The Effect of Exercise Training on Cognitive Function in Older Adults with Mild Cognitive Impairment: A Meta-analysis of Randomized Controlled Trials

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Objectives: *Investigations of exercise and cognition have primarily focused on healthy or demented older adults, and results have been equivocal in individuals with mild cognitive impairment (MCI). Our aim was to evaluate efficacy of exercise on cognition in older adults with MCI.* **Design:** *We conducted a meta-analysis of random controlled trials (RCTs) of exercise effects on cognitive outcomes in adults with MCI. Searches were conducted in Medline, EMBASE, CINAHL, PEDro, SPORTSDICUS, PsychInfo, and PubMed.* **Participants:** *Adults aged over 65 years with MCI or Mini-Mental State Exam mean score 24–28 inclusive.* **Measurements:** *Study quality was assessed using the PEDro scale; data on participant and intervention characteristics and outcomes were extracted, followed by meta-analysis.* **Results:** *Fourteen RCTs (1,695 participants; age 65–95 years) met inclusion criteria. Quality was modest and under-powering for small effects prevalent. Overall, 42% of effect sizes (ESs) were potentially clinically relevant (ES >0.20) with only 8% of cognitive outcomes statistically significant. Meta-analysis revealed negligible but significant effects of exercise on verbal fluency (ES: 0.17 [0.04, 0.30]). No significant benefit was found for additional executive measures, memory, or information processing. Overall results were inconsistent with benefits varying across exercise types and cognitive domains.* **Conclusions:** *There is very limited evidence that exercise improves cognitive function in individuals with MCI, although published research is of moderate quality and inconclusive due to low statistical power. Questions remain regarding the magnitude, generalization, persistence, and mechanisms of benefits. Large-scale, high-quality RCTs are required to determine if exercise improves cognition or reduces dementia incidence in those with MCI.* (Am J Geriatr Psychiatry 2013; ■:■–■)

Key Words: Exercise, cognition, MCI

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Physical exercise has well-documented benefits for general health and well-being, and more recently has been shown to benefit cognition.[1–4] Epidemiological evidence consistently links physical exercise with cognitive benefits,[1] lower risk for dementia, and reduced pathological changes.[2,5,6] A recent meta-analysis of 16 prospective studies including patients with neurodegenerative diseases found that higher physical activity was associated with a 28% reduction in incident dementia.[7] Frequent exercisers (>3/wk) have been reported to exhibit stable or improved cognitive health over 5 years.[8] Additionally, higher muscle mass is associated with a 43% decreased risk of Alzheimer disease.[9] It has been estimated from prospective cohort studies that reducing inactivity by 25% would prevent 1 million cases of dementia worldwide.[10]

The main area of uncertainty over the efficacy of prescribed physical activity is for adults with cognitive impairment but no dementia.[11] One challenge is a lack of objective cognitive criteria to distinguish "healthy" cognitive function from impairment. For example, a Cochrane review of exercise in older adults used "cognitively impaired in any way" as exclusion criteria, but provided no objective definition.[12] In another review of older adults with "normal" cognitive function, neurological patients were included,[2] and in a recent review of exercise in cognitively impaired and intact subjects no objective criteria were cited.[13]

Mild cognitive impairment (MCI) is often used as an intermediate diagnosis between normal cognitive function and dementia.[14] Multiple diagnostic criteria for MCI are available,[15] however, limiting consistency across studies. A recent non-systematic review of exercise identified only three clinical trials in MCI, with mixed results.[1] Lack of diagnostic clarity may have contributed to this heterogeneity. In addition, previous reviews of physical exercise in at risk individuals have included mixed samples,[1,3,13] Consequently, the overall evidence of exercise benefit in MCI and other individuals at risk of cognitive decline is equivocal and largely unknown.[16]

Cognitive risk for dementia includes many syndromes. For example, a recent review of progression from MCI to dementia identified age-associated memory impairment, cognitive impairment no dementia, and limited cognitive disturbance syndromes,[15] among others. In order to increase the scope and sensitivity of this systematic review, we adopted a general definition of MCI as that of mild but measurable cognitive changes prior to the onset of significant functional decline (not normal cognitive function but not dementia; functional activities preserved or at least minimal impairment; and evidence of cognitive decline)[14,17] and included those with clinical diagnosis of MCI using any criteria and those with mild cognitive deficits on the Mini-Mental State Exam (MMSE; score range: 24−28 inclusive). The purpose of this review was to determine if physical exercise improves objective cognitive function by analyzing all available randomized controlled trials of physical exercise in individuals at risk for dementia defined by the presence of MCI.

METHODS

Data Sources and Searches

We performed a systematic review consistent with the preferred reporting items for systematic reviews (PRISMA).[18] An electronic database search was originally performed in June 2012 and updated in December 2012 using Medline (1996−first week December 2012), EMBASE (1980−first week December 2012), CINAHL (1980−first week December 2012), PEDro (first week December), SPORTSDICUS (first week December), PsychInfo (1806−first week December 2012), PubMed (first week December 2012). The exercise intervention search terms were: [Exercise] [Aerobic] [Resistance training] [Strength training] [Physical activity] [exertion] [weight lifting] [walking] [fitness] [muscle strength] [stretching] and [recreation], combined with "or". Cognitive outcomes terms, combined with "or", were: [Cognition] [Cognitive] [Memory] [Brain] [Executive] [Neuropsychological]. Intervention and outcome terms were combined with "AND" and then searched in "All Fields" with the limits human, English language, adults 65 years and older, peer reviewed and randomized controlled trial. The full electronic search strategy for Medline is presented in Table 1. Identified papers were then reviewed (title /abstract) by NG to identify potentially relevant studies and exclude older adults defined as either cognitively intact or diagnosed with dementia. Remaining papers were retrieved and reviewed by NG and MFS. All authors reviewed and reached consensus on those studies where the sample was not explicitly defined. Bibliographies of eligible papers and reviews were manually searched for additional citations.

