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Author(s): Rintala, Aki; Hakala, Sanna; Paltamaa, Jaana; Heinonen, Ari; Karvanen, Juha; Sjögren, Tuulikki

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

5 Aki Rintala, MSc^{1,2}, Sanna Hakala, MSc¹, Jaana Paltamaa, PhD³, Ari Heinonen, PhD¹, Juha
6 Karvanen, DSc⁴, and Tuulikki Sjögren, PhD¹

7
8 ¹ Faculty of Sport and Health Science, University of Jyväskylä, Jyväskylä, Finland

9 ² Center for Contextual Psychiatry, KU Leuven, Leuven, Belgium

10 ³ School of Health and Social Studies, JAMK University of Applied Sciences, Jyväskylä, Finland

11 ⁴ Department of Mathematics and Statistics, University of Jyväskylä, Jyväskylä, Finland

12
13 Corresponding author:

14 Aki Rintala, MSc, PT; Postal address: Avenue de l’Héliport 32 69, 1000 Brussels, Belgium;
15 telephone number: +32 474 13 23 88; E-mail address: akirintala@gmail.com
16

37 **ABSTRACT**

38

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

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

44 **Methods:** Methodological quality of the studies was determined and a meta-analysis was performed.
45 In addition, a subanalysis of technologies and an additional analysis comparing to no treatment were
46 conducted.

47 **Results:** The meta-analysis consisted of 11 studies. The methodological quality was good (8/13). The
48 Internet, telephone, exergaming and pedometers were the technologies enabling distance physical
49 rehabilitation. Technology-based distance physical rehabilitation had a large effect on physical
50 activity (Standard mean difference (SMD) 0.59; 95% confidence interval (95% CI) 0.38 to 0.79;
51 $p < 0.00001$) compared to control group with usual care, minimal treatment, and no treatment. A large
52 effect was also observed on physical activity (SMD 0.59; 95% CI 0.34 to 0.83; $p < 0.00001$) when
53 compared to no treatment alone. There were no differences in walking and the subanalysis of
54 technologies.

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

57

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

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71 **Introduction**

72

73 Multiple sclerosis (MS) is a progressive neurological disease of the central nervous system (CNS)
74 [1]. Symptoms are individual and include functional, psychological and cognitive limitations.
75 Reduced walking ability [2,3], depression [4,5] and fatigue [6,7] are the most common symptoms of
76 MS. Other frequent symptoms are bladder and bowel symptoms, cognition, cerebellar and sensory
77 symptoms, motor weakness and spasticity, sexual dysfunction and visual loss [8]. Various symptoms
78 have different effects among persons with MS (PwMS) on activities of daily living, level of well-
79 being and satisfaction in life and overall on quality of life [1]. In the early stage of MS there is reduced
80 physical activity and walking compared to the general population [9,10]. In addition, previous
81 systematic reviews with meta-analysis reported that PwMS are less physically active compared to
82 healthy populations [11] and exercise training is associated with improvement in walking in MS [12].
83 However, there is a lack of evidence on the effect of technology-based distance physical rehabilitation
84 interventions in MS.

85

86 Only one previous systematic review of randomized control trials (RCTs) and controlled clinical trials
87 investigated the effect of distance rehabilitation conducted with telerehabilitation in MS [13]. In a
88 review consisting of 469 participants, Khan et al. [13] found limited evidence for the efficacy of
89 telerehabilitation in improving physical activity, balance capacity, postural control, fatigue, and
90 quality of life. Interventions varied in their rehabilitation components, including ones other than
91 physical rehabilitation interventions, such as nursing and fatigue management. In addition,
92 technology consisted only of the telephone, control groups were heterogeneous and the included
93 RCTs scored low on methodological quality. Khan et al. [13] concluded that there were limited data
94 on the process evaluation and cost-effectiveness.

95

96 To conclude, there is a need to build evidence for the use of technology in distance physical
97 rehabilitation interventions. The objective of this study was to investigate the effectiveness of
98 technology-based distance physical rehabilitation interventions on physical activity and walking in
99 MS compared to other treatment or no treatment (wait-list, minimal treatment, hippotherapy, and
100 usual care).

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104

105 **Methods**

106

107 *Search strategy for identification of the studies*

108

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

119

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

130

131 *Data extraction*

132

133 Only RCTs investigating the effect of technology-based distance physical rehabilitation interventions
134 were included in this systematic review. Further inclusion criteria according to the PICOS (Patient,
135 Intervention, Comparison, Outcome, Study design) framework were as follows: (P) PwMS; (I) any
136 technology used to promote or increase any physical activities or participation to enable distance
137 physical rehabilitation (e.g., wearable device, Internet, telephone, or smartphone); (C) no treatment
138 (i.e., wait-list), or face-to-face physical rehabilitation interventions or other treatments to promote or

139 increase activities or participation without distance physical rehabilitation approach and the use of
140 technology; (O) an outcome measure describing physical activity or walking; (S) the study design of
141 RCTs. Only RCTs published in English, Finnish, Swedish or German were included in the review.
142 Non-randomized or non-controlled experimental studies, longitudinal studies and protocols were
143 excluded. Studies including other diagnoses without separate analysis of MS were excluded.

144

145 In line with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [14],
146 two reviewers (AR and TS) independently screened all the titles and abstracts of the studies. After
147 the title and abstract phase, potentially relevant studies were independently evaluated for full-text
148 assessment by two assessors (AR and TS) of the research team. In case of disagreement, a third
149 reviewer (SH) evaluated the studies.

150

151 For this review and meta-analysis, only studies with technology-based distance physical rehabilitation
152 interventions and outcome measures describing valid measures of either physical activity or walking
153 were included. Outcome measures describing walking were linked to the International Classification
154 of Functioning, Disability and Health (ICF) chapter for mobility (d4) in activity and participation by
155 two researchers (AR and JP) [15, 16]. On physical activity measures, several ICF categories based
156 on the activities were captured, while linking the physical activity outcome measures to the ICF. Both
157 physical activity and walking measures were interpreted as activities and participation.

