Revista ARACÊ
ISSN: 2358-2472

INFLUENCE OF PHYSICAL EXERCISE ON MOTOR AND COGNITIVE FUNCTION OF ELDERLY PEOPLE WITH ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW

https://doi.org/10.56238/arev7n4-176

Date of submission: 16/03/2025 **Date of publication:** 16/04/2025

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ABSTRACT

Introduction: Alzheimer's disease is neurodegenerative and results in the progressive death of neurons in regions responsible for memory, learning, and emotional behavior. The aging process favors the emergence of chronic noncommunicable diseases (NCDs) due to exposure to agents throughout life. With physical deterioration and loss of muscle mass, the risk of falls and fractures increases, leading to a worsening of quality of life and dependence on care. Therefore, the practice of physical exercise can help in the treatment of this disease, as well as in the prevention of falls and fractures. Objective: To evaluate the effectiveness of physical exercise, with the aim of improving cognitive motor coordination in elderly individuals diagnosed with Alzheimer's disease. Methods: This qualitative systematic review used the Medline/PubMed, Embase, Cochrane, Web of Science, and Scopus, databases and was guided by the PICOT question. Results: A total of 860 articles were found with the selected keywords, seven of which were found to be eligible for the criteria. Conclusion: The practice of physical exercise as a nonpharmacological treatment in the progression of Alzheimer's disease contributes to positive effects on motor and cognitive function in elderly individuals. However, the level of confidence in the conclusions regarding the outcomes examined shows low reliability, that is, little power of effectiveness.

Keywords: Physical exercise. Alzheimer's disease. Motor and cognitive function.

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ISSN: 2358-2472

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia and one of the most common neurodegenerative pathologies in elderly individuals, accounting for approximately 90% of dementia cases in this population [1]. It is a multifactorial disease, resulting from genetic and environmental factors, and characterized by cognitive and motor decline [2].

A more accurate method for identifying AD is the disease's classic triad, which involves the presence of senile plaques containing β-amyloid, neurofibrillary tangles with Tau protein, and neuronal loss in the hippocampus region [3]. However, a definitive diagnostic protocol for Alzheimer's disease can be performed only post mortem, when it is possible to detect amyloid and tau neurofibrillary tangles in the brains of deceased patients [4]. Clinically, impairment of episodic memory or involvement of other cognitive, behavioral, and neuropsychiatric domains are key criteria that must be met for a definitive diagnosis [5].

Thus, dementia is one of the leading causes of disability in elderly individuals, with significant impacts on the autonomy and quality of life (QoL) of people with dementia and their families [6]. The causes may stem from personal and contextual factors, contributing to the emergence of chronic noncommunicable diseases (NCDs), as well as Alzheimer's disease, which develops silently, causing a decline in cognitive and motor functions [7].

Owing to these significant impacts on the autonomy and QoL of elderly individuals [6], the physical deterioration caused by AD may increase the risk of falls and fractures, in addition to the loss of mobility, leading to greater dependence on care [8].

Current treatments for Alzheimer's disease aim to improve symptoms but do not cure dementia, as no cure has yet been found [9]. Therapeutic clinical treatment for AD focuses on improving the behavioral, cognitive, and noncognitive symptoms of the disease [3].

In Brazil, the Unified Health System (UHS), in Portuguese, *Sistema Único de Saúde* (SUS), provides free treatment for patients with AD, including medications such as memantine, galantamine, donepezil, and rivastigmine [10]. However, despite decades of research aimed at discovering drugs for AD and billions of dollars spent on clinical trials, there is still no single effective anti-AD drug [11]. New strategies to develop drugs to treat AD continue to fail in clinical trials [10, 11].

Growing evidence suggests that nonpharmacological interventions, specifically combining cognitive and physical training, may be effective in protecting against the decline in cognitive and brain functions in healthy aging, as well as in neurodegenerative diseases such as AD [12].

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ISSN: 2358-2472

Studies have confirmed that physical exercise can help in the treatment of Alzheimer's disease and that aerobic exercise in animal models beneficially modifies toxic proteins, such as β-amyloid and tau proteins, which are found in the brain [13, 14]. In this context, physical exercise has emerged as a tool for treating AD, mainly because it is capable of delaying the neurodegenerative process [15, 16].

Through a systematic review, it was possible to gather and analyze existing studies, providing a comprehensive view of the effects of exercise in elderly people with Alzheimer's disease. This review may contribute to the development of more efficient intervention protocols, aiming to identify exercises that provide superior results compared with those already studied in this population.

To assess the reliability of the results obtained, the Grade tool was used, which aims to analyze the level of scientific evidence and methodological quality of the selected studies, thereby determining the level of confidence in the conclusions presented regarding the outcomes examined. Thus, it was possible to classify the reliability of the information into categories such as high, moderate, low, or very low.

MATERIALS AND METHODS

STUDY DESIGN

This is a descriptive qualitative systematic review, in which, through the Picot strategy, the following question that guided us in this research was formulated: “What is the effectiveness and reliability of physical exercise aimed at improving motor and cognitive function in elderly individuals with Alzheimer’s disease?”

REGISTRATION AND PROTOCOL

This review was developed according to the *Cochrane Handbook for Systematic Review of Interventions* [17] and the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) [18]. The protocol of the review was registered in Prospero (International Prospective Register of Systematic Reviews), nº CRD42023437300.

