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ORIGINAL RESEARCH

Physical therapy in patients with Alzheimer's disease: a systematic review of randomized controlled clinical trials

Fisioterapia em pacientes com doença de Alzheimer: uma revisão sistemática de ensaios clínicos randomizados controlados

Fisioterapia en pacientes con enfermedad de Alzheimer: una revisión sistemática de ensayos clínicos aleatorizados controlados

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ABSTRACT | The objective of this study is to evaluate the effects of physical therapy on the cognitive and functional capacity of patients with Alzheimer's Disease (AD). This is a systematic review of randomized or *quasi*-randomized clinical trials, using the descriptors: AD, dementia and physical therapy. Two studies were included with a total of 207 participants. In study 1, no statistically significant difference was found on the mini-mental state examination (MMSE) (MD 0.0, 95%CI −5.76 to 5.76), neuropsychiatric inventory (MD −4.50, 95%CI −21.24 to 12.24) and Pfeffer instrumental activities questionnaire (MD 0.0 95%CI −6.48 to 6.48). In study 2, there was no statistically significant difference on the MMSE (MD −1.60, 95% CI −3.57 to 0.37), clock-drawing test (MD −0.20, 95%CI −0.61 to 0.21) and Alzheimer's Disease Assessment Scale – cognitive subscale (MD 1.0, 95%CI −2.21 to 4.21) after 12 months. There was no consistent evidence on the effectiveness of physiotherapeutic intervention in improving cognitive function and functional capacity of patients with AD. More studies should be conducted for better evidence.
Keywords | Alzheimer's Disease; Cognition; Activities of Daily Life; Physical Therapy; Systematic Review.

RESUMO | O objetivo do estudo é avaliar os efeitos da fisioterapia na capacidade cognitiva e funcional de pacientes com doença de Alzheimer (DA). Trata-se de revisão sistemática de ensaios clínicos randomizados ou *quasi*-randomizados utilizando os descritores: DA, demência e fisioterapia. Dois estudos foram incluídos, com um total de 207 participantes. No Estudo 1, não houve diferença estatisticamente significativa no miniexame do estado mental (MEEM) (MD 0,0, IC 95% 5,76–5,76), inventário neuropsiquiátrico (MD −4,50, IC 95% 12,24–21,24) e questionário de atividades instrumentais Pfeffer (MD 0,0 IC 95% −6,48 a 6,48). No Estudo 2, não houve diferença estatisticamente significativa no MEEM (MD −1,60, IC 95% −3,57 a 0,37), teste do desenho do relógio (MD −0,20, IC95% −0,61 a 0,21) e escala de avaliação da doença de Alzheimer – subitem cognição (MD 1,0, IC95% −2,21 a 4,21) após 12 meses. Não houve evidência consistente da eficácia da intervenção fisioterapêutica na melhora da função cognitiva e capacidade funcional na DA. Recomenda-se a produção de mais estudos para encontrar possíveis evidências.
Descritores | Doença de Alzheimer; Cognição; Atividades da Vida Diária; Fisioterapia; Revisão Sistemática; Ensaios Clínicos.

RESUMEN | El presente estudio tiene como objetivo evaluar los efectos de la fisioterapia en la capacidad cognitiva y funcional de pacientes con enfermedad de Alzheimer (EA). Se trata de una revisión sistemática de ensayos clínicos aleatorizados o casi-aleatorizados, en que se utilizó los descriptores: EA, demencia y fisioterapia. Se incluyeron dos

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estudios, con un total de 207 participantes. En el Estudio 1, no hubo diferencias estadísticamente significativas en el Miniexamen del estado mental (MEEM) (MD 0,0, IC 95%: 5,6 –5,76), en el inventario neuropsiquiátrico (MD –4,50, IC 95%: 12,24 –21,24) y en el cuestionario de actividades instrumentales de Pfeffer (MD: 0,0 IC 95% IC: –6,48 a 6,48). En el Estudio 2, no hubo diferencias estadísticamente significativas en el MEEM (MD –1,60, IC 95% –3,57 a 0,37), el test de diseño del reloj (MD –0,20, IC 95% –0,61 a 0,21) y la escala de evaluación de la enfermedad de Alzheimer: subítem de cognición (MD 1,0, IC 95% –2,21 a 4,21) tras 12 meses. No hubo evidencia consistente de la eficacia de la intervención fisioterapéutica en la mejora de la función cognitiva y de la capacidad funcional en la EA. Se recomienda realizar estudios adicionales para encontrar posibles evidencias.

Palabras clave | Enfermedad de Alzheimer; Cognición; Actividades de la Vida Diaria; Fisioterapia; Revisión Sistemática.

