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Research

Physical exercise improves strength, balance, mobility, and endurance in people with cognitive impairment and dementia: a systematic review

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KEY WORDS

Dementia
Exercise
Mild cognitive impairment
Physical fitness
Quality of life

ABSTRACT

Question: Does physical exercise training improve physical function and quality of life in people with cognitive impairment and dementia? Which training protocols improve physical function and quality of life? How do cognitive impairment and other patient characteristics influence the outcomes of exercise training? **Design**: Systematic review with meta-analysis of randomised trials. **Participants**: People with mild cognitive impairment or dementia as the primary diagnosis. **Intervention**: Physical exercise. **Outcome measures**: Strength, flexibility, gait, balance, mobility, walking endurance, dual-task ability, activities of daily living, quality of life, and falls. **Results**: Forty-three clinical trials (n = 3988) were included. According to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system, the meta-analyses revealed strong evidence in support of using supervised exercise training to improve the results of 30-second sit-to-stand test (MD 2.1 repetitions, 95% CI 0.3 to 3.9), step length (MD 5 cm, 95% CI 2 to 8), Berg Balance Scale (MD 3.6 points, 95% CI 0.3 to 7.0), functional reach (3.9 cm, 95% CI 2.2 to 5.5), Timed Up and Go test (–1 second, 95% CI –2 to 0), walking speed (0.13 m/s, 95% CI 0.03 to 0.24), and 6-minute walk test (50 m, 95% CI 18 to 81) in individuals with mild cognitive impairment or dementia. Weak evidence supported the use of exercise in improving flexibility and Barthel Index performance. Weak evidence suggested that non-specific exercise did not improve dual-tasking ability or activity level. Strong evidence indicated that exercise did not improve quality of life in this population. The effect of exercise on falls remained inconclusive. Poorer physical function was a determinant of better response to exercise training, but cognitive performance did not have an impact. **Conclusion**: People with various levels of cognitive impairment can benefit from supervised multi-modal exercise for about 60 minutes a day, 2 to 3 days a week to improve physical function. **[Lam FMH , Huang MZ, Liao LR, Chung RCK, Kwok TCY, Pang MYC (2018) Physical exercise improves strength, balance, mobility, and endurance in people with cognitive impairment and dementia: a systematic review. *Journal of Physiotherapy* XX: XX–XX]**

Introduction

Dementia is an increasingly important public health concern.[1] It is estimated that by 2050 the number of people with dementia will reach 131.5 million worldwide.[1] Apart from deficits in cognition and behaviour,[2] deficits in balance, gait, and movement coordination are also found in people with mild dementia and mild cognitive impairment.[3,4] People with dementia are less likely to participate in regular physical exercise when compared with their counterparts with normal cognition.[5] Physical inactivity may give rise to further decline in physical functioning.[6] These factors may partially explain the higher risk of falls and hip fractures in people with dementia compared with their peers without dementia.[7,8]

Exercise training improves cognitive[9] and physical[10–12] functions in healthy older adults and is feasible for people with cognitive impairment.[13,14] Previous reviews have attempted to examine the effects of exercise on physical function in individuals with dementia, but the heterogeneous participant groups and different outcome measures that were used made conducting and interpreting meta-analyses difficult.[13–21] Meta-analyses were conducted in seven reviews to quantify the amount of improvement gained after exercise training.[14–16,20,22–24] However, non-randomised trials were included in some reviews, which compromised the quality of evidence.[16,23] Other reviews focused on one type of exercise training, one patient subgroup,[14,24] or few domains of physical function.[15,20,22,23] None of the existing systematic reviews conducted sensitivity analysis to specifically examine the effect of subject characteristics (eg, cognitive impairment level) on training efficacy – probably due to the small number of trials included in the reviews. Thus, the existing reviews have not provided a comprehensive understanding of the effect of physical exercise on physical function in people with cognitive impairment. Moreover, a good number of new exercise trials on people with mild cognitive impairment or dementia have been

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published in the last few years, and it is thus timely to conduct a systematic review on this topic to address the knowledge gaps identified above.

Therefore, the research questions for this systematic review were:

1. Does physical exercise training improve physical function and quality of life in people with cognitive impairment and dementia?
2. Which training protocols improve physical function and quality of life?
3. How do cognitive impairment and other patient characteristics influence the outcomes of exercise training?

Method

Identification and selection of trials

MEDLINE, CINAHL, PubMed, PsycINFO, and The Cochrane Library Databases of Systematic Reviews were searched electronically with search terms related to *cognitive impairment*, *dementia*, *exercise*, *rehabilitation*, and *randomised trial*. An example of the search strategy for one database is provided in Appendix 1 on the eAddenda. Two independent researchers screened the search results for publications about the effect of physical exercise in people with mild cognitive impairment or dementia. Potentially eligible trials were selected for further assessment of eligibility. Relevant reviews and the reference lists of all selected articles were then examined to look for potentially eligible articles. Finally, a forward search was performed on all articles selected in the above process using the Science Citation Index. The last search was performed in May 2016. The inclusion criteria for trials to be included in the review are presented in Box 1. However, trials were excluded if they were published only in conference proceedings or books. Disagreements about eligibility were resolved by the principal researcher.

Assessment of characteristics of trials

Quality

The PEDro score, obtained by searching the PEDro website (www.pedro.org.au), was used to assess the methodological quality of each selected trial. For trials that were not originally listed on the PEDro website, the PEDro team was contacted via email to request them to examine these trials and provide the PEDro scores. Hence, the PEDro scores of all trials included in this review were based on the information obtained from the PEDro website, where studies are rated in duplicate by trained raters.

Participants

To describe the participants in each trial, the following information was extracted from the published report: sample size, mean age, gender ratio, location of participants (community, institution), diagnosis, and cognitive impairment test scores (eg, Mini Mental State Examination).

Intervention

The details extracted from each included study about the exercise intervention were: frequency, intensity, duration and type of physical exercise.

Outcome measures

Outcome data were extracted from each included study if they pertained to any domain of physical function or quality of life.

Corresponding authors were contacted via email in case information needed for the meta-analysis could not be acquired from the original articles. When there were discrepancies between the two researchers responsible for data extraction, the information extracted was confirmed by the principal investigator.

Data analysis

Meta-analysis was performed for a given outcome only if at least three similar trials used the same outcome measure. Meta-analyses were conducted using RevMan software.[a] Random-effect models were used in all meta-analyses, given the large variation in study design across trials (eg, participants' characteristics, exercise protocols).[25] The existence of publication bias was examined using Egger's regression asymmetry test using Comprehensive Meta-analysis software.[b] A *p*-value of <0.1 (two-tailed test)

Box 1. Inclusion criteria.

Design
- Randomised trial
- English language

Participants
- People with a primary diagnosis of mild cognitive impairment or dementia

Intervention
- Physical exercise

Outcome measures
- Measures of physical function
- Measures of quality of life

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

Box 2. Criteria used to downgrade ratings in the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system. See the Methods section for further details.

