Title

Effects of non-pharmacological interventions on functioning of people living with dementia at home: a systematic review of randomised controlled trials

Running title: Interventions to improve function in people with dementia

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Word count for main body of text: 3877

Data sharing statement
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Acknowledgements/Funding

This work was carried out within the UCL Alzheimer's Society Centre of Excellence for Independence at home, NIDUS (New Interventions in Dementia Study) programme (Alzheimer's Society Centre of Excellence grant 330).

Kenneth Rockwood is President and Chief Science Officer of DGI Clinical, which in the last five years has contracts with pharma and device manufacturers (Baxter, Baxalta, Shire, Hollister, Nutricia, Roche, Otsuka) on individualized outcome measurement. In 2017 he attended an advisory board meeting with Lundbeck. Otherwise all personal fees are for invited guest lectures and academic symposia, received directly from event organizers, chiefly for presentations on frailty. He is Associate Director of the Canadian Consortium on Neurodegeneration in Aging, which is funded by the Canadian Institutes of Health Research, and with additional funding from the Alzheimer Society of Canada and several other charities, as well as, in first phase (2013-2018), from Pfizer Canada and Sanofi Canada. He receives career support from the Dalhousie Medical Research Foundation as the Kathryn Allen Weldon Professor of Alzheimer Research, and research support from the Canadian Institutes of Health Research, the Nova Scotia Health Research Foundation, the Capital Health Research Fund and the Fountain Family Innovation Fund of the Nova Scotia Health Authority Foundation.

Abstract

Objective: Slowing functional decline could enable people living with dementia to live for longer and more independently in their own homes. We aimed to update previous syntheses examining the effectiveness of non-pharmacological interventions in reducing functional decline (activities of daily living, activity-specific physical functioning or function-specific goal attainment) in people living in their own homes with dementia.

Methods: We systematically searched electronic databases from January 2012 to May 2018; two researchers independently rated risk of bias of Randomised Controlled Trials (RCTs) fitting predetermined inclusion criteria using a checklist; we narratively synthesised findings, prioritising studies judged to have a lower risk of bias.

Results: Twenty-nine papers (describing 26 RCTs) met eligibility criteria, of which we judged 13 RCTs to have a lower risk of bias. Study interventions were evaluated in four groups: physical exercise, occupational, multicomponent and cognition-oriented interventions. 4/13 RCTs reported functional ability as a primary outcome. In studies judged to have a lower risk of bias, in-home tailored exercise, individualised cognitive rehabilitation, and in-home activities-focussed occupational therapy significantly reduced functional decline relative to control groups in individual studies. There was consistent evidence from studies at low risk of bias that group-based exercise and reminiscence therapies were ineffective at reducing functional decline.

Conclusion: We found no replicated evidence of intervention effectiveness in decreasing functional decline. Interventions associated with slower functional decline in individual trials have been individually-delivered and tailored to the needs of the person with dementia. This is consistent with previous findings. Future intervention trials should prioritise these approaches.

Key words
dementia, function, activities of daily living, community care

Key points
1. All interventions that have significantly improved functioning in people living with dementia in the community have been individual rather than group interventions.
2. This may be because they can be individually tailored, and most took place in the homes of people living with dementia.
3. Components of successful individual interventions have included tailored exercise and activity programmes, cognitive rehabilitation and environmental adaptations.
4. Interventions appear to be most effective when delivered to dyads of people living with dementia and family carers.

Introduction

Around 850,000 UK people live with dementia. This is forecast to increase to over two million people by 2051 [1]. Dementia is a leading global cause of disability and dependence [2 3]. Living well with dementia has been conceptualised as living with quality of life, greater autonomy and independence, and staying at home for longer [4 5]. There can be a tension between striving for independence as an expression of full autonomy [4] and supporting interdependence that can enable people to live in their own homes for longer [5]. Nonetheless, less dependency on others for daily activities is associated with higher quality of life in people with dementia [6 7], and living at home for longer [2 7], so delaying functional dependence is an important target for care interventions.

UK and global policies call for strategies to enable people with dementia to remain engaged in everyday activities [2 8 9]. Basic Activities of Daily Living (ADLs) include self-care activities such as bathing, dressing, eating and toileting; and Instrumental ADLs (IADLs) are more complex activities such as household tasks, shopping, and managing finances [10]. Traditional assumptions that IADLs require a higher level of functioning were unsupported by a recent study, which conceptualised functional dependency as a continuum; from highest-order activities such as outside maintenance and tax arrangements, to basic ADLs such as eating [11]. Delaying such functional decline (i.e. maintaining or improving functional ability) could potentially transform the lives of the individuals with dementia, their families and society. With a dearth of new pharmacological interventions, and existing treatments only achieving modest symptomatic benefits, the importance of non-pharmacological treatment is clear [1 3].

Various non-pharmacological approaches have been trialled for managing functional decline in dementia. Existing syntheses conclude that evidence is strongest for exercise programmes (group or individual) involving aerobic exercise and strength training [12-15]. Occupational therapies, where both the person with dementia and their carer receive ADL training and environmental adaptations, have demonstrated positive effects [14 16 17]. Previous reviews found no good evidence that cognitive training or cognitive stimulation therapy improve functioning, and limited evidence that individual cognitive rehabilitation is efficacious [17-19]. Generic measures of functional ability evaluate performance on, or level of assistance required to carry out common ADLs; other instruments measure activity-specific physical functioning or function-related goal attainment [20 21].