INTRODUCTION

As a consequence of changes in the epidemiological and demographic profiles of the population, there was an increase in the number of chronic diseases, mainly cognitive diseases including Alzheimer's disease (AD)[1-3]. AD is characterized by neurodegenerative changes associated with gradual deficits in cognitive function, memory, and behavioral changes. AD has a slow and progressive evolutionary characteristic, leading to a decline in the long-term functional capacity[4]. The main pathophysiological finding is the deposition of beta-amyloid protein, abnormal protein filaments, and synaptic decline with the activation of glial cells, including inflammatory processes in the central nervous system[5].

During the neuropathological progression of AD, the cholinergic activity is reduced, thereby affecting cognitive function and behavior owing to the lack of cholinergic neurons in the nucleus basalis of Meynert and significant reduction of gray matter in the bilateral prefrontal cortex, parietal lobe, and cingulate gyrus[6]. Genetic aspects are of great importance in the etiopathogenesis of AD, leading to somatic mutation in the tissues[7]. Among the main disabilities observed in AD, dementia, which affects about one in six individuals over 80 years of age, decreases the functional capacity, autonomy, and quality of life, thereby creating a great socioeconomic impact on the public health system.

AD must be approached by a multidisciplinary team using pharmacological and non-pharmacological interventions aimed at delaying the reduction in cognitive function, minimizing functional disabilities, as well as treating the non-cognitive manifestations. Among the non-pharmacological treatments, physical therapy plays an important role in reducing complications of AD. It mainly involves the use of aerobic or anaerobic exercises aimed to improve functional capacity, reduce medication used, decrease the risk of falls, and minimize the functional deficits during the course of the disease[8].

Multiple factors involved in AD lead to reduced autonomy and independence, thus increasing the risk of hospitalization, institutionalization, and death. Physical exercise can reduce the risk of disability and prevent cognitive decline and memory[9,10]. Although current evidence remains insufficient to conclude that physical therapy is effective for AD, the non-pharmacological approach continues to be a promising area of research for AD treatment. This review is important for physical therapists to be aware of evidence-based strategies available to provide the most effective physical therapy in AD.

Therefore, the aim of the review is to evaluate the efficacy of physical therapy in the cognitive and functional aspects of AD.

METHODOLOGY

We adhered to methods described in the Cochrane Handbook for Systematic Reviews of Interventions[11]. Our report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

Eligibility criteria

- Study designs: randomized controlled trials (RCTs) and quasi-randomized controlled trials (RCTs)
- Participants: patients with Alzheimer's disease
- Interventions: physical therapy involving aerobic or anaerobic exercises versus control group; physical therapy involving multimodal interventions; and physical therapy associated with drug treatment versus physical therapy alone.
- Control groups: placebo or standard rehabilitation
- Outcomes:
    - Global cognitive function tests: Any test or measure that evaluates cognitive function, such as the mini mental state examination (MMSE); Wechsler memory digit span forward and

digit span backward tests; Montreal cognitive assessment (MOCA); clock-drawing test; or neuropsychiatric inventory.
- Functional skills measured by any specific instrument, such as the timed up and go test, or the 6-minute walk test;
- Functional ability through activities of daily living measured by validated instruments such as the Barthel index or Pfeffer functional activities questionnaire;
- Balance measured by the Berg scale or Tinetti test;
- Quality of life measured through short form health survey (SF-36);
- Adverse events (such as orthostatic hypotension, fatigue, vertigo, dehydration, insomnia, syncope, etc).

Data sources and electronic searches

Using the Medical Subject Headings (MeSH), the terms selected were "Alzheimer's disease," "dementia," "physiotherapy", "non-pharmacological", "exercise", "rehabilitation", "therapy", "training", and "physical activity". The search strategy was run in Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, and Scopus. The search strategy for Ovid MEDLINE was: (Alzheimer Disease OR Alzheimer Sclerosis OR Alzheimer Syndrome OR Alzheimer Type Senile Dementia OR ATD OR Alzheimer Type Dementia OR Senile Dementia OR Primary Senile Degenerative Dementia OR Acute Confusional Senile Dementia OR Presenile Dementia OR Late Onset Alzheimer Disease OR Focal Onset Alzheimer Disease OR Familial Alzheimer Disease OR FAD OR Presenile Alzheimer Dementia OR Early Onset Alzheimer Disease) AND (Physical Therapy Specialty OR Physiotherapy Specialty). This strategy was adapted for the other databases and run up to October 2018. No language restrictions were imposed.

Selection of studies

Two authors of the review selected the titles and abstracts of the articles obtained from the electronic databases and excluded those that presented irrelevant outcomes for the review. Only complete articles were selected. Two independent authors screened the articles to identify the inclusion criteria and the studies that were ineligible for this review. If there was disagreement between the evaluators of the articles, a third evaluator was consulted.