Risk of bias
- for outcomes where meta-analysis was possible, fewer than half of the trials included in the primary analysis had a PEDro score of $\geq$6
- for outcomes where meta-analysis was not possible, fewer than half of the trials included for outcome evaluation had a PEDro score of $\geq$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 less than that required by a conventional sample size calculation for a single trial
- the 95% CI spanned zero

Publication bias
- $p < 0.1$ on the two-tailed Egger's regression asymmetry test

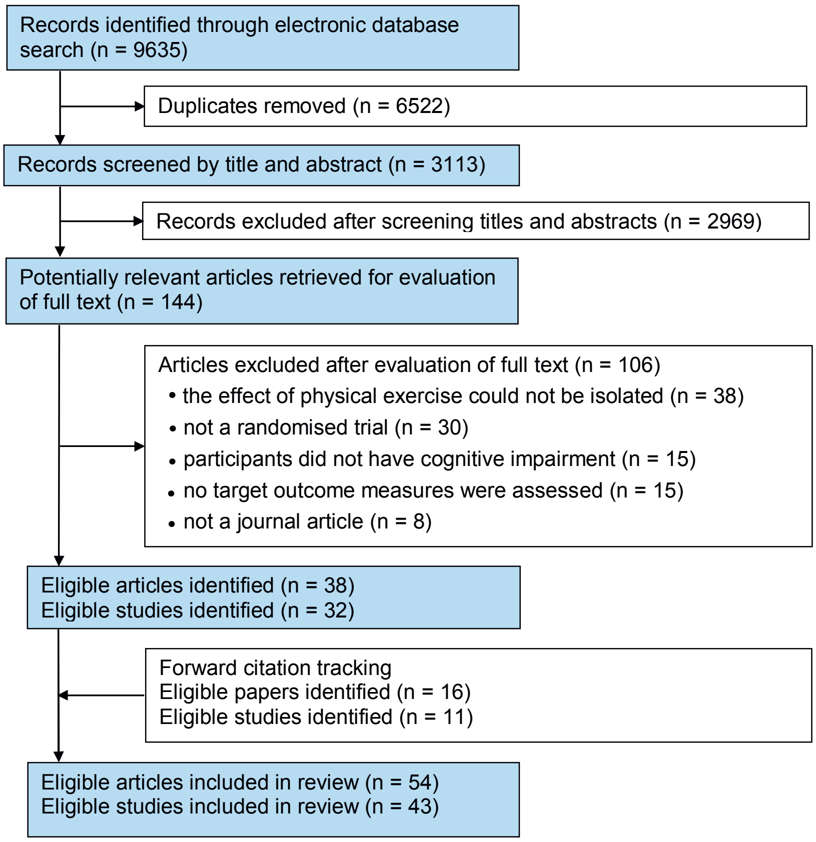

Figure 1. Flow of studies through the review.

indicated the presence of publication bias. The mean difference provided a summary measure of the effect of exercise. Sensitivity analyses were conducted based on different patient subgroups, outcome mono-dimensionality, and methodological quality, if three or more trials remained eligible for the additional analyses.

The level of evidence for each outcome measure was then calculated according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system.[26] The rating for each level of evidence started with 'high quality', as only randomised, controlled trials were included in this review. It was downgraded by one level for each of the criteria shown in Box 2. The quality of evidence was downgraded by two levels if less than half of the trials included in the primary meta-analysis had a PEDro score of $\geq$4. For outcomes for which meta-analysis was not possible, the same criteria were adopted with reference to the total number of trials reviewed for that particular outcome. Evidence quality was upgraded by one level if the effect size was large. After considering the balance of desirable and undesirable aspects of the available evidence, a strong or weak recommendation would be given according to existing evidence.[26]

Results

Flow of trials through the review

The database searches identified 6935 records. After screening titles and abstracts, 144 potentially relevant articles were obtained in full text and evaluated for eligibility. The 38 articles that were eligible for the review were supplemented by 16 more identified through the reference lists searches. Therefore, 54 articles were included in the review.[27–80] These reported on 43 trials involving a total of 3988 subjects (Figure 1). Three papers were excluded from some of the meta-analyses, as the required information was missing despite efforts to contact the original authors.[36,48,58]

Characteristics of included trials

The methodological quality of the included studies is summarised in Table 1. A more detailed version of this table is available in Appendix 2 on the eAddenda. The characteristics of their study populations are summarised in Table 2. The physical exercise protocols assessed in the included studies are summarised in Table 3. More details about the study populations, the intervention protocols, and the outcome measures are available in Appendix 3 on the eAddenda.

Quality

The quality of evidence assessed according to the GRADE is provided in Table 4. The results were organised according to the three levels of functioning described in the International Classification of Functioning, Disability, and Health (ICF), namely: body functions and structures, activities, and participation.[81] Outcomes that were reported by less than three trials are listed in Appendix 4 on the eAddenda.

Effect of exercise on body functions and structures

Body mass index (moderate-quality evidence)

Body mass index (BMI) was assessed in three trials (173 participants).[30,35,50] Multimodal exercise[30,50] or specific aerobic train-

Table 1
Methodological quality of the included trials (n = 43).

PEDro total score	Trials n (%)	References
excellent (9 to 10)	0 (0)	
good (6 to 8)	30 (70)	27,28,30–35,37–42,44,45,47,50–53,57,60,61,63–69,71–80
fair (4 to 5)	11 (26)	29,36,38,46,48,49,54–56,59,62,70
poor (0 to 3)	2 (5)	43,58

Percentages do not sum to 100, due to the effects of rounding.

Table 2
Characteristics of the participants in the included trials (n = 43).

Characteristic	Trials n (%)	References
Sample size		
≤50	18 (42)	34,35,44,46–50,52,53,55,56,58,59,61,62,79,80
>50	25 (58)	27–33,36–43,45,51,54,57,60,63–78
Cognitive impairment level		
mild cognitive impairment (mean MMSE > 24)	11 (26)	27–40,74,79
mild dementia (mean MMSE 20 to 24)	11 (26)	41,42,45–53,63,64,80
moderate dementia (mean MMSE 10 to 20)	16 (37)	43,44,54–62,65,71–73,75–78
severe dementia (mean MMSE < 10)	5 (12)	66–70
Setting of the trial		
residential care units	20 (47)	29,43,44,47,49,51,54,56,59,61,65,66,68–71,75–79
community	19 (44)	27,28,30–40,45,46,48,50,52,53,55,60,62,72–74,80
hospital respite care	1 (2)	67
mixed	3 (7)	41,42,57,58,63,64

Percentages may not sum to 100, due to the effects of rounding. MMSE = Mini Mental State Examination.

ing[35] (45 to 90 minutes per session, 2 to 7 sessions per week for 4 to 12 months) were compared to usual care,[50] health promotion,[30] or low-intensity stretching and balance exercise.[35] All three trials reported no significant change in BMI after physical exercise relative to the control intervention.[30,35,50]

Strength (moderate-quality evidence)

