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Effectiveness of technology-based distance physical rehabilitation interventions on physical activity and walking in multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: To determine the effectiveness of technology-based distance physical rehabilitation intervention in multiple sclerosis (MS) on physical activity and walking.

Data sources: A systematic literature search was conducted in seven databases for January 2000–September 2016. Randomized controlled trials of technology-based distance physical rehabilitation interventions on physical activity and walking outcome measures were included.

Methods: Study quality was determined by Furlan (2015) and a meta-analysis was performed. In addition, a subanalysis of technologies and an additional analysis comparing to no treatment were conducted.

Results: The meta-analysis consisted of 11 studies. The methodological quality was good (8/13). The Internet, telephone, exergaming and pedometers were the technologies enabling distance physical rehabilitation. Technology-based distance physical rehabilitation had a large effect on physical activity (Standard mean difference (SMD) 0.59; 95% confidence interval (95% CI) 0.38 to 0.79; \( p < 0.00001 \)) compared to control group with usual care, minimal treatment, and no treatment. A large
effect was also observed on physical activity (SMD 0.59; 95% CI 0.34 to 0.83; \(p<0.00001\)) when compared to no treatment alone. There were no differences in walking and the subanalysis of technologies.

**Conclusion:** Technology-based distance physical rehabilitation increased physical activity among persons with MS, but further research on walking in MS is needed.

**Keywords:** systematic review, rehabilitation technology, distance physical rehabilitation, multiple sclerosis, walking, physical activity

**Introduction**

Multiple sclerosis (MS) is a progressive neurological disease of the central nervous system (CNS). [1]. Symptoms are individual and include functional, psychological and cognitive limitations. Reduced walking ability [2,3], depression [4,5] and fatigue [6,7] are the most common symptoms of MS. Other frequent symptoms are bladder and bowel symptoms, cognition, cerebellar and sensory symptoms, motor weakness and spasticity, sexual dysfunction and visual loss [8]. Various symptoms have different effects among persons with MS (PwMS) on activities of daily living, level of well-being and satisfaction in life and overall on quality of life [1]. In the early stage of MS there is reduced physical activity and walking compared to the general population [9,10]. In addition, previous systematic reviews with meta-analysis reported that PwMS are less physically active compared to healthy populations [11] and exercise training is associated with improvement in walking in MS [12]. However, there is a lack of evidence on the effect of technology-based distance physical rehabilitation interventions in MS.

Only one previous systematic review of randomized control trials (RCTs) and controlled clinical trials investigated the effect of distance rehabilitation conducted with telerehabilitation in MS [13]. In a review consisting of 469 participants, Khan et al. [13] found limited evidence for the efficacy of telerehabilitation in improving physical activity, balance capacity, postural control, fatigue, and quality of life. Interventions varied in their rehabilitation components, including ones other than physical rehabilitation interventions, such as nursing and fatigue management. In addition, technology consisted only of the telephone, control groups were heterogeneous and the included RCTs scored low on methodological quality. Khan et al. [13] concluded that there were limited data on the process evaluation and cost-effectiveness.
To conclude, there is a need to build evidence for the use of technology in distance physical rehabilitation interventions. The objective of this study was to investigate the effectiveness of technology-based distance physical rehabilitation interventions on physical activity and walking in MS compared to other treatment or no treatment (wait-list, minimal treatment, hippotherapy, and usual care).

Methods

Search strategy for identification of the studies

A systematic literature search was performed of studies published between January 2000 and December 2015 from the following databases: Cochrane Controlled Trials Register (CENTRAL), Comprehensive Biomedical Literature Database (EMBASE), The National Library of Medicine (Ovid MEDLINE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Behavioral and Social Science Research (PsycINFO), Web of Science (WOS) and Physiotherapy Evidence Database (PEDro). Updated search was conducted from the same databases from studies published between January and September 2016. Figure 1 presents the combined flow chart of the study selection. Details of the protocol for this systematic review were registered on PROSPERO International prospective register of systematic reviews and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016038225.

Two information specialists performed the searches in the selected databases in collaboration with the research team. The search strategy was designed to include a wide range of technology terms and study types (i.e. RCT or clinical trial). In addition, comprehensive keywords describing physical rehabilitation interventions were used (e.g. exercise, exercise therapy, therapies, therapy modalities, rehabilitation, multidisciplinary therapy, motor activity, participation and physical activity). The original search strategy is available in Appendix 1. The search strategy used either MeSH or keyword headings. The original search strategy did not include or exclude any diagnosis, symptoms or disorders. In addition, a supplementary manual search was conducted using the reference lists from the retrieved studies. If needed, the authors of the included studies were contacted for further information.
**Data extraction**

Only RCTs investigating the effect of technology-based distance physical rehabilitation interventions were included in this systematic review. Further inclusion criteria according to the PICOS (Participants, Interventions, Comparisons, Outcomes, Study design) framework were as follows: (P) PwMS; (I) any technology used to promote or increase any physical activities or participation to enable distance physical rehabilitation (e.g., wearable device, Internet, telephone, or smartphone); (C) no treatment (i.e., wait-list), or face-to-face physical rehabilitation interventions or other treatments to promote or increase activities or participation without distance physical rehabilitation approach and the use of technology; (O) an outcome measure describing physical activity or walking; (S) the study design of RCTs. Only RCTs published in English, Finnish, Swedish or German were included in the review. Non-randomized or non-controlled experimental studies, longitudinal studies and protocols were excluded. Studies including other diagnoses without separate analysis of MS were excluded.

In line with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [17], two reviewers (AR and TS) independently screened all the titles and abstracts of the studies. After the title and abstract phase, potentially relevant studies were independently evaluated for full-text assessment by two assessors (AR and TS) of the research team. In case of disagreement, a third reviewer (SH) evaluated the studies.

For this review and meta-analysis, only studies with technology-based distance physical rehabilitation interventions and outcome measures describing valid measures of either physical activity or walking were included. Outcome measures describing walking were linked to the International Classification of Functioning, Disability and Health (ICF) chapter for mobility (d4) in activity and participation by two researchers (AR and JP) [20, 21]. On physical activity measures, several ICF categories based on the activities were captured, while linking the physical activity outcome measures to the ICF. Both physical activity and walking measures were interpreted as activities and participation.