Existing reviews have either investigated a specific type of intervention alone (e.g. exercise) or not distinguished participants who were living in care homes from those living in community settings [13 17 22]. This is potentially an important omission, as intervention attendance, adherence and support may differ significantly between these different contexts. We aimed to update, to our knowledge, the only previous systematic review of Randomised Controlled Trial (RCT) evidence for interventions to prevent functional decline specifically in people with dementia living in their own homes [14]. We synthesised findings of RCTs published from 2012 onwards that have reported the effectiveness of non-pharmacological interventions on functional ability (ADLs, activity-specific physical functioning or function-related goal attainment) of people living in their own homes with dementia.

Methods

We followed AMSTAR guidelines for systematic reviews of randomised studies of healthcare interventions [23], and registered our protocol with the PROSPERO Prospective Register of Systematic Reviews (CRD42018091625).

Search strategy

We searched PubMed, EMBASE (Ovid) and PsychINFO (Ovid) from 1/1/2012 to 16/5/18, (to update the search of the previous review [14], with no limits on language. We applied key terms for the databases that incorporated word combinations relating to or describing: dementia and non-pharmacological intervention, with relevant MeSH terms to improve the accuracy of the searches. We based our search strategy on the previous review [14]; deviations from this were that we did not restrict by intervention type (applying only population and intervention key terms), or use the term "cognitive impairment" as a population descriptor, as we only included studies where participants had a dementia diagnosis. We also included additional intervention terms ("psychotherapy" and "goal attainment") and omitted the term "motor activity"; these changes reflected intervention approaches that the co-author group judged to have been prevalent in the arena of interventions targeting functioning in people with dementia in recent years.

The population terms were (dementia) OR (Alzheimer*), combined with the intervention terms (non-pharmacologic*) OR (nonpharmacologic*) OR (psychotherapy) OR (rehabilitation) OR ('physical therapy') OR ('goal attainment'). A backwards search of the included papers was carried out and relevant systematic reviews were hand searched.

Protocols or pilot studies retrieved that were relevant but not eligible (e.g. due to small sample size), were also checked for updated publications by forward citation searching and contacting authors.

Study inclusion and exclusion criteria

We included RCTs where (a) all participants had a dementia diagnosis and lived in their own homes; (b) the intervention was non-pharmacological; (c) the control group received treatment as usual or placebo; and (d) measures of ADL/IADL functional performance or dependency; function-related goal attainment; or activity, goal, role or task specific physical functioning were primary or secondary outcomes. We excluded studies that evaluated nutritional interventions (as fitted our focus on psychological interventions) or interventions targeting caregiver-focussed outcomes only, which did not include components targeting care recipient-focussed outcomes;measures of general rather than specific physical functioning (e.g. mobility or balance); and studies where either the intervention or control group had less than 15 participants to minimise bias [24].

Procedures

IS conducted the searches and assessed eligibility of all retrieved abstracts. ML independently assessed eligibility of 10% of retrieved abstracts. Inter-rater agreement for abstract screening was substantial (Cohen's k=.77). IS reviewed the full text of all potentially eligible papers and ML independently assessed 10%. Inter-rater agreement for full text screening was very high (Cohen's k=.86). PR also reviewed all papers identified as potentially eligible and authors resolved discrepancies by consensus. IS then extracted study characteristics from all eligible full-texts (see Tables 1-3).

Assessing Risk of Bias (ROB)

IS and PR rated the risk of bias of included papers independently, based on responses to six standard quality criteria developed by our group [24-26], and incorporated AMSTAR guidelines for randomised-study quality assessment [23]. Each question from the quality tool checklist scored 1 point:

1. Were participants randomised to intervention and control groups?
2. Were participants and clinicians, as far as possible, masked to treatment allocation?
3. Were all participants who entered the trial accounted for and an intention-to-treat analysis conducted?
4. Was follow-up and data collection processes the same for all participants?
5. Was a power calculation carried out based on one of our specified outcomes of interest (dependency/ function)?
6. Were results reported based on an explicit analysis plan with specified outcomes?

Possible scores ranged from 0 to 6, with higher scores indicating lower ROB and therefore higher quality. Papers were judged to have a lower ROB if the response to questions: 1, 3, 4 and 6 above were affirmative. This prioritisation (of questions 1, 3 and 4) was based on a previous study [25]. We additionally prioritised question 6 as this is consistent with the AMSTAR guidelines for RCTs. IS and PR discussed any discrepancies in ratings and reached consensus.

Synthesis and analysis

In our narrative synthesis, we prioritised results from studies with lower ROB. We decided *a priori* to meta-analyse findings where three or more RCTs had sufficiently homogenous interventions and outcomes (a criteria used in previous reviews [27]). No intervention met these criteria. We tabulated all statistical comparisons between groups.

Results

We included 29 papers describing 26 studies (Figure 1 shows PRISMA diagram). We rated 13/26 studies as having lower ROB and describe these in the narrative synthesis and in Tables 1-3. We describe studies rated as having higher ROB in Tables 4-5. As shown in Tables 1-3, most studies with lower ROB enrolled between 100 and 250 participants, while one smaller pilot involved 30 participants and one larger with 494 participants. Most studies included people with mild and/or moderate dementia. One study also recruited people with very mild dementia [28] and one study compared people with mild and advanced dementia [29].

Description of lower ROB studies

The 13 studies with lower ROB were conducted in the UK [30-34], USA [35 36], Netherlands [37 38], Finland [28 29 39], Germany [40 41], Denmark [42] and France [43]. They evaluated functional ability using informant or self-report scales that measured: patient performance and dependency on others to perform ADLs [28-37 39-43], activity-specific goal setting [37], and physical

role function [38]. We divided the included studies into four groups: physical exercise therapies, Occupational Therapy (OT) interventions, multicomponent interventions and cognition-oriented or reminiscence therapies.