Meta-analysis of four trials (278 participants) showed a significant effect of exercise on improving 30-second sit-to-stand performance by 2.1 repetitions (95% CI 0.3 to 3.9).[48,49,71,77] See Figure 2, or for a more detailed forest plot see Figure 3 on the eAddenda. The result remained significant in sensitivity analyses that included only those trials that involved participants in institutionalised settings (three trials, 258 participants). The heterogeneity across trials was high in both the primary and sensitivity analysis, with I^2 values of 82% and 88%, respectively. Together with four other trials that assessed other types of sit-to-stand performance (eg, five times sit-to-stand test),[41,50,52,55] all trials that reported significant training effects adopted multimodal training with a resistance exercise component (30 to 120 minutes per session, 2 to 4 sessions per week, for 9 weeks to 4 months).[41,49,50,71] The intensity of the resistance training was not specified. The training effect appeared to diminish starting at 9 weeks and 3 months after training.[42,71]

Upper limb strength was reported in four trials.[39–42,49] Three of these trials assessed handgrip strength and one used the arm-curl test. The one trial that incorporated resistance training reported results in favour of the exercise group.[49] The other three trials, which all lacked specific upper limb resistance training, reported no significant effects.[39–42]

Flexibility (very-low-quality evidence)

Flexibility was assessed in three trials.[49,58,62] All trials incorporated multimodal exercise with a flexibility training component (2 to 3 sessions per week, 16 weeks to 12 months), and reported significant improvements in the intervention group. Of these, two reported that the improvements in the intervention group were significantly greater than no-intervention controls

Table 3
Characteristics of the physical exercise protocols used in the included trials (n = 43).

Characteristic	Trials n (%)	References
Mode of exercise [a]		
aerobic exercise	11 (23)	34–38,43,45,47,48,61,71,75
walking exercise	3 (6)	39,65,70
dual-task walking	2 (4)	65,69
multimodal	21 (45)	27,28,30,31,40–42,46,49–56,58,60,62–64,66,70–74,76–78
ADL/functional training	2 (4)	57,68
strengthening exercise	2 (4)	36,79
others	6 (13)	29,32,33,44,59,67,80
Duration of session *(min)*		
<30	3 (7)	34,59,75
30 to 40	10 (23)	29,47,48,53,61,65,67,69,71,80
45 to 60	15 (35)	27,36–38,45,54–58,60,66,72–74,76–79
75 to 150	5 (12)	28,30,31,39–42,49,63,64,68
variable (15 to 60)	6 (14)	32,33,35,43,44,62,70
unclear	4 (9)	46,50–52
Frequency *(sessions/week)* [b]		
1 to 2	17 (39)	28,30,31,34,36–42,44,45,48,53,55,57,58,60,63,64,66,72,73,76–78
3 to 4	15 (34)	27,35,43,47,49,51,54,56,59,61,65,71,74,79,80
5 to 7	8 (18)	29,50,52,54,68–70,75
variable or unclear	4 (9)	32,33,46,62,67
Duration [c]		
single session	1 (2)	34
8 to 15 weeks	16 (36)	39,41–47,49,55–57,59,63,64,71,76,77,79,80
16 to 24 weeks	18 (40)	27–29,31,32,35,36,40,48,50,52–54,58,61,65,68–70,78
≥12 months	9 (20)	30,33,37,38,51,60,62,66,72–75
unclear	1 (2)	67

Percentages may not sum to 100, due to the effects of rounding. ADL = activities of daily living.
[a] n = 47. Four of the trials had two exercise groups in addition to the control group: Nagamatsu[36] had aerobic and strengthening groups; Roach[70] had walking and multimodal groups; Tappen[65] had walking and dual-task walking groups; and Bosser[71] had aerobic and multimodal groups.
[b] n = 44. Apart from the control group, Christofoletti[54] had two exercise groups, which had different numbers of exercise sessions per week: 3 and 5.
[c] n = 45. Two trials used interim evaluation: in the 12-month trial by Uemura,[30] a 6-month interim evaluation was reported by Doi,[28] Makizako[40] and Suzuki.[31] Similarly, in the 12-month trial by Lam,[32] a 6-month interim evaluation was also reported.[33]

Table 4
Grades of Recommendation, Assessment, Development and Evaluation (GRADE) quality of evidence.

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size	GRADE quality	Direction of recommendation
Body mass index	0	0	0	–1[f]	0	0	Moderate	Against
Strength: 30-s sit to stand test	0	–1[b]	0	0	0	0	Moderate	For
Flexibility	–2[a]	0	0	–1[f]	0	0	Very low	For
Step length	0	0	0	0	0	0	High	For
Balance: Berg Balance Scale	0	0	0	0	0	0	High	For
Balance: Functional reach test	0	0	0	0	0	0	High	For
Mobility: Timed Up and Go test	0	0	0	–1[g]	0	0	Moderate	For
Mobility: Walking speed	0	–1[b]	0	0	0	0	Moderate	For
Walking endurance: 6-minute walk test	0	–1[b]	0	0	–1[h]	+1[i]	Moderate	For
Dual-task ability	0	–1[c]	0	–1[f]	0	0	Low	Against
Activities of daily living: Barthel index	0	–1[b]	0	0	–1[h]	0	Low	For
Activity level	0	–1[c]	0	–1[f]	0	0	Low	Against
Quality of life	0	0[d]	0	–1[f]	0	0	Moderate	Against
Falls	0	0	–1[e]	–1[g]	0	0	Low	No recommendation

[a] More than half of the trials included for outcome evaluation had a PEDro score ≤ 4.
[b] $I^2 \geq 50\%$ in the primary and high methodological quality analysis.
[c] Mixed result reported across trial and meta-analysis was not possible.
[d] Quality of life is not rated down here, considering that all studies involving multi-modal exercise reported non-significant effect.
[e] The method of collecting falls outcome by the trials may undermine the actual effect of exercise.
[f] Insufficient studies for meta-analysis.
[g] The effect size overlapped zero in the primary or high methodological quality analysis.
[h] Publication bias present.
[i] Large effect size detected.

as assessed by the chair sit-and-reach test[49,58] and back scratch test.[49] Between-group analysis was not conducted in one of these trials.[62]

Step length (high-quality evidence)

Meta-analysis of five trials (296 participants) revealed a significant effect of exercise on improving step length by 5 cm (95% CI 2 to 8).[28,41,56,64] See Figure 4, or for a more detailed forest plot see Figure 5 on the eAddenda. The heterogeneity across trials was low (I^2 = 29%). Sensitivity analyses that included only trials with high methodological quality (four trials, 265 participants), or individuals with mild cognitive impairment and mild-grade dementia (three trials, 183 participants) remained significant and the I^2 was reduced to 0%. Those trials that reported positive outcomes adopted multimodal exercise with walking, aerobic training, or functional training components, or specific aerobic training (60 to 120 minutes per session, 2 to 3 sessions per week for 15 weeks to 6 months).[28,41,56,64] One of the three trials performed long-term follow-up assessments and reported that the improvement was diminished and returned to baseline values 9 months after the intervention.[41,42]

Effect of exercise on activity

Balance (high-quality evidence)

The primary analysis of the effect of exercise on the Berg Balance Scale (six trials, 722 participants) revealed that exercise significantly improved scores by 3.6 points (95% CI 0.3 to 7.0).[33,45,54,59,77,78] See Figure 6, or for a more detailed forest plot see Figure 7 on the eAddenda. Publication bias was noted for this meta-analysis. A sensitivity analysis that included only trials with high methodological quality (four trials, 673 participants) markedly reduced the heterogeneity across trials, with I^2 value dropping from 91 to 17%. There was no publication bias in this analysis but the mean improvement found was reduced to 1.5 points (95% CI 0.1 to 3.0). Another sensitivity analysis that included only studies involving participants with moderate-grade dementia and living in institutions (four trials, 376 participants) also yielded significant results in favour of the exercise group, but the I^2 value was high (80%).

