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REVIEW

The effect of physical activity on cognitive function after stroke: a systematic review

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ABSTRACT

Background: Research in both humans and animals indicates that physical activity can enhance cognitive activity, but whether this is true in patients with stroke is largely unknown. We aimed to evaluate the relationship between increased physical activity after stroke and cognitive performance.

Methods: A systematic review was conducted of MEDLINE, EMBASE, PsycINFO and other electronic databases. All randomized controlled trials and controlled clinical studies that evaluated the effect of physical activity or exercise on cognitive function in stroke were included. Study quality was assessed using four criteria concerning sources of bias (use of randomization, allocation concealment, blinding of outcome assessment, whether all patients were accounted for in outcome data).

Results: The literature search (first run in 2008, updated in 2011) yielded 12 studies that satisfied inclusion criteria. Exercise interventions were heterogeneous; some studies compared different intensities of movement rehabilitation, others included a specific exercise program. Cognitive function was rarely the primary outcome measure, and cognitive assessment tools used were generally suboptimal. Nine studies had sufficient data to be included in a meta-analysis, which indicated a significant benefit of intervention over control (SMD = 0.20, 95% CI: 0.04–0.36; z = 2.43, p = 0.015). Studies that met all four quality criteria reported smaller treatment benefit than studies that did not.

Conclusions: There is some evidence that increased physical activity after stroke enhances cognitive performance. The pool of studies identified, however, was small and methodological shortcomings were widespread.

Key words: cerebrovascular disease, exercise, physical therapy, neuropsychology, cognition

Introduction

The healthy human brain is capable of carrying out complex mental tasks that rely on processes such as perception, attention, executive function, memory and language. When the brain is affected by stroke, these cognitive processes are often impaired. Approximately 5.5 million people worldwide die each year from either the primary insult or secondary complications of stroke (WHO, 2003), and many more are left with chronic disability. Cognitive deficits make a major contribution to stroke-related disability, with approximately two-thirds of stroke survivors experiencing cognitive impairments (Jin *et al.*, 2006). Not only is cognitive impairment a major problem in itself but it is also associated with other negative outcomes including death and disability (Patel *et al.*, 2002), greater rates of institutionalization (Pasquini *et al.*, 2007) and poorer quality of life (Hochstenbach *et al.*, 2001). While a range of treatments have been proposed to help reduce cognitive impairment after stroke, these have so far been poorly tested and have not yielded definitive findings (Lincoln *et al.*, 2000; das Nair and Lincoln, 2007).

Approaches to cognitive rehabilitation can be classified broadly into two groups: (a) *restorative*, where the aim is to reinforce, strengthen or re-establish previously learned cognitions or behavior, and (b) *compensatory*, where new patterns of cognitive activity are established (Cicerone *et al.*,

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2000). Compensatory approaches have had some success in helping people cope with daily challenges (e.g. list-writing for a dementia patient), but do not have a direct bearing on acquired cognitive deficits (i.e. the underlying memory impairment remains). Only limited evidence exists to support the efficacy of restorative interventions for cognitive impairments (Cicerone *et al.*, 2005). One approach that may prove to be restorative is to increase physical activity levels. Longitudinal epidemiological data indicate that exercise reduces the risk of cognitive decline in healthy older people (Fratiglioni *et al.*, 2004), and meta-analyses of intervention studies demonstrate a link between physical activity and cognition in older people (Colcombe and Kramer, 2003; Angevaren *et al.*, 2008). Physical activity can also be beneficial for cognitive performance in older adults with cognitive impairment (Heyn *et al.*, 2004), in those at risk of Alzheimer's disease (Lautenschlager *et al.*, 2008) and in patients with multiple sclerosis (Prakash *et al.*, 2007). Findings from animal studies provide further support: physical activity can reduce the risk of cognitive decline in mice (Cotman and Engesser-Cesar, 2002) and rats (Griesbach *et al.*, 2004).

Despite the recent research interest in this area (van Uffelen *et al.*, 2008; Devine and Zafonte, 2009; Smith *et al.*, 2010), no review to date has focused on patients with stroke and the effect of physical activity on cognitive function in this population. Exercise (e.g. walking, cycling) represents a simple, feasible, and potentially broadly applicable intervention for people with stroke. Thus, the aim of this systematic review was to determine whether increasing physical activity after stroke leads to improvements in cognitive performance. For the purposes of this review, we use the terms "exercise" and "physical activity" interchangeably and define them broadly as "any bodily movement produced by skeletal muscles that substantially increases energy expenditure over resting expenditure level" (Bouchard *et al.*, 2007).

Methods

Inclusion criteria

Study designs

All randomized controlled trials (RCTs) and controlled clinical trials that evaluated the effects of a physical activity or exercise-based intervention were included in the review. Other study designs (e.g. cohort studies, observational studies) were captured but not included in the analysis. We did not restrict the search to studies reported in English, and used translation where possible.

Types of participants

The target population was human adults who had suffered stroke. Studies of patients with traumatic brain injury (TBI), slow-onset progressive neurological syndromes (e.g. Parkinson's disease, multiple sclerosis), seizure-related conditions (e.g. epilepsy) or infections (e.g. meningitis) were excluded. Studies that investigated patients with acquired brain injury of various etiologies were included if stroke patients made up more than one-third of the sample.

Types of interventions

Studies that contained any intervention that aimed to increase levels of physical activity or exercise (e.g. walking, therapeutic exercise, participation in sport, active leisure pursuits) were included. Any form of intervention was considered, irrespective of type, frequency, duration or the person delivering the intervention. The experimental group could be compared to either a control condition (normal practice or no intervention) or a different intervention.

Types of outcome measures

The primary outcome measure was change in cognitive performance from pre-intervention to post-intervention. Tests of cognitive function could include assessments in the domains of visuospatial ability, attention, executive function, memory, language, arithmetic or abstract reasoning. Assessments might include a global measure of cognitive function (e.g. Mini-Mental State Examination), individual tests (e.g. Trail-Making Test) or a neuropsychological test battery (a combination of individual cognitive tests). Secondary outcome measures were depression and anxiety.