Physical Exercise Interventions (Table 1)

Four RCTs evaluated interventions that used a variety of forms of exercise and delivery. All reported good to high adherence rates to the interventions.

Only one of the RCTs [29 39] reported functional ability as a primary outcome. It compared two intervention conditions against Treatment As Usual (TAU) in people with Alzheimer's disease: (1) a group-based exercise programme at adult day care centres, and (2) a goal-oriented, individually tailored home exercise programme. Both were delivered for one-hour, twice a week for a year by dementia specialist physiotherapists. They involved endurance, balance and strength training and dual-tasks for executive function. Functional ability declined significantly less in the individual, but not the group intervention condition relative to TAU.

Three RCTs reported that there were no significant differences between intervention and control groups on secondary outcomes of ADL performance. Two RCTs evaluated four months of physiotherapist delivered, moderate-to-high intensity aerobic group exercise against TAU. This was delivered as three, one-hour sessions a week within memory clinics [42]; and as two, one-hour sessions in a gym, with additional strength training and one-hour of independent home exercises each week [30]. The third RCT was a small pilot study (n=30), comparing an in-home Wii-fit video game-led exercise programme (involving yoga, strength, aerobics, balance and dual-task exercise) for 20 minutes, 5 days a week for eight weeks and a walking-based control in people with mild dementia [35]. The intervention was supervised by family carers.

Summary

- There was consistent evidence from three trials that group-based exercise did not improve functioning.
- One trial reported that in-home individually tailored, physiotherapist-delivered exercise programme was associated with decreased functional dependence relative to a control group. This was contradicted by one smaller pilot study, in which the intervention was not tailored or supervised by experts.

Occupational Therapy interventions

Three RCTs examined the effects of ADL-focussed occupational therapy interventions on functional ability. All three evaluated interventions that trained people with dementia to perform specific ADL tasks and developing compensatory strategies to improve performance.

One RCT [40] reported functional ability as a primary outcome. The study compared an 'errorless learning' (help and instruction with a task before or as the patient makes mistakes) individual intervention focussed on two ADL tasks, against a control condition in which participants received no instruction during learning. ADL tasks were selected from a manual, which included 43 household, leisure and more complex tasks such as using the internet. Both conditions comprised 11, one-hour sessions delivered over eight weeks at participating services by an occupational therapist, nurse, psychologist or social worker. Adherence levels to the intervention were good. There were no significant between-group differences in ADL performance or dependence, with both groups improving on task performance.

Two RCTs reported outcomes of interest to this review as secondary outcomes. One compared an eight session, in-home OT programme (Tailored activity program; TAP-VA) over four months, to a telephone attention control [36]. Occupational therapists taught family carers to set activity goals that were appropriate to care recipients' capabilities and deficits and plan specific steps to set up activities. Adherence to the protocol was monitored. Levels of ADL dependence and the number of ADLs requiring assistance decreased in the intervention compared to the control group at four months. In the second paper, a cluster RCT compared the effects of a five week (10, one-hour sessions) in-home OT program (COTiD program) in which occupational therapists with additional training and support worked with people with mild to moderate dementia and their family carers to identify meaningful activities and to set appropriate intervention goals [37]. Usual care was delivered by staff who received usual postgraduate training. There were no significant between-group differences in ADL performance or dependence, or in self-perceived goal setting performance in meaningful ADLs at follow-ups.

Summary

- One trial reported that the Tailored activity program (TAP-VA), which involved in-home training of ADLs and environmental strategies delayed functional dependence relative to an attentional control.
- Two trials demonstrated no evidence for the benefit of enhanced ADL-OT (delivered at services, through errorless learning techniques or with improved staff training) compared to their standard ADL-OT programme delivery.

Multicomponent Interventions

Two RCTs examined the effects of multicomponent interventions on functional ability. The studies were diverse in therapeutic combinations. Both reported moderate to high adherence rates. One study, which reported functional ability as a primary outcome, compared an in-home multicomponent dyadic intervention delivered to carer-care recipient dyads by a personal coach (eight, one hour sessions, over three months), comprising physical exercise training, psycho-education, communication skills and training to increase pleasant activities, to a control intervention of general advice and monthly telephone emotional support. There were no significant, between-group differences in physical role functioning [38]. The other RCT [28] reported functional ability as a secondary outcome. It compared 16 days of psychosocial rehabilitation at a rehabilitation centre to a basic counselling control condition, for people with mild Alzheimer's Disease and their caregivers within two years of diagnosis. The courses aimed to enhance knowledge; reduce social isolation with group discussions and social activities; and support functional ability with individual counselling. Functional ability declined significantly more in the *intervention group,* compared to the control condition over 36 months.

Summary

- Two trials evaluating diverse multicomponent interventions demonstrated no beneficial effects on functional ability compared to controls, and in one of the trials, the intervention group participants declined more in functioning relative to the control group.

Cognition-oriented or Reminiscence Therapies

Four RCTs examined the effects of cognition-oriented or reminiscence therapies. One study reported high adherence [41], while the others highlighted poor adherence as a limitation [31-34] or did not report it [43].

One RCT reported on functional ability as a primary outcome [41]. It was the only study included in this synthesis to report sufficient power to detect a minimally clinically significant finding on a measure of functioning. It compared individual cognitive rehabilitation for personally identified problems (using external memory aids and introducing daily behavioural routines) and Cognitive-Behavioural Therapy (CBT: involving day structuring, activity planning and reminiscence) to a TAU control, in people with mild Alzheimer's disease. Behavioural therapists delivered 12 weekly, one-hour sessions over 3 months. There were no significant between-group differences in ADL measures or in client or carer-rated functional ability.