The primary analysis of the effect of exercise on the functional reach test (six trials, 242 participants) showed that exercise significantly improved the reaching distance by 3.9 cm (95% CI 2.2 to 5.5).[45,48,50,52,55,79] See Figure 8, or for a more detailed forest plot see Figure 9 on the eAddenda. Similar results were obtained in sensitivity analyses that included only those trials with: high methodological quality (four trials, 199 participants), participants with mild cognitive impairment and mild-grade dementia participants (five trials, 219 participants), or community settings (five trials, 197 participants). The heterogeneity across trials in all analyses was minimal with I^2 ranging from 0 to 1%.

Together with other trials that used clinical balance assessment scales as outcomes (eg, Tinetti balance assessments), it was found that various types of exercise interventions were effective in improving balance, including multimodal exercise, Tai Chi, resistance and functional training, and walking (20 to 120 minutes per session, at least 2 sessions per week, for a total of 9 weeks to 12 months).[32,33,41,45,48–52,54,58,59,71,77,78] Four trials with follow-up assessments suggested that the training effect was found to diminish at 9 weeks,[71] 3 months,[41,42] or 6 months,[45,76] although the outcomes remained significantly better than controls in three of the trials.[41,42,45,76]

Mobility (moderate-quality evidence)

Meta-analysis (11 trials, 606 participants) showed that exercise significantly reduced the time required to complete the Timed Up and Go (TUG) test by 1 second (95% CI –2 to 0).[41,47,50–55,71,75,79] See Figure 10, or for a more detailed forest plot see Figure 11

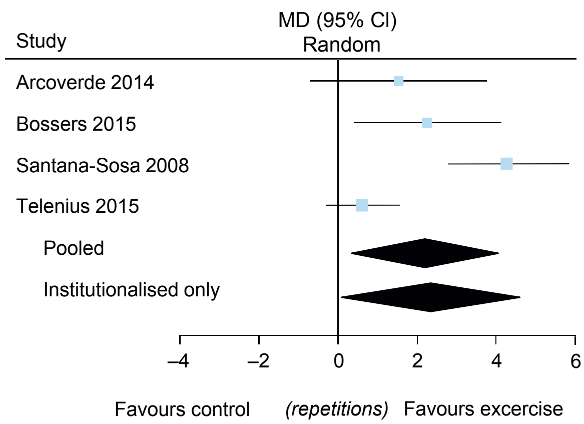

Figure 2. Weighted mean difference (95% CI) in 30-second sit-to-stand test performance (number of repetitions) due to exercise, pooling data from four studies (278 participants).

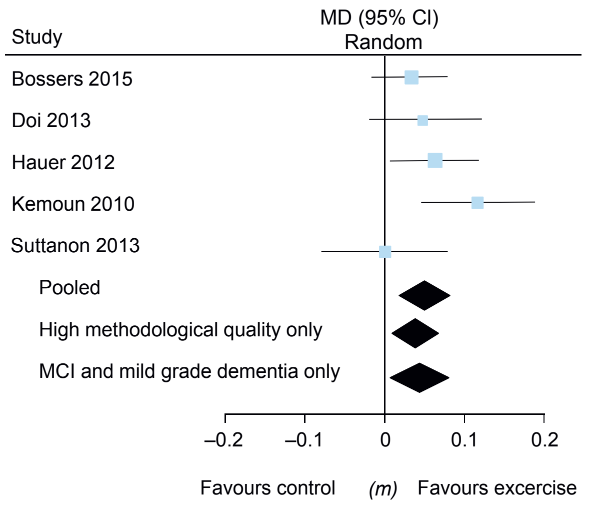

Figure 4. Weighted mean difference (95% CI) in step length (m) due to exercise, pooling data from five studies (296 participants). MCI = mild cognitive impairment.

on the eAddenda. Upon examination of trials that reported significant benefits,[39,41,48–50,58,75,79] most adopted multimodal exercises[41,49,50,58] (15 to 120 minutes per day, at least 2 days/week for a minimum of 12 weeks). The result became marginally significant when only high methodological quality trials (nine trials, 553 participants) were included ($p = 0.08$). The improvement found was also reduced to –1 seconds (95% CI –1 to 0). The group with moderate-grade dementia (four trials, 249 participants) had a tendency to benefit more from training with a marginally significant improvement of –2 seconds (95% CI –5 to 0) compared with individuals with mild cognitive impairment and mild-grade dementia (seven trials, 357 participants) (–1 second, 95% CI –1 to 0). Overall, it was found that aerobic exercise alone (three trials, 236 participants) did not significantly improve TUG performance ($p = 0.35$). The heterogeneity across trials was low, with I^2 ranging from 0 to 32%.

Meta-analysis (seven trials, 568 participants) revealed that exercise improved walking speed by 0.13 m/s (95% CI 0.03 to 0.24).[28,41,52,56,66,71,77] See Figure 12, or for a more detailed forest plot see Figure 13 on the eAddenda. Sensitivity analysis that included only trials with high methodological quality (six trials, 537 participants) yielded a significant but slightly smaller improvement of 0.08 m/s (95% CI 0.01 to 0.15). Improvement in walking speed among individuals with mild cognitive impairment and mild-grade dementia (three trials, 183 participants) was not significant ($p = 0.19$), whereas that in those with moderate-to-severe-grade dementia (four trials, 385 participants) was marginally significant (mean difference 0.14 m/s, 95% CI –0.01 to 0.29). It should be noted that the trials were highly heterogeneous in all analyses ($I^2 \geq 74\%$). The trials that reported significant training effects all adopted multimodal training, with a balance, walking, or functional training component (45 to 90 minutes per day, 2 to 3 days per week for a minimum of 15 weeks).[28,40,41,56,58,64]

Walking endurance (moderate-quality evidence)

Meta-analysis (seven trials, 402 participants) revealed that exercise significantly increased the distance covered in the 6-minute walk test by 50 m (95% CI 18 to 81).[30,45,61,62,65,70,71] See Figure 14, or for a more detailed forest plot see Figure 15 on the eAddenda. Publication bias was noted for this meta-analysis. The results were similar and remained significant in sensitivity analyses that included only trials with: high methodological quality (five trials, 318 participants), participants with moderate-to-severe-grade dementia (five trials, 229 participants), community settings (three trials, 203 participants), or aerobic and walking exercises only (five trials, 283 participants). The effect of exercise on the 6-minute walk distance among patients in an institutionalised setting (four trials, 199 participants) did not reach statistical significance ($p = 0.10$). It was found that aerobic exercise (three trials, 187 participants) led to the largest improvement in 6-minute-walk distance of 75 m (95% CI 25 to 125). The heterogeneity across trials was high in all analyses ($I^2 \geq 56\%$). Trials that reported positive findings adopted either specific aerobic training,[35,36,38,45,61] walking exercise,[65] or multimodal exercise,[30,49,62,71] with a training duration ranging from 30 to 90 minutes/session, 2 to 4 sessions/week, for a total of 9 weeks to 12 months. Reported effective training intensity was 30 to 60% VO_{2max},[62] or 40% of heart rate reserve that gradually progressed to 85%.[30,35,36]

