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EFFECT OF EXERCISE ON COGNITIVE FUNCTION IN PERSONS WITH DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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EFFECT OF EXERCISE ON COGNITIVE FUNCTION IN
PERSONS WITH DEMENTIA: A SYSTEMATIC REVIEW

AND META-ANALYSIS

BY

SOUTHEY F. SAUL

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE

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DOCTOR OF PHILOSOPHY

OF

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2019

ABSTRACT

As the population ages, the number of people suffering from dementia will rise significantly. Current estimates of total societal cost of dementia exceed \$8 billion dollars (US). Epidemiological studies have shown that increased lifetime engagement in exercise reduces cognitive decline and the incidence of dementia in normal older adults. While existing research suggests that lifelong exercise may be preferable, the adoption of exercise at any age and stage of dementia-onset to delay or reverse cognitive decline is worthwhile given the prevalence of sedentary lifestyle, and the increasing proportion of older adults and dementia incidence. Recently, trials have started to explore the impact of exercise on cognitive symptoms in individuals diagnosed with dementia. These studies are reporting promising findings, which call for further meta-analytical review. The primary objective of this meta-analysis is to examine the effects of exercise interventions on cognitive function compared to standard care in older persons with dementia. The secondary objectives are to identify covariates and/or moderators that affect the effectiveness of these exercise programs. The trials included in this meta-analytic review were identified from systematic searches of major medical and psychological databases, including EMBASE, PubMed/MEDLINE, PsycARTICLES, and Cochrane Central Register of Controlled Trials (1966-2018) on 30 April 2018 using the concepts of dementia, cognitive function, and exercise. Trials were selected in which older people, diagnosed with dementia, were allocated either to exercise programs or to control groups (standard care) with the aim of improving cognition. One rater retrieved the articles, assessed for inclusion and methodological quality, and extracted the data. Data was analyzed for summary effects using mean difference (MD) and standardized mean difference (SMD). Data was

synthesized for each outcome using a random-effects model. Exploration of heterogeneity was planned in relation to type, frequency and duration of exercise program. The collected data were analyzed by *Review Manager* (5.3). This review evaluated the results of 21 trials, including 1548 participants, that tested whether exercise programs could improve cognition (which includes such things as memory, learning, attention) in older people with dementia. The included trials were heterogeneous in terms of participant characteristics, and type, duration, and frequency of exercise. Meta-analysis demonstrated positive effects of exercise on cognitive function in older adults with dementia (SMD = 0.49, 95% CI [0.24 - 0.75], $P = 0.0002$). Fifteen trials demonstrated that exercise improves cognitive function for individuals with dementia, while the remaining six studies did not display a beneficial effect of exercise on cognitive function. This analysis revealed substantial heterogeneity ($I^2 = 79\%$), most of which could not be explained, and the quality of evidence was rated as low. Thus, findings should be interpreted with caution. This meta-analysis and systematic review revealed some evidence supporting the benefit of exercise programs in improving cognitive ability or slowing the decline of cognition in people with dementia. Future well-designed RCTs with clear intervention criteria, large samples, and long-term follow-up are needed to enhance the quality of such a review by assessing the exercise programs that are best for people with various types and severity of dementia and by addressing additional outcomes (e.g., mortality, quality of life, healthcare service use, expenditures).

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As secondary data analysis that did not access participant personal health information (PHI), the Institutional Review Board (IRB) granted this project an exemption. All statistical procedures were conducted with *Review Manager* (5.3), and all literature was accessed through the URI library reference databases.

DEDICATION

To my husband, family, and friends.

Your support cannot be quantified.

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CHAPTER 1:

STATEMENT OF THE PROBLEM

1. Dementia: description of the disease

Dementia is a clinical syndrome characterized by cognitive decline, motor deficits and/or behavioral problems, resulting in a decline in daily functioning (Scott & Barrett, 2007). With advancing age as the main risk factor, and an aging population worldwide, the prevalence of dementia worldwide is expected to double from approximately 50 million cases in 2019 to 65.7 million in 2030 (Prince et al., 2013). The total global societal cost of dementia was estimated to be US\$ 818 billion in 2015, equivalent to 1.1% of global gross domestic product (GDP). This expected increase in prevalence of dementia will thus have increasingly dramatic social and financial consequences. WHO has denoted dementia as a public health priority (Wortmann, 2012). No disease modifying drugs for dementia are currently available, and pharmacological treatment is restricted to medications that may alleviate symptoms. As a first approach, best practice guidelines currently recommend that behavioral and psychological interventions be explored before initiating pharmacological interventions, due to the limited benefits of pharmacological treatments in reducing functional decline and their possible side effects (Hogan et al., 2008). Thus, exercise treatment may be an appealing alternative or adjunct to medication (Deslandes et al., 2009). Furthermore, in addition to the preventative benefits exercise has on dementia, exercise is among the potential protective lifestyle factors identified as a strategy for treating the symptoms of dementia or delaying its progression (Lautenschlager et al., 2010).

CHAPTER 2:

JUSTIFICATION FOR AND SIGNIFICANCE OF THE STUDY

1. Exercise for the prevention and treatment of chronic disease.

The World Health Organization (WHO) reported that physical inactivity is the fourth leading risk factor for global mortality, accounting for 6% of deaths globally (World Health Organization, 2010). Moreover, a 25% decrease in physical inactivity could prevent 1.3 million deaths annually (Lee et al., 2012), which could contribute to dramatic reductions in healthcare costs. Such findings have led to the development of randomized controlled trials (RCTs) assessing exercise's preventative, and more recently, treatment benefits in those at risk or already diagnosed with chronic disease (e.g., Belardinelli et al., 2012; Zwisler et al., 2008).

Multifaceted benefits of exercise.

Despite the variability of exercise effects in preventing, slowing the progress of, or improving various chronic diseases, it is important to note that the biomedical model of disease does not account for the complex factors associated with living with chronic diseases (e.g. medication side-effects, costs). This demonstrates the need for a broader more integrative framework in the treatment of chronic health conditions that includes lifestyle interventions, like exercise, to decrease disease-related morbidity, improve quality of life and physical and psychological health outcomes. Population-level exercise interventions have a multiplicity of benefits across a variety of populations, diseases, and domains (i.e. physical and mental health) while being relatively low cost compared to the healthcare and medical expenses in treating these diseases.

2. Description of the intervention.

In 2019, the *World Health Organization (WHO)* released the *WHO Guidelines on risk reduction of cognitive decline and dementia* (2019) providing evidence-based recommendations on lifestyle behaviors and interventions to delay or prevent cognitive decline and dementia. Approximately 50 million people have dementia worldwide. With one new case every three seconds, the number of people with dementia is set to triple by 2050. The growing prevalence of dementia, its considerable social and economic impact and lack of curative treatment, make it imperative for countries to direct their resources to reducing modifiable risk factors for dementia. Action area 3 of the *Global Action Plan on the Public Health Response to Dementia 2017–2025* is risk reduction. These *WHO Guidelines* are an important tool for health care providers as well as governments, policy-makers and other stakeholders to strengthen their impact in response to the dementia challenge.

Exercise and cognitive functioning in older adults.

In recent years, exercise programs for healthy older adults without dementia have demonstrated improvement in cognitive function and prevention of the onset of dementia (Erickson et al., 2011; Tseng, Gau, & Lou, 2011). Many such studies used a 60-minute exercise regimen scheduled three times per week for 24 weeks (Tseng, Gau, Lou, 2011). For example, Hamer and Chida (2009) conducted a systematic review that included 16 prospective studies (163,797 participants without dementia at baseline with 3,219 with dementia at follow-up). The relative risk (RR) of dementia in the highest exercise category compared with the lowest was 0.72 (95% CI [0.60 - 0.86], $P < 0.001$) and for

Alzheimer's disease (AD) the RR was 0.55 (95% CI [0.36 - 0.84], $P = 0.006$), suggesting such exercise reduces the likelihood of dementia.

Further, other research shows that mid-life exercise may contribute to maintenance of cognitive function and may reduce or delay the risk of late-life dementia (Chang et al., 2010). Exercise is one lifestyle factor that has recently been identified as a potential means of reducing or slowing the progression of dementia symptoms, including cognitive performance. Animal model studies demonstrate that exercise may slow the progress of existing dementia, and an increasing amount of trials are examining the impact of exercise on individuals with dementia and are reporting promising findings. For example, such as work by Intlekofer and Cotman (2012) suggests that evidence is starting to emerge that exercise supports brain health, even when initiated after the appearance of Alzheimer's disease pathology.

Exercise and cognitive functioning in persons with dementia.

The existing RCTs on exercise treatment for dementia are mixed with some demonstrating enhanced brain vitality (Farina et al., 2014; Hess et al., 2014), while others do not (Forbes et al., 2015). For example, Groot et al. (2015) performed a meta-analysis of RCTs investigating effects of physical activity on cognitive function in patients with dementia. The findings suggest that exercise interventions led to improved cognitive function in patients with dementia. This effect was found across various types of dementia and different exercise frequencies. Conversely, a Cochrane systematic review of exercise RCTs for dementia treatment failed to find exercise benefits in cognition, neuropsychiatric symptoms, and depression (Forbes et al., 2015). This study included 11 RCTs examining cognitive function. Given the growing research base and increasing

interests in lifestyle interventions for chronic disease prevention and treatment, it would be reasonable to expect that there are a number of additional RCTs from the last four years that should be accounted for in these collective analyses.

With a burgeoning scientific literature on exercise and dementia, further justified by the recent release of the *WHO Guidelines on risk reduction of cognitive decline and dementia* (2019), a mechanism is needed to objectively synthesize data across the accumulating research. Fortunately, systematic review and meta-analysis can operate as this mechanism.

Furthermore, while exercise interventions for the treatment of dementia are becoming more prevalent, evidence varies across some effects and outcomes, and the mechanisms of exercise for the treatment of dementia remain inconclusive. For example, why do certain exercise interventions demonstrate beneficial effects on cognitive function while others fail to do so? What are the common factors underlying these exercise interventions that are effective in treating dementia?

There is a scarcity of review and meta-analytic studies that try to answer these questions. Many meta-analyses are looking at more global cognitive effects of exercise on dementia and other chronic diseases. However, the field now needs to look at the variables (e.g. recruitment, duration, exercise type) producing differential effect sizes to examine *where* exercise is making a difference in cognitive outcomes in people with dementia. Furthermore, progress in policy is hindered by the absence of clarity on actions most likely to make exercise effective and feasible in a given context (e.g. health status).

3. How the intervention might work.

Exercise mechanisms.

Physical activity refers to “body movement that is produced by the contraction of skeletal muscles and that increases energy expenditure” (Chodzko-Zajko et al., 2009). Exercise refers to “planned, structured, and repetitive movement to improve or maintain one or more components of physical fitness” (Chodzko-Zajko et al., 2009). Detailed exploration and explanations of the potential mechanisms of physical activity and exercise is beyond the scope of this paper. For additional information, the reader is directed to two recent reviews by Erickson, Weinstein, and Lopez (2012) and Davenport et al. (2012). Briefly, exercise improves vascular health by decreasing blood pressure, arterial stiffness, oxidative stress, inflammation, and strengthens endothelial function (Fleg, 2012; Ghisi et al., 2010), all of which are associated in the maintenance of cerebral perfusion (Davenport et al., 2012). Recent evidence has shown a strong association between cerebral perfusion (i.e. balance between the supply and demand of nutrients to the brain), cognitive function, and fitness in older healthy adults (Brown et al., 2010). Glucose intolerance or insulin resistance is linked with the formation of amyloid plaque (Watson 2003), which is a notable feature of Alzheimer’s Disease. Exercise may also keep neuronal structure intact, as well as promote neurogenesis, synaptogenesis, and capillarization (formation of nerve cells, the gaps between them, and blood vessels, respectively, which may be associated with exercise-induced increases in brain-derived neurotrophic factor (BDNF), and insulin-like growth factors (Colcombe et al., 2003). Studies suggest that BDNF supports the health and growth of neurons and may regulate neuroplasticity (adaptability of the brain) through aging (Cheng, 2003). More recently, Intlekofer et al. (2012) reported that exercise reinforces hippocampal function, which is responsible for memory, by strengthening the expression of BDNF to promote

neurogenesis, the formation of blood vessels, and synaptic plasticity. In summary, animal and human studies indicate that exercise can facilitate a process counteracting the progressive memory loss in older age and Alzheimer's Disease (Erickson et al., 2012).

4. Justification for review and meta-analysis.

One in four American adults has multiple chronic conditions (e.g. depression, cancer, type 2 diabetes) that last one year or more and require ongoing medical attention and/or limit activities of daily living (U.S. Department of Health & Human Services, 2010). Such statistics have broad implications for rising healthcare costs and call for innovative health behavior interventions. Certain lifestyle behaviors can reduce risk for developing many of these diseases. Exercise represents one lifestyle behavior that can reduce risk in disease development and is useful against a broad range of diseases and risk factors (Di Raimondo et al., 2016). For example, a multitude of meta-analyses and systematic reviews have examined exercise effects for the prevention and treatment of common chronic diseases, such as depression (Cooney et al., 2013), kidney disease (Heiwe & Jacobson, 2011), and type 2 diabetes (Thomas et al., 2006).

However, unlike other highly researched chronic diseases, much less is known about the relationship between exercise and dementia in regards to slowing cognitive decline. A more detailed exploration into the optimal “prescription” of exercise for cognitive health is needed for those suffering from dementia.

5. Current review.

Aim and scope.

This study aims to assess the effects of exercise interventions for the treatment of cognitive symptoms in dementia, one of the most pervasive and increasingly burdensome

chronic diseases. The study will compare the exercise effects across a variety of cognitive outcomes and exercise interventions among individuals with dementia. Evaluating the effectiveness of exercise interventions for the treatment of dementia may not only reveal if exercise is having an effect, but also reveal *when* exercise is having an effect. That is, research has yet to determine how exercise intensity, duration, frequency or mode influence exercise effects on cognitive outcomes. Findings may contribute in developing more effective and affordable evidence-based interventions for treating, managing and delaying the often devastating effects of dementia. Published meta-analyses in this area have often targeted specific modes of exercise (e.g., aerobic exercise), restricted their inclusion criteria to a single cognitive outcome (e.g., MMSE), or investigated participants with either mild cognitive impairment (MCI) or dementia (Farina, Rusted, & Tabet, 2014; Song et al., 2018; Young, et al., 2015; Zheng, et al., 2016), which tends to restrict their meta-analyses to a handful of studies rendering incomplete summaries of the available evidence on exercise effects on cognitive functioning specifically in individuals with dementia. Many reviews do not examine or account for exercise prescription variables, though a more thoughtful examining of these variables may help clinicians and policymakers establish and disseminate more thoughtful guidelines on the type, intensity, duration and frequency of exercise that is recommended for dementia patients.

Research objectives and hypotheses.

Objective 1) Examine the effects of exercise interventions on cognitive functioning in individuals with dementia. Exercise effects on cognitive functioning from

the included trials will be pooled across all trials to calculate a pooled mean effect size using a common effect size (SMD).

Hypothesis 1) Based on the existing literature exploring exercise for healthy older adults (Erickson et al., 2011; Northey et al., 2018; Tseng, Gau, & Lou, 2011) and adults with MCI (e.g., Hess et al., 2014; Song, Yi, Li, & Lei, 2018) it is hypothesized that exercise interventions will slow the progression of cognitive decline relative to the cognitive decline in control groups.

Objective 2) Examine the effects of exercise interventions within specific cognitive assessment measures/instruments. Mean exercise effects will be calculated within each specific cognitive outcome measure represented in the included studies.

Hypothesis 2) It is hypothesized that exercise interventions will slow cognitive decline relative to control groups within each cognitive outcome measure.

Objective 3) Differentiate the effects of exercise interventions on the six domains of cognition (e.g., Attention; Executive function; Language; Memory and learning; Social cognition; Perceptual-motor function). Calculate pooled mean exercise effects within each domain of cognition.

Hypothesis 3) It is hypothesized that exercise interventions will slow cognitive decline relative to control groups (e.g., usual care) within each domain of cognition represented in the included studies.

Objective 4) Examine the influence of exercise variables (duration, frequency, volume, intensity, length, type) on cognitive functions, by identifying covariates and/or moderators that affect effectiveness of exercise interventions. Which intervention variables (e.g. exercise type, exercise intervention intensity) interact with the exercise

effect on cognitive outcomes? What are the strongest non-causal predictors of the exercise effect? Are there variables that, when changed, are independently responsible, or causal, for changes in the exercise effect?

Hypothesis 4) It is hypothesized that exercise interventions with greater frequency, intensity, and duration will be most effective in slowing cognitive decline.

Objective 5) Examine the impact of study design (e.g., dementia type, dementia severity at baseline).

Hypothesis 5) It is hypothesized that exercise interventions with participants with less severe types and forms of dementia will experience greater improvement (or slowed progression) in cognitive function.

Such analyses have the potential to determine which variables are likely to predict successful treatment and possibly help to further elucidate the mechanisms of exercise interventions. These findings may identify ways to tailor the exercise intervention delivery to maximize effects for different groups. Building upon existing findings from 1) meta-analyses exploring the role of exercise in preventing dementia in those without dementia, and 2) newer and novel RCTs exploring exercise effects in treating dementia, this study will examine the collective effectiveness of exercise interventions in the treatment of cognitive symptoms in individuals with dementia, while also identifying what type of exercise interventions are most effective in treating dementia.

To examine mechanisms and/or predictors of successful exercise interventions, RCT variables can be coded to determine covariates within each RCT and across the included RCTs. Meta-analysis can be used to analyze which intervention variables

influence effect size for a specific intervention and compare how intervention variables affect effect size. One such meta-analysis assessed mean effect sizes across health behavior RCTs and moderator variables, such as recruitment type (Noar, Benac, & Harris, 2007). The need to improve exercise intervention accessibility, feasibility, and impact (reach x engagement) is clear. Meta-analysis can: 1) calculate and compare exercise effects across diseases using a pooled mean exercise effect across the included RCTs; 2) calculate and compare the pooled mean exercise intervention effect within each domain of cognition. 3) determine which of variables shared across RCTs are most influential on the mean effect. This may contribute to more impactful exercise intervention tailoring for subgroups.

CHAPTER 3: METHODOLOGY

1. Design

Meta-analysis and systematic review will be used to: 1) calculate the pooled effect of all included exercise interventions for the treatment of cognitive symptoms in individuals with dementia; 2) calculate the pooled exercise intervention effect within each cognitive outcome measure; 3) calculate the pooled exercise intervention effect within each domain of cognition; and 4) identify any exercise intervention characteristics and study design characteristics that are moderators affecting intervention effectiveness.

2. Criteria for considering studies for this review.

Types of studies.

Only studies examining the effects of an exercise intervention in the treatment/management of dementia will be included. Older people (60+) diagnosed with dementia must be allocated to either an exercise program or a control program (usual care or social contact/activities). Only studies providing pre- and post-intervention primary outcome measures will be included.

Cross-over trials were eligible for inclusion, but only data from the first treatment phase (prior to the cross-over) was considered for inclusion. Non-blinded trials were included, as it was unrealistic to expect blinding of the participants and those who conducted the exercise interventions (for further details, see *Assessment of risk of bias in included studies*). Outcome assessors were expected to be blinded to treatment allocation, however, studies without blinding of outcome assessors were not excluded. Studies were rated for blinding.

Types of participants.

The majority of participants had to be older than 60 years of age, diagnosed with dementia using accepted criteria such as the Diagnostic and Statistical Manual of Mental Disorders (APA, 2013), the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (McKhann, 1984), ICD-10 (World Health Organization, 1992), or CERAD-K (Hwang, 2010).

Types of interventions.