Search strategy

The initial literature search was carried out in 2008 and included studies of TBI as well as stroke, in an attempt to capture all the information relevant to these types of acquired brain injury. The following electronic bibliographic databases were searched: MEDLINE (1950–2008), EMBASE (1980–2008), CINAHL (1982–2008), SPORTDiscus (1985–2008), PsycINFO (1967–2008), AMED (1985–2008) and the Cochrane Library (up to 2008). The three key search terms – physical activity, cognitive function, stroke/TBI – and their synonyms were combined to identify relevant articles. The initial MEDLINE search strategy was modified to suit other databases (e.g. "exp Motor Activity" became "motor activit*.mp"). The full list of search terms is available from the authors. Once the yield was narrowed down to relevant included studies only, citation tracking on these studies was

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performed using the following electronic databases: the Science Citation Index Expanded (1975–2009), Social Sciences Citation Index (1975–2009) and the Arts and Humanities Citation Index (1975–2009). A search of the reference lists of the relevant included studies was also undertaken.

The initial search yield was considered to be insufficient, and closer inspection of the included studies led us to question the appropriateness of combining the two diverse populations of stroke and TBI. A subsequent search was undertaken in early 2011 using the same search strategy, but this time TBI studies were excluded.

Study selection

All studies identified using the methods outlined above were considered for inclusion in the review. A reviewer (KT) read the titles of each reference and eliminated any studies that were clearly irrelevant. Abstracts for the remaining studies were obtained. Further elimination occurred and full articles were obtained for any potentially relevant studies. Based on the criteria set out above (types of studies, types of participants, types of interventions, outcome measures), a reviewer (TC) classified these references as relevant, possibly relevant or not relevant. Where necessary, authors of studies that were possibly relevant were contacted and asked to provide additional information or data. Studies classified as possibly relevant were included or excluded on the basis of a consensus meeting with all authors.

Assessment of study quality

Use of randomization, allocation concealment, blinding of outcome assessment, and whether all the randomized patients were accounted for in the outcome data were examined for each study. These four quality criteria were selected as they are important sources of bias in research trials (Higgins and Green, 2008).

Data extraction and analysis

Relevant data were extracted from the included studies using a standard data recording form. If cognitive outcomes were reported from more than one time point post-intervention, results from the earliest time point were used (enabling us to maximize the available data in cases where there were losses to follow-up over time). In some cases this was immediately post-intervention, in other cases it was up to 12 months post-intervention. For both intervention and control groups, the change score was defined as the difference between the pre-intervention mean and the post-intervention mean. If the review yielded sufficient information, we planned to divide cognitive outcomes into separate domains (e.g. executive function, memory, visuospatial ability). If there were not enough studies that incorporated multiple cognitive outcomes, we would calculate standardized values for each cognitive outcome and then average across these to get a single change score. Baseline standard deviations for both groups were used together with the change scores as input for the meta-analysis (Morris and DeShon, 2002). Data from studies that contained sufficient information on means and variance were pooled and analyzed using the DerSimonian and Laird random-effect model in STATA version 11.0 (Stata Corp, College Station, TX, USA). The resulting meta-analysis yielded an overall standardized mean difference (SMD). Heterogeneity among studies was tested using the χ^2 test, variation in SMD attributable to heterogeneity was estimated using the I^2 index, and publication bias was assessed using both Begg's test and Egger's test (Egger *et al.*, 2001).

Results

The initial 2008 search yielded 1730 studies, of which 12 satisfied review inclusion criteria (7 stroke, 4 TBI, 1 mixed brain injury). The heterogeneity of these populations precluded a meaningful meta-analysis, and a subsequent search was conducted in 2011 that excluded TBI studies. This search yielded 328 additional studies, of which four satisfied inclusion criteria. Thus, the final yield was 12 studies (7 stroke, 1 mixed brain injury from initial search; 4 stroke from subsequent search). Several studies were relevant to the research question but were excluded as they did not test interventions, reporting associations only (Heinemann *et al.*, 1995; Horn *et al.*, 2005); were retrospective in design (Keith *et al.*, 1995); did not include a control group (Pyun *et al.*, 2009; Rand *et al.*, 2010); were still ongoing (MacKay-Lyons *et al.*, 2010); or did not report the cognitive aspect of the Functional Independence Measure (FIM) separately, and this information could not be ascertained from the authors directly (Katz-Leurer *et al.*, 2003; Wilson *et al.*, 2006). Details of the 12 included studies (Ruff *et al.*, 1999; Wolfe *et al.*, 2000; Bateman *et al.*, 2001; Nilsson *et al.*, 2001; Özdemir *et al.*, 2001; Fang *et al.*, 2003; Studenski *et al.*, 2005; Chen, 2006; Mead *et al.*, 2007; Pyoria *et al.*, 2007; Ploughman *et al.*, 2008; Quaney *et al.*, 2009) are presented in Table 1. All but one of these studies included only stroke patients in their sample; Bateman *et al.* (2001) included 157 patients with mixed brain injury (70 stroke, 44 TBI, 15 subarachnoid haemorrhage, 12 space occupying lesion, 16 other).

