported, most likely indicating under-

representation of these minority groups. White individuals accounted for 86% (n=3669) of the participants in over 80% (n=45) of the interventions. Below we summarize key findings and knowledge gaps, and make recommendations for future work to advance the field of MS rehabilitation.

4.1. Key findings and knowledge gaps

Despite increasing awareness that MS is prevalent across many racial and ethnic groups [1-3], we found little targeted recruitment of non-White participants into the studies included in this review. This finding is consistent across the general health literature [113-115], exercise trials in populations with various neurological conditions [116], and MS drug trials [25, 29], and highlights the possible limitations of traditional strategies for recruiting racial and ethnic minority groups into MS rehabilitation trials. Specifically, studies in this review recruited predominantly through MS clinics and/or MS organizations, thereby excluding people who are not able to access these services. Further, studies had eligibility criteria that tended to exclude people based on social determinants of health. Indeed, some studies targeted people based on geographical location (e.g., residing near a large MS clinical center for receipt of interventions), language eligibility (e.g., reads, speaks and understand English), or absence of comorbidity (e.g., depressive symptoms). The use of such eligibility criteria has important implications for the generalizability of interventions evaluated in MS rehabilitation trials.

We know that racial, ethnic, and sociodemographic characteristics are significantly associated with lack of geographic proximity to rehabilitation centers [117]. We also know that the prevalence of comorbidities in non-White individuals, including those with MS is higher than

among White individuals [118], and that racial and ethnic minority groups with MS experience lower engagement in health behaviours [119]. Taken together, these findings suggest that MS rehabilitation researchers may be implicitly excluding non-White individuals who are largely underserved by healthcare systems, have limited access to services, and likely have the most to gain clinically from rehabilitation interventions.

We found that knowledge about the effect of race and ethnicity on rehabilitation outcomes and intervention adherence in people with MS is virtually non-existent. Only one protocol study [72] planned to examine the heterogeneity of treatment effect in a racially diverse sample in order to understand for whom the intervention is effective. Studies in people with other chronic health conditions have shown that race and/or ethnicity can affect treatment outcome, adherence, and maintenance of treatment effect [120-122]. Reporting the race and ethnicity of enrolled participants without examining the possible mediating or moderating effects that these variables have on intervention outcomes or adherence creates an immediate challenge for researchers and clinicians in the field to evaluate rehabilitation treatments that are effective for all people with MS. Given the disproportionate impact of MS on racial and ethnic minority groups [9-14, 16, 17], and the importance of rehabilitation for improving key outcomes for all people with MS [33], "evidence-based" interventions that have generalizability and applicability across a diverse range of racial and ethnic groups, are a critical first step to addressing existing disparities in MS patient care.

4.2. Recommendations for future work to advance the field of MS rehabilitation

Herein, we provide recommendations to advance MS rehabilitation research. First, we recognize that researchers may need to grapple with a complex interplay of factors relative to recruitment and enrollment of non-White populations, such as links to relevant community networks (e.g., faith-based organizations), historical mistreatment of non-White people in past trials, cultural competency of researchers, and additional resources beyond what is typically required for recruitment [28, 123, 124]. However, we believe that a significant opportunity exists for MS rehabilitation researchers to optimize the recruitment and enrollment of diverse racial and ethnic groups. This can be done by incorporating best practices, as outlined, for example, in recently developed recruitment toolkits and frameworks [123, 125, 126], alongside resources specifically developed to address health inequalities (e.g., The For Equity Guidance Inventory – FOR-EQUITY https://forequity.uk/guidance-inventory/).

Such practices include, but are not limited to, embedding input from members of target communities into trial materials and processes (e.g., building input from racial and ethnic minority groups with MS into the recruitment strategy and/or piloting materials and procedures with them), offering written and spoken aspects of MS rehabilitation interventions in a language other than English, and using interventionists drawn from the target cultural communities. We urge the MS rehabilitation research community to focus on identifying meaningful ways of working holistically to address individual and external factors that impede participation of racial and ethnic minorities with MS in rehabilitation trials. The emphasis on patient and public involvement in research [127], as seen for example, in the TEAMS trial [72, 128]

aligns with this recommendation. As with other researchers [124], we highlight the potential for radical collaborations between the MS rehabilitation research community and community organizations (e.g., The Centre for Ethnic Health Research, UK; Multiple Sclerosis Minority Research Engagement Partnership Network of the Accelerated Cure project, US etc.), whose remit is to promote research that reduces ethnic health inequalities. Such collaborations will allow rehabilitation researchers to further leverage available expertise to develop innovative trial and intervention processes fit for diverse racial and ethnic groups with MS.

Second, we call on the MS rehabilitation research community, and to funders to support them, in prioritizing the conduct of larger global, multisite (with inclusion of cross-national enrollment sites), pragmatic trials that include a wider range of participants. Despite ever increasing ethnic diversity in Europe and North America due to international migration, we must acknowledge the inherent bias that is introduced when studies (93% of all included in this review) are conducted in regions where the majority of the population are White. There is an urgent need for the conduct of global MS trials. It is only by ensuring recruitment at sites across countries in which individuals from Black, Latina/Hispanic, Asian, Arab or Indigenous racial and ethnic groups predominate, that better representation of those considered a "minority" in Europe and North America can be achieved. Despite the complexity of conducting global, multisite, pragmatic trials, such a design will maximize generalizability and applicability, and will provide opportunities for conducting subgroup analyses to understand how diverse racial and ethnic groups affected by MS respond to treatment [72, 124]. Here again, the MS rehabilitation research community must consider opportunities to invest in improving the local research infrastructure, integrating diverse patient perspectives into trial design and processes and training

investigators and research staff in Lower and Middle Income Countries where Black, Latina/Hispanic, Asian, Arab or Indigenous racial and ethnic groups are part of the population majority. We believe that doing so will generate valuable insights to inform the selection of meaningful outcome measures, support intervention delivery, and ensure appropriate approaches to promote adherence and retention.

Finally, although MS rehabilitation researchers tend to incorporate aspects of reporting guidelines (e.g., CONSORT [129]), which advocate reporting baseline demographic and clinical characteristics for each group in an RCT, it is important to note that the CONSORT statement does not specify how race and ethnicity variables should be captured and described. The recently developed CONSORT-Equity 2017 [130], an extension to CONSORT, provides guidelines to improve the reporting of items specific to health equity (e.g., socioeconomic status and ethnicity) in RCTs. We urge the MS rehabilitation research community (including methodologists, trialists, journal editors etc.) to endorse and adopt the use of these guidelines in future MS rehabilitation trials.

We recognize that health equity is multidimensional, and therefore, propose that the MS rehabilitation research community converge on the most important sociodemographic characteristics that should be reported (e.g., in an updated checklist) in MS rehabilitation trials. The use of the GRADE Equity Guidelines [131] may support these efforts by ensuring appropriate consideration of health equity in checklist development, and ultimately promoting relevance for target populations. Importantly, such a checklist would assist in examining crucial relationships between sociodemographic variables, including race and ethnicity, and

intervention outcomes [113], further promoting consistency across MS rehabilitation trials. Given the inherent complexity of rehabilitation trials, consideration of social and cultural contexts, aligned to program theories is warranted to facilitate intervention reach, and an understanding of when specific interventions need further adaptation, to ensure fit for the target population [132].

4.3. Limitations

This review has several limitations that warrant consideration. First, we focused on RCTs without including other designs. Although RCTs are considered the gold standard for effectiveness research [47], the strategy could have reduced the number of included studies for this review. We are aware of only two pilot feasibility studies [133, 134], using one-group pretest-posttest design, that examine a self-management/behaviour change intervention for Blacks with MS. Whilst there may well be published qualitative or observational studies that provide an indication of ways in which rehabilitation could be more inclusive of the MS population, we argue that these approaches should also be considered in RCTs where there is the greatest potential impact on health services delivery.

Second, we included only English-language articles, due to a lack of resources for translation. There is a possibility that studies that should have been included in the review were omitted (e.g., those from countries where Black, Latina/Hispanic, Asian, Arab or Indigenous racial and ethnic groups predominate and/or where English is not the language of communication). Findings may be different if we included such studies. However, research indicating that the

exclusion of non-English studies across Cochrane reviews did not significantly alter findings [135], suggests that this is unlikely to be a key issue.

Finally, since there is no unified definition for MS rehabilitation, the applied definition could have excluded studies that others might consider as rehabilitation intervention trials. We attempted to minimize this risk by working with an experienced health sciences librarian to generate comprehensive search terms, and utilizing multiple search databases that provide broad coverage of the rehabilitation sciences.