In this review, RCTs in which older people diagnosed with dementia were allocated to either an exercise program or a control group (usual care, standard care, or social contact/activities). Searches will be limited to trials with physical activity interventions, defined by the American College of Sports Medicine as “body movement that is produced by the contraction of skeletal muscles and that increases energy expenditure” (Chodzko-Zajko et al., 2009).

Exercise refers to “planned, structured, and repetitive movement to improve or maintain one or more components of physical fitness” (Chodzko-Zajko et al., 2009). Searches were limited to interventions lasting 2 weeks or more with the aim of improving cognitive or neuropsychiatric symptoms in older people with dementia. Included interventions were both supervised and unsupervised programs.

Trials will be included where the only difference between groups was the exercise intervention, and the types, frequencies, intensities, duration, and settings of the exercise programs were described. In order to isolate exercise treatment effects, an experimental arm had to involve an intervention that solely delivers exercise (in addition to

usual/standard care). For example, a study with an intervention arm that involves both exercise *and* an additional non-exercise component (e.g., exercise with occupational therapy, exercise with experimental medication, exercise with nutrition intervention) were excluded unless they also had an exercise-only intervention arm. Each RCT's experimental exercise arms had to be compared to a non-exercise "control condition," defined as usual or standard care. That is, though both groups are likely to be receiving the "usual care" given the current standards of care for dementia, the exercise effect could still be extracted given both groups will receive "usual care." During an RCT intervention period, the control group could not receive any form of physical exercise therapy other than that provided in "standard" or "usual care" for dementia. The Cochrane Review or the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009) was used as a framework to guide item selection and discuss the limitations of inclusion criteria accordingly.

Outcome measures.

Primary outcomes included: cognition and neuropsychiatric symptoms. Cognitive screening is common in primary care and community settings (Morley et al., 2015). While assessments of dementia were variable across preliminary review of the literature, dementia outcomes may be assessed by changes in measures of cognitive functioning, such as: Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975); MiniCog (Borson, Scanlan, Brush, Vitaliano, & Dokmak, 2000); Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005); the Cognitive Memory Performance Scale; the Clock Drawing Test (Paula et al., 2013); Rapid Evaluation of Cognition Functions Test; or Eight Words Test. Assessments used for cognitive symptom

assessment for dementia will largely be determined by the frequency of the different measures used across RCTs.

3. Search methods for identification of studies.

Electronic searches.

Studies were identified through selected major medical and psychological databases, which included EMBASE, PubMed, MEDLINE, PsycARTICLES, and Cochrane Central Register of Controlled Trials (CENTRAL). The author (SS) devised a search strategy based on a combination of free-text keywords and subject headings that describe exercise and dementia. These databases were searched to identify RCTs published in any language between January 1, 1960, and April 30, 2018. Only peer-reviewed articles were included. Animal studies were excluded. Additional relevant studies were retrieved from lists of references of related studies.

A more detailed search strategy, including a record of specific keyword terms, was established in Appendix A ('Search strategy results by database').

4. Data collection and analysis.

Study selection.

After merging search results and discarding duplicates, the author (SS) reviewed results of the search strategy by examining titles and abstracts of citations. Due to resources available, this research had to rely on a single rater. If the title or abstract appeared to represent the inclusion criteria, the full article was retrieved for further assessment. The retrieved articles were then assessed for inclusion according to the eligibility criteria.

Data extraction and management.

The methodology for data extraction and analysis was based in the Cochrane Handbook of Systematic Reviews of Interventions (Higgins & Green, 2011). Once the full text of selected RCTs were obtained, information was extracted using the predefined data extraction form (Appendix B). This form summarized key information, including details of the participant population (e.g., severity of dementia), sample size, the intervention(s) including intervention details (e.g., exercise type, duration), the comparison group (e.g., standard care), and cognitive outcome measures and relevant data. If a study included multiple cognitive outcome measures, the form also included the study's "primary" cognitive outcome measure of interest if identified in the study. If studies included multiple measures of cognition, the author decided a priori to include the study's "primary" cognitive outcome in the main analysis across all studies. If a primary outcome of interest was not identified, the most commonly used measure was used to maximize comparability between studies.

The mean change from baseline to measurement at the conclusion of the intervention, and the number of participants for each group was extracted. Data is presented in a series of summary tables and figures.

Assessment of risk of bias in included studies.

The methodological quality of the evidence in included RCTs was assessed based on the Cochrane collaboration tool for assessing risk of bias and any summary of findings tables within them using a criteria list (Higgins & Green, 2011) (see Appendix C. 'Cochrane risk of bias tool for randomized controlled trials'). Criteria for judging risk of bias were based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2011). This assessment tool was used to determine whether there was

a low, high, or unclear risk of bias for each factor (Higgins & Green, 2011). The identity of the publication and author information for each trial report was not masked. If the description of a process or outcome was unclear or missing, the original author of the trial was contacted in an attempt to retrieve the required information. The following criteria were assessed:

1. Selection bias - systematic differences between baseline characteristics of the groups being compared, including:

- i) random sequence generation;
- ii) allocation concealment.

2. Performance bias - systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest, this includes:

- i) Blinding of participants and personnel.

3. Detection bias - systematic differences between groups in how outcomes are determined, this includes:

- i) blinding of outcome assessments.

4. Attrition bias - systematic differences between groups in withdrawals from a study, this includes:

- i) incomplete outcome data.

5. Reporting bias - systematic differences between reported and unreported findings, that is:

- i) outcome reporting bias.
- ii) publication bias.

6. Other bias (i.e., bias due to other problems)

Of note, blinding participants and personnel (performance bias) is inherently a problem when conducting rehabilitation trials, such as exercise interventions. Blinding of participants and personnel to the exercise intervention is not possible due to the nature of exercise interventions (e.g., exercises, devices, manual therapy), blinding for physiotherapists and personnel and patients may be challenging to impossible. Blinding for health care providers, patients, and outcome assessors is less frequently reported in trials involving nonpharmacological interventions (Boutron, Tubach, Giraudeau, et al., 2003). Thus, a high risk of bias assessment on this domain was not weighed in for final judgment for each study's total risk of bias.

Measures of treatment effect.

Effect sizes standardize findings across RCTs for direct comparison. Effect sizes represent the magnitude and direction of the exercise intervention effects within and across RCTs. Summary statistics were required for each included trial and outcome. For continuous data, the mean difference (MD) was used when the pooled trials used the same rating scale or test to assess an outcome. Standardized mean difference (SMD) was calculated and reported to compare the effectiveness across different outcomes. Both effect sizes were calculated and provided when possible.

SMD was used when the pooled trials used different rating scales or tests for continuous outcomes that were conceptually the same but measured in different ways. The particular definition of SMD used in Cochrane reviews and implemented in *Review Manager 5.3* software is the effect size known in social science as Hedges' (adjusted) g , which is very similar to Cohen's d , but includes an adjustment for small sample bias

$$SMD_i = \frac{m_{1i} - m_{2i}}{s_i} \left(1 - \frac{3}{4N_i - 9} \right),$$

with standard error

$$SE\{SMD_i\} = \sqrt{\frac{N_i}{n_{1i}n_{2i}} + \frac{SMD_i^2}{2(N_i - 3.94)}}.$$

Post-intervention effect sizes were collected from each study. SMD was computed using *Review Manager 5.3* meta-analysis software using the statistical data provided, such as mean, standard deviation, *F*-, or *t*-tests statistics. Based on the magnitude of effect sizes found in population-based health RCTs, 0.15, 0.20 and 0.25 represented small, medium, and large effects (Rossi, 2013).

An SMD of zero means that the new treatment and the control have equivalent effects. If improvement is associated with higher scores on the outcome measure, SMDs greater than zero indicate the degree to which treatment is more efficacious than control, and SMDs less than zero indicate the degree to which treatment is less efficacious than control. If improvement is associated with lower scores on the outcome measure, SMDs lower than zero indicate the degree to which treatment is more efficacious than control and SMDs greater than zero show the degree to which treatment is less efficacious than control.

The inverse variance method was used in this meta-analysis. All outcomes were reported using 95% confidence intervals (CI). None of the trials included in the review reported dichotomous data of interest to this review.

Dealing with missing data.

Reasons for missing data were extracted from original studies. Many types of information could not be identified from the published articles, such as descriptions of the

process of randomization, blinding of outcome assessors, attrition and adherence to the exercise intervention, reasons for withdrawing, and statistical data (i.e., means, SDs). Author contacts were emailed and asked to provide the missing data. The possible impact of the missing data on the results depended on the extent of missing data, the pooled estimate of the treatment effect, and the variability of the outcomes. The variation in the degree of missing data was also considered as a potential source of heterogeneity. If available, intention-to-treat (ITT) data was used to best account for noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. If these data were not available, only the reported completers' data was used in the analyses.

Assessment of heterogeneity.

Homogeneity analysis was used to test the assumption that all of the effect sizes are estimating the same population mean. Clinical heterogeneity could be assessed by inspecting the type of participants, details of the interventions, and outcomes within each study. Trials demonstrating clinical homogeneity, such that they tested an exercise intervention and examined similar cognitive outcome measures, were considered as potentials for this meta-analysis. Heterogeneity was initially explored through visual exploration of the forest plots. A test for statistical heterogeneity (a consequence of clinical or methodological diversity, or both, among trials) using the Chi^2 test (with a $P < 0.10$ indicating significance) and I^2 analysis was then performed. The I^2 analysis (Cochrane's Q test) is a useful statistic for quantifying inconsistency ($I^2 = [(Q - df)/Q] \times 100\%$, where Q is the Chi^2 statistic and df is its degrees of freedom (Higgins & Thompson, 2002; Higgins et al., 2003). This describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (i.e., chance).

Values greater than 50% are considered to represent substantial heterogeneity. If there was evidence of heterogeneity of the population or treatment effect, or both, between trials, random-effects model was used, for which the confidence intervals are broader than those of a fixed-effect model (Higgins & Green, 2011). If the value was less than 30%, the overall estimate would be presented as a fixed-effect model. Funnel plots were used to examine heterogeneity of effect sizes.

Assessment of reporting biases.

Funnel plots were examined to look for indications of publication bias. To investigate reporting biases within the included studies, the outcomes listed in the methods sections were compared with reported results.

Data synthesis.

A random-effects model was used when the I^2 measure of heterogeneity was greater than 30% indicating significant diversity between studies in participants or interventions. The overall quality of the evidence associated with the result of each meta-analysis was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. This gives an indication of the confidence that can be placed in the estimate of treatment effect. The effect estimates and GRADE ratings for primary outcomes were summarized and in a summary of findings table for the main comparison of exercise for dementia.

If a trial included multiple cognitive outcome measures, the outcome of primary interest in that trial was used in the overall pooled mean of cognitive function across the trials (SMD), and any remaining cognitive outcome measures were used in the subgroup

analyses within their respective specific cognitive outcome measure, and respective cognitive domain category.

Data is presented as a meta-analysis and systematic review with tabulated data of the statistical outcomes reported in the original RCTs. Comparisons were determined by the data in the original RCTs. Where possible, data was grouped by specific cognitive outcome measure (e.g. MMSE), and also by specific cognitive domain (e.g., attention). Outcomes of interest were continuous. The PRISMA (Liberati et al., 2009) statement was used as a framework to guide the selection of RCTs for the meta- analysis and systematic review. Another list was constructed with excluded studies and reasons for exclusion.

Subgroup analyses and investigation of heterogeneity.

If there was sufficient data, it was decided a priori that the following subgroup analyses would be conducted to explore possible causes of heterogeneity. In accordance with Objective 4 of this review and meta-analysis, the characteristics of the exercise intervention were coded into categorical variables. These were coded according to published guidelines that reconcile differences in the terminology used to describe components of exercise (ACSM, 2013; Norton, Norton, & Sadgrove, 2010).

Exercise moderators:

Type of exercise program:

1. aerobic (cardiorespiratory);
2. resistance training (strength, endurance, power);
3. balance;
4. flexibility (stretching);
5. combination of 2+ of the above types;
6. other.

Frequency of exercise program (# sessions per week):

1. up to 3 times per week;
2. more than 3 times per week.

Duration (minutes per session):

1. 30 minutes or less;
2. 31 or more minutes.

Volume (total exercise minutes per week):

1. 60 minutes or less;
2. 61 - 120 minutes;
3. 121 - 150 minutes;
4. >150 minutes.

Length of exercise intervention:

1. up to 12 weeks;
2. more than 12 weeks.

Due to the likelihood that the measures of exercise intensity would vary across RCTs, it was decided that exercise intensity would be coded based on the exercise intensity criteria used within each study. While this may interfere with best practices, we assume it will allow an exploration of an exercise prescription variable that has been cited as having particularly strong benefits in comparison to exercise duration and frequency.

Exercise intensity:

1. Low;
2. Moderate;
3. High;
4. Unclear / Not reported.

In accordance with Objective 3 of this review, the cognitive outcome measures were classified according to the domain of cognition being assessed (if not classified as a measure of global cognition). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) defines six key domains of cognitive function, including: 1) attention, 2) executive function, 3) language, 4) learning and memory, 5) social cognition, 6) and perceptual-motor function.

Characteristics of the baseline status of the participants were categorized in accordance with Objective 5, including type and severity of dementia at baseline, and

nature of the control group. Study design moderators: Similar to exercise intensity, it was decided that dementia severity would be coded based on the criteria used within each study. Preliminary review of the existing literature revealed a variety of measures used to identify dementia severity.

Disease type:

1. Alzheimer's disease (AD);
2. vascular dementia (VD);
3. mixed dementia (MD);
4. unclassified or other dementia (UD);
5. multiple types.

Setting/location:

1. Care facility;
2. Hospital;
3. Community;
4. Other.

Moderator and subgroup effects.

These predetermined exercise intervention variables (type, frequency, session duration, volume, length, intensity) and participants' dementia severity and type were coded to determine predictors of improved (or slowed progression) cognitive function. This coding was determined based on how common these outcomes and variables were represented within and across the included studies.

Sensitivity analysis.

Sensitivity analyses were also considered and used to explore possible causes of methodological heterogeneity, such as including studies at high risk of bias due to extreme effect sizes and small sample sizes that could distort the mean effect size or variance. Forest plots were used for outlier analysis and assessment of publication bias.

CHAPTER 4: RESULTS

1. Description of studies.

Please see Appendix D ('Characteristics of included studies').

2. Results of the search.

Database searches located a total of 1033 articles; after duplicates were removed, the abstracts and titles of 882 articles of these were screened for inclusion. 71 full-text articles were retrieved and rated. 21 articles met the inclusion criteria (Arcoverde et al., 2014; Barnes et al., 2015; Cheng et al., 2014; Christofolletti et al., 2008; Coehlo et al., 2012; Eggermont et al., 2009a; Eggermont et al., 2009b; Hernandez et al., 2010; Hoffman et al., 2016; Holthoff et al., 2014; Kemoun et al., 2010; Kwak et al., 2008; Lamb et al., 2008; Lee et al., 2018; Miu et al., 2008; Prick et al., 2017; Thurm et al., 2011; Toots et al., 2017; Van de Winckel et al., 2004; Venturelli et al., 2011; Vreugdenhil et al., 2011). See Figure 1 for a study flow diagram.

3. Included studies.

Please see Appendix D ('Characteristics of included studies') for the following details of each study:

1. Country;
2. Location of intervention;
3. Dementia type;
4. Dementia severity;
5. Sample size;
6. Percentage of male participants;

7. Mean age;
8. Inclusion criteria;
9. Exclusion criteria;
10. Exercise intervention type and description;
11. Exercise intervention frequency (sessions per week);
12. Exercise intervention duration (minutes per session);
13. Exercise intervention volume (total minutes exercised per week);
14. Exercise intervention intensity;
15. Intervention time period (weeks);
16. Attrition rate;
17. Exercise program adherence;
18. Therapy for controls;
19. Outcome measures of cognitive function.

Each study's characteristics table is accompanied by a risk of bias table.

The included studies were published between 2004 and 2018. One trial was conducted in the USA (Barnes et al., 2015;), four in Brazil (Arcoverde et al., 2014; Christofolletti et al., 2008; Coehlo et al., 2012; Hernandez et al., 2010), two in China (Cheng et al., 2014; Miu et al., 2008), three in the Netherlands (Eggermont et al., 2009a; Eggermont et al., 2009b; Prick et al., 2017); two in Germany (Holthoff et al., 2014; Thurm et al., 2011); and one each in Australia (Vreugdenhil et al., 2011), Denmark (Hoffman et al., 2014), France (Kemoun et al., 2010), Italy (Venturelli et al., 2011), S. Korea (Kwak et al., 2008), Republic of Korea (Lee et al., 2018), England (Lamb et al., 2018), Sweden (Toots et al., 2017), and Belgium (Van de Winckel et al., 2004).

Figure 1. Study flow diagram

Figure 2. Risk of bias summary: review author's judgments about each risk of bias item for each included trial

Study or Subgroup	Risk of Bias						
	A	B	C	D	E	F	G
Arcoverde et al., 2014	?	+	-	?	+	+	+
Barnes et al., 2015	+	-	-	+	+	+	+
Cheng et al., 2014	+	-	-	?	?	-	+
Christofoletti et al., 2008	?	+	-	+	-	+	+
Coelho et al., 2012	?	?	-	?	+	+	+
Eggermont et al., 2009a	+	?	-	+	+	+	-
Eggermont et al., 2009b	?	?	-	+	+	+	+
Hernandez et al., 2010	+	?	-	?	+	+	+
Hoffman et al., 2016	+	+	-	+	+	+	+
Holthoff et al., 2014	?	?	-	?	+	+	+
Kemoun et al., 2010	?	?	-	+	-	+	+
Kwak et al., 2008	?	?	-	?	?	+	+
Lamb et al., 2018	+	+	-	?	+	+	+
Lee & Kim, 2018	?	?	-	?	+	+	+
Miu, Szeto, & Mak, 2008	?	?	-	+	-	+	+
Prick et al., 2017	+	+	-	+	+	+	+
Thurm et al., 2011	+	-	-	?	+	+	+
Toots et al., 2017	+	+	-	+	-	+	+
Van de Winckel, Feys, & Weerd, 2004	+	?	-	-	+	+	?
Venturelli, Scarsini, & Schena, 2011	?	+	+	?	+	+	+
Vreugdenhil et al., 2011	+	+	-	+	+	+	+

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Participants.

Please see Appendix D ('Characteristics of included studies').

Trial participants had been recruited from nursing homes (Arcoverde et al., 2014; Barnes et al., 2015; Cheng et al., 2014; Eggermont et al., 2009a; Eggermont et al., 2009b; Kemoun et al., 2010; Holthoff et al., 2014; Lee & Kim, 2018; Thurm et al., 2011; Toots et al., 2017; Venturelli et al., 2011), psychiatric facilities (Christofolletti et al., 2008; Van de Winckel et al., 2004), and their own home settings (Coelho et al., 2010; Hernandez et al., 2010; Hoffman et al., 2016; Kwak et al., 2008; Lamb et al., 2018; Miu, Szeto, & Mak, 2008; Prick et al., 2017; Vreugdenhil et al., 2012).

Four of the included trials had 20 or fewer participants (Arcoverde et al., 2014; Barnes et al., 2015; Hernandez et al., 2010; Thurm et al., 2011); 13 trials recruited between 21 and 100 participants (Cheng et al., 2014; Christofolletti et al., 2008; Coelho et al., 2012; Eggermont et al., 2009b; Kemoun et al., 2010; Kwak et al., 2008; Hoffman et al., 2016; Holthoff et al., 2014; Lee & Kim, 2018; Miu, Szeto, & Mak, 2008; Van de Winckel et al., 2004; Venturelli et al., 2011; Vreugdenhil et al., 2012); and the four remaining trials recruited 100 or more participants (Eggermont et al., 2009a; Lamb et al., 2018; Prick et al., 2017; Toots et al., 2017).

