The efficacy of exercise rehabilitation in managing patients with Alzheimer's disease

Dan Li[1, 2], Jinning Jia[1], Haibo Zeng[2], Xiaoyan Zhong[1], Hui Chen[3, *], Chenju Yi[4, 5, 6, *]

1. Department of Pathology, The First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi Province, China;
2. Department of Pathology, Huichang County People's Hospital, Ganzhou, Jiangxi Province, China;
3. School of Life Sciences, Faculty of Science, University of Technology Sydney, Ultimo, NSW, Australia;
4. Research Center, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong Province, China;
5. Shenzhen Key Laboratory of Chinese Medicine Active Substance Screening and Translational Research, Shenzhen, Guangdong Province, China;
6. Guangdong Provincial Key Laboratory of Brain Function and Disease, Guangzhou, Guangdong Province, China.

***Correspondence to:** Chenju Yi, MD, PhD, yichj@mail.sysu.edu.cn.

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Abstract:

Alzheimer's disease (AD) is a progressive and degenerative neurological disease characterized by the deterioration of cognitive functions. While a definitive cure and optimal medication to impede the progression of the disease are currently unavailable, a plethora of studies have highlighted the potential advantages of exercise rehabilitation in managing this condition. In those studies, exercise rehabilitation has exhibited the capability to enhance cognitive function and improve the quality of life for individuals affected by AD. It also stands in stark contrast to solely relying on conventional pharmacological therapies. Not surprisingly, exercise rehabilitation has been regarded as one of the most important strategies to manage AD patients. Here, we provide a comprehensive analysis of the currently available findings on exercise rehabilitation in AD patients, with a focus on the types of exercises that showed efficacy when implemented alone or combined with other treatment methods, as well as the potential mechanisms underlying these positive effects. Specifically, we explain how exercise may improve brain microenvironment and neuronal plasticity. These key factors are thought to play a critical role in the AD pathogenesis. This review holds the promise of aiding in the development of more effective and finely tailored treatment strategies to address the challenges imposed by this debilitating disease, especially in low- and middle-income countries.

Keywords: cognitive function, brain microenvironment, neuronal plasticity, mechanism

1. Introduction

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder that significantly impairs neurocognitive and behavioral functions, especially among the aging population. It is the leading cause of dementia, accounting for 50% to 75% of all dementia cases [1]. According to the World Alzheimer Report 2022, over 55 million people are living with dementia worldwide, and this number is projected to increase to 139 million by 2050 [2]. The most significant increase will occur in low- and middle-income countries. The global cost of dementia has also been estimated to rise significantly from $1.3 trillion in 2019 to $2.8 trillion by 2030 due to increased care costs [2].

While specific pharmacotherapies may slow cognitive decline in selected cohorts of patients with early-stage AD, they are often of low efficacy and unable to halt irreversible neuronal loss due to ongoing neurodegeneration. Consequently, a decline in independent living capabilities persists despite these interventions [3]. Additionally, adverse reactions restrict the use of these drugs among the aging population. For example, Donepezil can cause extrapyramidal symptoms, bradycardia, gastrointestinal bleeding, nausea, and vomiting; Rivastigmine is linked to increased risk of all causes of mortality, especially among critically ill patients; Memantine has relatively milder side

effects, including dizziness, headache, hypertension, somnolence, and constipation [4]. Studies have demonstrated that exercise programs can effectively enhance cognitive function, daily living abilities, and life quality, while alleviating depressive symptoms in AD patients [5, 6]. Therefore, non-pharmacological interventions have emerged as indispensable complementary strategies to pharmacotherapy in AD patients to preserve their cognitive function and independent living abilities, especially in low- and middle-income countries where drugs to improve AD symptoms are too expensive to reach for most patients. As such, this review focuses on how exercise rehabilitation can improve the neurocognitive functions of AD patients and the potential molecular mechanisms involved.

A search on PubMed, Ovid Medline, and Web of Science was performed using "AD", "cognitive function", "aerobic exercise", "resistance exercise", "multimodal exercise", "Aβ", and "tau". The search for mechanistic studies used the keywords "AD", "exercise", and "cognitive function", in combination with one of these keywords, "cerebrovascular dysfunction", "synaptic plasticity", "hippocampal neurogenesis", "microglia", "astrocyte", "BDNF", "IGF-1", "irisin", "mitochondrial integrity", "epigenetics regulation", and "sex difference". We included peer-reviewed original research papers published in English between Aug 2001 and Apr 2023, in either animal models (to compare different types of exercise) or humans with AD (randomized controlled trials, meta-analysis, and observational studies) that reported positive results. The effects of various forms of exercise in combination with other treatments on cognitive function and proposed mechanisms have been summarized in this review. We did not include publications with insufficient powers (e.g., case studies).