ELIGIBILITY CRITERIA

For eligibility criteria, we present Figure 1, in the form of a flowchart, which illustrates the inclusion and exclusion criteria, formulated on the basis of the acronym Picot:

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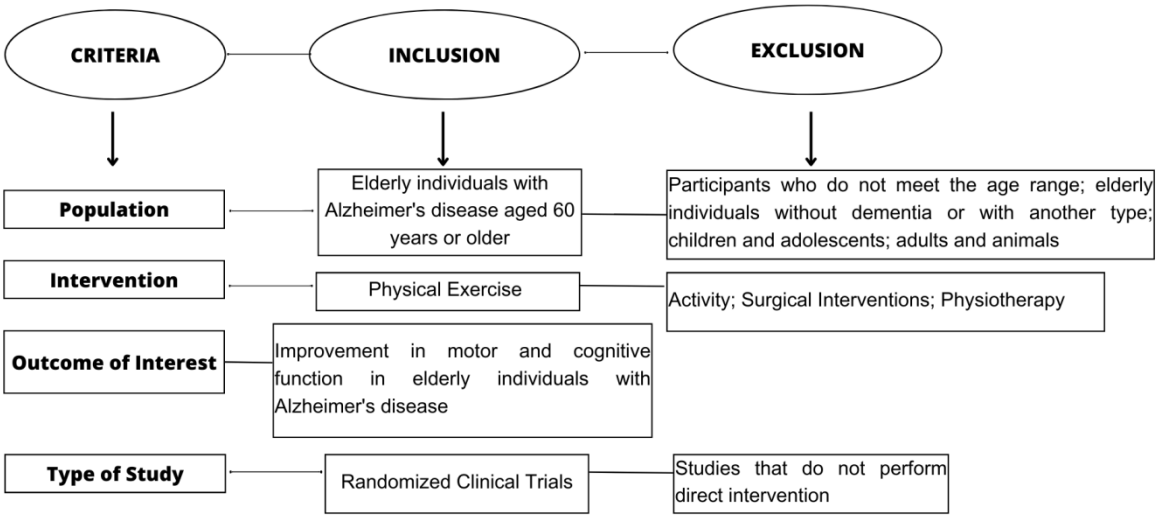
ISSN: 2358-2472

Figure 1. Flowchart — Inclusion and exclusion criteria.



SEARCH STRATEGY

The search and selection of articles were conducted by trained researchers with experience in systematic reviews and in physical exercise practices. The databases used for the research were *PubMed*, *Embase*, *Cochrane*, *Web of Science* and *Scopus*. There were no language restrictions, and no time duration was imposed as a criterion, since the number of studies is limiting and to avoid eliminating important information on the topic; however, for contextualization purposes, the years of each selected article will be presented. The descriptors chosen from the Health Sciences Descriptors (HSD) were employed and *medical subject headings* (MeSH) were used for each database: *"Elderly AND Exercises", "Elderly AND Physical Activity", "Elderly AND Aerobic Exercise", "Exercise Training AND Alzheimer Dementia"* and *"Elderly AND Alzheimer Dementias"*. From this search, articles that met the inclusion criteria mentioned in Figure 1 were included for full reading. Articles that did not have full text or whose access was private were contacted for requests for the complete article. The search for new studies was not updated, and the references of the selected articles were not explored to identify other studies as additional sources.

SELECTION OF STUDIES

The studies identified in the *PubMed*, *Embase*, *Cochrane*, *Web of Science* and *Scopus* databases were exported to the Rayyan platform (https://rayyan.ai/) [19].

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The initial search identified 860 publications. After the removal of duplicates, manual selection was performed by researchers on the basis of the inclusion and exclusion criteria. The full texts of the selected publications were evaluated for eligibility. Articles that did not meet the inclusion criteria were excluded and are presented in Table 1. Seven publications were included after the entire selection and extraction evaluation. The selection process of the studies is described in the flowchart (Figure 2).

DATA EXTRACTION

A guide was used to develop the data extracted from Cochrane for the following articles: study eligibility and setting and methods. The results were subsequently evaluated, and the studies were excluded, as shown in Table 2.

ASSESSMENT OF METHODOLOGICAL QUALITY (RISK OF BIAS)

For the risk of bias, the PEDro Scale was used, which was developed by Verhagen *et al*. (1998), with the purpose of assessing the methodological quality of clinical trials. The PEDro Scale was designed to be used in the evaluation of studies cited in articles indexed in the Physiotherapy Evidence Database (PEDro) [20]. The scale consists of 11 items divided into three categories, but only item 1 is not included in the evaluation count, as it is used to analyze the external validity of the studies, for example, if the eligibility criteria are specified in the text. Items 2 to 9 pertain to the analysis of risk of bias, and items 10 and 11 relate to statistical description. The methodological quality was assessed by two independent authors, who assigned a score to each item when it was satisfactory in the text. After each item was scored, conflicts were resolved by consensus. According to the final score, the methodological quality of a clinical trial is considered poor (<4); fair (4-5); good (6-8); or excellent (9-10) [21].

QUALITY OF EVIDENCE (GRADE TOOL)

The Grade tool (*Grading of Recommendations Assessment, Development and Evaluation*) [22] was used to assess the level of evidence and present the quality of the selected articles, clarifying if the confidence in the information provided for each analyzed outcome would be high, moderate, low, or very low. These levels represent the reliability of the presented effects. The assessment of methodological quality was conducted through

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the following domains: Nº of studies; study design; risk of bias; inconsistency; indirect evidence; imprecision; and publication bias.

