

Effects of Physical Activity on Poststroke Cognitive Function

A Meta-Analysis of Randomized Controlled Trials

Lauren E. Oberlin, MS; Aashna M. Waiwood, BS; Toby B. Cumming, PhD;
Anna L. Marsland, PhD; Julie Bernhardt, PhD; Kirk I. Erickson, PhD

Background and Purpose—Despite the social, health, and economic burdens associated with cognitive impairment poststroke, there is considerable uncertainty about the types of interventions that might preserve or restore cognitive abilities. The objective of this systematic review and meta-analysis was to evaluate the effects of physical activity (PA) training on cognitive function poststroke and identify intervention and sample characteristics that may moderate treatment effects.

Methods—Randomized controlled trials examining the association between structured PA training and cognitive performance poststroke were identified using electronic databases EMBASE and MEDLINE. Intervention effects were represented by Hedges' *g* and combined into pooled effect sizes using random- and mixed-effects models. Effect sizes were subjected to moderation analyses using the between-group heterogeneity test.

Results—Fourteen studies met inclusion criteria, representing data from 736 participants. The primary analysis yielded a positive overall effect of PA training on cognitive performance (Hedges' *g* [95% confidence interval]=0.304 [0.14–0.47]). Mixed-effects analyses demonstrated that combined aerobic and strength training programs generated the largest cognitive gains and that improvements in cognitive performance were achieved even in the chronic stroke phase (mean=2.6 years poststroke). Positive moderate treatment effects were found for attention/processing speed measures (Hedges' *g* [confidence interval]=0.37 [0.10–0.63]), while the executive function and working memory domains did not reach significance ($P>0.05$).

Conclusions—We found a significant positive effect of PA training on cognition poststroke with small to moderate treatment effects that are apparent even in the chronic stroke phase. Our findings support the use of PA training as a treatment strategy to promote cognitive recovery in stroke survivors. (*Stroke*. 2017;48:3093-3100. DOI: 10.1161/STROKEAHA.117.017319.)

Key Words: cognition ■ exercise ■ meta-analysis ■ physical activity ■ stroke ■ systematic review

Cognitive impairment occurs in up to 83% of stroke survivors and is associated with reduced quality of life, accelerated functional decline, and increased risk of dependent living and mortality.^{1–3} Given the lack of successful pharmaceutical treatments for cognitive decline and dementia, identifying alternative treatment strategies that mitigate cognitive deficits after stroke is a public health imperative.

Physical activity (PA) holds promise as a widely accessible, low-cost treatment that may preserve or restore cognitive abilities poststroke. Randomized controlled trials suggest that structured PA training improves cognitive function in other populations susceptible to cognitive decline, including neurologically healthy older adults⁴ and those with dementia.⁵ According to data from randomized controlled trials, stroke survivors may also achieve cognitive gains through PA training. One meta-analysis to date has synthesized data from randomized controlled trials to quantitatively evaluate the impact of PA training on cognitive outcomes poststroke.⁶ Results revealed a small but

significant benefit of PA training on a domain-general estimate of global cognition across the 9 included studies. However, since this publication in 2012, the number of PA intervention trials investigating this relationship in stroke survivors has nearly doubled.^{7–13} Furthermore, in contrast to earlier studies^{14–19}, cognition has been the primary outcome of interest in recent trials, and thus, more comprehensive neuropsychological batteries have been used.^{9–12,20} Given the increase in available data, an updated quantitative synthesis incorporating the latest studies and investigating the domain specificity of PA effects on cognition is warranted. In addition to characterizing the effects of PA training on cognition after a stroke, there is also a need to identify the population characteristics and particular training parameters that may generate the largest cognitive gains.

Here, we provide a meta-analytic review of the effects of PA training on cognition in stroke survivors. In addition to determining whether cognition is enhanced with PA training, we also examine whether PA has broad or selective effects on

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From the Department of Psychology (L.E.O., A.M.W., A.L.M., K.I.E.), and Center for the Neural Basis of Cognition (L.E.O., K.I.E.), University of Pittsburgh, PA; and The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia (T.B.C., J.B.).

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Correspondence to Lauren Oberlin, MS, Department of Psychology, University of Pittsburgh, 210 South Bouquet St, 3211 Sennott Square, Pittsburgh, PA 15260. E-mail leo11@pitt.edu

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cognitive function by assessing 3 domains characteristically affected in stroke: executive function, attention and processing speed, and working memory. Finally, for the first time, we evaluate study and sample characteristics that might moderate the efficacy of PA training, including intervention length, the mode of PA, and time from stroke onset to initiation of the intervention. Determining the particular intervention and population characteristics that are most likely to maximize cognitive gains could have important implications for cognitive and functional recovery after a stroke.

Methods

Search Criteria

We conducted a systematic search of the literature using electronic databases MEDLINE and EMBASE for human studies published in English or Chinese in peer-reviewed journals from the earliest available record up to November 14, 2016. The keywords of the search were combined with the following terms: (physical activity OR physiotherapy OR fitness OR aerobic OR exercise OR resistance training) AND (cognitive function OR cognition OR attention OR memory OR executive function OR neuropsychological test) AND (stroke OR cerebrovascular accident OR brain ischemia OR poststroke OR post-stroke). Reference lists from included articles were manually examined to identify other potentially relevant manuscripts.

Study Selection

Studies were selected for inclusion according to the following criteria: (1) recruitment of stroke survivors ≥ 18 years old (ischemic or hemorrhagic stroke, any location, number of strokes), (2) randomized controlled trials that included a clearly defined control condition and an experimental condition that included a component that aimed to increase PA (aerobic exercise, resistance training, or physiotherapy), (3) duration of training >4 weeks to provide sufficient time for benefits to accrue, and (4) included a validated neuropsychological test of cognition with data reported at baseline and postintervention. Because of the limited number of studies, no restrictions were placed on the characteristics of control groups. Studies including subjects with other neurological conditions were excluded unless separate data were provided for the stroke subset. For studies in which training participation was not monitored (ie, home-based), a change in physical function from pre- to postintervention, represented by changes in performance on objective PA or fitness tests, must have been observed. This was to increase the likelihood that adherence to PA recommendations were followed. Two studies included in a prior meta-analysis⁶ did not meet these inclusion criteria and were excluded from the present study (see the [online-only Data Supplement](#)).

