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Research

Physical exercise attenuates cognitive decline and reduces behavioural problems in people with mild cognitive impairment and dementia: a systematic review

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KEY WORDS

Exercise
Dementia
Cognitive dysfunction
Systematic review
Meta-analysis

ABSTRACT

Questions: What is the effect of physical exercise on cognitive decline and behavioural problems in people with mild cognitive impairment (MCI) or dementia? What is the effect of physical exercise on particular domains of cognitive function? How do training protocols and patients' characteristics influence the outcomes? **Design**: Systematic review and meta-analysis of randomised trials. **Participants**: People with MCI or dementia as their primary diagnosis. **Intervention**: Physical exercise. **Outcome measures**: Cognitive function including global cognition, memory, executive function, reasoning, attention, language, and behavioural problems. **Results**: Forty-six trials involving 5099 participants were included in this review. Meta-analysis of the data estimated that aerobic exercise reduced the decline in global cognition, with a standardised mean difference (SMD) of 0.44, 95% CI 0.27 to 0.61, I^2 = 69%. For individual cognitive functions, meta-analysis estimated that exercise lessened working memory decline (SMD 0.28, 95% CI 0.04 to 0.52, I^2 = 40%). The estimated mean effect on reducing the decline in language function was favourable (SMD 0.17), but this estimate had substantial uncertainty (95% CI –0.03 to 0.36, I^2 = 67%). The effects of exercise on other cognitive functions were unclear. Exercise also reduced behavioural problems (SMD 0.36, 95% CI 0.07 to 0.64, I^2 = 81%). **Conclusion**: Physical exercise can reduce global cognitive decline and lessen behavioural problems in people with MCI or dementia. Its benefits on cognitive function can be primarily attributed to its effects on working memory. Aerobic exercise at moderate intensity or above and a total training duration of > 24 hours can lead to a more pronounced effect on global cognition. **[Law C-K, Lam FMH, Chung RCK, Pang MYC (2020) Physical exercise attenuates cognitive decline and reduces behavioural problems in people with mild cognitive impairment and dementia: a systematic review. *Journal of Physiotherapy* 66:9–18]**

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Introduction

Due to its increasing prevalence, dementia has become a major public concern in recent years. In 2010, it was estimated that 36 million people were suffering from dementia worldwide. The number is anticipated to increase to 115 million by 2050.[1]

Decline in cognitive functions and behavioural problems are the common and inter-related symptoms of dementia.[2–4] Progression of behavioural problems in people with dementia is associated with a higher rate of cognitive decline.[5] Cognitive and behavioural problems can induce diverse issues such as reduced daily function and independence, which substantially increase the risk of institutionalisation and caregiver burden.[6–14] Effective intervention is needed to reduce the deterioration of cognitive functions and behavioural problems in people with cognitive impairment.

Exercise improves cognition,[15–21] but most of the evidence[15–18,21] relates to global cognition, which is a summary measure of diverse cognitive functions such as attention, executive function, memory, language and reasoning.[22,23] These cognitive functions are managed by different areas of the brain and are known to decline at different rates throughout the disease progression.[24–26] The areas and severity of cognitive decline also vary greatly among patients. Knowing that exercise improves global cognition is important but insufficient. Imaging studies have found that exercise has a particularly potent effect on certain brain regions[27] (eg, hippocampus[28]); this suggests that the effect of exercise could vary across the different cognitive functions. The effect of exercise on individual cognitive functions has been widely evaluated in people without cognitive decline or with mild cognitive impairment (MCI)[20,29–31] but limited in people with dementia. An existing systematic review[19] that included studies of people with dementia failed to delineate the effect of physical exercise by including trials that adopted multiple interventions[32,33] and no meta-analysis was conducted. The effect of exercise on individual cognitive functions in people with dementia remains unclear.

While it was suggested that exercise can alleviate behavioural problems, the evidence is seldom reviewed.[34,35] The most recent reviews[16,17] that have attempted to investigate the influence of exercise on behavioural problems did not draw a solid conclusion.

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Therefore, the research questions for this systematic review were:

1. What is the effect of physical exercise on cognitive decline and behavioural problems in people with mild cognitive impairment (MCI) or dementia?
2. What is the effect of physical exercise on particular domains of cognitive function?
3. How do training protocols and patients' characteristics influence the outcomes?

Methods

Identification and selection of trials

PubMed, CINAHL, MEDLINE, PsycINFO, and The Cochrane Database of Systematic Reviews were searched electronically using terms including *Alzheimer*, *dementia*, *mild cognitive impairment*, *physical exercise*, *randomized*, *clinical trial*, etc. (see Appendix 1 on the eAddenda). Two independent researchers screened the retrieved studies for eligibility. In cases of disagreement, the senior researcher was consulted for a final decision. The reference lists of all included studies and related review articles were screened to identify potentially eligible studies. Forward searching based on all studies that were selected in the process mentioned above was conducted using Science Citation Index. The last search was conducted in September 2018. The inclusion criteria are presented in Box 1. Exclusion criteria were reports in books, studies in which the effect of physical exercise could not be delineated due to the study design, and conference proceedings.

Box 1. Inclusion criteria.

Design
- Randomised controlled trial
- Published in English

Participants
- People with mild cognitive impairment (MCI) or dementia as the primary diagnosis

Intervention
- Physical exercise

Outcome measures
- Measures of cognitive functions
- Measures of behavioural problems

Comparisons
- Exercise versus no intervention/placebo
- Exercise plus other intervention versus other intervention only

Assessment of characteristics of studies

Two researchers extracted data independently. From each selected study, they extracted the characteristics of the study population, outcome measures and details of the intervention (ie, type, frequency, intensity and duration of training). All types of physical exercise – including aerobic exercise, walking exercise and resistance exercise – were included in this review. Physical exercise that could not be classified into these basic categories was grouped into other exercises (eg, Tai Chi, handball training). If a study combined different types of exercise, it was regarded as integrated exercise. Cognitive function was classified into global cognition, memory, executive function, reasoning, attention and language. Different assessments examining the same cognitive function were grouped together for analysis. The operational definitions of different types of exercises and cognitive functions are presented in Appendix 2 (see eAddenda for Appendix 2). The PEDro score, obtained by searching the PEDro website, was used to assess the methodological quality of each selected trial.