5. Conclusion

Given the disproportionate burden of MS among non-White individuals with MS, we call on the MS rehabilitation research community, and to funders, to pay attention to ensuring that trial and intervention processes accommodate the needs of diverse racial and ethnic groups both in terms of design and their reporting. Doing so will ensure that interventions are generalizable and applicable across diverse groups affected by MS, and further help to address some of the inequities in rehabilitation care for these individuals.

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Pullattayil: Data curation, Methodology, Writing – review & editing. **Monica Busse:** Conceptualization, Writing – original draft, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

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Table 1: Description of included studies

Ref. (quality)	Country	Int types	Control group	Int duration (weeks); session length (min)	Delivery mode; format	Primary outcome measure	Adherence strategies	Retention strategies	Reporting Guidelines
Effectiveness/Efficacy (n=36)									
1. Barlow 2009 MMAT= Moderate-High	UK	SM	Waitlist	6; >60	Face to face; Group	11-item Liverpool Self-Efficacy Scale; Hospital Anxiety and Depression Scale	Not reported	Not reported	CONSORT Flow diagram
2. Bombardier 2008 MMAT= High	US	SM	Waitlist	12; 30-60	Combined; Individual	Health Promoting Lifestyle Profile-II	Not reported	Not reported	CONSORT Flow diagram
3. Bombardier 2013 MMAT= High	US	SM	Waitlist	12; 30-60	Combined; Individual	Hamilton Rating Scale for Depression	Not reported	Not reported	CONSORT Flow diagram

4.	Charvet 2017 MMAT= High	US	Cog. Rehab	Active control	12; 30-60	Web based/online; Individual	Neuropsychological Composite Score (Paced Auditory Serial Addition Test, WAIS-IV Letter Number Sequence, WAIS-IV Digit Span Backwards, Selective Reminding Test, Brief Visuospatial Memory Test-Revised, Delis-Kaplan Executive Function System Trails)	Follow-up check-in calls for missed sessions/ troubleshooting issues with intervention or practice activities	Not reported	CONSORT explicitly stated
5.	Egner 2003[†] MMAT= Moderate	US	SM	Usual care	9; 30-60	Telephone/Videoconference; Individual	Fatigue Severity Scale; Quality of Well-Being Scale; Center for Epidemiologic Studies Depression Scale	Not reported	Not reported	Not reported

6.	Ehde 2017* MMAT= NA	US	SM	Usual care	16; 30-60	Combined; Individual	Brief pain inventory 4-item pain intensity scale; Hopkins symptom checklist-20 version B; Brief pain inventory-interference scale; Composite of medical services utilization and medication data; Major Depressive Episode & Dysthymia modules of the MINI International Neuropsychiatric Interview	Other	Financial incentive	CONSORT explicitly stated
7.	Ehde 2015 MMAT= High	US	SM	Active control	8; 30-60	Telephone/Videoconference; Individual	Modified Fatigue Impact Scale; Modified Brief Pain Inventory Inference Scale; Patient Health Questionnaire 9	Follow-up check-in calls for missed sessions/trouble shooting issues with intervention or practice activities	Not reported	CONSORT Flow diagram
8.	Ehde 2019* MMAT = NA	US	SM	Usual care	8; >60	Telephone/Videoconference; Group	11-point Numeric Rating Scale	Logbooks	Financial incentive and schedule flexibility	CONSORT explicitly stated

9.	Finlayson 2011 MMAT= High	US	SM	Waitlist	6; >60	Telephone/Video conference; Group	Fatigue Impact Scale; Fatigue Severity Scale; SF-36	Follow-up check-in calls for missed sessions/trouble shooting issues with intervention or practice activities	Not reported	CONSORT Flow diagram
10.	Goodwin 2020 MMAT= Moderate	UK	Cog Rehab	Active control	8; NR	Telephone/Videoconference; Individual	Everyday Memory Questionnaire self-report version	Not reported	Not reported	CONSORT Flow diagram
11.	Goverover 2018 MMAT= Moderate-High	US	Exs	Placebo	3; 60	Face to face; Individual	Contextual Memory Test; Self-Regulation Skills Interview	Not reported	Not reported	CONSORT Flow diagram

12. Hansen 2015 MMAT= Moderate-High	Belgium	Exs	Usual care	24; >60	Face to face; NR	Oxygen uptake (VO2, ml/min), carbon dioxide output (VCO2, ml/min), expiratory volume (VE, l/min), respiratory rate (RR), expiratory tidal volume (Vt, l/min), dead space/tidal volume ratio (Vd/Vt, %), oxygen uptake (VE/VO2) and carbon dioxide output equivalent (VE/VCO2), end-tidal oxygen (PETO2, KPa) and carbon dioxide pressure (PETCO2, KPa), oxygen pulse (VO2/HR)	Not reported	Not reported	CONSORT Flow diagram
13. Houniet-deGier 2020* MMAT = NA	Netherlands	SM	Active control	20; 30-60	Face to face; Individual	Checklist Individual Strength-Fatigue Severity Subscale	Logbooks	Make-up sessions/ FU calls	SPIRIT
14. Hugos 2019 MMAT= High	US	SM	Active control	6; >60	Face to face; Group	Modified Fatigue Impact Scale	Not reported	Financial incentive and Make-up sessions/ FU calls	CONSORT Flow diagram

15.	Jeong 2021 MMAT= Moderate	US	Exs	Contact control	12; NR	Telephone/Videoconference; Individual	Multiple Sclerosis Quality of Life-54	Not reported	Not reported	Not reported
16.	Kargarfard 2018[†] MMAT= High	Iran	Exs	Waitlist	8; 30-60	Face to face; Individual	Six-minute walk test; Berg Balance Scale; Modified Fatigue Impact Scale; sit-to-stand test; push-up test	Not reported	Not reported	CONSORT Flow diagram
17.	Lincoln 2020 MMAT= High	UK	Cog Rehab	Usual care	10; >60	Face to face; Group	Multiple Sclerosis Impact Scale Psychological	Logbooks and review of practice activities	Financial incentive and Schedule flexibility	CONSORT Flow diagram

18.	Martini 2018[†] MMAT= High	US	Neuro Rehab	Usual care	6; 30-60	Face to face; Individual	Self-report falls calendars; International Physical Activity Questionnaire short form; Timed Up and Go; Timed 25-foot walk; 2-minute walk test; Four Square Step Test; Quebec User Evaluation of Satisfaction with Assistive Technologies; Multiple Sclerosis Walking Scale-12; Activities-Specific Balance Confidence Scale; Multiple Sclerosis Impact Scale-29	Not reported	Schedule flexibility	CONSORT Flow diagram
19.	Mathiowetz 2005 MMAT= High	US	SM	Waitlist	6; >60	Face to face; Group	Fatigue Impact Scale; SF-36 health survey	Not reported	Make-up sessions/ FU calls	CONSORT Flow diagram

20.	McAuley 2007[†] MMAT= Moderate	US	SM	Usual care	12; 30-60	Face to face; Group	Six-item Exercise Self-Efficacy scale; Five-item Satisfaction with Life Scale; 12-item Short Form Survey; Daily attendance logs; Enjoyment Scale; Feeling Scale; Borg's RPE scale	Logbooks	Not reported	CONSORT Flow diagram
21.	McGibbon 2018 MMAT= High	Canada and US	Neuro Rehab	Cross-over	6; <30	Face to face; Individual	6 Minute Walk Test; Timed Up-and-Go; Timed Stair Test; Actigraph GT3X; Keeogo Usability Survey	Logbooks	Not reported	CONSORT Flow diagram
22.	Miller 2011[†] MMAT= High	US	SM	Active control	24; NR	Web-based/online; Individual	Sickness Impact Profile; MS Functional Composite; Control Subscale of the MS Self-Efficacy Scale; Seniors' General Satisfaction and Physician Quality of Care; Euro-Quality of Life	Reminders	Not reported	CONSORT Flow diagram
23.	Mohr 2004 MMAT= Moderate-High	US	SM	Active control	16; >60	Face to face; Hybrid	Beck Depression Inventory; Arizona Social Support Interview Schedule	Not reported	Not reported	Not reported

24.	Mohr 2007[†] MMAT= High	US	SM	Active control	16; 30-60	Telephone/Videoconference; Individual	Guy's Neurological Disability Scale; Beck Depression Inventory; telephone-administered version of the Hamilton Rating Scale for Depression; Fatigue Impact Scale	Not reported	Financial incentive	CONSORT Flow diagram
25.	Mohr 2012 MMAT= High	US	SM	Waitlist	24; 30-60	Face to face; Individual	Cumulative number of new gadolinium-enhancing (Gd+) brain lesions on MRI	Not reported	Not reported	CONSORT Flow diagram
26.	Moss-Morris 2013 MMAT= High	UK	SM	Active control	10; >60	Combined; Individual	General Health Questionnaire; Work; Social Adjustment Scale	Not reported	Not reported	CONSORT Flow diagram
27.	Motl 2019[*] MMAT= NA	US	Exs	Active control	16; 30-60	Combined; Individual	Timed 25-Foot Walk	Not reported	Financial incentive and Reminder calls	Not reported