All trials required a diagnosis of dementia for recruitment. All trials required participants to be 60 years or older. Eggermont et al. (2009a) and Eggermont et al. (2009b) required participants to be 70 years or older.

The DSM-IV set of criteria for diagnosis of dementia were the most commonly used in the included studies (Coelho et al., 2012; Eggermont et al., 2009a; Eggermont et al., 2009b; Hernandez et al., 2010; Kemoun et al., 2010; Miu, Szeto, & Mak, 2008;

Thurm et al., 2011; Toots et al., 2017; Venturelli, Scarsini, & Schena, 2011; Vreugdenhil et al., 2012). Other authors used the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable or possible AD as eligibility for inclusion (Arcoverde et al., 2014; Hoffman et al., 2016; Holthoff et al., 2014; Van De Winckel et al., 2004; Vreugdenhil et al., 2012); the International Statistical Classification of Diseases, 10th revision (ICD-10) definition of dementia (Christofolletti et al., 2008; Lamb et al., 2018); the Clinical Dementia Rating (CDR3-CDR4) for late stage AD (Cheng et al., 2014; Lee & Kim, 2018; Venturelli et al., 2011); the Modified Mini Mental State Examination (3MS) (Barnes et al., 2015); and physicians (general practitioner, psychiatrist, geriatrician, or a neurologist) (Prick et al., 2017). Kwak et al. (2014) did not report which set of diagnostic criteria they used for diagnosis of dementia.

Seven trials included participants with AD (Coehlo et al. 2012; Hernandez et al., 2010; Hoffman et al., 2016; Holthoff et al., 2015; Kemoun et al., 2010; Venturelli et al., 2011; Vreugdenhil et al., 2012). Several trials had two or more dementia diagnoses represented (Arcoverde et al., 2014; Cheng et al., 2014; Christofolletti et al., 2008; Lee & Kim, 2018); Miu, Szeto, & Mak, 2008; Prick et al., 2017), including a trial of participants with Multiple Infarct Dementia and AD (Van de Winckel et al., 2004). In the remaining trials, the participants' type of dementia was not specified (Barnes et al., 2015; Eggermont et al., 2009a; Eggermont et al., 2009b; Kwak et al., 2008; Lamb et al., 2018; Thurm et al., 2011; Toots et al., 2017).

Two of the trials had participants with “mild” dementia (Arcoverde et al., 2014; Lee & Kim, 2018). Participants were defined as having “mild to moderate” dementia in

thirteen of the studies (Barnes et al., 2015; Cheng et al., 2014; Coelho et al., 2012; Eggermont et al., 2009a; Eggermont et al., 2009b; Hernandez et al., 2010; Hoffman et al., 2016; Holthoff et al., 2018; Lamb et al., 2018; Miu, Szeto, & Mak, 2008; Prick et al., 2017; Toots et al., 2017; Vreugdenhil et al., 2012). Three trials had participants with “moderate” dementia (Christofolletti et al., 2008; Kwak et al., 2008; Thurm et al., 2011), and one trial had participants with “moderate to severe” dementia (Venturelli et al., 2011). Two of the trials had participants with “mild to severe” dementia (Kemoun 2010; Van de Winckel et al., 2004).

Exercise programs.

Exercise interventions were most likely to include multiple modes of exercise (Christofolletti et al., 2008; Coelho et al., 2012; Hernandez et al., 2010; Holthoff et al., 2018; Kwak et al., 2008; Lamb et al., 2018; Lee & Kim, 2018; Prick et al., 2017; Thurm et al., 2011; Toots et al., 2017; Van de Winckel Feys, & Weerdt, 2004; Vreugdenhil et al., 2011). Aerobic-only exercise interventions were the second most common (Arcoverde et al., 2014; Eggermont et al., 2009a; Hoffman et al., 2016; Kemoun et al., 2010; Miu, Szeto, & Mak, 2008; Venturelli et al., 2011). Only one trial used resistance training (Barnes et al., 2015). Two interventions were categorized as “other.” The program used by Cheng et al. (2014) used seated Tai Chi (Cheng et al., 2014), and the intervention employed by Eggermont et al. (2009b) included a hand movement activity group performing activities such as “finger movement, pinching a soft ball, or handling a rubber ring.”

The administration frequency of the exercise programs ranged from twice a week (Arcoverde et al., 2014; Barnes et al., 2015; Kwak et al., 2008; Lamb et al., 2018; Miu,

Szeto, & Mak, 2008; Thurm et al., 2011; Toots et al., 2017); to three times a week (Cheng et al., 2014; Christofolletti et al., 2008; Coelho et al., 2012; Hernandez et al., 2010; Hoffman et al., 2016; Holthoff et al., 2018; Kemoun et al., 2010; Lee & Kim, 2018; Prick et al., 2017), four times a week (Venturelli et al., 2011), five times a week (Eggermont et al., 2009a; Eggermont et al., 2009b), to daily (Van de Winckel, Feys, & Weerdt, 2004; Vreugdenhil et al., 2011).

Each session varied in length from 30 minutes (Arcoverde et al., 2014; Eggermont et al., 2009a; Eggermont et al., 2009b; Holthoff et al., 2018; Lee & Kim, 2018; Prick et al., 2017; Van de Winckel Feys, & Weerdt, 2004; Venturelli et al., 2011; Vreugdenhil et al., 2012); 45 minutes (Barnes et al., 2015; Kwak et al., 2008; Thurm et al., 2011; Toots et al., 2017); and 60 minutes (Cheng et al., 2014; Christofolletti et al., 2008; Coelho et al., 2012; Hernandez et al., 2010; Hoffman et al., 2016; Kemoun et al., 2010; Lamb et al., 2018; Miu, Szeto, & Mak, 2008).

The total volume of weekly exercise minutes ranged from 60 minutes (Arcoverde et al., 2014), 90 minutes (Barnes et al., 2015; Holthoff et al. 2018; Kwak et al., 2008; Lamb et al., 2018; Lee & Kim, 2018; Prick et al., 2017; Thurm et al., 2011), 120 minutes (Miu, Szeto, & Mak, 2008; Venturelli et al., 2011), 150 min (Eggermont et al., 2009a; Eggermont et al., 2009b), 180 minutes (Christofolletti et al., 2008; Coelho et al., 2012; Hernandez et al., 2010; Hoffman et al., 2016; Kemoun et al., 2010), to 210 minutes (Van de Winckel, Feys, & Weerdt, 2004; Vreugdenhil et al., 2011).

The intensities of the exercise programs were reported less frequently in the trials. Of those that reported intensity of exercise, most were qualified as “moderate” intensity (Arcoverde et al., 2014; Cheng et al., 2014; Coelho et al., 2012; Hernandez et al., 2010;

Hoffman et al., 2016; Kemoun et al., 2010; Kwak et al., 2008; Thurm et al., 2011; Vreugdenhil et al., 2011). Two exercise programs were “moderate to high intensity” (Holthoff et al., 2018; Lamb et al., 2018), and one other study was “high” intensity (Toots et al., 2017). One study was described as “low” intensity (Eggermont et al., 2009b). For the remaining studies, exercise intensity was either not reported, self-selected or unclear (Barnes et al., 2015; Christofolletti et al., 2008; Eggermont et al., 2009a; Lee & Kim, 2018; Miu, Szeto, & Mak, 2008; Prick et al., 2017; Van de Winckel, Feys, & Weerdt, 2004; Venturelli et al., 2011).

The period of time that the exercise programs were offered varied greatly, ranging from six weeks (Eggermont et al., 2009a; Eggermont et al., 2009b), 8 weeks (Lee & Kim, 2018), 10 weeks (Thurm et al., 2011), 12 weeks (Cheng et al., 2014; Holthoff et al., 2018; Miu, Szeto, & Mak, 2008; Prick et al., 2017; Van de Winckel Feys, & Weerdt, 2004;), 15 weeks (Kemoun et al., 2010), 16 weeks (Arcoverde et al., 2014; Coelho et al., 2012; Hoffman et al., 2016; Lamb et al., 2018; Toots et al., 2017; Vreugdenhil et al., 2011), 26 weeks (Hernandez et al., 2010), 18 weeks (Barnes et al., 2015), six months (Christofolletti et al., 2008; Hernandez et al., 2010; Venturelli et al., 2011), and 12 months (Kwak et al., 2008).

Control groups.

The control groups for 14 of the studies received usual care with no additional interventions (Arcoverde et al., 2014; Barnes et al., 2015; Christofolletti et al., 2008; Coelho et al., 2012; Hernandez et al., 2010; Hoffman et al., 2016; Kemoun et al., 2010; Kwak et al., 2008; Lamb et al., 2018; Miu, Szeto, & Mak, 2018; Prick et al., 2017; Thurm et al., 2011; Venturelli et al., 2011; Vreugdenhil et al., 2012). The control group for six

studies included social contact (Cheng et al., 2014; Eggermont et al., 2009a; Eggermont et al., 2009b; Lee & Kim, 2018; Toots et al., 2017; Van de Winckel et al., 2004). The control group in one trial received psychoeducation about healthy lifestyle (Holthoff et al., 2016).

Primary Outcome: Cognitive functioning.

Mini-Mental State Examination (MMSE) (Global cognitive function). 12 trials used the *Mini Mental State Exam (MMSE)* test to assess cognitive functioning (Arcoverde et al., 2014; Cheng et al., 2014; Christofolletti 2008; Hernandez et al., 2010; Hoffman et al., 2016; Holthoff et al., 2014; Kwak et al., 2008; Miu, Szeto, & Mak, 2008; Toots et al., 2017; Van deWinckel et al., 2004; Venturelli et al., 2011; Vreugdenhil et al., 2011). The MMSE is an established measure of cognitive function used extensively in clinical and research settings to measure cognitive impairment (Tombaugh & McIntyre, 1992). It is commonly used in medicine and allied health fields to screen for dementia. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes over time, which makes it effective in documenting an individual's response to treatment. Questions relate to a variety of domains, including attention, language, word recall, and orientation to time and place. The MMSE is composed of questions grouped into seven categories, each one designed to evaluate specific cognitive functions: time orientation, place orientation, three-word register, attention and calculation, immediate and delayed recall of the three words, language, and visuoconstructive praxis (Folstein, Folstein, & Mchugh, 1975). Scores range from 0 to 30 points and lower values represent a possible cognitive decline.

Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) (Global cognitive function). Following the MMSE, *ADAS-Cognitive Score* was used in a total of seven trials (Barnes et al., 2015; Hoffman et al., 2016; Lamb et al., 2018; Miu et al., 2008; Thurm et al., 2011; Toots et al., 2017; Vreugdenhil et al., 2011), The ADAS-Cog is one of the most commonly used primary outcome measures in dementia trials. The ADAS-Cog was designed to improve assessment of subtle changes in symptoms. The ADAS-Cog can both be used as an overall measure of cognitive functioning, and as a direct assessment of different cognitive domains, including learning (word list), naming (objects), following commands, constructional praxis (figure copying), ideational praxis (mailing a letter), orientation (person, time, plan), recognition memory and remembering test instructions (Rosen, Mohs, & Davis, 1984). The ADAS-Cog is a 70-point scale, with a higher score indicating greater impairment.

Category Verbal Fluency (CVFT) (Language). CVFT was represented in seven trials (Arcoverde et al., 2014; Christofolletti et al., 2008; Eggermont et al., 2009a; Eggermont et al. 2009b; Hoffman et al., 2016; Prick et al., 2017; Toots et al., 2017). This is a subtest from the *Groninger Intelligence Test* (GIT; Snijders & Verhage, 1983) that assesses the language domain of cognitive function. In this test the participant is asked to name as many animals and professions within one (separate) minute (Lezak, Howieson, & Loring, 2004). The outcome measure is the total number of animals and professions produced (range 0 - infinity).

Clock Drawing Test (CDT) (Executive Function). The CDT was used by Arcoverde et al. (2014), Christofolletti et al. (2008), Coelho et al. (2012), and Lee & Kim (2018). The Clock Drawing Test is an instrument used to evaluate executive functions,

including planning, abstraction, logical sequencing, and monitoring of the executive processing (Sunderland, Hill, & Mello, 1989).

Digit Span (Learning & Memory; Executive Functioning). *Digit Span* was used by Arcoverde et al. (2014), Eggermont et al., (2009a), and Eggermont et al. (2009b), and Prick et al. (2017). *Digit Span* is a subtest from the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987). A participant is asked to repeat series of digits read aloud by the examiner (*Digit Span Forward*), and the outcome measure is the number of series correctly reproduced (score range 0-21). This part of the *Digit Span* Test appeals to short-term memory cognitive domain of cognitive function. Subsequently, the participant is asked to repeat series of digits in the reverse order (*Digit Span Backward*). *Digit Span Backward* is considered to appeal to executive functioning cognitive domain. The outcome measures of both conditions are the number of series correctly reproduced. The total outcome measure is the number of series correctly reproduced (score range 0-21).

8 Words Test (Learning & Memory). The *8 Words Test* (8WT), including each of its three parts (Immediate, Delayed Recall, Recognition) was used in three trials (Eggermont et al., 2009a; Eggermont et al., 2009b; Prick et al., 2017). The *8 Words Test* of the Amsterdam Dementia Screeningtest (ADS; Lindeboom & Jonker, 1989) is used to measure episodic anterograde memory and learning domain of cognitive function. During the first part, eight unrelated words are read aloud to the subject five times. Immediately after each presentation, recall is tested, with the total number of words recalled after the five trials being used as the score (*immediate recall*, score range 0-40). In addition, recall is again tested after a delay of 10 minutes (*delayed recall*, score range 0-8). Next, a

recognition test is followed in which the eight words are intermixed with eight “distractor” words (*recognition score*, score range 0 - 16).

Stroop Color and Word Test (SCWT) (Executive functioning). The *Stroop Test* was used in two trials (Arcoverde et al., 2014; Hoffman et al., 2016). The Stroop Color and Word Test is a neuropsychological test extensively used to assess the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute (well-known as the “Stroop Effect”) (Golden, 1978). It appeals to the executive functioning domain of cognition.

Cambridge Cognitive Examination (CAMCOG) (Global cognitive function). The CAMCOG was used in one study (Arcoverde et al., 2014); The CAMCOG is a brief neuropsychological battery designed to assess global cognitive function by evaluating the range of cognitive functions required for a diagnosis of dementia, and to detect mild degrees of cognitive impairment (Roth et al., 1986).

Rapid Evaluation of Cognitive Function (ERFC) (Global cognitive function)). The *ERFC* was used in one study (Kemoun et al., 2010). The test consists of 12 subtests: spatial orientation, attention span, immediate and deferred memory, mental calculation, reasoning and judgment, comprehension, denomination, repetition, a written order, verbal fluency, apraxia, visual decoding and writing. The maximum score is 50, and a score lower than 46 indicates a significant probability of cognitive deficit (Gil, et al., 1986). In this way, this test measures global cognitive function taken as a whole.

Loewenstein Occupational Therapy Cognitive Assessment for Geriatric Population (LOTCA-G) (Global cognitive function). The LOTCA-G battery was used in one study (Lee & Kim, 2018). The LOTCA-G is a tool to assess cognitive functions that was developed for rehabilitation in a hospital in Israel in 1974 (Katz, Elazar, & Itzkovich, 1996). The LOTCA-G has subsequently been used widely in many countries, including the USA. It is for adults and has been adjusted for the elderly population. The LOTCA-G is an assessment of global cognitive function, and assesses six cognitive areas: orientation, visual perception, special perception, praxis, visuomotor organization, and thinking operation.

Functional Independence Measure - Cognitive Scale (FIM-Cog) (Global cognitive function). The FIM-Cog was used in one study (Lee & Kim, 2018). The FIM refers to the assessment tool to measure daily living operations, which consists of either tests of self-care, five tests of mobility, and five tests of communication and social cognition (Granger et al., 1990). The score criteria consist of seven-point scales from one, which is a total dependent operation, to seven, which is independent operation without the help of others. The higher the score, the more the patient can perform daily living operations independently. From the full FIM score, the FIM- Cognitive Scale was used to assess global cognition. The intra-rater reliability for the cognition area is 0.83.

Frontal Assessment Battery (FAB) (Executive functioning). The FAB was used in one study (Coehlo et al., 2012). The FAB is an assessment of frontal cognitive functions (executive functions) for patients with neurodegenerative disorders. The battery consists of six subtests: (i) similarities (abstract reasoning); (ii) lexical fluency (mental flexibility); (iii) series motor (motor programming); (iv) conflicting instructions

(sensitivity to interference); (v) go-no go (inhibitory control); (vi) conflicting instructions (sensitivity to interference); and (vi) prehension behavior (primitive reflex). It varies on a scale of 0-18 points, and higher scores represent better performance in frontal functions (Beato, Nitrini, Formigoni, & Caramelli, 2007).

Symbol Search-Subtest (Attention). Symbol Search was used in one study (Coelho et al., 2012). The Wechsler Adult Intelligence Scale-III Symbol Search-Subtest assesses focused attention (Wechsler, 2004).

Symbol Digit Modalities (SDMT) (Attention). Symbol Digit Modalities was used in one study (Hoffman et al., 2016). This measure assesses the cognitive domain of mental speed and attention (Smith, A., 1982). Using the number and symbol key at the top of the test page, participants are asked to correctly decode several lines of symbols. The total number of correct de-codings in 120 seconds is used as the outcome.

4. Excluded studies.

48 studies were excluded for the following reasons:

1. Eight did not include people diagnosed with dementia (Andrieu et al., 2017; Anon, 1986; Conradsson et al., 2010; Cancela et al., 2016; Hariprasad et al., 2013; Littbrand et al., 2006; Tortosa-Martinez, Clow, Caus, et al., 2014; Volkers et al., 2012).
2. Six were complex, multimodal interventions in which exercise was combined with additional non-exercise treatments or training so that groups did not differ in exposure to exercise alone (Bayer et al., 2017; Bossers et al., 2016; Pitkala et al., 2013; Schwenk et al., 2010; Tanaka et al., 2017; Yoon et al., 2013).

3. 14 studies did not include an exercise program (Andersen et al., 2012; Beishuizen, Coley, Moll van Charante, et al., 2017; de Souto, Barreto, et al., 2018; Doi, Verghese, Tsuitsuimoto, et al., 2017; Dominguez, Del Moral, De Guzman, et al., 2017; Gu et al., 2014; Kim, Han, So, et al., 2017; Hauer et al., 2017; Lazaroud et al., 2017; Lee et al., 2017; Perttila, Ohman, Strandberg, et al., 2017; Rudiger, Stuckenschneider, Vogt, et al., 2017; Yaguez et al., 2011; Yokoyama et al., 2015). For example, one study explored the effects of acupuncture on cognitive function (Gu et al., 2014), while several others involved cognitive training and exercises (Yaguez et al., 2011; Yokoyama et al., 2015).
4. 14 studies examined outcomes that were not of interest to this review (Abreu & Hartley, 2013; de Sousa, et al., 2017; Littbrand et al., 2011; Lowery et al., 2013; Padala et al., 2012; Rolland et al., 2007; Roach et al., 2011; Rodriguez-Ruiz et al., 2013; Steinberg et al., 2009; Stevens & Killeen, 2006; Suttanon, Hill, Said, et al., 2013; Varma, Tang, & Carlson, 2016; Volkers et al., 2012; Williams & Tappen, 2007).
5. Six studies were intervention protocols and did not include outcomes (Boss, Van Schaik, Deijle, et al., 2014; Devenney, Sanders, Lawlor, et al., 2017; Kolanowski, Fick, Litaker, et al., 2011; Makizako, Tsutsumimoto, Doi, et al., 2015; Morris et al., 2017; van Uffelen, Hopman-Rock, Chin, et al., 2005).

5. Risk of bias in included studies.

See ‘Cochrane risk of bias tool for randomized controlled trials’ (Appendix C), ‘Characteristics of included studies’ (Appendix D) and ‘Risk of bias summary: review author’s judgments about each risk of bias item for each included trial’ (Figure 2).