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Table 1. Details of included studies

STUDY	SAMPLE SIZE	MEAN AGE	TIME FROM STROKE TO INTERVENTION	LENGTH OF INTER-VENTION	COGNITIVE ASSESSMENT	PRIMARY RESULT
Bateman *et al.* (2001)	157 (78 E, 79 C)	41.7 (E), 44.7 (C)	Mean weeks: 22.2 (E), 25.5 (C)	12 weeks	FIM-cog	Week 12: E mean 27.5 (SD 6.6), C mean 26.6 (SD 6.4); n.s.
Chen (2006)	45 (25 E, 20 C)	66.2 (E), 67.3 (C)	<6 months: n = 13, 6–12 months: n = 8, >12 months: n = 4	3 months	MMSE	3 months: E mean 26.6 (SD 4.6), C mean 22.9 (SD 6.7); t = 2.1, p<0.05
Fang *et al.* (2003)	156 (78 E, 78 C)	65.5 (E), 61.8 (C)	Within first week	4 weeks	MMSE	30 days: E mean 23.4 (SD 7.7), C mean 21.9 (SD 9.8); n.s.
Mead *et al.* (2007)	66 (32 E, 34 C)	72.0 (E), 71.7 (C)	Median days: 178 (E), 162 (C)	12 weeks	FIM memory, problem solving questions	Post-intervention: E mean 12.9 (SD 1.2), C mean 13.2 (SD 1.0); n.s.
Nilsson *et al.* (2001)	73 (36 E, 37 C)	Median: 54 (E), 56 (C)	Median days: 22 (E), 17 (C)	Median days: 68 (E), 66 (C)	FIM-cog	10 months: E mean 32.0 (SD 5.0), C mean 31.5 (SD 6.6); n.s.
Özdemir *et al.* (2001)	60 (30 E, 30 C)	59.1 (E), 61.8 (C)	Mean days: 41 (E), 36 (C)	Mean days: 64 (E), 64 (C)	MMSE	Pre-post change score: E mean 4.8 (SD 5.0), C mean 2.0 (SD 2.1); 95% CI 1.05–5.34, p = 0.024
Ploughman *et al.* (2008)	21 (cross-over AB study design)	61.4	Mean months: 20.1	20 minutes	Trail-making A and B, Symbol-digit test, PASAT	Pre-post change: No group difference on any cognitive outcome (p = 0.36–0.75)
Pyoria *et al.* (2007)†	80 (40 E, 40 C)	72 (E), 72 (C)	Within first week	12 months	Memory, language, visuospatial function, visual inattention	Baseline-12m change: Improvement in all 4 domains in E group (all p<0.02) but not in C group (all p>0.10); between group differences on memory (p = 0.001) and language (p = 0.078)
Quaney *et al.* (2009)	38 (19 E, 19C)	64.1 (E), 59.0 (C)	Mean years: 4.6 (E), 5.1 (C)	8 weeks	WCST, Stroop task, Trail-making (B-A), SRTT repeated, SRTT random	Post-intervention: group difference on SRTT repeated (p = 0.024), but not on WCST (p = 0.14), Stroop (p = 0.13), Trails (p = 0.28), SRTT random (p = 0.20)
Ruff *et al.* (1999)†	113 (56 E, 57 C)	71.0 (E), 79.0 (C)	Not specified (inpatient rehabilitation)	Mean days: 20	FIM problem solving question	Post-intervention: E mean 3.07, C mean 3.00; n.s.
Studenski *et al.* (2005)	100 (44 E, 49 C, 7 losses to follow-up)	68.5 (E), 70.4 (C)	Mean days: 77.5 (E), 74.1 (C)	3 months	FIM-cog, 2 SIS domains (memory and thinking, communication)	Post-intervention FIM-cog: E mean 33.7 (SD 1.1), C mean 33.6 (SD 1.2); difference −0.05, 95% CI −0.44–0.34, SMD −0.04, n.s.
Wolfe *et al.* (2000)†	43 (23 E, 20 C)	72 (E), 76 (C)	Not specified (patients not admitted to hospital)	Maximum 3 months	MMSE	12 months: E median 29 (range 22–30), C median 27.5 (range 15–30); p = 0.27

E = experimental group; C = control group; n.s. = not significant; FIM-cog = Functional Independence Measure cognitive subsection; MMSE = Mini-Mental State Examination; SIS = Stroke Impact Scale; WCST = Wisconsin Card Sorting Test; SRTT = Serial Reaction Timed Task; PASAT = Paced Auditory Serial Addition Test.
*Lower scores on FIM-cog; MMSE indicate greater impairment.
†Indicates study not included in meta-analysis.

Interventions

All the interventions used had some impact on level of exercise or physical activity and can be divided into two groups (Table 2). Six studies (Ruff *et al.*, 1999; Wolfe *et al.*, 2000; Özdemir *et al.*, 2001; Fang *et al.*, 2003; Chen, 2006; Pyoria *et al.*, 2007) compared different levels and intensities of movement rehabilitation; some provided specialized community-based rehabilitation to the intervention group and standard care to the control group (Wolfe *et al.*, 2000; Chen, 2006), whereas another study compared 7-days-a-week rehabilitation to 6-days-a-week rehabilitation (Ruff *et al.*, 1999). The second group consisted of six studies (Bateman *et al.*, 2001; Nilsson *et al.*, 2001; Studenski *et al.*, 2005; Mead *et al.*, 2007; Ploughman *et al.*, 2008; Quaney *et al.*, 2009) that included a specific exercise program. These studies focused mainly on aerobic training, such as treadmill walking (Nilsson *et al.*, 2001; Ploughman *et al.*, 2008) and cycling on a stationary bicycle (Bateman *et al.*, 2001; Quaney *et al.*, 2009). No standard measure of physical activity was applied across studies.

Cognitive assessments

Four studies (Wolfe *et al.*, 2000; Özdemir *et al.*, 2001; Fang *et al.*, 2003; Chen, 2006) employed the Mini-Mental State Examination (MMSE) and five studies (Ruff *et al.*, 1999; Bateman *et al.*, 2001; Nilsson *et al.*, 2001; Studenski *et al.*, 2005; Mead *et al.*, 2007) employed cognitive questions from the FIM. One study (Studenski *et al.*, 2005) that included the FIM also incorporated the Stroke Impact Scale (SIS), which has memory/thinking and communication subscales. Other studies used more detailed cognitive measures. Pyoria *et al.* (2007) administered a battery of neuropsychological tests, with either two or three individual tests being combined to generate a sum score for each of four domains: memory, language, visuospatial function and visual inattention. Quaney *et al.* (2009) focused on executive function and included the Wisconsin Card Sorting Task, a Stroop task, Trail-Making tasks (B-A) and two Serial Reaction Timed Tasks (repeated and random). Similarly, Ploughman *et al.* (2008) concentrated on attentional and executive tasks, incorporating Trail-Making A and B, Symbol Digit Substitution and the Paced Auditory Serial Addition Test. Unfortunately, too few studies incorporated measures of individual cognitive domains to make grouping by domain feasible. In those studies that did report multiple cognitive outcomes, standardized values for each outcome were averaged to obtain a single change score.