Data Collection and Extraction

One member of the research team (L.E. Oberlin) performed the initial search and removed titles and abstracts that were clearly outside of the scope of the review. Two members of the research team (L.E. Oberlin and A.M. Waiwood) independently assessed remaining titles and abstracts and obtained the full text for all abstracts that (1) did not provide enough data for exclusion or (2) appeared potentially eligible for inclusion. L.E. Oberlin and A.M. Waiwood then independently assessed full text articles and selected studies for inclusion based on information within the full text. Any conflicts in article selection were resolved by consensus among the primary raters, and Dr Erickson was consulted if further clarification was required. Data were extracted from the full texts by one member of the review team (L.E. Oberlin) using a standard template and was independently verified by a second member of the research team (A.M. Waiwood). The extracted data included study, participant, and intervention characteristics and cognitive outcome data (for more detail, see the [online-only Data Supplement](#)). To achieve a high standard of reporting, we

followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²¹

Quality Assessment

The methodological quality of included trials was evaluated using the Cochrane risk-of-bias tool.²² The Cochrane collaboration specifies 6 potential sources of bias, including sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and selective outcome reporting. Risk of bias and quality of evidence were independently assessed by 2 members of the research team (L.E. Oberlin and A.M. Waiwood) and was rated per domain based on the published study reports (or, if applicable, based on information from related protocols) as low, unclear (insufficient detail or not reported), or high risk of bias, according to Section 8.5 of the Cochrane handbook.²² This tool is commonly used to assess bias in PA intervention studies and conforms to the PRISMA guidelines.²¹

Calculation of Effect Sizes

Data were entered into an electronic database and analyzed using Comprehensive Meta-Analysis software, version 2.²³ Intervention effects of each study were represented by Hedges' *g*, a bias-adjusted estimate of the standardized mean difference that applies an additional correction for small sample sizes. Hedges' *g* was calculated by subtracting the mean change in performance from baseline in the control group from the experimental group and dividing the difference by the pooled standard deviation of the change from baseline. Using Cohen's criteria, effect sizes were interpreted as small (≤ 0.2), moderate (0.5), or large (≥ 0.8).²⁴ Weighted mean effect size values, along with standard errors and 95% confidence intervals (CI), were estimated using random-effects or mixed-effects models. Random-effects models are considered more conservative than a fixed-effects approach and assume that the true treatment effect may differ across studies because of expected variations in sample, intervention, and assessment characteristics. Mixed-effects models were used for all moderation analyses because this approach assumes that variability between studies may be attributable to fixed and random components, as well as subject-level sampling error.²⁵ Data were analyzed using an intent-to-treat framework, and therefore, sample sizes at baseline, rather than postintervention, were considered in the calculation of effect size. The sign of the effect was calculated so that positive effect sizes were indicative of an improvement in cognitive performance among the experimental groups, relative to controls.

Quantitative Data Synthesis and Analysis

Using a random-effects model, we first assessed whether participation in PA training resulted in significant cognitive gains relative to control samples. For trials reporting multiple cognitive outcomes, effect sizes were calculated separately for each test and averaged together to obtain an overall effect size estimate for each study. This approach ensured that each study was represented by no more than one effect size and allowed us to assess the overall or domain-general effect of PA on cognition poststroke. Heterogeneity was evaluated using the chi-squared (*Q*) and *I*² statistics, according to procedures outlined in the Cochrane handbook.²² Consistent with these guidelines, a *P* value of <0.10 indicated statistically significant heterogeneity between studies.

In addition, several a priori analyses were conducted to investigate whether sample and study characteristics moderate the effects of PA training on cognitive performance. Intervention characteristics included trial duration (<3 months or ≥ 3 months), mode of exercise (aerobic, stretching and toning/physiotherapy, or combined aerobic and stretching and toning), and type of cognitive assessment (objective versus subjective). We also examined whether the time from stroke to initiation of the intervention (≤ 3 months poststroke, >3 months poststroke) affected the magnitude of the effect size. Moderation effects were analyzed in mixed-effects models using the

between-group heterogeneity (I^2) test, which provides an estimate of the between-groups variance. Significance was set at $P < 0.05$.

We also evaluated whether there were domain-specific effects of PA training on cognitive performance. Of the 14 studies included in the meta-analysis, 5 used multiple neuropsychological assessments that could be classified into different cognitive domains. Studies were not represented by a single effect size; instead, an effect size estimate was calculated for all cognitive outcomes within each study. The analysis included tests that could be classified into the following categories: attention and information processing speed, working memory, and executive function (Table I in the [online-only Data Supplement](#)).

Finally, a post hoc subgroup analysis assessed the overall effect of PA training on cognitive performance among studies that screened for and included participants with motor impairments (eg, chronic hemiparesis, including upper or lower limb paralysis, inability to walk without an assistive device [cane, walker]). This allowed us to assess whether stroke survivors with significant motor limitations were able to engage in PA training to the extent needed to generate cognitive gains.

Results

Characteristics of Included Studies

The initial search yielded a total of 956 potentially relevant studies, which was further refined to the retrieval of 143 full-text articles. Of these, 14 randomized controlled trials met all inclusion criteria, representing data from 736 participants. The study selection process, including reasons for exclusion at the full-text level, is summarized in a PRISMA study flow diagram (Figure 1). All included studies had been published between November 2000 and October 2016. The studies varied in size, duration, and intervention type. Study sizes ranged from 14 to 156, and the average age was 62.5 (6.44), with a large range across studies (21–80 years). Mean age

was similar across PA (61.93; SD, 6.62) and control groups (63.11; SD, 6.67). Men comprised $\approx 59\%$ of the sample across all studies. Among the PA training conditions, 5 studies involved stretching and toning/physiotherapy without a primary aerobic component, 3 trials consisted only of aerobic exercise training (eg, treadmill, bicycle training), and 6 studies included a combined PA training program, involving a mixture of both aerobic exercise and stretching and toning activities. Six studies included control groups that received standard medical practice or wait-list control, 2 studies contained an active control condition that did not involve any form of PA (social communication, progressive muscle relaxation), and 6 studies included a control condition that involved PA without a primary aerobic component (stretching, toning, and balance). The effect size estimates stratified by control group can be found in the [online-only Data Supplement](#) (Table II in the [online-only Data Supplement](#)).

