International Psychogeriatrics (2014), 26:1, 9–18 © International Psychogeriatric Association 2013
doi:10.1017/S1041610213001385

REVIEW

The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review

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ABSTRACT

Background: Non-pharmacological interventions may have a role in both the prevention and slowing down of disease progression in Alzheimer's disease (AD). The role of exercise in disease prevention, for example, has been extensively evaluated in large epidemiological studies. Much less is known about the potential benefit of exercise in patients already diagnosed with AD. It was therefore the aim of this systematic review to assess the effectiveness of exercise in attenuating cognitive decline within AD.

Method: A systematic review was conducted statistically accompanied by a meta-analysis. Publications between January 1991 and October 2012 were identified by searching the electronic databases PubMed, Science Direct, Web of Knowledge, and PsychINFO. Selected studies required AD patients to take part in an exercise-based randomized controlled trial (RCT) and have a cognitive outcome measure.

Results: Six RCTs were identified that exclusively considered the effect of exercise in AD patients. Exercise generally had a positive effect on rate of cognitive decline in AD. A meta-analysis found that exercise interventions have a positive effect on global cognitive function, 0.75 (95% CI = 0.32–1.17).

Conclusions: From the six studies reviewed, the evidence suggests that exercise can have a positive effect on rate of cognitive decline in AD. However, the variation between study designs makes conclusions regarding the optimum intervention on cognitive outcome in AD difficult. Well-designed and powered RCTs are still needed to ascertain the efficacy of exercise in slowing down cognitive impairment in AD patients. However, a positive initial indication for exercise efficacy justifies such efforts.

Key words: exercise, intervention, Alzheimer's disease, cognition, physical activity

Background

It is currently estimated that 35.6 million people globally have dementia. The most prevalent subtype of dementia is Alzheimer's disease (AD), accounting for up to 65.0% of all dementia cases (Brunnström *et al.*, 2009). Cognitive deficits in dementia are associated with functional impairment in everyday activities (Royall *et al.*, 2007) often leading to the inability to function independently. Currently, the efficacy of pharmacological treatments is limited to symptomatic management, and hence there is a crucial need for alternative treatment methods to help those already diagnosed with AD, along with the projected 106.2 million new AD cases that will be diagnosed by 2050.

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To date, several research studies have been carried out into modifiable lifestyle factors that might prevent or delay the onset of dementia. Factors that have been implicated in positively affecting outcome include diet (Barberger-Gateau *et al.*, 2007; Gu *et al.*, 2010), cognitive activities (Verghese *et al.*, 2003; Akbaraly *et al.*, 2009), and social environment (Fratiglioni *et al.*, 2000; Wang *et al.*, 2002). Perhaps one of the most researched lifestyle factors over the past 20 years is exercise. Research has shown that being physically active may both delay the onset of developing dementia (Larson *et al.*, 2006) and reduce the risk of dementia (Laurin *et al.*, 2001; Andel *et al.*, 2008; Ravaglia *et al.*, 2008; Buchman *et al.*, 2012). Though exercise as a preventative approach is important, there is also a need to investigate the impact of exercise post-diagnosis. Due to the pathological differences between a healthy population (generally used in prevention studies) and a dementia population, efficacy of exercise as a treatment, and particularly

its impact on rate of decline, cannot be inferred. Therefore, it is important that the effects of exercise on cognitive decline in an AD population are explored.

This review into the effects of exercise in AD addresses a gap in previous literature. It focuses purely on exercise interventions, compared to previous reviews that have incorporated exercise interventions with additional social or cognitive activities (Penrose, 2005; Coelho *et al.*, 2009) precluding conclusions about the explicit role of exercise in the outcome. Further, previous reviews have neglected to differentiate between subtypes of dementia (Forbes *et al.*, 2008; Littbrand *et al.*, 2011). Determining the specific effects of exercise interventions on the cognitive outcome of AD patients will inform management strategies.

Objectives

The purpose of this review was to evaluate the efficacy of evidence for the influence of exercise interventions on the cognitive outcome of AD patients. This review will synthesize and evaluate the studies highlighted to determine whether exercise interventions are effective in combating cognitive decline in AD.