Allocation: Random sequence generation (selection bias).

In 13 trials the methods used to generate allocation sequence were not described or were unclear (Arcoverde et al., 2014; Christofolletti 2008; Coelho et al., 2012; Eggermont et al., 2009b; Holthoff et al., 2014; Kemoun et al., 2010; Kwak et al., 2008; Lee & Kim, 2018; Miu, Szeto, & Mak, 2008; Venturelli, Scarsini, & Schena, 2011). Eight trials were judged to be at low risk of bias for this domain, as sufficient information about the way the allocation sequence was generated was available (Barnes et al., 2015; Cheng et al., 2014; Eggermont et al., 2009a; Hoffman et al., 2016; Lamb et al., 2018; Prick et al., 2017; Toots et al., 2017; Thurm et al., 2011; Van de Winckel et al., 2004; Vreugdenhil et al., 2012).

Allocation: Selection bias.

In 10 of the trials the methods used to conceal allocation sequence were unclear or not described (Coelho et al., 2012; Eggermont et al., 2009a; Eggermont et al., 2009b; Hernandez et al., 2010; Holthoff et al., 2014; Kemoun et al., 2010; Kwak et al., 2008; Lee & Kim, 2018; Miu, Szeto, & Mak, 2008; Van de Winckel et al., 2004). For eight trials, allocation concealment was adequate and, due to this factor, the risk of selection bias was ranked as low (Arcoverde et al., 2014; Christofolletti et al., 2008; Hoffman et al., 2016; Lamb et al., 2018; Prick et al., 2017; Toots et al., 2017; Venturelli et al., 2011; Vreugdenhil et al., 2012). Three trials were deemed high risk (Barnes et al., 2015; Cheng et al., 2014; Thurm et al., 2011). For example, "group assignment was randomly assigned by residency" in the trial by Thurm et al., 2011).

Blinding of participants and personnel (performance bias).

With the exception of one trial, trials were at high risk of performance bias, as blinding of participants and personnel to the intervention was not possible, due to the nature of rehabilitation trials. In the trial by Venturelli et al. (2011, members of the research team did not know to which group each participant had been assigned and one on the research team was present during the walking exercise.

Blinding of outcome assessment (detection bias).

It was not clear whether and how outcome assessments had been blinded in multiple trials (Arcoverde et al., 2014; Cheng et al., 2014; Coelho et al., 2012; Hernandez et al., 2010; Holthoff et al., 2014; Kwak et al., 2008; Lamb et al., 2018; Lee & Kim, 2018; Thurm et al., 2011; Venturelli et al., 2011). Van de Winckel et al. (2004) was rated as being at high risk for detection bias for cognition outcomes as “the physiotherapist who was conducting both treatments evaluated the patients on cognition. However, the nurses who scored the patients were all blind to the group assignment.” Remaining trials were deemed low risk for detection bias since outcome assessors were blinded (Christofolletti et al., 2008; Eggermont et al., 2009a; Eggermont et al., 2009b; Kemoun et al., 2010; Vreugdenhil et al., 2012).

Incomplete outcome data (attrition bias).

Attrition rates (drop-outs from the trials) varied from 0% to 38.8% in the included trials. The drop-out rates were higher in the experimental arms for Christofolletti et al., (2008) (29% experimental versus 15% control), Kemoun et al. (2010) (20% experimental versus 17% control, and Eggermont et al. (2009b) (12% experimental versus 3% control). Attrition was higher in the control groups for Van de Winckel et al. (2004) (0% experimental versus 10% control) and Venturelli et al. (2011) (8% experimental versus 17% control). Arcoverde et al. (2014), Barnes et al. (2015), Coelho et al., (2012),

Holthoff et al. (2018), Lee & Kim (2018), Kwak et al. (2008), Vreugdenhil et al. (2011) had 0% attrition in both experimental and control arms. Reasons for attrition were provided, including: death, illness, increased disability, disinterest, physician's disapproval, family withdrawal of consent, moving, and refusal to continue to participate.

In summary, the majority of the trials were found to be at low risk of attrition bias. Several trials had unclear risk. A high risk of attrition bias was reported for five of the included studies for a variety of reasons that included: failure to report attrition rates for individual groups; a high attrition rate; or an imbalance of attrition between the groups, or failure to provide reasons for attrition, or both (Christofoletti et al. 2008; Kemoun et al., 2010; Miu, Szeto, & Mak, 2008; Toots et al., 2017); see Appendix D. 'Characteristics of included studies').

No trials used ITT principles of analysis to estimate missing data. Eggermont et al. (2009a) and Eggermont et al. (2009b) did report running modified ITT analyses, but did not include all randomized participants. Eggermont et al. (2009a) enrolled 103 nursing home residents with dementia in the study, though included only 97 participants in the modified ITT analysis. Similarly, Eggermont et al. (2009b) enrolled 66 participants, but only 61 were included in the ITT analysis. The reported completers' data from the included studies was used in the analyses. Thus, there was a potential risk of attrition bias in these studies.

Selective reporting (reporting bias).

With the exception of Cheng et al. (2014), all included trials were deemed to be at low risk of reporting bias.

Other potential sources of bias.

See Figure 2. ‘Risk of bias summary: review author’s judgments about each risk of bias item for each trial.’

6. Main analysis: Pooled exercise intervention effects on overall cognitive function.

See: ‘Summary of findings for the main comparison: Exercise programs for dementia’ (Table 1) and ‘Forest plot: Exercise vs usual care: Cognition’ (Figure 3).

Primary outcome - Cognition.

Each of the 21 studies in this meta-analysis included at least one cognitive outcome. Data from these 21 studies were included in the meta-analysis of the overall pooled exercise effect on cognition. Both pre- and post-intervention cognitive measures were required to be included in the meta-analyses of overall cognition (Objective 1), as well as meta-analyses by specific cognitive measure (Objective 2) and cognitive domain (Objective 3), as applicable to outcomes available in each study. If a study included multiple outcome measures of cognition, the outcome of primary interest (“primary outcome”) identified in that study was used in the overall pooled mean of cognitive function across all studies. This was in accordance with the cognitive outcome criteria determined a priori and outlined in Chapter 2. Pre- and post-intervention measures following six weeks to 12 months of exercise intervention were included.

The author assumed that the effect sizes of individual studies would be comparable but not identical across studies due to expected heterogeneity across studies (different intervention types and outcomes of cognitive function), and therefore a random-effects model was used. The estimated SMD between exercise and control groups was 0.49 (95% CI [0.24 - 0.75], $P = 0.0002$, 21 studies; Figure 3. ‘Forest plot:

Table 1. Summary of findings for main comparison: Exercise programs for dementia

Patient or population: people with dementia Settings: long-term care, community programs, home Intervention: exercise program Comparison: usual care					
Outcomes	Illustrative comparative risks* (95% CI)		Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	[control]	[experimental]			
Cognition, SD units, investigator measured cognition using different instruments. Higher scores represent better cognitive function, Follow-up: 6-52 weeks		Mean score for cognition in the intervention groups was 0.49 SD units higher (0.24 lower to 0.75 higher)	1548 (21 studies)	⊕⊕⊕⊕ ^a low	0.15, 0.20 and 0.25 represented small, medium, and large treatment effects
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk Ratio; [other abbreviations, eg. OR, etc]					
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.					

Footnotes

a – I-squared = 79% and imprecision

Exercise vs usual care: Cognition'), with 21 studies and 1548 participants. Outcomes demonstrate a large treatment effect showing a statistically significant difference in cognitive functioning between the exercise intervention and control groups, supporting better cognitive functioning in the exercise intervention group.

However, based on visual inspection of forest plots and statistical tests, heterogeneity was very substantial ($I^2 = 79\%$; $\text{Chi}^2 = 93.94$, $P < 0.00001$). Thus, a clear conclusion cannot be drawn from this result because of the imprecision. The quality of this evidence was rated low because of the imprecision, inconsistency between studies, and risk of bias (see Table 1. 'Summary of findings for the main comparison: Exercise programs for dementia').

Further exploration revealed very large effect sizes for two studies with very small sample sizes (Thurm et al., 2011; Venturelli et al., 2011). Asymmetrical funnel plots (Egger et al., 1997) revealed additional evidence of "small-sample bias" and imprecision, as well as publication bias (Figure 3.1. 'Funnel plot: Exercise vs usual care: Cognition'). That is, if Thurm et al. (2011) and Venturelli et al. (2011) has not found significant effect sizes, it is likely they would not have been published due to such small sample size (publication bias). Based on visual inspection, and the very large sample sizes and low power of these two outliers, both studies were then excluded from the analysis since they were at considerable risk for bias and/or heterogeneity.

Sensitivity analysis excluding these two studies was used to assess whether this reduced the large heterogeneity across study effect sizes. Sensitivity analysis revealed a positive overall random effect of exercise interventions on cognitive function; $\text{SMD} = 0.37$ (95% CI [0.14 - 0.60], $P = 0.002$, 19 studies; Figure 3.2. Exercise vs usual care:

Figure 3. Main analysis: Overall effect of exercise interventions on cognitive function in dementia (all 21 studies)

Figure 3.1. Funnel plot: Overall effect of exercise interventions on cognitive function in dementia (all 21 studies)

Cognition - 19 studies), representing a large size treatment effect although slightly smaller than the treatment effect calculated from all 21 studies. This reduced the heterogeneity slightly ($I^2 = 74\%$), though it remained substantial.

Heterogeneity was further investigated in subgroup analyses.

7. Main analysis: Pooled exercise effects by cognitive measure.

In accordance with Objective 2 of this meta-analytic review, exercise effects were then assessed within each measure of cognitive function that was represented in the included studies using MD. SMD was also reported to compare intervention effectiveness across different outcomes. Measures represented by at least two studies were analyzed. Measures that were only used by a single study were not analyzed for MDs.

Mini-Mental State Examination (MMSE) (Global cognitive function). The data from the MMSE showed that exercise was associated with improved scores compared to

Figure 3.2. Main analysis: Overall effect of exercise interventions on cognitive function in dementia (sensitivity analysis

- 19 studies)

the control groups; MD = 1.57 (95% CI [0.54 - 2.61], $P = 0.003$; Figure 4.1. Cognition: Mini Mental State Examination). Heterogeneity was very substantial ($I^2 = 85\%$).

Reported alternatively, SMD = 0.50 (95% CI [0.14 - 0.86], $P = 0.006$).

Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) (Global cognitive function). The data from the ADAS-Cog showed that exercise was not associated with improved scores (lower scores for ADAS-Cog) compared to control groups; MD = -2.38 (95% CI [-5.02 - 0.26], $P = 0.08$; Figure 4.2. Cognition: ADAS-Cog). Heterogeneity was very substantial ($I^2 = 80\%$). Reported alternatively, SMD = -0.19 (95% CI [-0.47 - 0.10], $P = 0.20$).

Category Verbal Fluency (Language). The data showed that exercise was not significantly associated with improved scores; MD = -0.54 (95% CI [-1.11 - 0.04], $P = 0.07$; Figure 4.3. Cognition: Category Verbal Fluency). Heterogeneity was not notable ($I^2 = 12\%$). Reported alternatively, SMD = -0.14 (95% CI [-0.31 - 0.04], $P = 0.13$).

Clock Drawing Test (CDT) (Executive Function). Data from the CDT demonstrated that exercise was associated with improved performance on the CDT; MD = 0.58 (95% CI [0.07 - 1.09], $P = 0.02$; Figure 4.4. Cognition: Clock Drawing Test). Heterogeneity was moderate ($I^2 = 47\%$). Reported alternatively, SMD = 0.63 (95% CI [0.28 - 0.97], $P = 0.00004$).

Digit Span (Leaning & Memory; Executive Functioning). Data showed that exercise was not associated with improvement in performance on the *Digit Span - Forward*; MD = 0.04 (95% CI [-0.70 - 0.77], $P = 0.92$; Figure 4.5. Cognition: Digit Span - Forward) or *Digit Span - Backward*; MD = -0.01 (95% CI [-0.37 - 0.34], $P = 0.94$;

Figure 4.6. Cognition: Digit Span - Backward). Heterogeneity was substantial ($I^2 = 66\%$) and not notable ($I^2 = 0\%$), respectively. Reported alternatively, SMD = 0.04 (95% CI [-0.37 - 0.44], $P = 0.87$, and SMD = -0.02 (95% CI [-0.25 - 0.21], $P = 0.86$, respectively.

8 Words Test (Learning & Memory). Data from the 8 Words Test showed that exercise did not improve performance on: *Immediate Recall*; MD = -1.16 (95% CI [-2.79 - 0.46], $P = 0.16$; Figure 4.7. Cognition: 8 Words Test - Immediate); *Delayed Recall*; MD = -0.22 (95% CI [-0.57 - 0.014], $P = 0.24$; Figure 4.8. Cognition: 8 Words Test - Delayed Recall); or *Recognition*; MD = -0.56 (95% CI [-1.27 - 0.15], $P = 0.12$; Figure 4.9.

Cognition: 8 Words Test - Recognition). Heterogeneity ranged from not notable ($I^2 = 0\%$), substantial ($I^2 = 54\%$), to moderate ($I^2 = 32\%$), respectively. Reported alternatively, SMD = -0.17 (95% CI [-0.41 - 0.07], $P = 0.16$), SMD = -0.21 (95% CI [-0.52 - 0.10], $P = 0.18$), and SMD = -0.22 (95% CI [-0.49 - 0.04], $P = 0.09$), respectively.

Stroop Color and Word Test (SCWT) (Executive functioning). Data demonstrated that exercise was not associated with improved performance on the SCWT; MD = 0.79 (95% CI [-1.52 - 3.09], $P = 0.50$; Figure 4.10. Cognition: Stroop Color and Word Test). Heterogeneity was moderate ($I^2 = 57\%$). Reported alternatively, SMD = 0.41 (95% CI [-0.72 - 1.55], $P = 0.47$).

The remaining measures were each used in a single trial, and therefore results could not be pooled from multiple studies. This included the: *Cambridge Cognitive Examination (CAMCOG)*; *Rapid Evaluation of Cognitive Function (ERFC)*; *Loewenstein Occupational Therapy Cognitive Assessment for Geriatric Population (LOTCA-G)*; *Functional Independence Measure - Cognitive Scale (FIM-Cog)*; *Frontal Assessment Battery (FAB)*; *Symbol Search-Subtest*; and *Symbol Digit Modalities (SDMT)*.

Figure 4.1. Cognition: Mini-Mental State Examination (MMSE)

*Standardized Mean difference (SMD) = 0.50 (95% CI [0.14 - 0.86], $P = 0.006$).

Figure 4.2. Cognition: ADAS-Cog

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Figure 4.3. Cognition: Categorical Verbal Fluency (CVF)

Figure 4.4. Cognition: Clock Drawing Test (CDT)

Figure 4.5. Cognition: Digit Span - forward

Figure 4.6. Cognition: Digit Span - backward

*Standardized Mean difference (SMD) = -0.02 (95% CI [0.25 - 0.21], $P = 0.86$)

Figure 4.7. Cognition: 8 Words Test - immediate

*Standardized Mean difference (SMD) = -0.17 (95% CI [-0.41 - 0.07], $P = 0.16$)

Figure 4.8. Cognition: 8 Words Test (8WT) - delayed recall

*Standardized Mean difference (SMD) = -0.21 (95% CI [-0.52 - 0.10], $P = 0.18$)

Figure 4.9. Cognition: 8 Words Test (8WT) - recognition

*Standardized Mean difference (SMD) = -0.22 (95% CI [-0.49 - 0.04], $P = 0.09$)

Figure 4.10. Cognition: Stroop Color and Word Test

*Standardized Mean difference (SMD) = 0.41 (95% CI [-0.72 - 1.55], $P = 0.47$)

8. Main analysis: Pooled exercise intervention effects by cognitive domain.

In accordance with Objective 3 of this meta-analytic review, exercise effects within different domains of cognition were examined by pooling means of measures assessing the respective cognitive domains. This was also intended to target anticipated heterogeneity across studies.

Attention.

Three studies used measures of attention in assessing cognitive function (Coelho et al., 2012; Hoffman et al., 2016; Lee & Kim, 2018). Exercise was not statistically significant for the attention domain of cognitive function; SMD = 0.55 (95% CI [-0.08 - 1.18], $P = 0.09$; Figure 5.1. Cognition: Attention). Heterogeneity was very substantial ($I^2 = 77\%$).

Memory and Learning.

Six studies used measures within the memory and learning cognitive domain (Arcoverde et al., 2014; Christofolletti et al., 2008; Eggermont et al., 2009a; Eggermont et al., 2009b; Lee & Kim, 2018; Prick et al., 2017). Effect of exercise on cognition for the memory and learning domain was not statistically significant; SMD = -0.28 (95% CI [-0.57 - 0.01], $P = 0.06$; Figure 5.2. Cognition: Memory and learning). Heterogeneity was moderate ($I^2 = 43\%$).

Executive functioning.

Eight studies examined cognitive measures specific to executive functioning (Arcoverde et al., 2014; Christofolletti et al., 2008; Coelho et al., 2012; Eggermont et al., 2009a; Eggermont et al., 2009b; Hoffman et al., 2016; Lee & Kim, 2018; Prick et al.,

2017). Effect of exercise on cognition for the executive functioning domain was not statistically significant; SMD = 0.21 (95% CI [-0.05 - 0.48], $P = 0.11$; Figure 5.3.

Cognition: Executive functioning). Heterogeneity was moderate ($I^2 = 55\%$).

Language.

Ten studies examined cognitive measures specific to the language domain of cognition (Arcoverde et al., 2014; Christofolletti et al., 2008; Coelho et al., 2012; Eggermont et al., 2009a; Eggermont et al., 2009b; Hoffman et al., 2016; Lamb et al., 2018; Lee & Kim, 2018; Prick et al., 2017; Toots et al., 2017). The effect of exercise on cognition for the language domain of cognition was not statistically significant; SMD = -0.02 (95% CI [-0.22 - 0.18], $P = 0.86$; Figure 5.4. Cognition: Language). Heterogeneity was moderate ($I^2 = 56\%$).

No cognitive measures used were specific to the perceptual-motor function/visuospatial cognitive domain or social cognitive domain.

9. Secondary analyses: Subgroup analyses.

In accordance with Objective 4 and Objective 5 of this meta-analytic review, pre-specified exercise intervention variables and study design variables were examined as potential causes of heterogeneity. Potential reasons for high heterogeneity were explored by conducting meta-analyses that included only trials with:

- 1) aerobic-only exercise interventions;
- 2) exercise interventions using multiple, combined types of exercise (e.g., strength and aerobic exercises, balance and aerobic exercises);
- 3) 3 or less exercise sessions per week;
- 4) 4 or more exercise sessions per week

Figure 5.1. Cognition: Attention

Figure 5.2. Cognition: Memory and learning

Figure 5.3. Cognition: Executive functioning

Figure 5.4. Cognition: Language

- 5) 30-minute sessions only;
- 6) sessions longer than 30-minutes;
- 7) 150 or more minutes per week;
- 8) less than 150 minutes per week;
- 9) only moderate intensity exercise programs;
- 10 exercise interventions for more than 24 weeks;
- 11) exercise programs less than 24 weeks;
- 12) participants with mild-to-moderate dementia severity;
- 13) participants diagnosed with AD only.

None of these analyses reduced the heterogeneity below 65% (moderate range).

Exercise moderators.

Type. Subgroup analyses were performed for “combined type” and “aerobic-only type” exercise programs (Figure 6.1. Exercise type - combined type; Figure 6.2. Cognition: Exercise type - aerobic-only). Combined type revealed a significant exercise effect; SMD = 0.63 (95% CI [0.28 - 0.98], $P = 0.0004$). Heterogeneity remained very substantial ($I^2 = 80\%$ or above). Aerobic-only interventions did not show a significant exercise effect.