Data extraction

Reviewers underwent calibration exercises, and worked in pairs to independently extract data from included studies. They resolved disagreement by discussion or, if necessary, with third party adjudication. Data were extracted using a pre-tested data extraction form: study design; participants; interventions; comparators; outcome assessed; and relevant statistical data. The authors of the included studies were contacted via e-mail for clarification on missing data or for more information.

Risk of bias assessment

Two review authors (CLSM and GJL) independently assessed the risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[12] and PEDro score (high quality=PEDro score 6-10; fair quality=PEDro score 4-5; poor quality=PEDro score≤3). We resolved disagreements by discussion or by consultation with another review author (RB). We assessed risk of bias according to the following domains.
- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded the risk of bias for each domain as high, low, or unclear and provided information from the study report, together with justification for our judgment, in the "Risk of bias" tables.

Data synthesis and statistical analysis

We analyzed all outcomes as continuous variables. We presented the results as mean of differences (MD) along with 95% confidence intervals, using fixed-effects models. The unit of analysis was each participant recruited for review.

We assessed variability in results across studies by using the I^2 statistic and the p-value for the chi square test of heterogeneity provided by Review Manager. We used Review Manager (RevMan) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses.

As we identified an inadequate number of studies, we did not perform a sensitivity (e.g., low versus high risk of bias) nor a subgroup analysis.

RESULTS

Study selection

A total of 38 articles (21 in Medline, 12 in EMBASE, 2 in CENTRAL and 3 in LILACS) were identified in the databases (Figure 1). After analyzing the titles and abstracts, full copies of the 13 complete studies eligible for inclusion in the review were obtained. Eleven studies were excluded[12-22] from the review because they were experimental studies, case series or cohort studies, or reviews. Two studies[23,24] – one[23] randomized clinical trial and one[24] quasi-randomized clinical trial – with a total of 207 participants achieved the minimum methodological requirements and were included in this review.

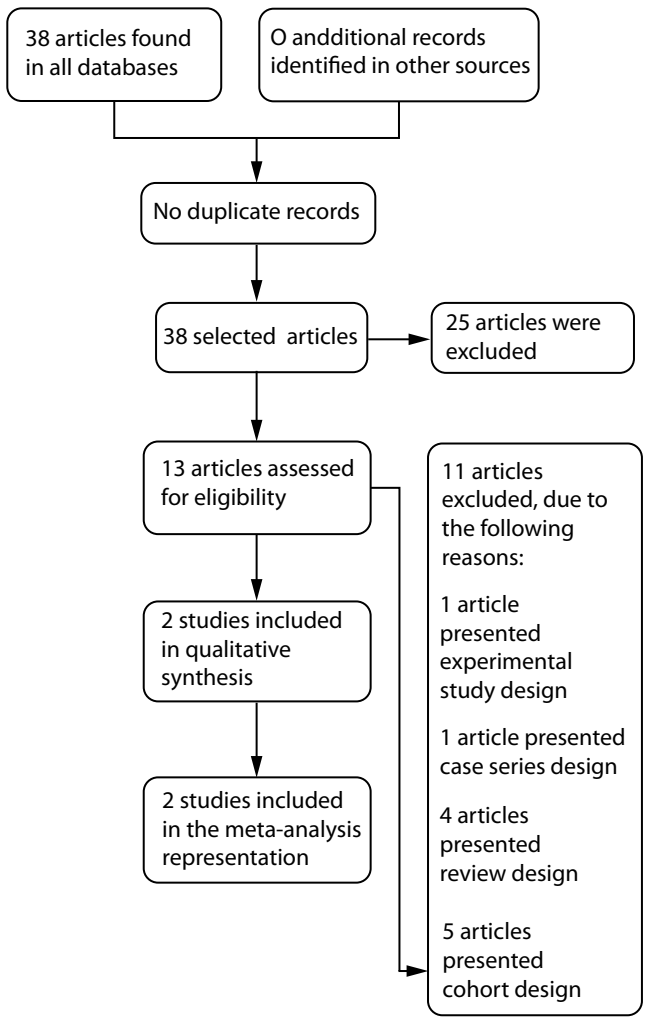

Figure 1. Flowchart of systematic review

Study characteristics

Andersen et al.[24] evaluated the use of donezepil (once a day, 5 to 10 mg) associated with the stimulation program (maximum of 250 sessions per year) compared to the placebo group in 180 participants with AD and MMSE score greater than or equal to 10 points. The age range was 65-100 years[23]. Nascimento et al.[25] evaluated an interdisciplinary rehabilitation program compared to the group that did not receive rehabilitation in 27 patients with Diagnosis of AD, dementia and hearing ability sufficient to comply with the procedures[24].