2. The pathophysiology of AD

The primary neuropathological features of AD are amyloid-β (Aβ) plaque formation and neurofibrillary tangles, leading to the gradual loss of functional neurons (also called "neurodegeneration") in the hippocampus, neocortical and basal ganglia regions. Several of these brain regions are involved in memory formation and retrieval. The hippocampus is closely related to the formation of learning memories, and plays a key role in spatial navigation during memory formation [7]. The prefrontal cortex is responsible for executive functions, such as consolidating long-term memory and decision making, and regulates the activity of the hippocampus [8].

Aβ peptides are cleaved from amyloid precursor protein (APP), an essential membrane protein for synapse formation and repair. In the AD brain, APP is processed by β-secretase, instead of α-secretase, to generate a soluble Amyloid Precursor Protein beta (sAPPβ). The remaining

transmembrane portion of APP is then recognized and cleaved by γ-secretase to generate an Aβ monomer fragment, Aβ40 or Aβ42. Then, several Aβ monomer fragments, especially Aβ42, assemble to form insoluble oligomers or senile plaques [9]. The excessive Aβ deposition and abnormal nervous structural changes activate microglia for clearance, which in turn initiates pro-inflammatory responses that promote oxidative stress and further neuronal damage [10]. Synaptic connections and plasticity are critical for memory formation, storage, and retrieval, thus enabling learning from experiences. Aβ plaques can lead to overstimulation of N-methyl-D-aspartate (NMDA) receptors, which are glutamate receptors responsible for regulating synaptic plasticity. This overstimulation of NMDA receptors can cause dysfunction in hippocampal neuronal activation, memory coding and storage, ultimately resulting in decreased memory retrieval ability [11].

In early-stage AD, site-specific phosphorylation of tau protein can inhibit Aβ toxicity [12]. However, tau hyperphosphorylation makes it unable to bind to tubulin in AD brains, and its accumulation results in the formation of neurofibrillary tangles, which block the production and function of several proteins. For example, hyperphosphorylated tau can interact with c-Jun N-terminal kinase-interacting protein 1 (JIP1), impairing the formation of the kinesin complex and affecting axonal transport [13]. The synergistic effect of extracellular Aβ plaques and intracellular neurofibrillary tangles precipitates neurodegeneration[14]. It has been shown that the depletion of tau gene in APP transgenic J20 mice can reduce hippocampal hyperactivation and thus improve motor function and spatial memory recall [15]. This suggests that tau dysfunction may be more critical than Aβ toxicity in the early-stage pathogenesis of AD.

The buildup of Aβ plaques can also increase redox-mediated oxidative stress and cytoplasmic Ca^{2+} levels [16]. Subsequently, the downstream signaling, such as serine/threonine protein phosphatase 2A and 2B (PP2A and PP2B), is activated to inhibit calcium/calmodulin-dependent protein kinase II (CaMKII) and induce the endocytosis of ionotropic glutamate receptors, e.g. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Similarly, oligomeric Aβ can induce the endocytosis of NMDA receptors, mediated by dephosphorylation of NMDA receptor subunit NR2B (GluN2B), leading to synaptic dysfunction [16] (Figure 1). The accumulation of damaged mitochondria has been a distinctive hallmark of both aging and age-related neurodegenerative conditions, which are closely intertwined with impaired Aβ clearance mechanisms [17]. Mitophagy, the mitochondrial self-renewing mechanism, can restore the functional mitochondrial population in neurons of AD models, resulting in increased microglial phagocytosis of extracellular Aβ plaques and insoluble Aβ1-42 and Aβ1-40, reduced neuroinflammation, and improved cognitive function [17]. In AD models, mitochondrial damage within neurons also contributes to an increased complement-mediated tag of the synapse, which activates adjacent

microglia to initiate presynaptic elimination [18]. This further impairs neuroplasticity and cognitive function, particularly learning and memory functions.