Three RCTs reported secondary functioning outcomes. Amieva et al [43] examined three different therapies against TAU: (1) cognitive rehabilitation with ADL training tailored to the person with dementia and their carer, (2) group cognitive training for standard ADL tasks, and (3) group reminiscence therapy. Psychologists delivered these interventions for 90 minutes per week over three months with maintenance sessions for 21 months every six weeks. ADL ability and dependency declined significantly less in the individual cognitive rehabilitation group relative to TAU over two years. There were no significant differences between the other conditions and TAU.

The other two RCTs reported no significant differences between intervention and TAU groups in functional outcomes. One assessed home-based individual Cognitive Stimulation Therapy (iCST), involving different themed activity sessions (e.g. being creative, word games and current affairs) with caregivers supported to deliver sessions for 30 minutes, two-three times a week over 25 weeks [31 32]. The other study evaluated group reminiscence therapy involving, art, cooking physical re-enactment of memories, singing and oral reminiscence and led by trained facilitators and volunteers at participating services (two hours, weekly across 12 weeks plus monthly maintenance sessions for seven months) [33 34].

Summary

- Group reminiscence therapy did not reduce functional decline in two trials reporting secondary outcomes

- There were mixed results for individualised cognitive rehabilitation tailoring ADL training; it was associated with less decline in functional ability and dependency in one trial reporting this as a secondary outcome over two years, but was not beneficial when combined with CBT in one trial which reported functioning as a primary outcome over three months.
- Neither individual cognitive stimulation therapy nor group cognitive training were shown to improve functioning in individual trials.

Evidence from studies with higher risk of bias (Tables 4-5)

Findings from these studies were broadly concordant with those from studies with lower ROB. Two studies evaluated in-home, individual physical activity programmes; both demonstrated improved ADL/IADL functioning for up to 4 months, relative to control conditions. One study evaluating an in-home OT intervention did not demonstrate efficacy over 24 months, although the authors note results are indeterminate as 95% confidence intervals include clinically significant between-group differences [44]. Multi-component interventions were diverse in both delivery and results, with 2 of 3 small studies demonstrating functional benefits [45 46]. A reminiscence therapy study demonstrated no effects [47]. Cognitive training and stimulation therapies provided mixed results, with 3/6 studies demonstrating evidence of efficacy of individual or group interventions.

Discussion

We synthesised RCT evidence from the last 6 years, to update an existing review of non-pharmacological interventions to improve, maintain or delay functional decline among people with dementia living in their own homes. Only three of the included RCTs that we judged to have a low risk of bias described interventions that were associated with significantly improved functioning. These were: a one year, in-home physical exercise programme [29 39]; an in-home ADL training and environmental strategy intervention [36]; and three months of cognitive rehabilitation and ADL training [43]. All were delivered individually and tailored to the person living with dementia' functional needs.

The most consistent evidence we found was from three trials that reported that group exercise did not delay functional decline. Group reminiscence, cognitive and multicomponent therapies were also found to be ineffective in reducing functional decline in individual trials. OT programmes based in services were also ineffective, so the message from existing evidence would appear to indicate that, interventions to improve functioning need to be delivered in people's homes. This may be because it allows therapists to evaluate and adapt the home environment, and because it is easier for carers and people with dementia to put learning into practice if they do not need to translate it to a different environment.

The review we updated reported evidence of efficacy for exercise and occupational therapy interventions, concluding that the literature supports a "proof of concept that the functional decline associated with dementia can be delayed". Our findings concord with and add to these earlier findings [14]. Other reviews that did not distinguish participants living in their own homes and 24-hour care settings [13 17 22] concluded that there was evidence that exercise programmes are effective at reducing functional decline in people with dementia. Only two studies included in a Cochrane review recruited people with dementia living at home. In both, interventions were delivered individually by family carers improved functioning [13]. Perhaps group interventions work in care homes but are less effective for people living with dementia in community settings.

The finding from one study in our review that in-home OT training and environmental strategies were effective [36] accords with the previous evidence base, that dyadic interventions encompassing activity interventions and environmental adaptations are effective [22]. Previous reviews reported that Cognitive Stimulation Therapy and Cognitive training are not effective at reducing cognitive decline, while there was some evidence for individual cognitive rehabilitation from a single trial [48]. In the current review, we found one additional trial in which individual, cognitive rehabilitation reduced functional decline [43].

Our findings are in line with current theoretical models describing how best to support people with dementia to live at home. Person-centred approaches, which optimise the environment and activities, support family carers, and are needs and goal-based, enable self-management where possible, and are underpinned by a responsive, case management service model; are the models that appear to be most likely to be effective [49].

While there remains a paucity of evidence about how clinical teams can best support people living at home with dementia to delay functional decline, the existing evidence is consistent and should inform future intervention studies. Our findings would support further trials of interventions that are specially tailored to activities that are meaningful to the participant and delivered in-home. Our findings indicate that individual interventions are more likely to be effective than group formats, particularly for exercise and reminiscence therapies due to replicated demonstration of lack of efficacy and low engagement from this particular population. The time and cost benefits of group therapy are apparent, but there could be longer term service benefits if individual therapy is more likely to enable people with dementia to retain functional abilities for longer. The relative efficacy of in-home interventions could be explained by higher attendance and adherence rates [39], a higher utility to learning skills in the environment you will use them, and perhaps learning in a more enabling environment is more effective.