TABLE 1. Database Search of MEDLINE

#	Searches	Results
1	(Exercise or Aerobic or 'Resistance training' or 'Strength training' or 'Physical activity' or exertion or 'weight lifting' or walking or fitness or 'muscle strength' or stretching or recreation).mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	333469
2	(Cognition or Cognitive or Memory or Brain or Executive or Neuropsychological). mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1124583
3	1 and 2	13525
4	Limit 3 to (English language and humans and "all aged (65 and over)" and clinical trial all)	25

Inclusion Criteria

Studies were selected from the initial search if they met the following criteria:

i) Population: Persons with MCI either via clinical diagnosis of MCI on documented criteria or MMSE mean score of 24−28 inclusive.
ii) Intervention: Physical exercise training consistent with the definition of the American College of Sports Medicine: Planned, structured, and repetitive physical activity which has as a final or intermediate objective, the improvement or maintenance of physical fitness.[19] Studies of less than four weeks exercise did not meet criteria for training and were excluded. No limitations were imposed based on modality, dose, intensity, or supervision, but exercise had to be prescribed specifically. Multi-modal interventions were potentially eligible for inclusion as long as a comparison arm would have allowed assessment of the isolated effects of exercise (e.g., exercise plus pharmacotherapy versus pharmacotherapy alone).
iii) Control group: Any kind of control group was eligible, including no contact, no treatment, waiting list, attention control, sham exercise, or alternative active treatment.
iv) Outcomes: Any validated neuropsychological test of cognition reported at baseline and follow-up.
v) Study design: Random controlled trial (RCT), full-length article published in a peer-reviewed English language journal.

Data Extraction and Quality Assessment

Key data were extracted by two reviewers (NG and MFS) onto a standard template. Quality assessment of eligible trials was independently rated on the 11-item quality rating Physiotherapy Evidence Database scale (PEDro).[20] An additional item ("Exercise supervised: yes/no") was included to identify this important component of exercise, providing a final possible score of 12. Differences in ratings were resolved by consensus.

Data Synthesis and Analysis

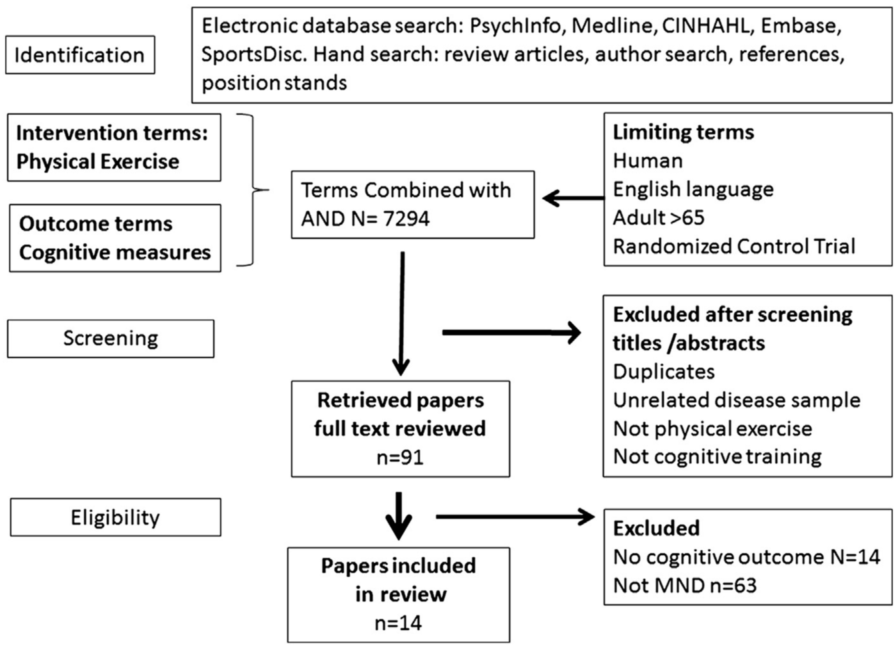
Baseline and outcome data were extracted and participant, intervention (training type, delivery, volume, and duration), and outcome measures are reported as means and standard deviations (SDs). Meta-analyses were conducted on the standard mean difference when combining disparate tests, and using the mean difference when combining identical outcomes. All meta-analyses used a random effects model and 95% confidence intervals (CIs) (RevMan 5.1),[21] and compared exercise with control at the end of intervention. The diversity between studies (Heterogeneity I^2 statistic) was examined to pool only those studies where I^2 was less than 75%. Effect sizes (ESs) were interpreted according to Cohen's scale of 'trivial' (<0.20), 'small' (≥0.20 to <0.50), 'moderate' (≥0.50 to <0.80), and 'large' (>0.80).[22] Power calculations to determine required sample size for a 'small' effect (ES 0.2) were made with GPower Analysis Version 3.1.[23]

Unpublished data (means and SDs) of cognitive outcomes were solicited from two authors.[24,25] The author of one RCT of MCI[26] did not publish or respond to requests for raw change score data, precluding effect size calculations comparable to the other trials.

