Effectiveness of Exercise Interventions for Adults over 65 with Moderate to Severe Dementia in Community Settings: A Systematic Review

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Key Summary Points

Aim: To review the literature on the effectiveness of exercise interventions for people with moderate to severe dementia in community settings

Findings: The literature was of low quality but suggested exercise programs may improve physical function of people with moderate to severe dementia. There was no evidence that exercise programs improve mood.

Message: More research is needed to improve the quality of the evidence to better understand the effectiveness of exercise programmes in community-dwelling older people with moderate to severe dementia.

Abstract

Purpose

To conduct a systematic review of the literature to evaluate the effectiveness of exercise interventions for people with moderate to severe dementia in community settings.

Methods

Eight electronic databases (MEDLINE, Embase, CINAHL, AMED, PsycINFO, PEDro, The Cochrane Library and BNI) were searched from inception to July 2018. Snowball searching identified additional articles not identified initially. Articles were included if they: reported randomised or quasi-randomised controlled trials comparing exercise with usual care or no treatment; and involved people over 65 with moderate to severe dementia in community settings. Outcome measures of interest were strength, endurance, mobility, mood and quality of life. Titles and abstracts of all studies were screened by one reviewer. Two reviewers independently screened full text articles for all eligible studies, extracted data and assessed quality and risk of bias.

Results

~~Seven~~ Eight studies with ~~737~~ 819 participants were included. Interventions were variable in terms of content, duration and frequency. There was some evidence exercise programs may improve physical function of people with moderate to severe dementia, with significant effects seen for gait speed and endurance, and a trend towards improvement in strength. There was little evidence to suggest exercise programs improve mood. Most studies were of low quality.

Conclusion

Exercise was associated with improvements in gait speed and endurance for older people with moderate to severe dementia living in the community but the quality of evidence

was low. There was no conclusive evidence regarding effect on strength or mood. Findings are limited by the quality of the available evidence.

Keywords
Dementia; Aged; Exercise; Systematic Review

Introduction

Dementia encompasses a range of cognitive and behavioural symptoms including memory loss, judgement and changes in personality that can lead to decline in function and difficulties with activities of daily living [1]. 47 million people with dementia worldwide were affected by activity limitation in 2015, a figure predicted to increase to 75 million by 2030 [2].

People with dementia have increased risk of falls and fractures, whilst some of the morbidity of dementia is related to declining performance status associated with loss of muscle strength and ~~endurance~~endurance [3]. Exercise, by improving muscle strength and endurance and reducing risk of falls, has the potential to mitigate against this morbidity and provide physical and mental wellbeing benefits for people living with dementia [4].

The Physical Activity Guidelines Advisory Committee [5] stated the benefits of exercise and physical activity include the potential to increase strength, balance, mobility and cardiovascular fitness, which may lead to subsequent improvements in function and therefore independence [6]. Previous systematic reviews [7] have found evidence to support these physical benefits in older people without cognitive impairment, whilst separate research has suggested that it may also improve psychological wellbeing and health-related quality of life. [8,9]

A previous Cochrane review [6] found evidence that exercise interventions in people with dementia were associated with improvement in activities of daily living but that there was no clear evidence of benefit for cognition, neuropsychiatric symptoms or depression. The studies included showed wide heterogeneity and many of the trials focused on people with mild to moderate cognitive impairment. The authors concluded that more work was needed to understand what type of exercise would be most beneficial in people with dementia, at what dose, and whether specific subgroups of dementia patients demonstrated particular benefit. [4,6]

Patients with more advanced dementia are differently able to engage with exercise programmes. There may be need to modify or attenuate interventions to account for this.

[11,12]. It is also possible that the efficacy and effectiveness of exercise interventions are attenuated by the more advanced frailty found in people with advanced dementia. This group therefore needs to be considered separately [4,6]. This review set out to consider the effectiveness of exercise interventions for people living with moderate to severe dementia focusing on physical benefits such as muscle strength and endurance, and mental wellbeing benefits, such as mood, and quality of life.

Methods

The protocol for this systematic review has been registered on PROSPERO (CRD42018096194) [13].

The search strategy used a previous Cochrane Review on Exercise Programmes for People with Dementia [6] as a starting point for search terms, these were then adapted to include exercise-, dementia-, ageing- and care home-related terms which were customised for each database. No language or date limits were set. A full search string is available as an online appendix.