Type of intervention and follow-up

Patients in the study by Andersen et al.[24] underwent treatment with a program of stimulation therapy including physical, cognitive, sensory, and social stimulation activities. The program systematically included activities of daily living such as walking, housework, regular reading of books and newspapers, training in specific rooms, dancing, crossword puzzles, music therapy, and regular participation in community social life. More sophisticated activities such as reminiscence groups, Sudoku, aromatherapy, and sensory garden were also added, which allowed participants to move freely. This therapy was performed for a minimum of 30 minutes, 5 days a week, for a year (maximum of 250 sessions per year). All participants were prescribed donepezil or placebo (5 mg) once a day, progressing to 10 mg after 4 days. Adverse events were systematically recorded and the patients were monitored for 12 months[23].

Patients in the study by Nascimento et al.[25] underwent treatment through an interdisciplinary program that consisted of cognitive therapy, occupational therapy, and aerobic physical activity (moderate intensity). The intervention was performed three times a week in sessions composed of activities that benefited functional capacity, such as flexibility (stretching), muscular endurance, and balance. Various types of stimulation were applied, such as different photos placed on the wall and objects of different colors to be identified, memory sets and simple calculations, all combined with exercises. All participants performed the tasks together to stimulate social interaction and under the supervision of 3 to 6 physical educators or physical therapists. The heart rate during the session remained between 60% and 80% of the maximum heart rate. The follow-up lasted 6 months for all participants[24].

Type of study participants

Participants in the study by Andersen et al.[24] were individuals aged 65-100 years with a recent diagnosis of AD and an MMSE score greater than or equal to 10 points. In the initial evaluation, 43 participants had an MMSE between 10 and 20 points, 92 participants scored between 21 and 25 points, and 52 participants scored 26 or higher. Nascimento et al.[25] assessed patients with a clinical diagnosis of AD according to the NINCDS-ADRDA Alzheimer's criteria (1984) and dementia assessment according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R); ability to travel, preserved vision, and hearing ability sufficient to comply with the test procedures (spectacles and/or hearing aids were admissible). A physician trained in geriatric psychiatry confirmed the diagnosis and included patients with mild or moderate AD, and supervised all cognitive and neuropsychiatric evaluations while blinded to the allocation of patients in the treatment groups.

Type of outcomes

Andersen et al.[24] assessed patients using the following tests/metrics: changes in the MEEM score; Alzheimer's disease assessment scale, cognition (ADAS-Cog); and clock-drawing test. Nascimento et al.[25] evaluated the MMSE, neuropsychiatric inventory (NPI), and Pfeffer functional activity questionnaire.

Risk of bias in included studies

Figure 2 describes the risk of bias assessment for the RCTs. The major issues regarding risk of bias were problems of generation of allocation, concealment of randomization and blinding of participants and personnel in the study by Nascimento et al.[24] The PEDro score for Andersen et al.[24] was 9 (high quality) and for Nascimento et al.[25] was 7 (high quality).

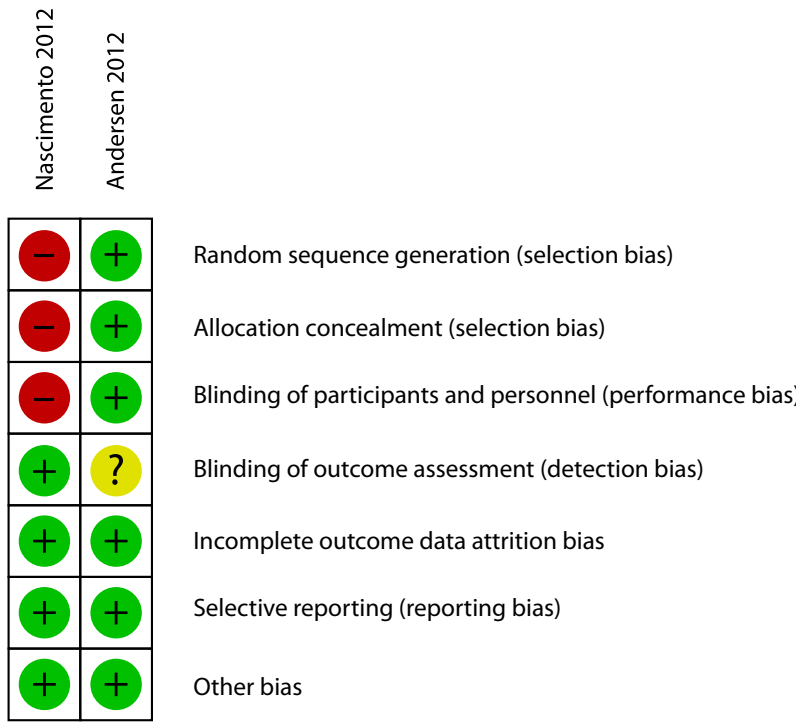

Figure 2. Risk of bias in included studies

Outcomes

Cognitive function

A statistically significant difference was found in the neuropsychiatric inventory for the pre-treatment physical activity group compared to control (MD, 11.0; 95% confidence interval [CI], 2.27-19.73). However, no statistically significant difference was found related to the MMSE scores or the neuropsychiatric inventory between the pre- and post-treatment groups (MMSE: MD, 0.0; 95% CI, -5.76-5.76; NPI: MD, -4.50; 95% CI, -21.24-12.24; Figure 3A)[24].