Methods

Type of studies

All selected studies implemented an exercise intervention. Only randomized controlled trials (RCTs) were included in this review. The only requirement of the exercise interventions was that they lasted a minimum of four weeks and were solely exercise-based. Whilst many exercise tasks have some social and cognitive elements, interventions were only excluded if they actively combined exercise with cognitive or social task. There were no limitations to the measurements taken as long as quantitative and objective measures of cognition (e.g. executive function, language, and memory) were recorded. All included studies had to be published and written in English.

Types of participants

All participants were required to have a diagnosis of AD, though there was no limitation on dementia severity or duration of the disorder. The age of participants in studies was not restricted. Participants with vascular dementia, Lewy body dementia, fronto-temporal dementia, and other rarer forms of dementia were excluded.

Types of outcome measures

Any quantitative, objective measure of cognitive performance, or cognitive subdomain.

Search methods for identification of studies

A series of medical, scientific, and psychology databases were searched, including: PubMed, Science Direct, Web of Knowledge, and PsychINFO. The following search terms were used: exercise, physical, training, walk*, danc*, movement, Alzheimer's, dementia, intervention, and program. Several search terms were employed to exclude irrelevant studies: "cognitive training," "memory training," "language training." Papers were restricted to those published in English between 1991 and 2012.

Assessment of risk of bias in included studies

Research quality was assessed by author NF, and confirmed by an independent researcher, using the Quality Assessment Tool for Quantitative Studies (Thomas *et al.*, 2004). The Quality Assessment Tool for Quantitative Studies covers several components of bias: (1) selection bias – the use of a sample representative of the target population; (2) study design – participant allocation and randomization; (3) confounders – controlling for factors related to the outcome; (4) blinding – the blinding of participants and assessors; (4) data collection – the use of valid and reliable outcome measures; (5) withdrawal –description and numbers of withdrawals and drop-outs. Each component was rated strong, moderate, or weak. A global rating of paper quality was derived by taking into account all the component ratings. A strong global rating was assigned if four components were rated strong with no weak ratings. The paper was deemed to have a moderate global rating if less than four components were rated strong and at least one weak. A weak global rating was assigned to papers that had two or more components with a weak rating. Studies that did not have a moderate or strong global rating were excluded from the review.

A funnel plot was used to assess publication bias in which the effect sizes of individual studies are plotted against the studies precision. An asymmetrical plot is representative of publication bias.

Data extraction

A table of predefined criteria was developed to ensure that data extraction was focused and accurate. Participant numbers, diagnosis, severity, intervention type and schedule, cognitive measures, and key cognitive outcomes were recorded. Where available, the means and standard deviations were

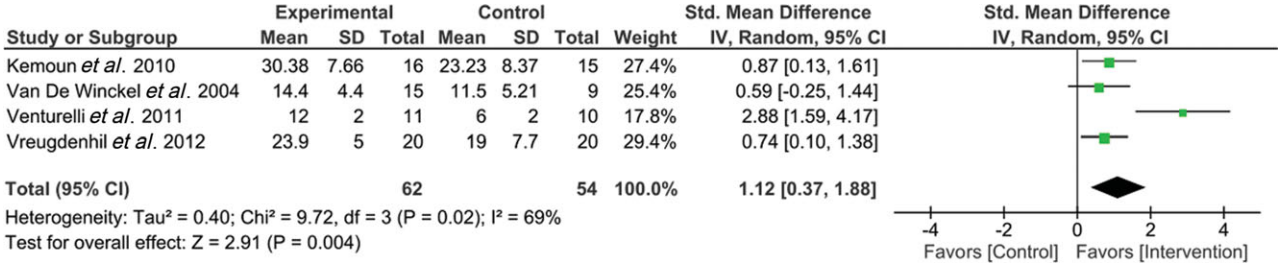

Figure 1. (Colour online) A forest plot of the meta-analysis of RCT studies that have measured global cognitive outcome. Exercise interventions were found to have a positive effect on global cognitive outcome.