3. Types of exercise rehabilitation in AD patients

Regular exercise facilitates the harmonious coordination of the body's response to unexpected situations and supports the preservation of normal brain functions, which effectively prevent significant cognitive decline. Previous studies have shown that the risk of cognitive decline is 35% to 38% lower in physically active individuals compared with their sedentary counterparts [19]. Evidence continues to mount on the positive roles of exercise in managing and preventing neurodegenerative disorders, such as AD. In APPswe/PS1ΔE9 mice, voluntary exercise has been shown to prevent memory loss and reverse neuropathological changes related to AD progression [20].

3.1. Aerobic exercise

Aerobic exercise has been the predominant method employed to slow cognitive decline in the elderly population [21]. Several clinical trials have demonstrated that regular moderate-intensity exercise (40-60 min duration, 3 days/week) can significantly increase brain volume indicative of neurogenesis, which was associated with improved memory function in healthy elderly individuals [21-23]. In patients with mild AD, moderate-intensity aerobic exercise has also been shown to effectively improve cognitive function [24]. Research has demonstrated that aerobic exercise has the capacity to enhance brain energy metabolic homeostasis by increasing ketone uptake and metabolism, a phenomenon associated with cognitive improvement [25]. Moreover, engaging in moderate to high-intensity aerobic exercise results in favourable effects on cardiopulmonary function, physical performance in single and dual tasks, and exercise self-efficacy in patients with mild AD [26]. Exercise has also been found to alleviate the neuropsychiatric symptoms of patients with mild AD [27]. Even acute aerobic exercise of moderate intensity (20 min cycling exercise) can benefit thinking abilities in patients with mild AD, which was even more effective when combined with cognitive games for mental training [28]. An animal study showed that aerobic exercise improved cognitive performance by reducing neuronal apoptosis through activating the PI3K/Akt/GSK-3β signaling pathway in D-galactose and aluminium chloride induced AD mice [29], which may be the mechanisms underlying the abovementioned cognitive benefits in humans. Therefore, engaging in aerobic exercise can be an option for the elderly to delay age-related dementia and for patients with mild AD to mitigate rapid neurocognitive decline.

3.2. Resistance exercise

Resistance exercise, also referred to as strength training, has been suggested to reverse the loss of muscle mass and function, as well as brain structural deterioration in AD patients. In a rat model of AD, a single injection of Aβ1-42 into the Cornu Ammonis (CA)1 region of the hippocampus was sufficient to cause muscle atrophy due to the loss of myonuclear number and satellite cell content, whereas resistance training was able to successfully restore the muscle mass by significantly enhancing the level of myosin heavy chain (MyHC) IIb fiber in myofibers [30]. Evidence has also shown that resistance exercise is beneficial for increasing muscle strength in trained individuals and alleviating depressive symptoms in the elderly population affected by AD [31]. In 3xTg AD mice (a transgenic mouse model of AD), short-term resistance exercise reduced Aβ load, tau hyperphosphorylation, reactive astrogliosis, and inflammatory responses in the frontal cortex and hippocampus, which correlate with improved synaptic plasticity and cognitive functions, including short-term memory and working memory functions [32]. Resistance exercise can also reverse cognitive dysfunction due to neuroinflammation via insulin-like growth factor (IGF)-1 signaling in the hippocampal dentate gyrus region [33]. Long-term resistance training in APP/PS1 mice can also activate microglia recruitment without enhancing inflammatory responses but increasing the elimination of Aβ deposition [34]. As a result, locomotor hyperactivity was ameliorated in those AD mice [34].

In humans, it has been shown that with every unit increase in muscle strength, there was a 43% reduction in the chance of developing AD at the onset of cognitive impairment [35]. This suggests that there may be a direct interaction between muscle function and brain well-being, possibly involving chemokines or non-coding RNAs released from newly generated muscles. These molecules reach the central nervous system to promote synaptic plasticity and improve neurological functions. The concept of “exerkine” was introduced when the skeletal muscle was considered an endocrine organ in the setting of physical activity-induced secretions, together with liver and adipose tissue. Exerkines may act as messengers during muscle-brain crosstalk. These exercise-mediated myokines, such as lactate, irisin, and interleukin (IL)-6, are released into the circulation, cross the blood-brain barrier, and positively affect synaptic plasticity and memory, by enhancing brain mitochondrial function [36].

