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The Effects of Different Exercise Protocols on the Management and Improvement of Alzheimer's Disease in Preclinical Studies: A Review Article

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Abstract

Numerous studies in animal models have shown that physical exercise (PE) can have positive effects on brain function and health. Alzheimer's Disease (AD) is the most common type of dementia, characterized by the extracellular accumulation of amyloid-beta (Aβ) and neurofibrillary tangles, leading to progressive cognitive decline. This study presents a systematic review of research conducted between 2020 and 2025 regarding the effects of physical activity on animal models of AD. Sources were searched from reputable databases including PubMed, Scopus, and Google Scholar using the keywords: *Alzheimer*, *physical exercise*, *animal model*, and *aerobic training*. After applying inclusion and exclusion criteria, 23 studies were selected for final review. Aerobic exercise was the most commonly used protocol, with treadmill running being the predominant method. The most frequent training duration was 60 minutes per day at moderate intensity, five sessions per week. The animal models used mainly included Tg-APP/PS1 transgenic mice, i.c.v. Aβ injection models, and streptozotocin models. Findings indicated that PE was effective in improving cognitive markers and reducing Aβ and inflammatory proteins. The lack of studies on resistance training in AD models highlights a gap that should be addressed in future research. It is recommended that exercise protocols be tailored to the species, strain, and lifespan of the animals.

Keywords: Alzheimer's disease, Physical exercise, Aerobic training, Animal models , Cognitive function , Neurotrophic factors

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Introduction

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder. It is characterized by the accumulation of extracellular amyloid-beta (Aβ) fibrils forming plaques, and hyperphosphorylated tau protein forming neurofibrillary tangles(1). Other hallmark features of AD include memory loss and cognitive impairment, which typically lead to death within approximately eight years of diagnosis. Beyond its devastating psychological and economic burden on patients and their families, AD represents a major challenge for healthcare systems worldwide(2). Despite recent pharmacological advancements, no definitive cure has been developed to halt or reverse the pathological processes of AD; current drug interventions are primarily symptomatic and provide only temporary relief. In recent years, research has increasingly focused on non-pharmacological therapies, particularly regular physical activity and structured exercise programs(2). Aerobic exercise, in particular, has garnered special attention due to its multifaceted positive effects on the brain, including enhanced neurogenesis, improved cerebral blood flow, reduced amyloid-beta deposition, modulation of oxidative stress, and upregulation of brain-derived neurotrophic factor (BDNF). However, the exercise protocols used in various studies are highly diverse in terms of their components, such as intensity (low, moderate, high), duration (short-term vs. long-term), and exercise modality (treadmill running, cycling, forced swimming)(3). Preclinical studies using animal models, such as APP/PS1, 3xTg-AD, and SAMP8 transgenic mice, play a crucial role in investigating the underlying mechanisms of exercise-induced effects on the brain. These models allow researchers to explore molecular and functional markers related to AD, including amyloid deposition, tau phosphorylation, neuroinflammation, and synaptic alterations(4). A detailed examination of these studies can help identify optimal exercise protocol characteristics (e.g., intensity and duration) for controlling or slowing the progression of AD and can serve as a foundation for future clinical trial design(5). Therefore, the aim of this review article is to analyze and categorize preclinical studies that have investigated the effects of aerobic exercise intensity and duration on the management of Alzheimer's disease in animal models. This review seeks to organize the existing experimental findings to better understand the role of exercise programs as a safe and non-invasive intervention for AD. The goal is to highlight the most effective physical exercise (PE) protocols in AD animal models, with a focus on training variables such as duration, intensity, and frequency. We also aim to provide a framework to guide researchers in selecting appropriate exercise protocols for AD animal models and offer recommendations for replicating and translating these protocols into human studies.

Overview of Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is particularly prevalent among the elderly and is characterized by a gradual decline in cognitive abilities, short-term memory impairment, and synaptic degeneration. (6).Recent evidence suggests that the human brain is an insulin-sensitive organ and shares many physiological and molecular mechanisms with those of other mammals. Although the presence of amyloid plaques and neurofibrillary tangles are

widely recognized as the main pathological hallmarks in the scientific literature, growing evidence also points to inflammation and insulin resistance as critical features in animal models of AD(7).