**Methodological quality and the risk of bias**

The methodological quality of the RCTs was evaluated using the Furlan method guideline for systematic reviews [18]. The updated Furlan method guideline for systematic reviews consists of 13 items and rates RCTs based on (1) adequate randomization, (2) treatment allocation concealed, (3)
blinding the patient, (4) blinding the care provider, and (5) blinding the outcome assessor, (6) dropout rate described and acceptable, (7) participants analyzed in the groups they were allocated, (8) suggestion of selective outcome reporting, (9) the similarity of the groups at baseline, (10) co-intervention avoided or similar, (11) compliance, (12) timing of the outcome assessment and (13) other sources of potential bias unlikely [18]. One item is scored positive (“yes”) if the criterion was fulfilled, negative (“no”) if the criterion was not fulfilled or unclear (“unsure”) if required information was adequately reported. The methodological quality was evaluated by two blinded and independent reviewers (AR and SH). In case of disagreements, a third reviewer (TS) was consulted to solve the disagreement. The total score of a study is the sum of the positive scores. The maximum score for a single study in the updated Furlan method guideline for systematic reviews is 13 points. In an adaptation of the Furlan et al. [18] method guideline and the criteria method of Anttila et al. [19], the methodological quality of a study was considered to be high, moderate or poor. A study was rated as high quality when the following criteria were fulfilled: overall at least 6 or more “yes” scores, at least 30 or more participants in the study, and “yes” scores for items (1) randomization method adequate, (2) treatment allocation concealed, (6) drop-outs described and acceptable and (9) group similarity at the baseline. A study was considered to have moderate quality when it fulfilled the following criteria: at least 4 or more “yes” scores and item (1) method of randomization was adequate. The study was evaluated as having poor quality if there were at least 4 or more “yes” scores, but the method of randomization was not adequately reported (a score of “no” or “unsure” on item (1) or there were only 0-3 “yes” scores, or the study included fewer than five participants in the experimental group or in the control group [19].

**Statistical synthesis**

The meta-analysis was performed separately for the outcome variables on physical activity and walking. In addition, a subanalysis of technologies and an additional analysis comparing these two outcome variables to wait-list were conducted. If adequate post-treatment values (mean and standard deviation; SD) were not reported, a request was sent to the corresponding author of the original study. If not answered, the RCT was not taken into account in the meta-analysis. If study was reported standard error (SE) instead of SD, SD was obtained from the standard error of a mean by multiplying the standard error by the square root of the sample size within an intervention group. Standardized mean differences (SMD) between the experimental and control groups were calculated for each study. In accordance with the Cochrane guidelines for systematic reviews and meta-analysis, the values of the outcome variables were multiplied by -1 when needed so that the higher values reflect better
physical activity and walking [22]. A random effects model was used in the meta-analysis. Cochrane Collaboration’s Review Manager 5.1.3 statistical software analysis package was used to calculate the pooled effect estimates for the combination of the single effects of the RCTs. SMD between the groups were considered to be large > 0.5, moderate 0.3–0.5, small 0.1–0.2 or insubstantial < 0.1 [23]. The results of the meta-analysis are presented using forest plots of the SMD. Statistical heterogeneity was evaluated with the \(I^2\) statistic, where a value closer to the zero of \(I^2\) indicates less heterogeneity [24].

**Results**

The search identified overall 2309 studies which 309 studies focused on MS. The screening of 50 full-text studies revealed 11 potentially eligible studies. Three studies had the same source or original data as another included study [25-27] providing no additional data to this systematic review (i.e., same outcome measures), and therefore they were excluded from the qualitative analysis. A total of 11 studies [28-38] published between 2007 and 2016 fulfilled the inclusion criteria and were included in the qualitative and quantitative analysis. A flow chart of the review process is presented in Figure 1 and specific details of included studies can be found in Table 1.

**Description of the participants**

The selected studies included a total of 657 PwMS, which consisted of 308 participants in the experimental group and 349 in the control group (Table 1). The mean (SD) age of the participants was 47 (4.6) years. From the total sample, mean (SD) disease duration since diagnosis was 11 (3.5) years with a range of 6–22 years. Of the participants, 75 % were women, and 73 % had relapsing-remitting MS. Two studies out of 11 included clinical course of relapsing-remitting [29-30], and other studies included several clinical courses of MS (i.e., relapsing-remitting, progressive or benign) [28,31-38]. In all of the included studies PwMS were ambulatory. Seven studies [28,31-33,35-37-38] used the Expanded Disability Status Scale (EDSS) [39], with the inclusion criterion of an EDSS score of 6.5 or lower. The four remaining studies [29-31,34,36] used the Patient Determined Disease Steps (PDDS) scale, which in a previous study has reported linearity and strong relation with the EDSS scores [40]. Participants in these included studies had a minimal to moderate level of disease severity with a PDSS score of 6.0 or lower, where the range was 0.0 to 7.0.
Methodological quality and the risk of bias

The methodological quality of the studies was good (median: 8) with interquartile range of 7 to 9 (Table 2). Overall, using the interpretation of the Furlan method guideline [18] and the method outlined by Anttila et al. [19], five studies were classified as high [32,34,36-38], five as moderate [28,30-31,33,35] and one as poor [29]. The most common methodological fault was no reporting or no blinding of the participants and the care providers, no reporting of selective outcomes, and no reporting of avoiding co-interventions. While ten out of 11 studies used an adequate randomization method (Item 1; 91 %), only seven studies reported concealed treatment allocation (Item 2: 64 %). All of the studies used similar timing of the outcome and did not include any other sources of likely potential bias (Items 12-13: 100 %). In addition, six of the studies [28,30-31,36-38] conducted intention-to-treat (ITT) analysis (Item D7: 55 %), and the smallest sample size was in two studies [33,35], ranging from 16 to 29 participants. Interrater reliability was good among the two assessors, having no disagreements on the methodological quality assessment.

Description of the technologies used in distance physical rehabilitation interventions

Mean (SD) duration of the intervention was 11 (3.5) weeks. The most used technology in distance physical rehabilitation interventions was the Internet. It was used in five studies with either only Internet-based e-training [35] or the Internet in combination with other technology such as a pedometer [29-30,34] or a telephone [33]. Two studies used only a telephone [28,31] and four studies used telephone in a combination with a pedometer [36], unsupervised exercises using the Nintendo Wii Balance Board or interactive exergames [32,37], or telehealth monitoring [38]. All of the included studies enabled interaction of two-way communication between the caregiver and the participant either by the Internet, a telephone [28-37], or telephone with the combination of telehealth monitoring [38]. Internet-delivered interventions used either Skype [34], online chat sessions [29], video-couching [30] or a feedback platform on a website [35]. Self-monitoring devices with one-way communication included a pedometer for independently controlling physical activity levels [29-30,34] or by using interactive exergames such as the Nintendo Wii Balance Board for balance exercises [32] or physical exercises [37].
Content of the interventions in experimental and control groups