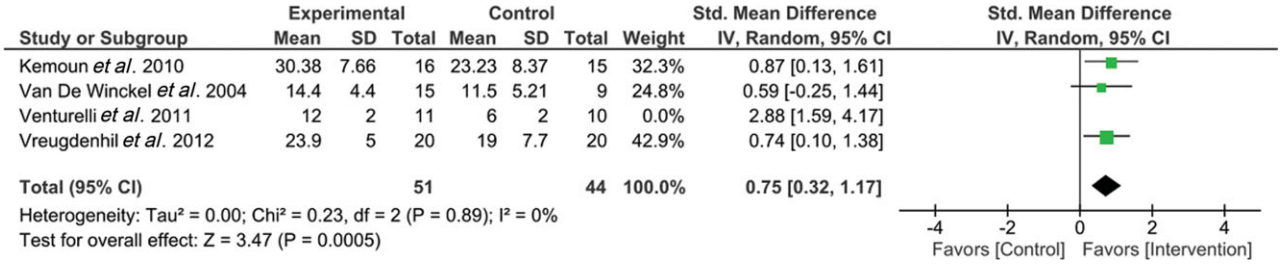

Figure 2. (Colour online) A forest plot of the meta-analysis intervention-controlled studies that have measured global cognitive outcome following the removal of a single study (Venturelli *et al.*, 2011). Exercise interventions were found to have a positive effect on global cognitive outcomes.

extracted from each cognitive measure at baseline and end of the study. All data were extracted by a single author (NF).

Results

Five-hundred and ninety papers were initially identified using the above search terms in the various databases. Following the removal of duplicates, poster abstracts, and those that were not published in English, 360 papers remained. Two-hundred and eighty-six studies were subsequently excluded because they did not implement an exercise intervention. Thirty-five studies were excluded because they did not use an AD population. Seven studies were excluded because they combined exercise interventions with another intervention, whilst two studies were excluded because the intervention duration was less than four weeks. Nineteen studies were excluded because they did not use a quantitative, objective cognitive outcome measure. Of the 11 studies remaining, five studies were excluded because they did not have an RCT design. A total of six studies met the inclusion criteria and were included in this review. Key information about the RCTs design (Table 1) and cognitive outcomes from the studies were extracted and tabulated (Table 2). Study quality was then subsequently assessed using the Quality Assessment Tool for Quantitative Studies (Table 3). All the studies were deemed to have a moderate to strong research quality.

A meta-analysis was subsequently carried out across four of the RCTs that assessed global cognitive outcome (Figure 1). Two studies were not entered into the meta-analysis, one due to a lack of publication of cognitive outcome means (Steinberg *et al.*, 2009) and the other due to exclusively reporting domain-specific cognitive outcomes (Yágüez *et al.*, 2010). The meta-analysis of the remaining studies reported a positive effect size, with an average effect of 1.12 (95% CI = 0.37–1.88). Heterogeneity among the studies was statistically significant ($I^2 = 69\%$, $p = 0.02$). Running a leave-one-out sensitivity analysis revealed that by removing the study by Venturelli and colleagues, heterogeneity became non-significant ($I^2 = 0\%$, $p = 0.89$). The study was likely to increase heterogeneity due to its substantially longer intervention duration compared to the next longest intervention (24 weeks vs. 16 weeks). The subsequent model, comprising of three studies, revealed that exercise significantly improved global cognitive performance compared to controls, 0.75 (95% CI = 0.32–1.17, $p < 0.001$) (Figure 2).

To evaluate whether publication bias existed amongst the studies within the final model, a funnel plot was conducted (Figure 3.) As there was no evidence of skew or asymmetry in the funnel plot, it was interpreted that there was no evidence of publication bias in the three studies.