The average time since stroke was ≈ 1.9 years (range 1 week to 5.1 years). Regarding stroke characteristics, all but 3 studies^{7,12,20} included subjects with ischemic and hemorrhagic stroke subtypes. Recurrent stroke was an exclusion criterion in 4 studies.^{7,10,15,20} In 7 studies, those with a history of dementia or probable clinically significant cognitive impairment were excluded,^{7,9,13,14,17,18,20} and in 3 studies, individuals with mild cognitive impairment or dementia were included.^{10,12,16} Baseline cognitive status was not reported in 4 studies.^{8,11,15,19} Attrition occurred in 8 studies and ranged from 3% to 18%. Further details regarding study characteristics can be found in the [online-only Data Supplement](#) (Table III in the [online-only Data Supplement](#)).

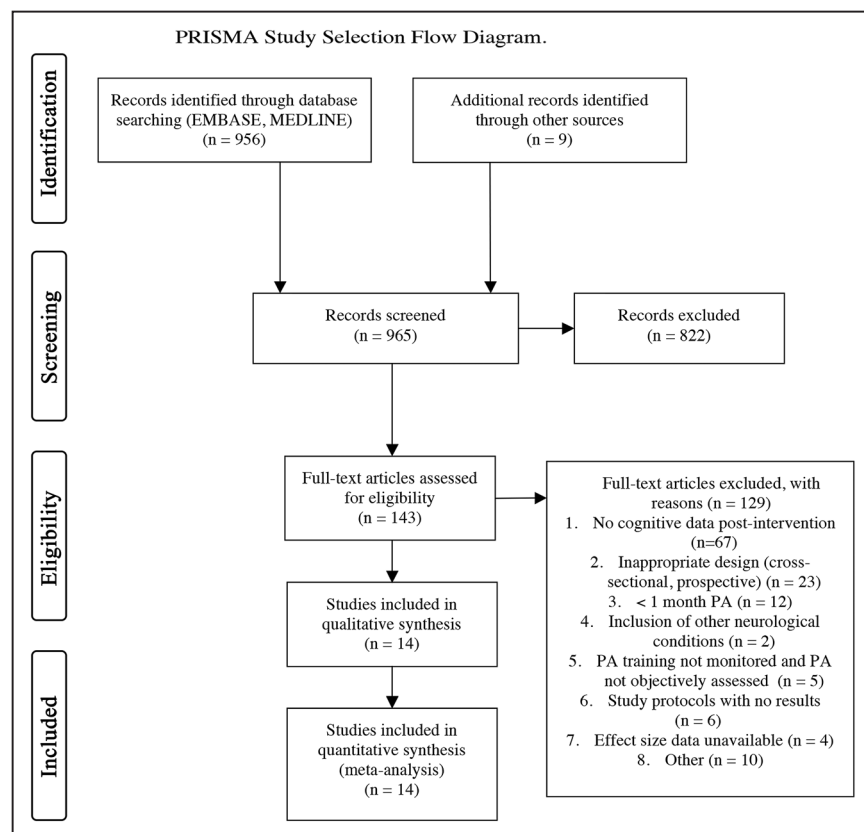


Figure 1. PRISMA study selection flow diagram. PA indicates physical activity; and PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table. Quality of Intervention Trials Included in the Meta-Analysis, Judged According to the Cochrane Risk-of-Bias Tool

References	Sequence Generation	Allocation Concealment	Blinding (Participants)	Blinding (Assessors)	Incomplete Outcome Data
Chen ¹⁹	Low	NR	NR	NR	Low
El-Tamawy et al ⁷	NR	NR	NR	NR	Low
Fang et al ¹⁸	Low	Low	NR	Low	High
Fernandez-Gonzalo et al ⁹	Low	Low	NR	Low	Low
Immink et al ⁸	Low	Low	NR	Low	Low
Liu-Ambrose and Eng ¹⁰	Low	Low	Low*	Low	Low
Mead et al ¹⁷	Low	Low	NR	Low	Low
Moore et al ¹³	Low	NR	Low*	Low	Low
Nilsson et al ¹⁵	Low	Low	Low	Low	High
Ozdemir et al ¹⁶	High	NR	NR	High	Low
Quaney et al ²⁰	Low	NR	Low	Low	Low
Schachten and Jansen ¹¹	Low	NR	NR	NR	Low
Studenski et al ¹⁴	Low	NR	Low*	Low	Low
Tang et al ¹²	Low	Low	Low*	Low	Low

NR indicates not reported.

*Liu-Ambrose and Eng,¹⁰ Moore et al,¹³ Studenski et al,¹⁴ Tang et al¹² were single-blind, but the reviewer judged that outcome measures were not likely to be influenced by lack of blinding.

Quality Assessment

In total, 2 of the 14 studies were judged to be of high methodological quality because they scored positively on all 6 of the quality criteria. The remainder of studies varied in the amount of methodological detail reported, with several quality indices not fully discussed in many trials. Information on allocation concealment was not reported in 50%, and blinding of participants and study assessors was not reported in 57% and 21% of trials, respectively. The randomization method led to a high risk of bias in only 1 of the included studies. Although attrition occurred in 8 studies, only 2 met criteria for high risk of bias in outcome reporting according to the Cochrane guidelines. Details on the methodological quality of each study are presented in the Table. Selective outcome reporting did not seem to occur in any of the included studies and was, therefore, not included in the Table.

Effects of PA Training on Cognition

Using data from 14 randomized controlled trials, we first investigated whether stroke survivors experienced cognitive gains after structured PA training relative to controls. Results revealed a significant and positive effect of PA training on cognitive performance, with a small to moderate mean effect size (Hedges' g [CI] =0.304 [0.14–0.47]; *P*<0.001; Figure 2). The significance remained when any 1 trial was removed from the analysis. The assumption of homogeneity was met for the full sample (*Q* (*df*)=15.36 (13); *P*=0.29).

Moderation Analyses

Intervention and Outcome Characteristics

Mixed-effects analysis revealed that longer intervention trials were not associated with a greater magnitude of cognitive gains relative to brief interventions (*Q_B*=0.82; *P*=0.367).