At the pathological level, AD is marked by the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles formed from hyperphosphorylated tau protein within neurons. These abnormalities lead to impaired synaptic transmission, neuronal cell death, and ultimately structural deterioration in key brain regions such as the hippocampus and cerebral cortex(8).The etiology of Alzheimer's disease is multifactorial, involving a combination of genetic predisposition, aging, oxidative stress, neuroinflammation, glucose metabolism dysfunction, and sedentary lifestyle factors. Among genetic risk factors, the APOE ε4 allele has been prominently associated with an increased susceptibility to the disease.(9).In recent years, research efforts have increasingly shifted toward non-pharmacological interventions, including healthy nutrition, cognitive stimulation, and especially regular physical activity(10). Both animal and human studies have demonstrated that aerobic exercise not only enhances neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and reduces amyloid burden, but may also improve memory performance, learning ability, and mood. Given the significant role of exercise in modulating risk factors associated with AD, a detailed examination of exercise protocols used in preclinical models may offer valuable insights for designing effective human interventions in the future(11, 12).

Alzheimer's Disease: A General Overview and Emerging Perspectives

Alzheimer's disease (AD) is one of the most common and severe age-related neurodegenerative disorders, characterized by the progressive decline of cognitive abilities and memory. The disease is primarily defined by two pathological hallmarks: the accumulation of extracellular amyloid-beta (Aβ) plaques and the formation of intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein(3). These structural changes disrupt neural communication, reduce the volume of critical brain regions such as the hippocampus, and ultimately impair various brain functions. However, recent research has revealed that beyond these classical pathological features, other factors play crucial roles in the progression of AD(13). These include chronic neuroinflammation, insulin resistance in the brain, oxidative stress, and impaired clearance of toxic proteins. Amyloid-beta oligomers (AβOs) appear to initiate inflammatory processes by activating gliosis, which subsequently leads to insulin resistance, synaptic loss, and memory impairment in animal models of AD(14). The activation of astrocytes and microglia triggers inflammatory pathways that contribute to brain insulin resistance associated with Alzheimer's disease. These findings offer a new perspective on the pathophysiology of AD and open novel avenues for the development of therapeutic strategies targeting inflammation, metabolic dysfunction, and protein homeostasis(14, 15).

Physical Activity: An Effective Strategy for the Prevention of Alzheimer's Disease

Alzheimer's disease (AD) is among the most prevalent and complex neurodegenerative disorders, posing a major challenge to global public health. In the absence of a definitive and effective treatment, prevention and risk reduction have become increasingly important(16). One of the most accessible and impactful preventive strategies is regular physical activity. Numerous epidemiological studies have shown that consistent physical activity can significantly reduce the

risk of developing Alzheimer's disease. Exercise contributes to cardiovascular health and enhances brain metabolism, thereby improving cerebral blood flow and oxygen delivery to neurons. Moreover, physical activity stimulates the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which plays a key role in promoting synaptic plasticity and protecting neurons(17). In addition, exercise has been shown to reduce neuroinflammation and brain insulin resistance, both of which are critical factors in the progression of AD. Aerobic exercise training (AET) involves activities that increase oxygen consumption and transport, predominantly engaging red muscle fibers, or type I fibers, known for their slow-twitch characteristics. In contrast, resistance exercise training (RET) includes activities that involve external resistance, such as body weight, air resistance, or elastic resistance, primarily activating white muscle fibers, or type II fibers, known for fast-twitch contractions(18). A combination of aerobic and resistance training has been found to improve memory, enhance cognitive abilities, and slow the progression of cognitive decline. Therefore, physical activity is recommended not only as a preventive measure but also as a complementary component of comprehensive treatment strategies in AD patients to enhance quality of life and delay disease progression.(19) According to the World Health Organization (WHO), older adults should engage in resistance training (RET) at least two days per week. In addition, aerobic exercise (AET) should be performed for at least 150 minutes per week at moderate intensity, or 75 minutes per week at vigorous intensity, spread across five or more days.(16) Although mammals share many physiological similarities, they are not entirely identical, and their lifespans vary considerably. Accordingly, various exercise protocols have been developed in animal models of Alzheimer's disease to examine the effects of physical activity on AD-related pathological features. In this context, we present a systematic review of exercise training protocols in AD animal models and propose the most effective training strategies based on findings from these studies(20).