RESULTS

Results of the search strategy are presented in Figure 1. The combined search yielded 7,294 potentially

FIGURE 1. Flow of trials into review.



eligible papers, was reduced to 102 after reviewing titles and abstracts, which were reviewed in full to determine suitability. Fourteen RCTs met criteria, comprising 1,695 subjects with MCI, with three trials including individuals with documented MCI,[24,27,28] two with diagnosis of amnestic-MCI,[26,29] and one with memory impairments and memory complaint with MMSE within normal limits.[30] The remaining trials included participants with MMSE scores in the range 24–28 inclusive,[25,30–35] one trial describing "probable MCI,"[36] and another included mixed data from individuals with diagnosed MCI and "at risk" individuals.[37] Most studies excluded were non-MCI with MMSE greater than or equal to 28 (N = 68).

Quality Assessment*

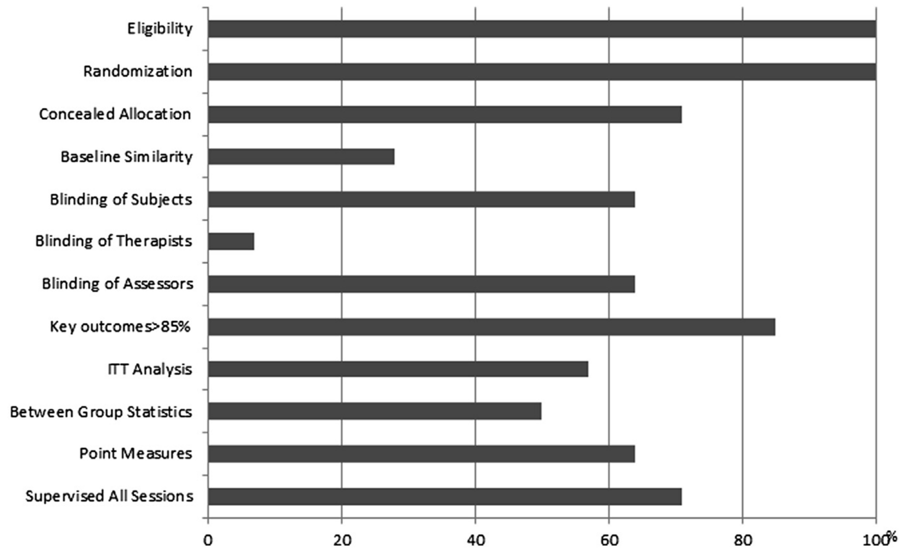
Overall the quality of included trials was moderate, and Figure 2 depicts the percentage of trials fulfilling each criterion of the modified PEDro scale. Average study quality was 6/12, range 4–9. Common limitations in quality were: lack of blinded assessors in 11 trials,[25–28,31–34,36,37] lack of therapists blinded to hypotheses in 13 trials,[24–33,36,37] absence of intention-to-treat analysis in 7 trials,[24,28,29,32,33,36] and insufficient available information regarding baseline matching between groups in 8 trials.[24,26,28,29,31,32,34,36]

Cohort Characteristics

A summary of cohort characteristics for each trial is presented in Table 2. The pool of 1,695 participants (894 in exercise intervention arms) were drawn from residential aged care facilities;[27–29,31,32] community-dwelling and recruited from memory clinics, falls clinics, and elderly clubs;[26,33,35–37] or advertising.[24,25,37] Recruitment method was unspecified in two trials.[30,34]

Severity of cognitive impairment was measured with the MMSE in nine trials,[25–27,29,31–33,35,36] with mean scores between 24–28 inclusive, with the exception of one trial with clinically diagnosed MCI.[27] Two studies used modified or shortened forms of the MMSE,[28,34] and although MMSE scores were inclusion criteria for two studies the actual scores were not provided.[24,30] Participants were predominantly female, two studies included only women,[31,36] and age ranged from 65–95 years (mean: 76 years). All trials provided exclusion criteria, indicating that participants were either physically

FIGURE 2. Bar graph representing the percentage of trials reporting information fulfilling each individual PEDro Quality Criteria. PEDro: Physiotherapy evidence database scale; ITT: intention to treat.



healthy and mobile without physical or cardiovascular conditions preventing exercise,[25–27,30–32,34,37] without other neurological conditions such as Parkinson disease or stroke,[24,28,32,34] and/or in good health.[24,26,28,30,33,37] One trial was specifically targeted to frail elderly.[28]

Total samples (mean N = 121, range: 29–389), were divided into intervention and control groups varying between 10 and 218 participants, with the larger groups participating in home or residential programs.[29,32,37]

Intervention Characteristics

Characteristics of exercise interventions are presented in Table 3.

Modality. Four trials tested the effect of isolated moderate intensity aerobic exercise,[24–26,37] while moderate and high intensity training were compared with control,[27] and one prescribed low intensity walking.[35] Only one trial used exclusively resistance training,[30] although four additional trials combined resistance training with balance and aerobic training,[32,34] or balance and coordination training.[31,33] Lower intensity interventions included Tai Chi,[29] low intensity walking with an aid or hand and face exercises for frail elderly.[28] One trial included resistance and aerobic training in separate groups to compare them against the control.[36]

Exercise dose and intensity. Exercise volume varied from 30–90 minutes per session, two to four sessions per week, and duration of interventions ranged from 6 to 52 weeks. The intensity of resistance training varied from high[30] in the exclusive resistance training trial to low to moderate intensity in the mixed resistance and other exercise conditions.[31–34] Three trials of aerobic exercise used exercise equipment at high,[26,27] or moderate[25,27] intensity, whereas moderate[24,37] or low[25] intensity walking was prescribed in the other aerobic trials.