Eight electronic databases (MEDLINE, Embase, CINAHL, AMED, PsycINFO, Physiotherapy Evidence Database, and British Nursing Index) were searched for primary studies. Search dates ranged from database inception to June 2018. The Cochrane Database of Systematic Reviews was searched for any related reviews. Both searches were conducted in June 2018. Reference lists of relevant reviews were checked for other relevant studies.

Randomised and quasi-randomised, including cluster randomised, controlled trials of adults over the age of 65 with moderate to severe dementia in community settings were included. Community settings were defined as being all settings other hospital, including participants' own homes, care homes and nursing homes. Studies were included where the dementia severity for the study population was stated as being moderate or severe. Where the severity of dementia in the study population was mixed, studies were included where 70% of the participants were classed as being affected by moderate to severe dementia. We accepted author classifications of dementia severity. Where no classification of severity was specified in the articles, we used the previously published cut-offs, used by Forbes, and colleagues [6] of <10, 10-17 and 17-26, to represent severe, moderate and mild dementia respectively. Interventions included were those involving any form of physical activity or exercise, such as walking or strength exercises. Articles which did not report the severity of dementia in the study population were excluded. There were no exclusion criteria for the type, frequency, intensity or duration of exercise. The comparator was usual care or no treatment control.

Primary outcomes were physical outcome measures, including timed up and go, 30 second [illegible] as the Montgomery-Ashberg Depression Rating Scale), and Quality of Life (, such as the Dementia Quality of Life [DEMQoL] measure) (DEMQoL). Only studies with standardised outcome measures were included.

Following de-duplication, titles and abstracts of all studies were screened by one reviewer (AL) to determine whether they met the inclusion criteria. Full text articles for all potentially eligible studies were retrieved and assessed by two reviewers (AL and KR) independently to determine whether they met the inclusion criteria.

Data were extracted using the Cochrane data extraction form [14], which was piloted before revision to extract data on population characteristics, settings, study methods used, intervention and controls used, outcome measures and any effect sizes shown. Two reviewers (AL and KR) extracted data independently and subsequently came together to discuss results and findings.

Each included study was assessed for risk of bias by the two reviewers using the Cochrane Collaboration Tool for assessing Risk of Bias [14]. Blinding was only assessed in relation to outcome assessors, because the nature of exercise interventions characteristically makes blinding of subjects and researchers delivering the intervention difficult.

The raw data on treatment effect was extracted as means for the intervention groups and compared with the control groups with 95% confidence intervals (CIs). Clinical heterogeneity was evaluated by looking at the diversity in participant characteristics, intervention and control characteristics and outcome measures in different studies. Methodological heterogeneity was evaluated by looking at diversity in study designs and risk of bias.

A narrative synthesis of the study results was conducted.

Results

516 studies were identified. 126 were duplicates, 311 were excluded based upon title and abstract, with a further 55 excluded at full text review. 24 articles were reviewed in full by both reviewers, of which seven eight met all inclusion criteria and have been reported in the narrative review. A PRISMA diagram is shown in figure 1.

The seven eight studies included had a total of 737 819 participants. Characteristics of the included studies are presented in Table 1 below. Two Three studies [15{Roach, 2011 #14895},16,17{Roach, 2011 #14895}{Roach, 2011 #14895}] had a mixed-age population but means and standard deviations indicated at least 70% of participants were over the age of 65. One study [1718] included people with moderate to severe dementia

only, the remaining six had a mixed population in terms of levels of dementia. The means and standard deviations of these studies suggested at least 70% of the participants had been classed as moderate to severe. The Mini Mental State Examination (MMSE) was used in all studies to establish criteria for judging level of dementia. There was variability in the cut-off points used in different studies so, for consistency, the cut-off points for mild (17 – 26), moderate (10 – 17) and severe (<10) dementia were taken from a previous Cochrane Review [6].