28.	Pinto 2019[*†] MMAT= NA	Brazil	Neuro Rehab	Active control	9; 30-60	Face to face; Individual	Surface electromyograph; Force platform EMG balance evaluation; Cosmed MicroQuark Spirometer; Analogue manovacuometer; Peak Flow Meter, NCS expiratory flow meter; common metric tape (1.5m); Infrared thermographic camera; frequency meter; lactometer with lactate reagent tapes; 6-minute walk test (Adapted); Short Form 36; Mini-Mental State Examination	Not reported	Not reported	CONSORT Flow diagram
29.	Plow 2019 MMAT= Moderate-High	US	SM	Contact control; Active control	12; >60	Telephone/Videoconference; Hybrid	Fatigue Impact Scale; Godin Leisure-Time Exercise Questionnaire	Logbooks	Make-up sessions/ FU calls	CONSORT Flow diagram
30.	Plow 2020[*] MMAT= NA	US	SM	Active control	6; >60	Combined; Hybrid	Fatigue Impact Scale	Not reported	Not reported	Not reported

31.	Rimmer 2018* MMAT= NA	US	Exs	Active control	12; 30-60	Combined; Individual	36-Item Short Form Survey; Modified Fatigue Impact Scale; Godin Leisure Time Exercise Questionnaire	Follow-up check-in calls for missed sessions/trouble shooting issues with intervention or practice activities; education about intervention components; Reminders; Logbooks;	Schedule flexibility; Financial incentive; Make-up sessions/ FU calls	Not reported
32.	Stuifbergen 2003 MMAT= High	US	SM	Waitlist	20; >60	Combined; Hybrid	Health Promoting Lifestyle Profile II; Medical Outcomes Study 36-Item Short-Form Health Survey	Not reported	Financial incentive	CONSORT Flow diagram

33.	Stuifbergen 2018[†] MMAT= High	US	Cog Rehab	Usual care	8; >60	Combined; Hybrid	Minimal Assessment of Cognitive Function in MS; Controlled Oral Word Association Test; California Verbal Learning Test, 2nd ed; Brief Visuospatial Memory Test – Revised; Paced Auditory Serial Addition Test; Symbol Digit Modalities Test; Everyday Problems Test-Revised; 17-item General Self-Efficacy Scale; Center for Epidemiologic Studies Depression Scale; Strategy Subscale of the Multiple-Factorial Memory Questionnaire; PROMIS v1.0; Applied Cognition-Abilities-Short Form	Not reported	Not reported	CONSORT Flow diagram

34. Thomas 2013 MMAT= High	UK	SM	Usual care	6; >60	Face to face; Group	Global Fatigue Severity subscale of the Fatigue Assessment Instrument; Disease-specific quality of life (QOL); Self-Efficacy Scale	Not reported	Not reported	CONSORT explicitly stated
35. Turner 2016 MMAT= High	US	SM	Active control	24; >60	Telephone/Videoconference; Individual	Mobility Item of the Performance Scales; Modified Fatigue Impact Scale	Follow-up check-in calls for missed sessions/trouble shooting issues with intervention or practice activities; Reminders; Logbooks	Not reported	CONSORT Flow diagram
36. Young 2019 MMAT= Moderate-High	US	Exs	Waitlist	12; 30-60	Face to face; Group	Timed Up and Go; 6-minute walk test; 5 times sit-to-stand test	Not reported	Not reported	CONSORT Flow diagram

Pilot/Feasibility (n=20)										
37. Block 2021 MMAT= Moderate-High	US	SM	Usual care	12; NR	Telephone/Video conference	Feasibility metrics (recruitment rates, retention rates, reasons for dropouts, adherence rate, study acceptability, adverse events)	Reminders	Not reported	CONSORT Flow diagram
38. Bogosian 2015 MMAT= High	UK	SM	Waitlist	8; >60	Telephone/Video conference	General Health Questionnaire	Not reported	Not reported	CONSORT Flow diagram
39. Cederberg 2021 MMAT= High	US	SM	Waitlist	16; 30-60	Web-based	International Restless Legs Syndrome Study Group Scale; Restless Legs Syndrome Rating Scale-6; Pittsburgh Sleep Quality Index; Sleep Satisfaction (RLS-6 Item 1); Seven-Day Diary; Home-based accelerometry; 8-item Epworth Sleepiness Scale	Follow-up check-in calls for missed sessions/trouble shooting issues with intervention or practice activities	Not reported	CONSORT explicitly stated

40.	dasNair 2016 MMAT= Moderate-High	UK	SM	Active control	16; NR	Face to face	Feasibility metrics (recruitment rate, acceptability of randomization and the intervention and adaptability for individual delivery)	Not reported	Not reported	CONSORT Flow diagram
41.	Hugos 2017[†] MMAT= High	US	SM	Usual care	6; >60	Face to face	Multiple Sclerosis Spasticity Scale-88; Multiple Sclerosis Walking Scale-12; Modified Fatigue Impact Scale; Multiple Sclerosis Impact Scale; Beck Depression Inventory II; Modified Ashworth Scale; Timed Up and Go; Timed 25 Foot Walk; 2-Minute Walk Test	Logbooks	Not reported	CONSORT Flow diagram
42.	Kannan 2019 MMAT= Moderate	US	SM	Waitlist	8; NR	Web-based	Survey of prospectively counted falls	Not reported	Make-up sessions/ FU calls	CONSORT Flow diagram
43.	Klaren 2014 MMAT= Moderate-High	US	SM	Waitlist	24; NR	Telephone/Video conference	International Physical Activity Questionnaire; Patient-Determined Disease Steps scale	Not reported	Financial incentive	Not reported

44.	Learmonth 2017 MMAT= High	US	SM	Waitlist	16; 30-60	Telephone/Video conference	ActiGraph GT3X accelerometers	Not reported	Not reported	CONSORT Flow diagram
45.	Learmonth 2021[*] MMAT= NA	Australia	Exs	Usual care	16; NR	Combined	Godin Leisure-Time Exercise Questionnaire	Reminders	Not reported	CONSORT Flow diagram
46.	Molton 2019[†] MMAT= Moderate-High	US	SM	Usual care	6; NR	Combined	Two-item, in-house treatment benefit scale; Single item overall satisfaction measure; Intolerance of Uncertainty Scale; Acceptance of Chronic Health Conditions; General Anxiety Disorder-7	Not reported	Not reported	Not reported
47.	Plow 2014[†] MMAT= Moderate-High	US	SM	Waitlist	24; 30-60	Combined	Physical Activity and Disability Survey-revised; Godin Leisure-Time Exercise Questionnaire; SF-12 physical composite; Multiple Sclerosis Scale; Symptoms of Multiple Sclerosis Scale	Logbooks	Not reported	CONSORT Flow diagram

48.	Ryan 2017[*†] MMAT= NA	UK	SM	Usual care	12; 30-60	Face to face	ActiGraph-activPAL3u monitor; International Physical Activity Questionnaire Short-form; 12-item MS Walking Scale; Modified Fatigue Impact Scale; Multiple Sclerosis Self-Efficacy Scale; Impact on Participation and Autonomy Questionnaire; ED-5D (EQ-5D-5L); Client Service Receipt Inventory	Not reported	Not reported	CONSORT Flow diagram
49.	Schirda 2020[†] MMAT= High	US	SM	Waitlist	4; >60	Face to face	Difficulties in Emotion Dysregulation Scale; Ruminative Responses Scale; Penn State Worry Questionnaire; World Health Organization Quality of Life, Survey; Beck Depression Inventory-II; Worry and Rumination Task	Logbooks	Financial incentive	CONSORT Flow diagram

50.	Sebastiao 2018 MMAT= Moderate	US	Exs	Contact control	12; 30-60	Combined	Timed 25-foot Walking; Six-minute Walk; Timed Up and Go; Symbol Digit Modalities Test; Brief Visuospatial Memory Test; California Verbal Learning Test; Short Physical Performance Battery	Follow-up check-in calls for missed sessions/trouble shooting issues with intervention or practice activities; Logbooks	Financial incentive	CONSORT Flow diagram
51.	Siengsukon 2020 MMAT= High	US	SM	Active control	6; 30-60	Face to face	Insomnia Severity Index; Pittsburgh Sleep Quality Index; Modified Fatigue Impact Scale; Fatigue Severity Scale	Not reported	Not reported	CONSORT Flow diagram