Setting and supervision. Exercise was predominantly provided in groups[24,26,29–33,35,36] versus individual[28,37] or mixed format.[34] Exercise sites were gymnasiums or YMCA,[25,26,30] local community,[35] mixed gym and community,[36] home and care center or residential site,[29,32–34] or home,[37] and was not reported in four studies.[24,27,28,31] Level of supervision varied depending upon setting, with constant supervision provided in exercise or residential facilities, whereas mixed and home-based programs provided initial training,[37] then weekly review[26] or follow-up.[34]

Control Characteristics

Control conditions were highly variable and included social visits or no contact,[28] education

TABLE 2. Participant Characteristics of Physical Exercise Trials on Cognitive Function in Individuals with MCI

Citation	Inclusion Criteria	Condition (N)	Age, years (SD)	% Female	MMSE (SD)
Molloy et al. 1988[31]	Women >70 years	Mixed training (23)	82.0	100	24.7 (4.8)
		Control (22)	83.3	100	24.9 (4.4)
Scherder et al. 2005[28]	Frail elderly, MCI ≥7 on 12-item MMSE	Walking (15)	84 (6.3)	86	MMSE 12-item, 9.73
		Hand and face (13)	89 (2.4)	84	MMSE 12-item, 9.23
		Control (15)	86 (5.0)	93	MMSE 12-item, 9.87
Brown et al. 2009[32]	Residents of retirement facilities	Mixed training (82)	79.5 (5.9)	87	26.6 (2.7)
		Control flexibility (34)	81.5 (6.9)	93	26.0 (2.9)
		Control no activity (38)	78.1 (6.4)	87	26.2 (2.9)
Busse et al. 2008[30]	SMC and memory deficit	Resistance (14)	70.4 (3.6)	57	NR
		Control (17)	73.3 (6.4)	88	NR
Lautenschlager et al. 2008[37]	≥24 MMSE, CDR ≥1, ICD-10 diagnoses	Aerobic (85)	68.6 (7.7)	49	ADAS Cog 7.0 (1.7)
		Control (85)	68.7 (8.5)	52	ADAS Cog 7.0 (1.8)
Muscari et al. 2009[25]	Community dwelling, age ≥65 years	Aerobic (60)	68.8 (2.5)	47	26.7
		Control (60)	69.6 (2.8)	50	27.0
Williamson et al. 2009[34]	Age 70−89 years, <20 min/wk exercise	Mixed training (50)	76.8 (4.37)	72	mMMSE 89.88 (6.1)
		Control (52)	78.6 (4.11)	69	mMMSE 90.67 (6.6)
Baker et al. 2010[26]	aMCI	Aerobic (19)	Female 65.3 (9.4)	53	28.4
			Male 70.9 (6.7)		25.6
		Control (10)	Female 74.6 (11.1)	50	28.6
			Male 70.6 (6.1)		27.2
Kimura et al. 2010[33]	Community dwelling, age >65 years	Resistance (65)	73.6 (4.7)	56	27.8 (1.8)
		Control (54)	72.0 (3.9)	72	27.9 (2.1)
Lam et al. 2010[29]	Age >65 years, aMCI CDR 0.5	Tai Chi (171)	77.2 (6.3)	73	24.7
		Control (218)	78.3 (6.6)	78	24.3
Van Uffelen et al. 2008[24]	Age 70−80 years, MCI, ≥24 MMSE, ≥19 TICS	Aerobic (77)	Female 76 (2.9)	52	NR
			Male 74 (2.7)		
		Control (75)	Female 75 (2.9)	36	NR
			Male 75 (2.8)		
Maki et al. 2012[35]	≥ 1 SCD, no dementia, age <80 years	Walking (75)	71.9 (4.1)	69	27.7 (1.9)
		Control (75)	72.0 (3.9)	62	27.9 (2.1)
Nagamatsu et al. 2012[36]	Women, age 70−80 years, <26 on cognitive assessment scale	Aerobic (30)	75.6 (3.6)	100	27.4 (1.5)
		Resistance (28)	73.9 (3.4)	100	26.0 (5.6)
		Control (75)	75.1 (3.6)	100	27.1 (1.7)
Valera et al. 2011[27]	MCI, age >65 years, residing in care homes	Aerobic at 40%HR (27)	79.24 (10.07)	NR	19.86 (5.12)
		Aerobic at 60%HR (26)	76.44 (11.38)	NR	20.81 (4.69)
		Control (15)	79.40 (6.72)	NR	21.80 (3.23)

Notes: MCI: mild cognitive impairment; MMSE: Mini Mental State Exam; aMCI: amnesic mild cognitive impairment; CDR: Clinical Dementia Rating scale; TICS: Telephone Interview for Cognitive Status; ICD-10: International Classification of Disease 10th Edition; mMMSE: modified Mini Mental State Exam; SMC: subjective memory deficit; SCD: subjective cognitive decline; HR: heart rate; NR: not reported.