A summary of risk of bias is~~are~~ presented in Figures 2 and 3 below. The methods used to generate the allocation sequence were well described in five trials [15,16,18-~~19~~20], allocation concealment was adequate in four trials [15,~~17~~18,~~18~~19,~~20~~21] and outcome assessors were blinded in ~~five~~ six trials. These attributes were unclear for the remaining studies. Attrition rates varied from 0% to 46% in the included trials. One trial did not specify the drop-out rates for control and intervention arms separately [~~21~~22]. The dropout rates were higher in the control group than the intervention group in ~~five~~ six trials [15- ~~1~~198, ~~20~~21]. Kemoun [~~19~~20] was the only study where attrition was higher in the intervention group. All studies provided reasons for attrition including: death, medical reasons, no longer resident, not adhering, no longer interested/declining to participate further, and hospitalisation.

Intention-to-treat analysis was used in two trials [15,~~18~~19]. There was no selective reporting bias with all included trials reporting on all planned outcome measures.

Effect of Interventions

Primary Outcomes

Eight physical and four mood outcome measures were used in the included studies but none of the reported outcome measures were the same between studies. ~~Six~~ Seven studies looked at the physical effects of the intervention with two also looking at the effect on mood. One reported using the 6-minute walk as a measure of functional exercise capacity, but reported on the effect of the intervention on mood only.

Physical Effects

The results of the ~~6~~ 7 studies [15-2~~1~~0] which looked at the physical effects of the intervention are summarised in table 2.

Three studies [16,~~18,~~19] used an endurance intervention - either walking or recumbent cycling. There was a mixed effect on endurance outcomes with one study [1~~8~~7] demonstrating an improvement in the six minute walk test (20% increase in walking

distance, p <0.05), whilst another found no effect on the 2-minute walking test performance [16]. One study used the timed up-and-go test, which mainly assesses gait and balance, as an outcome and did find a significant difference in favour of the intervention (F = 5.43, p = 0.03) [18]. There was risk of bias in all three studies, and not all studies included an endurance outcome measure. We consider the evidence with regard to endurance to be of low quality.

One study [210] used a strength intervention consisting of resistance band exercises for people in wheelchairs. The outcome measures were hand grip strength and arm muscle endurance. The pre- and post-test means showed a trend towards improvement in the intervention group (10% increase in grip strength and 46% increase in arm muscle endurance, no p values provided) and a trend toward deterioration in the control group. (11% decrease in grip strength and arm muscle endurance, no p values provided). Effect sizes reported were small for grip strength (0.13) and very small for arm muscle endurance (0.04). Raw standard deviations were not provided in the article. Although the outcome measures used were appropriate for the intervention, this was considered to be a very low quality of evidence with only one study and incomplete outcome data.

~~Two~~ Three studies [15,17,~~19~~20] looked at multi-component exercise programmes which included strength, endurance and balance exercises. ~~Both~~ Two studies [15,20] used walking speed as an outcome measure (10m walk and 6m walk respectively) and both found that there was a significant increase in gait speed associated with the intervention (increase of 1.02 m/s, p< 0.01 and increase of 0.41 m/s, p = 0.02 respectively). One of these [15] also used the timed get up-and-go outcome measure and found no improvement. The third study [17] used an endurance outcome measure (6 min walk test) and found no significant differences between the groups. ~~Both~~ All studies used appropriate outcome measures for their interventions but there was a significant risk of bias in one study [~~19~~20]. Overall, the evidence here was, again, of low quality.

Mood

The results of the 3 studies which looked at the effects on mood [15,~~18~~19,~~21~~22] are presented in table 3 below.

Two studies [15,~~18~~19] found no significant difference in mood between intervention and control using the Cornell Scale for Depression in dementia and the Montgomery-Asberg Depression Rating Scale respectively. One study [~~21~~22] showed a mixed pattern with no significant differences seen between the groups for the positive domains (p = 0.38) but some differences for the negative domains of the Alzheimer's Mood Scale (p = 0.004).

There were also some differences, favouring the intervention, in Dementia Mood Assessment scores (p = 0.007). Means and standard deviations were not provided for this study. There was risk of bias in all three of these studies with incomplete data for one, [~~21~~22] with a range of different measures used. Hence, this was considered to be very low-quality evidence.

Quality of Life

No included studies used quality of life as an outcome measure.

Heterogeneity

The included studies were clinically and/or methodologically heterogeneous, hence neither a meta-analysis nor tests for statistical heterogeneity were appropriate.