52.	Stuifbergen 2012† MMAT= High	US	Cog Rehab	Waitlist	8; >60	Combined	Self-Administered Expanded Disability Status Scale; Minimal Assessment of Cognitive Function in MS; Self-Efficacy Scale (MSSE-Control); Strategy Subscale of the Multifactorial memory Questionnaire (MMQ-Strategy); Multiple Sclerosis Neuropyschological Screening Questionnaire	Not reported	Financial incentive	CONSORT Flow diagram
53.	Suh 2015† MMAT= High	US	SM	Contact control	6; NR	Combined	Godin Leisure-Time Exercise Questionnaire; Exercise Self-Efficacy Scale; Multidimensional Outcomes Expectations for Exercise Scale; Late-Life Function and Disability Instrument; Goal-setting Scale; Social Support and Exercise Survey; Patient Determined Disease Steps	Follow-up check-in calls for missed sessions/trouble shooting issues with intervention or practice activities	Financial incentive	CONSORT Flow diagram

54.	Thomas 2017[†] MMAT= Moderate	UK	SM	Waitlist	24; NR	Combined	Two-minute walk test; Step test; Steady stance test; Instrumented Timed Up and Go; Gait stride-time rhythmicity; Static posturography (Limits of Sway); Godin Leisure-Time Exercise Questionnaire; ActivPAL; Nine-hole peg test; Multiple Sclerosis Self-Efficacy Scale; Hospital Anxiety and Depression Scale; EuroQual 5 Dimensions-5 Levels; Multiple Sclerosis Impact Scale; Fatigue Symptom Inventory; Medical Outcomes Short-Form Survey V.2	Not reported	Not reported	CONSORT explicitly stated

55. Tosh 2014 MMAT= Moderate-High	UK	Exs	Usual care	12; 30-60	Face to face	Self-report physical activity questionnaire; accelerometry; Leisure Score Index; Godin Leisure Time Exercise Questionnaire	Not reported	Not reported	Not reported
56. vanKessel 2016 MMAT= Moderate	New Zealand	SM	Active control	8; 30-60	Web-based	Chalder Fatigue Scale; Modified Fatigue Impact Scale	Reminders	Not reported	CONSORT Flow diagram

*indicates protocol papers; †indicates that the primary outcome was not reported

MMAT – Multiple Methods Assessment Tool; Int – Intervention; SM – Self management; Cog Rehab – Cognitive rehabilitation; Exs – Exercise training; Neuro Rehab – Neurological rehabilitation

Table 2: Participant eligibility criteria and recruitment strategies

Ref	Inclusion criteria	Exclusion criteria	Recruitment strategies
Effectiveness/Efficacy (n=36)			
1. Barlow 2009	Aged 18+ years; diagnosis of MS; ability to communicate in and understand English; Ability to complete the questionnaire	Inability to understand and participate in a programme delivered in English	Media; MS organization
2. Bombardier 2008	Aged 18+ years; physician-confirmed diagnosis of MS; able to walk 90m (300ft) without assistance (equating to an EDSS score of 5.5 or better); endorsed interest in 1 or more of the health promotion target areas	Significant depressive symptoms; medical conditions that were contraindications to increased exercise	Media; Clinical records/visits/Physician referral; MS organization; Existing list of research volunteers
3. Bombardier 2013	Aged 18-70 years; physician-confirmed diagnosis of MS; EDSS ≤ 5.5; significant depressive symptoms; diagnosis of major depressive disorder or dysthymia; currently not meeting physical activity guidelines (exercising <150 min per week).	Cardiovascular, balance, or bone/joint problem that would make exercise unsafe; extreme heat intolerance or Uhthoff effect; prior diagnosis of schizophrenia, paranoid disorder, or bipolar disorder; active suicidal ideation; current alcohol dependence; unable to complete forms without assistance	Media; Mail; Clinical records/visits/Physician referral; MS organization
4. Charvet 2017	Aged 18-70; definite MS diagnosis, any subtype; probable cognitive impairment; concurrent medications to be kept constant over three months (as possible); no relapse or steroids in previous month; reading score on WRAT-3 of 37 or greater; visual, auditory and motor capacity to operate computer software, as judged by treating neurologist or study staff	History of mental retardation, pervasive developmental disorder or other neurological condition associated with cognitive impairment; primary psychiatric disorder that would influence ability to participate; other serious uncontrolled medical condition (e.g., cancer or acute myocardial infarction); alcohol or other substance use disorder; history of computer-based training manufactured by Posit Science; learned English language after 12 years of age	Clinical records/visits/Physician referral

5.	Egner 2003	Experience of a recent functional setback in the disease process, such as a severe exacerbating episode or an increase or start of chemotherapy treatment; EDSS score of 7 or greater	Not reported	Clinical records/visits/Physician referral
6.	Ehde 2015	Aged 18+ years; Physician-confirmed diagnosis of MS; plans to continue to receive care at the UQ Medicine MS Center during the enrollment period to ensure integration of services; has access to and is able to communicate over the telephone to facilitate the telehealth components of the intervention and outcome assessments; reads, speaks and understands English; reports a clinically significant problem in pain or depression, specifically (a) chronic pain: average pain intensity in the past week of at least moderate severity (defined as 3 or greater on 0-10 numeric rating scale) and pain of at least six months duration, with pain reportedly present greater than or equal to half of the days in the past six months or (b) depression: depressive symptoms over the past two weeks in the range of probable depressive symptoms over the past two weeks in the range of probable major depression on Patient Health Questionnaire-9 and endorsement of depressed mood and/or anhedonia (i.e., one of the cardinal symptoms of depression) present more than half the days in the past two weeks	Presence of a severe psychiatric disorder as evidenced by (a) high suicide risk (i.e., current intent or plan, or thoughts of suicide in the past month with at least one suicide attempt in the past), (b) diagnosis of bipolar disorder with current psychotic features, or (c) symptoms of a current psychotic disorder at the time of screening; severe cognitive impairment, resulting in inability to provide informed consent; Self-reported active substance abuse within the past month; patient reports a planned major surgery scheduled in the next 10 months; ongoing psychiatric (> once a month) care of depression provided by a psychiatrist	Clinical records/visits/Physician referral

7.	Ehde 2018	Aged 18+ years; self-reported diagnosis of MS, and 1 of the following - moderate depressive symptoms suggested by a score between 10 and 14 on the Patient Health Questionnaire-9; existence of chronic pain defined as 3 average pain intensity in the past week on a 0 to 10 pain intensity numerical rating scale (NRS); presence of significant fatigue symptoms defined as 10 on the 5-item short version of the Modified Fatigue Impact Scale (MFIS)	Significant cognitive impairment defined as errors on the 6-item Cognitive Screener receiving psychotherapy more than once a month at time of screening, or moderate to severe or severe depressive symptoms on the Patient Health Questionnaire-9.	Mail; Clinical records/visits/Physician referral; MS organization; Existing list of research volunteers
8.	Ehde 2019	Aged 18+ years; physician-confirmed diagnosis of clinically definite MS; presence of chronic pain, and pain of at least 3 months duration, with pain reportedly present on at least half the days in the past 3 months; reads and speaks English; has access to and is able to communicate over the telephone; and has a computer or digital device with video capabilities (any operating system) with Internet access	Severe cognitive impairment; currently in psychotherapy or counseling for pain more than once a month; and previously participated in a pain study that used CBT or MBCT.	Word of mouth/Snowball sampling; Online; Posters; Clinical records/visits/Physician referral; MS organization; Existing list of research volunteers
9.	Finlayson 2011	Aged 18+ years; living within the state of Illinois; self-reported diagnosis of MS; functional English literacy (i.e. able to read course materials and carry on telephone conversations in English); Fatigue Severity Scale score of 4 or greater (i.e. moderate to severe fatigue); weighted score of at least 12 on the short version of the Blessed Orientation Memory Concentration test	Not reported	Mail; MS organization

10.	Goodwin 2020	Aged 18+ years; had been diagnosed with MS more than 12 months before joining the study; self-reported memory problems, defined as a score more than 20 on the self-report version the Everyday Memory Questionnaire; gave informed consent	Cognitive, visual or motor impairment, such that they were unable to use a pager or mobile phone; another concurrent neurological diagnosis, e.g., epilepsy; concurrent severe medical or psychiatric diagnosis; concurrently taking part in other psychological intervention studies; did not understand English	Clinical records/visits/Physician referral; MS organization
11.	Goverover 2018	Aged 31-65 years; clinically definite MS with documented memory impairment based on the Selective Memory Test (SRT); free from any history of neurological injuries or illnesses (aside from MS); had no reported history of alcohol or drug abuse and/or major psychiatric illnesses; sufficient vision (assessed by paragraph reading); English as their primary language; at least 1-month post most recent exacerbation; free of corticosteroid use	Not reported	MS organization; Advertisements; Existing list of research volunteers
12.	Hansen 2015	Aged 18-75 years; sedentary (<2h sports activities/week; diagnosed for at least 12 months by a neurologist according to the McDonald criteria	Diagnosed with cardiovascular, renal or pulmonary disease	Word of mouth/Snowball sampling
13.	Houniet-deGier 2020	Aged 18-70 years; definitive diagnosis of MS; severely fatigued; ambulatory; no evident signs of an exacerbation and no corticosteroid treatment in the past 3 months; no current infections; no anemia; normal thyroid function	Depression; primary sleep disorders; other severe somatic or psychiatric co-morbidity; current pregnancy or having given birth in the past 3 months; pharmacological treatment for fatigue that was started in the past 3 months; non-pharmacological therapies for fatigue that took place in the last 3 months; having received CBT in the TREFAMS trial	Clinical records/visits/Physician referral; MS organization