158

159 *Methodological quality and the risk of bias*

160

161 The methodological quality of the RCTs was evaluated using the Furlan method guideline for
162 systematic reviews [17]. The updated Furlan method guideline for systematic reviews consists of 13
163 items and rates RCTs based on (1) adequate randomization, (2) treatment allocation concealed, (3)
164 blinding the patient, (4) blinding the care provider, and (5) blinding the outcome assessor, (6) drop-
165 out rate described and acceptable, (7) participants analyzed in the groups they were allocated, (8)
166 suggestion of selective outcome reporting, (9) the similarity of the groups at baseline, (10) co-
167 intervention avoided or similar, (11) compliance, (12) timing of the outcome assessment and (13)
168 other sources of potential bias unlikely [17]. One item is scored positive (“yes”) if the criterion was
169 fulfilled, negative (“no”) if the criterion was not fulfilled or unclear (“unsure”) if required information
170 was adequately reported. The methodological quality was evaluated by two blinded and independent
171 reviewers (AR and SH). In case of disagreements, a third reviewer (TS) was consulted to solve the
172 disagreement. The total score of a study is the sum of the positive scores. The maximum score for a

173 single study in the updated Furlan method guideline for systematic reviews is 13 points. In an
174 adaptation of the Furlan et al. [17] method guideline and the criteria method of Anttila et al. [18], the
175 methodological quality of a study was considered to be high, moderate or poor. A study was rated as
176 high quality when the following criteria were fulfilled: overall at least 6 or more “yes” scores, at least
177 30 or more participants in the study, and “yes” scores for items (1) randomization method adequate,
178 (2) treatment allocation concealed, (6) drop-outs described and acceptable and (9) group similarity at
179 the baseline. A study was considered to have moderate quality when it fulfilled the following criteria:
180 at least 4 or more “yes” scores and item (1) method of randomization was adequate. The study was
181 evaluated as having poor quality if there were at least 4 or more “yes” scores, but the method of
182 randomization was not adequately reported (a score of “no” or “unsure” on item (1) or there were
183 only 0-3 “yes” scores, or the study included fewer than five participants in the experimental group or
184 in the control group [18].

185

186 *Statistical synthesis*

187

188 The meta-analysis was performed separately for the outcome variables on physical activity and
189 walking. In addition, a subanalysis of technologies and an additional analysis comparing these two
190 outcome variables to wait-list were conducted. If adequate post-treatment values (mean and standard
191 deviation; SD) were not reported, a request was sent to the corresponding author of the original study.
192 If not answered, the RCT was not taken into account in the meta-analysis. If study was reported
193 standard error (SE) instead of SD, SD was obtained from the standard error of a mean by multiplying
194 the standard error by the square root of the sample size within an intervention group. Standardized
195 mean differences (SMD) between the experimental and control groups were calculated for each study.
196 In accordance with the Cochrane guidelines for systematic reviews and meta-analysis, the values of
197 the outcome variables were multiplied by -1 when needed so that the higher values reflect better
198 physical activity and walking [19]. A random effects model was used in the meta-analysis. Cochrane
199 Collaboration’s Review Manager 5.1.3 statistical software analysis package was used to calculate the
200 pooled effect estimates for the combination of the single effects of the RCTs. SMD between the
201 groups were considered to be large > 0.5, moderate 0.3–0.5, small 0.1–0.2 or insubstantial < 0.1 [20].
202 The results of the meta-analysis are presented using forest plots of the SMD. Statistical heterogeneity
203 was evaluated with the I^2 statistic, where a value closer to the zero of I^2 indicates less heterogeneity
204 [21].

205

206 **Results**

207

208 The search identified overall 2309 studies which 309 studies focused on MS. The screening of 50
209 full-text studies revealed 11 potentially eligible studies. Three studies had the same source or original
210 data as another included study [22-24] providing no additional data to this systematic review (i.e.,
211 same outcome measures), and therefore they were excluded from the qualitative analysis. A total of
212 11 studies [25-35] published between 2007 and 2016 fulfilled the inclusion criteria and were included
213 in the qualitative and quantitative analysis. A flow chart of the review process is presented in Figure
214 1 and specific details of included studies can be found in Table 1.

215

216 *Description of the participants*

217

218 The selected studies included a total of 657 PwMS, which consisted of 308 participants in the
219 experimental group and 349 in the control group (Table 1). The mean (SD) age of the participants
220 was 47 (4.6) years. From the total sample, mean (SD) disease duration since diagnosis was 11 (3.5)
221 years with a range of 6–22 years. Of the participants, 75 % were women, and 73 % had relapsing-
222 remitting MS. Two studies out of 11 included clinical course of relapsing-remitting [26-27], and other
223 studies included several clinical courses of MS (i.e., relapsing-remitting, progressive or benign)
224 [25,28-35]. In all of the included studies PwMS were ambulatory. Seven studies [25,28-30,32,34-35]
225 used the Expanded Disability Status Scale (EDSS) [36], with the inclusion criterion of an EDSS score
226 of 6.5 or lower. The four remaining studies [26-28,31,33] used the Patient Determined Disease Steps
227 (PDDS) scale, which in a previous study has reported linearity and strong relation with the EDSS
228 scores [37]. Participants in these included studies had a minimal to moderate level of disease severity
229 with a PDDS score of 6.0 or lower, where the range was 0.0 to 7.0.

230

231 *Methodological quality and the risk of bias*

232

233 The methodological quality of the studies was good (median: 8, interquartile range: 7 to 9) (Table 2).
234 Overall, using the interpretation of the Furlan method guideline [17] and the method outlined by
235 Anttila et al. [18], five studies were classified as high [29,31,33-35], five as moderate [25,27-
236 28,30,32] and one as poor [29]. The most common methodological fault was no reporting or no
237 blinding of the participants and the care providers, no reporting of selective outcomes, and no
238 reporting of avoiding co-interventions. While ten out of 11 studies used an adequate randomization
239 method (Item 1; 91 %), only seven studies reported concealed treatment allocation (Item 2: 64 %).
240 All of the studies used similar timing of the outcome and did not include any other sources of likely

241 potential bias (Items 12-13: 100 %). In addition, six of the studies [25,27-28,33-35] conducted
242 intention-to-treat (ITT) analysis (Item D7: 55 %), and the smallest sample size was in two studies
243 [30,32], ranging from 16 to 29 participants. Interrater reliability was good among the two assessors,
244 having no disagreements on the methodological quality assessment.