programs,[25,33−35,37] "normal" activities,[31] or "recreational activities."[27] Five trials had active or sham exercise control conditions including stretching, flexibility[24,26,29,36] or low intensity aerobic exercise.[32] One trial did not describe the control condition.[30] Nine trials reported participants were blinded to investigators' hypotheses regarding the superior intervention, whereas blinding of subjects was not possible in four trials.[30,31,35,36]

Outcome Measures

A total of 28 different cognitive outcome measures were administered (average 6/study, range: 1−11). Data from nonsignificant findings were not always provided.[26] General cognitive function was measured using MMSE,[24,25,27,29,31,34] ADASCog,[29,37] and CAMCOG,[30] and fluid intelligence with subtests of the WAIS-R.[32] The majority of trials administered standardized neuropsychological tests with executive function the most frequently measured domain,[24,26,28,29,32−37] followed by memory[24,26,28−32,34−37] and information processing.[24,30,31] Only one trial[31] specified the delay between last bout of exercise and assessment (3−7 days), a potentially important variable given the known acute bout effects of exercise. Only three trials had longitudinal follow-up after intervention at 6

TABLE 3. Intervention and Control Characteristics of Physical Exercise Trials on Cognitive Function in Individuals with MCI

Citation	Intervention Modality	Format	Setting	Intensity	Volume (minutes)	Frequency (days/week)	Duration (weeks)	Control Condition
Aerobic								
Lautenschlager et al. 2008[37]	Walking	Individual	Home	Moderate	50	3	24	Education
Muscari et al. 2009[25]	Cycle ergometer, treadmill, free-body	NR	Gym	Moderate	60	3	52	Education
Baker et al. 2010[26]	Treadmill, stationary bike, elliptical trainer	Group	YMCA	High	45–60	4	26	Group stretching
Van Uffelen et al. 2008[24]	Walking	Group	NR	Moderate	60	2	52	Non aerobic exercise
Maki et al. 2012[35]	Walking	Group	Community	Light	90	1	12	Education
Nagamatsu et al. 2012[36]	Walking Machine and free weights	Group Group	Community Gym	Moderate	60 60	2 2	26 26	Balance and tone
Valera et al. 2012[27]	Cycling	NR	NR	Moderate	30	3	12	Activities
Resistance								
Busse et al. 2008[30]	Machine-based	Group	Gym	NR	60	2	36	NR
Mixed								
Molloy et al. 1988[31]	Balance, coordination, resistance (unspecified)	Group	NR	Light	10–35	3	12	Normal activities
Brown et al. 2008[32]	Resistance (unspecified), aerobic (walk), balance	Group	Trial site	Moderate	60	2	26	Flexibility or no activity
Williamson et al. 2009[34]	Aerobic, strength, and flexibility, balance	Individual and group	Mixed	Moderate	40–60	3	26	Education
Kimura et al. 2010[33]	Strength (machine based) and balance	Group	Facility	Moderate to high	90	2	12	Education
Other								
Scherder et al. 2005[28]	Walking or hand and face	Individual	NR	Light	30	3	6	No contact
Lam et al. 2010[29]	Tai Chi	Group	Mixed	Light	≥30	≥3	52	Stretch and tone

Notes: NR: not reported.

weeks,[28] 24 weeks,[27] and 12 and 18 months;[37] the latter reporting that participants were encouraged to continue exercise.[37]

Synthesis of Results

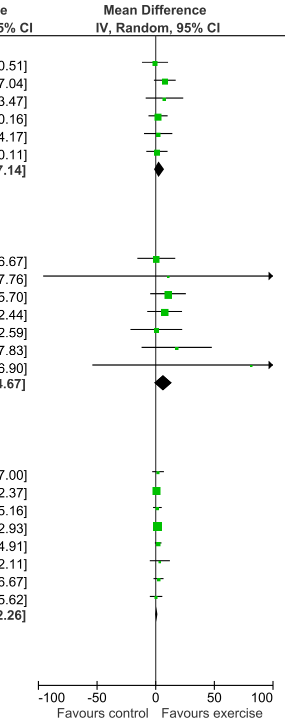
Nine of the 14 trials (69%) reported significant benefits for at least one outcome; no significant effects were found in five trials,[24,27,28,33,34] however. Exercise was reported to result in improved verbal fluency,[29,31,35] global cognition,[25,29,37] and fluid intelligence,[32] executive function,[26,36] and memory.[9,30,36] Overall, only 8% of outcomes were significant across all trials.

Relative effect sizes were calculated for all cognitive outcome measures. Effect sizes were classified as trivial (60.5%), small (33.3%), moderate (4.3%), or large (1.7%) and the complete data set of means (SDs) and effect sizes are presented in Supplementary Table 1 (available online). We conservatively considered an effect size of 0.20 (small) to represent the lower threshold of a clinically meaningful effect, acknowledging the uncertainty of any threshold. Power calculations indicated that a sample size of 601 per group (1,202 total) would be required to detect an ES of this magnitude with a power of 80% and α of 0.05. Using this principle, none of the outcomes with effect sizes of this magnitude or lower (constituting 58% of all outcomes) were tested within adequately powered studies.

Meta-analysis was performed on three measures of executive function (Stroop, Trail Making Test B, and verbal fluency), sensitive to progressive cognitive decline associated with aging and dementia,[38] and common to five trials. In addition, a timed task-switching test of executive function[33] was included being comparable to Trail Making Test B. Effects could not be pooled for a total executive domain as the sample size would be inflated by the repetition of several studies with multiple tests of executive

FIGURE 3. Meta-analysis of exercise on executive function in MCI. Note domain effect not pooled because several studies repeated and sample would be counted more than once, thus inflating total sample size.