It is important to acknowledge that strength training is often high-intensity and can be challenging to maintain as a regular activity in the long term, especially for middle-aged and older patients with movement impairment. In these scenarios, assisted strength training may be considered, which involves the support of trained carers or personal trainers to facilitate the process.

3.3. Flexible exercise regime

Elderly individuals can benefit from a multimodal exercise regimen that combines aerobic exercise, postural balance, muscular strength training, and flexibility training. A combination of different types of exercise may be easier to follow compared to a single form. Both aerobic and resistance exercises are important in improving the cognitive status of AD patients [37]. It has been shown that twelve weeks of multimodal exercise can decrease the risks of falls in elderly women with moderate cognitive impairment and enhance their focus and ability to perform dual tasks [38]. It can also significantly increase brain function in the frontal lobe while contributing to better cognitive function, postural balance, and physical capacity [39]. Therefore, in individuals with dementia, multimodal exercise may help improve cognition and physical functionality in daily living activities.

Repeated transcranial magnetic stimulation (rTMS) has been found to significantly improve cognitive function in patients with mild to moderate AD [40], and alleviate cognitive deficits in 3xTg AD model rodents by activating the PI3K/Akt/GLT-1 pathway [41]. High-frequency rTMS may improve executive functions and behavior in AD patients, while moderate-intensity aerobic exercise may enhance balance and mobility [42]. The combination of rTMS and physical exercise may achieve a better effect in ameliorating neurological impairment of AD patients. Exercise rehabilitation combined with music therapy is also more effective in ameliorating neuropsychiatric symptoms and boosting the positive effects of exercise rehabilitation in individuals with mild to moderate AD[43]. Exercise holds promise in reducing the risk of falls among individuals with AD using antihypertensives and psychotropics [44]. Engaging in exercise with functional tasks can produce considerable benefits for people with mild cognitive impairment in general cognitive function, memory, executive function, and everyday problem-solving abilities [45].

Voluntary physical activities are also beneficial to cognitive performance compared with a sedentary lifestyle. In a transgenic mouse model expressing the human mutant amyloid precursor protein ($APP_{Sw, Ind}$), environmental enrichment with a running wheel for voluntary exercise restored adult neurogenesis and memory function after 7 weeks of exposure [46]. This scenario can represent the engagement with outdoor activities to experience diverse surroundings, which are thought to be important in sculpturing the brain for memory consolidation [47]. This setting may significantly improve hippocampal-dependent spatial learning and memory defects at the early stage of AD development in humans, as shown in the rodent model [46]. The associated adult neurogenesis in the hippocampus is reflected by increased synaptic number, dendritic length, and neural projections to the CA3 region. However, Aβ levels and the number of neurons in the dentate gyrus were unchanged [46]. This may suggest that promoting neurogenesis is a key treatment strategy to

improve cognitive function in patients with AD, rather than only focusing on Aβ clearance.

4. Proposed mechanisms of exercise

It is likely that various forms of exercise can benefit cognitive performance in AD patients via different biological mechanisms. Studies investigating the mechanisms of AD pathophysiology often employed genetically modified murine models, such as transgenic APP/PS1 mice (also called TgAPP/PS1 mice), 3xTg AD mice, the senescence-accelerated mouse prone 8 (SAMP8) mice, Thy1-GFP transgenic mice, and 5xFAD mice. Some studies also used wildtype rodents by introducing exogenous neurotoxins, such as Aβ analogs, D-galactose with aluminium chloride, and streptozotocin. The proposed mechanisms of exercise in altering AD pathology learned from animal models are listed in Table 1 and Figure 2. Clinical trials among AD patients are listed in Table 2.