Due to heterogeneity of interventions and effects measured, we were unable to meta-analyse findings and conclusions are based on a narrative synthesis. This breadth in scales used to measure calls for adopting a more standardised outcome measure in future studies to facilitate effective synthesis and comparison of results. All but one study employed generic, as opposed to activity-specific measures of functioning, which were proxy reported by a carer. In the study that found a greater decline in functioning in the intervention relative to the control group, the authors hypothesised that greater awareness of dementia-related symptoms might have accounted for their findings [28]. No studies used direct observation of functioning, which could have eliminated rater bias; advances in technology may allow this in future trials. While it is possible that ceiling effects may have reduced sensitivity of functioning measures to detect change, most of the lower risk of bias studies that reported positive effects were in populations with mild dementia, suggesting this is less likely [28 29 38]. Only one study which found a significant effect in favour of the intervention included participants who had on average moderate dementia [36].

There was a dearth of good quality evidence regarding how interventions might reduce functional decline; the majority of studies only reported on functional ability as a secondary outcome. Individualised measures, such as goal attainment may more often show evidence of efficacy [50]. Some studies did not report intervention adherence. We excluded three studies of interventions delivered directly to family carers, though none found a significant effect of the intervention on functioning of the person living with dementia. While we based our definitions of higher and lower risk of bias on previous work, this dichotomisation is a potential source of bias, so we evaluated the evidence from higher ROB studies and compared it with the evidence base from studies judged to be at lower risk of bias.

Conclusion

Findings from our review and the previous literature indicate that future interventions to improve functioning of people living with dementia at home should focus on individually tailoring exercise and activity programmes, cognitive rehabilitation and environmental adaptations. These appear to be most effective when delivered to dyads of people living with dementia and family carers.

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Table 1: Characteristics, results and quality assessment of physical exercise therapy studies identified as having low risk of bias

Study/ Country	Inclusion criteria/ Recruitment	Intervention group (IG)	n	Control group (CG)	n	Significance of differences between groups (intervention vs control)				Quality rating (see methods)					
						Outcome of interest		Mean difference at follow-up (95% CI) P-value	Other 1ry outcomes	1	2	3	4	5	6
Physical Exercise Therapies															
Hoffman [42] Denmark	Mild AD from memory clinics	Moderate-high intensity, group exercise programme; 1 hour long, 3/week for 16 weeks)	107	TAU	93	ADCS-ADL (mean change difference from baseline)		16 weeks: –0.1 (–1.8, 1.5) p=0.868	Mental speed and attention	y	y	y	y	n	y
Lamb [30] UK	Mild-moderate dementia; from community services & registries	Group exercise; 1-1.5 hours, 2/week for 4 months + 1hr home exercise)	329	TAU + counselling/ for carers families.	165	BADL ‡ (mean difference)		6 months: 0.8 (−0.3, 2.0), p=0.15 12 months: 0.3 (−1.7, 1.2), p=0.70	Severity of dementia	y	y	y	y	n	y
Pitkala, [39]**; Ohman** [29] Finland	People with AD and spousal caregivers; from drug reimbursement registries	Endurance, balance, strength and dual-task training: group vs individually tailored home exercise conditions; 1 hour, 2/week for 1 year	Home 70 Group 70	TAU – with similar advice	70	**FIM †** (mean change difference from baseline)	Home	6 months: **p=0.001*** IG -6.5(-4.4, -8.6), CG -11.8 (-9.7, -14.0); 12 months: **p=0.004*** IG -7.1(-3.7, -10.5), CG -14.4(-10.9, -18.0)	Mobility and complications e.g. fall, fractures, hospitalisations, compliance, care costs	y	n	y	y	y	y
							Group	6 months: p=0.07 IG -8.9(-6.7, -11.2), CG -11.8(-9.7, -14.0); 12 months: p=0.12 IG -10.3(-6.7,-13.9), CG -14.4(-10.9,-18.0)						
	Sub-analysis of participants with mild and advanced AD	Participation in either of exercise groups in main trial	Mild 44 Advanced 85		Mild 22 advanced 43	**FIM †**	Mild	6 months: **p=0.003*** IG –3.3(–1.5, –5.2), CG –8.9(–5.2, –12.7) 12 months: **p<0.001*** IG -2.7(–0.5, –4.9), CG –10.1(–7.0, –13.3)							
							Advanced	6 months: p=0.82 IG –13.3(–7.8, –19), CG –12.7(–9.0,-16.3) 12 months: p=0.18 IG –9.9(–7.0,– 1 2.7), C CG –14.6(–8.6,–20.6)							
Padala [35] USA	People with mild AD; from clinic	In-home Wii-Fit interactive video-game-led exercise program; 20 minutes, 5 days a week for 8 weeks	15	Placebo walking control; 30 minutes, 5/week	15	ADL (mean change difference from baseline)		8 weeks: 0.1 (-0.4, 0.6), p=0.708; 16 weeks: -0.2 (-0.7, 0.4), p=0.499	Balance impairment	y	n	y	y	n	y
						IADL		8 weeks: 0.7 (-0.7, 2.0), p=0.316; 16 weeks: 0.7(-0.6, 2.1), p=0.267							

† Primary outcome, ‡ Higher scores indicate lower functional ability

*** Significant difference**

AD= Alzheimer's Disease, ADCS-ADL=Alzheimer's Disease Cooperative Study - Activities of Daily Living, BADL= Bristol activity of daily living index, CI = Confidence Interval, FIM=Functional Independence Measure, ADL=Katz's Activities of Daily Living, IADL=Lawton and Brody's Instrumental Activities of Daily Living; IG = Intervention Group; CG = Control Group