Data analysis

Meta-analysis was only conducted if an outcome measure was or similar outcome measures were adopted in at least five studies. A list of which outcome measures were categorised as similar is provided in Appendix 3 (see eAddenda for Appendix 3). Meta-analysis was performed using Comprehensive Meta-analysis[a], while forest plots of meta-analyses were generated using Review Manager[b]. A random-effects model was used to combine the results because different study designs (eg, exercise protocol, participant characteristics) were used across studies. The summarised effect of exercise was denoted by the standardised mean difference (SMD). Egger's regression asymmetry test was used to examine the existence of publication bias. Separate sensitivity analyses were performed for studies that: had good methodological quality, were conducted in similar patient subgroups, or adopted similar intervention, as long as five or more studies were available for inclusion. In cases where the information required for meta-analysis could not be obtained from the original studies, corresponding authors were contacted through email.

The level of evidence for each individual outcome measure was rated by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system.[36] Since only randomised trials were included in the present review, the initial score for each outcome was assigned as 'high quality' and any condition listed in Box 2 would downgrade the quality of evidence by one level. If less than half of the participants included in the primary meta-analysis were from trials with a PEDro score of ≥ 4, the quality of evidence was downgraded by two levels. For outcomes that had insufficient studies for meta-analysis ($<$ five trials), the same criteria were administered on the basis of the total number of trials examining those particular outcomes. The quality of evidence was upgraded by one level when a large effect size was detected or a dose-response relationship was found.

Results

Flow of studies through the review

Electronic searches identified 9635 records. After screening, 144 potentially relevant papers were extracted. Thirty-four eligible papers were identified and an additional 16 eligible papers were identified by forward citation tracking. Finally, 46 trials (50 articles)[37–86] involving a total of 5099 participants were included in this review (Figure 1). Nine papers were excluded from the meta-analyses because the necessary information was not available even after making requests to the original authors.[39,46,49,52,56,60,72,79,80]

Characteristics of the included trials

The mean age of the participants in the included trials ranged from 68 to 86 years and the severity of cognitive impairment varied from MCI to severe dementia (MCI: 14 trials; mild: seven trials; moderate: 19 trials; severe: two trials; not reported: four trials). Different types of exercise were adopted (aerobic: 17 trials; integrated: 15 trials; resistance: three trials; walking: four trials; others: seven trials). Detailed study characteristics are summarised in Table 1. The results of the primary meta-analyses and related sensitivity analyses are presented Table 2. The quality of the evidence is summarised in Table 3.

Effect of exercise on cognitive functions

Global cognition

Assessments for global cognition were reported in 35 trials.[37,38,40–44,46,48–57,60,61,64–66,73,75,77–86] Meta-analysis (26 trials, 2079 participants) showed that exercise improved global cognition (SMD 0.44, 95% CI 0.27 to 0.61) (Figure 2 and Table 2).[37,38,41–43,48,50,51,53–57,60,61,64,66,75,77,80–86] See Figure 3 on the eAddenda for a detailed forest plot. Different sensitivity analyses (Table 2) were conducted and all reported results in favour of exercise. Notably, aerobic exercise might lead to a more potent improvement in global cognition (SMD 0.45, 95%

Box 2. Criteria used to downgrade one level of rating in the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system.

Risk of bias	• for outcomes where meta-analysis was possible, less than half of the participants included in the primary analysis were from trials with a PEDro score of ≥ 6 • for outcomes where meta-analysis was not possible, less than half of the participants included for outcome evaluation were from trials with a PEDro score of ≥ 6
Inconsistency	• for outcomes where meta-analysis was possible, $I^2 \geq 50\%$ in the primary meta-analysis and the meta-analysis that involved only trials with high methodological quality • for outcomes where meta-analysis was not possible, mixed results were reported
Indirectness	• the participants, intervention, comparator intervention, outcome measure or study design did not match between the included studies and the eligibility criteria for this review
Imprecision	• insufficient studies for meta-analysis • the number of subjects included in the primary meta-analysis was < 800 • the 95% CI spanned 0
Publication bias	• $p < 0.1$ on the two-tailed Egger's regression asymmetry test

CI 0.15 to 0.76). In particular, aerobic exercise with moderate to high intensity further augmented this improvement (SMD 0.60, 95% CI 0.21 to 0.98). Sensitivity analyses of studies with participants possessing Mini Mental State Exam (MMSE) baseline score of 10 to 20 (SMD 0.54, 95% CI 0.18 to 0.89) and studies adopting exercise with total training duration > 24 hours (SMD 0.66, 95% CI 0.32 to 0.99) also resulted in a more prominent effect than the primary meta-analysis.

Memory

For memory, assessments of delayed memory were reported in 15 trials.[43–46,48,49,52,56,57,60,65,67,69,74,86] The primary meta-analysis (11 trials, 1294 participants; SMD 0.15, 95% CI –0.04 to 0.34) (Figure 4 and Table 2) and sensitivity analyses did not provide a clear estimate of the effect (Table 2).[43–45,48,56,57,65,67,70,74,86] See Figure 5 on the eAddenda for a detailed forest plot. The meta-analysis on recognition (six trials, 291 participants) also did not provide a clear estimate of the effect (SMD 0.33, 95% CI –0.25 to 0.92) (Figure 6 and Table 2).[41,43–45,51,70] See Figure 7 on the eAddenda for a detailed forest plot. Six trials assessed other memory functions.[39,43,51,56,57,68] One trial showed that exercise could significantly improve associative memory.[68] No significant effect of exercise on declarative memory,[39,43] incidental memory,[39,43] short-term memory[51] and subjective cognitive complaints[56,57] was reported.

Executive function

For executive function, meta-analysis (eight trials, 646 participants) revealed that exercise could significantly improve working memory, although the effect may be small (SMD 0.28, 95% CI 0.04 to 0.52) (Figure 8 and Table 2).[38,41,45,48,51,57,64,85] See Figure 9 on the eAddenda for a detailed forest plot. Sensitivity analysis (Table 2) of high methodological quality trials showed that exercise might improve working memory moderately, but the possibility of a trivial negative effect was not excluded (SMD 0.14, 95% CI –0.03 to 0.30). Seventeen trials assessed cognitive flexibility.[38–41,46,48,51,56,57,60,62,64,65,68,70,79,86] The primary analysis (seven trials, 544 participants; SMD 0.03, 95% CI –0.14 to 0.20) (Figure 10 and Table 2) showed no worthwhile effect.[38,41,48,51,62,68,79] See Figure 11 on the eAddenda for a detailed forest plot. No worthwhile effect of exercise on cognitive flexibility was found even when sensitivity analyses were conducted (Table 2). Inhibition was not examined among the included trials in this review. Hence, there was no evidence regarding the effect of exercise on inhibition.