14. Hugos 2019	Aged 18+ years; definite MS of any subtype; moderate-to-severe fatigue; EDSS <6.5 5; Beck Depression Inventory II <28; stable on disease modifying medications for at least 3 months; free of relapses for the prior 30 days; not pregnant; able to comply with study procedures, and complete measures independently	Not reported	Clinical records/visits/Physician referral
15. Jeong 2021	Not reported	Not reported	Not reported
16. Kargarfard 2018	MS of a minimum of 2 years; no relapses in the past month, and; able to exercise regularly	A relapse during the intervention; developed any comorbidities during the intervention or both	MS organization
17. Lincoln 2020	Aged 18-69 years; diagnosed with relapsing remitting or progressive multiple sclerosis; diagnosed at least three months prior to the screening assessment; reported having cognitive problems; impaired on at least one of the Brief Repeatable Battery of Neuropsychological tests; able to attend group sessions; able to speak English sufficiently to complete the cognitive assessments; gave written informed consent	Had vision or hearing problems, such that they were unable to complete the cognitive assessments; had concurrent severe medical or psychiatric conditions, which prevented them from engaging in treatment; were involved in other psychological intervention trials.	Clinical records/visits/Physician referral; MS organization; MS Register
18. Martini 2018	Aged 18+ years; confirmed MS of any type; self-reported current intermittent or constant use of unilateral or bilateral assistance for walking; able to walk at least 25 feet; no relapse in prior 30 days; self-reported history of 1 or more falls in the previous year	Reporting receiving more than 1 hour of walking aid training within the previous 3 years; serious conditions that would preclude reliable study participation (e.g., dementia, deafness, and blindness)	Clinical records/visits/Physician referral

19. Mathiowetz 2005	Aged 18+ years; diagnosis of MS; reported being functionally literate in English (i.e., able to read course materials); Fatigue Severity Scale score of 4 or greater; lived independently in the community; and agreed to attend at least five out of six EC sessions	Failed more than one subtest of the Neuropsychological Screening Battery for Multiple Sclerosis	MS organization
20. McAuley 2007	Definite diagnosis of MS; ambulatory with minimal assistance; sedentary (defined as being physically active less than three times per week for 30 minutes each bout); willing to commit to the length of the program	Not reported	Media; MS organization; Existing list of research volunteers
21. McGibbon 2018	Aged 21+ years; diagnosed > 1 yr. ago with multiple sclerosis; able to read and understand informed consent form and study instructions; waist and leg circumference and lower extremity lengths appropriate for a comfortable and safe fit in the Keeogo device; able to walk 25 m without stopping, without human assistance, using assistive devices and ankle-foot-orthoses, as necessary; can complete a 10 step stair test; Score > 23 on the Mini-Mental State Examination; Modified Ashworth Score < 3 for knee or hip, and < 3 for ankle if no AFO is used; Recent (< 12mo) EDSS evaluation on record, with EDSS <6.5	Legally blind; pregnant or lactating; skin condition that contraindicates use of orthotics or support braces; recent (< 6 months) lower-body hospitalizations or active treatments due a joint, muscle, bone, nerve or vascular injury or condition; scheduled for major surgery within next 4 months; lower-extremity amputation above or below the knee - uncontrolled hypertension; recent (< 1 year) heart attack; uncontrolled diabetes; diagnosed with other health condition(s) that affect mobility and balance, including chronic obstructive pulmonary disease; peripheral arterial disease; vestibular disorders; cerebellar disease; cerebral palsy; muscular dystrophy; spinal cord injury; stroke or other brain injury	Clinical records/visits/Physician referral

22. Miller 2011	Clinically definite MS; resided in the county where the Mellen Center is located or in one of the five surrounding counties; had completed at least two appointments with a physician or an APC at our center in the 12 months previous to enrollment; demonstrate that they could turn a computer on and off, send an e-mail message, and pass a typing test	Not reported	Clinical records/visits/Physician referral
23. Mohr 2004	Confirmed diagnosis of MS; relapsing-remitting or secondary progressive disease course confirmed by a neurologist; a score of 16 or greater on the Beck Depression Inventory; willingness to abstain from psychological or pharmacological treatment for depression other than that provided in the study during the treatment period	Other serious psychological disorders for which treatment would be inappropriate, including psychotic disorders, bipolar disorders, or active substance abuse; meeting criteria for dementia by falling below the 5th percentile in three out of six areas of neuropsychological functioning, including attention and concentration, speed of processing, executive functioning, verbal memory and visual processing; severe suicidality including ideation, plan, and intent; treatment with corticosteroids within previous 14 days; initiation of treatment with an interferon medication within previous 2 months; current MS exacerbation; other disorders of the central nervous system in addition to MS; current or planned pregnancy; current psychological or pharmacological treatment for depression	Not reported

24. Mohr 2007	Aged 18+ years; physician confirmed diagnosis of MS; functional impairment resulting in limitations in activity as measured by a score of at least 3 of a total possible score of 6 (indicating marked impact on activity) on one or more areas of functioning on Guy's Neurological Disability Scale); score of 16 or above on the Beck Depression Inventory and 14 or above on the Hamilton Rating Scale of Depression; ability to speak and read English	Met criteria for dementia; currently in psychotherapy; severe psychopathology, including psychosis, current substance abuse, or plan and intent to commit suicide; current MS exacerbation, defined as a sudden increase in symptoms within 24 hr. that had not yet remitted; physical deficits that prevented participation in treatment or assessment including inability to speak or read and write; on medications other than antidepressants that affect mood (e.g., steroidal anti-inflammatories)	Clinical records/visits/Physician referral; MS organization
25. Mohr 2012	Aged 18+ years; diagnosed with MS according to the MacDonald criteria and had documented evidence of clinical exacerbation or at least 1 Gd+ MRI brain lesion within 12 months prior to enrollment. The qualifying exacerbation or Gd+ lesion had to have occurred at least 1 month after initiation of an interferon drug or 6 months after initiation of glatiramer acetate; able to speak and read English; A score of 0-6.5 EDSS	Received corticosteroids in the past 28 days, were treated with a cytotoxic agent or natalizumab, had other autoimmune or endocrine disorders; unable to undergo GD+ MRI; pregnant or planning pregnancy; diagnosed using the Mini International Neuropsychiatric Interview with any severe psychiatric disorder (e.g., psychotic disorders, bipolar disorder), or were currently receiving or planning to being psychotherapy; met criteria for dementia, defined consistent with previous trials as being below the fifth percentile on 3 or more of the following: Symbol Digit Modalities, Digit Span, Hopkins Verbal Learning Test, Controlled Word Association Test, Similarities, and the 10/36 test	Clinical records/visits/Physician referral; MS organization

26.	Moss-Morris 2013	Definite diagnosis of MS within the last 10 years; ability to walk a short distance (with a stick or crutches if needed; equivalent to a score of 6.5 or less on the EDSS; willingness to abstain from new psychological or pharmacological treatment during the course of the study where possible	Comorbid serious, life-threatening health problems or severe mental health problems (e.g., psychotic disorders or substance abuse); current psychological treatments or treatments received in the last 2 months; severe cognitive impairment, as assessed by a score of less than 20 on the Telephone Interview for Cognitive Status Modified	Clinical records/visits/Physician referral
27.	Motl 2019	Aged 18-65 years; self-reported diagnosis of MS; accessible, technological platform for GEMS-5 (i.e. computer or DVD player and TV, and telephone); able and willing to travel to a site for testing and/or training; score between 25 and 75 on the MSWS-12; score between 3 and 6 (inclusive) on the PDDS; medically stable as determined by the Exercise Preparticipation Health Screening or approval from physician to participate in exercise studies; EDSS score of 4.0 through 6.5; T2FW time between 6s and 3 min	Documented MS relapse in the past 30 days; occurrence of falls in the past three months that the study investigator determines makes participation unsafe; Unable to walk 25 ft; not proficient in English; Other neurological (e.g., stroke) or musculoskeletal conditions or other comorbidities; Any other concerns that the investigators deem would jeopardize the safety of the potential participant; Score of 25 or higher based on Health Contribution score from the GLTEQ; Cognitive difficulties as determined by a Mini Mental Status Exam score < 19; Any other concern that the investigator deem would jeopardize the safety of the potential participant	Word of mouth/Snowball sampling; Clinical records/visits/Physician referral; Existing list of research volunteers