Table 1. A descriptive overview of exercise interventions with control group

STUDY	POPULATION	TREATMENT/ CONTROL SAMPLE SIZE	DEMENTIA SEVERITY	INTERVENTION	SCHEDULE	CONTROL	COGNITIVE MEASURES
Kemoun *et al.* (2010)	31 AD	16/15	MMSE < 23	1 hour exercise sessions, including: articular mobilization, muscle stimulation, walking, ergocycling, dance and stepping	3 sessions/week 15 weeks	No physical activity	ERFC
Steinberg *et al.* (2009)	27 AD	14/13	MMSE > 9	Combination of aerobic fitness, strength training and balance/flexibility training	A single session daily for 12 weeks	Home safety assessment	MMSE, BNT, HVLT
Van de Winckel *et al.* (2004)	25 AD	15/10	MMSE < 24	30 minutes of music based exercise	A single session daily for 12 weeks	Daily one-to-one conversation	MMSE, ADS-6
Venturelli *et al.* (2011)	21 AD	11/10	MMSE 5–15	30 minutes of walking	4 sessions/week for 24 weeks	Daily activity	MMSE
Vreugdenhil *et al.* (2012)	40 AD	20/20	MMSE 10–28	A series of exercises focussing on upper and lower body strength and balance training in addition to 30 minutes of walking	A single session daily for 16 weeks	Routine treatment	MMSE, ADAS-Cog
Yágüez *et al.* (2010)	27 AD	15/12	MMSE 17–29	A series of 15 exercises composed of muscle stretching, circular movements of extremities and isometric tensions of muscles. Each session lasted 2 hours including a 30 minute break	A single session per week for 6 weeks	Support group	CANTAB-Expedio

BNT = Boston Naming Task; HVLT = Hopkins Verbal Learning Test; ERFC = Rapid Evaluation of Cognitive Functions; MMSE = Mini-Mental State Examination; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Sub-Scale; ADS-6 = Amsterdam Dementia Screening Test 6; CANTAB = The Cambridge Neuropsychological Test Automated Battery.

Table 2. The means (and standard deviations) of cognitive outcomes from the reviewed RCTs. The main statistical analyses described in the studies are also reported

		CONTROL		INTERVENTION		
STUDY	COGNITIVE TASK	BASELINE	FOLLOW-UP	BASELINE	FOLLOW-UP	STATISTICAL ANALYSIS
Kemoun *et al.* (2010)	ERFC	28.33 (7.11)	26.81 (6.42)	23.23 (8.37)	30.38 (7.66)	After 15 weeks, the intervention group improved ERFC score ($p < 0.01$).
Steinberg *et al.* (2009)	MMSE	15.5 (5.4)	–	20.1 (5.1)	–	No significant group × time interaction in BNT ($p = 0.26$) and HVLT ($p = 0.19$) after controlling for baseline MMSE score.
	BNT	12.1 (7.7)	–	15.0 (8.3)	–	
	HVLT	8.1 (3.8)	–	10.2 (5.6)	–	
Van de Winckel *et al.* (2004)	MMSE	10.80 (5.01)	11.00 (4.30)	12.87 (5.01)	15.53 (4.44)	A significant improvement in MMSE ($p < 0.01$) and category fluency subtest of the ADS-6 ($p < 0.01$) in the intervention group. No significant difference was found in the control group.
Venturelli *et al.* (2011)	MMSE	12 (2)	6 (2)	13 (2)	12 (2)	The intervention group did not show a significant change in MMSE scores before and after the training period, whereas the control group showed a decrease in MMSE scores during the same period ($p < 0.05$)
Vreugdenhil *et al.* (2012)	MMSE	21.0 (6.3)	19.0 (7.7)	22.9 (5.0)	23.9 (5.0)	Participants in the treatment group showed a significant mean improvement in MMSE and ADAS-Cog performance compared to control group which showed a decline ($p = 0.001$)
	ADAS-Cog	26.6 (16.6)	30.6 (17.9)	22.7 (9.7)	18.5 (9.8)	
Yágüez *et al.* (2010)	Motor Control	1,396.23 (461.70)	1,424.31 (425.93)	1,381.90 (350.77)	1,372.55 (449.09)	The exercise group reported a significant improvement in sustained attention ($p < 0.01$) and visual memory ($p < 0.05$) compared to controls following the intervention.
	Matching to sample simultaneous	81.68 (18.00)	71.67 (13.37)	89.34 (12.80)	90.67 (14.86)	
	Matching to sample delayed	61.67 (17.78)	65.58 (11.74)	63.99 (12.80)	67.56 (20.76)	
	Paired associate learning	105.67 (33.98)	107.84 (35.76)	85.47 (39.33)	88.80 (39.20)	
	Working memory	67.84 (12.16)	65.58 (11.74)	66.54 (18.60)	59.27 (14.95)	
	Pattern recognition	64.58 (11.85)	62.50 (14.97)	68.89 (14.93)	73.33 (10.77)	
	Rapid visual information processing	31.47 (15.05)	42.14 (13.02)	34.84 (12.32)	37.78 (16.07)	

BNT = Boston Naming Task; HVLT = Hopkins Verbal Learning Test; ERFC = Rapid Evaluation of Cognitive Functions; MMSE = Mini-Mental State Examination; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Sub-Scale; ADS-6 = Amsterdam Dementia Screening Test 6.