Meta-analysis

Of the 12 studies, nine contained sufficient data to allow inclusion in a meta-analysis. The test for heterogeneity among the nine included studies indicated no significant heterogeneity ($\chi^2 = 5.36$, $p = 0.72$; $I^2 = 0$). There was a significant benefit favoring intervention across the nine studies (SMD = 0.20, 95% CI: 0.04–0.36; $z = 2.43$, $p = 0.015$). An effect size of 0.20 means the score of the average person in experimental groups was 0.20 standard deviations above the average person in control groups. The forest plot is presented in Figure 1. Neither Begg's test ($z = 1.77$, $p = 0.08$) nor Egger's test ($t = 1.56$, $p = 0.16$) indicated publication bias.

Studies excluded from meta-analysis

Three studies could not be included in meta-analysis. Ruff *et al.* (1999) reported only means and no measure of variability. Wolfe *et al.* (2000) reported medians and no common measure of variance. This study did contain sufficient information to compute an effect size, using group difference at follow-up, and it favored the intervention group ($\theta = 0.40$). Pyoria *et al.* (2007) reported medians and interquartile ranges at baseline and median changes with 95% confidence intervals at 12 months for their four cognitive measures. Their between-group analysis indicated a significant treatment benefit for memory ($p = 0.001$), borderline for language ($p = 0.078$) but no difference for visuospatial function ($p = 0.17$) or visual inattention ($p = 0.45$).

Secondary outcomes

Three studies included depression or anxiety assessment, and the results are summarized in Table 3.

Study quality

Table 4 outlines the performance of the 12 studies on each of the four specified quality criteria. Matching this to the meta-analysis results reveals that studies meeting all quality criteria reported smaller treatment benefit. The two studies with the biggest intervention effects (Özdemir *et al.*, 2001; Chen, 2006) both failed to report whether group allocation was concealed or whether outcome assessment was blinded.

Discussion

Despite our broad inclusion criteria, only 12 studies could be included in the review. All included studies were published in the past 12 years, reflecting the recent interest in effects of exercise on cognition

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Table 2. Details of interventions used, with studies sorted by type of intervention

STUDY	EXPERIMENTAL GROUP	CONTROL GROUP
(a) Altering the intensity of rehabilitation		
Chen (2006)	Community-based rehabilitation. Included balance training, sit-to-stand, step training, walking, stair-climbing, ADL training. Dose: Twice a week.	Standard care. Dose: NR.
Fang *et al.* (2003)	Additional early physiotherapy. Provided by 2 experienced rehabilitation therapists. Dose: 45 minutes a day, 5 days a week.	Routine therapy. Dose: received no professional or regular physiotherapy during the hospitalization period.
Özdemir et al. (2001)	Intense interdisciplinary rehabilitation as inpatients, with therapeutic exercises (range of motion, passive stretching, muscle strengthening, mobilization) and neuromuscular facilitation exercises (Davies model). Dose: 2 hours a day, 5 days a week.	Conventional exercises with family caregiver in the home. Dose: at least 2 hours a day, 7 days a week. Supervised and instructed by rehabilitation doctor and physiotherapist once a week.
Pyoria *et al.* (2007)	Activating therapy: aim is to reduce passive handling techniques and emphasise manual, verbal and visual guidance. Training focusses on control of balance and posture in first 3 months followed by progressive strength and endurance training. Two periods of intensive rehabilitation (12 days at 6 months, 3 days at 10 months) were delivered to support patients' independent training at home. Dose: mean of 72 physiotherapy sessions, plus a mean of 25 physiotherapy sessions in intensive rehabilitation.	Standard care: comprehensive multidisciplinary treatment for stroke patients according to Finnish recommendations. Dose: mean of 70 physiotherapy sessions.
Ruff et al. (1999)	Rehabilitation treatments (occupational, physical, speech therapy) 7 days a week. Dose: NR.	Standard 6 day a week rehabilitation services, with 7th day for rest and visitation. Dose: NR.
Wolfe et al. (2000)	Community rehabilitation team comprising senior physiotherapist, occupational therapist, therapy aide and half-time speech therapist. Maximum of one daily visit from each therapist. Dose: NR.	Usual care in the home. Maximum of 3 1-hour visits daily by home help for personal care, meals on wheels, and a community nurse for specific tasks. Dose: NR.
(b) Introducing a specific exercise program		
Bateman *et al.* (2001)	Aerobic training consisting of active resisted exercise on a cycle ergometer. Supervised by senior physiotherapist. Dose: 30 minutes, 3 times a week.	Relaxation training consisting of breathing exercises, visualisation, muscle relaxation techniques. Supervised by senior physiotherapist. Dose: 30 minutes, 3 times a week.
Mead *et al.* (2007)	Exercise training, including progressive endurance and resistance training (e.g., cycle ergometry, star climbing, weights, sit-to-stand). Dose: 75 minutes (including 'tea and chat'), 3 times a week.	Seated relaxation intervention that included deep breathing and progressive muscular relaxation. Dose: 75 minutes (including 'tea and chat'), 3 times a week.
Nilsson *et al.* (2001)	Treadmill walking training with body weight support. Dose: 30 minutes a day, 5 days a week.	Walking training on the ground with a physiotherapist. Dose: 30 minutes a day, 5 days a week.
Ploughman *et al.* (2008)	Treadmill walking with body weight support. Dose: 1 20 minute session at 70% of estimated heart rate reserve or level 13 on Borg perceived exertion scale.	Review of home exercise program with a physiotherpist. Dose: 1 20 minute session.
Quaney *et al.* (2009)	Progressive resistive stationary bicycle training at 70% maximal heart rate. Dose: 45 minute sessions, 3 times a week for 8 weeks.	Stretching exercises at home. Dose: 45 minute sessions, 3 times a week for 8 weeks.