Table 2: Characteristics, results and quality assessment of occupational therapy and multicomponent intervention studies identified as having low risk of bias

Study/ Country	Inclusion criteria/ Recruitment	Intervention group (IG)	n	Control group (CG)	n	Significance of differences between groups (intervention vs control)			Quality rating (see methods)					
						Outcome of interest	Mean difference at follow-up (95% CI)	Other primary outcomes	1	2	3	4	5	6
Occupational Therapies (OT)														
Dopp (32) Netherlands	Mild-moderate dementia and carers; from outpatient services	OT training of ADL tasks in-home (COTiD programme); 10, 1 hour sessions over 5 weeks, when delivered by service staff who received multi-faceted teaching of COTiD to enhance adherence	44 (28 units)	Service staff received usual 3-day postgraduate training course	27 (17 units)	AMPS process (mean difference)	6 months: -0.26(-0.86, 0.33) 12 months: -0.21(-0.50, 0.93) §, p>0.05	Adherence	y	y	y	y	n	y
						IDDD performance ‡ ''	6 months: 0.32(-0.28, 0.92) 12 months: 0.39(-0.32, 1.11) §, p>0.05							
						COPM performance ''	6 months: -0.30(-0.90, 0.30) 12 months: -0.30(-1.01, 0.41) §, p>0.05							
Gitlin [36] USA	People with dementia and carers; from geriatric services	OT training of ADL tasks in-home (TAP-VA programme); 8 sessions over 4 months	76	Attention via telephone and basic dementia advice	84	CAFU: dependence in ADL/IADL (mean change difference from baseline)	4 months: 4.09(1.06, -7.13), **p=0.009***	behaviour symptoms	y	y	y	y	n	y
						CAFU: number of ADL/ IADLs requiring assistance	4 months: -0.80(-1.41, -0.20), **p=0.009***							
Voigt-Radloff [40] Germany	Mild-moderate dementia; from memory centres	OT training of ADL tasks (REDALI-DEM programme) using 'errorless learning'; 9, 1-hour sessions of 2 tasks over 8 weeks	81	OT training with 'trial and error learning' placebo control	80	**CEM †** (time x group effect) — Task A	16 weeks 0.3 (–0.3, 0.9) 26 weeks 0.3 (–0.5, 0.8), p>0.05		y	y	y	y	n	y
						CEM † (time x group effect) — Task B	16 weeks –0.1 (–0.5, 0.7) 26 weeks –0.2 (–0.9, 0.5), p>0.05							
						IDDD performance ‡ ''	16 weeks 0.0 (–3.0, 2.9) 26 weeks 1.4 (–2.1, 4.8), p>0.05							
Multicomponent Interventions														

Koivisto [28] Finland	Very mild to mild AD and carers; from memory clinics	Psychosocial rehabilitation courses, incl. education, counselling and social support for patient and caregiver; across 16 days	84	TAU + basic counselling	152	ADCS-ADL (mean change difference from baseline)	36 months: **p=0.014*** IG -25.25(-29.62, -20.87), CG -19.20(-23.28, -15.11)	Moving to care home over 36 months	y	y	y	y	n	y
Prick [38] Netherlands	People with dementia and carers; from community	Home physical exercise training, with psycho-education, communication skills and pleasant activities training; 8, 1 hour sessions, over 3 months	57	Usual care + monthly support calls (10 minutes)	54	**SF-36 physical role function subscale †** (time x group effect)	3 months: -1.17 (-10.60, –8.23), p=0.81 6 months: -1.52 (-10.91, –7.87), p=0.75 Overall: -1.04 (-10.49, –8.41), p=0.83	Depression	y	y	y	y	n	y

† Primary outcome

‡ Higher scores indicate lower functional ability

§ Calculated standardised difference

*** Significant difference**

AMPS=Assessment of Motor and Process Skills, CI = Confidence Interval, IDDD= Interview for Deterioration of Daily Activities, COPM=Canadian Occupational Performance Measure, CAFU=Caregiver Assessment of Function and Upset Scale, CEM=Core Element Method, ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living, SF-36=36 Item Short Form Health Survey

Table 3: Characteristics, results and quality assessment of cognition-oriented therapy studies identified as having low risk of bias

Study/ Country	**Sample/ Recruitment**	**Intervention group (IG)**	**n**	**Control group (CG)**	**n**	**Significance of differences between groups (intervention vs control)**				**Quality assessment (see methods)**					
						Outcome of interest i.e. measure of functional ability		**Mean difference at follow-up (95% Confidence Interval) P-value**	**Primary outcomes**	**1**	**2**	**3**	**4**	**5**	**6**
Cognition-oriented therapies															
Amieva [43] France	653 participants with mild-moderate AD (>50yrs) and caregivers; from memory centres or geriatric day-care units	Group cognitive training (CT), group reminiscence therapy (RT), individualized cognitive rehabilitation (ICR); all 90 minutes, weekly for 3 months, with maintenance sessions every 6 weeks for 21 months.	CT 170 RT 172 ICR 157	TAU	154	DAD (mean difference)	CT	3 months: 0.06(-0.17, 0.29) 24 months: -0.05(-0.30, 0.21) § p>0.05	Rate of survival without moderately severe to severe dementia at 2 years	y	y	y	y	n	y
							RT	3 months: 0.13(-0.10, 0.36) 24 months: 0.16(-0.10, 0.42) § p>0.05							
							ICR	3 months: 0.13(0.10, 0.36) 24 months: 0.12(-0.14, 0.38) § p>0.05							
						AGGIR ‡ ''	CT	3 months: 0.05(-0.18, 0.28) 24 months: -0.01(-0.26, 0.25) § p>0.05							
							RT	3 months: 0.05(-0.17, 0.29) 24 months: 0.02(-0.24, 0.28) § p>0.05							
							ICR	3 months: -0.02(-0.26, 0.21) § p>0.05 24 months: -0.21(-0.47, 0.04) § **p=0.02***							
Kurz [41] German y	Mild AD and caregivers; from outpatient units	Individual cognitive rehabilitation and cognitive-behavioural therapy; 12 weekly sessions over 3 months.	100	TAU	101	**B-ADL † ‡** (mean change difference from baseline)		3 months: -0.11(-0.40, 0.18) § p=0.438 9 months: -0.08(-0.38, 0.22) § p=0.640		y	y	y	y	y	y
						AFIB self rated ‡ ''		3 months: -0.05(-0.34, 0.23) § p=0.702 9 months: -0.09(-0.39, 0.21) §							