245

246 *Description of the technologies used in distance physical rehabilitation interventions*

247

248 Mean (SD) duration of the intervention was 11 (3.5) weeks. The most used technology in distance
249 physical rehabilitation interventions was the Internet. It was used in five studies with either only
250 Internet-based e-training [32] or the Internet in combination with other technology such as a
251 pedometer [26-27,31] or a telephone [30]. Two studies used only a telephone [25,28] and four studies
252 used telephone in a combination with a pedometer [33], unsupervised exercises using the Nintendo
253 Wii Balance Board or interactive exergames [29,34], or telehealth monitoring [35]. All of the included
254 studies enabled interaction of two-way communication between the caregiver and the participant
255 either by the Internet, a telephone [25-34], or telephone with the combination of telehealth monitoring
256 [35]. Internet-delivered interventions used either Skype [31], online chat sessions [26], video-
257 coaching [27] or a feedback platform on a website [32]. Self-monitoring devices with one-way
258 communication included a pedometer for independently controlling physical activity levels [26-
259 27,31] or by using interactive exergames such as the Nintendo Wii Balance Board for balance
260 exercises [29] or physical exercises [34].

261

262 *Content of the interventions in experimental and control groups*

263

264 The content of the interventions in the experimental group were heterogeneous. Six out of 11
265 interventions focused on increasing or promoting physical activity either with social-cognitive theory
266 (SCT) [26-27,31,33] or with a motivational interview (MI) [28,35]. The SCT approaches included
267 manuals for stretching, physical activity in everyday life, goal-setting and outcome expectations [26-
268 27,31,33]. The MI interview consisted of tailored home- or community-based physical activity or
269 exercises based on individual needs in the participants' daily life, physical abilities, environment
270 resources, and motivation [28,35]. Two interventions included home training exercise programs for
271 either balance, postural control and strength exercises [32] or balance, strength and cardiovascular
272 exercises [30]. Another two studies included virtual games for the Nintendo Wii Balance Board or
273 other interactive exergames involving balance and physical exercises [29,34]. One intervention
274 included an MI approach for increasing health promotion activities such as exercise, fatigue

275 management, social support, anxiety, and drug use [25]. The content of the intervention in the control
276 groups was also heterogeneous consisting of no treatment (i.e., wait-list), usual care, minimal
277 treatment, or hippotherapy without the use of technology relating to distance physical rehabilitation.
278 Usual care consisted of either general advice on exercise [30], physical activity [34] or general advice
279 excluding physical activity (e.g. on allergies, blood pressure, alcohol use, cholesterol, nutrition and
280 stress management) [33]. Minimal treatment included the similar home DVD program as in the
281 experimental group to facilitate motivation, to promote self-efficacy, and provide examples of in-
282 home exercises to overcome barriers to participation [35]. Other treatments included a comparison of
283 hippotherapy [32].

284

285 *Description of the outcome measures*

286

287 A total of eight different outcome measures was identified from the selected studies (Table 2). The
288 results of the outcome variables in the selected studies are presented in Table 3. Six out of 11 studies
289 investigated physical activity with the self-reported questionnaires either with the Godin Leisure-
290 Time Exercise Questionnaire (GLTEQ) [26-27,33,35], International Physical Activity Questionnaire
291 (IPAQ) [31], or the 7-Day Physical Activity Readiness (PAR) questionnaire [28]. Values in GLTEQ
292 were measured in total leisure physical activity in METs per minutes per week (MET/min/wk) [26-
293 27,35] or in total leisure physical activity in scores between 0 and 119 in arbitrary units [33]. In IPAQ,
294 overall physical activity was measured with scores 0 to 117 where a higher score indicated more
295 physical activity [31]. Values in PAR were reported in total energy expenditure in kilocalories per
296 kilogram per week (kcal/kg/week) [28]. A higher score on MET/min per week, arbitrary units and in
297 kcal/kg/week signify better physical activity. Seven out of ten studies used outcome measures to
298 describe walking as follows: a 90-meter walk test measured in seconds [25], the Multiple Sclerosis
299 Walking Scale-12 (MSWS-12) on a scale of 0 to 80 [27], the Timed 25-Foot Walk test (25-FW)
300 measured in meters per second [29-30], the 6-Minute Walk test (6MW) measured in meters [31,34]
301 and the Dynamic Gait Index (DGI) on a scale of 0 to 24 [32]. A higher score on 25FW, 6MW, and
302 DGI signify better walking. In contrast, a lower score in the 90-meter walking test and on the MSWS-
303 12 scale signify better walking.

304

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

306

307 The data (post-treatment value with mean and SD) needed for the estimations of ES were reported in
308 10 studies, and in one study the authors provided this data on request. In one study SD was obtained

309 from the standard error [35]. In one cross-over trial, only data from phase 1 of 0–12 weeks was taken
310 into account, because of possible carryover effect [29]. Therefore, the meta-analysis was conducted
311 from all of the included studies [25-35] (Figures 2–4). Subanalyses of different technologies were
312 conducted based on the interactive role of the main technology. Due to the lack of studies, only the
313 comparison of wait-list was included in the additional analysis (Figure 4 & 5). Funnel plots of the
314 meta-analyses are in Appendices 2–5.