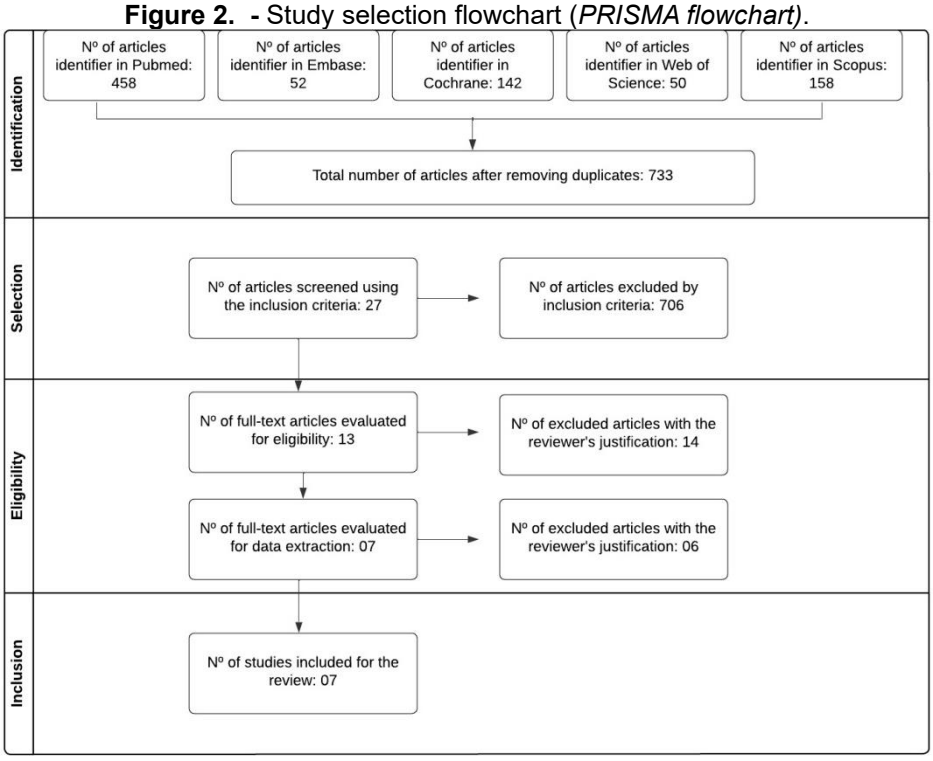
RESULTS

SEARCH RESULTS

A total of 860 records were identified from the initial search, combining all the prespecified databases. After 127 duplicates were removed, 733 articles remained, of which 127 records were excluded following title and abstract screening by two review authors on the Rayyan platform.

With the application of the inclusion criteria filters, 27 studies were selected for full-text review and subjected to eligibility assessment and data extraction. Figure 2 (*Prisma Flow*) outlines the process undertaken for study selection.

Figure 2. - Study selection flowchart (*PRISMA flowchart*).



For the eligibility process, 13 of the 27 selected studies were included, and 14 were excluded, as shown in Table 1. Three articles did not match the age range (Zhu *et al.*, 2022; Vidoni E. D. *et al.*, 2020; Yang Y. S. *et al.*, 2015); five studies had a mixed population or another type of dementia (Zhu *et al.*, 2022; Sanders L. *et al.*, 2020; Vijen I. L. *et al.*, 2020; Silva O. de F. *et al.*, 2019; Doi T. *et al.*, 2012); three trials did not match the outcome

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(Pedrinolla A. *et al.*, 2020; Yu F. *et al.*, 2012; Cezar C. de O. A. *et al.*, 2021) and four studies were not randomized clinical trials (Kin A. *et al.*, 2022; Panza A. G. *et al.*, 2018; Ben-Sodoun G. *et al.*, 2014; Ben-Sodoun G. *et al.*, 2016).

Table 1 – Articles excluded in the eligibility criteria

Authors	Title	Justification
Zhu *et al.* (2022)	Effect of 3-month Aerobic Dance on Hippocampal Volume and Cognition in Elderly people with Amnestic Mild Cognitive Impairment: A Randomized Controlled Trial.	–Population diagnosed with amnestic mild cognitive impairment. –Age range between 50 and 85 years.
Sanders L. *et al.* (2020)	Effect of low-and higt-intensidy physical exercise on physical and cognite function in older persons with dementia: A Randomized Controlled Trial.	–The study population includes all types of dementia, not just Alzheimer's disease.
Vijen I. L. *et al.* (2020)	Individual differences in the effects of physical activity on cognitive function in people with mild to moderate dementia.	–Study population diagnosed with vascular dementia, mixed type, and unspecified dementia.
Kin A. *et al.* (2022)	The molecular effects of environmental enrichment on Alzheimer's disease.	–It is not a randomized clinical trial.
Vidoni E. D. *et al.* (2020)	Aerobic exercise sustains performance of instrumental activities of daily living in early-stage Alzheimer's disease.	–Age range of 55 years or older.
Pedrinolla A. *et al.* (2020)	Exercise training improves vascular function in patients with Alzheimer's disease.	–The study outcome is to investigate the effects induced by exercise on vascular function.
Yu F. *et al.* (2012)	Improving recruitment, retention and adherence to 6-month cycling in Alzheimer's disease.	–The study outcome does not aim to improve cognitive motor coordination.
Cezar C. de O. A. *et al.* (2021)	Feasibility of reducing frailty components in older adults with Alzheimer's dementia: A Randomized Controlled Trial.	–The study outcome does not aim to improve cognitive motor coordination.
Panza A. G. *et al.* (2018)	Can exercise improve cognitive symptoms of Alzheimer's disease?	–Case-control study. Secondary research.
Silva O. de F. *et al.* (2019)	Three months of multimodal training contributes to mobility and executive function in elderly individuals with mild cognitive impairment, but not in those with Alzheimer's disease.	–The study population is not exclusively elderly individuals with Alzheimer's disease.
Ben-Sodoun G. *et al.* (2014)	Activité aérobie et environnement enrichi: perspectives pour le patient Alzheimer.	–It is not a randomized clinical trial.