Discussion

This systematic review has extended our understanding of the evidence on the effectiveness of exercise in people with dementia by focusing specifically on studies which aimed to support those with moderate to severe dementia. Only ~~seven~~ eight studies were suitable for inclusion in the review. The interventions were extremely variable in both content and duration and, with one exception [~~17~~18], were targeted at all people with dementia without respect to severity. There was some evidence that exercise programs may have a role in improving the physical function of people with moderate to severe dementia [15, ~~17~~18, ~~19~~20] but there was little evidence to suggest that exercise programs may improve mood. ~~Overall, the evidence was~~Most of the studies retrieved were of either very low, or low, quality.

The strengths of this review are that it was conducted systematically according to the guidelines laid out in the Cochrane Handbook for Systematic Reviews of Interventions [14] to minimise bias during the review process. Two reviewers independently extracted the data and assessed risk of bias and the protocol was registered on PROSPERO prior to searches commencing. Hand searching of reference lists was used to maximise coverage. As with all such reviews, there may be additional research classified under alternate search headings that was not included. It is also possible that important research conducted using methodologies other than randomised controlled trials was missed. A limitation is that different types of physical outcome measure were included in the analysis, including those, such as endurance, which would be described by some authors as physical performance rather than physical function measures. We have not, however, conflated results using different types of measures and presenting these studies together here serves to underscore how little work has been done regarding exercise in people with

moderate to severe dementia. There are acknowledged limitations of using the MMSE – which was used in most of the included studies – to classify severity of dementia, in part because of its lack of sensitivity to change and in part because it focusses exclusively on progression of cognitive symptoms [2~~2~~3]. We are, however, as limited as reviewers to what is available in the published literature. Including up to 30% of patients with mild dementia may have skewed our findings somewhat. A broader limitation across the literature is that most studies did not consider whether statistically significant improvements were clinically meaningful – more work is required as part of empirical studies with patient, family carer and professional consultees, to work out what constitutes clinically meaningful change.

All previous reviews have focused mainly on people with mild to moderate cognitive impairment with very few trials containing participants with moderate to severe dementia. Depression was considered by two previous reviews [6, 2~~3~~4~~2~~] and found no clear evidence of the benefit of exercise for depression in people with dementia. Three reviews looked at physical function [2~~3~~4~~2~~-2~~5~~6~~4~~] and again showed similar results to those identified here, with no clear evidence of benefit. One review [2~~3~~4~~2~~] assessed the benefit of exercise on quality of life and provided weak evidence in favour of the intervention. A systematic review did not find changes in Behavioural and Psychological Symptoms of Dementia (BPSD) in response to exercise interventions but again found a scarcity of studies of variable quality [2~~6~~7]. Given the overall low quality of the evidence to date, further research is needed to examine the effect of exercise on physical function, depression and quality of life in people with dementia at all stages. ~~-~~This review confirms that this is also the case when people with moderate-severe dementia are considered separately.

Future research should focus on people with moderate to severe dementia as a separate group~~, should modify interventions to take account of cognitive impairment and prevalent frailty in this group,~~ and should consider outcomes that are important to this group and which have sensitivity and specificity in the context of cognitive impairment and advanced frailty. More generally, outcome measures should match the intervention, with endurance measures used for endurance exercise and strength and balance measures used for strength and balance exercise.

Author Contributions

All authors wrote the protocol for the review, contributed to the analysis and wrote the manuscript. AL and KR conducted the review and led the analysis.

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Disclosure

The authors declare that there is no conflict of interest.