There was no statistically significant difference at baseline between the experimental and placebo groups in the MMSE (MD, -0.40; 95% CI, -2.22-1.42),

clock-drawing test (MD, 0.0; 95 % CI, –0.45-0.45), and ADAS-Cog (MD, 2.10; 95% CI, –1.13-5.33) scores (Figure 4A). After 4 months of treatment, there was no statistically significant difference in the MMSE (MD –0.90; 95% CI, –2.58-0.78), clock-drawing test (MD, –0.30; 95% CI, –0.71-0.11), and ADAS-Cog (MD, 2.90; 95% CI, –0.06-5.86) scores between the groups (Figure 4B). After 8 months of treatment, there was no statistically significant difference in the MMSE (MD, –0.70; 95% CI, –2.53-1.13) and ADAS-Cog (MD, 0.90; 95% CI, –2.58-4.38) scores between groups. The clock-drawing test score was significantly different between the groups (MD, –0.50; 95% CI, –0.96 to –0.04) (Figure 4C). After 12 months of treatment, there was no statistically significant difference in the MMSE (MD, –1.60; 95% CI, –3.57-0.37), clock test (MD, –0.20; 95% CI, –0.61-0.21), and ADAS-Cog (MD, 1.0; 95% CI, –2.21-4.21) scores between groups (Figure 4D)[23].

Activities of daily living

No statistically significant difference was found in the Pfeffer instrumental activities questionnaire between the pre- and post- treatment groups (MD, 0.0; 95% CI, –6.48-6.48) (Figure 3B). (A) Differences between control and experimental groups for cognitive function before and after treatment with physical activity; (B) Differences between control and physical activity groups for activities of daily living before and after treatment with physical activity