28. Pinto 2019	Aged 18-65 years; people with stroke, traumatic brain injury, spinal cord injury, brain tumor postoperative period, chronic nonprogressive encephalopathy, and multiple sclerosis; chronic neurological diseases, from 6 months of injury; Caucasian individuals; both sexes; preserved cognition; able to wander on the treadmill voluntarily or through assistance of the Brain Mov Rehabilitation and Physical Activity Station; continuous and regular use of medications prescribed by the physician for the control and/or treatment of chronic diseases; the release of the cardiologist for rehabilitation	Not meeting the inclusion criteria; active smokers; carriers of chronic respiratory diseases, such as chronic obstructive pulmonary disease, asthma and bronchiectasis; decompensated heart disease; obesity grade II - body mass index greater than 34.99kg/m^2; spinal cord injury above sixth thoracic vertebra, who present with autonomic dysreflexia; American Spinal Injury Association Impairment Scale A or B Impairment; patients with multiple sclerosis who are in the onset period; patients who use beta-blocking drugs; hemorrhagic encephalic vascular accident	Clinical records/visits/Physician referral; Existing list of research volunteers
29. Plow 2019	Aged 18-65 years; physician-confirmed diagnosis of MS and physician consent to initiate a physical activity program; ability to walk 25 or more feet with or without a cane; ability to carry on telephone conversations in English; PDDS score between 1 (mind disability) and 5 (unilateral support required); current sedentary lifestyle (i.e. purposeful exercise less than or equal to 2 days / wk. for 30 min); moderate to severe fatigue (a score of 4 or greater on the Fatigue Severity Scale)	Pregnancy; cardiopulmonary diseases that would hinder engagement in physical activity; uncontrolled diabetes (hospitalized within the last 6 months); >3 falls in the past 6 months; severe cognitive deficits (weighted score of less than 12 on the short version of the Blessed Orientation memory Concentration test); unable to contact physician/treating clinician to confirm MS diagnosis and reasonable risk for the walking program	Mail; MS organization
30. Plow 2020	Aged 18+ years; self-reported diagnosis of MS; moderate-to-severe fatigue (i.e., Fatigue Severity score greater or equal to 4); ability to speak and read English (i.e., confirmed via phone conversation and self-report)	Inability to understand the consent form (e.g., assessed with five questions about the study); inability to participate in the intervention (e.g., unwilling or unable to travel outside the home)	Word of mouth/Snowball sampling; Online; Clinical records/visits/Physician referral; MS organization

31.	Rimmer 2018	Aged 18-70 years; mild to moderate disability (PDDS 0-7); able to use both arms/legs for exercise while standing or seated (this would include people with hemiparesis); physician permission to participate in the study	Significant visual acuity that prevents seeing a tablet screen in order to follow home exercise program; cardiovascular disease event within the past six months; severe pulmonary disease; renal failure; active pressure ulcer; currently pregnant; within 30 days of receiving a rehabilitation session; already meeting physical activity guidelines (GLTEQ ≥ 24)	Clinical records/visits/Physician referral; posters; MS organization; community organizations; community social events; social media
32.	Stuifbergen 2003	Aged 20-70 years; female; physician-diagnosed MS for at least 6 months	Pregnant; concurrent medical conditions for which changes in exercise or diet would be contraindicated	Posters; MS organization; Existing list of research volunteers
33.	Stuifbergen 2018	Aged 18-60 years; able to understand and comply with the study protocol; visual acuity with correction sufficient to work on a computer screen; clinically definite MS for at least 6 months; exacerbation free for 90 days; Perceived Deficits Questionnaire score of ≥10 (indicating some problems in at least 5 areas)	Not reported	Clinical records/visits/Physician referral; MS organization

34. Thomas 2013	Aged 18+ years; providing written informed consent; clinical diagnosis of relapsing-remitting or progressive multiple sclerosis; score on the FSS >4; ambulatory (score on the Adapted PDDS < 8); able to attend the intervention sessions; English speaking	Attended a specific fatigue management programme within the last year; Received a substantive, specific, fatigue intervention from an Occupational Therapist (OT) or other health professional, consisting of more than general advice, within the previous 3 months; already involved in another research study; Individuals who have cognitive deficits such that they would not be able to engage in the group format or benefit from the program; a relapse within the previous three months; on a disease-modifying drug (such as Beta-Interferon, Glatiramer Acetate) or an anti-depressant for < 3 months; Individuals who are known to be currently under the care of a psychiatrist or under the care of addiction services	Clinical records/visits/Physician referral; MS organization
35. Turner 2016	Aged 18-80 years; physician-confirmed diagnosis of MS; sufficient ambulatory ability (EDSS <6.5); willingness to complete a physical activity program but currently exercising less than 300 min per week; Having telephone access; Currently reporting fatigue (MFIS score ≥20)	MS exacerbation (relapse) in the past 30 days; health conditions for which aerobic exercise might be contraindicated (e.g., cardiopulmonary difficulties, significant balance problems, bone and joint disorders) as assessed by the Physical Activity Readiness Questionnaire; exercise-induced MS symptoms (such as extreme heat insensitivity); psychosis or unmanaged bipolar disorder; active suicidal ideation; current or active substance use disorder	Mail; Clinical records/visits/Physician referral; MS organization

36.	Young 2019	Aged 18-65years; self-reported a diagnosis of MS, with a PDDS score 0-6; ability to exercise with arms and/or legs; physician clearance	Participation in a similar intervention in the last 6 months; use of tobacco products in the last 6 months; unstable weight; cognitive impairment (MMSE score<24); active pressure ulcer; any contraindications to exercise based on the ACSM guidelines	Word of mouth/Snowball sampling; Clinical records/visits/Physician referral; MS organization
Pilot/Feasibility (n=20)				
37.	Block 2021	EDSS score of 1.5-6.5; Bladder Control Scale score of >2; Neurostatus Ambulation score of >1; CES-D score of mild depression or worse; at least 2 of the 3 Bladder Ambulation and Mood symptoms	No access to a smartphone/personal computer or Internet connectivity; cognitive impairment severe enough to preclude participation; an Inability to understand the study protocol and/or consent autonomously	Clinical records/visits/Physician referral
38.	Bogosian 2015	Diagnosis of PPMS or SPMS; internet access; some level of distress determined by a score of ≥3 on the GHQ-12	Severe cognitive impairment; high suicide risk; self-reported serious psychological disorders (e.g. psychosis, substance abuse); severe hearing impairment; attending other psychological therapies or prior formal training in mindfulness	Online
39.	Cederberg 2021	Aged 18+ years; confirmed diagnosis of MS; relapse free for the past 30 days; Internet and email access; non-active defined as not engaging in regular activity (i.e., 30 minutes accumulated per day) on more than 2 days of the week for the previous six months; ambulatory without assistance; positive screen for RLS diagnostic criteria based on affirmative responses to the Cambridge-Hopkins Restless Legs Syndrome Short Form Diagnostic Questionnaire that excludes common mimics of RLS; RLS severity of moderate-to-very severe (i.e., International Restless Legs Syndrome Study Group Scale score of 15 or higher)	Moderate or high risk for undertaking strenuous or maximal exercise (i.e., more than one affirmative response on the Physical Activity Readiness Questionnaire); diagnosis of radiculopathy, peripheral edema, peripheral neuropathy, iron deficiency anemia, renal disease, or diabetes	Mail; Posters

40. dasNair 2016	Diagnosis of MS; ≥3 out of 12 on the GHQ-12 or ≥8 out of 21 on the HADS Anxiety or Depression subscales	Did not speak English; unable to attend group sessions (if they were to be allocated to group treatment)	Clinical records/visits/Physician referral; MS organization
41. Hugos 2017	Aged 18+ years; physician-confirmed diagnosis of MS; able to provide informed consent and comply with study procedures; able to walk 25 feet independently with or without assistive devices; fluent in written and spoken English as program materials are not provided in other languages; self-reported lower-extremity spasticity interfering with daily activities; willing to not change medications during the study	Other medical or mental conditions that would interfere with participation	Clinical records/visits/Physician referral
42. Kannan 2019	Aged 18+ years; physician-confirmed diagnosis of MS of any subtype; no MS relapse in the previous month; self-reported history of two or more falls in the previous two months; ability to walk at least 100 m with or without intermittent or constant unilateral assistance (EDSS ≤6.0); daily access to a computer and willingness to respond to a daily online fall survey	Conditions that would preclude reliable participation or increase risk of injury during the program	Clinical records/visits/Physician referral
43. Klaren 2014	Aged 18-64 years; physician-diagnosed MS; relapse-free for the past 30 days; ability to walk with or without an assistive device; willingness to complete in-person assessments; physical inactivity defined as <60 minutes/week of PA; low risk for contraindications of PA based on the Physical Activity Readiness Questionnaire; and physician's approval for participation	Not reported	MS organization; Existing list of research volunteers