Dual-task ability (low-quality evidence)

Five trials examined the effect of exercise on dual-task ability.[39,40,48,52,63] A dual-task training component was incorporated into the overall exercise program in two trials.[40,63] Only one

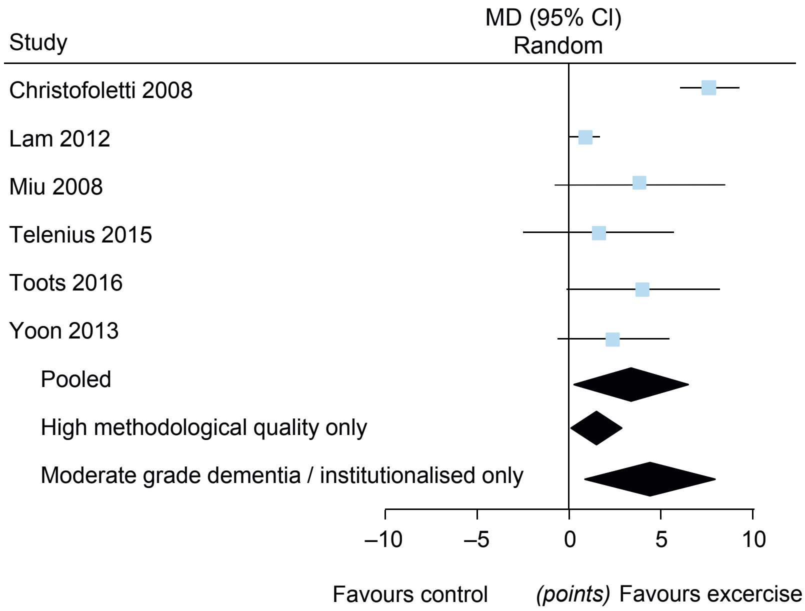

Figure 6. Weighted mean difference (95% CI) in Berg Balance Scale performance (0 to 56) due to exercise, pooling data from six studies (722 participants).

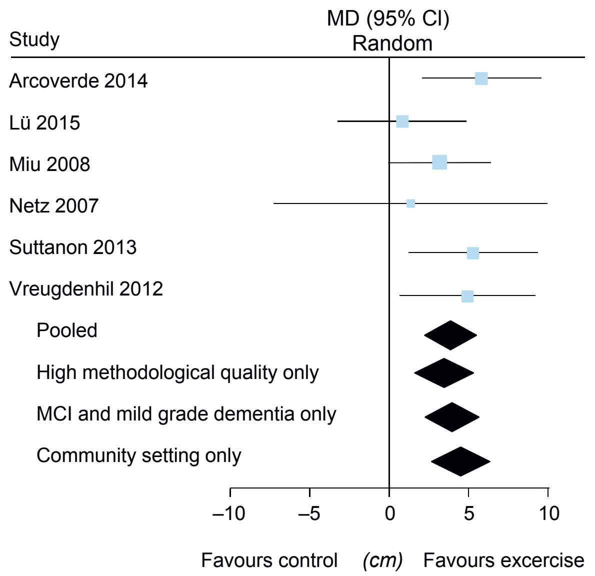

Figure 8. Weighted mean difference (95% CI) in functional reach test result (cm) due to exercise, pooling data from six studies (242 participants). MCI = mild cognitive impairment.

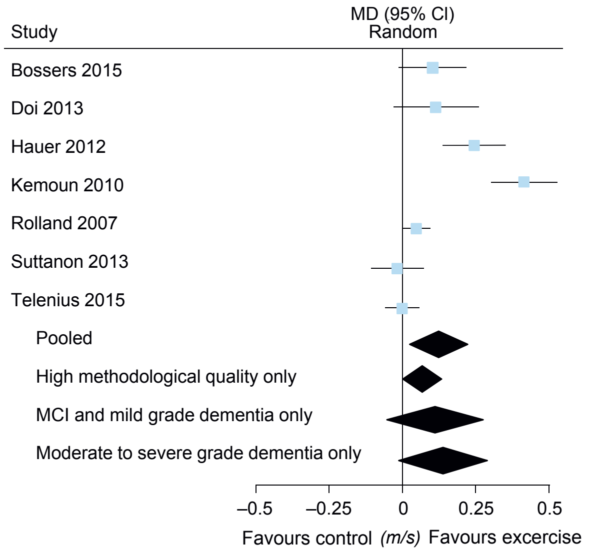

Figure 12. Weighted mean difference (95% CI) in walking speed (m/s) due to exercise, pooling data from seven studies (568 participants). MCI = mild cognitive impairment.

of these trials reported results that favoured the training group.[63] Significantly greater improvements in dual-task gait speed, cadence, stride length, and single support duration were reported in the dual-task training group when compared with non-specific low-intensity exercise. No significant results were found in the other four trials.[39,40,48,52]

Activities of daily living (low-quality evidence)

Twenty-two trials assessed the effect of exercise on activities of daily living (ADL) performance.[29,39,43,44,46,49,50,53,57,59–62,66,68–70,74,75,77,78,80] Sixteen trials reported significant benefits in at least one outcome measure in the ADL category.[29,39,43,44,46,49,50,59–61,66,68,70,75,77,80] Meta-analysis (four trials, 237 participants) found that exercise significantly improved the Barthel Index by 10 points (95% CI 3 to 16).[49,50,61,77] See Figure 16, or for a more detailed forest plot see Figure 17 on the eAddenda. Publication bias was noted for this meta-analysis. Sensitivity analyses that involved only trials with high methodological quality (three trials, 221 participants) or those that were conducted in institutionalised settings (three trials, 197 participants) also yielded results in favour of exercise. The heterogeneity across trials was high in all analyses ($I^2 \geq 72\%$). A wide selection of exercise protocols (eg, ADL training, multimodal exercise, aerobic exercise) were found to improve ADL performance (20 to 150 minutes per session, at least 2 sessions per week, for 12 weeks to 15 months).[29,39,46,49,50,59,61,62,66,68,70,75,80]

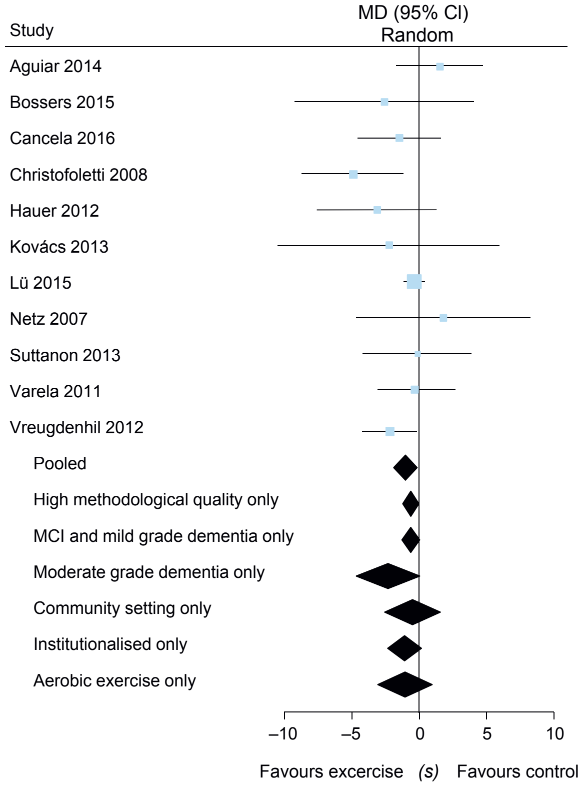

Figure 10. Weighted mean difference (95% CI) in Timed Up and Go test performance (s) due to exercise, pooling data from 11 studies (606 participants). MCI = mild cognitive impairment.