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Table 2. Continued.

STUDY	EXPERIMENTAL GROUP	CONTROL GROUP
Studenski *et al.* (2005)	Progressive exercise program targeting strength, balance, endurance and upper extremity function. In the home, supervised by physiotherapist or occupational therapist. Equipment included stationary bicycle and elastic bands of varying resistance. Dose: 3 times a week for 36 sessions.	Could receive home rehabilitation as ordered by their doctor. A study researcher visited every 2 weeks to provide education about stroke prevention and take physiological measurements. Dose: NR, but 54% of controls received some home rehabilitation during the trial.

ADL = activities of daily living; NR = not reported.

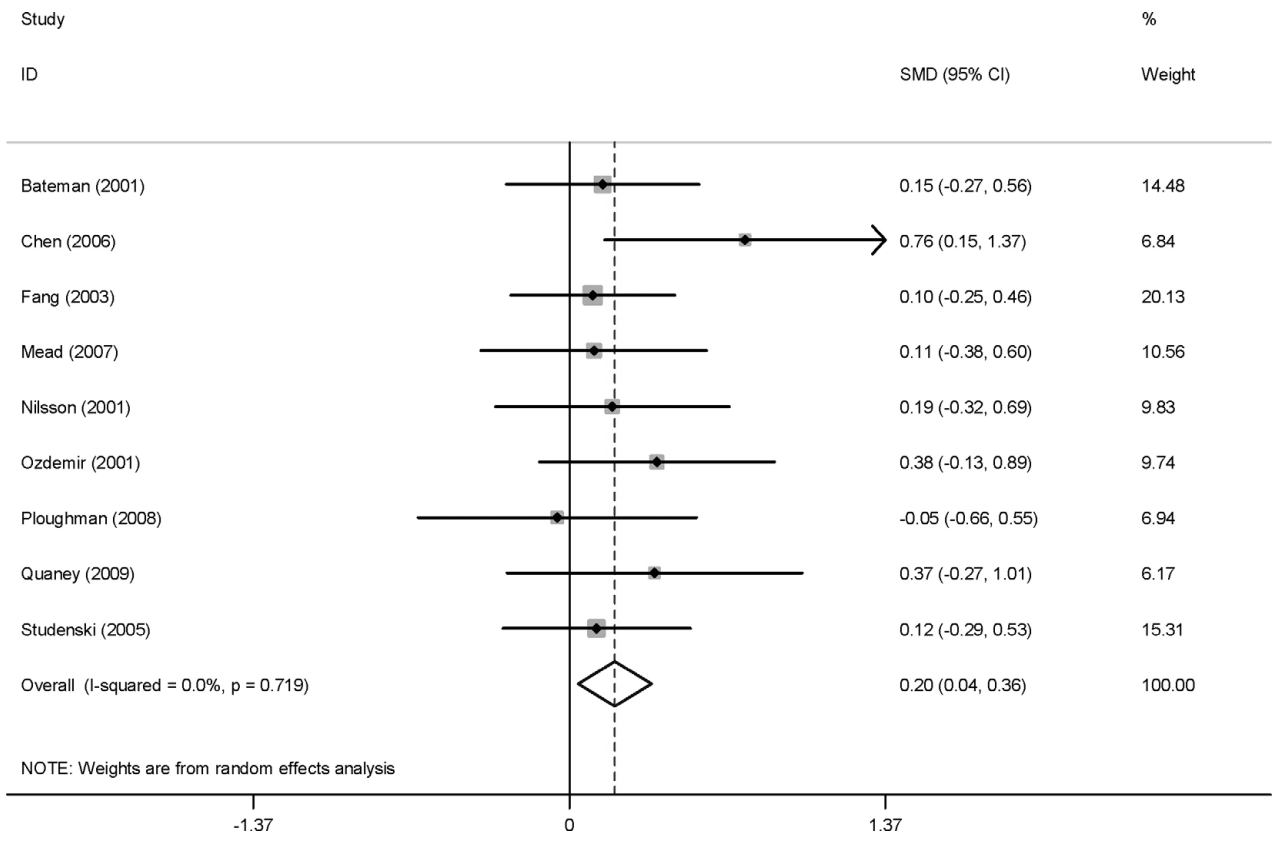


Figure 1. Forest plot of the nine studies included in meta-analysis.

after stroke. Most were relatively small trials that did not specify cognitive function as the primary outcome measure. Exercise or physical activity interventions were heterogeneous across studies, and in several cases were only one aspect of a multifaceted rehabilitation intervention. These methodological issues contributed to individual studies lacking the power to demonstrate a difference in cognitive outcome, and meta-analysis is a useful tool in this situation. We identified a significant benefit favoring intervention in the nine studies that were combined in meta-analysis, with a pattern of reasonably consistent and relatively small positive effects of exercise on cognition.

Several potential mechanisms exist that may explain why physical activity can improve cognitive performance after stroke. One possibility is that exercise enhances cognitive activity and information processing by increasing arousal and wakefulness, perhaps via increases in brain neurotransmitters such as dopamine and norepinephrine (McMorris *et al.*, 2008). A second explanation is that exercise reduces depressive symptoms, which in turn leads to better cognitive performance. The findings of Lai *et al.* (2006), in a follow-up publication from the Studenski *et al.* (2005) cohort, support this explanation. Positive effects of exercise on cognition were seen only in the subgroup with depressive

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Table 3. Secondary outcome measures: depression and anxiety

STUDY	SCALE	TIME POINT	EXPERIMENTAL	CONTROL
Bateman *et al.* (2001)	Depression (HADS), *mean (SD)*	Baseline	5.7 (4.2)	6.6 (3.9)
		Post-intervention	5.5 (3.8)	5.8 (4.0)
	Anxiety (HADS), *mean (SD)*	Baseline	5.6 (3.6)	6.1 (4.1)
		Post-intervention	5.0 (3.9)	5.5 (3.5)
Mead *et al.* (2007)	Depression (HADS), *adj mean (95% CI)*	3 months	4.1 (3.0–5.3)	3.5 (2.6–4.6)
		7 months	4.2 (3.2–5.4)	4.0 (3.1–5.1)
	Anxiety (HADS), *adj mean (95% CI)*	3 months	3.7 (2.6–4.8)	4.0 (3.0–5.2)
		7 months	4.0 (2.9–5.2)	4.2 (3.2–5.4)
Wolfe *et al.* (2000)	Depression (HADS), *median (min-max)*	Baseline	6 (1–14)	6 (0–17)
		12 months	4 (0–11)	6 (0–15)
	Anxiety (HADS), *median (min-max)*	Baseline	2 (0–15)	5 (0–14)
		12 months	1 (0–18)	3 (0–18)

HADS = Hospital Anxiety and Depression Scale (higher scores indicate greater depression, anxiety).
*None of the differences between experimental and control groups reached significance.