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Tables

Table 1 Characteristics of Included Studies

Study	Setting	Participants Mean (SD)	Inclusion Criteria	Intervention	Control	Dropout Rates	Outcomes
Cancela 2016	Spain: Elderly care facility	IG: n = 73, age 80.63 (8.32), MMSE 15.16 (2.54). CG n = 116, age 82.90 (7.42), MMSE 14.95 (2.44)	Over 65; diagnosis of dementia; able to stand & walk 30 m without assistance or shortness of breath	Continuous cycling on a recumbent bike at constant self-selected pace (15 months, 15 mins x daily). Monitored by a physiotherapist	Usual care	IG = 30% CG =46%	Timed up and go, Cornell Scale for Depression in Dementia.
Cott 2002	Canada: Long-term care facilities	Total n = 86, age 82 (8), MMSE 6 (6)	Medical diagnosis of AD; score of <20 on MMSE with a score of <3 on Item 8; able to walk 5 m with or without assistive device or supervision	IG: Supervised walking and talking. (16 wks, 30 mins x 5pw) AC: Talking only (16 wks, 30 mins x 5pw)	Usual care	IG = 0% CG (incl. AC) =14%	2 min walk test.
Kemoun 2010	France: Nursing Home	Figs only for those who completed. Age 81.8 (5.3) IG: n = 16, MMSE 12.6 (7 – 20) CG: n = 15, MMSE 12.9 (8 – 19)	Diagnosis of AD according to DSM IV criteria; MMSE <23; able to walk 10 m without aid	Multicomponent exercise program including walking x 1pw, equilibrium x 1pw and stamina x 1pw. (15 wks, 1 hr x 3pw)	Usual care	IG = 20% CG = 17%	10m walk test.
Meng-Chun 2016	Taiwan: Nursing Homes	IG: n = 76 CG: n = 74 Age 81.07 (7.13),	Over 65; mobility with wheelchair; diagnosed with cognitive	Elastic Band exercises groups sat in wheelchair (6 months, 40	Usual care	IG = 4% CG = 12%	Grip Strength, Arm Muscle Endurance measured by

		MMSE 11.49 (4.32)	impairment by physician or MMSE <23	mins x 3pw) Instructors were volunteers from nursing home that were trained			the Arm Curl Test.
Roach 2011	USA: Long term care facilities	Figures for those who completed IG n = 28 age 89.12 (6.54), MMSE 8.71 (7.83) AC n = 29 age 87.31 (6.08), MMSE 12.20 (7.47) CG n = 25 age 88.24 (5.80), MMSE 9.44 (7.21)	Residence in a long term care facility; clinical evidence of AD based on NINCD criteria; dependence in at least one of bed mobility, transfers, gait or balance; ability to walk with or without assistance.	Multicomponent exercise group including strength, balance, flexibility and endurance led by graduate nursing and physical therapy students trained and supervised by the investigators (16 wks, up to 30 mins x 5pw)	Social conversation (16wks, up to 30 mins x 5pw)	IG = 18% AC = 27% CG = 19%	6 min walk test.
Rolland 2007	France: Nursing Homes	IG: n = 67 CG: n = 67 Age 83 (7.4), MMSE 8.8 (6.6)	Diagnosis of AD according to NINCD criteria; lived in the nursing home for 2 months; able to transfer and walk 6 m without human assistance	Multicomponent exercise group including aerobic, strength, flexibility and balance training led by OT; walking trail created to encourage adherence (12 months, 1 hr x 2pw)	Usual care	IG = 16% CG = 19%	6 m walk test, get up and go, Montgomery -Asberg Depression Rating Scale.
Venturelli 2011	Italy: Alzheimer's Care Unit	IG: n = 12, age 83 (6), MMSE 13 (2)	Over 65: assistance with 2 or more ADL's on Barthel; MMSE 15 – 5; POMA	Walking arm in arm with relative (24 wks, 30 mins x 4pw)	Usual care	IG = 8% CG = 17%	6 minute walk test.

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		CG: n = 12, age 85 (5,) MMSE 12 (2)	min score 23; CDR 3 or more.				
Williams 2007	USA: Long-term care facilities	Figures only for those who completed. Age 88 (6.32), MMSE 44% - 0 - 9, 42% - 10 - 19, 10% - 20 - 23, 3% - 24 – 28. IG: n = 30, AC: n = 31, CG: n = 29	Evidence of AD according to NINCD criteria; dependence in at least one of: bed mobility, transfers, gait or balance; able to walk with assistance.	IG: Individual Supervised Multicomponent exercise program (16 wks, up to 30 mins x 5pw) AC: Supervised walking (16 wks, up to 30 mins x 5pw) Generally conducted indoors on nursing home units	Casual conversation (16wks, up to 30 mins x 5pw)	Not specified	Dementia Mood Assessment Scale, Alzheimer's Mood Scale.

IG = Intervention Group, CG = Control Group, AC = Active Control, MMSE = Mini Mental State Examination, AD = Alzheimer's Disease, OT= Occupational Therapist, NINCD = National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer Disease and Related Disorders Association, ADL = Activities of Daily Living, POMA = Performance Orientated Mobility Assessment.