315

316 *Physical activity*

317

318 Technology-based distance physical rehabilitation interventions had a large effect on physical activity
319 when compared to control groups with no treatment, usual care and minimal treatment without the
320 use of technology (SMD 0.59; 95 % confidence interval (CI) 0.38 to 0.79; $p < 0.00001$). In
321 subanalyses of different technologies, the Internet and the use of a pedometer (SMD 0.68; 95 % CI
322 0.37 to 0.99; $p = 0.0001$) had a large effect when compared to no treatment. In addition, in the use of
323 a telephone alone or telephone with a combination of a telehealth monitoring or a pedometer, a
324 moderate effect was captured (SMD 0.53; 95 % CI 0.21 to 0.84; $p = 0.001$) when compared to no
325 treatment, usual care and minimal treatment. The studies were homogeneous according to the overall
326 meta-analysis result ($I^2 = 0\%$) (Figure 2). Low level of heterogeneity was observed in a subanalysis
327 in the use of a telephone alone, or with telehealth monitoring or pedometer ($I^2 = 26\%$)

328

329 *Walking*

330

331 Technology-based distance physical rehabilitation interventions had no effect on walking when
332 compared to control group with no treatment, usual care, and hippotherapy without the use of
333 technology (SMD -0.09; 95 % CI -0.29 to 0.11, $p = 0.39$). In the subanalysis of different technologies,
334 the use of the Internet alone and in combination with a pedometer or telephone (SMD 0.01; 95 % CI
335 -0.29 to 0.32; $p = 0.94$) had no effect when compared to the control group with no treatment, usual
336 care and hippotherapy without the use of technology. In addition, no effect was captured in the use
337 of telephone alone (SMD -0.10; 95 % CI -0.45 to 0.24; $p = 0.57$) when compared to no treatment or
338 in the use of exergames with the use of telephone (SMD -0.29; 95 % CI -0.74 to 0.16; $p = 0.20$) when
339 compared to usual care and no treatment. The studies were homogeneous according to the meta-
340 analysis ($I^2 = 0\%$) (Figure 3).

341

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

343

344 Technology-based distance physical rehabilitation intervention had a large effect on physical activity
345 when compared to no treatment alone (SMD 0.59; 95 % CI 0.34 to 0.83; $p < 0.00001$) (Figure 4). No
346 effect was observed on walking (SMD -0.05; 95 % CI -0.28 to 0.19; $p = 0.70$). The studies were
347 homogeneous according to the meta-analysis ($I^2 = 0\%$) (Figure 5).

348

349 **Discussion**

350

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

365

366 The distance physical rehabilitation interventions on physical activity used technology in
367 combinations of the Internet, telephone alone, telephone and pedometer, or telephone and telehealth
368 monitoring [26-28,31,33,35]. All included studies had a similar aim of increasing or promoting
369 physical activity among PwMS, used self-reported physical activity questionnaires, and four out of
370 six studies had similar interventions based on SCT [26-27,31,33]. These similarities between the
371 studies might support the low level of heterogeneous findings on meta-analysis. Furthermore,
372 subanalysis of different technologies on physical activity were unable to determine if the technologies
373 lead to differing outcomes when comparing to control groups with no treatment and usual care
374 without the distance approach and the use of technology. This might suggest that similar effect might
375 occur regardless of the technology being used when promoting physical activity in MS. However,
376 small number of participants ranging from 82 to 108 and only six included studies in the subanalysis

377 might limit this indication. Thus, future RCT studies might help to inform if a difference in
378 interventions exists.

379

380 There was no effect of technology-based distance physical rehabilitation interventions between the
381 groups in any meta-analysis on walking outcomes [25,27,29-32,34], and there were no differences
382 between the technologies in the subanalysis. The meta-analysis did not capture heterogeneous results,
383 although distance physical rehabilitation interventions differed in the content of exercises programs,
384 technologies, and control groups. Exercise programs included home-based balance training or step
385 training with the use of exergames [29,34], Internet-based home training to improve balance [32],
386 physical activity intervention with the use of the Internet and a pedometer [27,31], telephone
387 counselling for health promotion [25], and individual web-based physiotherapy [30]. Although
388 studies used different measurements to capture walking in MS, all of the measurements investigated
389 the functional performance on walking. This might partly explain the null heterogeneous finding in
390 the meta-analysis. Further analysis to explain the heterogeneous findings could not be made due to
391 the lack of included studies. The results of our meta-analysis on walking with no effect observed
392 should be viewed critically because the findings are based on a range from 40 to 82 participants from
393 seven studies.

394

395 Two previous systematic reviews with meta-analysis have investigated physical activity and walking
396 among PwMS [11-12], but without the focus on distance physical rehabilitation with technologies.
397 One previous systematic review using remote physical activity monitoring in neurological diseases
398 reported that physical activity monitoring is feasible in people with a moderate to severe neurological
399 disability [38]. This supports our meta-analysis findings in MS. However, a review by Block et al.
400 [38] consisted of different neurological disorders, including 61 studies of MS with study settings of
401 RCTs, non-randomized controlled studies, cross-sectional studies and longitudinal studies. Only one
402 previous systematic review has investigated the technology-based distance rehabilitation
403 interventions on telerehabilitation in MS [13]. A systematic review by Khan et al. [13] with qualitative
404 analysis indicated a low effect of telerehabilitation interventions in reducing short-term disability and
405 improving long-term functional abilities, quality of life and psychological outcomes. However, Khan
406 et al. [13] could not conduct a meta-analysis from the selected studies. Furthermore, Khan et al. [13]
407 differs from our review in the content of inclusion criterion and in the use of technology. In our
408 review, only interventions with physical rehabilitation were included and the use of the technology
409 was not limited. In contrast, Khan et al. [13] included only studies with telerehabilitation, regardless
410 of the intervention content, and the use of a telephone. However, in both our review and in Khan et

411 al. [13], none of the included studies addressed cost-effectiveness. This lack indicates a need for
412 future studies to investigate more reliable recommendations of the technology in clinical use among
413 PwMS, as well as cost-effectiveness.