Reasoning

Reasoning was assessed in two trials conducted in community-dwelling older people with MCI.[46,65] One study[46] reported that 6 months of resistance training could have a small effect on reasoning, while the other study[65] showed that a 3-month walking program had no clear effect.

Attention

Attention was examined in 20 trials.[38–46,48,51,52,56,57,60,64,65,70,85,86] The meta-analysis (15 trials, 1264 participants) demonstrated that exercise had no clear effect on attentional performance and suggested that any possible effect would be small (SMD 0.04, 95% CI –0.08 to 0.15) (Figure 12 and Table 2).[38,40–45,48,51,57,64,65,70,85,86] See Figure 13 on the eAddenda for a detailed forest plot. No clear effect was found in sensitivity analyses (Table 2).

Language

Language ability was assessed in 20 trials.[38–41,43–46,48–51,56,57,60,65,70,72,77,79] The meta-analysis (14 trials, 1593 participants) suggested that exercise might improve language ability moderately, although the possibility of a trivial harmful effect was not excluded

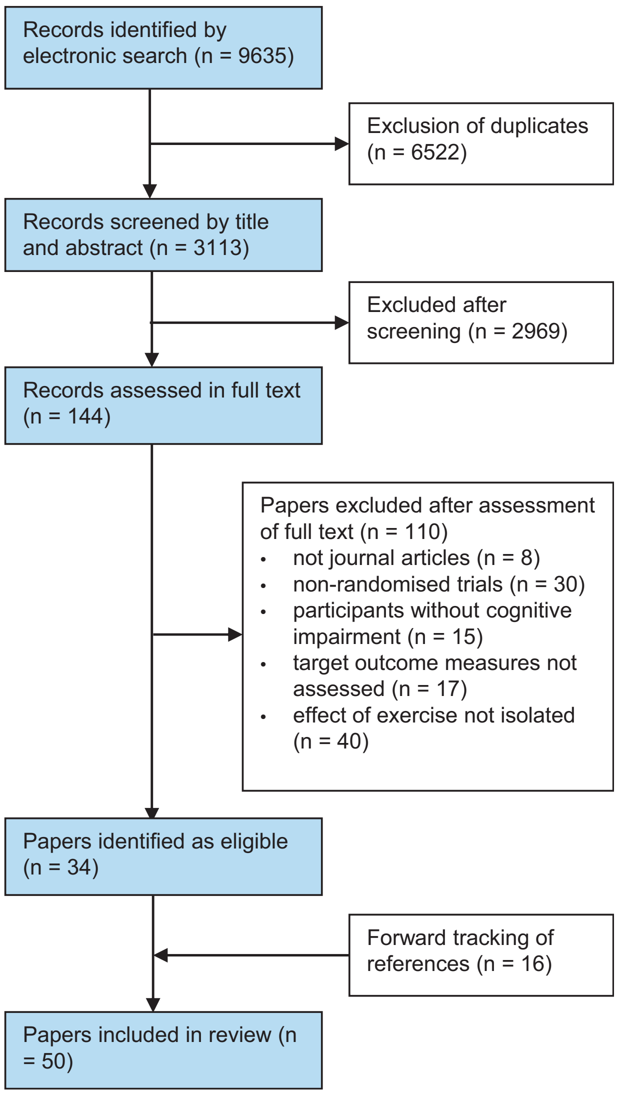

Figure 1. Flow of studies through the review.

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Table 1
Study characteristics.

Study	Quality[a]	N	Cognitive impairment[b]	Study setting	Type of exercise	Exercise intensity	Total training duration *(hr)*
Aguiar 2014[37]	Good	34	Mild	Other	Integrated[c]	NR	27
Arcoverde 2014[38]	Fair	20	Mild	Other	Aerobic	Moderate	16
Baker 2010[39]	Good	29	MCI	Community	Aerobic	High	≥ 72
Barnes 2013[40]	Good	126	MCI	Community	Aerobic	Low to moderate	36
Bossers 2015[41]	Good	109	Moderate	Residential care units	Aerobic	Moderate to high	18
Cancela 2016[42]	Good	114	Moderate	Residential care units	Aerobic	Self-paced	≥ 105
Christofoletti 2008[43]	Fair	54	Moderate	Residential care units	Integrated[d]	NR	72
Eggermont 2009a[44]	Good	61	Moderate	Residential care units	Others	NR	15
Eggermont 2009b[45]	Good	97	Moderate	Residential care units	Walking	NR	15
Fiatarone Singh 2014[46]	Good	100	MCI	Community	Resistance	High	≥ 48
Fleiner 2017[47]	Good	85	Moderate	Residential care units	Integrated[d]	NR	8
Hoffmann 2016[48]	Good	200	Mild	Others	Aerobic	Moderate to high	48
Hokkanen 2008[49]	Fair	29	Moderate	Residential care units	Others	NR	≥ 4
Holthoff 2015[50]	Good	30	Mild	Community	Resistance	NR	18
Hong 2018[51]	Fair	22	NR	Others	Resistance	NR	24
Hu 2014[52]	Fair	204	NR	Community	Aerobic	NR	36
Kemoun 2010[53]	Fair	31	Moderate	Residential care units	Integrated[c]	High	45
Kim 2016[54]	Good	33	Moderate	Residential care units	Aerobic	Low	120
Kwak 2008[55]	Fair	30	Moderate	Community	Integrated[d]	Low to moderate	NR
Lam 2015[56]	Good	555	MCI	Community	Integrated[c]	NR	48
Lam 2011[57]	Good	389	MCI	Community	Others	NR	≥ 18
Lam 2012[58]	Good	389	MCI	Community	Others	NR	≥ 18
Landi 2004[59]	Poor	30	Moderate	Residential care units	Integrated[c]	NR	NR
Lautenschlager 2008[60]	Good	170	MCI	Community	Integrated[c]	Moderate	60
Lee 2018[61]	Fair	60	NR	Residential care units	Integrated[d]	NR	12
Liu-Ambrose 2016[62]	Good	70	MCI	Others	Aerobic	Moderate to high	72
Lowery 2014[63]	Good	131	Moderate	Community	Walking	NR	≥ 20
Lü 2015[64]	Good	45	MCI	Community	Others	Tailored to participants' capabilities	36
Maki 2012[65]	Good	150	MCI	Community	Walking	NR	18
Miu 2008[66]	Good	85	Moderate	Community	Aerobic	NR	≥ 18
Nagamatsu 2013[67]	Good	86	MCI	Community	Aerobic	Moderate to high	48
Nagamatsu 2012[68]	Fair	86	MCI	Community	Aerobic	Moderate to high	48
Rolland 2007[69]	Good	134	Severe	Residential care units	Integrated[c]	NR	96
Scherder 2005[70]	Fair	43	Severe	Residential care units	Walking	NR	9
Sobol 2018[71]	Good	52	MCI	Others	Aerobic	Moderate to high	48
Steinberg 2009[72]	Fair	27	Moderate	Community	Integrated[c]	NR	NR
Stevens 2006[73]	Poor	75	NR	Residential care units	Aerobic	NR	≥ 18
Sungkarat 2017[74]	Good	66	MCI	Community	Others	NR	18
Telenius 2015a[75]	Good	163	Moderate	Residential care units	Integrated[d]	High	≥ 20
Telenius 2015b[76]	Good	170	Moderate	Residential care units	Integrated[d]	High	≥ 20
Toots 2017[77]	Good	186	Moderate	Residential care units	Integrated[d]	High	30
Toulotte 2003[78]	Poor	20	Moderate	Others	Integrated[d]	NR	24
van Uffelen 2008[79]	Good	152	MCI	Community	Aerobic	Moderate	96
Varela 2012[80]	Good	48	Mild	Residential care units	Aerobic	High	18
Venturelli 2011[81]	Good	21	Moderate	Residential care units	Aerobic	Moderate	48
Vreugdenhil 2012[82]	Good	40	Mild	Community	Integrated[c]	NR	NR
Wei 2014[83]	Fair	60	MCI	Residential care units	Others	Low	60
Yang 2015[84]	Fair	50	Mild	Community	Aerobic	Moderate	24
Yoon 2013[85]	Fair	20	Moderate	Residential care units	Aerobic	Low	12
Zhu 2018[86]	Good	60	MCI	Community	Others	Moderate to high	21