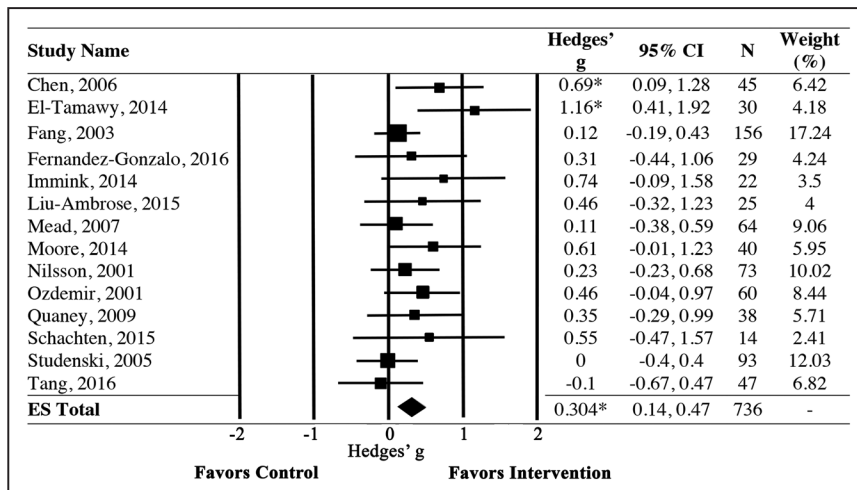


Figure 2. Forest plot showing individual study and pooled effects of physical activity (PA) training on cognitive function. Positive values of Hedges' g reflect improvements in cognitive performance among those in the PA group relative to controls. Random effects model used. **P*<0.05. CI indicates confidence interval; and ES, effect size.

Specifically, PA training lasting <3 months (Hedges' g [CI] =0.39 [0.14–0.63]) and interventions involving at least 3 months of PA training (Hedges' g [CI] =0.23 [0.01–0.46]) were associated with improvements in cognitive performance compared with controls (Figure 3).

To assess the influence of the type of training, studies were stratified based on whether the PA training involved (1) a combination of aerobic and strength/balance training (6 studies; 297 participants), (2) aerobic exercise only (3 studies; 158 participants), or (3) stretching/toning/balance training without an aerobic component (5 studies; 281 participants). Participants in combined strength and aerobic training programs experienced the largest cognitive benefits (Hedges' g [CI] =0.43 [0.09–0.77]), although cognitive gains were also apparent among subjects who underwent a PA regimen involving only strength/balance training (Hedges' g [CI] =0.28 [0.05–0.52]). The effect size for aerobic-only trials was not significantly different from zero (Hedges' g [CI] =0.16 [–0.15 to 0.47]), and the between-groups difference did not reach statistical significance ($Q_B=1.35$; $P=0.508$).

The type of cognitive assessment was significant such that positive, moderate effects were observed among studies that

used objective cognitive assessments (Hedges' g [CI] =0.39 [0.18–0.59]), while the pooled effect size for trials using subjective cognitive measures did not significantly differ from zero (Hedges' g [CI] =0.16 [–0.09 to 0.40]). However, the interaction effect did not reach statistical significance ($Q_B=1.93$; $P=0.165$).

A post hoc subgroup analysis assessed whether cognitive gains were observed specifically in studies that screened for and included subjects with mobility limitations, including chronic hemiparesis and an inability to ambulate without an assistive device. Across the 8 included studies, results revealed a moderate, positive treatment effect in favor of the PA group (Hedges' g [CI] =0.33 [0.10–0.56]; $I^2=0\%$).

Time From Stroke to Intervention

We also investigated whether the magnitude of cognitive gains differed depending on when a PA regimen was introduced in the course of stroke recovery. Among the 4 studies initiated within 3 months poststroke (382 participants), one started PA training within 1 week poststroke,¹⁸ one began, on average, 3 weeks after a stroke,¹⁵ and 2 began ≈6 to 10 weeks poststroke,^{14,16} with a pooled average of ≈35 days poststroke. The time from stroke to intervention among the 10 trials including chronic stroke survivors (>3 months poststroke;

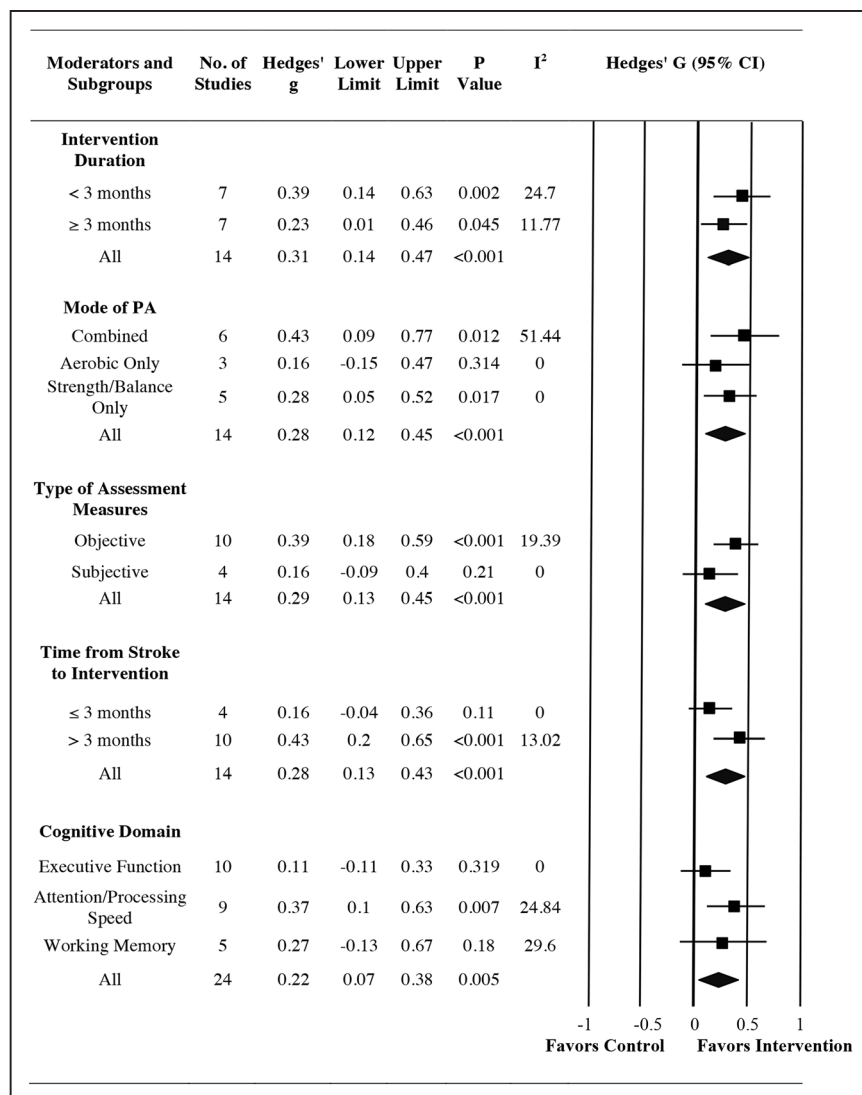


Figure 3. Forest plot showing results from moderation analyses, including pooled effects for subgroups. Positive values of Hedges' g reflect improvements in cognitive performance among those in the physical activity (PA) group relative to controls.