414

415 Overall, the methodological quality of the studies was good and sample sizes ranged from 16 to 130
416 participants. Regarding physical activity, all of the included studies had sufficient statistical power
417 for drawing fair conclusions [26-28,31,33,35]. However, only two out of seven studies had sufficient
418 statistical power on measures describing walking [25,27,29-32,34]. This might partly explain our
419 findings in the meta-analysis on walking. A previous review of the challenges in designing trials has
420 reported that the studies to be included should have adequate power, a suitable study setting, proper
421 inclusion and exclusion criteria, reasonable outcomes to fit with the study aim, and proper time-points
422 for assessments [39]. The studies included in this review had insufficient methodological quality in
423 blinding participants and care providers, selection bias and avoiding co-intervention. The difficulty
424 in blinding patients and care providers in studies of different physical rehabilitation interventions is
425 understandable. However, most of the studies reported no suggestions of selective outcomes or
426 avoidance of co-interventions. In addition, if concealed treatment allocation was not properly
427 reported, the study setting might be questionable. All of the included studies were reported to be
428 RCTs. Proper reporting in concealed treatment allocation should be taken into account when planning
429 a protocol or study setting, or when reporting results.

430

431 Ten out of 11 studies reported the clinical course of relapse-remitting MS (RRMS), and overall 73 %
432 of the participants had RRMS. In addition, all of the participants were ambulatory at the baseline,
433 with a mean disease duration of 11 years. This meta-analysis result on physical activity might be
434 generalized to ambulatory persons with RRMS. However, more MS studies focusing on technology-
435 based distance physical rehabilitation are needed, taking into account the factors regarding the clinical
436 course of MS, and disease duration.

437

438 In this systematic review, technology-based distance physical rehabilitation interventions were
439 determined as interventions that used a technological device to enable the full intervention to be
440 conducted without a care provider present. All of the included studies enabled interaction with two-
441 way communication between the caregiver and the participant either via the Internet or a telephone
442 [25-34]. Nine out of 11 studies used a combination of two different technologies [26-31, 33-35],
443 which makes it difficult to separate the advantage of any single technology in our findings. To
444 conclude, there is not enough evidence to make a firm conclusion on the use of any particular

445 technology in a distance physical rehabilitation setting in MS. With better evidence, there is the
446 possibility to more precisely determine the clinical benefits of using technology in distance physical
447 rehabilitation among PwMS.

448

449 *Strengths and limitations of the systematic review and meta-analysis*

450

451 The strength of this systematic review and meta-analysis is its focus on technology-based distance
452 physical rehabilitation in MS. To our knowledge, this is the first systematic review with meta-analysis
453 exploring the use of technology in distance physical rehabilitation interventions among PwMS. The
454 meta-analysis did not indicate major statistical heterogeneity, and funnel plots did not suggest
455 publication bias. If publication bias existed, it might have indicated, for example, an author's
456 publishing of portions of the study based on only the magnitude, direction, or statistical significance
457 of the results [21]. PICOS criteria were determined quite strictly by including only technology-based
458 distance physical rehabilitation interventions in the systematic review and excluding the technology
459 from the control groups to capture the effect on technology-based distance physical rehabilitation
460 interventions. The study population was targeted to be PwMS, and the study settings (i.e. RCTs) were
461 similar among the included studies. Both physical activity and walking measures were interpreted as
462 activities and participation in the ICF framework. Although the measures differed in the terms of the
463 values described within one outcome, all of the measures represented movement either focusing on
464 physical activity or on walking.

465

466 However, this systematic review and meta-analysis has its limitations. Due to the lack of studies in
467 technology-based distance physical rehabilitation interventions among PwMS, the content of the
468 treatments in the experimental and control groups were clinically heterogeneous. Intervention
469 consisted of different aspects of physical rehabilitation, targeting, for example, only physical activity
470 [26-28,31,33,35], balance and strength [29-30,32,34], and general health promotion for exercise,
471 fatigue, social support, anxiety and drug use [25]. Comparison in the control groups also consisted of
472 several different approaches, including no treatment, usual care, minimal treatment, and hippotherapy
473 [25-35]. Furthermore, small range of the participants and the number of studies might have an impact
474 for not distinguishing the differences between the technologies in the subanalyses. Also, there was
475 substantial variety in the kinds of technology used as a different combination or as a single
476 technology. In the subanalyses, the selection was made based on the most interactive role of the
477 technology that provided the distance physical rehabilitation intervention. However, some studies
478 used a combination of technologies, which might have an impact on the results. Due to these facts,

479 the results of this systematic review and meta-analysis should be interpreted with caution.
480 Nevertheless, this study provides promising results regarding the use of technology in distance
481 physical rehabilitation among PwMS on physical activity. Further studies are needed to more
482 precisely determine the use of technology in distance rehabilitation in MS, especially on walking.

483

484 **Conclusions**

485

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

492

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494

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498

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500

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503

504 **Declaration of interest**

505

506 No potential conflict of interest was reported by the authors.

507

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611 Figure 1. Flow chart of the study selection.

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613 Figure 2. Meta-analysis on physical activity compared to the control group with no treatment,
614 minimal treatment, and usual care without the use of technology. The squares and diamonds represent
615 the test values for individual studies and overall effectiveness; standard mean difference with 95%
616 confidence interval (CI). Abbreviations: SD: standard deviation; IPAQ: International Physical
617 Activity Questionnaire; GLTEQ: Godin Leisure-Time Exercise Questionnaire; MET/min/week:
618 METs per minutes per week; PAR: Physical Activity Recall; kcal/kg/week: total energy expenditure
619 in kilocalories per kilogram per week; df: degrees of freedom.

620

621 Figure 3. Meta-analysis on walking compared to the control group with no treatment, usual care, and
622 hippotherapy without the use of technology. The squares and diamonds represent the test values for
623 individual studies and overall effectiveness; standard mean difference with 95% confidence interval
624 (CI). Abbreviations: SD: standard deviation; DGI: Dynamic Gait Index; 6MW: 6-Minute Walk; m:
625 meters; 25FW: 25-Foot Walk; m/s: meters per second; MSWS-12: The Multiple Sclerosis Walking
626 Scale-12; df: degrees of freedom.