Table 4. Quality assessment results

STUDY	RANDOMIZATION?	ALLOCATION CONCEAL-MENT?	BLINDED OUTCOME ASSESSMENT?	ALL PATIENTS ACCOUNTED FOR IN OUTCOME DATA?
Bateman *et al.* (2001)	Yes (blocked)	Yes	Yes	142/175 at week 12 follow-up (most dropouts were early discharges), but only 88 on FIM-cog (reasons NR)
Chen (2006)	Yes	NR	NR	45/45
Fang *et al.* (2003)	Yes	Yes	Yes	128/156 (28 could not tolerate intervention)
Mead *et al.* (2007)	Yes	Yes	Yes	65/66 (1 withdrew)
Nilsson *et al.* (2001)	Yes	Yes	Yes	60/73 (2 deaths, 11 dropouts)
Özdemir *et al.* (2001)	Yes	NR	NR	NR
Ploughman *et al.* (2008)	Within-subject AB design, with order randomized	No	No	21/21
Pyoria *et al.* (2007)	No (patients divided according to their local healthcare centre)	No	NR	73/80 (6 deaths, 1 dropout), but only 68/77 on cognitive measures (3 refusals)
Quaney *et al.* (2009)	Yes	NR	Yes	38/38
Ruff *et al.* (1999)	Quasi-random (7day/wk group for all Medi-Cal patients)	NR	NR	87/113 (reasons NR)
Studenski *et al.* (2005)	Yes	NR	Yes	93/100 (reasons NR)
Wolfe *et al.* (2000)	Yes	Yes	Yes (but patient revealed group membership occasionally)	32/43 (5 deaths, 6 dropouts)

NR = not reported; FIM-cog = Functional Independence Measure cognitive subsection.

symptoms at baseline. Another possibility is that aerobic exercise increases cerebral blood volume and thus enhances cognitive function (Pereira *et al.*, 2007); there is even evidence that exercise may increase brain volume in older adults (Colcombe *et al.*, 2006). A prominent molecular hypothesis relates to the expression of growth factors in the brain: animals that exercise show an increase in brain-derived neurotrophic factor (BDNF), a molecule that increases neuronal survival, improves learning, and protects against cognitive decline (Cotman and Engesser-Cesar, 2002). In a group of young and healthy human males, vocabulary learning was 20% faster after intense physical exercise, and this condition also elicited the strongest increases in BDNF levels (Winter *et al.*, 2007). There is some evidence from rats that the beneficial effects of exercise on BDNF and

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cognition are also evident after brain injury (Griesbach *et al.*, 2004).

As a group, the studies included in this review had several notable limitations. Although we found no significant heterogeneity between studies and no evidence of publication bias (possibly due to cognitive measures rarely being the primary outcome), it is difficult to draw firm conclusions from a meta-analysis that includes only nine datasets. The exercise interventions varied considerably between studies in terms of type (e.g. therapeutic exercises, treadmill walking, cycle ergometer), dose (e.g. 45 minutes a day, 5 days a week for 4 weeks; 30 minutes a day, 3 days a week for 12 weeks; a single 20-minute session) and setting (e.g. community-based rehabilitation, inpatient rehabilitation, the patient's home). Details of how the dose of intervention was measured and monitored were often poorly reported. Given the variability, it was not possible to draw conclusions on the most effective type of exercise, let alone the optimal amount or timing of physical activity.

Cognitive assessment was limited in the majority of studies. The MMSE, used in four studies (Wolfe *et al.*, 2000; Özdemir *et al.*, 2001; Fang *et al.*, 2003; Chen, 2006), is a brief global screening tool and was not designed to be sensitive to change in specific cognitive domains. Particularly in patients with stroke, the MMSE is far from an ideal measure of cognition (Blake *et al.*, 2002; Nys *et al.*, 2005). The FIM, used in five studies (Ruff *et al.*, 1999; Bateman *et al.*, 2001; Nilsson *et al.*, 2001; Studenski *et al.*, 2005; Mead *et al.*, 2007), is a clinical observation scale rather than a direct test of cognitive function. As such, the sensitivity of the FIM to detect cognitive changes is highly questionable, especially given that it is subject to ceiling effects. Ideally, we would have been able to analyze different cognitive domains separately across studies, but only three studies included more targeted and sophisticated cognitive measures (Pyoria *et al.*, 2007; Ploughman *et al.*, 2008; Quaney *et al.*, 2009). Out of necessity, we condensed multiple cognitive measures into a single summed score for each of these three studies. It should also be noted that even the more detailed cognitive measures still often suffer from not being designed for serial testing and are therefore subject to practice effects (e.g. Trail-Making, Symbol digit test).

Study quality was evaluated on the basis of randomization, allocation concealment, blinded outcome assessment and all patients being accounted for in the outcome data. The most striking finding was that the two studies that documented the largest intervention effects in the meta-analysis (SMD = 0.76, 0.38) both failed to report whether group allocation was concealed or whether outcome assessment was blinded (Özdemir *et al.*, 2001; Chen, 2006). The next largest intervention effect (SMD = 0.37) was from a study with blinded outcome assessment but no reported allocation concealment (Quaney *et al.*, 2009). The studies that reported concealed group allocation and blinded outcome assessment were more equivocal (SMD = 0.15, 0.10, 0.19, 0.11) in terms of exercise benefit (Bateman *et al.*, 2001; Nilsson *et al.*, 2001; Fang *et al.*, 2003; Mead *et al.*, 2007). An inverse relationship between study quality and effect size has been documented in a number of areas, and continued attention to trial quality must be a priority.