	Exercise			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.1.1 Stroop								
Brown 2009	3.2	27	66	3.8	26.78	34	14.0%	-0.60 [-11.71, 10.51]
Nagamatsu Resist 2012	9.13	19.88	28	1.37	15.26	28	20.1%	7.76 [-1.52, 17.04]
Nagamatsu Aerobic 2012	8.83	41.86	30	1.37	15.26	28	6.8%	7.46 [-8.55, 23.47]
Van Uffelen 2008 men	2.6	17	36	0.6	20.45	45	26.1%	2.00 [-6.16, 10.16]
Van Uffelen 2008 women	2.5	23	35	0.4	22.4	22	11.9%	2.10 [-9.97, 14.17]
Williamson 2009	-0.5	20.4	45	-1.54	23.91	47	21.1%	1.04 [-8.03, 10.11]
Subtotal (95% CI)			**240**			**204**	**100.0%**	**2.97 [-1.19, 7.14]**
Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 5 (P = 0.85); I² = 0%								
Test for overall effect: Z = 1.40 (P = 0.16)								
1.1.2 TMTB								
Brown 2009	2.8	35.7	66	2.3	40.7	34	23.9%	0.50 [-15.67, 16.67]
Kimera 2010	58.2	300.35	54	47.3	290.9	65	0.5%	10.90 [-95.96, 117.76]
Lam 2010	-1.7	62.8	135	-12.2	77.5	194	27.0%	10.50 [-4.70, 25.70]
Maki 2012	9.9	40.7	66	2.3	46.45	67	28.4%	7.60 [-7.24, 22.44]
Nagamatsu Resist 2012	0.91	43.91	28	0.39	40.27	28	12.8%	0.52 [-21.55, 22.59]
Nagamatsu Aerobic 2012	18.28	72.55	30	0.39	40.27	28	7.0%	17.89 [-12.05, 47.83]
Scherder 2005	38.33	234	15	-43.1	130	15	0.3%	81.43 [-54.04, 216.90]
Subtotal (95% CI)			**394**			**431**	**100.0%**	**6.76 [-1.14, 14.67]**
Heterogeneity: Tau² = 0.00; Chi² = 2.83, df = 6 (P = 0.83); I² = 0%								
Test for overall effect: Z = 1.68 (P = 0.09)								
1.1.3 Fluency								
Brown 2009	3.6	11.25	66	1.6	12.5	34	3.5%	2.00 [-3.00, 7.00]
Lam 2010	2.5	7.75	135	1.8	7.35	194	31.8%	0.70 [-0.97, 2.37]
Lautenschlager 2008	1.88	11.5	85	0.43	13.1	85	6.4%	1.45 [-2.26, 5.16]
Maki 2012	1.2	4.4	66	-0.2	4.6	67	37.8%	1.40 [-0.13, 2.93]
Molloy 1988	-0.3	4.6	23	-2.4	5	22	11.2%	2.10 [-0.71, 4.91]
Scherder 2005	2.2	10.5	15	-1.33	13.3	15	1.2%	3.53 [-5.05, 12.11]
Van Uffelen 2008 men	2.2	8.95	36	-0.2	10.65	45	4.9%	2.40 [-1.87, 6.67]
Van Uffelen 2008 women	6.4	10.25	35	6.1	9.8	22	3.1%	0.30 [-5.02, 5.62]
Subtotal (95% CI)			**461**			**484**	**100.0%**	**1.32 [0.38, 2.26]**
Heterogeneity: Tau² = 0.00; Chi² = 1.56, df = 7 (P = 0.98); I² = 0%								
Test for overall effect: Z = 2.75 (P = 0.006)								
Test for subgroup differences: Chi² = 2.32, df = 2 (P = 0.31), I² = 13.9%								



function. Similarly, effects of exercise on immediate and delayed memory could not be pooled due to high heterogeneity ($I^2 = 82\%$) due to one trial producing significant large effects.[30] Meta-analysis was conducted on two measures of information processing (Digit Symbol Substitution Test and Digit Span) providing a pooled domain effect. Meta-analysis results are presented in Figures 3–6.

Effects of training on specific cognitive domains. Exercise training had a trivial but positive significant effect on verbal fluency (ES: 0.17; 95% CI: 0.04, 0.30), but not cognitive flexibility (TMTB ES: 0.13; 95% CI: −0.01, 0.27) nor response inhibition (SCWT ES: 0.12; 95% CI: −0.07, 0.31). Similarly, there was no significant effect of exercise on delayed memory (ES: −0.01; 95% CI: −0.16, 0.14), nor information processing domain (ES: 0.57; 95% CI: −0.11, 0.42).

Effects of isolated aerobic training on cognition. Aerobic exercise was the training regime in 50% (N = 7) of trials. Global cognitive function significantly improved in three trials [(ES: 0.74; 95% CI: 0.43, 1.05),[37] (ES: 0.56; 95% CI: 0.19, 0.92),[25] and (ES: 0.69; 95% CI: 0.03, 1.32)]—although nonsignificant results were found in another.[24] Trivial, nonsignificant effects were found for executive function[24,35] and memory.[24,37] Thus, the effect of aerobic exercise was heterogeneous and inconclusive.