627

628 Figure 4. Additional meta-analysis on physical activity compared to no treatment alone. The squares
629 and diamonds represent the test values for individual studies and overall effectiveness; standard mean
630 difference with 95% confidence interval (CI). Abbreviations: SD: standard deviation; IPAQ:
631 International Physical Activity Questionnaire; PAR: Physical Activity Recall; kcal/kg/week: total
632 energy expenditure in kilocalories per kilogram per week; GLTEQ: Godin Leisure-Time Exercise
633 Questionnaire; MET/min/week: METs per minutes per week; df: degrees of freedom.

634

635 Figure 5. Additional meta-analysis on walking compared to no treatment alone. The squares and
636 diamonds represent the test values for individual studies and overall effectiveness; standard mean
637 difference with 95% confidence interval (CI). Abbreviations: SD: standard deviation; 6MW: 6-Minute
638 Walk; m: meters; 25FW: 25-Foot Walk; m/s: meters per second; MSWS-12: The Multiple Sclerosis
639 Walking Scale-12; df: degrees of freedom.

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- 645 APPENDIX 1. Search strategy.
- 646 APPENDIX 2. Funnel plot of the meta-analysis on physical activity.
- 647 APPENDIX 3. Funnel plot of the meta-analysis on walking.
- 648 APPENDIX 4. Funnel plot of the meta-analysis on physical activity compared to no treatment.
- 649 APPENDIX 5. Funnel plot of the meta-analysis on walking compared to no treatment.
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652 Table 1. Summary of randomized controlled trials (RCTs) on technology-based distance physical rehabilitation interventions with outcomes related
 653 to physical activity and walking compared to wait-list, minimal treatment, hippotherapy, or usual care without the use of technology.

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

							Intervention consisted 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.		
Frevel & Mäurer 2015 Germany	12 weeks	18 (17)	9 (22)	9 (11)	44/47	Persons with MS	<p>Internet-based home-training program.</p> <p>Balance, postural control and strength exercises with unstable surface under the feet.</p> <p>One training (45 min) consists 5-8 exercises with moderate intensity, 8-15 repetitions and 2-3 sets.</p>	Hippotherapy	<p>The Dynamic Gait Index (DGI)</p> <p>2-minute walk test (2MWT)</p> <p>Timed Up and Go (TUG)</p>
Suh et al. 2015 United States	6 weeks	68 (18)	34 (12)	34 (24)	50/48	Physically inactive persons with MS	<p>Behavioral intervention based on SCT delivered by newsletters and phone calls for increasing physical activity.</p> <p>Pedometers and log-books were delivered to the intervention group for the purpose of self-monitoring and tracking physical activity.</p>	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

								stress management)	
Paul et al. 2014 United Kingdom	12 weeks	30 (20)	15 (20)	15 (20)	51/53	Persons with MS	Individualized web-based physiotherapy completed twice per week. Online exercise diaries were monitored; participants were telephoned weekly by the physiotherapist and exercise programmes altered remotely by the physiotherapist as required.	Usual care	The Timed 25 Foot Walk test (25-FW)
Sandroff et al. 2014 United States	6 months	76 (25)	37 (27)	39 (23)	49/50	Persons with mild or moderate disability status of MS	SCT-based program for increasing physical activity behavior delivered via the Internet. Website consisted teaching behavioral strategies of self-monitoring and goal-setting and information, instructions and examples using pedometer. Behavioral intervention involved weekly one-on-one coaching sessions via Skype consisting support, goal-setting, goal attainment, strategies and facilitators. During intervention there were 15 Skype coaching	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.		
Bombardier et al 2013 United States	12 weeks	92 (14)	44 (11)	48 (17)	47/50	Persons with MS and major depressive disorder (MDD) or dysthymia	<p>MI-based promotion of physical activity.</p> <p>7 telephone counselling sessions for Weeks 1, 2, 3, 4, 6, 8, and 10 each lasting 30min and final lasting up to 60min.</p> <p>Counselling consisted individual feedback on PA levels and barriers and menu options of stretching, range-of-motion, strength, aerobic, athletic, lifestyle PA exercises.</p>	No treatment (i.e., wait-list)	7-Day Physical Activity Recall (PAR)
Prosperini et al 2013 Italy	24 weeks	36 (31)	Group A 18 (28) Group B 18 (33)	-	Group A 35 Group B 37	Persons with MS	<p>Daily sessions (with the exception of the weekend) of home-based rehabilitation of balance using the Nintendo Wii Balance Board System (WBBS).</p> <p>Phone calls every week to remind patients to complete the logbook and encourage them to perform the training.</p>	No treatment (i.e., wait-list)	The Timed 25 Foot Walk test (25-FW)

Dlugonski et al 2012 United States	12 weeks	45 (13)	22 (18)	23 (9)	49/45	Physically inactive, ambulatory persons with MS	<p>Internet-delivered and SCT-based behavioral intervention that was supplemented with video coaching for increasing and sustaining physical activity.</p> <p>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).</p> <p>Website and pedometer.</p>	No treatment (i.e., wait-list)	<p>the Godin Leisure-Time Exercise Questionnaire (GLTEQ)</p> <p>The Multiple Sclerosis Walking Scale-12 (MSWS-12)</p>
Motl et al 2011 United States	12 weeks	48 (10)	23 (9)	25 (12)	46/46	Persons with MS	<p>Internet intervention based on SCT for favorably increasing PA.</p> <p>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.</p>	No treatment (i.e., wait-list)	the Godin Leisure-Time Exercise Questionnaire (GLTEQ)

							Website and pedometer.		
Bombardier et al 2008 United States	12 weeks	130 (22)	70 (24)	60 (20)	48/45	Persons with MS	MI followed by 5 telephone counseling sessions to facilitate improvement in 1 of 6 health promotion areas: exercise, fatigue management, communication and/or social support, anxiety and/or stress management, and reducing alcohol or other drug use.	No treatment (i.e., wait-list)	Self-selected walking speed (90-meter)

654 Abbreviations: MS = Multiple Sclerosis; RRMS = Relapse-remitting MS, MI = Motivational Interview, SCT = Social Cognitive Theory

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667 Table 2. Methodological quality assessment of included randomized controlled trials (RCTs) (n=10) concerning technology-based distance physical
 668 rehabilitation interventions on physical activity and walking among PwMS.