In conclusion, there is some evidence that increased physical activity after stroke optimizes cognitive performance. The pool of studies identified, however, was small and methodological shortcomings were widespread. There is a need for more comprehensive randomized trials to address this key question. Given that different cognitive tests assess different cognitive skills and that each stroke impacts upon a different area of the brain and that different modes of exercise may have differential effects on brain function, we may need many studies before meaningful effects are identified. Perhaps the most important step in progressing from the studies reported here is to specify cognitive function as the primary outcome measure. The benefit of this would be two-fold: valid, reliable and repeatable cognitive assessments could be used and an appropriate power calculation could be performed to ensure adequate sample size. Many unknowns remain regarding the optimal type, timing and duration of physical activity interventions for patients with stroke. Focused dosing studies should precede a suitably randomized and controlled study with concealed allocation and blinding of outcome assessment. Such studies have the potential to increase our limited knowledge regarding the effect of physical activity on cognitive function after stroke.

Conflict of interest

None.

Description of authors' roles

T. Cumming conceived the study, assisted with the literature search, helped analyze the results and wrote the paper. K. Tyedin conducted the literature search and helped draft the paper. L. Churilov was responsible for statistical analysis and interpretation

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of results. M. Morris and J. Bernhardt both helped draft the inclusion criteria for the review, had input into which articles satisfied these criteria and also helped revise the paper.

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References

Angevaren, M., Aufdemkampe, G., Verhaar, H. J., Aleman, A. and Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Systematic Reviews*, CD005381.

Bateman, A., Culpan, F. J., Pickering, A. D., Powell, J. H., Scott, O. M. and Greenwood, R. J. (2001). The effect of aerobic training on rehabilitation outcomes after recent severe brain injury: a randomized controlled evaluation. *Archives of Physical Medicine & Rehabilitation*, 82, 174–182.

Blake, H., McKinney, M., Treece, K., Lee, E. and Lincoln, N. B. (2002). An evaluation of screening measures for cognitive impairment after stroke. *Age & Ageing*, 31, 451–456.

Bouchard, C., Blair, S. N. and Haskell, W. L. (2007). *Physical Activity and Health*. Champaign, IL: Human Kinetics.

Chen, X. (2006). Effect of community-based-rehabilitation on activities of daily life and cognitive function in stroke patients. *Chinese Journal of Clinical Rehabilitation*, 10, 4–6.

Cicerone, K. D. *et al.* (2000). Evidence-based cognitive rehabilitation: recommendations for clinical practice. *Archives of Physical Medicine & Rehabilitation*, 81, 1596–1615.

Cicerone, K. D. *et al.* (2005). Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Archives of Physical Medicine and Rehabilitation*, 86, 1681–1692.

Colcombe, S. and Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological Science*, 14, 125–130.

Colcombe, S. J. *et al.* (2006). Aerobic exercise training increases brain volume in aging humans. *Journals of Gerontology, Series A: Biological Sciences & Medical Sciences*, 61, 1166–1170.

Cotman, C. W. and Engesser-Cesar, C. (2002). Exercise enhances and protects brain function. *Exercise & Sport Sciences Reviews*, 30, 75–79.

das Nair, R. D. and Lincoln, N. B. (2007). Cognitive rehabilitation for memory deficits following stroke. *Cochrane Database of Systematic Reviews*, CD002293.

Devine, J. M. and Zafonte, R. D. (2009). Physical exercise and cognitive recovery in acquired brain injury: a review of the literature. *Pm & R*, 1, 560–575.

Egger, M., Smith, G. D. and Altman, D. G. (2001). *Systematic Reviews in Health Care: Meta-analysis in Context*. London: BMJ.

Fang, Y., Chen, X., Li, H., Lin, J., Huang, R. and Zeng, J. (2003). A study on additional early physiotherapy after stroke and factors affecting functional recovery. *Clinical Rehabilitation*, 17, 608–617.

Fratiglioni, L., Paillard-Borg, S. and Winblad, B. (2004). An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurology*, 3, 343–353.

Griesbach, G. S., Hovda, D. A., Molteni, R., Wu, A. and Gomez-Pinilla, F. (2004). Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. *Neuroscience*, 125, 129–139.

Heinemann, A. W., Hamilton, B., Linacre, J. M., Wright, B. D. and Granger, C. (1995). Functional status and therapeutic intensity during inpatient rehabilitation. *American Journal of Physical Medicine & Rehabilitation*, 74, 315–326.

Heyn, P., Abreu, B. C. and Ottenbacher, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Archives of Physical Medicine & Rehabilitation*, 85, 1694–1704.

Higgins, J. and Green, S. (eds.) 2008. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1*. Cochrane Collaboration.

Hochstenbach, J. B., Anderson, P. G., van Limbeek, J. and Mulder, T. T. (2001). Is there a relation between neuropsychologic variables and quality of life after stroke? *Archives of Physical Medicine and Rehabilitation*, 82, 1360–1366.

Horn, S. D., DeJong, G., Smout, R. J., Gassaway, J., James, R. and Conroy, B. (2005). Stroke rehabilitation patients, practice, and outcomes: is earlier and more aggressive therapy better? *Archives of Physical Medicine & Rehabilitation*, 86, S101–S114.

Jin, Y. P., Di Legge, S., Ostbye, T., Feightner, J. W. and Hachinski, V. (2006). The reciprocal risks of stroke and cognitive impairment in an elderly population. *Alzheimer's and Dementia*, 2, 171–178.

Katz-Leurer, M., Carmeli, E. and Shochina, M. (2003). The effect of early aerobic training on independence six months post stroke. *Clinical Rehabilitation*, 17, 735–741.