							p=0.584							
						AFIB caregiver rated ‡ ,,	3 months: -0.01(-0.30, 0.27) § p=0.948; 9 months: 0.09(-0.20, 0.40) § p=0.521							
Orgeta [31]; Orrell [32] UK	Mild-moderate dementia and carers; from memory and outpatient clinics	Individual Cognitive Stimulation Therapy (iCST); 30 minutes, 2-3 times weekly over 25 weeks.	180	TAU	176	BADL ‡ (mean difference)	13 weeks: –0.20 (–1.44, 1.04) p=0.75 26 weeks: –0.66 (–2.07, 0.75) p=0.36	Severity of dementia, quality of life	y	y	y	y	n	y
Woods [33 34] UK	Mild-moderate dementia and carers; from memory clinics & community mental health teams	Group reminiscence therapy; 2 hours, weekly for 12 weeks; then monthly maintenance sessions for 7 months.	268	TAU	230	BADL ‡ (mean difference)	3 months: 0.48 (-0.83, 1.79) p=0.47 10 months: -1.13 (-2.50, 0.24) p=0.11	Quality of life, psychological distress for carer	y	y	y	y	n	y

† Primary outcome

‡ Higher scores indicate lower functional ability

§ Calculated standardised difference

*** Significant difference**

B-ADL=Bayer Activities of Daily Living, AFIB=Aachen Functional Item Inventory, DAD=Disablement Assessment for Dementia, AGGIR=Grille d'Autonomie Gérontologique-Groupes Iso-Ressources, BADL=Bristol activity of daily living index (BADL),

Table 4*: Characteristics and quality ratings of physical exercise, occupational and multicomponent therapy studies identified as having higher risk of bias*

Study Country	Sample/ Recruitment	Intervention group (IG)	n	Control group (CG)	n	Significance of differences between groups (intervention vs control)			Quality assessment (see methods)					
						Outcome of interest i.e. measure of functional ability	Difference/effect at follow-up (95% Confidence Interval) P-value	Other primary outcomes	1	2	3	4	5	6
Physical Exercise Therapies														
Holthoff [51] Germany	Mild-moderate AD and caregivers; from memory clinic	In-home physical activity program with leg and movement training; 30 minutes, 3/week, for 12 weeks.	15	TAU	15	**ADCS-ADL †** (time x group effect)	12 weeks: 4.89 (2.30, 7.48) p>0.05 **24 weeks: 7.76 (5.01, 10.51) p<0.05***		y	y	n	y	n	n
Vreugdenhil [52] Australia	AD, and caregivers, recruited from a hospital outpatient memory clinic	In-home strength and balance training plus walking programme; 10 exercises + 30 minutes walking, daily, for 4 months	20	TAU	20	BIADL (mean change difference)	**4 months: 2.6 p=0.047***	Cognitive function, physical function, depression, global change function, carer burden	y	y	n	y	n	y
						IADL	**4 month: 1.6 p=0.007***							
Occupational Therapies (OT)														
Callahan [44] USA	AD and caregivers; from primary or senior care practices	In-home ADL-focused OT; 90 minutes, 24 sessions over 2 years	91	TAU	89	**ADCS-ADL †** (time x group effect)	6 months: 1.92(−3.49, 7.32) p=0.49 12 months: 3.89(−2.24, 10.01) p=0.21 18 months: 2.78 (−3.71, 9.27) p=0.40 24 months: 2.34 (−5.27, 9.96) p=0.54	Physical performance	y	y	n	y	y	y
Multicomponent Therapies														