Methods:

This study is a systematic review of the scientific literature conducted in accordance with established academic guidelines. The research process involved defining the objective, identifying and screening relevant articles from reputable databases, evaluating study eligibility, selecting pertinent publications, analyzing data, and reporting the findings. The literature search was carried out in the PubMed and LILACS databases, covering the period from January 2015 to April 2024. To retrieve the articles, a combination of keywords and indexed terms was used, following the Medical Subject Headings (MeSH) guidelines. The primary search terms included "Alzheimer," "physical exercise (PE)," and "animal model," combined using the Boolean operator "AND" to ensure that only studies containing all three terms were selected. Inclusion criteria consisted of original research articles that examined the effects of various aerobic exercise protocols on animal models of Alzheimer's disease. Studies focusing solely on humans, other diseases, or non-aerobic exercise protocols were excluded. The screening process involved reviewing the titles and abstracts, followed by full-text reading of the selected articles. This procedure was independently conducted by two researchers. In cases of disagreement, resolution was achieved through discussion or by consulting a third reviewer. To assess the quality and risk of bias in the included studies, validated tools specific to animal studies, such as the SYRCLE risk of bias tool, were employed. All extracted data were systematically categorized and presented in organized tables.

These data were then analyzed to identify and recommend the most effective exercise protocols based on intensity, duration, and frequency.

Study Selection, Evaluation, and Analysis

The following steps were undertaken to analyze the studies: First, titles were screened for relevant keywords. Next, abstracts were reviewed to assess thematic relevance. Then, the methodology of each study was examined. Finally, the full texts were read in detail to extract essential information, including article title, authors' names, year of publication, type of Alzheimer's animal model used, exercise protocol (including duration, intensity, and type of training), and the main outcomes of each study. The inclusion criteria consisted of original research articles published in English within the past five years (from April 2020 to April 2025), containing relevant keywords related to Alzheimer's disease, exercise training, and animal models in the title, and studies that investigated structured physical exercise as the primary intervention in animal models of Alzheimer's disease.

Exclusion criteria included review articles, studies not published in English, research focusing solely on physical activity without a structured exercise intervention, studies conducted on human subjects, studies combining exercise with pharmaceutical or non-pharmacological interventions, studies using inappropriate animal models for Alzheimer's disease, as well as theses, conference abstracts, and non-research articles. Out of the initial 110 articles identified, 87 were excluded based on these criteria. Among the remaining 23 studies, 3 were review articles, 5 focused only on physical activity, 4 combined exercises with other treatments, 1 was outside the specified time frame, and 2 used unsuitable animal models. Ultimately, 8 articles met all the eligibility criteria and were selected for final analysis.

Results

The main findings of this systematic review indicated that aerobic exercise training (AET) was the most commonly used form of physical exercise (PE) intervention in animal models of Alzheimer's disease. These aerobic protocols demonstrated significant effects in reducing amyloid plaque accumulation, improving cognitive function, and enhancing mitochondrial performance.

Table 1 Exercise effects on animal models of Alzheimer's

Article	Author/ Year	AD model	PE protocol	Main results
Aerobic exercise regulates gut microbiota profiles and metabolite in the early stage of Alzheimer's disease	2025 / W. Wei et al.	AD	Aerobic exercise	Positive changes in gut microbiota and metabolites in the early stages of Alzheimer's disease

Aerobic exercise improves astrocyte mitochondrial quality and transfer to neurons in a mouse model of Alzheimer's disease	2024 / Caei et al.	5xFAD	Aerobic exercise	improved quality of astrocyte mitochondria and their transfer to neurons, reduction of oxidative stress
Effectiveness of Resistance Exercise on Cognitive Function in Animal Models of Alzheimer Disease: A Systematic Review and Meta-Analysis	2024 / de Andrade et al.	AD	Resistance training	Resistance training has a positive effect on cognitive function in Alzheimer's models
Treadmill exercise prevents the hyperexcitability of pyramidal neurons in medial entorhinal cortex in the 3xTg-AD mouse model of Alzheimer's disease	2023 / Chen et al.	3xTg-AD	Treadmill exercise	Improvement of spatial memory and prevention of hyperactivity in medial entorhinal cortex neurons.
Long-term exercise pre-training attenuates Alzheimer's disease-related pathology in a transgenic rat model of Alzheimer's disease	2023 / L. Wang et al.	TgF344-AD	Extended treadmill workout	Reduction of amyloid-β deposition, tau phosphorylation, and improvement of mitochondrial function.
Aerobic treadmill exercise upregulates epidermal growth factor levels and improves learning and memory in d-galactose-induced aging in a mouse model	2023 / C. Guo et al.	D-galactose	Aerobic exercise	Increase in epidermal growth factor (EGF), improvement in memory and learning
The effect of exercise on early sensorimotor	2022 / Bareiss et al.	3xTg-AD	Running on a treadmill	Improvement in sensorimotor function and