The content of the interventions in the experimental group were heterogeneous. Six out of 11 interventions focused on increasing or promoting physical activity either with social-cognitive theory (SCT) [29-30,34,36] or with a motivational interview (MI) [31,38]. The SCT approaches included manuals for stretching, physical activity in everyday life, goal-setting and outcome expectations [29-30,34,36]. The MI interview consisted of tailored home- or community-based physical activity or exercises based on individual needs in the participants’ daily life, physical abilities, environment resources, and motivation [31,38]. Two interventions included home training exercise programs for either balance, postural control and strength exercises [35] or balance, strength and cardiovascular exercises [33]. Another two studies included virtual games for the Nintendo Wii Balance Board or other interactive exergames involving balance and physical exercises [32,37]. One intervention included an MI approach for increasing health promotion activities such as exercise, fatigue management, social support, anxiety, and drug use [28]. The content of the intervention in the control groups was also heterogeneous consisting of no treatment (i.e., wait-list), usual care, minimal treatment, or hippotherapy without the use of technology relating to distance physical rehabilitation. Usual care consisted of either general advice on exercise [33], physical activity [37] or general advice excluding physical activity (e.g. on allergies, blood pressure, alcohol use, cholesterol, nutrition and stress management) [36]. Minimal treatment included the similar home DVD program as in the experimental group to facilitate motivation, to promote self-efficacy, and provide examples of in-home exercises to overcome barriers to participation [38]. Other treatments included a comparison of hippotherapy [35].

Description of the outcome measures

A total of eight different outcome measures was identified from the selected studies (Table 2). The results of the outcome variables in the selected studies are presented in Table 3. Six out of 11 studies investigated physical activity with the self-reported questionnaires either with the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [29-30,36,38], International Physical Activity Questionnaire (IPAQ) [34], or the 7-Day Physical Activity Readiness (PAR) questionnaire [31]. Values in GLTEQ were measured in total leisure physical activity in METs per minutes per week (MET/min/wk) [29-30,38] or in total leisure physical activity in scores between 0 and 119 in arbitrary units [36]. In IPAQ, overall physical activity was measured with scores 0 to 117 where a higher score indicated more physical activity [34]. Values in PAR were reported in total energy expenditure in kilocalories per
kilogram per week (kcal/kg/week) [31]. A higher score on MET/min per week, arbitrary units and in kcal/kg/week signify better physical activity. Seven out of ten studies used outcome measures to describe walking as follows: a 90-meter walk test measured in seconds [28], the Multiple Sclerosis Walking Scale-12 (MSWS-12) on a scale of 0 to 80 [30], the Timed 25-Foot Walk test (25-FW) measured in meters per second [32-33], the 6-Minute Walk test (6MW) measured in meters [34,37] and the Dynamic Gait Index (DGI) on a scale of 0 to 24 [35]. A higher score on 25FW, 6MW, and DGI signify better walking. In contrast, a lower score in the 90-meter walking test and on the MSWS-12 scale signify better walking.

**Effectiveness of the technology-based distance physical rehabilitation interventions**

The data (post-treatment value with mean and SD) needed for the estimations of ES were reported in 10 studies, and in one study the authors provided this data on request. In one study SD was obtained from the standard error [38]. In one cross-over trial, only data from phase 1 of 0–12 weeks was taken into account, because of possible carryover effect [32]. Therefore, the meta-analysis was conducted from all of the included studies [28-38] (Figures 2-4). Subanalyses of different technologies were conducted based on the interactive role of the main technology. Due to the lack of studies, only the comparison of wait-list was included in the additional analysis (Figure 4). Funnel plots of the meta-analyses are in Appendix 2.

**Physical activity**

Technology-based distance physical rehabilitation interventions had a large effect on physical activity when compared to control groups with no treatment, usual care and minimal treatment without the use of technology (SMD 0.59; 95 % confidence interval (CI) 0.38 to 0.79; *p* < 0.00001). In subanalyses of different technologies, the Internet and the use of a pedometer (SMD 0.68; 95 % CI 0.37 to 0.99; *p* = 0.0001) had a large effect when compared to no treatment. In addition, in the use of a telephone alone or telephone with a combination of a telehealth monitoring or a pedometer, a moderate effect was captured (SMD 0.53; 95 % CI 0.21 to 0.84; *p* = 0.001) when compared to no treatment, usual care and minimal treatment. The studies were homogeneous according to the overall meta-analysis result ($I^2 = 0\%$) (Figure 2). Low level of heterogeneity was observed in a subanalysis in the use of a telephone alone, or with telehealth monitoring or pedometer ($I^2 = 26\%$)
Walking

Technology-based distance physical rehabilitation interventions had no effect on walking when compared to control group with no treatment, usual care, and hippotherapy without the use of technology (SMD -0.09; 95 % CI -0.29 to 0.11, \( p = 0.39 \)). In the subanalysis of different technologies, the use of the Internet alone and in combination with a pedometer or telephone (SMD 0.01; 95 % CI -0.29 to 0.32; \( p = 0.94 \)) had no effect when compared to the control group with no treatment, usual care and hippotherapy without the use of technology. In addition, no effect was captured in the use of telephone alone (SMD -0.10; 95 % CI -0.45 to 0.24; \( p = 0.57 \)) when compared to no treatment or in the use of exergames with the use of telephone (SMD -0.29; 95 % CI -0.74 to 0.16; \( p = 0.20 \)) when compared to usual care and no treatment. The studies were homogeneous according to the meta-analysis (\( I^2 = 0\% \)) (Figure 3).

Additional meta-analysis of no treatment comparison on physical activity and walking

Technology-based distance physical rehabilitation intervention had a large effect on physical activity when compared to no treatment alone (SMD 0.59; 95 % CI 0.34 to 0.83; \( p < 0.00001 \)) (Figure 4a). No effect was observed on walking (SMD -0.05; 95 % CI -0.28 to 0.19; \( p = 0.70 \)). The studies were homogeneous according to the meta-analysis (\( I^2 = 0 \% \)) (Figure 4b).

Discussion

The purpose of this systematic review and meta-analysis was to determine the effects of technology-based distance physical rehabilitation interventions among PwMS on physical activity and walking, as measured by outcome measures linked to the ICF activities and participation component. In the meta-analysis, technology-based distance physical rehabilitation interventions had a large effect on physical activity when compared to control groups with no treatment, usual care and minimal similar treatment without the distance approach and the use of technology. In an additional meta-analysis, a large effect was observed on physical activity when compared to no treatment alone. No effect was captured in any meta-analysis on walking outcomes. Furthermore, none of the main analyses indicated heterogeneous results. Subanalysis of different technologies on physical activity showed slight heterogeneity in the use of a telephone alone, or telephone with the combination of telehealth monitoring or pedometer. However, the studies included in this systematic review and meta-analysis were clinically heterogeneous in terms of intervention content, control groups, and the use of outcome
variable on physical activity and walking. Despite this clinical heterogeneity, there are some general conclusions that can be drawn.