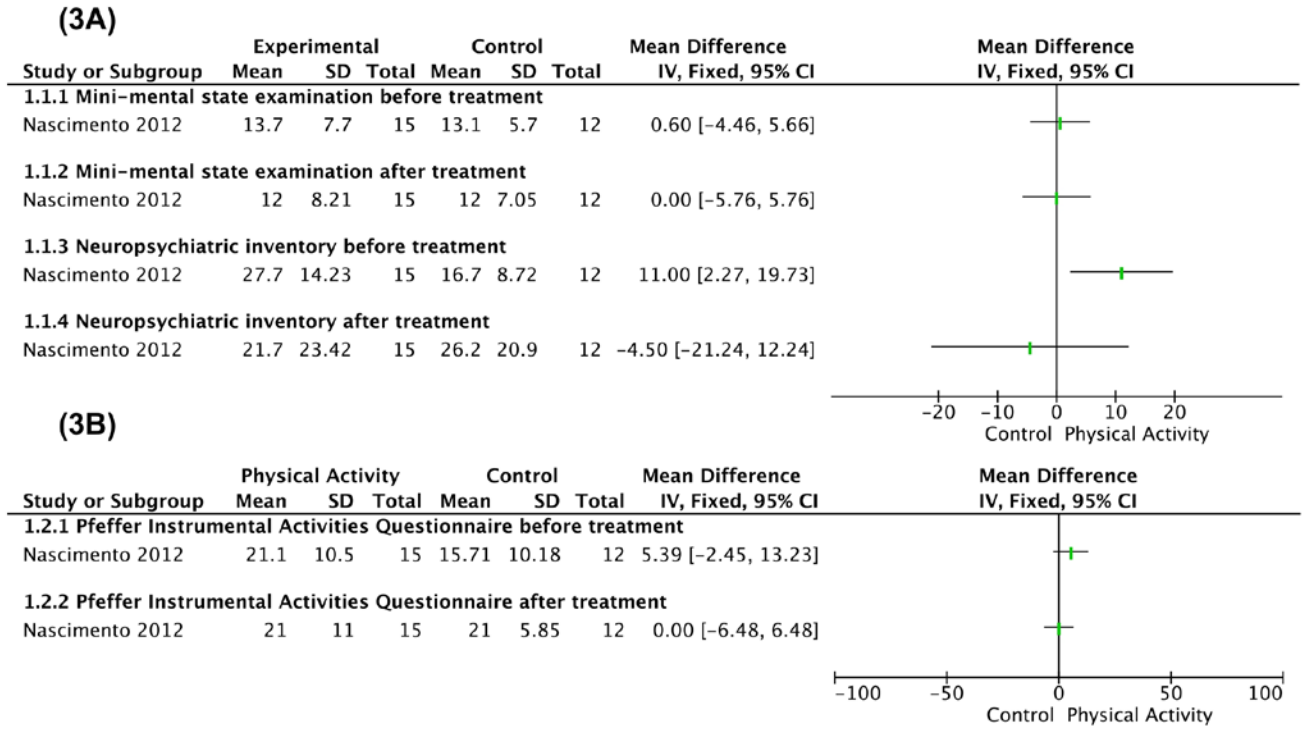

Figure 3. Cognitive and physical function before and after physical therapy

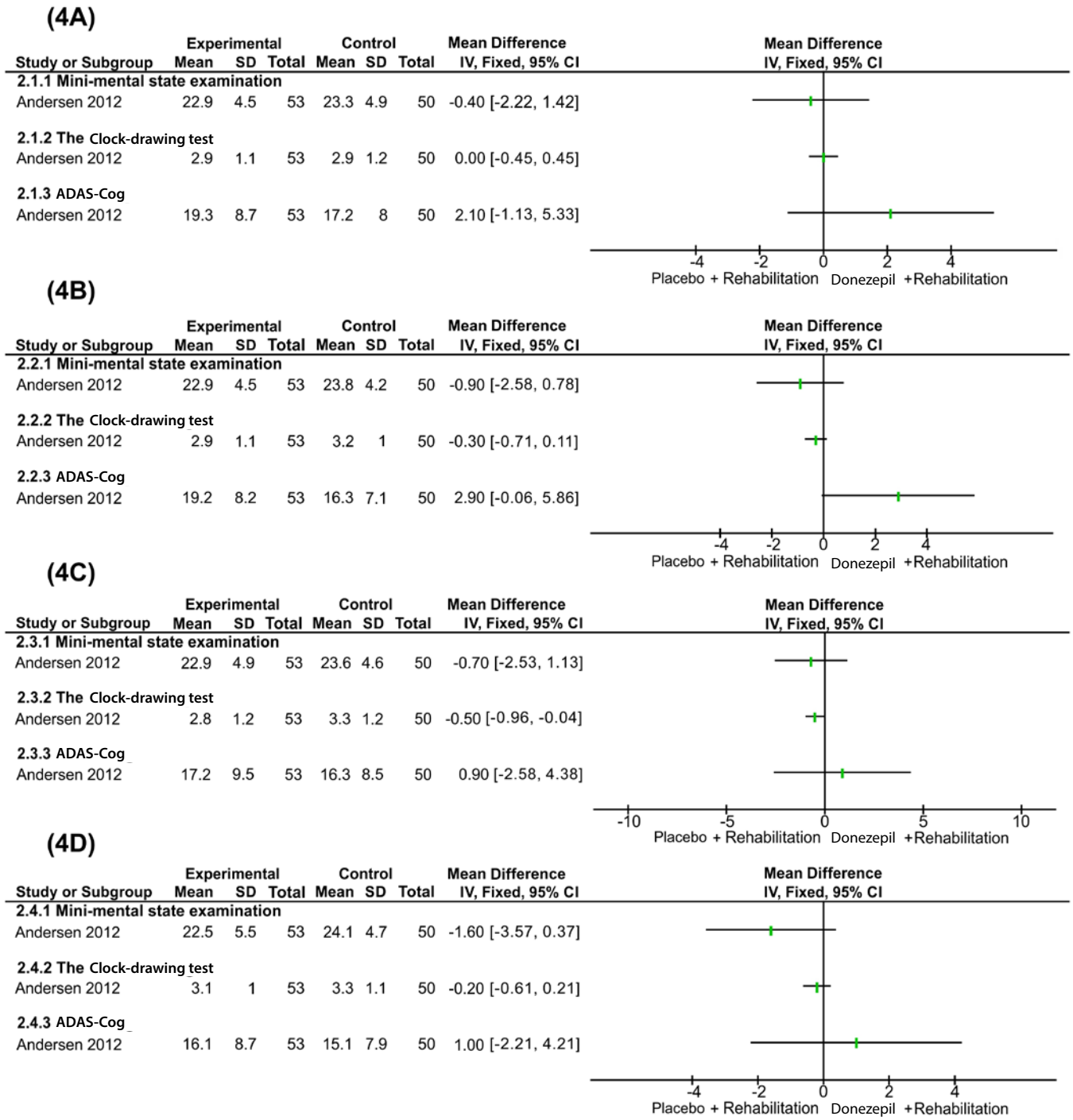

Figure 4. Cognitive function before and after physical therapy

(A) Cognitive function difference at baseline between the experimental and placebo groups; (B) Cognitive function difference at 4 months between the experimental and placebo groups; (C) Cognitive function difference at 8 months between the experimental and placebo groups; (D) Cognitive function difference at 12 months between the experimental and placebo group.