44. Learmonth 2017	Aged 18-64 years; diagnosis of MS; PDDS scale score ≤3.0; relapse free in past 30 days; willing and able to participate in the intervention; non-exercisers (i.e., not participating in 30 or more minutes of structured strength training AND, 30 or more minutes of brisk walking OR moderate exercise in the last 3- months); a PAR-Q score of ≤2 (physician approval was requested for participants who had a PAR-Q score of 2)	Not reported	Word of mouth/Snowball sampling; MS organization; Existing list of research volunteers
45. Learmonth 2021	Aged 18+ years; self-reported diagnosis of MS; relapse-free in past 30 days; PDDS score of ≤4	Not Reported	MS organization; Existing list of research volunteers
46. Molton 2019	Physician confirmed diagnosis of MS or clinically isolated syndrome (CIS; a single episode of MS-like symptoms), using the revised McDonald criteria; diagnosed within the past 36 months; have at least moderate psychological distress (on the basis of scoring > 10 on the GAD-7 or the PHQ-9; able to read, speak, and understand English	Not reported	Clinical records/visits/Physician referral; Existing list of research volunteers
47. Plow 2014	Aged 18-65 years; physician-confirmed diagnosis of RRMS; ability to walk 25 feet with or without a cane	Exercising for ≥150 per week; pregnancy; cardiopulmonary disease; ≥4 falls in the past six months; severe cognitive deficits; inability to read and speak English at a sixth-grade level; co-morbid condition leading to hospitalization in the past year	Online; Clinical records/visits/Physician referral; MS organization

48. Ryan 2017	Self-reported diagnosis of MS; relapse free for the past 3 months; a relapse will be defined as the appearance of new symptoms, or the return of old symptoms, for a period of 24hours or more, in the absence of a change in core body temperature or infection; independently ambulatory at a minimum within their home with or without a walking aid; free of unstable medical conditions, for ex-ample, unstable angina; able to travel to the Berkshire MS Therapy Centre for the intervention; fluent in English to a standard sufficient for completion of the trial assessment and intervention; ability to comprehend and follow all instructions relating to participation in the study including providing informed consent, completing the outcome measures or participating in the intervention	Pregnancy; ongoing participation in Other trials	Clinical records/visits/Physician referral; MS organization
49. Schirda 2020	Aged 30-59 years; clinically significant diagnosis of MS; relapse free for prior 30 days; absence of comorbid neurological disorder(s); score 23 on the MMSE; corrected visual acuity of at least 20/40; no experience with mindfulness mediation or cognitive training within the past year; and computer and Internet access at home	Not reported	Online; Posters; Clinical records/visits/Physician referral

50.	Sebastiao 2018	Aged 60+ years; clinically definitive diagnosis of MS; relapse-free for the past 30 days; ability to walk with or without assistive device (i.e., cane); willing and able to participate in a 12-week home-based exercise regimen using hybrid approach; non-exercisers (operationalized to be not engaging in structured exercise 2 + days/week); asymptomatic (i.e., one or fewer affirmatives on the PAR-Q or physician approval for undertaking exercise training for those with 2 or more affirmatives on the PAR-Q; scoring ≥13 points in the Telephone Interview for Cognitive Status, indicating no more than mild cognitive impairment	not reported	Online; Media; Mail; MS organization; Existing list of research volunteers
51.	Siengsukon 2020	Aged 18-64 years; RRMS or SPMS; report difficulty falling asleep, maintaining sleep, or waking up too early at least 3 nights/week for the past 6 months; Score ≥10 on Insomnia Severity Index; English speaking; Score ≥24 on the MMSE	Known untreated sleep disorder (i.e., sleep apnea or restless leg syndrome); Score >4 on STOP BANG (indicating elevated risk of sleep apnea); increased risk of restless leg syndrome on RLS-Diagnosis Index; Score of ≥15 on the PHQ-9) indicating severe depression or endorse any suicidal ideation; history of alcohol/drug dependence or nervous system disorder other than MS; severe neurological or sensory impairments that would interfere significantly with testing; relapse and/or corticosteroid use in past 8 weeks; performs shift work	Clinical records/visits/Physician referral; MS organization; Existing list of research volunteers

52. Stuifbergen 2012	Aged 18-60 years; able to understand and comply with the study protocol including reading and writing in English; visual acuity with correction sufficient to work on a computer screen; clinically definite multiple sclerosis for at least six months that was documented by a physician and stable disease status at the time of study entry	Other medical causes of dementia; other neurological disorders that might impact cognition; evidence of major psychiatric disorder; major functional limitations that precluded them from participating in the study	Clinical records/visits/Physician referral; MS organization
53. Suh 2015	Aged 18-64 years; definite diagnosis of RRMS; independently ambulatory or ambulatory with a single point assistance (e.g., cane); relapse free in the past 30 days; nonactive defined as not engaging in regular physical activity (i.e., 30 minute-accumulated per day) on > 3 days of the week during the previous 6 months); free of contraindications for physical activity (e.g., no underlying cardiovascular disease) based on PAR-Q; having the visual ability necessary to read 14 point font	Not reported	Existing list of research volunteers
54. Thomas 2017	Aged 18+ years; a clinically definite diagnosis of MS; satisfied a risk assessment - relatively physically inactive (active for a period of 30 min or more on <5 days per week); having a suitable television at home; living with Poole/Bournemouth conurbations	APDDS Scale score of 1 or ≥6 (equivalent to an EDSS score of 1 or ≥6; a relapse within the past 3 months that required treatment with corticosteroids and/or a hospital admission; already participating in exercise or rehabilitation research; a medical condition placing an individual at risk from exercise participation; owns a Wii and is currently using it on a weekly basis or more; unwilling or unable to comply with the protocol (e.g., long vacation planned).	MS organization

55. Tosh 2014	Aged 18-65 years; clinical diagnosis of MS with an EDSS score of between 1.0 and 6.5; able to walk 10 m distance; clinically stable for at least 4 weeks prior to entering the study; participants on disease modifying therapy (Interferon, Glatiramer Acetate, Mitoxantrone and Natalizumab) must have been stable on this treatment for at least 3 months prior to entering the study; physically able to participate in some form of exercise three times per week; able to provide written informed consent	Failure to meet any of the inclusion criteria; experiencing illness that impairs the ability to be physically active three times per week; unwilling to be randomized to either the exercise intervention or usual care control group; living more than 20 miles from the trial centre; already engaged in purposeful structured exercise or brisk walking ≥3 times per week for ≥30 min per session for at least 6-months	Clinical records/visits/Physician referral; MS organization
56. vanKessel 2016	A definite diagnosis of MS from a neurologist; ambulatory with or without a stick for at least 100m; A Chalder Fatigue Scale score of ≥4; willingness to abstain from any new psychological or pharmacological treatment for fatigue during the duration of the study; New Zealand resident	Not reported	Clinical records/visits/Physician referral; MS organization

Table 3: Description of enrolled participants

Ref	Total sample	No. of Groups	No. of Females (EG/CG/CG)			Mean Age in years (EG/CG/CG)			MS Phenotype	Race and/or ethnicity
Effectiveness/Efficacy (n=36)										
1. Barlow 2009	216	3	57	44	56	48± 10	51±12	55±14	Not reported	White: 207 Not reported: 9
2. Bombardier 2008[#]	130	2	53	48	-	48±41-54	45±41-52	-	RRMS: 91 PPMS: 7 SPMS: 13 Other: 3 Not reported: 17	White: 124 Black: 2 Latinx/Hispanic: 1 Arab: 2 Asian: 1 Not reported: 1
3. Bombardier 2013	92	2	39	40	-	47±9	50±8	-	RRMS: 68 RPMS: 1 PPMS: 3 SPMS: 13 Not reported: 7	White: 85 Indigenous: 2 Other/Did not disclose: 5
4. Charvet 2017	135	2	50	54	-	48±13	52±11	-	RRMS: 89 PPMS: 7 SPMS: 35 Not reported: 4	White: 114 Black: 10 Latinx/Hispanic: 10 Other/Did not disclose: 11
5. Egner 2003	27	3	6	5	6	41±9	49±10	48±5	Not reported	Black: 10 Not reported: 17
6. Ehde 2017[*]	190-200	2	-	-	-	-	-	-	-	-