NR = not reported, MCI = mild cognitive impairment.
[a] Better methodological quality is indicated by a higher PEDro score (9 to 10: excellent; 6 to 8: good; 4 to 5: fair; < 4: poor).
[b] Cognitive impairment level is classified by average Mini Mental State Exam score of participants (> 24: MCI; 20 to 24: mild; 10 to 20: moderate; < 10: severe).
[c] With aerobic component.
[d] Without aerobic component.

(SMD 0.17, 95% CI –0.03 to 0.36) (Figure 14 and Table 2).[40,41,43–45,48,50,51,56,57,65,70,77,79] See Figure 15 on the eAddenda for a detailed forest plot.

Behavioural problems

Behavioural problems were assessed in 11 trials.[42,47,48,50,57,59,63,69,72,75,84] The meta-analysis (nine trials, 1172 participants) demonstrated that exercise can reduce behavioural problems but the relatively wide confidence intervals indicated that the favourable effect may or may not be worthwhile (SMD 0.36, 95% CI 0.07 to 0.64) (Figure 16 and Table 2).[42,47,48,50,57,63,69,75,84] See Figure 17 on the eAddenda for a detailed forest plot.

Attendance and adverse events

Attendance to the intervention was reported in 14 trials.[38,41,42,47,48,60,62,65,69,74,77,79,81,86] The attendance rates had a wide range of 33 to 93% and all reported that attendance rates were > 60%, except that one trial[67] reported a particularly low attendance rate (33%). Reasons for low attendance included behaviour disorders, disagreement or unwillingness to continue, and acute disease. In addition, among the 37 trials that reported information about supervision of the intervention, only two of them[60,72] reported that participants underwent interventions without supervision. Otherwise, interventions were under the supervision of trainers or caregivers.

Data on adverse events were reported in 27 trials.[37,38,40–42,46–48,50,52,56–58,60,62–64,67,69,72,74,75,77,79,81,83,86] Nine trials[38,56,64,74,75,79,81,83,86] reported that there were no adverse events. Seven trials[42,47,57,58,60,63,72] reported adverse events that were regarded by the original authors as likely unrelated to the intervention. Seven trials[37,40,46,48,62,67,69] reported adverse events that were potentially related to the intervention (eg, acute episodes of shortness of breath,[67] fall,[40,46,62,67] pain,[40] dizziness,[40,48] hospitalisation,[40] erythema/itching,[37] exacerbations of pre-existing arthritis symptoms,[46] musculoskeletal problems,[48] faintness,[48] and atrial fibrillation[48]). In addition, the relationship between the intervention and adverse events was not mentioned in four trials.[41,50,52,77]

Table 2
Meta-analysis and sensitivity analysis results for different aspects of cognitive function.