Frequency. Subgroup analyses were performed for interventions with three or less sessions per week, revealing a significant exercise effect; SMD = 0.41 (95% CI [0.14 - 0.69], $P = 0.003$; Figure 6.3. Cognition: Exercise frequency - 3 sessions or less per week). Heterogeneity remained substantial ($I^2 = 77\%$). Subgroup analyses were performed for interventions with 4 or more sessions per week, also revealing a significant exercise effect; SMD = 0.83 (95% CI [0.08 - 1.57], $P = 0.03$; Figure 6.4. Cognition:

Exercise frequency - 4 or more sessions per week). Heterogeneity remained very substantial ($I^2 = 85\%$).

Duration of session. Subgroup analyses revealed significant overall random effects for exercise interventions with 30-minute sessions; SMD = 0.77 (95% CI [0.25 - 1.29], $P = 0.003$; Figure 6.5. Cognition: Exercise duration - 30-minute sessions), and exercise interventions with sessions over 30 minutes; SMD = 0.28 (95% CI [0.01 - 0.56], $P = 0.04$; Figure 6.6. Cognition: Exercise duration - sessions over 30 minutes). Results had very substantial heterogeneity ($I^2 = 84\%$) and substantial heterogeneity ($I^2 = 69\%$), respectively.

Volume. Subgroup analyses revealed significant overall random effects for exercise interventions with 150 or more minutes of exercise per week; SMD = 0.51 (95% CI [0.13 - 0.89], $P = 0.009$; Figure 6.7. Cognition: Exercise volume - 150 or more minutes of exercise per week), as well as exercise interventions under 150 minutes per week; SMD = 0.51 (95% CI [0.13 - 0.89], $P = 0.009$; Figure 6.8. Cognition: Exercise volume - < 150 minutes of exercise per week), and heterogeneity was substantial ($I^2 = 78\%$; $I^2 = 80\%$).

Intensity. Significant overall random effects were found for exercise interventions with moderate intensity; SMD = 0.65 (95% CI [0.20 - 1.10], $P = 0.004$; Figure 6.9. Cognition: Exercise intensity - moderate) with substantial heterogeneity ($I^2 = 75\%$).

Length of exercise intervention. Significant overall random effects were found for exercise interventions lasting less than 24 weeks; SMD = 0.40 (95% CI [0.14 - 0.65], $P = 0.002$; Figure 6.10. Cognition: Length of intervention - <24 weeks), and exercise interventions lasting 24 or more weeks; SMD = 1.04 (95% CI [0.04 - 2.05], $P = 0.04$;

Figure 6.11. Cognition: Length of intervention - < 26 weeks). These results had substantial heterogeneity ($I^2 = 78\%$; $I^2 = 79\%$).

Study design moderators.

Dementia severity. A majority of the trials included participants with “mild to moderate” dementia, which revealed significant random effects on cognitive performance; SMD = 0.36 (95% CI [0.12 - 0.61], $P = 0.004$, $I^2 = 76\%$; Figure 6.12. Cognition: Dementia severity - mild and moderate).

Dementia type. While multiple studies had participants representing multiple types of dementia or did not report dementia type, a majority of the trials included participants with AD. Subgroup analysis revealed positive overall random effects of exercise interventions on cognitive function in studies with AD patients only; SMD = 0.96 (95% CI [0.35 - 1.58], $P = 0.002$, $I^2 = 81\%$; Figure 6.13. Cognition: Dementia type - Alzheimer’s disease only).

It is important to note that despite multiple significant subgroup findings, the substantial heterogeneity ($I^2 > 70\%$) remained unresolved.

10. Final summary.

A summary of findings from all analyses can be found in Table 2 (‘Meta-analyses summary table: Exercise vs. usual care’)

Figure 6.1. Exercise - Combined type only

Figure 6.2. Exercise - Aerobic-only type

Figure 6.3. Exercise frequency - 3 or fewer sessions per week

Figure 6.4. Exercise frequency - 4 or more sessions per week

Figure 6.5. Exercise duration - 30-minute sessions

Figure 6.6. Exercise duration - sessions over 30 minutes

Figure 6.7. Exercise volume - 150 or more minutes of exercise per week

Figure 6.8. Exercise volume - less than 150 minutes per week

Figure 6.9. Exercise intensity - moderate only

Figure 6.10. Length of exercise intervention - < 24 weeks

Figure 6.11. Length of intervention - 24 or more weeks

Figure 6.12. Dementia severity - mild and moderate only

Figure 6.13. Dementia type - Alzheimer's disease only

Table 2. Meta-analyses summary table: Exercise vs. usual care

Analysis of cognitive function (exercise vs. usual care)	Studies (N)	MD, 95% CI	SMD, 95% CI
All studies	21	-	*0.49 [0.24 - 0.75], <i>P</i>=0.0002
Sensitivity analysis - 19 studies	19	-	*0.37 [0.14 - 0.60], <i>P</i>=0.002
Cognitive Test/Measure			
MMSE	12	*1.57 [0.54 - 2.61], <i>P</i>=0.003	*0.50 [0.14 - 0.86], <i>P</i>=0.006
ADAS-Cog	7	-2.38 [-5.02 - 0.26], <i>P</i> =0.08	-0.19 [-0.47 - 0.10], <i>P</i> =0.20
Category Verbal Fluency	7	-0.54 [-1.11 - 0.04], <i>P</i> =0.07	-0.14 [-0.31 - 0.04], <i>P</i> =0.13
Clock Drawing Test	4	*0.58 [0.07 - 1.09], <i>P</i>=0.02	*0.63 [0.28 - 0.97], <i>P</i>=0.00004
Digit Span - forward	4	0.04 [-0.70 - 0.77], <i>P</i> =0.92	0.04 [-0.37 - 0.44], <i>P</i> =0.87
Digit Span - backward	4	-0.01 [-0.37 - 0.34], <i>P</i> =0.94	-0.02 [-0.25 - 0.21], <i>P</i> =0.86
8 Words Test - immediate	3	-1.16 [-2.79 - 0.46], <i>P</i> =0.16	-0.17 [-0.41 - 0.07], <i>P</i> =0.16
8 Words Test - delayed recall	3	-0.22 [-0.57 - 0.014], <i>P</i> =0.24	-0.21 [-0.52 - 0.10], <i>P</i> =0.18
8 Words Test - recognition	3	-0.56 [-1.27 - 0.15], <i>P</i> =0.12	-0.22 [-0.49 - 0.04], <i>P</i> =0.09
Stroop Color and Word Test	2	0.79 [-1.52 - 3.09], <i>P</i> =0.50	0.41 [-0.72 - 1.55], <i>P</i> =0.47
Cognitive Domain			
Attention	3	-	0.55 [-0.08 - 1.18], <i>P</i> =0.09
Memory and Learning	6	-	-0.28 [-0.57 - 0.01], <i>P</i> =0.06
Executive functioning	8	-	0.21 [-0.05 - 0.48], <i>P</i> =0.11
Language	10	-	-0.02 [-0.22 - 0.18], <i>P</i> =0.86
Moderator analysis			
<i>Exercise Intervention</i>			
Combined type	12	-	*0.63 [0.28 - 0.98], <i>P</i>=0.0004
Aerobic-only type	6	-	0.45 [-0.12 - 1.01], <i>P</i> =0.12
Frequency- 3 or less sessions/week	16	-	*0.41 [0.14 - 0.69], <i>P</i>=0.009
Frequency - 4+ sessions/week	5	-	*0.83 [0.08 - 1.57], <i>P</i>=0.03
Duration - 30-minutes/session	9	-	*0.77 [0.25 - 1.29], <i>P</i>=0.003
Duration - 30+ minutes/session	12	-	*0.28 [0.01 - 0.56], <i>P</i>=0.04
Volume - 150+ minutes/week	11	-	*0.51 [0.13 - 0.89], <i>P</i>=0.009
Volume - <150 minutes/week	10	-	*0.51 [0.13 - 0.98], <i>P</i>=0.009
Intensity - moderate	9	-	*0.65 [0.20 - 1.10], <i>P</i>=0.004
Intervention length <24 weeks	17	-	*0.40 [0.14 - 0.65], <i>P</i>=0.002
Intervention length 24 or more weeks	4	-	*1.04 [0.04 - 2.05], <i>P</i>=0.04
<i>Participants</i>			
Dementia severity - mild/moderate only	18	-	*0.36 [0.12 - 0.61], <i>P</i>=0.004
Dementia type - Alzheimer's only	7	-	*0.96 [0.35 - 1.58], <i>P</i>=0.002

* Significant effect sizes are marked in bold and marked with an asterisk

CHAPTER 5:

CONCLUSION

1. Summary of main results.

This study conducted the most comprehensive systematic review and meta-analysis of RCTs exploring exercise intervention effects on cognitive functioning in adults >60 years of age with dementia to date. Importantly, it did not limit inclusion of studies by specific exercise type, publication date, or cognitive measure. The study also incorporated a multilevel meta-analysis method that included exploration of subgroups and moderator variables. The key finding from this study is that exercise interventions are effective in improving cognition or slowing the progression of cognitive decline in older adults with dementia.

This review included 21 trials (21 articles) with a total of 1548 participants. Most participants were women diagnosed with AD and living at a care facility. This review tested whether exercise interventions could improve cognitive function in older persons with dementia. The exercise interventions varied greatly; the length of time that they ran ranged from 8 weeks to 12 months, and activities varied (e.g., hand movements, sitting, walking, Tai Chi, walking, strength exercises). Independently, 15 of the included trials demonstrated that exercise improves cognitive function for individuals with dementia, while the remaining six studies did not display a beneficial effect of exercise on cognitive function in individuals with dementia.

Objective 1. The review supports the notion that exercise interventions may improve cognitive functioning in individuals with dementia, though there was considerable unexplained statistical heterogeneity observed in the analyses, which

suggests the need for caution in interpreting these results. Regardless, these are encouraging results for a disease that is debilitating with limited desirable treatment options. Meta-analysis demonstrated positive effects of exercise on cognitive function in older adults with dementia; SMD = 0.49, (95% CI [0.24 - 0.75], $P = 0.0002$). This analysis revealed very substantial heterogeneity ($I^2 = 79\%$), most of which the author was unable to explain despite investigation. The quality of evidence was rated as low due to publication bias, inconsistency and imprecision. Thus, some of these findings should be interpreted with caution.

Sensitivity analysis was conducted after examining the forest plot and funnel plot of the primary analysis. The removal of two studies (Thurm et al., 2011; Venturelli, et al., 2011) from the analysis resulted in a large treatment effect; SMD = 0.37, 95% CI [0.14 - 0.60], $P = 0.002$, 19 studies), again in favor of exercise effects on slowing the progression of cognitive decline and/or improving cognitive function. However, substantial heterogeneity remained ($I^2 = 74\%$).

Objective 2. Among the specific measures of cognition that were represented in the included studies, the Mini-Mental State Examination (MMSE) was used to measure cognitive function most frequently in the trials ($N = 12$). The MMSE and Clock Drawing Test (CDT) both demonstrated significant exercise treatment effects on cognition.

Objective 3. No evidence of exercise effects was found within the six specific cognitive domains that the review was intending to assess (attention, executive functioning, memory and learning, language, social cognition, visuospatial/perceptual-motor function).

Objective 4. Several exercise intervention and study variables were identified a priori as potential contributors to heterogeneity, and subgroup analyses were conducted

accordingly. These variables for subgroup analyses included exercise type (mode), frequency (number of exercise sessions per week), duration (minutes of exercise per session), volume (total minutes of exercise per week), length of exercise intervention, and exercise intensity. Interestingly, heterogeneity remained substantial throughout these subgroup analyses, while all but one of the planned subgroup analyses revealed a significant exercise effect. The significant subgroup analyses (moderators) included: type of exercise (combined-type only); three or fewer exercise sessions per week and four or more exercise sessions per week; 30-minute sessions and sessions over 30-minutes; total of 150+ minutes per week and under 150 minutes per week; moderate intensity exercise interventions; and interventions lasting 24 weeks or longer and those lasting less than 24 weeks. Subgroup analysis for aerobic-only type of exercise was not significant.

Objective 5. RCTs' specific type of dementia and severity of dementia at baseline were also variables coded for subgroup analyses. Subgroup analyses combining "mild-to-moderate" dementia severities revealed significant exercise effects on cognitive function (RCTs' pooled mean outcome measures of cognitive function). Similarly, subgroup analyses were performed using trials composed of Alzheimer's disease patients only (a majority of the trials), and this also revealed a significant exercise effect on pooled cognitive outcome measures. Given that Alzheimer's disease is the most common type of dementia, these results are promising. Given the exercise effects on cognitive function for mild-to-moderate dementia severity, this is also promising as individuals with less severe dementia may be more independent and capable of initiating, establishing, and maintaining a regular exercise program.

2. Overall completeness and applicability of evidence.

Clearly, additional research is needed that examines these important outcomes and provides the data needed for meta-analysis. Eight studies were based in the community/homes (Coehlo et al., 2012; Hernandez et al., 2010; Hoffman et al., 2016; Kwak et al., 2008; Lamb et al., 2018; Miu, Szeto, & Mak, et al., 2008; Prick et al., 2017; Vreugdenhil 2012), all others were conducted largely in care facilities/ institutions (Arcoverde et al., 2014; Barnes et al., 2015; Cheng et al., 2014; Christofolletti et al., 2008; Eggermont et al., 2009a; Eggermont et al., 2009b; Holthoff et al., 2018; Kemoun et al., 2010; Lee & Kim, 2018; Thurm et al., 2011; Toots et al., 2017; Van de Winckel, Fewys, & Weerdt, 2004; Venturelli et al., 2011).

The participants within the trials were not homogeneous in terms of their diagnosis (e.g., AD, vascular dementia, mixed dementia, other) though most were qualified as having “moderate” severity dementia. As dementia is not a singular disease entity, and there is some evidence that exercise might affect the risk of these conditions in different ways (Rockwood 2007).

Also, the exercise programs were not homogeneous in terms of the type (e.g. aerobic, strength, balance, combined), duration (range: 8 weeks to 12 months), frequency (range: two times per week to daily) of activities, and intensity (low to high). Therefore, type, duration (less than 12 weeks versus longer than 12 weeks), frequency (less than three times per week versus more than three times per week), and intensity of the exercise programs were compared in further subgroup analyses. However, the examination of moderators depended on the variables available in the studies selected, which is an inherent limitation of meta-analysis.

3. Potential biases and limitations.

This review was conducted as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011), therefore, the introduction of bias during the review process was minimized. However, not all of the included trials reported data that could be used in the meta-analysis (e.g., data pertinent to risk of bias assessment, exercise intensity), and most authors did not respond to requests for this data. This meant that the certain variables from these trials could not be included in the meta-analyses. This was unfortunate as the total number of trials that have examined the evidence of the benefit or lack of benefit of exercise programs in improving the symptoms of dementia is limited.

The limited number of studies included in this meta-analytic review resulted in even fewer variables in the subgroup analyses, as many of the included studies were missing variables of interest to this review (e.g., exercise intensity, exercise adherence, attrition). The Cochrane Handbook for Systematic Reviews of Interventions version 5.20 (2017) notes the importance of ensuring that there are adequate studies to justify subgroup analyses. The typical advice for undertaking simple regression analyses: that at least 10 observations (i.e. ten studies in the meta-analysis) should be available for each characteristic, and that even this will be too few when the covariates are unevenly distributed. The final number of studies included stands as a considerable weakness. However, this could not be fully anticipated or controlled for by the author.

As studies were included only if exercise was the sole intervention, a large number of studies were excluded that used exercise as an adjunct component to another intervention (e.g., combined cognitive and exercise program) were excluded. It is

unfortunate such studies did not have exercise-only intervention arms, as this would significantly have increased the number of included studies, and therefore strengthened the generalizability of our findings and allowed more robust subgroup and moderator analyses.

Another potential source of study bias involves the small sample sizes in half of the included studies (10 studies had fewer than 30 participants). Furthermore, two studies with very small sample sizes (under 20 participants) and very large treatment effects could likely be contributing to the large heterogeneity of effect sizes found in the analyses. If such small studies had not found significant effect sizes, it is likely that they would not have been published due to such small sample sizes. This contributes to inherent publication bias, such that studies with small sample sizes are only available if they also found a larger effect size in comparison to the population effect size, which secures effect size heterogeneity.

The constant of heterogeneity was evident in the included studies. Heterogeneity was present across a variety of variables involving participant variables, exercise intervention variables, and cognitive outcome measures. However, this weakness of heterogeneity could not be fully anticipated or controlled for by the author.

As the author was the only coder, interrater reliability could not be assessed to ensure consistency and clarity at the title/abstract screening, full text screening, and data extraction stages. To ensure rating consistency, the author blindly re-rated and re-coded several studies, as well as comparing several studies' risk of bias ratings to other authors' ratings of the same studies in other published reviews. However, to help ensure that these

judgements are reproducible, it is desirable for more than one author to repeat parts of the process at various stages in a systematic review to enhance quality appraisal.

While this meta-analysis did not find any exercise effects within any of the individual cognitive domains, this author's criteria for categorizing cognitive measures into different domains (DSM-V) may have differed from the study authors' criteria or definition. That is, the author of individual studies included in this meta-analysis may have categorized a measure into a different domain than the author of this meta-analysis. Perhaps the use of different definitions or categorizations of cognitive domains would have yielded different outcomes, including significant exercise effects.

Lastly, exercise influences cognitive function through multiple mechanisms. Without direct measurements of these pathways, we cannot discern from the current meta-analyses which mechanisms underlie these findings from individuals diagnosed with dementia.

4. Agreements and disagreements with other reviews.

The primary result of this study aligns with the findings from a recent meta-analysis by Panza et al. (2018), which examined nineteen studies and found a favorable effect of exercise on cognitive function (SMD = 0.47, 95% CI [0.26 - 0.68], $P = 0.00$). The exercise effect in this study (SMD = 0.49, 95% CI [0.24 - 0.75], $P = 0.0002$) is similar in magnitude to Panza et al.'s (2018) findings. However, Panza et al. (2018) included participants with and without AD (at risk of AD), while this study included only those with existing dementia diagnoses. In contrast to the findings of this study supporting exercise effects in combined-type (multimodal) but not aerobic-only exercise interventions, Panza et al. (2018) found aerobic exercise had the most favorable effect.

The findings from this study are of importance as they include new and additional relevant studies, multiple exercise intervention variables, a multilevel analysis examining outcomes by cognitive measure and domain, and are specific to those diagnosed with dementia. The findings of this meta-analysis are in contrast to a Cochrane Review by Forbes et al. (2015), which included nine trials examining exercise intervention effects on cognitive functioning and neuropsychiatric symptoms. Forbes et al. (2015) found no clear evidence of benefit from exercise (SMD = 0.43, 95% CI [-0.05 - 0.92], $P=0.08$).

5. Implications for practice.

The findings of this meta-analysis and systematic review could have implications contributing to future policy, practice, and research. The results reveal the collected findings of the best evidence available on exercise for the treatment or management of dementia, a debilitating major chronic disease. They may help to eventually inform clinicians and policymakers of the exercise conditions for which exercise provides an improvement in cognitive function, and those for which there is no clear benefit or where evidence of benefit is lacking. By taking a step toward quantifying the benefits of exercise in treating one of the most common deadly and costly chronic diseases, healthcare providers and policymakers may be more willing or likely to take action on implementing more accessible, feasible, and cost-effective exercise interventions delivered on a population level. Barriers to exercise interventions and implementation in practice may also be discussed. Further elucidating the influence of these variables could help in tailoring exercise programs for the maximal patient benefit.