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

669 Abbreviations: *The methodological quality of the studies was assessed with Furlan method guideline [17] including 13 items (1-13) rated as
 670 positive ("yes), negative ("no") or not fulfilled/unsure ("?"). †Methodological quality of level is based on the Anttila et al [18] criteria.

671 Table 3. Results of outcome variables in selected studies concerning technology-based distance physical rehabilitation interventions on physical
672 activity and walking among PwMS.

Study and year	Experimental			Control			Group differences (Effect /effect size)	Group differences p-value (95%CI)
	<i>n</i>	M1 mean (SD)	M2 mean (SD)	<i>n</i>	M1 mean (SD)	M2 mean (SD)		
Turner et al. 2016	30	0 wk	24 wk	33	0 wk	24 wk		
GLTEQ (total leisure physical activity in MET/min/wk)		16.4 (19.4)	31.1 (17.5)		14.8 (19.4)	15.4 (17.5)	ES = 0.92	<i>p</i> = 0.049
Hoang et al. 2016	23	0 wk	12 wk	21	0 wk	12 wk		
6MW (m)		277.0 (18.0)	279.0 (97.0)		295.0 (19.0)	308.0 (108.0)	ES = 0.16	<i>p</i> = 0.326
Frevel & Mäurer 2015	8	0 wk	10 wk	8	0 wk	10 wk		
DGI (0-24)		13.3 (6.6)	15.3 (6.5)		12.8 (6.4)	15.8 (6.6)	-	<i>p</i> > 0.05
Suh et al. 2015	34	0 wk	6 wk	34	0 wk	6 wk		
GLTEQ (total leisure time in the scale of 1-119)		19.1 (14.8)	27.4 (20.6)		22.7 (19.4)	20.3 (21.9)	<i>F</i> (1, 66) = 5.47* $\eta^2_p = 0.08$	<i>p</i> = 0.02
Paul et al. 2014	15	0 wk	12 wk	14	0 wk	12 wk		
25FW (m/s)		0.8 (0.4)	0.80 (0.4)		0.9 (0.5)	0.9 (0.4)	-	<i>p</i> = 0.170
Sandroff et al. 2014	37	0 wk	24 wk	39	0 wk	24 wk		
6MW (m)		444.7 (157.7)	457.1 (164.9)		429.7 (160.8)	420.0 (158.0)	<i>F</i> = 5,4* $\eta^2_p = 0.07$	<i>p</i> = 0.02
IPAQ (0-117)		17.4 (20.8)	29.7 (20.7)		22.8 (18.8)	19.3 (17.0)	<i>F</i> (1, 69) = 10.2* $\eta^2_p = 0.13$	<i>p</i> = 0.002
Bombardier et al. 2013	44	0 wk	12 wk	48	0 wk	12 wk		
7-Day PAR (kcal/kg/wk)		223.5 (8.2)	228.5 (9.9)		222.6 (6.9)	224.4 (9.2)	-	<i>p</i> = 0.0245
Prosperini et al. 2013 Group A vs. Group B (T0-T1)	17	0 wk	12 wk	17	0 wk	12 wk		
25FW (m/s)		8.5 (2.7)	7.8 (2.8)		9.5 (3.3)	8.7 (3.0)	<i>F</i> = 3.34	<i>p</i> = 0.048
Dlugonski et al. 2012	22	0 wk	12 wk	23	0 wk	12 wk		

MSWS-12 (0-80)		27.4 (22.0)	30.9 (22.1)		24.9 (25.0)	27.0 (25.6)	$F(2,86) = 0.01^*$ $\eta^2_p = 0.00$	$p = 0.99$
GLTEQ (total leisure physical activity in MET/min/wk)		13.6 (11.6)	28.2 (15.6)		16.1 (14.2)	15.4 (13.9)	$F(2, 86) = 8.77^*$ $\eta^2_p = 0.17$	$p = 0.001$
Motl et al. 2011	23	0 wk	12 wk	25	0 wk	12 wk		
GLTEQ (total leisure physical activity in MET/min/wk)		13.8 (15.2)	24.7 (18.8)		11.7 (16.3)	12.4 (14.2)	$F(1,52) = 4.85^*$ $\eta^2_p = 0.09$	$p = 0.03$
Bombardier et al. 2008	70	0 wk	12 wk	60	0 wk	12 wk		
90m walking test (s)		28.0 (8.1)	27.0 (7.2)		26.44 (6.0)	26.3 (6.6)	-	$p = 0.28$

673 Abbreviations: n = study sample; M1 = baseline value; SD = Standard deviation; M2 = post intervention end-point value; M2-M1 = change in the
674 intervention within the group, 95 % CI = 95% Confidential Interval; wk = week; 6MW = 6 meter walking test; m = meter; ES = Effect size as
675 Cohen's *d*; *p* = *p*-value; DGI = Dynamic Gait Index; GLTEQ = the Godin Leisure-Time Exercise Questionnaire, *F* = *F*-statistics; * = condition x
676 time; η^2_p = Effect sizes as partial eta-squared; 25FW = 25 Foot Walk test; m/s = meters/second; IPAQ = International Physical Activity
677 Questionnaire; 7-Day PAR = 7-Day Physical Activity Recall; kcal/kg/wk = total energy expenditure in kilocalories per kilogram per week; T0-
678 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 =
679 metabolic equivalent by minutes per week; s = seconds

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684 Appendix 1. Search strategy.