Outcome	Trials (n)	Participants (n)		SMD	95% CI	I^2	Publication bias
		Exp	Con				
Global cognition							
primary meta-analysis	26	1011	1068	0.44	0.27 to 0.61	69%	Yes
high quality only	17	852	905	0.29	0.11 to 0.47	68%	Yes
MMSE score > 24	6	396	444	0.39	0.07 to 0.70	75%	Yes
MMSE score 20 to 24	7	205	190	0.33	0.11 to 0.54	8%	Yes
MMSE score 10 to 20	11	370	392	0.54	0.18 to 0.89	80%	Yes
aerobic exercise only	11	352	352	0.45	0.15 to 0.76	71%	No
integrated exercise only	9	420	411	0.43	0.13 to 0.73	73%	Yes
aerobic exercise[a]	7	236	219	0.60	0.21 to 0.98	70%	Yes
total training time ≤ 24 hr	13	514	590	0.23	0.07 to 0.40	35%	Yes
total training time > 24 hr	12	477	458	0.66	0.32 to 0.99	81%	Yes
Delayed memory							
primary meta-analysis	11	624	670	0.15	−0.04 to 0.34	59%	Yes
high quality only	9	597	638	0.10	−0.06 to 0.25	41%	Yes
MMSE score > 24	6	428	480	0.14	−0.10 to 0.38	63%	Yes
total training time ≤ 24 hr	7	339	407	0.16	−0.04 to 0.36	35%	No
Recognition							
primary meta-analysis	6	141	150	0.33	−0.25 to 0.92	82%	No
Working memory							
primary meta-analysis	8	292	354	0.28	0.04 to 0.52	40%	Yes
high quality only	5	261	323	0.14	−0.03 to 0.30	0%	No
total training time ≤ 24 hr	7	270	331	0.30	0.02 to 0.58	48%	Yes
Cognitive flexibility							
primary meta-analysis	7	289	255	0.03	−0.14 to 0.20	0%	No
high quality only	5	269	233	0.05	−0.13 to 0.23	0%	Yes
aerobic exercise only	6	279	243	0.01	−0.16 to 0.19	0%	No
Attention							
primary meta-analysis	15	597	667	0.04	−0.08 to 0.15	0%	No
high quality only	10	539	604	0.05	−0.07 to 0.17	0%	No
MMSE score > 24	5	282	347	0.01	−0.15 to 0.17	0%	No
MMSE score 10 to 20	6	178	195	0.11	−0.19 to 0.41	47%	No
aerobic exerciser only	6	243	238	0.12	−0.06 to 0.30	<1%	No
total training time ≤ 24 hr	10	378	444	0.05	−0.09 to 0.19	0%	No
total training time > 24 hr	5	219	223	−0.01	−0.28 to 0.25	42%	No
Language							
primary meta-analysis	14	788	805	0.17	−0.03 to 0.36	65%	Yes
high quality only	11	751	761	0.05	−0.11 to 0.21	51%	Yes
MMSE score > 24	5	450	471	0.00	−0.19 to 0.19	43%	No
MMSE score 10 to 20	5	196	204	0.33	−0.14 to 0.80	79%	Yes
total training time ≤ 24 hr	9	425	490	0.22	0.02 to 0.42	47%	Yes
total training time > 24 hr	5	363	315	0.08	−0.28 to 0.43	77%	Yes
Behavioural problems							
primary meta-analysis	9	560	612	0.36	0.07 to 0.64	81%	No
high quality only	8	535	587	0.35	0.04 to 0.66	83%	No
total training time ≤ 24 hr	6	351	407	0.28	0.10 to 0.46	24%	No

SMD = standardised mean difference, MMSE = Mini Mental State Exam.
[a] moderate to high intensity.

Discussion

This is the first systematic review to estimate the effect of exercise on individual cognitive functions and behavioural problems among people with MCI or dementia. In line with previous reviews, exercise was estimated to be effective for global cognition.[15,17,18,20] However, it appears to selectively improve particular areas of cognitive function.

Among the various cognitive functions that were examined, the results revealed that physical exercise can improve working memory. Working memory is one of the cognitive functions that shows earlier decline among all cognitive functions in people with Alzheimer's disease,[26] and may thus be more sensitive to exercise intervention. There was also very low quality of evidence showing an improvement in language function in the exercise group. However, the possibility of a trivial negative effect could not be excluded. Also, the heterogeneity was still moderate to high in all sensitivity analyses. There could be unidentified factors affecting the participants' responsiveness to exercise training on language improvement. Upon scrutinising the individual studies included in the meta-analyses, most studies showed that the intervention group exhibited no improvement, while the control group demonstrated significant cognitive decline during the study period. Thus, exercise is effective in alleviating cognitive decline rather than enhancing cognitive functions.

There was a moderate level of evidence showing that exercise has minimal effect on cognitive flexibility and attention. The meta-analyses revealed no favourable effects with relatively low heterogeneity across studies. Nonetheless, when the characteristics of the trials (n = 7) that examined cognitive flexibility were scrutinised, those trials were found to be similar in the type of exercise adopted (aerobic = 6, resistance = 1) and severity of participants' cognitive impairment (baseline MMSE score ≥ 20 = 5, baseline MMSE score 10 to 20 = 1, not reported = 1). It remains unclear whether cognitive flexibility could be improved by other types of exercise or in people with more severe dementia. On the other hand, the trials examining attention were diverse in trial characteristics. This suggests that exercise in general does not have an effect on attention, regardless of the difference in exercise types and characteristics of the participants. Although the meta-analysis of delayed memory and recognition also yielded non-significant results, the effect of exercise on these cognition functions was highly uncertain because the heterogeneity across studies was very large. No concrete conclusion could be drawn. Other memory-related functions and reasoning were insufficiently studied to draw any conclusion.

This review also demonstrated that exercise significantly reduces behavioural problems assessed by the Neuropsychiatric Inventory, which measures various aspects of behavioural functioning (eg, apathy, agitation).[87] Failure in these aspects of behavioural

Table 3
Grades of Recommendation, Assessment, Development and Evaluation (GRADE) quality of evidence.

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size	Plausible residual confounding	Dose-response gradient	GRADE rating
Global cognition	0	–1[a]	0	0	–1[b]	0	0	0	Low
Global cognition (aerobic exercise only)	0	–1[a]	0	–1[c]	0	0	0	+1[d]	Moderate
Delayed memory	0	0	0	–1[e]	–1[b]	0	0	0	Low
Recognition	0	–1[a]	0	–1[e]	0	0	0	0	Low
Working memory	0	0	0	–1[e]	–1[b]	0	0	0	Low
Cognitive flexibility	0	0	0	–1[e]	0	0	0	0	Moderate
Reasoning	0	–1[f]	0	–1[e]	0	0	0	0	Low
Attention	0	0	0	–1[e]	0	0	0	0	Moderate
Language	0	–1[a]	0	–1[e]	–1[b]	0	0	0	Very low
Behavioural problem	0	–1[a]	0	0	0	0	0	0	Moderate
Associative memory	–1[g]	0	0	–1[h]	0	0	0	0	Low
Declarative memory	–1[g]	0	0	–1[h]	0	0	0	0	Low
Incidental memory	–1[g]	0	0	–1[h]	0	0	0	0	Low
Short-term memory	–1[g]	0	0	–1[h]	0	0	0	0	Low

[a] $I^2 \geq 50\%$ in the primary and high methodological quality analysis.
[b] Publication bias is present.
[c] Number of participants included in the analysis is < 800.
[d] Particular training intensity yielded a more prominent effect.
[e] Effect size overlaps 0 in the primary or high methodological quality analysis.
[f] Mixed results reported across trials, and meta-analysis is not possible.
[g] Fewer than half of the participants included for outcome evaluation were from trials with a PEDro score of ≥ 6.
[h] Insufficient studies for meta-analysis.