Table 2 Physical outcome measures results and findings of statistical significance

Study	Outcome Measure (including units)	Results: mean (SD)	Significant Difference between Groups	Effective
Cancela 2016	Timed up and Go: change from baseline (secs)	IG: -2.11 (7.5) CG: -0.56 (4.8)	Yes significant difference post intervention (ITT) F = 5.43, p = 0.03	Yes
Cott 2002	2 min walk test: post-test distance covered (m)	IG: 53.25 (27.53) AC: 56.42 (34.43) CG: 47.66 (33.75)	No paper states no significant differences between or within groups (no figures provided)	No
Kemoun 2010	10 m walk: post intervention score (m/s)	IG: 1.02 (0.24) CG: 0.75 (0.16)	Yes significant difference post intervention p< 0.01	Yes
Meng-Chun 2016	Grip Strength: post intervention score (kg)	IG: 11.48 CG: 10.16	Potentially - means and standard deviations of each group not provided individually – change between groups and effect sizes given β - 1.29 effect size 0.13 pre/post-test changes suggest a trend towards improvement	Potentially but have not provided statistical data in the same form as other studies and effect size is small
	Arm Muscle Endurance: post intervention score (no of reps)	IG: 6.73 CG: 6.35	Potentially - means and standard deviations of each group not provided individually – change between groups and effect sizes given β - 0.82 effect size 0.04 pre/post-test changes show a trend towards improvement	Potentially but they have not provided statistical data in same form as other studies and the effect size is very small.
Roach 2011	6 min walk test: post intervention distance covered (ft)	IG: 384.86 (217.56) AC: 324.80 (274.36) CG: 367.51 (300.15)	No not a significant difference between the groups p = 0.61	No

Rolland 2007	6 m walk: post intervention score (m/s)	IG: 0.41 (0.16) CG: 0.36 (0.19)	Yes significant difference post intervention p = 0.02	Yes
	Get up and go: post intervention score (range 1-5)	IG: 3.1 (1.1) CG: 3.2 (1.2)	No not a significant difference between groups p = 0.3	No
Venturelli 2011	6 min walk test: post intervention distance covered (m)	IG: 294 (49) CG: 168 (34)	Yes significant difference post intervention p <.05	Yes

IG = Intervention Group, CG = Control Group, AC = Active Control, F = p- value for ANCOVA for repeated measures

Table 3 Mood outcome measures results and findings of statistical significance

Study	Outcome Measure	Results mean (SD)	Significant Difference between Groups	Effective
Cancela 2016	Cornell Scale for Depression in Dementia: change from baseline	IG: 1.84 (11.32) CG: -2.71 (4.40)	No not a significant difference post intervention (ITT) F= 1.48 p = 0.22	No
Rolland 2007	Montgomery-Asberg Depression Rating Scale: post intervention score	IG: 13.4 (8) CG: 14.8 (7.2)	No not a significant difference post intervention p = 0.2	No
Williams 2007	Alzheimer's Mood Scale (Positive): post-test adjusted means	IG: 88.76 AC: 80.87 CG: 77.2	No not a significant difference post intervention (no figures provided)	No
	Alzheimer's Mood Scale (Negative): post-test adjusted means	IG: 46.91 AC: 53.04 CG: 64.2	Mixed significant difference between IG and CG p = 0.004 and AC and CG p = 0.04. no significant difference between IG and AC	Mixed however did show significant difference between intervention and usual care and active control and usual care
	Dementia Mood Assessment: post-test adjusted means	IG: 19.69 AC: 26.49 CG: 33.13	Mixed significant difference between IG and CG p = .007 all other comparisons not significant	Mixed

IG = Intervention Group, CG = Control Group, AC = Active Control, F = p- value for ANCOVA for repeated measures