Effects of isolated resistance training on cognition. Isolated resistance training was provided in two trials and produced significant large and moderate effects on memory [(ES: 3.37; 95% CI: 2.27, 4.47),[30] (ES: 0.54; 95% CI: 0.01, 1.08)[36]] but nonsignificant results on executive function.

Effects of other modalities or multi-modal training on cognition. Four trials administered multi-modal training regimes and negligible or nonsignificant results were reported for the majority (76%) of outcomes. A single trial of Tai Chi resulted in significant effects on two of nine cognitive outcomes: global cognition (ES 0.56; 95% CI: 0.34, 0.79) and visual attention (ES 0.32; 95% CI: 0.10, 0.55).[29] Nonsignificant results were found in a trial of low-intensity walking[28] and multi-modal training trials.[31,34]

FIGURE 4. Meta-analysis of exercise on information processing in MCI.

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Digit Symbol Substitution Test								
Brown 2009	-0.9	10.5	66	-1.3	10.35	34	0.4%	0.40 [-3.90, 4.70]
Lautenschlager 2008	2.62	15.1	85	3.43	14.1	85	0.4%	-0.81 [-5.20, 3.58]
Maki 2012	4	14.3	66	4	14.9	67	0.3%	0.00 [-4.96, 4.96]
Molloy 1988	1	6.35	23	-0.3	8.8	22	0.4%	1.30 [-3.20, 5.80]
Van Uffelen 2008 men	0.9	10.55	37	0.2	9.75	48	0.4%	0.70 [-3.68, 5.08]
Van Uffelen 2008 women	0.3	9.8	40	-0.3	11.55	27	0.3%	0.60 [-4.71, 5.91]
Williamson 2009	1.14	13.7	44	-1.19	12.94	48	0.2%	2.33 [-3.13, 7.79]
Subtotal (95% CI)			**361**			**331**	**2.2%**	**0.57 [-1.21, 2.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 6 (P = 0.99); I² = 0%								
Test for overall effect: Z = 0.63 (P = 0.53)								
1.4.2 Digit Span								
Brown 2009	-0.1	2.15	66	0	1.9	34	10.5%	-0.10 [-0.92, 0.72]
Lam 2010	0.1	1.3	135	0	1.45	194	79.1%	0.10 [-0.20, 0.40]
Molloy 1988	-0.2	2.1	23	-0.5	4.1	22	1.9%	0.30 [-1.62, 2.22]
Nagamatsu Resist 2012	-0.73	2.52	30	-2	3.14	28	3.3%	1.27 [-0.20, 2.74]
Nagamatsu Aerobic 2012	-0.54	4.77	30	-2	3.14	28	1.7%	1.46 [-0.61, 3.53]
Scherder 2005	0.33	3.6	15	0.13	2.82	15	1.3%	0.20 [-2.11, 2.51]
Subtotal (95% CI)			**299**			**321**	**97.8%**	**0.15 [-0.12, 0.42]**
Heterogeneity: Tau² = 0.00; Chi² = 4.26, df = 5 (P = 0.51); I² = 0%								
Test for overall effect: Z = 1.06 (P = 0.29)								
Total (95% CI)			**660**			**652**	**100.0%**	**0.16 [-0.11, 0.42]**
Heterogeneity: Tau² = 0.00; Chi² = 5.41, df = 12 (P = 0.94); I² = 0%								
Test for overall effect: Z = 1.15 (P = 0.25)								
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%								

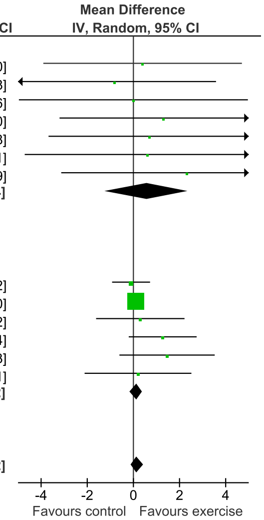


FIGURE 5. Effect size analysis of exercise on immediate memory in MCI. Note total meta-analysis effect not provided because pooled effect heterogeneity $I^2 = 82\%$.

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Std. Mean Difference IV, Random, 95% CI
1.2.1 Learning / Immediate memory							
Brown 2009	1	4.25	66	0.7	4.25	34	0.07 [-0.34, 0.48]
Busse 2008	3.9	1	14	-1.19	1.2	17	4.45 [3.07, 5.83]
Lautenschlager 2008	1.09	4.9	85	0.91	4.7	85	0.04 [-0.26, 0.34]
Molloy 1988	-0.4	1.4	23	-0.2	3.1	22	-0.08 [-0.67, 0.50]
Nagamatsu Resist 2012	0.61	0.72	28	0.23	0.66	28	0.54 [0.01, 1.08]
Nagamatsu Aerobic 2012	-0.09	0.82	30	0.23	0.66	28	-0.42 [-0.94, 0.10]
Scherder 2005	6.05	14.18	15	4.6	15.36	15	0.10 [-0.62, 0.81]
Van Uffelen 2008 men	-2.6	8.6	36	-0.1	7.95	45	-0.30 [-0.74, 0.14]
Van Uffelen 2008 women	-2.5	8.6	35	-1.3	8	22	-0.14 [-0.68, 0.39]
Williamson 2009	1.14	13.7	44	-1.19	14.44	47	0.16 [-0.25, 0.58]

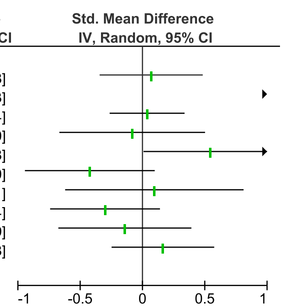
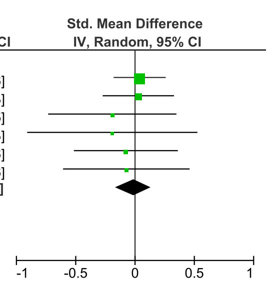


FIGURE 6. Meta-analysis of exercise on delayed memory in MCI.