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Doi T. *et al.* (2012)	Effects of multicomponent exercise on spatial-temporal gait parameters among the elderly with amnestic mild cognitive impairment: Preliminary results from a randomized controlled trial	–Population diagnosed with amnestic mild cognitive impairment.
Yang Y. S. *et al.* (2015)	The effects of aerobic exercise on cognitive function of Alzheimer's disease patients.	–Age range between 50 and 80 years.
Ben-Sodoun G. *et al.* (2016)	Physical and cognitive stimulation using an exergames in subjects with normal aging, mild and moderate cognitive impairment.	–It is not a randomized clinical trial.

For data extraction, out of the 13 included studies, seven full studies were accepted for review, and six were excluded, as shown in Table 2. Two articles included older adults who did not match the chosen age range (Morris *et al.*, 2017; Hoffmann K. *et al.*, 2015); one trial included older adults with another type of dementia (Arcoverde C. *et al.*, 2014); two studies were not completed (Blumen *et al.*, 2020; Yu F. *et al.*, 2014) and one study was not a randomized clinical trial (Frederiksen S. K. *et al.*, 2014).

Table 2 – Data extraction assessment.

Authors	Title	Justification
Blumen *et al.* (2020)	A social dancing pilot intervention for older adults at high risk for Alzheimer's disease and related dementias	–The study was not completed and has not yielded published results.
Morris *et al.* (2017)	Aerobic Exercise for Alzheimer's Disease: A Pilot Randomized Controlled Trial	–Adults aged 55 years in the early stages of cognitive decline related to Alzheimer's disease were included.
Yu F. *et al.* (2014)	Effects of aerobic exercise on cognition and hippocampal volume in Alzheimer's disease: study protocol of a randomized clinical trial	–The study was not completed.
Arcoverde C. *et al.* (2014)	Treadmill training as an additional treatment for Alzheimer's disease: A randomized controlled pilot study	–Elderly individuals with mixed dementia were included, in addition to those with Alzheimer's disease.
Hoffmann K *et al.* (2015)	Moderate to high intensity physical exercise in patients with Alzheimer's disease: a randomized clinical trial	–Elderly individuals aged between 50 and 90 years were included.
Frederiksen. S. K. *et al.* (2014)	Moderate to High Intensity Aerobic Exercise in Patients With Mild to Moderate Alzheimer's Disease: A Pilot Study	–It is not a randomized clinical trial.

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STUDIES INCLUDED

Seven articles were included; all were randomized clinical trials (RCTs), with a total sample size of 509 participants. Four trials have been conducted in the USA (Yu F. *et al.*, 2021, 2013, 2020; Padala K. *et al.*, 2017); one in Finland (Ohman H. *et al.*, 2016); one in Spain Santana-Sosa E. *et al.*, 2008); and one in Italy (Pedrinolla A. *et al.*, 2018). The sample size ranged from 16 participants (Santana-Sosa E. *et al.*, 2008) to 210 participants (Ohman H. *et al.*, 2016), all aged 60 years or older. The most commonly prescribed type of exercise for intervention was aerobic exercise, which varied between cycling and strength training, and was performed at least three times per week. Notably, none of the clinical trials included anaerobic interventions, as the proposed duration for each exercise was long.

The duration ranged from 20-90 minutes at moderate intensity, during which older adults were supervised by professionals in 100% of the trials.

PARTICIPANTS

The age of the participants ranged from 70 years (Santana-Sosa E. *et al.*, 2008) to 78±8 years (Yu F. *et al.*, 2013). The percentage of female participation in the trials ranged from 62.5% (Santana-Sosa E. *et al.*, 2008) to 81% (Padala K. *et al.*, 2017).

INTERVENTIONS

Among the seven included trials, three were conducted in a community setting (Ohman H. *et al.*, 2016; Pedrinolla A. *et al.*, 2018; Padala K. *et al.*, 2017), one in a nursing home (Santana-Sosa E. *et al.*, 2008) and three in a gym and elderly facility (Yu F. *et al.*, 2021, 2013, 2020).

Six studies implemented group interventions, and only one did not include a control group (Yu F. *et al.*, 2013). The most common intervention is aerobic exercise (cycling, walking) (Yu F. *et al.*, 2021; 2013; 2020; Ohman H. *et al.*, 2016; Pedrinolla A. *et al.*, 2018; Padala K. *et al.*, 2017). One trial included yoga as a physical exercise, combined with strength training (Padala K. *et al.*, 2017) and two trials included resistance training and other combinations (Ohman H. *et al.*, 2016; Santana-Sosa E. *et al.*, 2008). Five trials tested exercises three times per week (Yu F. *et al.*, 2021; 2013; 2021; Santana-Sosa E. *et al.*, 2008; Pedrinolla A. *et al.*, 2018); two trials tested exercises twice per week (Ohman H. *et al.*, 2016) and five days per week (Padala K. *et al.*, 2017).

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Two trials tested exercises lasting 20 to 50 minutes per session (Yu F. *et al.*, 2021; 2020); with the maximum time per training session being 90 minutes (Pedrinolla A. *et al.*, 2018). The duration of each study ranged from three months (Santana-Sosa E. *et al.*, 2008) to one year (Ohman H. *et al.*, 2016).