Moreover, dissemination and communication with the public can increase awareness about the potential benefits of exercise for those with dementia. Family

caregivers and providers may not be aware of these findings, or these findings may challenge existing beliefs about older adults with dementia and exercise (e.g., exercise is unsafe, exercise is not beneficial at this age). The promising evidence that exercise improves cognition may be added to exercise's synergistic impact on well-being. That is, exercise has been shown to prevent, delay or treat other chronic diseases, as well as increasing the likelihood of changing and engaging in other health behaviors (e.g., healthy diet, smoking cessation).

6. Implications for research and future directions.

The overview and results help to identify specific considerations that should be taken into account in future studies that contribute to a reliable basis for clinical application. Future studies should define, control for, and clearly report variables such as: dementia type; dementia severity; study location; exercise type, intensity, duration, frequency, volume; measurement of physical activity level; study follow up; and participant characteristics. Future well-designed RCTs with clear intervention criteria, larger samples, standardized outcome measures, and long-term follow-up are needed to enhance the quality of such a review by assessing the exercise programs that are best for people with various types and severities of dementia. Exploration of additional outcomes (e.g., mortality, quality of life, healthcare service use and expenditures) and use of technology in attaining more objective measures of exercise may add to the existing body of research. Including biomarkers in future studies may help us better understand the physiological mechanisms of the relationship between exercise and cognition.

While specific “doses” of health behaviors prevent and treat other chronic diseases, research has yet to determine the optimal exercise “dose” for treating or slowing

the progress of cognitive decline in persons with dementia. That is, aerobic exercise and “heart healthy foods” are often prescribed for heart disease, while a diet of complex carbohydrates, low glycemic foods, and avoiding processed carbohydrates and sugars is typically recommended for those with type 2 diabetes. Future studies incorporating the aforementioned recommendations may shed light on optimizing the exercise “dose” for the treatment of dementia and, more specifically, the unique and differing needs, preferences, and capabilities of the individuals diagnosed with dementia.

Regardless of the results from this individual study, researchers, health providers and policymakers must call for an increasing consensus in an increasingly important area tied to chronic disease, the aging population, lifestyle intervention, increasing healthcare costs, and Big Pharma. A recent report on pharmaceutical development in *New Scientist* (MacKenzie, 2019), discusses how all major pharmaceutical firms have closed their Alzheimer’s units, despite research supporting the potential use of an arthritis drug in significantly cutting the risk of developing Alzheimer’s. Major pharmaceuticals companies are opting out of organizing large, longitudinal studies on Alzheimer’s and dementia largely due to the financial risks. Such trends call for assistance in government funding and more non-pharmaceutical intervention research, including lifestyle interventions.

APPENDIX A

Search strategy and results by database

Inclusion Criteria

Participants: Adults (<60) who have been diagnosed with dementia

Interventions: Any intervention with at least one exercise of physical activity component that states improvement in cognitive functioning as goal

Comparison: No treatment, usual care, standard care, social control. Cannot have any exercise/ physical activity components, or components of cognitive activity.

Outcomes: Cognitive outcomes.

Study design: Randomized controlled trials in which participants were prospectively assigned to study groups and in which control group outcomes were measured concurrently with intervention group outcomes.

Exclusion Criteria

Participants: Adults <60 years old

Study design: Any study without a contemporaneous control group

Filter: Date (January 1, 1950 – current date), search performed April 30, 2018

Search String 1. Dementia terms (population/disease filter): dementia, Alzheimer

Search String 2. Exercise terms (intervention filter):

Search String 3. Cochrane published RCT filter (study design filter): (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])

Search String 4. Outcome:

Databases

1. PubMed
2. MEDLINE
3. EMBASE
4. PsycARTICLES
5. CENTRAL

PUBMED

Date Searched: April 30, 2018

Limits: None

Publication Date: No start date was applied, and databases were searched from their inception or date of the earliest available publication.

Returned Hits: 176

PubMed was searched with appropriate Medical Subject Headings (MeSH) incorporated into hedges. Filters were set for Humans:

("Dementia"[Mesh] OR dementia[ti] OR dement[ti] OR "Alzheimer Disease"[Mesh] OR alzheimer[ti] OR alzheimers[ti] OR alzheimer's[ti])

AND ("Exercise"[MAJR] OR exercise OR exercises OR running[ti] OR running[mesh] OR jogging OR walking OR bicycling OR cycling[ti] OR bicycling[mesh] OR bicycling OR treadmill OR treadmills OR ergometer OR ergometers OR "physical activity"[ti] OR "resistance training" OR "weight lifting" OR "weightlifting" OR "strength training" OR "workout" OR "workouts" OR dancing OR dance OR swim OR swimming OR yoga OR "tai chi" OR tai chi OR "t'ai chi" OR taijiquan OR qigong OR sport OR sports OR "physical activity"[ti])

AND ("intelligence"[MAJR:noexp] OR "intelligence"[ti] OR "IQ"[ti] OR "Cognition"[MAJR:noexp] OR cognition[ti] OR "Comprehension"[MAJR] OR cognitive[ti] OR neurocognition OR neurocognitive OR "neuro-cognition" OR "neuro-cognitive" OR "Executive Function"[MAJR] OR "executive function" OR "executive functions" OR "executive functioning" OR "Problem Solving"[MAJR] OR "problem solving" OR "Memory"[MAJR] OR memory[ti] OR "Attention"[MAJR] OR attention[ti] OR attentiveness[ti] OR concentration[ti] OR concentrate[ti] OR learn[ti] OR learning[ti] OR "brain development" OR "cognitive performance" OR "cognitive function" OR "cognitive functioning" OR "information retrieval" OR "information processing" OR "perceptual skills" OR "intelligence quotient")

AND (("clinical"[tiab] AND "trial"[tiab]) OR "clinical trials as topic"[mesh] OR "clinical trial"[pt] OR random*[tiab] OR "random allocation"[mesh] OR "therapeutic use"[sh])

NOT (cancer OR neoplasm* OR hypertensi* OR "high blood pressure" OR diabetes OR diabetic* OR HIV OR "acquired immunodeficiency syndrome" OR "cerebral palsy" OR parkinson's[ti] OR parkinson[ti])

EMBASE

Searched: 4/30/18

Search dates: Date of inception 1960 – April 30, 2018

Limits: Filter set for Document Type to include articles only

Returned Hits: 272

(in title) dementia OR Alzheimer OR alzheimers OR alzheimer's OR alzheimer

AND

(in title) exercise OR "physical activity"

OR

Running OR cycling OR jogging OR walking OR bicycling OR bicycling OR treadmill
OR treadmills OR ergometer OR ergometers OR "resistance training" OR "weight
lifting" OR "weightlifting" OR "strength training" OR "workout" OR "workouts" OR
dancing OR dance OR swim OR swimming OR yoga OR "tai chi" OR tai chi OR "t'ai
chi" OR taijiquan OR qigong OR dancing OR "resistance training" OR "weight lifting"
OR "strength training" OR sport OR sports

AND

(in title) intelligence OR "IQ" OR cognition OR cognitive OR brain OR memory OR
attention OR attentiveness OR concentration OR concentrate OR learn OR learning
OR cognitive OR attentiveness OR concentration OR concentrate OR learn OR
learning OR neurocognition OR neurocognitive OR neuro-cognition OR neuro-
cognitive OR "executive function" OR "executive functions" OR "executive
functioning" OR "problem solving" OR "brain development" OR "cognitive
performance" OR "cognitive function" OR "cognitive functioning" OR "information
retrieval" OR "information processing" OR "perceptual skills" OR "intelligence
quotient"

AND

Clinical AND trial

OR

random*

NOT

cancer OR neoplasm* OR hypertensi* OR "high blood pressure" OR diabetes OR
diabetic* OR HIV OR "acquired immunodeficiency syndrome" OR "cerebral palsy"
OR parkinson's OR parkinson

MEDLINE

Search Date: April 30, 2018

Search Dates: Date of inception 1960 – April 30, 2018

Returned Hits: 388

(in title) dementia OR Alzheimer OR alzheimers OR alzheimer's OR alzheimer

AND

(in title) exercise OR "physical activity"

OR

Running OR cycling OR jogging OR walking OR bicycling OR bicycling OR treadmill
OR treadmills OR ergometer OR ergometers OR "resistance training" OR "weight
lifting" OR "weightlifting" OR "strength training" OR "workout" OR "workouts" OR
dancing OR dance OR swim OR swimming OR yoga OR "tai chi" OR tai chi OR "t'ai
chi" OR taijiquan OR qigong OR dancing OR "resistance training" OR "weight lifting"
OR "strength training" OR sport OR sports

AND

(in title) intelligence OR "IQ" OR cognition OR cognitive OR brain OR memory OR
attention OR attentiveness OR concentration OR concentrate OR learn OR learning
OR cognitive OR attentiveness OR concentration OR concentrate OR learn OR
learning OR neurocognition OR neurocognitive OR neuro-cognition OR neuro-
cognitive OR "executive function" OR "executive functions" OR "executive
functioning" OR "problem solving" OR "brain development" OR "cognitive
performance" OR "cognitive function" OR "cognitive functioning" OR "information
retrieval" OR "information processing" OR "perceptual skills" OR "intelligence
quotient"

AND

Clinical AND trial

OR

random*

NOT

cancer OR neoplasm* OR hypertensi* OR "high blood pressure" OR diabetes OR
diabetic* OR HIV OR "acquired immunodeficiency syndrome" OR "cerebral palsy"
OR parkinson's OR parkinson

PsycARTICLES

Search Date: April 30, 2018

Search Dates: Date of inception – April 30, 2018

Returned Hits: 6

(in title) dementia OR Alzheimer OR alzheimers OR alzheimer's OR alzheimer

AND

(in title) exercise OR "physical activity"

OR

Running OR cycling OR jogging OR walking OR bicycling OR bicycling OR treadmill
OR treadmills OR ergometer OR ergometers OR "resistance training" OR "weight
lifting" OR "weightlifting" OR "strength training" OR "workout" OR "workouts" OR
dancing OR dance OR swim OR swimming OR yoga OR "tai chi" OR tai chi OR "t'ai
chi" OR taijiquan OR qigong OR dancing OR "resistance training" OR "weight lifting"
OR "strength training" OR sport OR sports

AND

(in title) intelligence OR "IQ" OR cognition OR cognitive OR brain OR memory OR
attention OR attentiveness OR concentration OR concentrate OR learn OR learning
OR cognitive OR attentiveness OR concentration OR concentrate OR learn OR
learning OR neurocognition OR neurocognitive OR "neuro-cognition" OR "neuro-
cognitive" OR "executive function" OR "executive functions" OR "executive
functioning" OR "problem solving" OR "brain development" OR "cognitive
performance" OR "cognitive function" OR "cognitive functioning" OR "information
retrieval" OR "information processing" OR "perceptual skills" OR "intelligence
quotient"

AND

Clinical AND trial

OR

random*

NOT

cancer OR neoplasm* OR hypertensi* OR "high blood pressure" OR diabetes OR
diabetic* OR HIV OR "acquired immunodeficiency syndrome" OR "cerebral palsy"
OR parkinson's OR parkinson

CENTRAL

Search Date: April 30, 2018

Search Dates: Date of inception – April 30, 2018

Returned Hits: 6

(in title, abstract, keyword) dementia OR Alzheimer OR alzheimers OR alzheimer's
OR alzheimer

AND

(in title, abstract, keyword) exercise OR "physical activity"

OR

Running OR cycling OR jogging OR walking OR bicycling OR bicycling OR treadmill
OR treadmills OR ergometer OR ergometers OR "resistance training" OR "weight
lifting" OR "weightlifting" OR "strength training" OR "workout" OR "workouts" OR
dancing OR dance OR swim OR swimming OR yoga OR "tai chi" OR tai chi OR "t'ai
chi" OR taijiquan OR qigong OR dancing OR "resistance training" OR "weight lifting"
OR "strength training" OR sport OR sports

AND

(in title, abstract, keyword) intelligence OR "IQ" OR cognition OR cognitive OR
brain OR memory OR attention OR attentiveness OR concentration OR concentrate OR
learn OR learning

OR cognitive OR attentiveness OR concentration OR concentrate OR learn OR
learning OR neurocognition OR neurocognitive OR "neuro-cognition" OR "neuro-
cognitive" OR "executive function" OR "executive functions" OR "executive
functioning" OR "problem solving" OR "brain development" OR "cognitive
performance" OR "cognitive function" OR "cognitive functioning" OR "information
retrieval" OR "information processing" OR "perceptual skills" OR "intelligence
quotient"

AND

Clinical AND trial

OR

random*

NOT

cancer OR neoplasm* OR hypertensi* OR "high blood pressure" OR diabetes OR
diabetic* OR HIV OR "acquired immunodeficiency syndrome" OR "cerebral palsy"
OR parkinson's OR parkinson

APPENDIX B

Data extraction form

STUDY ID:

DATE OF REVIEW:

YEAR OF PUBLICATION:

INITIAL SCREENING (Y/N):

1. Is this paper about exercise interventions for the treatment of cognitive function in persons with dementia?
YES = 1 or NO = 2
 2. Is this paper published in a peer-reviewed journal?
YES = 1 or NO = 2
-

ELIGIBILITY DECISIONS (Y/N):

1. DESIGN - Is it a randomized experiment?
YES = 1 or NO = 2
 2. POPULATION - Does it include adults w/dementia over 60 y/o?
YES = 1 or NO = 2
 3. INTERVENTION - Does intervention group include an exercise-only program?
YES = 1 or NO = 2
 4. COMPARISON - Does study include 2+ parallel cohorts (1 Intervention group; 1 "usual or standard care" group)?
YES = 1 or NO = 2
 5. OUTCOME - Does the primary outcome measure cognitive functioning?
YES = 1 or NO = 2
 - a. Primary cognitive outcome of interest: _____
-

INCLUDE? YES or NO

IF EXCLUDED, WHY? _____

GROUPS

1. How many intervention groups are relevant to this m-a?
2. How many different control/comparison groups were there?
3. How many control/comparison groups are relevant to this m-a?

SETTING/LOCATION

1. **COUNTRY:**
2. **LOCATION OF INTERVENTION:**
 1. = Care facility
 2. = Participant's home
 3. = Hospital
 4. = Other

SAMPLE

1. Sample size
Intervention group (N) =
Control group (N) =
2. Dementia type:
 1. = AD - Alzheimer's disease,
 2. = MD - mixed dementia,
 3. = VaD - vascular dementia,
 4. = UD - undefined dementia,
 5. = MID - Multiple Infarct Dementia
 6. = multiple types
3. Diagnostic criteria:
 1. = NINCDS-ADRDA (national institute of neurological and communicative disorder and stroke & Alzheimer's diseases and related disorders association)
 2. = ICD-10 = international classification of diseases and related health problems
 3. = DSM=diagnostic and statistical manual of mental disorders
 4. = Other diagnostic criteria
4. Dementia severity at baseline (Mean):
 1. = Mild (Mini Mental State Examination (MMSE) = 17 - 26,
 2. or similar scale; [Hogan 2007](#));
 3. = Moderate (MMSE 10 - 17, or similar scale; [Hogan 2007](#));
 4. = Severe (MMSE < 10, or similar scale; [Feldman 2005](#)).

OR... dementia severity as defined by study: _____

5. Sample characteristics?
 - a. Mean age (SD) =
 - b. % Male =
6. Control group:
 - a. Education;
 - b. Social;
 - c. Usual or standard care
7. Inclusion criteria:
8. Exclusion criteria:

INTERVENTION

1. Brief description of exercise intervention: _____

2. Type of exercise program:
 1. = aerobic-only (cardiorespiratory);
 2. = resistance training only (strength, endurance, power);
 3. = balance only;
 4. = flexibility (stretching) only;
 5. = combination of 2+ of the above;
 6. = other.
3. Frequency of exercise program (# sessions per week):
 1. = up to 3 times per week;
 2. = more than 3 times per week.
4. Duration (minutes per session):
 1. = 30 minutes or less;
 2. = 31 or more minutes.
 3. = >60 minutes;
5. Volume (total exercise minutes per week):
 1. 60 minutes or less;

2. 61 - 120 minutes
3. 121 - 150 minutes;
4. >150 minutes.

6. Time period (duration of exercise program):

1. = up to 12 weeks;
2. = more than 12 weeks.

7. Intensity of exercise program (as defined in RCT):

1. = Low
2. = Moderate
3. = High
4. = Unclear

SERVICES PROVIDED TO CONTROL CASES

1. Control group:

1. = Active;
2. = Education;
3. = No contact;
4. = Social;
5. = Nothing provided.

OUTCOMES

1. Information on program adherence/fidelity to exercise intervention?

2. Cognitive outcome measures used?

3. What were the pre-post cognitive outcome measures?

Intervention group =

Control group =

STUDY QUALITY STANDARDS

1. Random generation of allocation (assignment) to groups

1. = Low risk
2. = High risk
3. = Unclear risk

Notes:

2. Allocation concealment

1. = Low risk
2. = High risk
3. = Unclear risk

Notes:

3. Blinding patients/personnel
 1. = Low risk
 2. = High risk
 3. = Unclear risk

Notes:

4. Blinding outcome assessor
 1. = Low risk
 2. = High risk
 3. = Unclear risk

Notes:

5. Incomplete outcome data
 1. = Low risk
 2. = High risk
 3. = Unclear risk

Notes:

6. Selective reporting
 1. = Low risk
 2. = High risk
 3. = Unclear risk

Notes:

7. Other bias
 1. = Low risk
 2. = High risk
 3. = Unclear risk

Notes:

APPENDIX C

Cochrane risk of bias tool for randomized controlled trials

RANDOM SEQUENCE GENERATION Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.	
Criteria for a judgment of 'Low risk' of bias.	<p>The investigators describe a random component in the sequence generation process such as:</p> <ul style="list-style-type: none"> •Referring to a random number table; •Using a computer random number generator; •Coin tossing; •Shuffling cards or envelopes; •Throwing dice; •Drawing of lots; •Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgment of 'High risk' of bias.	<p>The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:</p> <ul style="list-style-type: none"> •Sequence generated by odd or even date of birth; •Sequence generated by some rule based on date (or day) of admission; •Sequence generated by some rule based on hospital or clinic record number. <p>Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:</p> <ul style="list-style-type: none"> •Allocation by judgement of the clinician; •Allocation by preference of the participant; •Allocation based on the results of a laboratory test or a series of tests; •Allocation by availability of the intervention.
Criteria for the judgment of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.

ALLOCATION CONCEALMENT Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	
Criteria for a judgment of 'Low risk' of bias.	<p>Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:</p> <ul style="list-style-type: none"> • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgment of 'High risk' of bias.	<p>Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:</p> <ul style="list-style-type: none"> • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
Criteria for the judgment of 'Unclear risk' of bias.	<p>Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.</p>
SELECTIVE REPORTING Reporting bias due to selective outcome reporting.	
Criteria for a judgment of 'Low risk' of bias.	<p>Any of the following:</p> <ul style="list-style-type: none"> • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgment of 'High risk' of bias.	<p>Any one of the following:</p> <ul style="list-style-type: none"> • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified
	<p>(unless clear justification for their reporting is provided, such as an unexpected adverse effect);</p> <ul style="list-style-type: none"> • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgment of 'Unclear risk' of bias.	<p>Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.</p>

OTHER BIAS Bias due to problems not covered elsewhere in the table.	
Criteria for a judgment of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgment of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: <ul style="list-style-type: none"> • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.
Criteria for the judgment of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: <ul style="list-style-type: none"> • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.
BLINDING OF PARTICIPANTS AND PERSONNEL Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: <ul style="list-style-type: none"> • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: <ul style="list-style-type: none"> • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: <ul style="list-style-type: none"> • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.