The distance physical rehabilitation interventions on physical activity used technology in combinations of the Internet, telephone alone, telephone and pedometer, or telephone and telehealth monitoring [29-31,34,36,38]. All included studies had a similar aim of increasing or promoting physical activity among PwMS, used self-reported physical activity questionnaires, and four out of six studies had similar interventions based on SCT [29-30,34,36]. These similarities between the studies might support the low level of heterogeneous findings on meta-analysis. Furthermore, subanalysis of different technologies on physical activity were unable to determine if the technologies lead to differing outcomes when comparing to control groups with no treatment and usual care without the distance approach and the use of technology. This might suggest that similar effect might occur regardless of the technology being used when promoting physical activity in MS. However, small number of participants ranging from 82 to 108 and only six included studies in the subanalysis might limit this indication. Thus, future RCT studies might help to inform if a difference in interventions exists.

There was no effect of technology-based distance physical rehabilitation interventions between the groups in any meta-analysis on walking outcomes [28,30,32-35,37], and there were no differences between the technologies in the subanalysis. The meta-analysis did not capture heterogeneous results, although distance physical rehabilitation interventions differed in the content of exercises programs, technologies, and control groups. Exercise programs included home-based balance training or step training with the use of exergames [32,37], Internet-based home training to improve balance [35], physical activity intervention with the use of the Internet and a pedometer [30,34], telephone counselling for health promotion [28], and individual web-based physiotherapy [33]. Although studies used different measurements to capture walking in MS, all of the measurements investigated the functional performance on walking. This might partly explain the null heterogeneous finding in the meta-analysis. Further analysis to explain the heterogeneous findings could not be made due to the lack of included studies. The results of our meta-analysis on walking with no effect observed should be viewed critically because the findings are based on a range from 40 to 82 participants from seven studies.

Two previous systematic reviews with meta-analysis have investigated physical activity and walking among PwMS [11-12], but without the focus on distance physical rehabilitation with
technologies. One previous systematic review using remote physical activity monitoring in neurological diseases reported that physical activity monitoring is feasible in people with a moderate to severe neurological disability [41]. This supports our meta-analysis findings in MS. However, a review by Block et al. [41] consisted of different neurological disorders, including 61 studies of MS with study settings of RCTs, non-randomized controlled studies, cross-sectional studies and longitudinal studies. Only one previous systematic review has investigated the technology-based distance rehabilitation interventions on telerehabilitation in MS [13]. A systematic review by Khan et al. [13] with qualitative analysis indicated a low effect of telerehabilitation interventions in reducing short-term disability and improving long-term functional abilities, quality of life and psychological outcomes. However, Khan et al. [13] could not conduct a meta-analysis from the selected studies. Furthermore, Khan et al. [13] differs from our review in the content of inclusion criterion and in the use of technology. In our review, only interventions with physical rehabilitation were included and the use of the technology was not limited. In contrast, Khan et al. [13] included only studies with telerehabilitation, regardless of the intervention content, and the use of a telephone. However, in both our review and in Khan et al. [13], none of the included studies addressed cost-effectiveness. This lack indicates a need for future studies to investigate more reliable recommendations of the technology in clinical use among PwMS, as well as cost-effectiveness.

Overall, the methodological quality of the studies was good and sample sizes ranged from 16 to 130 participants. Regarding physical activity, all of the included studies had sufficient statistical power for drawing fair conclusions [29-31,34,36,38]. However, only two out of seven studies had sufficient statistical power on measures describing walking [28,30,32-35,37]. This might partly explain our findings in the meta-analysis on walking. A previous review of the challenges in designing trials has reported that the studies to be included should have adequate power, a suitable study setting, proper inclusion and exclusion criteria, reasonable outcomes to fit with the study aim, and proper time-points for assessments [42]. The studies included in this review had insufficient methodological quality in blinding participants and care providers, selection bias and avoiding co-intervention. The difficulty in blinding patients and care providers in studies of different physical rehabilitation interventions is understandable. However, most of the studies reported no suggestions of selective outcomes or avoidance of co-interventions. In addition, if concealed treatment allocation was not properly reported, the study setting might be questionable. All of the included studies were reported to be RCTs. Proper reporting in concealed treatment allocation should be taken into account when planning a protocol or study setting, or when reporting results.
Ten out of 11 studies reported the clinical course of relapse-remitting MS (RRMS), and overall 73% of the participants had RRMS. In addition, all of the participants were ambulatory at the baseline, with a mean disease duration of 11 years. This meta-analysis result on physical activity might be generalized to ambulatory persons with RRMS. However, more MS studies focusing on technology-based distance physical rehabilitation are needed, taking into account the factors regarding the clinical course of MS, and disease duration.

In this systematic review, technology-based distance physical rehabilitation interventions were determined as interventions that used a technological device to enable the full intervention to be conducted without a care provider present. All of the included studies enabled interaction with two-way communication between the caregiver and the participant either via the Internet or a telephone [28-37]. Nine out of 11 studies used a combination of two different technologies [29-31,32-34, 36-37,38], which makes it difficult to separate the advantage of any single technology in our findings. To conclude, there is not enough evidence to make a firm conclusion on the use of any particular technology in a distance physical rehabilitation setting in MS. With better evidence, there is the possibility to more precisely determine the clinical benefits of using technology in distance physical rehabilitation among PwMS.

Strengths and limitations of the systematic review and meta-analysis

The strength of this systematic review and meta-analysis is its focus on technology-based distance physical rehabilitation in MS. To our knowledge, this is the first systematic review with meta-analysis exploring the use of technology in distance physical rehabilitation interventions among PwMS. The meta-analysis did not indicate major statistical heterogeneity, and funnel plots did not suggest publication bias. If publication bias existed, it might have indicated, for example, an author’s publishing of portions of the study based on only the magnitude, direction, or statistical significance of the results [24]. PICOS criteria were determined quite strictly by including only technology-based distance physical rehabilitation interventions in the systematic review and excluding the technology from the control groups to capture the effect on technology-based distance physical rehabilitation interventions. The study population was targeted to be PwMS, and the study settings (i.e. RCTs) were similar among the included studies. Both physical activity and walking measures were interpreted as activities and participation in the ICF framework. Although the
measures differed in the terms of the values described within one outcome, all of the measures represented movement either focusing on physical activity or on walking.