OUTCOME MEASURES

The main characteristics of each trial were separated into seven columns regarding physical exercise and Alzheimer's disease, as shown in Table 3. All trials reported results on the decline of global cognition and motor function in participants (Yu F. *et al.*, 2021; 2013; 2020; Ohman H. *et al.*, 2016; Santana-Sosa E. *et al.*, 2008; Pedrinolla A. *et al.*, 2018; Padala K. *et al.*, 2017); three studies reported outcomes related to behavioral and psychological symptoms (Yu F. *et al.*, 2021; 2013; Pedrinolla A. *et al.*, 2018); two trials reported improvements in quality of life (Yu F. *et al.*, 2021; Padala K. *et al.*, 2017); four trials reported improvements in the ability to perform activities of daily living (Yu F. *et al.*, 2013; Santana-Sosa E. *et al.*, 2008; Pedrinolla A. *et al.*, 2018; Padala K. *et al.*, 2017); and one study reported an improvement in VO2 max (Yu F. *et al.*, 2020).

Table 3 – Main features of the selected articles.

Authors	Sample (*n*)	Intervention	Frequency	Variables analyzed	Assessment tool	Results
Yu F. *et al.* (2021)	96 elderly	**Intervention Group (n=64)** Cycling **Control Group (n=32)** Stretching Range of Motion Exercises	**Intervention Group** • - 72 sessions (6 months) • - 3 times a week • - 20-50 minutes • - 50-75% HRR or 9-15 on the 6-20 RPE scale **Control Group** - <20% HRR or <9 RPE	- Global Cognition • - Episodic Memory • - Executive Function • - Attention • - Processing Speed • - Language	- ADAS-Cog - Logical Memory Subtest • - Verbal Learning Test Hopkins - Trail Making Test part b (TMT) - Exit Interview - 25 (EXIT-25) - Executive Clock Drawing Task - Wechsler Adult Intelligence Scale-Revised (WAIS-R) - WAIS-Third Edition Digit	- (+) Reduction in global cognition decline. - (+) Quality of life. - (+) Physical function. - (+) Behavioral and psychological symptoms.

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					Symbol e TMT part A - Controlled Oral Word Association	
Yu F. *et al.* (2013)	26 elderly	Cycling	- 65-75% HRR - 3 times a week. - 6 months. - 45 minutes. **Elderly individuals using medications that may alter heart rate or have irregular heartbeat** - 12-14 on the 6-20 RPE scale	- Global Cognition - Decline in the ability to perform daily activities • - Manifestation of behavioral and psychological symptoms of dementia • - Caregiver distress	- ADAS-Cog - Disability in Alzheimer's disease (DAD) - Severity of NPI-Q (BPSD) - NPI-Q Distress	• - (+) Reduction in cognitive decline. • - (+) Reduction in the decline of the ability to perform daily activities. • - (+) Manifestation of behavioral and psychological symptoms of dementia. • - (+) Reduction in caregiver distress.
Yu F. *et al.* (2020)	78 elderly	**Intervention Group (n=53)** Cycling **Control Group (n=25)** Stretching	**Intervention and Control Group** - 50-75% HRR or 9-15 on the 6-20 RPE scale. - 20-50 minute. - 3 times a week - 72 sessions (6 months)	-Aerobic Fitness - Global Cognition - Vo2max	- ADAS-Cog - SWT - 6MWT - Cycle ergometer - Polar Wireless HR Monitor	• - (+) Vo2max. • - (+) Aerobic fitness. • - (+) Global cognition.
Ohman H. *et al.* (2016)	210 elderly	**Home Exercise Group (n = 70)** and Exercise Group **(n=70)** Aerobic, resistance, balance, and strength training. **Control Group (n=70)** Usual care	**Home Exercise Group and Exercise Group** - 2 times a week - 1 year - 60 minute	- Cognitive function - Physical Fitness • - Executive Function • - Semantic Memory	- CDT - VF - CCD - MME - SPPB	• - (+) Physical functioning. • - Cognitive function.
Santana-Sosa E. *et al.* (2008)	16 elderly	**Exercise Group (n=8) and Control Group (n=8)** Resistance exercises, flexibility, joint mobility, and balance/coordination .	**Both** - 36 sessions - 12 weeks - 75 minute - 3 times a week	- Muscle strength and flexibility • - Agility and balance • - Endurance fitness	- Senior Fitness Test • - Katz Score • - Barthel Index • - Tinetti Scale	• - (+) Significant improvement in overall functional capacity. • - (+) Ability to

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				• - Ability to perform daily activities - Cognitive function		perform daily activities. • - Cognitive function.
Pedrinolla A. *et al.* (2018)	53 elderly	**Exercise Group (n=27)** Aerobic and Strength Training **Cognitive Training Group (n=26)** Cognitive Stimulation	**Both** - 72 sessions (6 months) - 70% HR - 90 minute - 3 times a week	- Gait (speed, stride length, single support, and double support). - Cw • - Cognitive stimulation	- Gait Rite System - WS1 - WS2 - WS3 - Cognitive Stimulation Therapy	• - (+) > Increased walking speed. • (+).> Increased ability to perform daily activities. • (+) < Decreased behavioral disturbances. • (+) < Slower natural progression of cognitive impairment.
Padala K. *et al.* (2017)	30 elderly	**Wii-fit Group (n=15)** Yoga, strength training, aerobic exercise, and balance. **Walking Group (n=15)** Walking at a self-selected pace.	**Both** - 16 weeks - 30 minute - 5 days a week	- Balance -Fear of falling - Quality of life - Cognitive -Functional status	- Berg Balance Scale • - Balance Confidence Scale • - Fall Efficacy Scale • - Quality of Life-AD • - Modified Mini-Mental State Examination	- (+) > Improved balance. - (+) < Reduced fear of falling. - (+) > Improved quality of Life. - Cognitive Decline. - (+) Functional status. - (+) Daily activity.