BLINDING OF OUTCOME ASSESSMENT Detection bias due to knowledge of the allocated interventions by outcome assessors.	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: <ul style="list-style-type: none"> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: <ul style="list-style-type: none"> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: <ul style="list-style-type: none"> Insufficient information to permit judgment of 'Low risk' or 'High risk'; The study did not address this outcome.
INCOMPLETE OUTCOME DATA Attrition bias due to amount, nature or handling of incomplete outcome data.	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: <ul style="list-style-type: none"> No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: <ul style="list-style-type: none"> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;

	<ul style="list-style-type: none"> • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
Criteria for the judgment of 'Unclear risk' of bias.	<p>Any one of the following:</p> <ul style="list-style-type: none"> • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.

Thresholds for Converting the Cochrane Risk of Bias Tool to AHRQ Standards (Good, Fair, and Poor)

Good quality: All criteria met (i.e. low for each domain)

Using the Cochrane ROB tool, it is possible for a criterion to be met even when the element was technically not part of the method. For instance, a judgment that knowledge of the allocated interventions was adequately prevented can be made even if the study was not blinded, if EPC team members judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.

Fair quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was **unlikely** to have biased the outcome, and there is no known important limitation that could invalidate the results

Poor quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was **likely** to have biased the outcome, and there are important limitations that could invalidate the results

Poor quality: Two or more criteria listed as high or unclear risk of bias

APPENDIX D

Characteristics of included studies

(-) = unknown, AD = Alzheimer's disease, MD = mixed dementia, VaD = vascular dementia, UD = undefined dementia, MID = Multiple Infarct Dementia, NINCDS-ADRDA = national institute of neurological and communicative disorder and stroke & Alzheimer's diseases and related disorders association, ICD-10 = international classification of diseases and related health problems, DSM=diagnostic and statistical manual of mental disorders.

Arcoverde et al. (2014)

Methods	16-week RCT
Participants	<p>Country: Brazil Location: Care facility (residence) Diagnosis: AD, MD; NINCDS-ADRDA diagnostic criteria. Dementia severity: mild Participants: N=20 Experimental Group: N = 10, Control Group: N = 10 Mean age (SD): M=78.8 years % Male: Total = 45%; Control=50%, Experimental=40% Inclusion criteria: 1) diagnosis of AD and MD according to NINCDS-ADRDA criteria; 2) MMSE score ≥ 15; 3) CDR score=1 (moderate memory loss); 4) regular use of anticholinesterase drugs or another type of pharmacological treatment to AD for at least 6 months; 5) cardiologist's authorization; 6) at least 6 months without practicing physical exercises. Exclusion criteria: if they presented: 1) clinical depression or Cornell Scale ≥ 720; 2) other types of dementia; 3) physical limitation due to other pathologies or associated neurological disease; 4) severe or uncontrolled arterial hypertension; 5) marked visual and/or auditory deficit; 6) incapacity to perform physical exercise due to neurological or neuromuscular impairments; 7) illiteracy; 8) less than 6 months of treatment at the outpatient unit.</p>
Interventions	<p>Experimental Group: supervised AET -Treadmill Type: Aerobic-only Frequency (sessions/week): 2 Duration: 30 min Volume (total exercise min/week): 60 Time period (weeks): 16 weeks Intensity: Moderate intensity (60% VO_{2max}) Attrition: 0% Exercise program adherence: 99.4% Control Group: Standard care (maintained only the clinical and pharmacological treatment along the 4 months of follow-up. These patients attending the hospital only to medical routine and did not do another type of intervention during this period.)</p>
Outcomes	<p>1) Mini-Mental State Examination (MMSE) 2) Cambridge -Cognitive Examination (CAMCOG), Brazilian validated version</p>

	3) Clock Drawing Test (CDT) 4) Verbal Fluency Test (animal category) 5) Digit Span (WAIS-R Scale subtest) 6) Stroop Test
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Randomization process not described. Arcoverde emailed on April 30, 2019, no response.
Allocation concealment (selection bias)	Low risk	Randomized with blind design by researcher who did not participate in initial assessments.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to attrition.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Barnes et al. (2015)

Methods	18-week RCT
Participants	Country: USA Location: Care facility Diagnosis: UD; diagnostic criteria via Modified Mini-Mental State Examination (3MS) Dementia severity: "mild to moderate" Participants: N=12 Experimental group N=6, Control group N=6 % Male: 18% Mean age (SD) = 84.4(4) years Inclusion criteria: Diagnosis of cognitive dementia or any type or severity, adult day program attendance at least 2 days/week, recommended by adult day staff, English language fluency and caregiver consent. Exclusion criteria: Lack of assess to study procedures
Interventions	Experimental Group: Participated in the PLIE (Preventing Loss of Independence through Exercise) program, which involved: repetition with variation; progressive, functional movements; slow-pace and step by step instruction; participant-centered goal orientation; body awareness, mindfulness, breathing; social interaction

	Type: Resistance/strength (functional movements) Frequency (sessions/week): 2 Duration (min/session): 45 min Volume (total exercise min/week): 90 min Time period (weeks): 18 weeks Intensity: - Attrition: 0% Exercise program adherence: -- Therapy for controls: Usual care
Outcomes	1) ADAS-Cog
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	Assigned based on attendance at the day program
Allocation concealment (selection bias)	High risk	See above
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Research assistants who collected outcome data were blinded to group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed 12-week intervention
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Cheng et al. (2014)

Methods	12-week cluster-randomized open-label controlled trial
Participants	Country: China Location: Care facility (nursing homes) Diagnosis: AD, VaD, UD; Clinical Dementia Rating 0.5 or more Dementia severity: mild to moderate Participants: 110 residents at baseline, 74 participants completed the study. Experimental: N=39, Control: N=35 % Male: 25% Mean age (SD): 81.4 years Inclusion criteria: MMSE = 10-24 and suffering from at least very mild dementia (Clinical Dementia Rating 0.5). Exclusion criteria: Being bedbound, audio/visual impairment, regular activity participation before study, or contraindications for physical or group activities.

Interventions	Intervention Group: seated Tai Chi Type: Other Frequency (sessions/week): 3 Duration (min/session): 60 min Volume (total exercise min/week): 180 min Time period (weeks): 12 weeks Intensity: "moderate" Attrition: -- Exercise program adherence: -- Therapy for Controls: Social control group (simple handicrafts)
Outcomes	1) MMSE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	"Residents recruited from 9 nursing homes were randomized by home"
Allocation concealment (selection bias)	High risk	"Cluster design deemed necessary to avoid treatment contamination within homes"
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated ("open-label design was inevitable because activities could not be masked and it was not possible to prevent residences from talking to interviewers about the activities")
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of the outcome assessors not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Few attritions over time"
Selective reporting (reporting bias)	High risk	Attrition not reported.
Other bias	Unclear risk	"Residents recruited from 9 nursing homes were randomized by home"

Christofolletti et al. (2008)

Methods	6-month RCT
Participants	Country: Brazil Location: Long-term psychiatric institution/care facility Diagnosis: AD, MD; (ICD-10 criteria) Dementia severity: "moderate stage" (baseline MMSE =13.7) Participants: 54 at baseline, and 41 completed Male %: 30% Mean age (SD): 74.3 years (1.4) (M=76.7 years for those who completed intervention) Group 1 (N = 17) was an interdisciplinary program Group 2 (N = 17) was physiotherapy Group 3 (N = 20) was the control

	<p>(Of the two experimental groups, only Group 2 was included in this review)</p> <p>Inclusion criteria: “primary diagnosis of dementia” using ICD-10 criteria and confirmed by MMSE and Katz ADL score, medically fit for participation in intervention, resident of psychiatric institution.</p> <p>Exclusion criteria: cognitive impairment associated with other neuropsychiatric conditions or neurological diagnosis; antidepressant prescriptions with sedative or anticholinergic actions; impairment of cognition or balance related to drugs</p>
Interventions	<p>Experimental Group: physiotherapy kinesio-therapeutic exercises-- strength, balance, memory, and recognition exercise using balls, elastic ribbons, and proprioceptive plates--provided by physiotherapist</p> <p>Type: Combined (strength/balance)</p> <p>Frequency (sessions/week): 3</p> <p>Duration (min/session): 60 min</p> <p>Volume (total exercise min/week): 180 min</p> <p>Time period (weeks): 24 weeks</p> <p>Intensity: --</p> <p>Attrition rate: 24.1% (29% experimental versus 15% control)</p> <p>Exercise program adherence: --</p> <p>Therapy for controls: Standard care</p>
Outcomes	<p>1) MMSE</p> <p>2) Brief Cognitive Screening Battery (BCSB)</p> <p style="padding-left: 40px;">a. Clock Drawing Test</p> <p style="padding-left: 40px;">b. Immediate memory</p> <p>3) Verbal Fluency (semantic, animals/minute)</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Unclear process of randomization: (quote) “A sealed envelope with an identification number was assigned to each subject, each one filled with a slip giving the group. When a patient was registered and given a number, the appropriate envelope was opened”
Allocation concealment (selection bias)	Low risk	Used sealed envelop, though did not specify if envelopes were opaque
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and personnel to the intervention allocated: "As a common bias presented on most rehabilitation trials, it was not possible to 'blind' the subjects regarding the treatments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessors.

Incomplete outcome data (attrition bias) All outcomes	High risk	Study attrition rate = 24.1% Attrition rate for each group: Experimental Group: 29.4% = 5 participants Control Group: 15.0% = 3 participants Reasons for attrition given, however, not specified according to group
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Coehlo et al. (2012)

Methods	16-week controlled trial
Participants	<p>Country: Brazil Location: Community-dwelling Diagnosis: AD; diagnostic criteria DSM-4-R. All of the patients underwent a clinical and a neuropsychological evaluation carried out by a trained team. CDR was used for the classification of dementia severity. The MMSE was also used, which is scored using a scale that ranges from 0 to 30 points. Dementia severity: mild to moderate</p> <p>Experimental group (n = 14; aged M=78.0 SD=1 7.3 years) Control group (n = 13; aged M=77.1 SD= 7.4 years) for convenience.</p> <p>Inclusion criteria: 27 patients with mild (CDR 1) and moderate (CDR 2) Alzheimer's disease who were capable of independent ambulation were included in the study. Exclusion criteria: Patients with severe dementia (CDR 3) or with other neuropsychiatric conditions were also excluded from the investigation.</p>
Interventions	<p>Intervention group: Type: Combined (multiple mode types) Frequency (sessions/week): 3 Duration (min/session): 60 min Volume (total exercise min/week): 180 min Time period (weeks): 16 weeks Intensity: "moderate" (65-75% of predicted max. heart rate for age)</p> <p>Attrition: 0% Exercise program adherence: --</p> <p>Therapy for Controls: Standard care (kept to their same daily routine and did not participate in any regular or structured exercise programs)</p>
Outcomes	<p>1) FAB (total score) 2) Clock Drawing Test (CDT) 3) Symbol Search (subtest)</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	No description of randomization process provided. Emailed April 30, 2019, no response.
Allocation concealment (selection bias)	Unclear risk	No description of methods used to conceal allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% of participants completed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Eggermont et al. (2009a)

Methods	12-week RCT
Participants	<p>Country: Netherlands Location: Care facility (23 nursing homes) Diagnosis: UD; DSM-4 and NINCDS-ADRDA diagnostic criteria Dementia severity: mild to moderate (baseline MMSE = 16.3) Participants: 103* *6 did not complete study protocol so number who actually took part in the study = 97</p> <p>Experimental Group: N = 51 Control Group: N = 46 Mean age (SD)=85.4 years % Male: 19% (79 women and 18 men)</p> <p>Inclusion criteria: Age > 70 years; diagnosis of dementia; able to walk for short distances with or without a walking aid; written consent from participants and relatives. Exclusion criteria: MMSE score of < 10 or > 24; visual disturbances; hearing difficulties; history of alcoholism; personality disorders; cerebral trauma; hydrocephalus; neoplasm; or disturbances of consciousness.</p>
Interventions	<p>Experimental Group: Walking group, walks occurred on unit wards and in public places Type: Aerobic-only Frequency (sessions/week): 5 Duration (min/session): 30 min Volume (total exercise min/week): 150 min Time period (weeks): 6 weeks Intensity: -- (unclear - "self-selected speed")</p> <p>Attrition: 5.8% Exercise program adherence: 100%</p>

	Therapy for Controls: Social control group - social visits (5 days a week, social visit duration = 30 minutes for 6 weeks)
Outcomes	1) Digit Span (Forward, Backward) 2) Eight Words Test (Recognition, Delayed Recall, Immediate) 3) Category (Verbal) Fluency
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	"By tossing a coin subjects were randomly allocated to either an experimental or control group."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and personnel to intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measures were evaluated by trained psychology student blinded to participants' intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study attrition rate = 5.8%. Authors did not report group attrition rates, or reasons for attrition. Modified ITT used in analysis, however 103 participants were enrolled in the study but only 97 participants were included in the modified ITT analysis.
Selective reporting (reporting bias)	Low risk	Used 2 rating scales to measure executive function, memory, and cognitive domains. Components of both scales were reported elsewhere: "The following tests were administered (details are published elsewhere)"
Other bias	High risk	Attendance and adherence not stated

Eggermont et al. (2009b)

Methods	6-week clustered-RCT
Participants	<p>Country: Netherlands Location: Care facility (10 nursing homes) Diagnosis: UD; dementia diagnosis using the DSM-4, NINCDS-ADRDA criteria Dementia severity: mild - moderate dementia (baseline MMSE = 17.7)</p> <p>Participants: 66 at baseline, and 61 completed Experimental: N=30, Control: N= 31 Mean age (SD): 84.6 years % Male: -</p> <p>Inclusion criteria: At least 70 years old, DSM-4 dementia diagnosis, no apparent disability in hand motor function Exclusion criteria: --</p>

Interventions	<p>Experimental Group: hand movement activity group performing activities such as “finger movement, pinching a soft ball, or handling a rubber ring”</p> <p>Type: Other</p> <p>Frequency (sessions/week): 5</p> <p>Duration (min/session): 30 min</p> <p>Volume (total exercise min/week): 150 min</p> <p>Time period (weeks): 6 weeks</p> <p>Intensity: low</p> <p>Attrition: 7.6%</p> <p>Exercise program adherence: 80%</p> <p>Therapy for Controls: Social control group - social contact plus read out loud program. Frequency: 5 days a week, duration = 30 minutes, Time period: 6 weeks</p>
Outcomes	<p>1) Digit Span (Forward, Backward)</p> <p>2) Eight Words Test</p> <p>3) Category Fluency</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Randomization process unclear. Emailed Eggermont on May 5, no response.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment process unclear
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants or personnel to intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition provided Used ITT analysis, though, 66 participants were enrolled in the study and only 61 were included in the ITT analysis Per-protocol analysis included participants that attended 80% of the sessions
Selective reporting (reporting bias)	Low risk	Reported all outcomes measured
Other bias	Low risk	None apparent

Hernandez et al. (2010)

Methods	6-month RCT
Participants	<p>Country: Brazil</p> <p>Location: Community</p> <p>Diagnosis: AD (DSM-IV diagnostic criteria)</p> <p>Dementia severity: mild - moderate</p> <p>Participants: N = 16 elderly patients</p>

	<p>Experimental: N=9, Control: N=7 Mean age (SD)=78.5(6.8) years % Male: --</p> <p>Inclusion criteria: diagnosed with AD according to DSM-IV Exclusion criteria: no AD diagnosis</p>
Interventions	<p>Experimental Group: stretching/weight training/circuits/dance Type: Combined (multiple types/modes) Frequency (sessions/week): 3 Duration (min/session): 60 min Volume (total exercise min/week): 180 min Time period (weeks): 26 weeks Intensity: moderate (60-80% maximum heart rate)</p> <p>Attrition: 20% Exercise program adherence: --</p> <p>Therapy for Controls: Standard care</p>
Outcomes	1) MMSE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	"Randomly divided into two groups . . . according to the availability of caregivers and patients for transport to the place of physical activity."
Allocation concealment (selection bias)	Unclear risk	No description of methods used to conceal allocation.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	20% total attrition rate. (Sample loss of 4 elderly patients due to health problems, followed by hospitalization. Study completed with 16 elderly patients with AD (IG; n=9 and RG; n=7)
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Hoffman et al. (2016)

Methods	16-week RCT
Participants	<p>Country: Denmark Location: Community Diagnosis: AD; NINDS-ADRDA diagnostic criteria Dementia severity: mild to moderate Participants: N=200 at baseline and in analyses, N=190 completed follow-up Experimental: N=102, Control: N=88</p>

	<p>Mean age (SD): 70.5 years % Male: 57%</p> <p>Inclusion Criteria: MMSE score >19, age 50-90 years, and a caregiver with regular contact (1+ visit per month) who was willing to participate in the study. If patients received anti-dementia medication or mood stabilizing medication, they had to be on a stable dose for at least 3 months before inclusion.</p> <p>Exclusion Criteria: 1) presence of cardiac or other medical diseases constituting a contraindication to physical activity or other neurological diseases causing cognitive decline; 2) severe psychiatric disease; 3) alcohol abuse within the last 2 years according to the national guidelines; 4) participation in regular physical activity of high intensity 2+ times weekly.</p>
Interventions	<p>Exercise Group: Type: Aerobic -only Frequency (sessions/week): 3 Duration (min/session): 60 min Volume (total exercise min/week): 180 min Time period (weeks): 16 weeks Intensity: moderate (target heart rate was 70-80% of maximal heart rate - [220 - person's age])</p> <p>Attrition: 4% Exercise program adherence: --</p> <p>Therapy for Controls: Standard care</p>
Outcomes	<p>1) MMSE 2) ADAS-Cog 3) Symbol Digit Modalities Test (SDMT) 4) Stroop Color and Word Test 5) Verbal Fluency - Categorical (semantic, animal)</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomized in blocks of 4-10 per participating center, using a computerized random-number generator.
Allocation concealment (selection bias)	Low risk	Assessors blinded to group assignment throughout the study period completed the baseline assessments.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Raters performing the outcome measurements were blinded to group assignment, and patients and caregivers were advised not to disclose group assignment during the test sessions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% total attrition. 76% of participants in intervention group attended more than 80% of exercise sessions, 78% exercised with intensity of more than 70% of

		maximal heart rate, 62% fulfilled both criteria ("high exercise subjects")
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Holthoff et al. (2018)

Methods	12-week RCT
Participants	<p>Country: Germany Location: Care facility Diagnosis: AD (NINCDS-ADRDA criteria) Dementia severity: mild - moderate Participants: N=30 Experimental group: N=15, Control group: N=15 Mean age (SD): 72.4 (4.3) years % Male: 50%</p> <p>Inclusion criteria: 55 years or older, mild-moderate AD. full capacity to consent, required to speak German, minimum of 8 years formal education, have a caregiver living at home Exclusion criteria: Participants with clinically relevant medical conditions (e.g., heart disease), history of alcohol or substance abuse, head trauma, psychiatric or neurological disorder preceding AD onset, major systemic disease affecting brain function</p>
Interventions	<p>Experimental group: Home-based physical activity program that changed between passive, motor-assisted or active resistive leg training and changes in direction on a movement trainer. Type: Combined (resistance training, aerobic circuit) Frequency (sessions/week): 3 Duration (min/session): 30 min Volume (total exercise min/week): 90 min Time period (weeks): 12 weeks Intensity: "moderate to high" (70-80% of maximal HR)</p> <p>Attrition: 0% Exercise program adherence: 90%</p> <p>Therapy for controls: Psychoeducation (received same monthly clinical visits and a counselling by the treating physician, which included specific advice how to change inactive habits and increase the PA level)</p>
Outcomes	1) MMSE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Randomization process not described. Emailed Holthoff on 3/5/19, no response.
Allocation concealment (selection bias)	Unclear risk	No description of methods used to conceal allocation

Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of methods used to blind outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the first follow-up 12 weeks after study inclusion
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Kemoun et al. (2010)