Effects of interventions

See summary of findings (Tables 1 and 2).

Table 1. GRADE evidence profile of cognitive function and activities of daily living in patients with AD for received physical therapy versus control group

Outcomes	Mean difference (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
Cognitive function Mini-mental state examination Neuropsychiatric inventory Nascimento 2012 study Follow-up: last day of therapy (discharge)	Before treatment MMSE 0.60 (−4.46 to 5.66) NPI 11.00 (2.27 to 19.73) After treatment MMSE 0.0 (−5.76 to 5.76) NPI −4.50 (−21.24 to 12.24)	27 (1 study)[a,b,c,d,e]	⊕⊖⊖⊖ **very low**
Daily life functions Pfeffer Instrumental Activities Questionnaire Nascimento 2012 study Follow-up: last day of therapy (discharge)	Before treatment Pfeffer 5.39 (−2.45 to 13.23) After treatment Pfeffer 0.00 (−6.48 to 6.48)	27 (1 study)[a,b,c,d,e]	⊕⊖⊖⊖ **very low**
GRADE Working Group grades of evidence **High quality:** Further investigations are very unlikely to change our confidence in the estimate of effect **Moderate quality:** Further investigations are likely to impact our confidence on the estimate of effect and may change the estimate **Low quality:** Further estimate of effect very likely to impact our confidence on the estimate of effect and is likely to change the estimate **Very low quality:** We are very uncertain about the estimate			

a: Meta-analysis could not be performed; only 1 study could be represented graphically; b: Quality was downgraded by 1 level because of very serious imprecision (selection bias, performance bias, small sample size); c: Although the confidence interval was narrow in some of the scales that evaluated the primary outcome, the magnitude of effect was controversial; d: Quality was downgraded by 1 level for uncertainty on both publication bias and heterogeneity (Heterogeneity: Chi^2=5.40, df=3 (p=0.14); I^2=44%), as included studies were insufficient to allow this analysis; e: Risk of bias in four domains was classified as low, and in three as high.

Table 2. GRADE evidence profiles of cognitive function in patients with AD for received physical therapy associated with drug treatment versus control group

Outcomes	Mean difference (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
Cognitive function Mini-mental state examination Cock-drawing test ADAS-Cog Andersen 2012 study Follow-up: 4 months, 8 months and 12 months after treatment	Baseline MMSE −0.40 (−2.22 to 1.42) Clock-drawing test 0.00 (−0.45 to 0.45) ADAS-Cog 2.10 (−1.13 to 5.33) 4 months MMSE −0.90 (−2.58 to 0.78) Clock-drawing test −0.30 (−0.71 to 0.11) ADAS-Cog 2.90 (−0.06 to 5.86) 8 months MMSE −0.70 (−2.53 to 1.13) Clock-drawing test −0.50 (−0.96 to −0.04) ADAS-Cog 0.90 (−2.58 to 4.38) 12 months MMSE −1.60 (−3.57 to 0.37) Clock-drawing test −0.20 (−0.61 to 0.21) ADAS-Cog 1.00 (−2.21 to 4.21)	180 (1 study)[a,b,c,d,e]	⊕⊕⊖⊖ **Moderate**
GRADE Working Group grades of evidence **High quality:** Further investigations are very unlikely to change our confidence in the estimate of effect **Moderate quality:** Further investigations are likely to impact our confidence on the estimate of effect and may change the estimate **Low quality:** Further investigations are very likely to important our confidence on the estimate of effect and is likely to change the estimate **Very low quality:** We are very uncertain about the estimate			

a: Meta-analysis could not be performed; only 1 study could be represented graphically; b: Quality was downgraded by 1 level because of very serious imprecision (detection bias and CI include effects suggesting benefits, as well as damage); c: The confidence interval was narrow in some of the scales that evaluated the primary outcome; the scores for the scales used in the study are similar for the two groups studied, at baseline and follow-up; d: There is no publication bias because unfavorable results and a low heterogeneity were presented: Chi^2=1.81, df=2 (p=0.40); I^2=0%; e: Risk of bias in all domains was generally classified as low.