Abbreviations: HRR = Heart Rate Reserve; RPE = Borg Ratings of Perceived Exertion; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognition; BPSD = Behavioral and Psychological Symptoms of Dementia; NPI-Q = Neuropsychiatric Severity Inventory; SWT = Shuttle Walk Test; 6MWT = 6-min walk test; VO2máx = Maximal Oxygen Consumption; CDT = Clock Design Test; VF = Verbal Fluency; CCD = Clinical Classification of Dementia; MME = Mini Mental Status Exam; SPPB = Short Physical Performance Battery; WS1 = First Walking Speed; WS2 = Second Walking Speed; WS3 = Third Walking Speed e CW = Cost of Walking.

Table 4 presents the risk of bias for each included trial, as assessed by seven criteria. The first criterion was not included in the final sum, but all seven trials were scored. From the second to the fifth criterion, only one trial did not score (Yu F. *et al.*, 2013); in the

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sixth criterion, four scored (Yu F. *et al.*, 2021; 2013; 2020; Pedrinolla A. *et al.*, 2018); in the seventh criterion, only two trials scored (Yu F. *et al.*, 2021; Pedrinolla A. *et al.*, 2018); in the eighth criterion, three scored points (Yu F. *et al.*, 2020; Santana-Sosa E. *et al.*, 2008; Padala K. *et al.*, 2017); in the ninth criterion, three studies scored (Yu F. *et al.*, 2013; Pedrinolla A. *et al.,* 2018; Padala K. *et al.*, 2017); in the tenth criterion, only one trial did not present satisfactory results (Yu F. *et al.*, 2013); and in the final criterion, two trials did not score (Yu F. *et al.*, 2020; Pedrinolla A. *et al.*, 2018).

In the end, the methodological quality of the trials varied from a high risk of bias (Yu F. *et al.*, 2013) to a low risk of bias (Yu F. *et al..*, 2021; Pedrinolla A. *et al.*, 2018; Padala K. *et al.*, 2017).

Table 4 – Assessment of Methodological Quality.

Authors	1	2	3	4	5	6	7	8	9	10	11	Total
Fang Yu *et al.* (2021)	1	1	1	1	1	1	1	0	0	1	1	8/10
Fang Yu *et al.* (2013)	1	0	0	0	0	1	0	0	1	0	1	3/10
Fang Yu *et al.* (2020)	1	1	1	1	1	1	0	1	0	1	0	7/10
Ohman H. *et al.* (2016)	1	1	1	1	1	0	0	0	0	1	1	6/10
Santana-Sosa E. *et al.* (2008)	1	1	1	1	1	0	0	1	0	1	1	7/10
Pedrinolla A. *et al.* (2018)	1	1	1	1	1	1	1	0	1	1	0	8/10
Padala K. *et al.* (2017)	1	1	1	1	1	0	0	1	1	1	1	8/10

The Grade tool was used to assess the quality of evidence of the trials, as presented in Table 5.

The quality of evidence was rated as "very low" because the results were classified as severe, very severe, or highly suspicious in three assessment domains.

For the risk of bias, two levels were downgraded for scores below seven, which were classified as serious, since out of the seven trials, only one scored three (Yu F. *et al.*, 2013) and the other scored six (Ohman H. *et al.*, 2016).

The inconsistency domain was rated as very serious because all seven trials exhibited heterogeneity, making it impossible to perform a meta-analysis of the studies. All trials involved the same population diagnosed with Alzheimer's disease and aimed at improving cognitive motor coordination; however, the interventions and assessment methods were conducted differently. Three studies used cycling as physical exercise (Yu F.

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et al., 2021; 2013; 2020), whereas four alternated with strength, endurance, and aerobic exercises (Ohman H. *et al.*, 2016; Santana-Sosa E. *et al.*, 2008; Pedrinolla A. *et al.*, 2018; Padala K. *et al.*, 2017). Finally, the protocol numbers for four articles were not found (Yu F. *et al.*, 2013; 2020; Ohman H. *et al.*, 2016; Santana-Sosa E. *et al.*, 2008); one trial did not present an evaluation listed in the protocol objectives (Yu F. *et al.*, 2021). According to these results, two levels were downgraded in the publication bias domain, which were considered highly suspicious.

Table 5 – Summary of Results – Grade.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study Design	Risk of Bias	Inconsistency	Indirect Evidence	Imprecision	Other considerations			Relative (95% CI)	Absolute (95% CI)		
Improvement of cognitive motor coordination (assessed with motor and cognitive tests)												
7	Randomized clinical trials	Severe[a]	Very Severe[b]	Not Severe	Not Severe	Highly suspicious publication bias [c]	509		-	Not Combined	⨁◯◯◯ Very Low	

CI: Confidence interval
Explanations
a. Yu F. *et al.* (2013) did not score in domains 2,3,4,5,7,8, and 10, whereas Ohman H. *et al.* (2016) did not score in domains 6,7,8 and 9 in the methodological evaluation.
b. The seven articles are heterogeneous, making it impossible to conduct a meta-analysis.
c. The protocol numbers for the authors Yu F. *et al.*, (2013; 2020), Ohman H. *et al.*, (2016) and Santana-Sosa E. *et al.*, (2008) were not found. In the study by Yu F. *et al.*, (2021) an evaluation that should have been in the study's objectives was not found in the results.