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.2 Delayed Memory								
Lam 2010	0.7	2.55	135	0.6	2.55	194	45.2%	0.04 [-0.18, 0.26]
Lautenschlager 2008	0.45	2.6	85	0.38	2.4	85	24.1%	0.03 [-0.27, 0.33]
Molloy 1988	-1.2	3.8	33	-0.4	4.55	22	7.5%	-0.19 [-0.73, 0.35]
Scherder 2005	0.14	4.83	15	1.06	4.5	15	4.2%	-0.19 [-0.91, 0.53]
Van Uffelen 2008 men	-0.8	2.7	36	-0.6	2.45	45	11.3%	-0.08 [-0.52, 0.36]
Van Uffelen 2008 women	-0.7	2.8	35	-0.5	2.5	22	7.7%	-0.07 [-0.61, 0.46]
Subtotal (95% CI)			**339**			**383**	**100.0%**	**-0.01 [-0.16, 0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 5 (P = 0.96); I² = 0%								
Test for overall effect: Z = 0.16 (P = 0.87)								
Test for subgroup differences: Not applicable								



CONCLUSIONS

This systematic review identified 14 RCT trials of exercise in individuals with MCI. The quality of this literature was moderate, and the majority of trials had samples too small for sufficient power to detect small effects. The vast majority of outcomes (92%) were nonsignificant, providing no strong or consistent evidence that exercise of any particular type significantly or robustly improves cognition in individuals at risk of dementia with MCI.

Relationship of Exercise Modality to Cognitive Outcomes

Prior systematic reviews and meta-analyses have mainly focused on aerobic exercise and linked it to improved executive function,[2,16,39] By contrast, this review found that the effect of aerobic exercise was limited to verbal fluency and no other executive function. Significant moderate-sized effects were reported for global cognition,[25,37] however. Although aerobic exercise did not benefit memory in any trial,[24,26,28,36,37] two trials of isolated resistance training resulted in large significant effects on memory,[30,36] suggesting that high intensity resistance training may specifically benefit memory. These significant results are consistent with a prior review in healthy older adults.[2] In contrast, lower intensity resistance training combined with other exercise modalities provided inconclusive results.

More research focusing on nonaerobic exercise is required for two reasons of clinical relevance. First, physical frailty, which is targeted by resistance training, has been specifically associated with increased risk of MCI.[40] Secondly, many older adults with co-morbidities may not tolerate moderate—high intensity aerobic exercise, but can tolerate high intensity resistance training. Currently, the American College of Sports Medicine recommends that exercise programs for older adults include both aerobic and nonaerobic physical activities, such as resistance training, balance training, and stretching,[19] for optimal general health. The relative lack of efficacy of multi-modal training for cognitive outcomes in this review, however, suggests that this general recommendation for older adults may not be optimal for targeting cognitive impairment specifically.

Mode of Delivery and Dose of Exercise

Most trials delivered exercise regimes in groups but the number of participants per training session was not reported.[24,26,27,29,30—33,35,36] Interestingly, group size may have an impact on results. A prior meta-analysis of exercise in cognitively impaired adults reported the greatest benefit in studies with groups of no larger than ten individuals.[4] Individuals with increasing cognitive difficulties may become overwhelmed in larger groups, or alternatively, larger groups may lead to insufficient personal training and feedback. Small group training optimizes the feasibility and adaptation to more intensive training, and so may lead to greater physiological and cognitive response. On the other hand, such training has logistical and economical drawbacks when considering population-based implementation. In general, much more research is required to understand dose—response linkages between exercise and cognitive change.

Limitations of the Current Review and Existing Evidence Base

Whereas this review attempted to increase its scope to include all individuals with subtle early cognitive changes, it was limited by the number of RCTs available for review. The application of a general construct of MCI also introduces the problematic issue that potentially different etiological processes and subtypes may have been mixed within the MCI diagnosis. Notably, unlike previous reviews that mixed healthy adults with those with MCI,[13] or MCI with dementia,[2] this review attempted to clearly delineate individuals at the transitional stage between cognitive health and dementia.

Several methodological shortcomings were noted in this emerging field. Negligible or nonsignificant effects were reported in a high proportion of cognitive outcomes, consistent with results from a previous systematic review of exercise that combined healthy and impaired adults.[13] Our calculations show that individually the 14 studies were underpowered on most outcomes. Given our overall finding was for no significant effect, the unavoidable issue of negative publication bias should not have impinged upon the outcome of this review.

Only two trials have reported longitudinal follow-up,[28,37] thus little is known regarding the persistence of putative therapeutic effects in MCI following the termination of exercise. In addition, the training regimes were relatively short and some lacked sufficient intensity to optimize neurophysiological or neuropsychological change. Future studies will also need to use cognitive measures more sensitive to longitudinal change.[13] Arguably the most salient issue for the field is the expansion of outcomes to assess transfer of cognitive gains to activities of daily living, quality of life, and psychological well-being.

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