354 participants) ranged from 3 months to nearly 5 years, with an approximate overall average of 2.62 years since stroke onset.

Results indicated that PA training introduced in the chronic stroke phase resulted in significant, moderate, and positive effects on cognition (Hedges' g [CI] =0.43 [0.20–0.65]), while the effect size for trials that initiated PA training within 3 months poststroke was not significantly different from zero (Hedges' g [CI]=0.16 [–0.04 to 0.36]). However, mixed-effects analysis did not demonstrate a significant between-group difference. Effect size estimates were statistically homogenous within subgroups for all moderation analyses, aside from the combined training subgroup ($I^2=51.44$; $P=0.069$). Primary and moderation analyses are represented in Figure 3 and in Table II in the [online-only Data Supplement](#).

Subgroup Analysis: Domain Specificity

We also examined the domain specificity of PA training. This mixed-effects analysis consisted of 24 effect sizes derived from 5 studies that used comprehensive neuropsychological batteries, representing data from 153 participants. Analyses were conducted on 10 measures of executive function, 9 assessments of attention/processing speed, and 5 measures of working memory, yielding a pooled effect size estimate for each domain. The overall effect size across all 3 domains was 0.22 (CI=0.07–0.38; $P=0.005$). Of the 3 domains, effects were only significantly different from zero for attention and processing speed (Hedges' g [CI] =0.37 [0.10–0.63]) and not for executive function (Hedges' g [CI] =0.11 [–0.11 to 0.33]) or working memory (Hedges' g [CI] =0.27 [–0.13 to 0.67]; Figure 4). When subjected to a between-group analysis, results revealed no significant difference in effect size across the 3 domains ($Q_B=2.18$; $P=0.336$).

Discussion

Poststroke cognitive impairment has gained increased attention in recent years because of its high prevalence, persistence, and implications on health, quality of life, and recovery among stroke survivors. Our results indicate that PA training enhances cognitive performance after a stroke. In particular, small to moderate cognitive gains were achieved among stroke survivors who participated in structured PA training relative to controls. These findings suggest that PA may reduce the burden of cognitive deficits in stroke survivors.

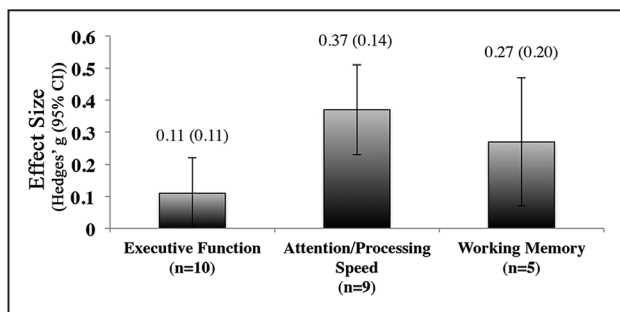


Figure 4. Mean effect (Hedges' g) of physical activity (PA) as a function of cognitive domain, based on a subgroup of included studies. No significant between-group difference ($P>0.05$) was observed. Error bars show standard errors. CI indicates confidence interval; and N, number of data points within each domain.

One prior meta-analysis assessed the effects of PA training on cognitive outcomes in stroke and found a small but significant benefit of structured PA training across the 9 included studies. Seven additional randomized controlled trials were published since this review, which allowed us to expand on the previous meta-analysis in several important ways. Specifically, we were able to impose stricter inclusion criteria, excluding studies with mixed populations and interventions consisting of a single bout of PA. Furthermore, we were able to (1) investigate factors influencing the efficacy of PA interventions and (2) evaluate and characterize the effects of PA training on different cognitive domains. We found that PA training resulted in moderate, positive improvements on measures of attention and processing speed, while the executive function and working memory domains did not reach statistical significance.

The findings should be interpreted with caution, however, as one study was overrepresented in the analysis because of the inclusion of a larger cognitive battery, and the working memory effect size estimate was based on only 5 evaluations. Furthermore, it is possible that exercise may improve performance in cognitive domains that are not well represented in the current literature, including language, visuospatial, and memory abilities, and may also preferentially influence subtypes of executive function. Therefore, this study is an important first step in elucidating domain-specific effects of PA training. However, future randomized controlled PA trials using detailed cognitive assessments of both global and focal (eg, aphasia, hemispatial neglect) cognitive deficits are needed to confirm and expand on these findings.

We evaluated several moderators to characterize the features of PA interventions that may maximize cognitive gains. Mixed-effects analysis demonstrated that PA had favorable effects regardless of program length. Importantly, this suggests that participation in brief structured PA programs is sufficient to induce cognitive gains. However, trials that were longer in duration (≥ 3 months) tended to involve fewer PA sessions per week, suggesting that a frequency-duration trade-off may have also contributed to the lack of effect size differences between the 2 groups.

We also investigated differences in effect size as a function of type of PA training. Our analysis indicated that strength/balance training and interventions that combined both aerobic and strength training protocols achieved significant effects, although the effect size for combined trials was nearly double that of strength/balance training-only studies. Interventions involving only aerobic exercise did not result in significant cognitive gains, although we may have been insufficiently powered to detect an effect in this subgroup ($n=3$ studies). The relative superiority of combined interventions is consistent with findings in healthy aging⁴ and has also been shown to yield the largest improvements in quality of life among stroke survivors.²⁶ Our results suggest that combined aerobic and strength training programs may generate the largest cognitive gains and support the recent guidelines highlighting the need for cardiovascular exercise protocols to be integrated into standard subacute and chronic stroke rehabilitation programs.²⁷

There are likely many cellular and molecular mechanisms by which PA influences cognitive function. Animal models have shown that aerobic exercise after a stroke increases

brain-derived neurotrophic factor, insulin-like growth factor-1, synaptogenesis, and dendritic branching,²⁸ reduces lesion volume in affected regions, and protects perilesional tissue from inflammation and oxidative damage.²⁹ Exercise training soon after stroke also exerts greater effects on many of the aforementioned processes than delayed initiation of PA training.^{28,29} Yet, here, only trials that introduced PA >3 months after stroke onset demonstrated a significant overall treatment effect. The modest effect size among trials introducing PA within 3 months poststroke may, in part, be a consequence of the small number of studies conducted within this time frame (4 studies; 382 participants), as well as the exclusive use of subjective neuropsychological assessments in half of the trials. According to our moderation analyses, subjective measures may not be as sensitive as objective assessments at detecting PA-induced changes in cognitive performance. Furthermore, 2 of the studies did not include an aerobic component, and only 1 trial involved a combined strength and aerobic training program. Determining whether cognitive recovery can be maximized by introducing PA during this critical window of heightened neuroplasticity constitutes an important focus for future work.