Baglio [53] Italy	Mild to moderate AD (65-85yrs); from a memory clinic	Multidimensional Stimulation group Therapy; 30 rehabilitation sessions; 2.5hrs, 3/week, for 10 weeks+	30	TAU	30	**FLSA †** (mean change difference)		10 weeks: R^2>0.60, IG=99.6 (SD=1.52), CG=98.5 (SD=1.69), p=0.649	Cognitive function, behavioural and psychological symptoms, quality of life, brain activation	y	y	n	y	n	n
Fernandez-Calvo [45] Spain	Mild AD, from details provided by the Alzheimer's Association of Salamanca	Multi-intervention programme of cognitive tasks, daily life training and recreational activities (individual); 90 minutes, 3/week, for 16 weeks	28	Wait-list	33	**RDRS-2 †** (time x group effect)		**16 weeks: F(1, 53)=23.36 p< 0.001***	Cognitive impairment, behavioural and psychological symptoms, Depression	y	y	n	y	n	n
Quintana [46] Spain	Probable AD (60yr+); recruited from memory problems detection unit Marjorie Warren of Canary Lydia Garcia Foundation.	Mindfulness, cognitive stimulation and muscle relaxation in groups; 90 minutes, weekly over 2 years	MF: 36 CS: 32 MR: 34	TAU	25	**RDRS-2 †** (mean difference)	Mindfulness	**12 months: X^2= 162,000; p=0.000*** 6, 18, 24 months: p>0.05	Cognitive efficiency, Psychopathological measures	y	y	n	y	n	n
							Relaxation	**24 months: X^2= 122,000, p=0.006*** 6, 12, 18 months: p>0.05							
							Cognitive stimulation	**24 months: X^2= 153,500, p = 0.002*** 6, 12, 18 months: p>0.05							

† Primary outcome
*** Significant difference**
ADCS-ADL=Alzheimer's Disease Cooperative Study - Activities of Daily Living, BIADL=The Barthel Index of Activities of Daily Living, IADL=Lawton and Brody's Instrumental Activities of Daily Living, FLSA=Functional Living Skills Assessment Scale, RDRD-2=Rapid assessment of disability scale.

Table 5: Characteristics and quality ratings of cognition-oriented therapy studies identified as having higher risk of bias

Study/ Country	Sample/ Recruitment	Intervention group (IG)	n	Control group (CG)	n	Significance of differences between groups (intervention vs control)			Quality assessment (see methods)					
						Outcome of interest i.e. measure of functional ability	**Difference/effect at follow-up (95% Confidence Interval) P-value**	**Other primary outcomes**	**1**	**2**	**3**	**4**	**5**	**6**
Barban [54] Italy, Greece, Norway, Spain	Mild AD; from medical centres and municipalities across the 4 countries.	Computerised process-based cognitive training combined with reminiscence therapy; in 24 1-hour sessions for 3 months, followed by 3 month rest	42	3 months rest (TAU), followed by 3 month training	39	IADL (time x group effect)	6 months: X^2 =3.190 p<0.07	Memory, executive functioning and global cognition	y	n	n	y	n	y
Charles worth [47] UK	Dementia; from local adverts, Alzheimer's Society network	Group reminiscence therapy; 12, 2-hour sessions/week then, 7 monthly, over 10 months	97	TAU	47	ADCS-ADL (mean difference)	12 months: -2.45(-5.95, 1.06) p=0.07	Patient quality of life, carers, mental-health related quality of life	y	y	n	y	n	y
Giuli [55] Italy	Mild-moderate AD; from Evaluation of Alzheimer's unit at hospital	Cognitive training (individual); 10, 45 minute sessions, /week, unreported duration	51	TAU + psycho-educatio n	50	ADL unspecified if primary (time x group effect)	**Treatment end: F=4.81 p<0.05; ηp^2=0.054***	Cognitive function, memory, executive function, fluency, cognitive decline, dementia severity+	y	n	n	n	n	n
						IADL ,,	**Treatment end: F =16.53 p<0.0001; ηp^2=0.162***							
Jelcic [56] **Italy**	AD; from Memory Unit of University	Cognitive Stimulation with focused lexical–semantic rehabilitation exercises; 2/week, for 3 months	20	Unstruct ured cognitive stimulati on	20	IADLs (time x group effect)	3 months: X^2 test, p>0.05	Global cognitive function, lexical-semantic abilities,	y	y	n	y	n	y

								fluency, episodic verbal memory							
Lin [57] China	AD; recruited from a university hospital	Chinese chess (Go-game) as cognitive stimulation; a) 1-hour Go-game b) 2 hour GO-game, daily for 6 months	a) 49 b) 49	TAU	49	GAF unspecified if primary (mean difference)		**6 months: 4.95(-1.37,-9.18) p<0.05***	Depression,, anxiety, life quality, Alexithymia, serum levels of BDNF	y	n	n	y	n	n
Poptsi [58] Greece	Mild AD; recruited from the Day Care Unit of Alzheimer Hellas	Cognitive training (executive functioning) group programme: 80, 2-hour sessions, /week for 2 years	32	TAU	23	FUCUS (mean difference)	Medication	**12 months: F=8.603, p-0.005***	Cognitive function, general functional performance, verbal learning, visual memory, executive function	y	y	n	y	n	y
							Telephoning	**12 months: F=7.417 p=0.009***							
							Orientation	**12 months: F=29.174 p=0.009***							
							Shopping	12 months: F=0.642, p =0.424							
							Hygiene	12 months: F=2.214, p= 0.143							
							Clothing	12 months: F=4.855, p=0.032							
Silva [59] Portugal	51 participants with mild AD; from psychiatric/ neurology services of University Hospitals and Alzheimer Disease Association	Cognitive training with a) Memo+ paper and pencil memory training program b) SenseCam wearable camera used as a passive external memory aid; all of 6 weeks, review 2/week	a) 17 b) 17	Written diary (a personal journal, used as cognitive training control)	17	IAFAI unspecified if primary (time x group effect)		$F(2,43)=8.71$, $p<0.01$, $n^2p = 0.29$	Depression, Quality of life	y	n	n	y	n	n

† Primary outcome

*** Significant difference**

ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living, IADL=Lawton and Brody's Instrumental Activities of Daily Living, ADL=Katz's Activities of Daily Living, GAF= global assessment of functioning, FUCAS= Functional Cognitive Assessment Scale, IAFAI= Functional Assessment Inventory