Table 3. The quality assessment of included RCT studies. All studies revealed a moderate to strong research quality

	SELECTION BIAS	STUDY DESIGN	CONFOUNDERS	BLINDING	DATA COLLECTION	WITHDRAWAL	OVERALL
Kemoun *et al.* (2010)	*	***	***	**	***	***	**
Steinberg *et al.* (2009)	**	***	***	**	***	***	***
Van de Winckel *et al.* (2004)	*	***	***	**	***	***	**
Venturelli *et al.* (2011)	**	***	***	**	***	***	***
Vreugdenhil *et al.* (2012)	**	***	***	**	***	***	***
Yágüez *et al.* (2010)	**	***	***	**	***	***	***

*Weak quality; **moderate quality; ***strong quality.

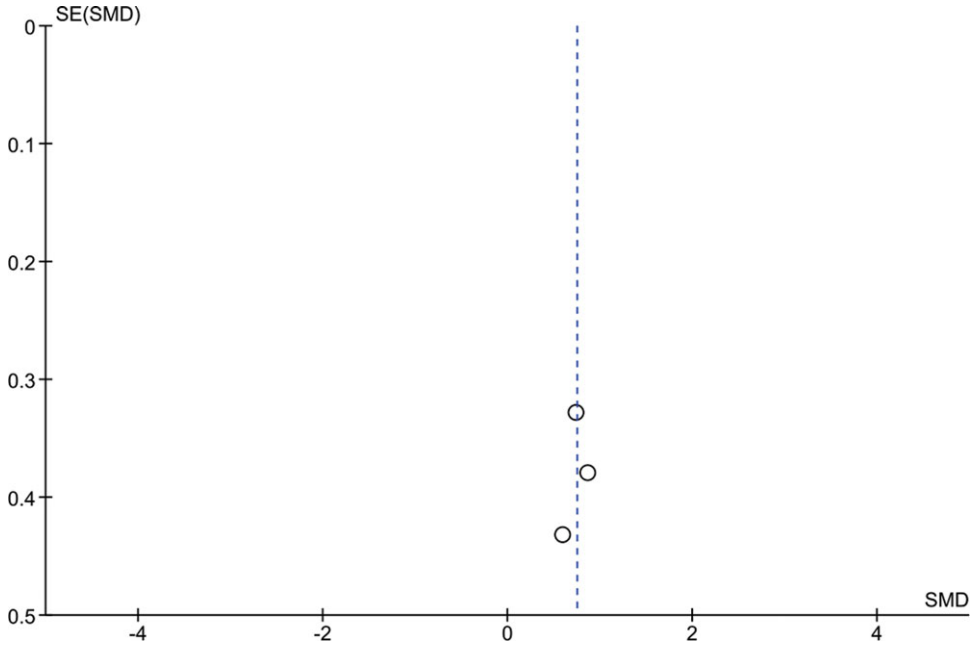

Figure 3. (Colour online) A funnel plot of the three studies included in the meta-analysis. Standard Error (SE) represents the precision of the estimate of the treatment effect, with the smaller the SE the more precise the estimate. The standard mean difference (SMD) measures the treatment effect size.

Discussion

The purpose of this review was to evaluate published research investigating the effects of exercise interventions exclusively on cognitive outcomes for individuals with a diagnosis of AD, to increase our understanding of the potential role that exercise may play on the rate of cognitive decline. The systematic review revealed preliminary evidence of the beneficial effects of exercise on cognition for people with AD, though methodological heterogeneity limits conclusions that can be made.