We report that PA training is capable of improving cognitive performance in chronic stroke. Participants within this subgroup began PA training, on average, ≈ 2.62 years after stroke, and our results showed positive and moderate treatment effects. These findings emphasize the importance of including both strength and aerobic training in standard postacute rehabilitation programs, including community and home-based services, in the interest of promoting cognitive recovery in chronic stroke.

Safety is an important consideration in this population, particularly given the prevalence of mobility impairments and heightened risk of injury and falls poststroke.²⁷ Unfortunately, many of the studies included here had inadequate reporting regarding adverse events and whether the events were serious, expected (eg, muscle soreness), or related/unrelated to the intervention protocol (see the [online-only Data Supplement](#)). Eight of the included trials, to some degree, reported on adverse events that occurred during intervention sessions and found no incidence of injury or serious adverse events during PA sessions. Improved reporting of adverse events in future studies is critical to determine interventions that minimize the likelihood of adverse events in this population. Notably, when we exclusively analyzed studies that included participants with motor impairments, we found that PA training led to improvements in cognitive performance that were moderate in magnitude. These results indicate that participants with motor deficits were successfully able to engage in PA training to such an extent that cognitive gains were achieved. Thus, determining safe, effective, and feasible methods of PA training and customizing these to the needs and abilities of the patient is an important area for future work.

The included studies varied in several population characteristics that we were unable to systematically study here but may influence the effect of PA training on cognition. These variables include age, baseline fitness levels, stroke characteristics, such as type, severity, and first versus

recurrent stroke, as well as the presence of comorbid cardiovascular and mental health conditions. In addition, we included trials involving cognitively healthy participants, as well as cognitively impaired samples. Favorable effects of PA on cognition have been found in neurologically healthy older adults,⁴ as well as in those with dementia,⁵ so PA training may exert similar cognitive benefits across a range of deficits poststroke. Nonetheless, the extent and specificity of PA-induced cognitive changes may differ depending on the level of cognitive dysfunction. Finally, many of the studies that included participants with motor impairments did not provide details regarding the specificity of these motor deficits, so whether these findings are generalizable to individuals with more severe mobility limitations is not well understood. Overall, further assessment of these population characteristics is needed to determine how these factors may influence treatment effects.

This literature is marked by methodological limitations, with only 2 studies meeting low risk of bias in all 6 quality domains. However, the small number of published interventions and inconsistent reporting across trials precluded our ability to examine whether these factors may have accounted for effect size variance across studies. The nature of the control group (eg, wait-list control, non-PA, or stretching/toning) may also impact the magnitude of effect sizes; however, we were underpowered to assess this in the present study. Similarly, adherence was only sporadically reported and, therefore, could not be taken into consideration. Finally, some moderation analyses included subgroups containing just 4 or 5 effect sizes. While there is no fixed minimum number of data points required for a meta-analysis, fewer data points may limit the precision of pooled estimates as well as the power to detect effects, particularly among studies with small sample sizes.²⁵

Summary

Results from our quantitative synthesis and analysis indicate that PA training enhances cognitive performance after a stroke. We found that cognitive benefits were achieved in as little as 12 weeks, and combined intervention programs yielded the largest cognitive gains. Further, PA training had favorable effects on cognition even when introduced during the chronic stroke phase. These findings also highlight several critical avenues for future work, including identifying the ideal window of time after a stroke and the optimal training parameters needed to maximize cognitive recovery. Included in these trials should be participants with more severe levels of cognitive and physical impairment to enhance generalizability and help inform the development of methods to customize PA to the needs and abilities of these patients.

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Disclosures

None.

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Lauren E. Oberlin, Aashna M. Waiwood, Toby B. Cumming, Anna L. Marsland, Julie Bernhardt and Kirk I. Erickson

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SUPPLEMENTAL MATERIAL

Effects of physical activity on post-stroke cognitive function: a meta-analysis of randomized controlled trials

Lauren E. Oberlin, M.S.,^{1,2} Aashna Waiwood,¹ Toby B. Cumming, Ph.D.,³ Anna L.

Marsland, Ph.D.,¹ Julie Bernhardt, Ph.D.,³ Kirk I. Erickson, Ph.D.^{1,2}

1. Department of Psychology, University of Pittsburgh
2. Center for the Neural Basis of Cognition, University of Pittsburgh
3. The Florey Institute of Neuroscience and Mental Health, University of Melbourne

Correspondence should be addressed to Lauren E. Oberlin, Department of Psychology,
University of Pittsburgh, 210 S. Bouquet St., 3211 Sennott Square, Pittsburgh, PA 15260.

Phone: (412) 624-4557 Email: leo11@pitt.edu

1.0 SUPPLEMENTAL METHODS

1.1 Study Selection

Two studies included in a prior meta-analysis¹ did not meet our inclusion criteria and were excluded from the present study. Specifically, Ploughman et al. (2008)² involved only one 20-minute bout of PA and Bateman et al., (2001)³ included a combination of subjects who had suffered a single-incident brain injury of any cause (i.e., stroke, TBI, other). Further, several single-group non-randomized trials were excluded from the present meta-analysis.^{4,7} Thus, the exclusion of these papers makes our approach more conservative because the absence of control conditions in these trials makes it difficult to account for confounding factors such as practice effects,⁸ and may also overestimate treatment effects.⁹

1.2 Data Collection and Extraction

Data extracted included: study characteristics (design, year, inclusion criteria, cohort size), participant characteristics (age, gender, time since stroke, stroke type/location, baseline physical and cognitive status), intervention characteristics (components of control and PA conditions, including the length, mode, and intensity of PA, session duration, frequency, adherence, attrition, adverse outcomes), outcome measures including physical activity data (fitness, balance, strength, walking speed), and cognitive data (screening criteria, cognitive measures, frequency of administration) and data on study quality. Study outcomes for which data were extracted include self-report estimates of cognitive function (e.g., the memory domain of the Stroke Impact Scale) and objective measures of cognitive abilities (e.g., Mini-Mental State Examination, Wisconsin Card Sorting Test, etc.). Authors of two trials that included median and range values of cognitive outcomes in the published reports were contacted and provided mean and standard deviation values.