DISCUSSION

Main findings

This review found a limited number of randomized clinical trials that demonstrate the efficacy of physical therapy treatment in improving the cognitive function of patients with Alzheimer's disease. In the study by Nascimento et al.[25], the authors observed that there was no benefit of physical therapy in improving the cognitive and functional function in patients with AD. While few studies have demonstrated the positive impact of physical therapy in patients with AD, we can infer that physical inactivity is related to risk factors such as smoking, inadequate eating habits, alcoholism, emotional stress, and cognitive impairment[24]. Some risk factors are also associated with a higher risk of cognitive decline, such as chronic diseases, hypercholesterolemia, and sedentary lifestyle, and may be reversed or attenuated by regular physical exercise[25].

Studies have shown that active people who perform some type of physical exercise have a lower risk of being affected by cognitive deficits than sedentary people, thereby acquiring increased brain plasticity process and resistance of the brain to lesions, as well as improving learning and functional capacity[26,27].

The benefit caused by physical exercise in cognitive functions is due to the improvement in cardiovascular function when there is a progressive decrease in oxygenation and tissue hypoxia over time leading to a cognitive decline. Physical activity and cardiorespiratory exercises minimize cognitive dysfunction in the acute phase of AD[28]. The maximal oxygen consumption (VO_2 max) is reduced in AD, and exercise has great benefit in cognition as it increases the VO_2 max in this population[29]. Studies have demonstrated an improvement in memory and executive function with an increase in the cardiorespiratory capacity, and its benefits are related with improvements in memory performance and changes in brain volume, manly in the bilateral hippocampus volume[30,31].

Regular physical activity has been recommended for the prevention and treatment of cardiovascular diseases (hypertension, insulin resistance, diabetes mellitus, dyslipidemia, and obesity), where physical inactivity and unfavorable habits are directly linked to the development of cognitive decline[32]. A meta-analysis of 54 randomized controlled trials examined the effect of aerobic exercise on blood pressure and found that this exercise modality reduces the systolic and diastolic pressures by 3.8 mmHg and 2.6 mmHg, respectively. In this sense, a reduction of only 2 mmHg in the diastolic pressure can substantially reduce the risk of chronic diseases and cognitive decline[33]. Aerobic exercise benefits the functional ability in individuals with early-stage AD. Furthermore, we found indirect evidence that exercise-related increases in cardiorespiratory fitness may be important to improve memory performance and reduce hippocampal atrophy[34].

In the study by Andersen et al.[24], donezepil associated with rehabilitation did not have a significantly different effect on the test scores, compared to when physical therapy was used alone. The multidisciplinary treatment for AD leads to improvement in the quality of life of the patient and his/her family, reducing cognitive deficits and behavioral changes. Over the years, pharmacotherapy in the treatment of AD has greatly evolved, with anticholinesterase drugs (donezepil, rivastigmine, epstatigmine, and galantamine) acting on the symptoms of the disease by improving the healthcare network. Complementing this therapy with rehabilitation could enhance the action of pharmacological treatment, leading to an improvement in cognitive performance, behavior, and quality of life[35]. However, these studies are limited by short follow-up period, retrospective design, poorly defined controls, and small sample sizes. In our study, there was no difference in cognitive performance between donepezil and placebo groups, regardless of standard pacing or therapy. The activities are very different in this study and do not follow the same line of learning; in this way, individuals would hardly have positive results regarding the effectiveness of the method.

Strengths and limitations

In the two studies included in this review, the patient groups, interventions, and relevant outcomes were addressed to prove the efficacy of physical therapy treatment using the MMSE score as the primary endpoint for cognitive function. The review does not report secondary outcomes such as disability and functional skills measured by specific instruments, as the timed up and go and 6-minute walk test scores; functional capacity through activities of daily living measured by validated instruments, such as the Barthel's index and Pfeffer functional activities questionnaire score; balance measured by the mean scores of the Berg and Tinetti scales; and quality of life through the SF-36 score.

Only two studies were included in this review; the total size was small, although a majority of the domains

evaluated were classified as presenting low risk of bias in relation to the methodological quality. The quality of evidence for the outcomes assessed in the two trials was very low, which lowered the quality from high to very low because of the presence of a serious risk of selection bias and inaccuracy (due to some events and small sample sizes). We cannot assess the publication bias and could not investigate heterogeneity as the included studies were insufficient to allow such analyses. The methodological quality of the two studies was reasonable, although the risk of selection bias was substantial (participants were distributed successively).

Implications

There was low quality of evidence to draw a consistent conclusion about the effectiveness and safety of physical therapy interventions in improving cognitive function and functional capacity in patients with Alzheimer's disease. The applicability of these results may be compromised as they were obtained from studies of small sample sizes. This evaluation underlines the need for well-designed trials in this area. Future clinical trials should be methodologically adequate and include standardized outcome measures such as functional skills, balance, and quality of life tests.

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