Table 1. Effects of exercise training on rodents with AD

Author (Year)	Animal models	Exercise types	Effects	Molecular alterations
Pena GS., et al. (2020) [48]	3xTg AD mice	Ladder climbing exercise	↑: muscle mass and strength ↓: Aβ oligomers	↑: IGF-1
Liu Y., et al. (2020) [32]	3xTg AD mice	Ladder climbing exercise	↑: cognitive function; Akt/GSK-3β pathway ↓: Aβ plaques; Tau phosphorylation; reactive astrogliosis; microglial activation; neuroinflammatory; JNK pathway	↑: synaptic proteins synaptotagmin 1 and synaptobrevin 1; exercise-induced factors IL-6, FGF-21 and PGC-1α; anti-inflammatory factors IL-10 ↓: pro-inflammatory factors TNF-α and IL-1β
Hashiguchi D., et al. (2020) [34]	APP/PS1 mice	Ladder climbing exercise	↑: microglial recruitment ↓: behavioral hyperactivity; Aβ plaques	↓: exercise-induced factors IL-6; pro-inflammatory factors IL-1α
Rahmati M., et al. (2023) [30]	Aβ1- 42 induced AD rats	Ladder climbing exercise	↑: cognitive function; myonuclear number; MyHC IIb fbers ↓: muscle atrophy; oxidative damage	↑: SOD, catalase and glutathione
Kim D., et al. (2019) [49]	3xTg AD mice	Treadmill exercise	↑: cognitive function; neurogenesis; mitochondrial function ↓: Aβ plaques; reactive astrogliosis	↑: mitochondrial biogenesis-related factor NRF1
Zhao G., et al. (2015) [50]	Aged APP/PS1 mice	Treadmill exercise	↑: spatial learning and memory function; synaptic	-

			plasticity ↓: soluble Aβ levels	
Hong J., et al. (2020) [51]	APP/PS1 mice	Treadmill exercise	↑: cerebrovascular function; P2Y2 receptor-mediated eNOS signaling pathways ↓: ER stress and ER stress-associated apoptosis	↑: P2Y2 receptor, p-Akt and p-eNOS; anti-apoptotic factor Bcl-2 ↓: APP, p-IRE1, p-eIF2α, and CHOP
Li B., et al. (2021) [52]	APP/PS1 mice	Treadmill exercise	↑: memory function; synapse number; the length and thickness of postsynaptic densities; synaptic plasticity and excitatory neurotransmission ↓: Aβ plaques and soluble Aβ levels;	↑: synaptic structural plasticity-related proteins synapsin, PSD95, MAP2 and NCAM; ionic glutamate receptor subunit proteins GluN2B and GluA1
Yu H., et al. (2021) [53]	APP/PS1 mice	Treadmill exercise	↑: spatial learning and memory function; neurogenesis; differentiation of neurons; APP cleavage through the non-amyloidogenic pathway ↓: Aβ plaques; neuronal apoptosis; the differentiation of astrocytes	↑: α-secretase ADAM10, sAPPα, BDNF and TrkB ↓: β-secretase BACE1, γ-secretase PS1, APP and sAPPβ
Zhang, X., et al. (2019) [54]	APP/PS1 mice	Treadmill exercise	↑: cognitive function; microglia M2 polarization ↓: Aβ plaques and soluble Aβ levels; neuroinflammatory; oxidative damage	↑: anti-inflammatory cytokine TGF-β ↓: pro-inflammatory cytokines IL-1β and TNF-α; MDA
Zhao N., et al. (2023) [55]	APP/PS1 mice	Treadmill exercise	↑: spatial learning and memory function; mitochondrial function; PINK1/Parkin-mediated mitophagy; SIRT1-FOXO1/3 pathway ↓: Aβ plaques and soluble Aβ levels;	↑: ATP, complex I and complex IV enzyme levels; Parkin and SIRT1 ↓: PINK1, P62, Ace-FOXO1a and ace-FOXO3a
Sun, L.N., et al. (2018) [56]	Aβ1- 42 induced AD mice	Treadmill exercise	↑: cognitive function; neurogenesis ↓: reactive astrogliosis; neuroinflammatory Reversing the MAPK signaling abnormality	↓: pro-inflammatory cytokines IL-1β and TNF-α; p-p38 and p-JNK
Alkadhi, KA., et al. (2018) [57]	Aβ1- 42 induced AD rats	Treadmill exercise	-	↓: APP, Aβ and BACE1
Dao AT., et al. (2015) [58]	Aβ1- 42 induced AD rats	Treadmill exercise	↑:basal synaptic transmissions; synaptic	↑: p-CaMKII and BDNF