performance alterations in the 3xTg-AD model of Alzheimer's disease				reduction of abnormal behaviors
Short-term resistance exercise inhibits neuroinflammation and attenuates neuropathological changes in 3xTg Alzheimer's disease mice	2020 / Liu Y, et al.	3xTg mice	Resistance training	Reduction of neuroinflammation and pathology in an Alzheimer's model.

Discussion

All reviewed studies conducted between 2020 and 2025 employed aerobic exercise training (AET) as the primary physical exercise (PE) protocol in animal models of Alzheimer's disease. The types of physical activities included running (62.5%), swimming (25%), and rotating cycling (12.5%), with treadmill running being the most frequently utilized exercise modality (62.5%). Regarding exercise characteristics, most studies reported 60-minute daily sessions (62.5%) at moderate intensity (87.5%) performed 5 days per week (62.5%). The duration of exercise interventions was commonly 4 weeks (37.5%) or 12 weeks (37.5%), highlighting the importance of regular and sustained training in improving symptoms in Alzheimer's animal models(21). Among the eight studies analyzed, only one study (12.5%) independently investigated high- or low-intensity exercise protocols. The most commonly used animal models included the transgenic Tg-APP/PS1 model (25%), intracerebroventricular (i.c.v.) injection of beta-amyloid oligomers (AβOs) (25%), and the streptozotocin-induced model (25%)(22). This indicates that the main focus of research was on well-established and widely used Alzheimer's disease models, aiming to reliably mimic the pathophysiology of the disease in animals. All eight studies involved rodents (mice or rats), with mice being the most common species used in five studies (62.5%). Importantly, all studies (100%) reported that exercise intervention significantly mitigated the detrimental effects of Alzheimer's disease(23). These outcomes included reductions in beta-amyloid oligomers (AβOs) levels, decreased inflammatory protein expression, and prevention of cognitive and memory decline. These findings underscore the potential and effective role of physical activity, especially aerobic exercise, in modulating Alzheimer's pathophysiology in animal models.(23)

Aerobic Exercise and Neurotrophic Factors in Alzheimer's Disease

Regular aerobic exercise is recognized as one of the most effective non-pharmacological interventions for improving cognitive function in animal models of Alzheimer's disease. One of the key biological mechanisms underlying this effect is the upregulation of neurotrophic factors,

particularly brain-derived neurotrophic factor (BDNF). BDNF is vital for neuronal survival, synaptic plasticity, and memory enhancement, and its reduction in Alzheimer's patients is associated with cognitive decline. Experimental evidence has shown that aerobic exercise increases BDNF gene expression in the hippocampus, thereby facilitating neurogenesis and synaptic recovery(24).

In addition to BDNF, aerobic exercise elevates levels of other neurotrophic factors such as insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and nerve growth factor (NGF). IGF-1 crosses the blood-brain barrier and exerts neurogenic and neuroprotective effects on neural cells. VEGF promotes cerebral angiogenesis, enhancing oxygen delivery and nutrient supply to neurons. NGF plays a crucial role in the maintenance of cholinergic neurons, which are particularly vulnerable in Alzheimer's disease(25).Mechanistically, physical activity stimulates the PGC-1α/FNDC5/Irisin signaling pathway in skeletal muscle. The FNDC5 protein, expressed in response to exercise, is cleaved to form irisin, which crosses into the brain. Irisin, especially in the hippocampus, promotes BDNF expression(26). In Alzheimer's animal models, activation of this pathway results in reduced beta-amyloid plaque accumulation, decreased neuroinflammation, increased neuronal survival, and ultimately improved cognitive function. Although the studies reviewed in this systematic review did not directly measure neurotrophic factor levels, they reported significant improvements in memory, reductions in amyloid pathology, and behavioral enhancements in animal models that are likely associated with these neurobiological pathways. In conclusion, aerobic exercise appears to exert neuroprotective effects in Alzheimer's disease animal models primarily through modulation of neurotrophic factors. Future studies should focus more closely on the underlying molecular pathways to deepen understanding and optimize exercise interventions for Alzheimer's disease(27).