Figure Captions

Figure 1 Flow Diagram of Study Retrieval and Selection

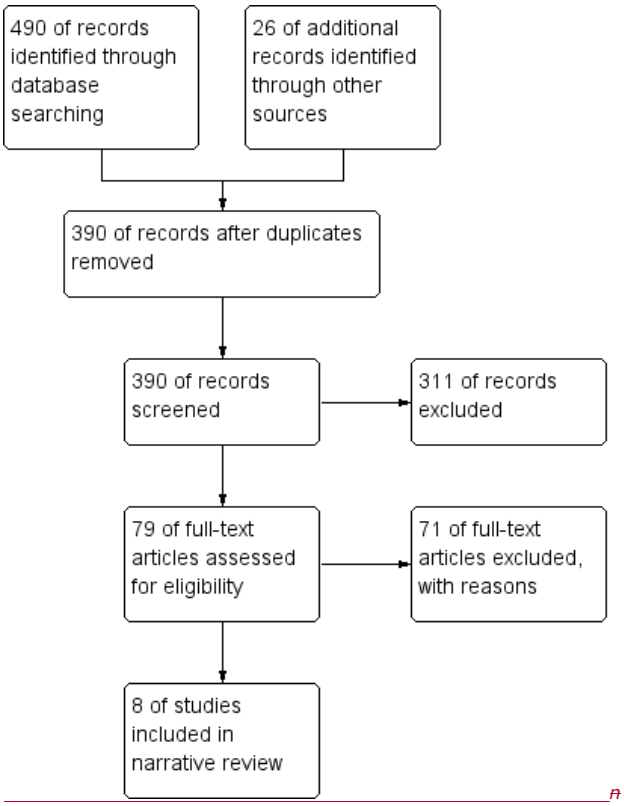


*Figure **Error! No text of specified style in document.** Risk of bias graph: review item presented as percentages across all authors' judgements about each risk of bias included trials*

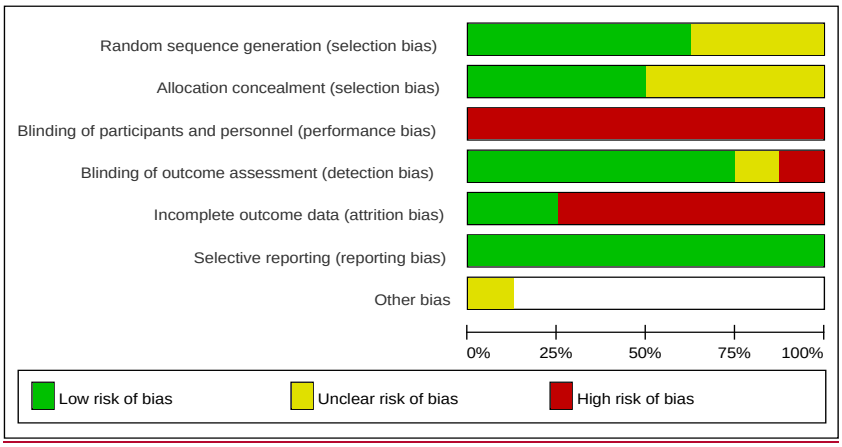
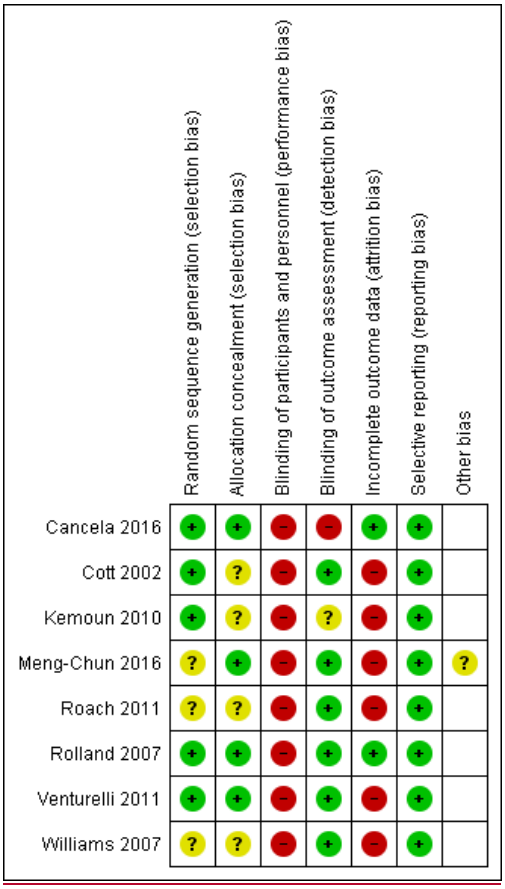


Figure 1 Risk of bias summary: review authors judgement about each risk of bias item for each included study


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Cancela 2016
Cott 2002
Kemoun 2010
Meng-Chun 2016
Roach 2011
Rolland 2007
Venturelli 2011
Williams 2007