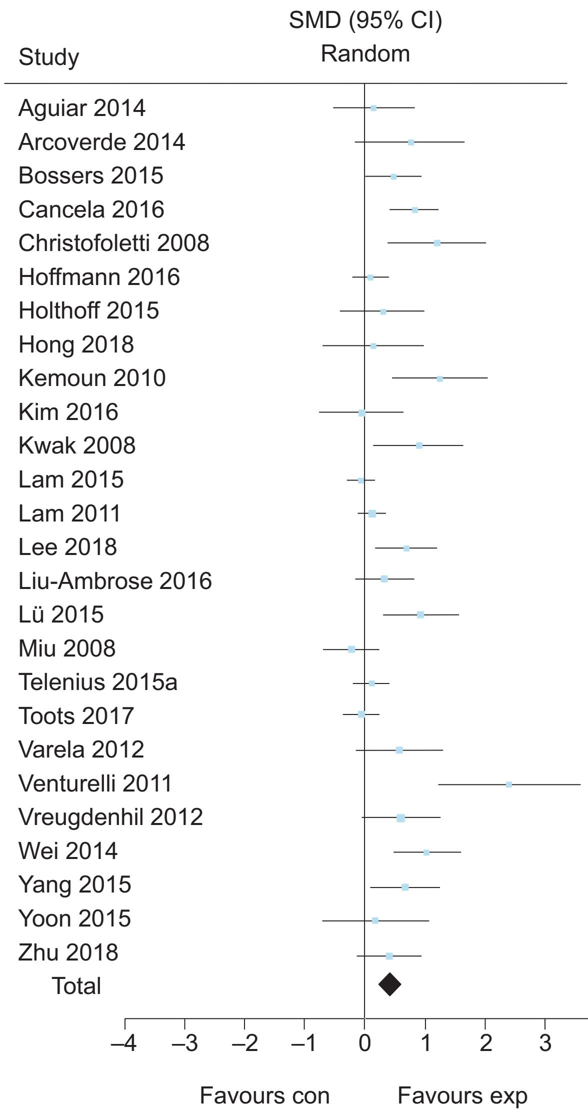

Figure 2. Standardised mean difference (95% CI) of the effect of exercise on global cognition by pooling data from 26 trials (n = 2079).

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functioning were found to be related to the defects of certain brain regions and neurotransmitter systems.[88] Exercise can induce the release of neurotrophic factor and certain neurotransmitters (eg, norepinephrine, serotonin) and facilitate brain plasticity and the balance of the neurotransmitter system,[89,90] which may alleviate behavioural problems.

Training duration and type of exercise appeared to be influential training parameters to prompt the favourable effect of exercise on global cognition. When the training duration of the included trials was divided according to median split (median = 24), the sensitivity analyses showed that a total training duration > 24 hours resulted in a more potent improvement in global cognition when compared with the primary meta-analysis. Additionally, it was found that aerobic exercise yielded a more pronounced beneficial effect on global cognition than the effect seen in the primary analysis that pooled all exercise types. The effect was further enhanced when only studies incorporating moderate to high intensity aerobic exercise were included. Unfortunately, no other types of exercise (eg, resistance training) could be singled out for sensitivity analysis. The improvement in cognition through aerobic exercise could be attributed to its facilitation on adult hippocampal neurogenesis.[90,91] The current positive finding agrees with this postulation but the included trials in this review did not aim to examine the neural mechanisms and thus a causal relationship could not be confirmed.[92–95] A similar trend could not be observed in other outcomes that reported positive findings, perhaps due to the insufficient number of trials for sensitivity analyses (ie, working memory and behavioural problems).

Baseline cognitive impairment level is another important factor in determining the treatment outcomes. The sensitivity analysis showed that people with more severe cognitive impairment tend to have a better outcome in global cognition with exercise. People with lower MMSE score at baseline also tend to have a steeper cognitive decline rate, and thus any therapeutic effect of exercise may be more apparent.[96] This has important clinical implications because people with more severe cognitive deficits can still benefit from exercise.

To evaluate the sustainability of the benefits from exercise, six trials included in this review conducted follow-up assessments on global cognition for a period of time (from 4 weeks to 12 months) after the exercise intervention had ceased.[41,46,49,50,60,86] Three of the trials reported that the improvement was not sustained when the follow-up assessment was conducted at ≤ 12 weeks (ie, 4, 9 and 12 weeks) after the end of the intervention,[41,49,50] whereas the other three trials showed that improvement was able to last for an

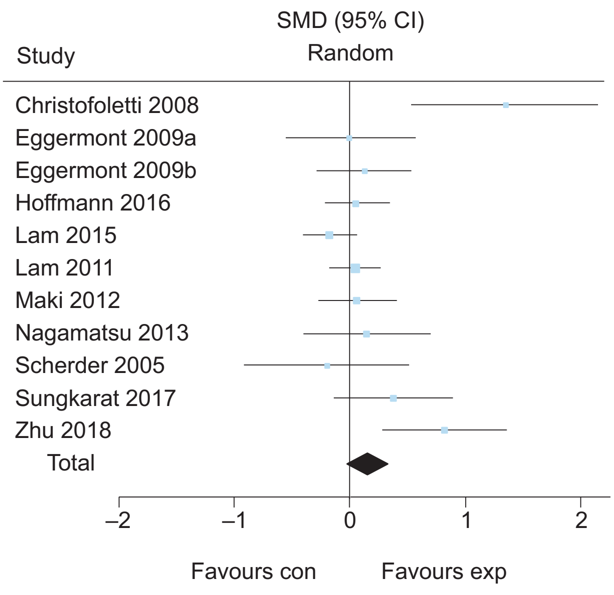

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Figure 4. Standardised mean difference (95% CI) of the effect of exercise on delayed memory by pooling data from 11 trials (n = 1294).

additional 12 weeks or more (ie, 12 and 48 weeks).[46,60,86] It is worth noting that all trials that reported sustained improvement in global cognition included people with MCI as participants and had longer total training durations (≥ 21 hours). On the contrary, in those trials that reported no sustained improvement, the participants had mild to moderate dementia and the total training duration was shorter (≤ 18 hours). However, the current results should be interpreted with caution, as there is insufficient data to estimate the effect of different trial characteristics (eg, participant population, training protocol) on the sustainability of improvement. Also, no study has examined the sustainability of the benefits of exercise on behavioural problems.