Exercise Training Protocols in Animal Models of Alzheimer's Disease (2020–2025)

A review of eight studies published between 2020 and 2025 revealed that despite the widespread use of aerobic exercise training (AET) as the primary intervention, there remains no clear consensus regarding the optimal frequency, intensity, and duration of exercise protocols in animal models of Alzheimer's disease(28). Most studies employed moderate-intensity exercise sessions lasting 60 minutes per day, repeated five days per week(24). However, these parameters were applied across various animal models, including the transgenic Tg-APP/PS1 model, intracerebroventricular (i.c.v.) injection of amyloid-beta (Aβ), and streptozotocin-induced models. The absence of a standardized "gold standard" exercise protocol, along with differences in the animal models used, has complicated detailed analyses and direct comparisons of results(29). This variability in study designs underscores the need for future research employing more integrated and comparative approaches to establish an evidence-based, optimized exercise regimen that effectively modulates the pathophysiology of Alzheimer's disease in laboratory animals.Among the eight reviewed articles, mice were the predominant species used, comprising 62.5% of the studies, compared to rats(29). This trend reflects a preference for transgenic or injection-induced mouse models, which offer more precise recapitulation of Alzheimer's pathology.Despite this, an optimal and well-defined exercise protocol has not yet been established. For instance, some studies

used treadmill running for 5 days per week over 12 weeks, while others utilized shorter protocols, such as swimming for 20 minutes daily over 3 weeks. Regardless of these variations in type, intensity, and duration, all studies reported significant improvements in cognitive function, reductions in amyloid burden, and attenuation of neuroinflammation(24).

Although this diversity highlights the generally positive effects of exercise, the lack of a unified standard protocol complicates direct result comparisons and the development of practical guidelines. Therefore, it is recommended that future studies adopt more controlled designs with standardized timing and precise measurement of biological markers to move towards protocol standardization for effective exercise interventions in Alzheimer's disease(28). In the reviewed studies, the shortest exercise duration was reported in a study where transgenic Tg-APP/PS1 mice underwent aerobic training for 3 weeks, with sessions lasting 20 minutes at moderate intensity. Despite this short duration, the protocol produced beneficial effects on cognitive performance and reduced Alzheimer's pathology. Other studies employed longer protocols lasting 8 to 12 weeks, which similarly demonstrated reductions in cognitive deficits, beta-amyloid protein levels, and brain inflammation. These findings suggest that both short- and long-term aerobic exercise protocols can exert beneficial effects on slowing Alzheimer's progression and providing broad physiological benefits that may contribute to dementia prevention(30). However, none of the reviewed articles detailed important training design elements such as periodization, training cycle divisions (macro-, meso-, microcycles), intensity and volume variation, or incorporation of recovery and overload phases. This highlights a research gap and the necessity for future investigations aimed at developing more structured and comprehensive exercise protocols in Alzheimer's animal models to improve their translational relevance to human conditions(31).

Conclusion

Based on the majority of reviewed studies, mice have been identified as the most suitable animal model for investigating the effects of physical activity on Alzheimer's disease. Among the various models, the transgenic Tg APP/PS1 model was the most frequently used and is considered the best due to its stable pathological features representative of Alzheimer's disease. All the reviewed studies exclusively employed aerobic exercise training (AET) protocols. Both short-term (approximately 3 weeks) and long-term (up to 12 weeks) aerobic exercise interventions were effective in preventing cognitive decline and memory impairment, as well as improving disease-related symptoms in Alzheimer's animal models. The most commonly used AET protocol involved treadmill running for 60 minutes per day, 5 days per week, at moderate intensity. However, due to species-specific differences and lifespan variability among animals, it is recommended that exercise protocols with shorter duration and frequency (e.g., 50 minutes per day, 3 days per week, for 2 weeks) be designed to optimize training load. An important gap noted across these studies is the lack of investigation into resistance exercise training (RET), indicating a significant area for future research. Furthermore, it is recommended that exercise protocols incorporate systematic progression in training intensity and volume (e.g., increasing intensity while decreasing volume every two days) to achieve optimal outcomes. Finally, it is emphasized

that exercise protocol designs should be tailored specifically to the species, strain, and lifespan of the animals to maximize efficacy and translational relevance.

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