Participation

Activity level (low-quality evidence)

Five trials examined the effect of exercise on activity level.[27,39,41,42,46,52] Four trials reported that the exercise training

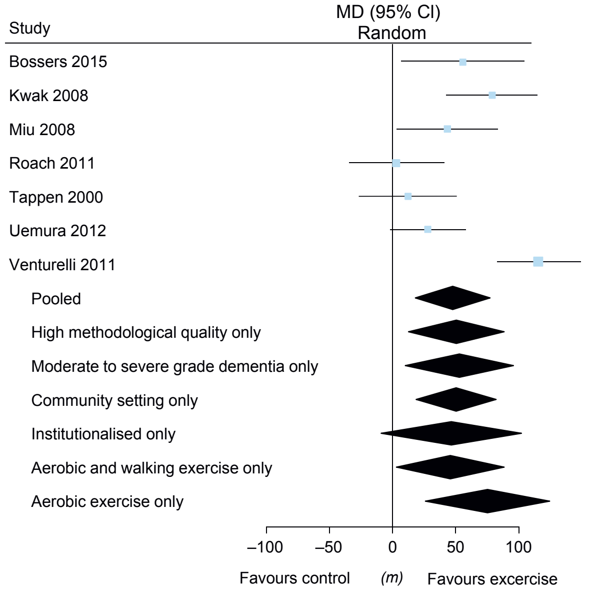

Figure 14. Weighted mean difference (95% CI) in 6-minute walk test results (m) due to exercise, pooling data from seven studies (402 participants).

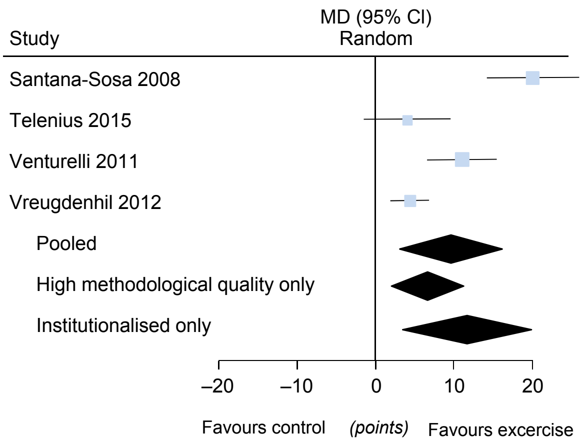

Figure 16. Weighted mean difference (95% CI) in Barthel Index score (0 to 100) due to exercise, pooling data from four studies (237 participants).

did not result in higher activity level than controls,[27,39,46,52] except for one of the outcome variables (ie, total steps per week) reported by Lautenschlager and colleagues.[27] One trial reported a significantly greater improvement in the exercise group immediately after training, but the effect was not maintained at 3 or 9 months.[41,42]

Quality of life (moderate-quality evidence)

Eight trials measured quality of life.[27,37,39,45,46,52,53,76] All six trials that used multimodal exercise as the experimental intervention (at least two 40 to 60 minute sessions/week for 12 weeks to 6 months) reported no significant results.[27,45,46,52,53,76] In the other two trials,[37,39] a walking program was adopted; one of these trials reported improvement in satisfaction in daily life.[39] While the trial that reported no significant improvement adopted moderate-intensity walking exercise (60 minutes/day, 2 days/week, 1 year),[37] the trial that reported significant improvement in quality of life administered a 90-minute walking program once a week for 3 months. In the latter program, the participants were also encouraged to walk daily and organise walking events with other group members.[39]

Falls (low-quality evidence)

Four trials examined the effect of exercise on falls.[42,51,52,60,72,73] Meta-analysis (three trials, 191 participants) showed that exercise did not reduce the number of fallers compared to controls (OR 0.98, 95% CI 0.49 to 1.95).[42,51,52] See Figure 18, or for a more detailed forest plot see Figure 19 on the eAddenda. The heterogeneity across trials was low in this analysis ($I^2 = 26\%$). For other fall-related outcomes, three trials reported that the exercise group did not differ from the controls in cumulative falls, fall rate, fall risk score and time to first fall.[42,51,52] Pitkälä and colleagues[60] reported that 12 months of multimodal exercise resulted in a significant lower number of falls per year when compared with no-intervention

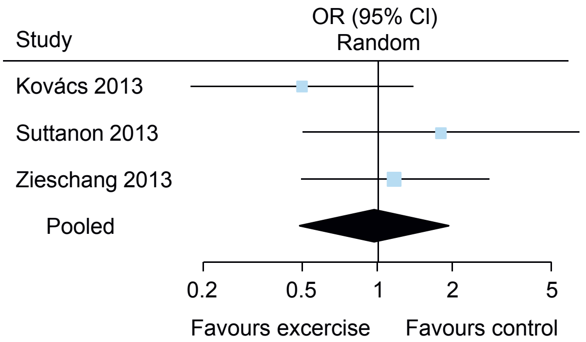

Figure 18. Odds ratio (95% CI) of number of fallers in the exercise versus control groups, pooling data from three studies (191 participants).

controls, while the incidence of fractures or hospitalisation did not differ between groups.

Attendance

Twenty-three trials reported participants' attendance to exercise.[27,28,30,31,36–40,46,48,49,52,55,60,61,63–67,71,74–80] Among these, the mean attendance rate ranged from 33 to 99%. Most trials reported an attendance rate between 70 and 90%.[27,28,30,31,38,39,46,55,60,65,67,71,74–80] Two trials reported an attendance rate <70%.[65,66] Three trials reported reasons for low attendance, which included acute disease, disagreement or unwillingness to continue,[66] behaviour disorders,[66] increased disability in ADLs,[66] and health-related problems.[37,52] One trial showed that women had a better attendance to exercise training than men.[74] Better baseline cognitive ability also showed a weak association with better attendance.[74]

Safety

In almost all of the reviewed trials, the exercise training was conducted under the supervision of either the caregiver (four trials)[46,50,52,61] or professional staff (eg, research staff, certified exercise instructors, therapists) (33 trials).[28–45,47–49,51,53–60,62–79] The only exception was the trial by Lautenschlager and colleagues,[27] in which the participants with mild cognitive impairment were taught the exercises and advised to do them independently at home. Of the four trials in which the caregiver provided supervision, three involved participants with mild-grade dementia[46,50,52] and one involved moderate-grade dementia.[61] The remaining trials did not provide information on supervision of the exercise.[44,56,59,62,80]