Most trials had acceptable attendance rates. The only trial[69] that had poor attendance (33%) included participants with a markedly low baseline MMSE score (8.8), while the participants of all other trials had baseline MMSE scores > 15. Severe cognitive impairment could be a potential cause of a low attendance rate.

Regarding safety, the adverse events that were considered to be potentially intervention-related were observed in few cases (n = 54) compared with the total number of participants exposed to the exercise intervention (n = 1850). Exercise intervention appears to be largely safe in people with MCI or dementia. However, it is recommended that exercise be administered with supervision.

The included studies had some common limitations. Most of the trials examined global cognition using MMSE. Nineteen of 30 scores in MMSE are related to language and working memory (10 from Orientation, five from Attention and Calculation and four from Language).[97] Improvement in MMSE may be induced predominantly by enhanced language ability and working memory. The conclusion that exercise improves global cognition has to be interpreted carefully as exercise may not benefit other cognitive functions, as shown in the present review. Also, most of the included studies recruited considerably more women than men. Finally, since not all of the included trials explicitly disclosed the type of dementia (eg, Alzheimer's, vascular) of the participants, the current review was unable to estimate the effect of exercise on various types of dementia.

This systematic review had some limitations. The mean baseline MMSE scores were used to classify the selected studies into different patient sub-groups. One potential problem for this classification is that it cannot take the heterogeneity of the sample within a study into account. The comparison of exercise effectiveness on people with different levels of cognitive impairment across studies is therefore compromised. Also, the influence of specific parameters of exercise protocols on training effect remains largely uninvestigated. There were large inter-study variations in training protocol. This study tried to reduce the heterogeneity by selecting trials that shared a particular parameter for sensitivity analysis (eg, total training duration). However, other dimensions of an exercise program might have also contributed to the difference in effect size obtained across analyses. In addition, the large inter-study variations in training protocol made it difficult to identify an 'optimal' training protocol in terms of training

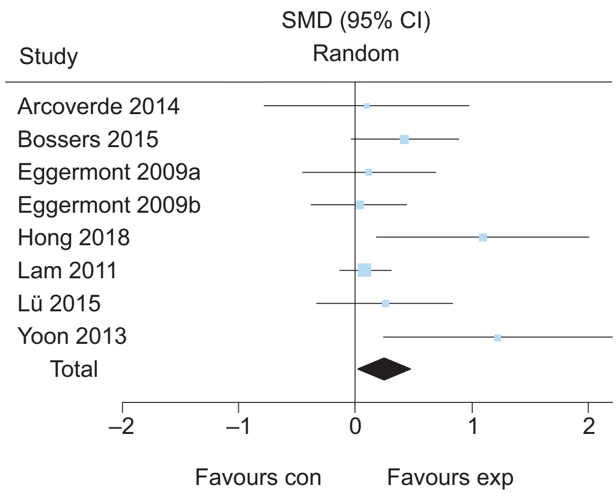

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Figure 8. Standardised mean difference (95% CI) of the effect of exercise on working memory by pooling data from eight trials (n = 646).

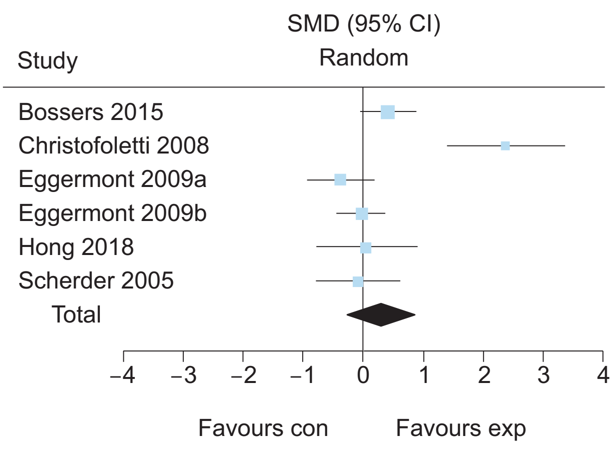

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Figure 6. Standardised mean difference (95% CI) of the effect of exercise on recognition by pooling data from six trials (n = 291).

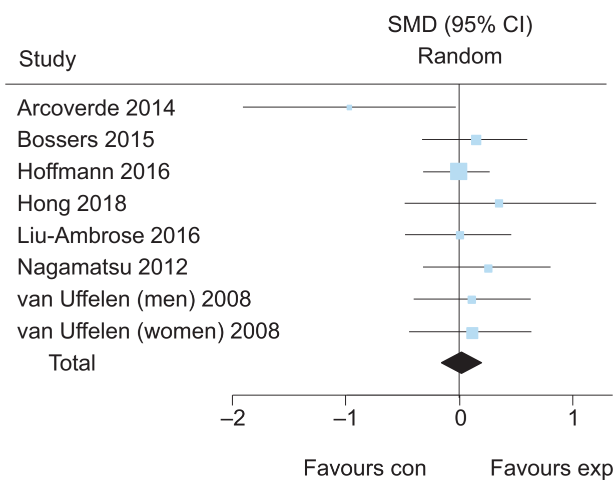

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Figure 10. Standardised mean difference (95% CI) of the effect of exercise on cognitive flexibility by pooling data from seven trials (n = 544).