However, this systematic review and meta-analysis has its limitations. Due to the lack of studies in technology-based distance physical rehabilitation interventions among PwMS, the content of the treatments in the experimental and control groups were clinically heterogeneous. Intervention consisted of different aspects of physical rehabilitation, targeting, for example, only physical activity [29-31,34,36,38], balance and strength [32-33,35,37], and general health promotion for exercise, fatigue, social support, anxiety and drug use [28]. Comparison in the control groups also consisted of several different approaches, including no treatment, usual care, minimal treatment, and hippotherapy [28-38]. Furthermore, small range of the participants and the number of studies might have an impact for not distinguishing the differences between the technologies in the subanalyses. Also, there was substantial variety in the kinds of technology used as a different combination or as a single technology. In the subanalyses, the selection was made based on the most interactive role of the technology that provided the distance physical rehabilitation intervention. However, some studies used a combination of technologies, which might have an impact on the results. Due to these facts, the results of this systematic review and meta-analysis should be interpreted with caution. Nevertheless, this study provides promising results regarding the use of technology in distance physical rehabilitation among PwMS on physical activity. Further studies are needed to more precisely determine the use of technology in distance rehabilitation in MS, especially on walking.

Conclusions

This systematic review and meta-analysis suggest that technology-based distance physical rehabilitation interventions have a large effect among PwMS on physical activity compared to usual care and no treatment. There was no effect observed in the technology-based distance physical rehabilitation interventions on walking compared to heterogeneous control groups. Further research on the effectiveness of technology-based distance physical rehabilitation interventions in MS, especially on walking, is needed.
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Declaration of interest

No potential conflict of interest was reported by the authors.

References


Figure 1. Flow chart of the study selection.

1. Identification
   - Medline (n = 954)
   - Embase (n = 981)
   - PsycInfo (n = 330)
   - Cinahl (n = 75)
   - CENTRAL (n = 164)
   - PEDro (n = 237)
   - WOS (n = 222)

2. Duplicates excluded (n = 608)

3. Studies excluded by title and/or abstract with reason (n = 2259):
   - Studies excluded as irrelevant or no sample of persons with multiple sclerosis n = 2000
   - No distance technology n = 206
   - No RCT n = 40
   - Protocol or study design n = 13

4. Studies screened (n = 2308)

5. Full-text studies assessed for eligibility (n = 30)

6. Studies included in qualitative and quantitative synthesis (meta-analysis) (n = 11)

7. Full-text studies excluded with reason (n = 29):
   - No distance technology in the intervention n = 11
   - No physical rehabilitation or treatment n = 7
   - No outcomes related to physical activity or walking ability n = 7
   - No RCT n = 5
   - Other diagnosis without a separate analysis of MS n = 4
   - Same source data as another included studies n = 3
   - Distance technology used in both treatments n = 2
Figure 2. Meta-analysis on physical activity compared to the control group with no treatment and usual care without the use of technology.

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<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Internet and the use of pedometer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bandoff et al. 2014 (IPAQ)</td>
<td>20.7</td>
<td>37</td>
<td>19.3</td>
<td>17</td>
<td>39</td>
<td>19.6</td>
<td>0.64</td>
<td>[0.05, 1.06]</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>Dlugonski et al. 2012 (GLTEQ-NETmin/week)</td>
<td>20.3</td>
<td>32</td>
<td>15.6</td>
<td>13.9</td>
<td>33</td>
<td>11.9</td>
<td>0.65</td>
<td>[0.14, 1.17]</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Moll et al. 2011 (GLTEQ)</td>
<td>24.7</td>
<td>38</td>
<td>15.2</td>
<td>14.2</td>
<td>35</td>
<td>12.0</td>
<td>0.73</td>
<td>[0.14, 1.32]</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>82</td>
<td>77</td>
<td>42.0</td>
<td>68</td>
<td>0.69</td>
<td>0.37, 0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 2 (P = 0.72), I² = 6% |
| Test for overall effect: Z = 4.46 (P < 0.0001) |

<table>
<thead>
<tr>
<th>Telephone alone, or with telehealth monitoring or pedometer</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner et al. 2016, GLTEQ (METmin/week)</td>
<td>31.1</td>
<td>30</td>
<td>15.4</td>
<td>17.5</td>
<td>33</td>
<td>15.3</td>
<td>0.89</td>
<td>[0.37, 1.41]</td>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>Shu et al. 2015, GLTEQ (O-110)</td>
<td>27.4</td>
<td>34</td>
<td>26.3</td>
<td>21.9</td>
<td>34</td>
<td>16.6</td>
<td>0.33</td>
<td>[0.15, 0.51]</td>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>Bombardier et al. 2013, T-DayPAR (kcal/kg/week)</td>
<td>220.5</td>
<td>44</td>
<td>224.4</td>
<td>9.2</td>
<td>44</td>
<td>29.1</td>
<td>0.43</td>
<td>[0.01, 0.84]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>108</td>
<td>115</td>
<td>57.4</td>
<td>93</td>
<td>0.53</td>
<td>0.95, 0.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Heterogeneity: Tau² = 0.02; Chi² = 1.71, df = 2 (P = 0.26), I² = 36% |
| Test for overall effect: Z = 3.00 (P < 0.001) |

| Total (95% CI) | 190 | 202 | 100.0 | 0.59 | 0.36, 0.76 | |

| Heterogeneity: Tau² = 0.00; Chi² = 3.94, df = 5 (P = 0.50), I² = 6% |
| Test for overall effect: Z = 5.66 (P < 0.0001) |
| Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.50), I² = 0% |

Abbreviations: the squares and diamonds represent the test values for individual studies and overall effectiveness; standard mean difference with 95% confidence interval (CI). SD: standard deviation; IPAQ = International Physical Activity Questionnaire; GLTEQ = Godin Leisure-Time Exercise Questionnaire; MET/min/wk = METs per minutes per week; PAR = Physical Activity Recall; kcal/kg/wk = total energy expenditure in kilocalories per kilogram per week; df = degrees of freedom.
Figure 3. Meta-analysis on walking compared to the control group with no treatment, usual care, and hippotherapy without the use of technology.

Abbreviations: the squares and diamonds represent the test values for individual studies and overall effectiveness; standard mean difference with 95% confidence interval (CI). SD: standard deviation; DGI = Dynamic Gait Index; 6MW = 6-Minute Walk; m = meters; 25FW = 25-Foot Walk; m/s = meters per second; MSWS-12 = The Multiple Sclerosis Walking Scale-12; df = degrees of freedom.
Figure 4a-b. Additional meta-analysis on physical activity and walking compared to no treatment alone.