DISCUSSION

SUMMARY OF THE MAIN RESULTS

The objective of this review was to analyze the effectiveness and reliability of physical exercise aimed at improving motor and cognitive function in elderly individuals with Alzheimer's disease. In addition to gathering and analyzing existing studies and ensuring a more comprehensive view of the effects of exercise on elderly individuals with AD, it aims to contribute to the development of more effective intervention protocols, where, through the analysis of the reliability of the results obtained, some of the exercises employed for this population should demonstrate a superior effect compared with others.

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After the intervention proposed by the authors was analyzed, moderate-intensity aerobic exercise, which was practiced three times a week with a duration varying from 20-90 minutes, was the most commonly prescribed exercise among the articles.

The seven articles showed positive results in motor function, whereas three did not demonstrate positive statistical power for improvement in cognitive function (Ohman H. *et al.*, 2016); (Santana-Sosa E. *et al.*, 2008) and (Padala K. *et al.*, 2017).

In the study by Ohman H. *et al.* (2016), the primary goal was to assess the physical functioning of elderly individuals; however, the cognitive aspects were limited, as cognitive domains such as semantic memory and executive function were not measured. However, they observed a small effect of the intervention on cognition, seen only in the clock drawing test, which is widely used in neuropsychological assessments aimed at investigating dementia syndromes in elderly individuals [23]. Although cognitive function is limited, this test assesses various cognitive dimensions [24].

The same occurred in the studies by Santana-Sosa E. *et al.* (2008) who reported clinically relevant findings in the improvement of the ability to perform daily activities. For a more conclusive response regarding the improvement in cognitive function, the authors suggest that more evidence is needed.

The study by Padala K. *et al.* (2017) prioritized working on balance as the main objective, and as secondary objectives, improvements in fall risk, functional status, quality of life, and cognition of elderly individuals.

According to the results, the authors achieved the proposed main objective. Although, for the secondary objectives, the fall risk and quality of life of the elderly were positive in the first eight weeks of the study, this effect was not sustained at 16 weeks. For cognition, this type of intervention and frequency did not have a significant effect between the groups, as duration of six months is considered insufficient to induce cognitive changes [25]. However, some authors have already shown that physical exercise of sufficient intensity and duration (i.e., approximately 3 months of moderate-intensity aerobic exercise, with sessions lasting no less than 20 minutes) seems capable of triggering neurogenesis, which enhances synaptic plasticity and creates new synapses and neural circuits that, ultimately, may contribute to optimizing brain plasticity and fitness [26].

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EFFECTS OF PHYSICAL EXERCISE ON GLOBAL COGNITION

The studies by Yu F. *et al.* (2013; 2020; 2021) used cycling as the intervention exercise, and performed three times a week, varying from 20-50 minutes in duration. In the study by Pedrinolla A. *et al.* (2018), a combination of aerobic exercises with strength training was used three times a week for 90 minutes. The four trials reported satisfactory results on global cognition, agreeing with authors who presented positive effects of exercise in previous trials on cognition, where the practice of exercise was daily or three times a week [27].

All of these studies used aerobic exercise as the means of intervention, which is consistent with the results of other clinical studies that demonstrated that aerobic activity improved or stabilized global cognition [28]; moreover, exercise has been demonstrated to mitigate cognitive decline and improve synaptic dysfunction [29]. Another study highlighted the benefits of aerobic exercise, such as cycling, which improved in cognitive function and quality of life in elderly individuals [30].

EFFECTS OF PHYSICAL EXERCISE ON PHYSICAL FUNCTION AND QUALITY OF LIFE IN ELDERLY PEOPLE WITH ALZHEIMER'S DISEASE

The seven articles reported positive results in the domains of physical function; in particular, two articles (Yu F. *et al.*, 2021); (Padala K. *et al.*, 2017) reported beneficial results in the quality of life of elderly individuals.

Studies in elderly individuals with Alzheimer's disease have also shown that aerobic exercise improves physical function and the behavioral and psychological symptoms of dementia [31]. Furthermore, as shown in the studies by Yu F. *et al.*, (2021), aerobic exercise has a low profile of adverse events in elderly individuals with AD.

Four studies adopted a combination of aerobic exercises with strength and resistance training, ranging from daily sessions (Padala K. *et al.*, 2017) to three times a week (Santana-Sosa E. *et al.*, 2008); (Pedrinolla A. *et al.*, 2018) with a duration of 30-90 minutes, showed positive effects on the physical function of elderly individuals. The literature indicates that programs combining aerobic exercises and muscle strengthening can improve strength, balance, and mobility [32].

Additionally, systematic reviews suggest that structured exercise, such as resistance and aerobic training, promotes not only physical function but also mood and quality of life [33].

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EFFECTS OF PHYSICAL EXERCISE ON BEHAVIORAL AND PSYCHOLOGICAL DISORDERS

Three studies (Yu F. *et al.*, 2021; 2013) and (Pedrinolla A. *et al.*, 2018) measured behavioral and psychological disturbances via the Neuropsychiatric Inventory-Caregiver. The practice of physical exercise strongly affects the mental health of individuals and, to some extent, can alleviate psychological problems [34]. Furthermore, higher levels of sedentary time and lower levels of physical fitness are associated with deterioration in mental health in the general population [35].

Both studies reported improvements in behavioral and psychological symptoms, confirming what a systematic review indicated about regular exercise practices and demonstrating a reduction in signs of aggression, anxiety, and depression, which are common symptoms in patients with AD [36].

Furthermore, the habit of engaging in physical exercise, with an emphasis on aerobic activity, may have a neuroprotective effect, helping to improve brain function [37], and the effects of exercise on brain oxygenation provide compelling evidence of the role of physical activity in maintaining and improving brain health [38].