A total of six eligible studies were identified in the search, which revealed generally positive effects. Though selection bias was the most common weakness, particular attention needs to be taken for confounding variables. Controlling for confounders was of a high standard, though only core factors were generally controlled for (e.g. age, gender, and Mini-Mental State Examination, MMSE) limiting the study outcome. For example, participants may have different exercise habits prior to the intervention and hence have different fitness levels at the outset. This would mask the impact of the exercise intervention. This has been resolved in a single RCT study (Kemoun *et al.*, 2010) and other non-RCTs (Palleschi *et al.*, 1996; Yu and Kolanowski, 2009; Hernandez *et al.*, 2010; Yu *et al.*, 2011) by implementing a target effort level for participants, this methodology should be a requirement in any exercise intervention study.

No two studies identified in this review implemented the same exercise intervention, though the interventions could broadly be categorized into three types: (1) aerobic exercise intervention such as walking (Venturelli *et al.*, 2011); (2) interventions that aimed to improve flexibility, balance, and

strengthen muscles (Van de Winckel *et al.*, 2004; Yágüez *et al.*, 2010; Vreugdenhil *et al.*, 2012); and (3) interventions that combine the previous two types (Steinberg *et al.*, 2009; Kemoun *et al.*, 2010). Heterogeneity was also observed in the exercise program schedule, both in the overall intervention duration and the number of intervention sessions conducted over this time period. Out of the studies reviewed, the longest intervention period lasted 24 weeks (Venturelli *et al.*, 2011) and the shortest lasting six weeks (Yágüez *et al.*, 2010). Yágüez *et al.* (2010) also implemented the least intensive program, with only a single exercise session per week, whereas several other studies had an exercise session daily (Van de Winckel *et al.*, 2004; Steinberg *et al.*, 2009; Vreugdenhil *et al.*, 2012). From this literature, it is impossible to make strong recommendations toward an optimal exercise intervention. Future research is needed to determine the effects of different exercise types on cognition, this is in line with previous conclusions made in a review focused on a cognitively healthy population (Voss *et al.*, 2011). It is likely that different exercise types are more effective in certain individuals, therefore engaging those with AD in a combined exercise type may prove to be more effective than any single exercise type alone. More importantly, comparisons are needed between low intensity (e.g. once a week) and high intensity (e.g. daily) exercise interventions to determine the optimum protocol.

Other lifestyle factors that have been implicated in cognitive outcomes include diet, cognitive activities, and social activities. It is therefore important that these factors are controlled for. Out of the six RCT studies, only four studies implemented an active control (Van de Winckel *et al.*, 2004; Steinberg *et al.*, 2009; Yágüez *et al.*, 2010; Venturelli *et al.*, 2011). An active control is important with regard to exercise studies as there is generally a cognitive or social (if group exercise) component to the activities. Not only is it important that certain activities are matched, it is essential that the control groups are not participating in similar levels of physical activity as the intervention group. Steinberg *et al.* (2009) was the only study that took into consideration that members of the control group may also be participating in non-interventional exercise.

Although a meta-analysis was conducted within RCTs, the cognitive outcomes were limited to measures of global cognition, as there were insufficient studies to explore individual cognitive subdomains. There are obvious benefits in using standardized global measures of cognition, particularly the ease of administration and comparability between studies. Unfortunately in the literature reviewed there is an over-reliance on global cognitive measures which was often used as the primary cognitive outcome measure (Van de Winckel *et al.*, 2004; Kemoun *et al.*, 2010; Venturelli, *et al.*, 2011, Vreugdenhil *et al.*, 2012). One commonly used global cognitive measure, the MMSE, though a quick method of providing a clinical screening of cognitive performance, has previously been criticized as overly reliant on language and education (Borson *et al.*, 2000). Perhaps more importantly, the total MMSE score reveals nothing of cognitive subdomain changes. It is therefore important that if general cognitive measures (e.g. MMSE and ADAS-cog) are taken that it should be alongside a more comprehensive cognitive battery. The need to improve cognitive measures used in exercise intervention studies is in line with conclusions made in a recent review (Yu, 2011).

An additional issue revealed by this review is that the majority of studies measure cognitive outcome exclusively at baseline and endpoint of the intervention. There are several problems with this design. First, as dementia is progressive in nature, the longer the intervention the more likely there will be a decline in cognition. It is therefore important that measures are taken throughout the intervention period, allowing researchers to be more effective in determining whether exercise at any point can alter the trajectory of cognitive decline. Only a single study (Van de Winckel *et al.*, 2004) implemented a cognitive measure prior to the end of the intervention. Second, no RCTs used a follow-up measure taken some time after the end of the exercise intervention, which would allow for researchers to determine the sustainability of any benefits gained through the intervention. Determining the sustainability of benefits is clearly an important factor when considering the practicalities of implementing an exercise intervention. It should be noted, also, that since physical disability increases with age (Jagger *et al.*, 1989), this could prevent the longer term adherence to an intervention.