7.	Ehde 2015	163	2	67	75	-	51±10	53±10	-	RRMS: 91 PPMS: 72	White: 136 Black: 19 Latinx/Hispanic: 3 Other/Did not disclose: 5
8.	Ehde 2019[*]	240	3	-	-	-	-	-	-	-	-
9.	Finlayson 2011[^]	181	2	143	-	-	56±9	-	-	RRMS: 95 RPMS: 11 PPMS: 16 SPMS: 39 Not reported: 20	White: 159 Black: 18 Other/Did not disclose: 3
10.	Goodwin 2020	38	2	11	17	-	49±13	47±10	-	RRMS: 22 PPMS: 4 SPMS: 10 Other: 1 Not reported: 1	White: 38
11.	Goverover 2018	35	2	13	13	-	50±9	49±9	-	RRMS: 24 PPMS: 4 SPMS: 7	White: 19 Black: 13 Latinx/Hispanic: 3
12.	Hansen 2015	27	2	10	6	-	46±11	48±10	-	RRMS: 18 RPMS: 1 PPMS: 3 SPMS: 3 Not reported: 2	White: 27
13.	Houniet-deGier 2020[*]	166	2	-	-	-	-	-	-	-	-

14.	Hugos 2019	218	2	80	77	-	54±10	54±11	-	RRMS: 127 PPMS: 52 SPMS: 36 Not reported: 3	White: 165 Black: 38 Other/Did not disclose: 15
15.	Jeong 2021	45	2	23	10	-	58±12	56±13	-	Not reported	White: 27 Black: 14 Latinx/Hispanic: 6 Asian: 2 Other/Did not disclose: 1
16.	Kargarfard 2018	32	2	17	15	-	37±9	36±7	-	RRMS: 32	Asian: 32
17.	Lincoln 2020	449	2	178	148	-	45±10	49±10	-	RRMS: 291 PPMS: 46 SPMS: 112	White: 432 Black: 6 Asian: 5 Other/Did not disclose: 6
18.	Martini 2018	40	2	1	1	-	56±9	55±1	-	Not reported	White: 2 Black: 4 Not reported: 34
19.	Mathiowetz 2005^	169	2	140	-	-	48±8	-	-	RRMS: 104 RPMS: 3 PPMS: 10 SPMS: 32 Not reported: 20	White: 157 Black: 7 Latinx/Hispanic: 2 Other/Did not disclose: 3
20.	McAuley 2007^	26	2	23	-	-	44±8	-	-	RRMS: 24 PPMS: 1 SPMS: 1	White: 24 Black: 2

21. McGibbon 2018	29	2	8	9	-	48±11	50±10	-	Not reported	White: 21 Black: 5 Latinx/Hispanic: 3 Asian: 1 Other/Did not disclose: 2
22. Miller 2011	206	2	88	73	-	48±10	48±9	-	Not reported	White: 158 Not reported: 48
23. Mohr 2004^	63	3	45	-	-	45±10	-	-	Not reported	White: 52 Black: 5 Latinx/Hispanic: 3 Asian/Other: 3
24. Mohr 2007	127	2	47	51	-	49±10	47±1	-	Not reported	White: 114 Black: 6 Latinx/Hispanic: 2 Asian: 1 Indigenous: 2 Other/Did not disclose: 2
25. Mohr 2012	121	2	51	50	-	42±9	43±11	-	RRMS: 118 SPMS: 2 Not reported: 1	White: 100 Not reported: 21
26. Moss-Morris 2013	94	2	35	30	-	40±9	43±11	-	RRMS: 73 PPMS: 12 SPMS: 9	White: 71 Not reported: 23
27. Motl 2019*	500	2	-	-	-	-	-	-	-	-

28. Pinto 2019*	90	3	-	-	-	-	-	-	-	-
29. Plow 2019	208	3	55	63	58	51±9	53±7	52±9	RRMS: 176 RPMS: 1 PPMS: 6 SPMS: 11 Not reported: 14	White: 187 Not reported: 21
30. Plow 2020*	582	3	-	-	-	-	-	-	-	-
31. Rimmer 2018*	820	2	-	-	-	-	-	-	-	-
32. Stuifbergen 2003	113	2	56	57	-	-	-	-	RRMS: 62 Not reported: 51	White: 92 Black: 13 Latinx/Hispanic: 3 Asian: 1 Other/Did not disclose: 4
33. Stuifbergen 2018	183	2	80	80	-	50±8	49±9	-	RRMS: 125 RPMS: 2 PPMS: 8 SPMS: 24 Other: 6 Not reported: 17	White: 137 Black: 34 Latinx/Hispanic: 18 Other/Did not disclose: 12
34. Thomas 2013	164	2	61	58	-	48±10	50±9	-	RRMS: 75 PPMS: 13 SPMS: 39 Other: 32 Not reported: 5	White: 149 Other/Did not disclose: 15

35. Turner 2016	64	2	9	14	-	53±12	54±13	-	RRMS: 42 Other: 22	White: 53 Other/Did not disclose: 11
36. Young 2019	81	3	22	20	24	50±27	48±26	47±10	Not reported	White: 44 Black: 35 Other/Did not disclose: 2
Pilot/Feasibility (n=20)										
37. Block 2021	22	2	11	7	-	48±12	47±9	-	RRMS: 10 PPMS: 9 SPMS: 1 Not reported: 2	White: 11 Black: 5 Latinx/Hispanic: 2 Asian: 1 Other/Did not disclose: 4
38. Bogosian 2015	40	2	9	13	-	53±8	51±10	-	PPMS: 17 SPMS: 23	White: 36 Other/Did not disclose: 4
39. Cederberg 2021	14	2	6	5	-	56±10	57±13	-	RRMS: 13 PPMS: 1	White:12 Black: 2
40. dasNair 2016	21	2	8	7	-	49±10	48±9	-	RRMS: 14 PPMS: 4 Other: 1 Not reported: 2	White: 18 Other/Did not disclose: 3
41. Hugos 2017	38	2	13	16	-	53±12	53±13	-	RRMS: 18 PPMS: 10 SPMS: 10	White: 36 Other/Did not disclose: 2

42. Kannan 2019	30	2	11	10	-	5411	58±10	-	RRMS: 8 PPMS: 9 SPMS: 13	White: 29 Not reported: 1
43. Klaren 2014	70	2	24	30	-	49±9	50±9		RRMS: 58 Not reported: 12	White: 68 Not reported: 2
44. Learmonth 2017	57	2	28	27	-	49±10	48±9	-	RRMS: 51 SPMS: 1 Not reported: 5	White: 38 Black: 17 Latinx/Hispanic: 1 Indigenous: 1
45. Learmonth 2021*	52	2	-	-	-	-	-	-	-	-
46. Molton 2019	48	2	16	19	-	40±11	36±11	-	Not reported	White: 41 Black: 1 Latinx/Hispanic: 3 Multi-racial: 6
47. Plow 2014	30	2	14	16	-	47±9	48±10	-	Not reported	Racial minority: 10 Not reported: 20
48. Ryan 2017*	382	2	-	-	-	-	-	-	-	-
49. Schirda 2020	61	3	16	16	15	47±7	45±9	46±8	RRMS: 59 PPMS: 1 Not reported: 1	White: 44 Black: 14 Other/Did not disclose: 3

50. Sebastiao 2018	25	2	13	9	-	64±4	65±5	-	RRMS: 23 SPMS: 2 Other: 1	White: 25
51. Siengsukon 2020	30	3	9	8	10	51±8	50±12	57±10	RRMS: 27 SPMS: 3	White: 28 Other/Did not disclose: 2
52. Stuifbergen 2012^	61	2	29	25	-	48±9	-	-	Not reported	White: 54 Black: 2 Other/Did not disclose: 5
53. Suh 2015	68	2	30	26	-	50±8	48±9	-	RRMS: 66 Other: 2	White: 65 Not reported: 3
54. Thomas 2017	30	2	14	13	-	51±8	48±9	-	RRMS: 21 PPMS: 1 SPMS: 5 Other: 1 Not reported: 2	White: 30
55. Tosh 2014	120	2	43	43	-	46±9	46±8	-	RRMS: 98 PPMS: 4 SPMS: 18	White: 111 Not reported: 9
56. vanKessel 2016	39	2	11	18	-	43±8	46±8	-	RRMS: 26 SPMS: 5 Other: 8	White: 39

Key: * indicates protocol studies; ^ indicates studies that reported total sample; # indicates median and IQR reported for age

Ref – Reference; EG – Experimental group; CG – Control group; MS – Multiple sclerosis; RRMS – Relapsing remitting multiple sclerosis; RPMS – Relapsing progressive multiple sclerosis; PPMS – Primary progressive multiple sclerosis; SPMS – Secondary progressive multiple sclerosis

Figure caption

Fig 1 Flow diagram of the study selection process