METHODOLOGICAL ASSESSMENT

For the analysis of the methodological evaluation of the seven selected clinical trials, four (Yu F. *et al.*, 2013; 2020); (Ohman H. *et al.*, 2016) and (Santana-Sosa E. *et al.*, 2008) presented scores below eight. One article (Yu F. *et al.*, 2013) presented high risk of bias, according to the PEDro judgment criteria, scoring below seven domains. The trials that scored six (Ohman H. *et al.*, 2016) or seven (Yu F. *et al.*, 2020); (Santana-Sosa E. *et al.*, 2008) did not implement blinding of the intervention and/or did not clearly present the outcome measures.

Only three articles (Yu F. *et al.*, 2021); (Pedrinolla A. *et al.*, 2018) and (Padala K. *et al.*, 2017) presented scores of eight. The first study (Yu F. *et al.*, 2021) had a sample loss of over 15% and did not clarify in its outcome measures whether the data for at least one key outcome were analyzed. The second study (Pedrinolla A. *et al.*, 2018), also had a sample loss of over 15%, failing to score on the eleventh statistical domain of the PEDro scale. The third study (Padala K. *et al.*, 2017) did not ensure the blinding of either the therapists or all the study assessors, raising concerns about bias.

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Another limiting factor was that, of the seven articles, only three (Yu F. *et al.*, 2021); (Pedrinolla A. *et al.*, 2018) and (Padala K. *et al.*, 2017) had registration numbers. Although the final average of the articles in the methodological evaluation was considered good, in terms of evidence quality, the articles presented a high risk of serious bias.

QUALITY OF EVIDENCE

The distinguishing factor of this review was the use of the Grade system to analyze the certainty of evidence in the articles, even without conducting a meta-analysis, owing to the lack of homogeneity among the articles included in the study.

With respect to the risk of bias, the articles presented proper randomization, however, five articles (Yu F. *et al.*, 2013; 2020); (Ohman H. *et al.*, 2016); (Santana-Sosa E. *et al.*, 2008) and (Padala K. *et al.*, 2017) did not ensure the blinding of subjects (Yu F. *et al.*, 2013), therapists (Ohman H. *et al.*, 2016), (Santana-Sosa E. *et al.*, 2008), (Padala K. *et al.*, 2017) and assessors (Yu F. *et al.*, 2013; 2020); (Ohman H. *et al.*, 2016); (Santana-Sosa E. *et al.*, 2008); and (Padala K. *et al.*, 2017).

In the Grade system, levels are downgraded when the score is below seven, which are evaluated as serious. Since it was not possible to perform a meta-analysis, the certainty of evidence among the articles was affected, with inconsistency being considered very serious, as the articles were classified as heterogeneous.

As shown in Table 5, the absence of registration numbers in four of the seven clinical trials compromised reliability, and publication bias was considered highly suspect.

Overall, Grade assessed the certainty of the evidence as very low, because of the analysis of blinding bias and key outcome measures, inconsistency (no meta-analysis generated), and publication bias.

LIMITATIONS

The major limitation of this review was the literature search, which resulted in 860 publications that used descriptors. However, after the process of removing duplicates, assessing eligibility, and extracting data, a total of 853 articles were excluded.

If the number of articles in the final sample were larger, there would be a greater chance of homogeneity among the studies, as well as the possibility of generating a meta-analysis, thereby strengthening the evidence power of the results found.

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In addition to the limited number of publications, another limitation was access to the articles, as some were behind pay walls. Although we contacted the authors, we did not receive any responses. We were able to access the articles through the libraries of the Federal University of São João del-Rei and the Federal University of Rio de Janeiro.

CONCLUSION

These results, suggest that physical exercise, particularly aerobic exercise, has positive effects on motor and cognitive function in elderly individuals with Alzheimer's disease. In addition, it significantly improves other aspects, such as quality of life and behavioral and psychological symptoms.

With respect to reliability, the results showed very low confidence. More and better randomized clinical trials are needed to increase this level.

Studies that test anaerobic exercises adapted for this population are also needed, so that they can be compared with aerobic exercises to find evidence of which is more effective, helping in the creation of intervention protocols.

As a recommendation for continuing the research, increasing the sample size in future studies will facilitate greater analysis of homogeneity, resulting in a meta-analysis, as well as standardizing intervention protocols to minimize heterogeneity in studies. Inclusion of objective and standardized measures of motor and cognitive function assessment, so that both can be measured and analyzed, in order to fulfill the primary objectives of the research and plan strategies to reduce selection and publication bias, in addition to implementing blinding in data collection and analysis. These points are crucial in the evaluation of evidence and consequently in the reliability of the results.

The research findings, even with the low reliability of evidence, can help in prescribing exercises for this type of population, since positive results were found for motor and cognitive function, regions affected by the disease, being performed by a specific exercise. In addition, it can help in future research, starting from an already structured base.

ACKNOWLEDGMENTS

I would like to thanks CAPES (Coordenação de Aperfeiçoamento de Pessoas de Nível Superior) for support through the scholarship provided in the Master's Program in Health Sciences at the Federal University of Lavras (UFLA) – Minas Gerais, Brazil.

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AUTHORS' CONTRIBUTIONS

LMA designed and supervised all aspects of the study, analyzed the results, interpreted the findings, and drafted the manuscript; CJN supervised all aspects of the study and interpreted the results; MPPN assisted in the study data search and analyzed the results; BDLCM supervised all aspects of the study; ACG supervised all aspects of the study, conducted the data analysis and drafted the manuscript. All the authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

COMPETING INTEREST

The authors declare that they have no competing interests.

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