Keith, R. A., Wilson, D. B. and Gutierrez, P. (1995). Acute and subacute rehabilitation for stroke: a comparison. *Archives of Physical Medicine & Rehabilitation*, 76, 495–500.

Lai, S. *et al.* (2006). Therapeutic exercise and depressive symptoms after stroke. *Journal of the American Geriatrics Society*, 52, 240–247.

Lautenschlager, N. T. *et al.* (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*, 300, 1027–1037.

Lincoln, N. B., Majid, M. J. and Weyman, N. (2000). Cognitive rehabilitation for attention deficits following stroke. *Cochrane Database of Systematic Reviews*, CD002842.

MacKay-Lyons, M. *et al.* (2010). Program of rehabilitative exercise and education to avert vascular events after non-disabling stroke or transient ischemic attack

https://doi.org/10.1017/S1041610211001980 Published online by Cambridge University Press

(PREVENT Trial): a multi-centred, randomised controlled trial. *BMC Neurology*, 10, 122.

McMorris, T., Collard, K., Corbett, J., Dicks, M. and Swain, J. P. (2008). A test of the catecholamines hypothesis for an acute exercise-cognition interaction. *Pharmacology,Biochemistry & Behavior*, 89, 106–115.

Mead, G. E. *et al.* (2007). Stroke: a randomized trial of exercise or relaxation. *Journal of the American Geriatrics Society*, 55, 892–899.

Morris, S. B. and DeShon, R. P. (2002). Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychological Methods*, 7, 105–125.

Nilsson, L. *et al.* (2001). Walking training of patients with hemiparesis at an early stage after stroke: a comparison of walking training on a treadmill with body weight support and walking training on the ground. *Clinical Rehabilitation*, 15, 515–527.

Nys, G. M., van Zandvoort, M. J., de Kort, P. L., Jansen, B. P., Kappelle, L. J. and de Haan, E. H. (2005). Restrictions of the Mini-Mental State Examination in acute stroke. *Archives of Clinical Neuropsychology*, 20, 623–629.

Özdemir, F., Birtane, M., Tabatabaei, R., Kokino, S. and Ekuklu, G. (2001). Comparing stroke rehabilitation outcomes between acute inpatient and nonintense home settings. *Archives of Physical Medicine & Rehabilitation*, 82, 1375–1379.

Pasquini, M., Leys, D., Rousseaux, M., Pasquier, F. and Henon, H. (2007). Influence of cognitive impairment on the institutionalisation rate 3 years after a stroke. *Journal of Neurology, Neurosurgery & Psychiatry*, 78, 56–59.

Patel, M. D., Coshall, C., Rudd, A. G. and Wolfe, C. D. (2002). Cognitive impairment after stroke: clinical determinants and its associations with long-term stroke outcomes. *Journal of the American Geriatrics Society*, 50, 700–706.

Pereira, A. C., *et al.* (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences of the United States of America*, 104, 5638–5643.

Ploughman, M., McCarthy, J., Bosse, M., Sullivan, H. J. and Corbett, D. (2008). Does treadmill exercise improve performance of cognitive or upper-extremity tasks in people with chronic stroke? A randomized cross-over trial. *Archives of Physical Medicine & Rehabilitation*, 89, 2041–2047.

Prakash, R. S. *et al.* (2007). Cardiorespiratory fitness: a predictor of cortical plasticity in multiple sclerosis. *Neuroimage*, 34, 1238–1244.

Pyoria, O., Talvitie, U., Nyrkko, H., Kautiainen, H., Pohjolainen, T. and Kasper, V. (2007). The effect of two physiotherapy approaches on physical and cognitive functions and independent coping at home in stroke rehabilitation: a preliminary follow-up study. *Disability & Rehabilitation*, 29, 503–511.

Pyun, S.-B., Yang, H., Lee, S., Yook, J., Kwon, J. and Byun, E.-M. (2009). A home programme for patients with cognitive dysfunction: a pilot study. *Brain Injury*, 23, 686–692.

Quaney, B. M., *et al.* (2009). Aerobic exercise improves cognition and motor function poststroke. *Neurorehabilitation & Neural Repair*, 23, 879–885.

Rand, D., Eng, J. J., Liu-Ambrose, T. and Tawashy, A. E. (2010). Feasibility of a 6-month exercise and recreation program to improve executive functioning and memory in individuals with chronic stroke. *Neurorehabilitation & Neural Repair*, 24, 722–729.

Ruff, R. M., Yarnell, S. and Marinos, J. M. (1999). Are stroke patients discharged sooner if in-patient rehabilitation services are provided seven v six days per week? *American Journal of Physical Medicine & Rehabilitation*, 78, 143–146.

Smith, P. J. *et al.* (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosomatic Medicine*, 72, 239–252.

Studenski, S., Duncan, P. W., Perera, S., Reker, D., Lai, S. and Richards, L. (2005). Daily functioning and quality of life in a randomised controlled trial of therapeutic exercise for subacute stroke survivors. *Stroke*, 36, 1764–1770.

van Uffelen, J. G. Z., Chin a Paw, M. J. M., Hopman-Rock, M. and van Mechelen, W. (2008). The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. *Clinical Journal of Sport Medicine*, 18, 486–500.

WHO (2003). *World Health Report*. Geneva: World Health Organization.

Wilson, D. J., Powell, M., Gorham, J. L. and Childers, M. K. (2006). Ambulation training with and without partial weightbearing after traumatic brain injury: results of a randomized, controlled trial. *American Journal of Physical Medicine & Rehabilitation*, 85, 68–74.

Winter, B. *et al.* (2007). High impact running improves learning. *Neurobiology of Learning & Memory*, 87, 597–609.

Wolfe, C. D., Tilling, K. and Rudd, A. G. (2000). The effectiveness of community-based rehabilitation for stroke patients who remain at home: a pilot randomized trial. *Clinical Rehabilitation*, 14, 563–569.

https://doi.org/10.1017/S1041610211001980 Published online by Cambridge University Press