It is important to note that the studies identified in this review do not directly address the mechanisms that mediate exercise and cognition in AD because they do not include objective indices of these mechanisms. Exercise has generally been reported to have a positive effect on various cognitive outcome measures in a healthy elderly population (van Gelder *et al.*, 2004; Etgen *et al.*, 2010). A systematic review of double-blinded exercise interventions in a healthy older adults concluded that exercise is beneficial to cognitive function, though the effects are modest (Angevaren *et al.*, 2008). Two mechanisms have

been proposed to mediate the effects of exercise on cognition. The first is that exercise has a nutritive influence on neuronal function. Exercise has been shown to promote neurotrophic effects, including synaptic plasticity, neurogenesis, and vascular function (Cotman and Berchtold, 2002, 2007; Ratey and Loehr, 2011). Second, regular exercise has been found to improve aerobic capacity and cerebral vascular perfusion (Rogers *et al.*, 1990). Such improvements to vascular health may be a significant feature for any intervention in AD, where poor vasculature represents a potential mechanism for disease (Kalaria and Ballard, 1999; Kalaria, 2002; De la Torre, 2004). These may not be the primary or exclusive mediators of exercise effects in an AD population. Cognitive decline in AD is attributable at least in part to the buildup of amyloid and tau proteins, which promote neuronal dysfunction and death (Hardy and Selkoe, 2002; Karran *et al.*, 2011). Evidence in transgenic mouse models of AD, in which the mice have artificially elevated amyloid load, suggests that exercise programs are able to improve cognitive function (Adlard *et al.*, 2005; Nichol *et al.*, 2007). Adlard and colleagues also determined that the improvement in cognitive performance occurred in conjunction with a reduced amyloid load. Research that includes direct indices of change in such biomarkers will help to determine the mechanisms by which exercise may act on cognition in AD.

Whilst the implementation of a more liberal study inclusion criterion allowed a better insight into the current state of literature, it is also responsible for a greater heterogeneity between studies. As such, a meta-analysis was only performed in a subgroup of studies that used a general cognitive outcome measure. Even within this subgroup, only following a sensitivity analysis and the removal of one study was homogeneity achieved. The validity of the meta-analysis performed may be compromised following the exclusion of a study if it seriously changes the overall result (Walker *et al.*, 2008). The large positive effect size that was reported in both meta-analyses ($d = 1.12$ vs. $d = 0.75$) reflects the robustness of the effect of exercise on general cognitive outcome in AD. Clearly, the data in this review should be interpreted cautiously; whilst there does not appear to be any publication bias, the review encompasses a limited number of studies with generally small sample sizes. Therefore, it is possible that other studies also with small sample sizes were not published as they failed to report a positive outcome.

In the most general terms, current research into the effects of exercise on the cognitive progression of AD has yielded positive results. Heterogeneity between study designs precludes comment on optimal interventions, cognitive domains affected, and underlying mechanisms. The consistency of positive findings, albeit in small sample sizes and varying design, does highlight that a range of exercise interventions can potentially be of benefit to AD populations. Future studies should use improved methodological designs, building upon previous intervention studies and theoretical knowledge. In particular, the role of other factors that may differ between patients such as diet, social interactions, and cognitive activities should be considered. The use of sensitive cognitive measures for a range of subdomains should also be developed. This will allow researchers to determine the potential role of exercise, to hone in on the underlying mechanism, and to further optimize interventions.

Conflict of interest

None.

Description of authors' role

N.F. completed the search, assessed the research quality, and wrote the first draft of the review. N.T. and J.R. provided input and amendments throughout the development of the paper.

Acknowledgments

We acknowledge the contribution of Jeremy Young, who independently evaluated the quality of the included studies.

This work was supported by the Economic and Social Research Council (ES/102803X/1) and the Sussex Partnership NHS Foundation Trust.

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