**a) Physical activity**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Bande et al. 2014, PAR-01 (117)</td>
<td>28.7</td>
<td>9.0</td>
<td>37</td>
<td>19.3</td>
</tr>
<tr>
<td>Bombardier et al. 2013, 7-Day PAR (kcal/kg/wk)</td>
<td>229.5</td>
<td>9.0</td>
<td>44</td>
<td>249.4</td>
</tr>
<tr>
<td>Dlugonski et al. 2012, GLTEQ (METs/min/wk)</td>
<td>92.2</td>
<td>15.0</td>
<td>22</td>
<td>15.4</td>
</tr>
<tr>
<td>Wolf et al. 2011, GLTEQ (0-119)</td>
<td>24.7</td>
<td>18.0</td>
<td>23</td>
<td>15.4</td>
</tr>
</tbody>
</table>

Total (95% CI): 1.19

Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 2 (P = 0.47), P = 0%
Test for overall effect: Z = 4.62 (P < 0.0001)

**b) Walking ability**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Sandoff et al. 2014, 6MW (m)</td>
<td>457.1</td>
<td>194.0</td>
<td>37</td>
<td>420.5</td>
</tr>
<tr>
<td>Prosperi et al. 2013, 25FW (m)</td>
<td>7.0</td>
<td>2.0</td>
<td>17</td>
<td>9.7</td>
</tr>
<tr>
<td>Dlugonski et al. 2012, MSWS-12</td>
<td>-16.8</td>
<td>22.1</td>
<td>22</td>
<td>-27</td>
</tr>
<tr>
<td>Bombardier et al. 2010, 6-12 m walking (s)</td>
<td>-17</td>
<td>7.2</td>
<td>10</td>
<td>-25.3</td>
</tr>
</tbody>
</table>

Total (95% CI): 1.28

Heterogeneity: Tau² = 0.00; Chi² = 2.31, df = 3 (P = 0.52), P = 0%
Test for overall effect: Z = 0.93 (P = 0.39)

Abbreviations: the squares and diamonds represent the test values for individual studies and overall effectiveness; standard mean difference with 95% confidence interval (CI). SD: standard deviation; IPAQ = International Physical Activity Questionnaire; PAR = Physical Activity Recall; kcal/kg/wk = total energy expenditure in kilocalories per kilogram per week; GLTEQ = Godin Leisure-Time Exercise Questionnaire; MET/min/wk = METs per minutes per week; 6MW = 6-Minute Walk; m = meters; 25FW = 25-Foot Walk; m/s = meters per second; MSWS-12 = The Multiple Sclerosis Walking Scale-12; s = second; df = degrees of freedom.
Table 1. Summary of randomized controlled trials (RCTs) on technology-based distance physical rehabilitation interventions with outcomes related to physical activity and walking compared to wait-list, minimal similar treatment, hippotherapy, or usual care without the use of technology.

<table>
<thead>
<tr>
<th>Study / Year / Country</th>
<th>Duration</th>
<th>Total N (% men)</th>
<th>Experimental N (% men)</th>
<th>Control N (% men)</th>
<th>Age (years)</th>
<th>Experimental / Control</th>
<th>Participants</th>
<th>Intervention in the experimental group</th>
<th>Control</th>
<th>Outcomes related to physical activity and walking ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner et al. 2016 United States</td>
<td>6 months</td>
<td>65 (64)</td>
<td>31 (71)</td>
<td>33 (58)</td>
<td>53/54</td>
<td>Persons with MS</td>
<td>Telephone counseling (MI-based) and home-based telehealth monitoring to improve physical activity with home DVD physical activity exercises. Telephone counseling consisted of 6 weekly sessions and following the first telephone counseling session. Participants received a home monitoring session to provide reminder alarms to engage in physical activity at desired times and received weekly information on physical activity and progress on their goals.</td>
<td>Minimal treatment of similar DVD exercises as experimental group</td>
<td>the Godin Leisure-Time Exercise Questionnaire (GLTEQ)</td>
<td></td>
</tr>
<tr>
<td>Hoang et al. 2016 Australia</td>
<td>12 weeks</td>
<td>50 (24)</td>
<td>28 (33)</td>
<td>22 (29)</td>
<td>53/51</td>
<td>Persons with MS</td>
<td>Home-based step training programme on balance, stepping, cognition functional performance</td>
<td>Usual physical activity with no intervention</td>
<td>6-minute walk (6MW) 10-meter walk test Timed Up and Go (TUG)</td>
<td></td>
</tr>
</tbody>
</table>
Intervention consisted of unsupervised two interactive exergames (i.e., playing of video games that also provide the player with physical exercise), with follow-up phone calls at first two weeks.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Participants</th>
<th>Follow-up</th>
<th>Intervention Details</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frevel &amp; Maurer 2015 Germany</td>
<td>12 weeks</td>
<td>18 (17)</td>
<td>9 (22)</td>
<td>Internet-based home-training program. Balance, postural control and strength exercises with unstable surface under the feet. One training (45 min) consists 5-8 exercises with moderate intensity, 8-15 repetitions and 2-3 sets.</td>
<td>Hippotherapy The Dynamic Gait Index (DGI) 2-minute walk test (2MWT) Timed Up and Go (TUG)</td>
</tr>
<tr>
<td>Suh et al. 2015 United States</td>
<td>6 weeks</td>
<td>68 (18)</td>
<td>34 (12)</td>
<td>Behavioral intervention based on SCT delivered by newsletters and phone calls for increasing physical activity. Pedometers and log-books were delivered to the intervention group for the purpose of self-monitoring and tracking physical activity.</td>
<td>Newsletters and phone calls included information regarding topics without physical activity (e.g. allergies, blood pressure, alcohol use, cholesterol, nutrition and the Godin Leisure-Time Exercise Questionnaire (GLTEQ) in total leisure activity in scores between 0 and 119 in arbitrary units</td>
</tr>
<tr>
<td>Study</td>
<td>Duration</td>
<td>Participants</td>
<td>Males</td>
<td>Females</td>
<td>Persons with MS</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>-------</td>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Paul et al. 2014 United Kingdom</td>
<td>12 weeks</td>
<td>30 (20)</td>
<td>15</td>
<td>15</td>
<td>51/53</td>
</tr>
<tr>
<td>Sandroff et al. 2014 United States</td>
<td>6 months</td>
<td>76 (25)</td>
<td>37</td>
<td>39</td>
<td>49/50</td>
</tr>
</tbody>
</table>