Nineteen trials explicitly reported if any adverse effects occurred.[27,29,31–33,36,37,41,42,46,48,49,52,53,60,61,63,64,66,72,74,76–79] Among these, 10 trials reported that no adverse event occurred.[29,37,41,42,46,48,49,61,63,64,74,76,77,79] Four trials reported few adverse events in the exercise group (ie, foot pain,[27] falls,[31,33,60,72] hospitalisation[31]) that were considered unlikely to be related to the intervention by the original authors.[27,33] Five trials reported adverse events that may be related to exercise.[36,52,53,66,78] These adverse events included a higher number of hospitalisations per patient,[66] falls,[36,66] shortness of breath,[36] erythema,[53] and pain or discomfort, which eased as time progressed or by slight modification of the exercise.[52] One trial reported that one of the participants fell ill one day after an exercise session and later passed away with a diagnosis of circulatory failure and general atherosclerosis.[78]

Discussion

This systematic review summarised the evidence on the effects of exercise on physical functioning and quality of life in individuals with mild cognitive impairment and dementia. The large number of trials involved in this review made sensitivity analyses possible, which was missing in previous reviews.[13–18,22,82–84] Sensitivity analysis allowed the effects of exercise on patient subgroups to be determined, and the potential factors that may affect training outcomes to be identified.

Overall, very few adverse events were reported with exercise. Hence, according to the quality and direction of the evidence, there was strong evidence to support the use of exercise in improving strength, step length, balance, TUG, walking speed, and endurance in people with mild cognitive impairment, or mild-to-moderate-grade dementia. On the other hand, the evidence for supporting the use of exercise in improving flexibility and ADL was weak. There was weak evidence against the use of non-specific exercise in improving BMI, dual-tasking ability and activity level, and strong evidence against the use of non-specific exercise in improving quality of life. The review provided no recommendations on the

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effect of exercise on falls, as most trials collected fall data during the intervention period.[51,52,60] This data collection method is prone to inaccuracy, as the effect of exercise may not appear in the initial periods of intervention. The meta-analysis also may not have had sufficient power to detect a significant between-group difference in fall rate, given the limited sample size. The results of this review can be generalised to people with mild cognitive impairment or mild-to-moderate-grade dementia.

Specificity of training appears to be an important factor in obtaining beneficial effects on impairment-level outcomes (eg, strength, flexibility) and certain activity-level outcomes (ie, walking endurance). For example, among all trials that reported favourable results on lower limb strength and walking endurance, 100% and 71% included specific training for the respective outcomes. Indeed, the sensitivity analysis showed that specific aerobic training led to the greatest improvement in the 6-minute walk distance. On the other hand, for lower limb strength, two[48,55] out of five trials[46,48,52,55,76,77] that did not identify a treatment benefit did not incorporate training that specifically targeted lower limb muscle strength. For endurance, all trials that did not identify a treatment benefit did not include an aerobic training component in their training program.[67,69,70] All trials that measured flexibility also included flexibility exercise as part of the overall training, and reported positive results.[49,58,62] For more complex activity-level outcomes such as balance, the specificity of training seemed to be less important. Sixty-four per cent of the trials that reported favourable results on balance outcomes incorporated specific balance training. However, two trials[45,48] that adopted aerobic exercise, and one trial that incorporated aerobic and resistance exercise[71] also reported positive effects on balance. On the other hand, although Tai Chi[33] and cycling exercise[59] were reported to induce significant effects on balance, the improvement was very small and markedly less than the minimal clinically important change.[85]

For even higher levels of function like ADL, various forms of exercise other than specific ADL training were found to be beneficial, including aerobic walking training,[61] cycling exercise,[75,80,59] multimodal training without a specific ADL training component,[18,46,49,50,66] handball training,[29] and dance and movement therapy.[44] This could be because ADL ability can be influenced by many impairment variables.

Based on the overall evidence, it can be deduced that regular multimodal exercise with a combination of resistance, aerobic, balance, flexibility and functional training for around 60 minutes a day, 2 to 3 days a week is effective in improving various aspects of physical functioning (lower limb strength, mobility, balance, walking endurance). Considering that specific training is more important for impairment level outcomes, a comprehensive assessment of physical functioning is required to determine the specific areas of deficit, so that the appropriate type of exercise (flexibility, aerobic, resistance) can be incorporated into the overall program to address the impairments identified. The training program duration varied (ie, 8 weeks to 15 months), but the overall evidence indicated that positive training effects on physical function can be obtained in 9 to 16 weeks. Based on the few trials that included follow-up assessment, the improvements in strength, step length and balance diminished from 9 weeks to 9 months after the intervention. Continuous exercise programs may be required to maintain the treatment effect.

With respect to the frequency, intensity and duration of training, no clear differences in these parameters were identified between the trials that yielded larger effect sizes and those with smaller effect sizes for all outcomes, except lower limb strength and walking endurance. For strength, one trial suggested that 30 minutes of specific strength training of 12 repetition-maximum could lead to significant strength improvement.[71] However, among the trials that incorporated multimodal exercise, those that reported no significant results tended to use a shorter total training duration per session (non-significant: 30 to 60 minutes;[48,55,76,77] significant: 75 to 120 minutes).[41,42,49] This suggests that the strength training component cannot be too short in a multimodal training program if benefits on muscle strength are desired. For walking endurance, trials that reported negative findings also tended to adopt a shorter training duration per session (10 to 30 minutes).[67,69,70] A longer exercise duration in each session (≥30 minutes of aerobic training) is required to induce a positive training effect.

With a large number of trials included in our review, it was possible to conduct sensitivity analyses for people with different levels of cognitive impairment. Indeed, sensitivity analyses that involved only people with mild cognitive impairment or mild-grade dementia did not show superior benefits of exercise in improving step length and functional reach when compared with the primary analysis. On the contrary, when compared with the primary analyses, the moderate dementia group tended to have a slightly better improvement in BBS and the moderate-to-severe dementia group had a better improvement in 6-minute walk distance. When compared with the mild cognitive impairment and mild-grade dementia group, the moderate dementia group also showed more improvement in TUG, while the moderate-to-severe dementia group showed slightly more improvement in walking speed. It should be noted that the response in the moderate-to-severe-grade dementia subgroup also tended to be more heterogeneous (eg, TUG, walking speed, 6-minute walk test). This finding challenges the previous finding that better cognitive ability is associated with greater improvement in TUG performance within a group of patients with mild cognitive impairment.[86] However, it should be noted that this comparison involved a much greater between-group difference in baseline cognitive ability (ie, mild cognitive impairment and mild-grade dementia versus moderate-to-severe-grade dementia) rather than comparing individuals within the same diagnostic category (eg, within mild cognitive impairment only). As the cognitive decline was found to be associated with poorer physical function, the group with more advanced cognitive impairment may indeed have a larger potential for improvement in physical function with exercise training. For example, a previous trial revealed that the effect of exercise on fall reduction is more potent in people with advanced dementia due to their inherent high fall rate.[73]

Taken together, these results suggest that people with moderate-grade cognitive impairment are still likely to respond positively to exercise training. The response to exercise training among people with severe-grade cognitive impairment remains largely uncertain, as only five trials[66–70] were conducted in this patient subgroup and only one was included in the meta-analysis of walking speed[66] and 6-minute walk test distance,[70] respectively.