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

686 Search Strategy:

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- 688 1 Exercise Therapy/ (27416)
- 689 2 exercise therapy.tw. (1900)
- 690 3 Physical Therapy Modalities/ (28897)
- 691 4 physical therapy.tw. (10161)
- 692 5 physiotherapy.tw. (10909)
- 693 6 functional therapy.tw. (295)
- 694 7 Occupational Therapy/ (10498)
- 695 8 Neuropsychology/ (2044)
- 696 9 dietician.tw. (576)
- 697 10 dietitian.tw. (1805)
- 698 11 Dietetics/ (5248)
- 699 12 Occupational Health Services/ (9835)
- 700 13 multidisciplinary therapy.tw. (270)
- 701 14 physical activity.tw. (55661)
- 702 15 Exercise/ (70603)
- 703 16 Exercise Movement Techniques/ (418)
- 704 17 Motor Activity/ (83150)
- 705 18 energy expenditure.tw. (17234)
- 706 19 "Delivery of Health Care"/ (68140)
- 707 20 public health service\$.tw. (5236)
- 708 21 Nursing Diagnosis/ (3863)
- 709 22 Nursing Informatics/ (1017)
- 710 23 Community Health Nursing/ (18608)
- 711 24 Nursing/ (50228)
- 712 25 Public Health Nursing/ (9754)
- 713 26 medical treatment\$.tw. (34601)
- 714 27 Psychiatry/ (32921)
- 715 28 Rehabilitation/ (17036)
- 716 29 Health Promotion/ (55591)
- 717 30 health counse?ling.tw. (556)
- 718 31 directive counse?ling.tw. (128)
- 719 32 coaching.tw. (2284)
- 720 33 health guidance.tw. (273)
- 721 34 "Activities of Daily Living"/ (52849)
- 722 35 adl.tw. (6077)
- 723 36 participation.tw. (91377)
- 724 37 cultural activities.tw. (158)
- 725 38 Leisure Activities/ (6678)
- 726 39 "Physical Education and Training"/ (12075)
- 727 40 Primary Prevention/ (14663)
- 728 41 Secondary Prevention/ (2154)
- 729 42 Tertiary Prevention/ (87)
- 730 43 Sports/ (24021)
- 731 44 active lifestyle.tw. (816)
- 732 45 physical lifestyle.tw. (27)
- 733 46 Physical Fitness/ (22813)
- 734 47 Health Education/ (53678)
- 735 48 Patient Education as Topic/ (72468)
- 736 49 Behavior Therapy/ (24576)
- 737 50 Cognitive Therapy/ (17151)
- 738 51 or/1-50 (863030)
- 739 52 mobile system\$.tw. (153)
- 740 53 Telemedicine/ (12179)
- 741 54 ehealth.tw. (644)
- 742 55 mobile health.tw. (424)
- 743 56 mhealth.tw. (184)

744 57 phealth.tw. (35)
745 58 mobile multimedia.tw. (10)
746 59 mobile communication\$.tw. (402)
747 60 mobile technolog\$.tw. (353)
748 61 Cellular Phone/ (4868)
749 62 cellular phone\$.tw. (551)
750 63 cell phone\$.tw. (1154)
751 64 cellular telephone\$.tw. (335)
752 65 mobile phone\$.tw. (2761)
753 66 mobile telephone\$.tw. (334)
754 67 Mobile Health Units/ (3053)
755 68 Computers, Handheld/ (2492)
756 69 communication technolog\$.tw. (1596)
757 70 technology integration.tw. (67)
758 71 web based communication\$.tw. (58)
759 72 web based organi?ation\$.tw. (0)
760 73 virtual communit\$.tw. (158)
761 74 e-learning environment\$.tw. (26)
762 75 User-Computer Interface/ (30035)
763 76 virtual learning environment\$.tw. (118)
764 77 acceleromet\$.tw. (6771)
765 78 mobile application\$.tw. (164)
766 79 web based interacti\$.tw. (126)
767 80 (mobile adj3 game\$.tw. (22)
768 81 mobile gaming.tw. (3)
769 82 pervasive game\$.tw. (0)
770 83 Geographic Information Systems/ (4803)
771 84 global positioning system\$.tw. (721)
772 85 telerehabilitation.tw. (218)
773 86 tele rehabilitation.tw. (40)
774 87 "web 2.0 intervention\$.tw. (4)
775 88 "web 2.0 application\$.tw. (29)
776 89 smart phone\$.tw. (207)
777 90 Remote Consultation/ (3752)
778 91 sms.tw. (2922)
779 92 Text Messaging/ (666)
780 93 text messag\$.tw. (918)
781 94 digital learning.tw. (21)
782 95 or/52-94 (71324)
783 96 Randomized Controlled Trials as Topic/ (98775)
784 97 Randomized Controlled Trial/ (396594)
785 98 Random Allocation/ (83641)
786 99 Double-Blind Method/ (131663)
787 100 Single-Blind Method/ (20356)
788 101 Clinical Trial/ (499445)
789 102 clinical trial, phase i.pt. (15178)
790 103 clinical trial, phase ii.pt. (24340)
791 104 clinical trial, phase iii.pt. (9914)
792 105 clinical trial, phase iv.pt. (1010)
793 106 controlled clinical trial.pt. (90437)
794 107 randomized controlled trial.pt. (396594)
795 108 multicenter study.pt. (186489)
796 109 clinical trial.pt. (499445)
797 110 exp Clinical Trials as Topic/ (293077)
798 111 or/96-110 (1081783)
799 112 (clinical adj trial\$.tw. (213285)
800 113 ((signl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. (118789)
801 114 Placebos/ (33931)
802 115 placebo\$.tw. (158807)
803 116 randomly allocated.tw. (16408)

804 117 (allocated adj2 random\$.tw. (18923)
805 118 or/112-117 (411822)
806 119 111 or 118 (1209420)
807 120 case report.tw. (189105)
808 121 letter/ (845830)
809 122 Historical Article/ (311099)
810 123 or/120-122 (1334329)
811 124 119 not 123 (1178568)
812 125 51 and 95 and 124 (2193)
813 126 limit 125 to (yr="2000 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)") and (english or
814 finnish or german or swedish) and humans) (1238)
815 127 intervention studies/ (7408)
816 128 intervention\$.tw. (541118)
817 129 127 or 128 (542366)
818 130 126 and 129 (68)
819