Usual care | The Timed 25 Foot Walk test (25-FW) | No treatment (i.e., wait-list) | International Physical Activity Questionnaire (IPAQ) | 6-minute walk (6MW)
sessions which decreased over the intervention: 7 in first 2 months, 6 in the second period of 2 months and 2 in the final 2 months.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Participants</th>
<th>Completed</th>
<th>Attendance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bombardier et al 2013 United States</td>
<td>12 weeks</td>
<td>92 (14)</td>
<td>44 (11)</td>
<td>48 (17)</td>
<td>MI-based promotion of physical activity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 telephone counselling sessions for Weeks 1, 2, 3, 4, 6, 8, and 10 each lasting 30min and final lasting up to 60min.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Counselling consisted individual feedback on PA levels and barriers and menu options of stretching, range-of-motion, strength, aerobic, athletic, lifestyle PA exercises.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No treatment (i.e., wait-list)</td>
</tr>
<tr>
<td>Prosperini et al 2013 Italy</td>
<td>24 weeks</td>
<td>36 (31)</td>
<td>-</td>
<td>Group A 18 (28) Group B 18 (33)</td>
<td>Phone calls every week to remind patients to complete the logbook and encourage them to perform the training.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group A 35 Group B 37</td>
<td>Daily sessions (with the exception of the weekend) of home-based rehabilitation of balance using the Nintendo Wii Balance Board System (WBBS).</td>
</tr>
<tr>
<td>Study</td>
<td>Duration</td>
<td>Sample Size</td>
<td>Sample Size Distribution</td>
<td>Intervention Details</td>
<td>Control Group Details</td>
</tr>
<tr>
<td>------------------</td>
<td>----------</td>
<td>-------------</td>
<td>---------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Dlugonski et al 2012 United States</td>
<td>12 weeks</td>
<td>45 (13)</td>
<td>22 (18) 23 (9) 49/45</td>
<td>Internet-delivered and SCT-based behavioral intervention that was supplemented with video coaching for increasing and sustaining physical activity. The content was text-based and supplemented by web-based video coaching (7x á 5-10 min) and portable document format (pdf) files and incorporated the principle elements of SCT (i.e., self-efficacy, outcome expectations, impediments, and goal setting). Website and pedometer.</td>
<td>No treatment (i.e., wait-list)</td>
</tr>
<tr>
<td>Motl et al 2011 United States</td>
<td>12 weeks</td>
<td>48 (10)</td>
<td>23 (9) 25 (12) 46/46</td>
<td>Internet intervention based on SCT for favorably increasing PA. Content was text-based and supplemented by chat video sessions (2 times/wk) and portable document format (PDF) files (i.e., multimedia), and incorporated the principle elements of SCT including self-efficacy, outcome expectations, impediments, and goal setting.</td>
<td>No treatment (i.e., wait-list)</td>
</tr>
<tr>
<td>Bombardier et al 2008 United States</td>
<td>12 weeks</td>
<td>130 (22)</td>
<td>70 (24)</td>
<td>60 (20)</td>
<td>48/45</td>
</tr>
</tbody>
</table>

Abbreviations: MS = Multiple Sclerosis; RRMS = Relapse-remitting MS, MI = Motivational Interview, SCT = Social Cognitive Theory
Table 2. Methodological quality assessment of included randomized controlled trials (RCTs) (n=10) concerning technology-based distance physical rehabilitation interventions on physical activity and walking among PwMS.

<table>
<thead>
<tr>
<th>Study and year</th>
<th>1: randomization method adequate</th>
<th>2: treatment allocation concealed</th>
<th>3: blinding of participants</th>
<th>4: blinding of care provider</th>
<th>5: blinding of outcome assessor</th>
<th>6: drop-outs described and acceptable</th>
<th>7: participants analyzed in the allocated groups</th>
<th>8: free of suggestion of selective outcome reporting</th>
<th>9: group similarity at the baseline</th>
<th>10: co-intervention avoided or similar</th>
<th>11: compliance</th>
<th>12: similar timing of the outcome assessment</th>
<th>13: other sources of potential bias unlikely</th>
<th>Number of &quot;yes&quot; scores (maximum of 13)*</th>
<th>Methodological quality level†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner et al. 2016</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
</tr>
<tr>
<td>Hoang et al. 2016</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
</tr>
<tr>
<td>Frevel &amp; Maurer 2015</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Suh et al. 2015</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Paul et al. 2014</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Sandroff et al. 2014</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Bombardier et al. 2013</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Prosperini et al. 2013</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Dlugonski et al. 2012</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Motl et al. 2011</td>
<td>?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Bombardier et al. 2008</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: *The methodological quality of the studies was assessed with Furlan method guideline [18] including 13 items (1-13) rated as positive (“yes”), negative (“no”) or not fulfilled/unsure (“?”). †Methodological quality of level is based on the Anttila et al [19] criteria.
Table 3. Results of outcome variables in selected studies concerning technology-based distance physical rehabilitation interventions on physical activity and walking among PwMS.