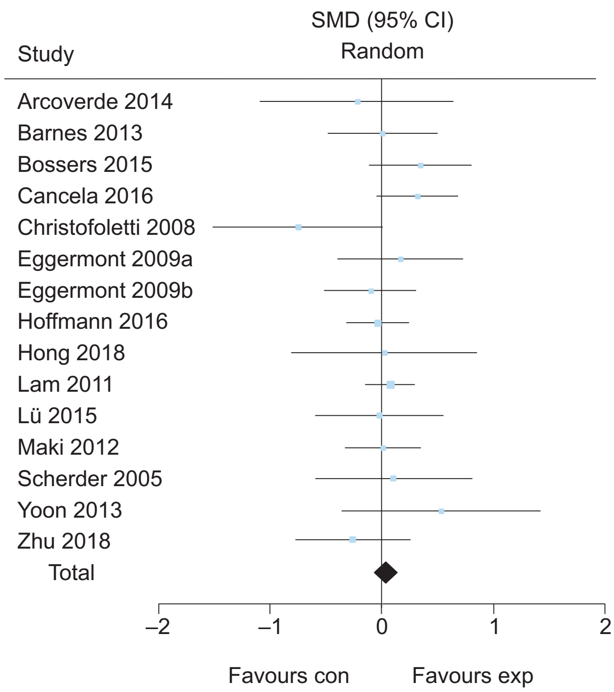

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Figure 12. Standardised mean difference (95% CI) of the effect of exercise on attention by pooling data from 15 trials (n = 1264).

frequency and duration. Therefore, analyses could only be conducted with total training duration, which can also shed some light on the proposed time of an 'optimal' training protocol. Finally, publication bias was present in most of the meta-analyses; this was taken into consideration in the rating of the quality of the evidence according to the GRADE system.

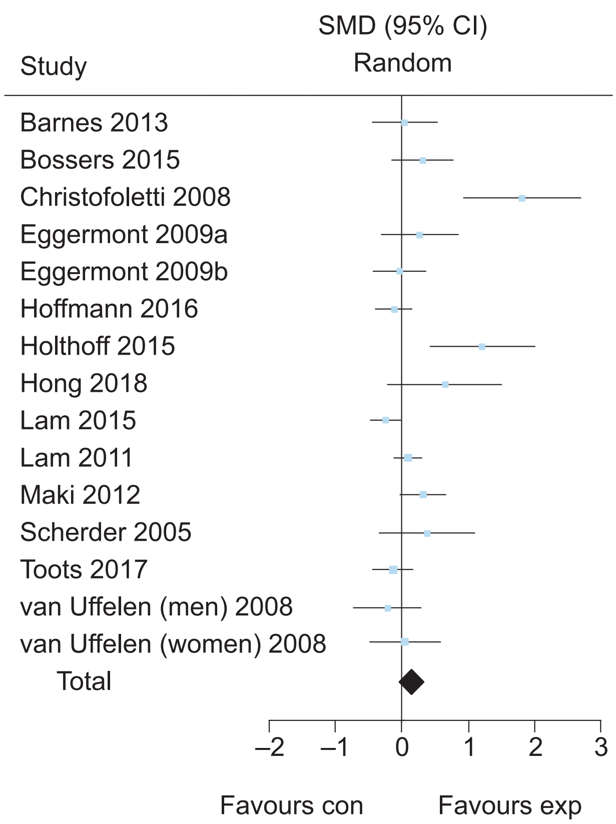

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Figure 14. Standardised mean difference (95% CI) of the effect of exercise on language by pooling data from 14 trials (n = 1593).

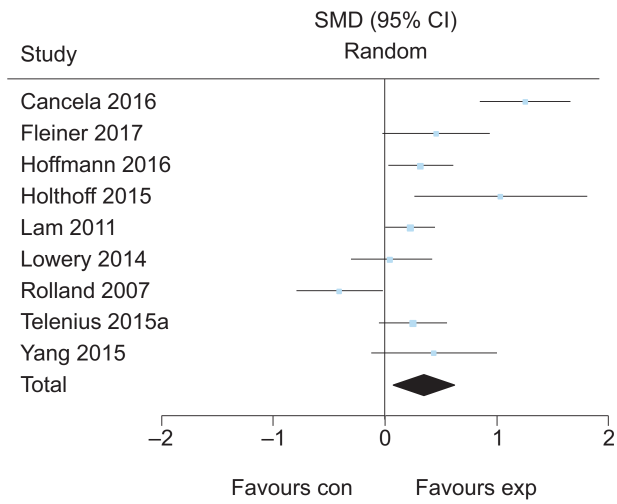

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Figure 16. Standardised mean difference (95% CI) of the effect of exercise on behavioural problem by pooling data from 9 trials (n = 1172).

In the future, more studies should be conducted to evaluate the effect of exercise on specific cognitive functions. The heterogeneity in most areas of cognitive functions remains large, while determinants of effective training remain unclear. More effort should be put into future studies to scrutinise the pivotal factors (eg, type of training, target population) that contribute to the favourable treatment outcomes. Research on people with a more severe grade of dementia is needed, especially considering that this review showed that people with moderate dementia tend to demonstrate greater improvement. Whether the effect of exercise on cognitive function and behavioural changes could last after discontinuing the exercise training also requires further investigation.

In conclusion, exercise appears to be safe in people with MCI and dementia when under supervision. There was low quality of evidence to support using non-specific physical exercise to reduce the decline in global cognition in people with MCI or dementia. The quality of evidence improved to moderate when aerobic exercise, particularly at moderate to high intensity, was adopted. The effect appeared to be more pronounced in those with moderate-grade dementia relative to those at an earlier stage. Total training duration of > 24 hours could lead to a greater training effect. For individual cognitive functions, there is low quality of evidence showing that exercise attenuates the decline in working memory. Moderate evidence was found that exercise in general has no substantial effect on attention. Aerobic exercise appears to have no substantial effect on cognitive flexibility in people with MCI or mild dementia. The effect of exercise on other cognitive functions was largely uncertain. It remains controversial whether the effect of exercise on cognitive function could last after the termination of exercise. There was also moderate quality evidence to support the use of exercise in alleviating behavioural problems.

What was already known on this topic: People with mild cognitive impairment and dementia exhibit deterioration in cognitive function and may have behavioural problems. Exercise improves cognition, but the evidence for this benefit focuses on global measures of cognitive function, which combine specific aspects such as attention, executive function, memory, language and reasoning.
What this study adds: Exercise reduces global cognitive decline and lessens behavioural problems in people with mild cognitive impairment or dementia. Its benefits on cognitive function are mainly due to its effects on working memory. The most pronounced effect on global cognition appears to arise from aerobic exercise at moderate or greater intensity with at least 24 hours of total training time.

Footnotes: [a] Comprehensive Meta-analysis Version 2, Biostat, Englewood, NJ, 2005. [b] Review Manager Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

eAddenda: Figures 3, 5, 7, 9, 11, 13, 15, 17 and Appendices 1, 2, 3 can be found online at https://doi.org/10.1016/j.jphys.2019.11.014.

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Competing interests: Nil.

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