Methods	15-week RCT
Participants	<p>Country: France Location: Care facility (nursing home) Diagnosis: AD; DSM-4 criteria Dementia severity: mild to severe (baseline MMSE = 12.8) Participants: N=38 at baseline, 31 completed</p> <p>Experimental Group: N = 20 (16 completed) Mean age (SD) = 82.0 years (5.8) % Male: 35% (23 women and 8 men) Control Group: N = 18 (n=15 completed) Mean age (SD) = 81.7(5.1) years</p> <p>Inclusion criteria: Diagnosis of Alzheimer dementia using DSM-IV criteria, MMSE < 23, able to walk 10 min without technical assistance. Exclusion criteria: --</p>
Interventions	<p>Experimental Group: Aerobic exercise program included three different sessions each week, i.e. 1) walking, 2) stamina exercise and 3) a combination of walking, stamina, and balance exercises. For the first 2 weeks of the program participants prepared for the routine program with specific muscles and joint exercises Type: Aerobic-only Frequency (sessions/week): 3 Volume (min/wk): 180 min Duration (minutes): 60 min Time period: 15 weeks Intensity: "Moderate"</p> <p>Attrition: 18.4%, 20% experimental versus 17% control Exercise program adherence: 90.2%</p> <p>Therapy for Controls: Standard care, no physical activity.</p>
Outcomes	1) Rapid Evaluation of Cognitive Functions Test (ERFC, French Version)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Randomization process not described. Email correspondence, Kemoun, 13 May 2018, description was as follows "The process of randomization was conducted by the randomization manager of the clinical investigation center of the university hospital of Poitiers. Each randomization number was given for each patient after he had been included in the study by the principal investigator."
Allocation concealment (selection bias)	Unclear risk	"Subjects were randomized into two groups using a permutation table." Methods used to conceal allocation not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and personnel in intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate = 18.4%: 4 participants lost from Experimental Group and 3 from Control Group. Reasons for attrition provided
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Kwak et al. (2008)

Methods	12-month RCT
Participants	<p>Country: S. Korea Location: Community Diagnosis: UD; Diagnostic criteria -- Dementia severity: moderate (baseline MMSE = 14.0) Mean age: M=81.0 years % Male: 0% Females N=30 Participants: Total N = 30 Exercise Group N = 15, Control Group N= 15</p> <p>Inclusion criteria: Women, postmenopausal status, age 60+ years, MMSE 10-26, free from any medical condition that would limit participation in light to moderate intensity exercise (i.e., walking), not engaged in regular physical activity in the previous 6 months, stable on all medications for at least the last 6 months Exclusion criteria: Men, no dementia diagnosis, medical condition preventing physical activity</p>
Interventions	<p>Experimental Group: Type: Combined (strength/resistance training, walking, stretching) Frequency (sessions/week): 2-3 Duration (min/session): 45 min (exercised 30 - 60 minutes per day) Volume (min/week): 90 min (average)</p>

	Time period (weeks): 52 weeks (12 months) Intensity: “moderate” (gradually increased from 30% to 60% of expected maximal oxygen consumption) Attrition: 0% Exercise program adherence: -- Therapy for Controls: Standard care
Outcomes	1) MMSE
Notes	

Risk of bias

Bias	Authors’ judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Randomization process not described. Emailed Kwak on 2/7/19, no response
Allocation concealment (selection bias)	Unclear risk	No description of methods used to conceal allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of methods use to blind outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Lamb et al. (2018)

Methods	4-month RCT
Participants	Country: England Location: Community Diagnosis: UD; ICD-10 diagnostic criteria for type of dementia; Dementia severity: mild to moderate Participants: Baseline: N= 494 Experimental N=329, Control N=165 Sample for primary analysis: N=415, Experimental N=277, Control N=137 Mean age(SD): 77.5(7.7) years % Male: 60.7% Inclusion criteria: People with dementia were eligible if they had a clinically confirmed diagnosis of dementia in accordance with DSM-4 and a standardized mini mental state examination score (sMMSE) >10, were able to sit on a chair and walk 10 feet without assistance, and lived in the community either alone or with others. Exclusion criteria: Excluded people with acute, unstable physical

	or terminal illness that would make participation in the exercise program unsafe.
Interventions	<p>Exercise Intervention:</p> <p>Type: Combined (aerobic/strength tailored to fitness and health status; static cycling)</p> <p>Frequency (sessions/week): 2</p> <p>Duration (min/session): 45 min average (60-90 minutes)</p> <p>Volume (total min/week): 90 min</p> <p>Time period: 16 weeks</p> <p>Intensity: "Moderate to high" (depending on tolerance level), intensity set using 6 minute walk test</p> <p>Attrition: Total = 16% (Control = 17% ; Exercise=15%)</p> <p>Exercise program adherence: 65%</p> <p>Therapy for Controls: Standard care</p>
Outcomes	1) ADAS-Cog
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	Independent telephone randomization system assigned participants to exercise training or usual care in a 2:1 ratio. Unbalanced randomisation used to minimize delays to starting exercise training.
Allocation concealment (selection bias)	Low risk	Independent statistician used computerized random number generator for the allocation sequence.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Researchers who undertook data entry and cleaning were unaware of treatment allocation (data was masked).
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Attrition: Total = 16%; Control = 17% ; Exercise=15%</p> <p>Reasons for attrition reported.</p> <p>"A few people with dementia withdrew themselves from the trial or were lost to follow-up. No people with dementia were withdrawn from the trial by investigators."</p> <p>"Used the published recommendations for dealing with missing items within scales."</p>
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Lee & Kim (2018)

Methods	18-week RCT
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Participants	<p>Country: Republic of Korea Location: Care facility (day care center for elderly) Diagnosis: AZ, VaD, UD; Clinical Dementia Rating (CDR) = 1 served as diagnostic criteria Dementia severity: mild Participants: Total N=60 Experimental Group N=30, Control Group N=30 Mean age (SD): 75.65(4.42) % Male: 43.3%</p> <p>Inclusion criteria: Clinical Dementia Rating (CDR) was 1, no problems with hearing and vision, able to walk independently Exclusion criteria: -</p>
Interventions	<p>Exercise intervention: Type: Combined (strength/balance re-training to prevent falls by the elderly) Frequency (sessions/week): 3 Duration (min/session): 30 min Volume (total min/week): 90 min Time period: 8 weeks Intensity: -</p> <p>Attrition: 0% Exercise program adherence: --</p> <p>Therapy for controls: Social visit</p>
Outcomes	<p>1) Loewenstein Occupational Therapy Cognitive Assessment for Geriatric Population (LOTCA-G), Total a. Clock Drawing Test (subtest) 2) Functional Independence Measure (FIM) - Cognition Total (subtest)</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Method of random selection not provided ("Divided randomly")
Allocation concealment (selection bias)	Unclear risk	No description of methods used to conceal allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition = 0%, all participants completed the program
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Miu, Szeto, & Mak (2008)

Methods	12-week RCT
Participants	<p>Country: China Location: Community Diagnosis: AD, VaD, MD; DSM-4 diagnostic criteria Dementia severity: mild - moderate (MMSE 10 - 26; baseline MMSE = 18.9) Participants: N=85 at baseline (Experimental: N=36; Control: N=49) N =52 total completed (Experimental: N=24; Control: N=28) Age (M): 76.6 years % Male: 46%</p> <p>Inclusion criteria: mild-to-moderate dementia, Cantonese version MMSE scores of 10 to 26, age >60, being community dwelling, ambulatory, and having a caregiver that was willing to participate and escort the patient to hospital for training and assessment. Exclusion criteria: Patients with severe dementia (MMSE<10) were excluded.</p>
Interventions	<p>Experimental Group: aerobic exercise with treadmill, bicycle, arm ergometry and flexibility exercise Type: Aerobic-only Frequency (sessions/week): 2 Duration (min/session): 60 min Volume (total min/week): 120 min Time period: 12 weeks Intensity: --</p> <p>Attrition: 38.8% Exercise program adherence: --</p> <p>Therapy for Controls: Standard care (conventional medical treatment)</p>
Outcomes	<p>1) MMSE 2) ADAS-Cog (subscale)</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Unclear process of randomization ("in the memory clinic of a regional hospital . . . consecutive patients with a diagnosis of dementia according to the DSM-IV-TR criteria were randomized into one of two groups")
Allocation concealment (selection bias)	Unclear risk	Methods to conceal allocation not described
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physiotherapist and occupational therapist who were blinded to allocation groups conducted the assessments at baseline and post-intervention.

Incomplete outcome data (attrition bias) All outcomes	High risk	Study attrition was 38.8%. 23% attrition rate for experimental group, and 43% attrition rate for control group.
Selective reporting (reporting bias)	Low risk	Reported all outcomes measured
Other bias	Low risk	None apparent

Prick et al. (2017)

Methods	3-month RCT
Participants	<p>Country: Netherlands Location: Homes of participants Diagnosis: UD; diagnosis of dementia made by a physician (for instance a general practitioner, psychiatrist, geriatrician or a neurologist) Dementia severity: mild to moderate Participants: N=111, intervention (N=57), control group (N=54) Mean age (SD): 77(7.46) % Male: --</p> <p>Inclusion criteria: people with dementia were a diagnosis of dementia made by a physician (for instance a general practitioner, psychiatrist, geriatrician or a neurologist), minimum age 55 years, and living at home with a caregiver willing to participate in the training sessions. Exclusion criteria: the use of antidepressants, the presence of psychotic symptoms, Mini Mental State Examination (MMSE) score < 14, and receiving more than two days care in a day care facility.</p>
Interventions	<p>Experimental group: Type: Combined (flexibility, strengthening, balance, endurance, related support existing of psycho-education) Frequency (sessions/week): 3 days/week Duration (min/session): 30 min Volume (total min/week): 90 min Time period: 12 weeks Intensity: --</p> <p>Attrition: 12% Exercise program adherence: 77.2%</p> <p>Control: Social visit</p>
Outcomes	<p>1) Eight Words Test (8WT) 2) Digit Span (subtest of WMS-R) (Backward, Forward, Total) 3) Category Verbal Fluency</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomly assigned by blocked randomization (block size 20) to intervention or comparison group.
Allocation concealment (selection bias)	Low risk	The allocation schedule was made by an independent researcher with a computer-generated block randomization using random Allocation Software (Version 1).

Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In total, 98 (88%) people with dementia completed post measurement.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None apparent

Thurm et al. (2011)

Methods	10-week randomized controlled trial
Participants	<p>Country: Germany Location: Care facility (nursing home) Diagnosis: UD; diagnosed using DSM-4-TR criteria Dementia severity: "moderate" Participants: N=19 at baseline, N=15 post-intervention Experimental Group: N=6, Control Group: N=9 Mean age: M=83.15 years % Male: 42% male</p> <p>Inclusion criteria: older adults with a record of dementia who were physically frail but cognitively and physically eligible for participating in the neuropsychological and physical examinations as well as in the physical movement training. Exclusion criteria: No indication of dementia (MMSE > 24, DSM-IV-TR criteria), salient behavioral problems or lack of minimally sufficient daily functioning, severe sensory impairments, absence of or severe impairments in written or spoken German and lack of minimal physical eligibility.</p>
Interventions	<p>Experimental Group: Type: Combined (physical exercise mainly conducted in a seated position but gradually increased in level of difficulty and complexity; the training combined strengthening, coordination, balance, flexibility, stamina) Frequency (sessions/week): 2 Duration (min/session): 45 min Volume (total min/week): 90 min Time period: 10 weeks Intensity: "moderate"</p> <p>Attrition: 21.2% Exercise program adherence: -- ("high" but not quantitatively specified)</p> <p>Control group: standard care</p>
Outcomes	1) ADAS-Cog (German version)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	"Group assignment randomly assigned by residency"
Allocation concealment (selection bias)	High risk	"Randomized allocation to groups was not possible as participants were not able to visit the other building for training because of their physical frailty"
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total study attrition rate was 21.1%. 25% of the training group (N=6), 19.2% of the control group (N=9).
Selective reporting (reporting bias)	Low risk	Reported all outcomes
Other bias	Low risk	None apparent

Toots et al. (2017)

Methods	16-week cluster-RCT
Participants	<p>Country: Sweden Location: Care facility (16 nursing homes) Diagnosis: VaD, AD, MD, UD; DSM-4-TR diagnostic criteria Dementia severity: mild to moderate Participants Baseline: N=186, (Experimental: N=93, Control: N=93) Mean age (SD): M=85.1(7.1) % Male: 24.2%</p> <p>Inclusion criteria: MMSE score$\geq$10, a dementia diagnosis, age$\geq$65 y, dependent on assistance in$\geq$1 personal activity of daily living according to the Katz Index [29], ability to stand up from a chair with armrests with assistance from$\leq$1 person, physician's approval, and ability to hear and understand spoken Swedish sufficiently to participate in assessments. All individuals included in the study gave informed oral consent to participation, which was confirmed by their next of kin. Exclusion criteria: --</p>
Interventions	<p>Exercise Intervention: Type: Combined (strength/balance/mobility, "high-intensity functional exercise program") Frequency: 115 min (five 45-minute sessions x 2 weeks) Duration: 16 weeks Intensity: High ("supervised individually to promote the highest possible exercise intensity" (8-12 repetition maximum, "High-Intensity Functional Exercise (HIFE) Program")</p> <p>Attrition: 28.5% (Intervention attrition = 27%, Control attrition = 30%) Exercise program adherence: 71.5%</p> <p>Therapy for Controls: Social activity</p>
Outcomes	1) MMSE

	2) ADAS-Cog 3) Verbal Fluency (VF), Categorical
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	Drawing lots "Clusters (N=36) of 3-8 participants each (that lived in same wing, unit, or floor) were formed. Randomization was stratified in all nursing homes except one, which had single cluster (aimed to have participants in both groups in each nursing home and reduce risk of factors associated with site to influence the outcome"
Allocation concealment (selection bias)	Low risk	Participants were randomized after completion of enrollment process and baseline assessment to ensure concealed allocation. "Researchers not involved in study performed randomization drawing lots using sealed opaque envelopes."
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Testers blinded to activity allocation and previous test results. Blinding preserved throughout all cognitive tests"
Incomplete outcome data (attrition bias) All outcomes	High risk	Intervention attrition = 27%, Control attrition = 30%
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Van de Winckel, Feys, & Weerdts (2004)

Methods	3-month RCT
Participants	Country: Belgium Location: Care facility (public psychiatric hospital) Diagnosis: MID (multiple infarct dementia) (3 participants), AD (22 participants); Diagnosed via NINCDS-ADRDA criteria Dementia severity: moderate to severe (baseline MMSE = 12.0) Participants: 25 at baseline, and 24 completed, Experimental Group (n = 15), Control Group (n = 10): Mean age: M = 81 years Inclusion criteria: diagnosed with probable AD using NINCDS-ADRDA criteria or multiple infarct dementia; MMSE < 24; able to follow verbal and visual commands; mimic movements; and hear music. Medically cleared by physician; consent signed by family. Exclusion criteria: unable to sit in chair for 30 minutes; apathetic; would require change in medication during intervention
Interventions	Experimental Group: Intervention focused on strength training, balance, trunk movements and flexibility. Exercise routine supported with music

	<p>(music-based dance therapy) Type: Combined (Strength/Balance/Flexibility/Aerobic) Frequency (sessions/week): Daily Duration (min/session): 30 min Volume (total min/week): 210 min Time period: 12 weeks Intensity: --</p> <p>Attrition: 4% (0% Experimental, 9% Control) Exercise program adherence: --</p> <p>Therapy for Controls: Social visits (Social contact 1-on-1 conversation with therapist). Frequency: daily, activity duration = 30 minutes. Time period: 3 months</p>
Outcomes	1) MMSE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	Coin flipping
Allocation concealment (selection bias)	Unclear risk	No description of methods used to conceal allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The physiotherapist who was conducting both treatments evaluated the patients on cognition. However, the nurses who scored the patients on behaviour were all blind to the group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in control group unable to complete 3-month MMSE and ADS 6 due to hip fracture
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Attendance and adherence not stated

Venturelli et al. (2011)

Methods	6-month, randomly assigned experimental trial
Participants	<p>Country: Italy Location: Care Facility (nursing home - specifically Alzheimer care unit) Diagnosis: AD (DSM-4 diagnostic criteria) Dementia severity: moderate to severe (MMSE 5-15) Participants: Baseline N=24, Completed: N=21 Mean age (SD): 84.0 years % Male: 0</p> <p>Inclusion criteria: 65 years or older; dependent on assistance in 2 or more personal ADLs according to the Barthel index; MMSE maximum score of 15 and minimum of 5; absence of mobility limitations, minimum score of 23, according to the Performance Oriented Mobility Assessment</p>

	(POMA) index; and constant oxygen saturation during walking (SpO2 > 85%). According to the clinical dementia rating scale, all nursing home residents had to be in the later stages (CDR3-CDR4) of AD. Exclusion criteria: None stated.
Interventions	Experimental Group: walking Type: Aerobic-only Frequency (sessions/week): 4 Duration (min/session): 30 min Volume (min/week): 120 minutes (minimum of 30 minutes of moderate walking 4 times a week) Time period: 24 weeks Intensity: -- Attrition: Experimental Group = 1 (8.4%); Control Group = 2 (16.7%) Exercise program adherence: 93% Therapy for Controls: Standard Care (usual care at the home, which consisted of bingo, sewing, music therapy)
Outcomes	1) MMSE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Method of random selection not described
Allocation concealment (selection bias)	Low risk	Quote: "The head nurse of the ACU (not involved in the residents assessments) did the participants' randomization using StatsPlus for Macintosh"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "... members of the research team did not know to which group each participant had been assigned ... No one on the research team was present during the walking exercise"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Evaluation was done before and after the experiment period in a blind way"- not described well
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition: Experimental Group = 1 (8.4%) ; Control Group = 2 (16.7%) Reasons for attrition stated for each group
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Vreugdenhil et al. (2011)

Methods	4-month RCT
Participants	Country: Australia Location: Community (home) Diagnosis: AD (DSM-4 and NINCDS-ADRDA diagnostic criteria) Dementia severity: mild to moderate Participants: N=40 at baseline (all of whom completed) Mean age(SD): 74.1 years % Male: 40% (24 women and 16 men)

	<p>Inclusion criteria: diagnosed with dementia using DSM-IV criteria; diagnosed with AD with NINCDS-ARDRA criteria; from outpatient memory disorder clinic; community dwelling with live-in care provider/caregiver who could visit daily.</p> <p>Exclusion criteria: physical condition that could prevent participation; evidence of neurodegenerative disorder (other than AD); already in exercise program more than once a week (resistance or aerobic training); started dementia medications in last 3 months.</p>
Interventions	<p>Experimental Group: 10 simple exercises and 30 minutes of brisk walking; home-based exercises-- progressively became more challenging, and targeted strength and balance--and brisk walking under supervision of carer</p> <p>Type: Combined (Aerobic/Strength/Balance)</p> <p>Frequency (sessions/week): daily</p> <p>Duration (min/session): 30 minutes</p> <p>Volume (min/week): 210 minutes</p> <p>Time period: 16 weeks</p> <p>Intensity: "Moderate"</p> <p>Attrition: 0%</p> <p>Exercise program adherence: --</p> <p>Therapy for Controls: Standard care, no activity reported</p>
Outcomes	<p>1) MMSE</p> <p>2) Alzheimer's Disease Assessment Scale (ADAS-Cog)</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	Used computer-generated random allocation sequence
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants and the personnel to the intervention allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% of participants completed trial
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

(-) = unknown, AD = Alzheimer's disease, MD = mixed dementia, VaD = vascular dementia, UD = undefined dementia, MID = Multiple Infarct Dementia, NINCDS-ADRDA = national institute of neurological and communicative disorder and stroke & Alzheimer's diseases and related disorders association, ICD-10 = international classification of diseases and related health problems, DSM=diagnostic and statistical manual of mental disorders.

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