Participants' physical ability at baseline also appears to influence training outcome. For TUG, the sensitivity analysis involving those trials that included only community-dwelling individuals yielded non-significant results. This could be because community-dwelling participants tended to have better baseline mobility level (mean TUG: 10 to 18 seconds) and thus have less room for improvement,[50,52,53,55] when compared with most of the other trials included in the primary meta-analysis (mean TUG: 15 to 33 seconds).[41,47,51,54,71,75] Perttila et al[72] also suggested that while the worsening of ADL performance was attenuated in both the prefrail and frail subgroups of people with dementia upon exercise training, a significant effect was achieved at the sixth month of training for the advanced frailty group but only at the twelfth month for the prefrail group. The fall reduction effect was also greater in the advanced frailty group (incidence rate ratio: advanced frailty: 0.43; prefrail: 0.63). This suggested that cognitively impaired individuals who have deteriorated physical performance could potentially benefit more from exercise training.

Exercise attendance appeared to be generally acceptable across trials. Two trials reported an attendance rate <70%.[65,66] Upon examining the training protocols and the participants' characteristics, no obvious relationship could be found between the training protocols used and attendance rates. However, in the

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two trials that reported exceptionally low attendance, the cognitive ability of the participants was also the poorest (mean MMSE = 8.8 and 11.1, respectively).[65,66] However, two other trials that involved participants with relatively low cognitive ability (mean MMSE = 13) reported good attendance.[55,61] Therefore, no consistent trend could be identified regarding the relationship between cognitive ability and exercise attendance. Taken together, the difference in attendance rate could possibly be due to complex interaction of factors such as the exercise training protocol adopted, cognitive ability, level of physical functioning and involvement of the family/caregiver.

Unfortunately, other aspects of adherence (eg, intensity level, training duration) were seldom reported in the included trials. Therefore, the influence of patient or intervention-related factors on patients' adherence to the prescribed protocol could not be deduced. The influence of exercise adherence to treatment outcomes also remains uncertain.

It is recommended that exercise training be supervised by professional staff. For those with mild cognitive impairment or mild dementia, the training may be supervised by a properly trained caregiver.[46,50,52,61] Less than half of the trials included in this review included information regarding adverse effects. Only five out of 14 trials reported adverse effects that were related to exercise.[36,52,53,66,78] Most adverse events reported were mild and subsided quickly.[36,52] A higher hospitalisation rate in the exercise group was reported by Rolland et al[66] but it remains unclear if the between-group difference in hospitalisation rate was already present prior to commencement of the exercise intervention. The single death event reported by one trial was not directly related to exercise training.[78] In summary, no evidence suggests that exercise poses an substantial risk to individuals with mild cognitive impairment or dementia.

Research in people with severe dementia is scarce. The results of this review are therefore better generalised to people with mild cognitive impairment, and mild or moderate dementia. Details on the training protocol, such as the specific exercises performed, training intensity and progression rules, and the time devoted to different types of exercise in a multimodal program are crucial pieces of information, but were seldom reported. Delineating the factors that are important determinants of successful training outcomes is therefore difficult. Detailed information on adherence to exercise training (ie, degree of deviation between the actual exercise conducted by the participants and the prescribed exercise protocol) was also rarely reported in the included trials. Long-term follow-up trials were few and so the carry-over effects of exercise were not well evaluated.

This review had some limitations. We used the mean baseline cognitive outcome scores to classify the selected trials into different patient sub-groups. There may be potential inaccuracy with this approach, as heterogeneity of the sample within the same trial was not considered. Most trials used multimodal exercise as the experimental intervention, and so it was difficult to single out the effect of a particular exercise type. We did not perform any economic analysis and hence could not comment on the cost-effectiveness of the exercise programs studied. We did not separate the trials that tended to examine 'efficacy' (training performed in a highly controlled environment) from those that tended to examine 'effectiveness' (training performed under real-world conditions) on the continuum from efficacy to effectiveness. To assist readers in judging whether the findings of the present review apply to 'real-world' conditions in their respective contexts, other relevant information of the trials (key subject characteristics, attendance, adverse effects, and supervision level) was provided. Many trials did not contain adequate details necessary for meta-analysis. Meta-analysis could not be performed for several outcomes, due to the small number of trials. Publication bias was present in a small number of analyses. A definite conclusion could not be made on the effect of exercise in severe-grade dementia because there is less research in this subgroup of the dementia population. This may also be due to the way that the different dementia grades were classified (Table 2). Finally, only trials reported in English were included in this review.

Despite the large number of trials that have been conducted, determinants of successful training outcomes are still unclear for many of the outcome measures. More effort could be put into identifying key factors (ie, training type, and parameters) that determine the favourable treatment outcomes. Good quality trials are needed to study the effects on exercise on falls and dual-tasking ability, which are important concerns in individuals with cognitive impairments. Mediators or strategies that are required to translate the improvement in body functions/structures-level outcomes into improvement in activity/participation-level outcomes should be identified. Long-term effects of exercise training also await further investigations. More economical ways of providing exercise training (eg, through educating the caregiver) should be further investigated. More research on people with severe dementia should be conducted.

In conclusion, this review demonstrated that physical exercise training is a feasible intervention for people with mild cognitive impairment and dementia, and that the benefits far outweigh the risks. Strong evidence was found to support the use of physical exercise in improving strength, step length, balance, mobility, and walking endurance. There was weak evidence supporting the use of exercise for improving flexibility and ADL, and against the use of non-specific exercise for improving dual-tasking ability and increasing activity levels. The evidence against the use of non-specific exercise alone for improving quality of life was strong. Taken together, supervised multimodal exercise for about 60 minutes a day and 2 to 3 days a week was beneficial in improving physical functioning in individuals with mild cognitive impairment or mild-to-moderate-grade dementia. The effect of exercise in severe-grade dementia was less certain, due to paucity of research.

What is already known on this topic: Exercise training improves cognitive and physical function in healthy older adults, and is feasible and beneficial for people with cognitive impairment. Patients with dementia are less likely to participate in regular physical exercise when compared with their counterparts with normal cognition.
What this study adds: Strong evidence now indicates that exercise for people with mild cognitive impairment or mild to moderate dementia improves sit to stand, step length, balance, mobility and walking endurance. People across these levels of cognitive impairment are more likely to achieve these benefits with supervised multi-modal exercise for about 60 minutes a day, 2 to 3 days a week.

Footnotes: [a] Review Manager 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark; [b] Comprehensive Meta-analysis version 3, Biostatc, Inc., Englewood, NJ, USA.

eAddenda: Figures 3, 5, 7, 9, 11, 13, 15, 17 and 19 and Appendices 1, 2, 3 and 4 can be found online at https://doi.org/10.1016/j.jphys.2017.12.001

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Competing interests: The authors declare that there is no conflict of interest.

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