1.3 Calculation of Effect Sizes

Data were entered into an electronic database and analyzed using Comprehensive Meta-Analysis (CMA) software, version 2. The software employs the same computational algorithms used by the Cochrane collaborators to weight studies by inverse variance methods.¹⁰ Only 6 trials had longitudinal follow-up after the intervention, therefore, for the purposes of consistency, effect size estimates were derived from cognitive outcome data collected immediately following the intervention.

1.4 Quantitative Data Synthesis and Analysis

We evaluated whether there were domain-specific effects of PA training on neurocognitive performance in a subgroup of studies that employed multiple neuropsychological assessments. The analysis included tests that could be classified into the following categories: attention and information processing speed, working memory, and executive function. Neuropsychological tests were categorized according to cognitive domains described by Lezak (2004).¹¹ Tests that were not included in this neuropsychological compendium were categorized based on 1) particular factor loadings from previous studies or 2) similar classification across a preponderance of studies. Two studies included outcome variables from neuropsychological tests that were not included

in the analysis, as they did not assess the domains specified above.^{12,13}

2.0 SUPPLEMENTAL RESULTS

2.1 Characteristics of included studies

Included trials were performed in nine countries, including four in North America, two in the United Kingdom and two in China, and one in Egypt, Germany, Turkey, Sweden, Spain, and Australia. The pool of 736 participants (363 in PA training conditions) was drawn from inpatient care facilities, medical and stroke centers, multi-site stroke databases, and community advertising. All trials provided exclusionary criteria, indicating that participants were stroke survivors aged 18 or over, frequently without other neurological or psychiatric conditions. The sample size within exercise or control conditions ranged from 7 to 78. Hemiparesis was an inclusionary criterion in three studies¹⁴⁻¹⁶ and an additional five studies included individuals that required an assistive device while walking due to motor impairments.^{12,13,17-19} The ability to walk independently was a requirement for inclusion in two studies^{20,21} and the absence of limb impairment was a requirement in one study.²² Baseline motor status was not reported in three studies.²³⁻²⁵

2.2 Intervention characteristics

Most interventions were conducted 2-3 times per week, and the average trial duration was 12.39 (5.91) weeks. Of the 14 included studies, six studies compared an experimental group with a control group that received standard medical practice or waitlist control.^{12,16,18,21,22,24} However, physical therapy and occupational therapy were considered part of standard care in a subset of participants in one trial, and therefore even participants within the control group may have received some form of PA training²¹. A majority of these studies did not explicitly state whether participants in control groups received physical or occupational therapy as part of standard care.^{12,16,18,22} Two studies contained an active control condition that did not involve any form of PA (social communication, progressive muscle relaxation).^{13,20} Finally, 6 studies included a control condition that involved PA without a primary aerobic component (stretching, toning, and balance).^{14,15,17,19,23,25} However, in 3 studies the stretching/toning conditions were home-based, and thus training participation was not directly monitored. These trials employed daily diaries and/or regular phone check-ins to assess adherence.^{14,17,23} Pooled effect size estimates stratified by type of control group are included in Table III. Among the PA training conditions, 5 studies involved stretching and toning/physiotherapy without a primary aerobic component, 3 trials consisted only of aerobic exercise training (e.g., treadmill, bicycle training), and 6 studies included a combined PA training program, involving a mixture of both aerobic exercise and stretching and toning activities. Four studies incorporated another component along with PA training into experimental conditions, including ADL training, occupational therapy, and social activities.^{13,18,23,24} Six studies included a follow-up assessment after the conclusion of the intervention, which ranged from 3 to 10 months post-intervention.^{14,15,18,20-22} Adherence rates were reported in 7 studies, and ranged from 80% to 100% within the exercise conditions, with an average of 89% adherence across all 7 studies. Cardiorespiratory fitness was assessed in 4

studies,^{14,17,19,20} 3 of which found an increase in fitness levels following the PA intervention.^{14,17,20}

2.2.1. Adverse Events

Eight studies reported on adverse events, although in most studies the criteria and methods used to define and assess adverse events were unclear and the information provided was often sparse. Four of the 8 studies reported no incidence of adverse events in PA conditions.^{12,16-18} No serious adverse events were reported in any study aside from one,¹⁵ which noted that two participants died over the course of the intervention. However, it was unclear if these participants were assigned to the exercise or control conditions, and whether these incidents were at all related to the intervention. One study found no differences in medical complications between PA and control groups aside from reported shoulder problems.²³ Mead et al.,²⁰ reported participant falls outside of the intervention sessions in both PA and relaxation control groups. Two studies reported falls that occurred during intervention sessions, although in both cases these falls took place during control sessions (relaxation condition and low-intensity PA condition).^{19,20} Given this lack of adverse event reporting in these studies it is impossible to determine the prevalence or incidence of adverse events resulting from an exercise intervention in individuals with stroke.

2.3 Cognitive Measures

Nine studies employed a single, global measure of cognitive function, specifically the Mini-Mental Status Exam (MMSE), the Functional Independence Measure (FIM), Addenbrooke's Cognitive Examination-Revised (ACE-R), the Montreal Cognitive Assessment (MOCA), or the Stroke Impact Scale (SIS). Five of these studies used objective measures, and four used subjective cognitive assessments (e.g., SIS, FIM). Finally, five studies administered multiple neuropsychological tests that allowed for an assessment across multiple domains.

3.0 SUPPLEMENTAL TABLES

Table I. Classification of neurocognitive tests by domain.

Neurocognitive Domain		
Executive Function (# studies)	Attention/Information Processing Speed (# studies)	Working Memory (# studies)
Trail Making Test, Part B (4)	Serial Repetition Task (repeated, random) (1)	Digit Span Backward (3)
Stroop Color-Word Interference (3)	Walking While Talking Test (1)	Symbol Span Backward (1)
Go/No-go (1)	Symbol Span Forward (1)	Block Tapping Test (1)
FAS (1)	Digit Span Forward (2)	
Wisconsin Card Sort Test (1)	Trail Making Test, Part A (1)	
	Stroop Color/Word Reading (1)	
	Continuous Performance Test (1)	

Values in parentheses reflect the number of studies that employed each cognitive test.

Table II. Meta-analytic results from all random and mixed-effects models.