<table>
<thead>
<tr>
<th>Study and year</th>
<th>Experimental</th>
<th>Control</th>
<th>Group differences (Effect/effect size)</th>
<th>Group differences p-value (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>M1 mean (SD)</td>
<td>M2 mean (SD)</td>
<td>M1 mean (SD)</td>
</tr>
<tr>
<td>Turner et al. 2016</td>
<td>30</td>
<td>0 wk</td>
<td>24 wk</td>
<td>33</td>
</tr>
<tr>
<td>GLTEQ (total leisure physical activity in MET/min/wk)</td>
<td>16.4 (19.4)</td>
<td>31.1 (17.5)</td>
<td>14.8 (19.4)</td>
<td>15.4 (17.5)</td>
</tr>
<tr>
<td>Hoang et al. 2016</td>
<td>23</td>
<td>0 wk</td>
<td>12 wk</td>
<td>21</td>
</tr>
<tr>
<td>6MW (m)</td>
<td>277.0 (18.0)</td>
<td>279.0 (97.0)</td>
<td>295.0 (19.0)</td>
<td>308.0 (108.0)</td>
</tr>
<tr>
<td>Frevel &amp; Maurer 2015</td>
<td>8</td>
<td>0 wk</td>
<td>10 wk</td>
<td>8</td>
</tr>
<tr>
<td>DGI (0-24)</td>
<td>13.3 (6.6)</td>
<td>15.3 (6.5)</td>
<td>12.8 (6.4)</td>
<td>15.8 (6.6)</td>
</tr>
<tr>
<td>Suh et al. 2015</td>
<td>34</td>
<td>0 wk</td>
<td>6 wk</td>
<td>34</td>
</tr>
<tr>
<td>GLTEQ (total leisure time in the scale of 1-119)</td>
<td>19.1 (14.8)</td>
<td>27.4 (20.6)</td>
<td>22.7 (19.4)</td>
<td>20.3 (21.9)</td>
</tr>
<tr>
<td>Paul et al. 2014</td>
<td>15</td>
<td>0 wk</td>
<td>12 wk</td>
<td>14</td>
</tr>
<tr>
<td>25FW (m/s)</td>
<td>0.8 (0.4)</td>
<td>0.80 (0.4)</td>
<td>0.9 (0.5)</td>
<td>0.9 (0.4)</td>
</tr>
<tr>
<td>Sandroff et al. 2014</td>
<td>37</td>
<td>0 wk</td>
<td>24 wk</td>
<td>39</td>
</tr>
<tr>
<td>6MW (m)</td>
<td>444.7 (157.7)</td>
<td>457.1 (164.9)</td>
<td>429.7 (160.8)</td>
<td>420.0 (158.0)</td>
</tr>
<tr>
<td>IPAQ (0-117)</td>
<td>17.4 (20.8)</td>
<td>29.7 (20.7)</td>
<td>22.8 (18.8)</td>
<td>19.3 (17.0)</td>
</tr>
<tr>
<td>Bombardier et al. 2013</td>
<td>44</td>
<td>0 wk</td>
<td>12 wk</td>
<td>48</td>
</tr>
<tr>
<td>7-Day PAR (kcal/kg/wk)</td>
<td>223.5 (8.2)</td>
<td>228.5 (9.9)</td>
<td>222.6 (6.9)</td>
<td>224.4 (9.2)</td>
</tr>
<tr>
<td>Prosperini et al. 2013</td>
<td>17</td>
<td>0 wk</td>
<td>12 wk</td>
<td>17</td>
</tr>
<tr>
<td>Group A vs. Group B (T0-T1)</td>
<td>25FW (m/s)</td>
<td>8.5 (2.7)</td>
<td>7.8 (2.8)</td>
<td>9.5 (3.3)</td>
</tr>
<tr>
<td>Dlugonski et al. 2012</td>
<td>22</td>
<td>0 wk</td>
<td>12 wk</td>
<td>23</td>
</tr>
<tr>
<td>Measure</td>
<td>Baseline M1</td>
<td>Baseline M2</td>
<td>Post 12 wk</td>
<td>Post 25 wk</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>MSWS-12 (0-80)</td>
<td>27.4 (22.0)</td>
<td>30.9 (22.1)</td>
<td>24.9 (25.0)</td>
<td>27.0 (25.6)</td>
</tr>
<tr>
<td>GLTEQ (total leisure physical activity in MET/min/wk)</td>
<td>13.6 (11.6)</td>
<td>28.2 (15.6)</td>
<td>16.1 (14.2)</td>
<td>15.4 (13.9)</td>
</tr>
<tr>
<td>Motl et al. 2011</td>
<td>23</td>
<td>0 wk</td>
<td>12 wk</td>
<td>25</td>
</tr>
<tr>
<td>GLTEQ (total leisure physical activity in MET/min/wk)</td>
<td>13.8 (15.2)</td>
<td>24.7 (18.8)</td>
<td>11.7 (16.3)</td>
<td>12.4 (14.2)</td>
</tr>
<tr>
<td>Bombardier et al. 2008</td>
<td>70</td>
<td>0 wk</td>
<td>12 wk</td>
<td>60</td>
</tr>
<tr>
<td>90m walking test (s)</td>
<td>28.0 (8.1)</td>
<td>27.0 (7.2)</td>
<td>26.44 (6.0)</td>
<td>26.3 (6.6)</td>
</tr>
</tbody>
</table>

Abbreviations: n = study sample; M1 = baseline value; SD = Standard deviation; M2 = post intervention end-point value; M2-M1 = change in the intervention within the group, 95% CI = 95% Confidential Interval; wk = week; 6MW = 6 meter walking test; m = meter; ES = Effect size as Cohen’s $d$; p = p-value; DGI = Dynamic Gait Index; GLTEQ = the Godin Leisure-Time Exercise Questionnaire, F = F-statistics; * = condition x time; $\eta^2_p$ = Effect sizes as partial eta-squared; 25FW = 25 Foot Walk test; m/s = meters/second; IPAQ = International Physical Activity Questionnaire; 7-Day PAR = 7-Day Physical Activity Recall; kcal/kg/wk = total energy expenditure in kilocalories per kilogram per week; T0-T1 = Cross over RCT time point of phase 1 from baseline and 12 week; MSWS-12 = the Multiple Sclerosis Walking Scale-12; MET/min/wk = metabolic equivalent by minutes per week; s = seconds
Appendix 1. Search strategy.

Database: Ovid MEDLINE(R) <1946 to October Week 1 2014>

Search Strategy:

1 Exercise Therapy/ (27416)
2 exercise therapy.tw. (1900)
3 Physical Therapy Modalities/ (28897)
4 physical therapy.tw. (10161)
5 physiotherapy.tw. (10909)
6 functional therapy.tw. (295)
7 Occupational Therapy/ (10498)
8 Neuropsychology/ (2044)
9 dietician.tw. (576)
10 dietitian.tw. (1805)
11 Dietetics/ (5248)
12 Occupational Health Services/ (9835)
13 multidisciplinary therapy.tw. (270)
14 physical activity.tw. (55661)
15 Exercise/ (70603)
16 Exercise Movement Techniques/ (418)
17 Motor Activity/ (83150)
18 energy expenditure.tw. (17234)
19 "Delivery of Health Care"/ (68140)
20 public health service$.tw. (5236)
21 Nursing Diagnosis/ (3863)
22 Nursing Informatics/ (1017)
23 Community Health Nursing/ (18608)
24 Nursing/ (50228)
25 Public Health Nursing/ (9754)
26 medical treatment$.tw. (34601)
27 Psychiatry/ (32921)
28 Rehabilitation/ (17036)
29 Health Promotion/ (55591)
30 health care$.tw. (556)
31 directive care$.tw. (128)
32 coaching.tw. (2284)
33 health guidance.tw. (273)
34 "Activities of Daily Living"/ (52849)
35 adl.tw. (6077)
36 participation.tw. (91377)
37 cultural activities.tw. (158)
38 Leisure Activities/ (6678)
39 "Physical Education and Training"/ (12075)
40 Primary Prevention/ (14663)
41 Secondary Prevention/ (2154)
42 Tertiary Prevention/ (87)
43 Sports/ (24021)
44 active lifestyle.tw. (816)
45 physical lifestyle.tw. (27)
46 Physical Fitness/ (22813)
47 Health Education/ (53678)
48 Patient Education as Topic/ (72468)
49 Behavior Therapy/ (24576)
50 Cognitive Therapy/ (17151)
51 or/1-50 (863030)
52 mobile system$.tw. (153)
53 Telemedicine/ (12179)
54 ehealth.tw. (644)
55 mobile health.tw. (424)
56 mhealth.tw. (184)
(allocated adj2 random$).tw. (18923)
or/112-117 (411822)
119 111 or 118 (1209420)
120 case report.tw. (189105)
letter/ (845830)
Historical Article/ (311099)
or/120-122 (1334329)
124 119 not 123 (1178568)
51 and 95 and 124 (2193)
limit 125 to (yr="2000 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)") and (english or finnish or german or swedish) and humans) (1238)
intervention studies/ (7408)
intervention$.tw. (541118)
127 or 128 (542366)
126 and 129 (681)
Appendix 2. Funnel plots of the meta-analyses.

a) Physical activity

b) Walking ability

c) Control comparison of no treatment