Model	N	Hedge's g	95%CI	P-value	Heterogeneity (Q)	I ²	Q P-value	Q _B	Q _B P-value
Overall	14	0.304**	(0.14; 0.47)	< .001	15.36	15.36	0.29	-	-
Exercise Mode	14							1.35	0.508
Combined	6	0.43*	(0.09; 0.77)	0.012	10.23	51.44	0.069		
Aerobic	3	0.16	(-0.15; 0.47)	0.314	1.21	0	0.546		
Stretching/Toning	5	0.28*	(0.05; 0.52)	0.017	2.97	0	0.563		
Cognitive assessment	14							1.93	0.165
Objective Outcomes	10	0.39**	(0.18; 0.59)	< .001	11.17	19.39	0.27		
Subjective Outcomes	4	0.16	(-0.09; 0.40)	0.21	2.61	0	0.46		
Length of Intervention	14							0.82	0.367
< 3 months	7	0.39**	(0.14; 0.63)	0.002	7.97	24.7	0.24		
≥ 3 months	7	0.23*	(0.01; 0.46)	0.045	6.8	11.77	0.34		
Time from stroke to intervention	14							2.89	0.089
≤ 3 months	4	0.16	(-0.04; 0.36)	0.11	2.11	0	0.549		
> 3 months	10	0.43**	(0.20; 0.65)	< .001	10.35	13.02	0.323		
Motor Limitations	8	0.33	(0.10; 0.56)	0.006	4.36	0	0.74	-	-
Cognitive Domains	24							2.18	0.336
Executive Function	10	0.11	(-0.11; 0.33)	0.319	4.87	0	0.85		
Processing Speed	9	0.37**	(0.10; 0.63)	0.007	10.64	24.84	0.22		
Working Memory	5	0.27	(-0.13; 0.67)	0.18	5.68	29.6	0.22		
Type of Control Condition	14								
Standard Care	6	0.27	(0.02; 0.53)	0.036					
Non-PA Controls	2	0.21	(-0.30; 0.71)	0.42					
PA component	6	0.39	(0.13; 0.66)	0.004					

• p < 0.05; **p < 0.01 CI = Confidence interval; PA = physical activity

Table III. Characteristics of included studies.

Study (Year)	N	Age (Mean)	Time from Stroke to Int.	Length of Intervention	Type of PA	PA Session Duration	PA Frequency	Control Type	Cognitive Outcomes
Chen, 2006	Ex: 25; Con: 20	Ex: 66.2; Con: 67.3	<6 mon (13); 6-12 mon (8); >12 mon (4)	12 weeks	Combined	-	2x week	Standard Care	MMSE
El-Tamawy, 2014	Ex: 15; Con: 15	Ex: 48.4; Con: 49.7	3-18 months	8 weeks	Combined	75 min/day	3x week	Stretching, gait, strength training	ACE-R
Fang, 2003	Ex: 78; Con: 78	Ex: 65.6; Con: 61.8	Within first week	4 weeks	Physiotherapy	45 min/day	5x week	Routine Therapy	MMSE
Fernandez-Gonzalo, 2016	Ex: 16; Con: 16	Ex: 61.2; Con: 65.7	Mean years: 3.91	12 weeks	Resistance Training	4 sets of 7 repetitions	2x week	Standard Care	CPT, Digit Span, FAS, RAVLT, Spatial Span, Stroop, Trail Making Test, WWTT
Immink, 2014	Ex: 11; Con: 11	Ex: 56.1; Con: 63.2	Mean months: 52.5	10 weeks	Yoga	40-90 min	90 min/1x week supervised, 40 min/day home-based	Waitlist Control	SIS – memory domain
Liu-Ambrose, 2015	Ex: 11; Con: 14	Ex: 62.9; Con: 66.9	Mean years: Ex: 2.4; Con: 2.9	24 weeks	Combined	60 min/day	2x week	Standard Care	Stroop, Trail Making Test, Digit Span
Mead, 2007	Ex:32; Con: 34	Median age: Ex: 72; Con: 71.7	Median days: Ex: 178; Con:162	12 weeks	Combined	75 min/day	3x week	PMR	FIM memory, problem solving questions
Moore, 2014	Ex: 20; Con: 20	Ex: 68; Con: 70	Mean months: Ex: 21; Con: 16	19 weeks	Combined	45-60 min/day	3x week	Stretching	ACE-R
Nilsson, 2001	Ex: 36; Con: 37	Median age: Ex: 54; Con: 56	Median days: Ex: 22; Con: 17	9.5 weeks	Aerobic treadmill walking	30 min/day	5x week	Track walking with physiotherapist	FIM-Cognitive
Ozdemir, 2001	Ex: 30; Con: 30	Ex: 59.1; Con: 61.8	Mean days: Ex: 41; Con: 36	9 weeks	Stretching, toning, neuromuscular facilitation exercises	120 min/day	5x week	Conventional PA at home	MMSE
Quaney, 2009	Ex: 19; Con: 19	Ex: 64.1; Con: 59	Mean years: Ex: 4.6; Con: 5.1	8 weeks	Aerobic	45 min/day	3x week	Home-based stretching exercises	WCST, Trail Making Test, Serial Reaction Time Test, Stroop,
Schachten, 2015	Ex: 7; Con: 7	Ex: 55.1; Con: 53.1	Mean years: Ex: 3.43; Con: 3.86	10 weeks	Golf training (coordinative exercises)	60 min/day	2x week	Social Communication	Block Tapping Test, Go/No-go, Mental Rotation Test
Studenski, 2005	Ex: 44; Con: 49	Ex: 68.5; Con: 70.4	Mean Days: Ex: 77.5; Con: 74.1	12 weeks	Combined	NR	3x week	Standard Care (some received PT/OT as part of standard care)	FIM-Cognitive
Tang, 2016	Ex: 22; Con: 25	Ex: 65.9; Con: 66.9	Mean years: Ex: 3.5; Con: 2.3	24 weeks	High intensity aerobic PA (40 – 80% HR reserve)	60 min/day	3x week	Stretching, balance, strength training (< 40% HR reserve)	Digit Span Forward, Digit Span Backward, Stroop Color-Word Interference Test, Trail Making Test Part B

WWTT = Walking While Talking Test; RAVLT = Rey Auditory Verbal Learning Test; CPT = Conners Continuous Performance Test-II; PMR = Progressive Muscle Relaxation ACE-R = Addenbrooke’s Cognitive Examination-Revised; FIM = Functional Independence Measure; HR= Heart Rate; MMSE = Mini-Mental State Examination; OT = Occupational Therapy; PT = Physical Therapy; SIS = Stroke Impact Scale

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