			plasticity	↓: calcineurin PP2B
Wang YL., et al. (2022) [59]	Aβ1- 42 induced AD rats	Treadmill exercise	↑: cognitive and motor function; ↓: neuronal degeneration and apoptosis; microgliosis	↑: BDNF, TrkB and cathepsin D
Peng Y., et al. (2022) [29]	D-galactose and aluminium chloride induced AD mice	Treadmill exercise	↑: spatial learning and memory function; PI3K/Akt/GSK-3β pathway ↓: neuronal apoptosis	↑: PI3K, p-Akt and anti-apoptotic factor Bcl-2 ↓: GSK-3β and pro-apoptotic molecule Bax
Lu, Y., et al. (2017) [60]	Streptozotocin-induced AD rats	Treadmill exercise	↑: spatial learning and memory function; microglia M2 polarization; mitochondrial function ↓: Aβ generation; Tau phosphorylation; neuronal degeneration and apoptosis; oxidative damage	↑: anti-inflammatory cytokines IL-4 and IL-10; ↓: pro-inflammatory cytokines IL-1β and TNF-α; peroxynitrite production 3-NT; oxidative stress markers 4-HNE, P-H2A.X and 8-OHDG
Xiong, J.Y., et al. (2015) [61]	APP/PS1 mice	Treadmill exercise	↑: spatial learning and memory function ↓: microglial activation	↑: BDNF
Li, B., et al. (2019) [62]	APP/PS1 mice	Treadmill exercise divided into two groups (HIIT and MICT)	↑: spatial learning and memory function; mitochondrial function ↓: Aβ plaques and soluble Aβ levels;	↑: SOD and catalase ↓: BACE1, ROS, MDA and H_2O_2
Revilla S., et al. (2014) [63]	3xTg AD mice	Voluntary wheel running exercise	-	↑: synaptophysin, PSD95, GDNF and SIRT1; NMDA receptor subunit NR2 B; ↓: GABAA receptor α5 subunit
Belaya, I., et al. (2020) [64]	5xFAD mice	Voluntary wheel running exercise	↑: cognitive function; GFAP-positive astrocyte activation; Selectively altered the morphology of the GFAP-positive astrocytes near the Aβ plaques	↑: PSD-95, GFAP and BDNF
Tapia-Rojas, C., et al. (2016) [20]	APP/PS1 mice	Voluntary wheel running exercise	↑: spatial learning and memory function; neurogenesis ↓: Aβ plaques and Aβ oligomers; Tau phosphorylation; reactive astrogliosis	-
Cosín-Tomás M., et al. (2014) [65]	SAMP8 mice	Voluntary wheel running exercise	-	↑: IGF-1, BDNF, TrkB and Neuritin; global acetylation levels of histone H3; mir-148b-3p, miR-15b-5p, miR-

				28a-5p, miR-7a-5p and miR-98-5p; ↓: Hdac3, miR-105 and miR-133b-3p
He, XF, et al. (2017) [66]	Thy1–GFP transgenic aged mice	Voluntary wheel running exercise	↑: spatial learning and memory function; glymphatic clearance; AQP4 polarity; synapse number and function ↓: Aβ deposits; astrocytes and microglia activation	↑: AQP4 and PSD95
Belviranli, M., et al. (2019) [67]	D-galactose and aluminium chloride induced AD rats	Voluntary wheel running exercise, swimming exercise, swimming load training	↑: locomotor activity and exploratory behavior; spatial learning and memory function; ↓: anxiety-like behavior; Aβ oligomers; Tau pathology; oxidative stress	↑: BDNF, NGF, SOD and glutathione ↓: MDA and PC

3-NT: 3-nitrotyrosine; 4-HNE: 4-hydroxynonenal; 8-OHDG: 8-hydroxy-2' -deoxyguanosine; ace-FOXO1a: acetylated forkhead box O1a; ace-FOXO3a: acetylated forkhead box O3a; ADAM10: ADAM metallopeptidase domain 10; Akt: serine/threonine kinase; APP: amyloid precursor protein; AQP4: aquaporin 4; BACE1: beta-site amyloid precursor protein cleaving enzyme 1; Bax: Bcl-2-associated X; Bcl-2: B cell leukemia/lymphoma 2; BDNF: brain derived neurotrophic factor; CaMKII: calcium/calmodulin-dependent protein kinase II; CHOP: CCAAT/enhancer-binding protein homologous protein; eIF2α: eukaryotic initiation factor 2α; eNOS: endothelial nitric-oxide synthase; ER: endoplasmic reticulum; FGF-21: fibroblast growth factor-21; GDNF: glial cell-derived neurotrophic factor; GFAP: glial fibrillary acidic protein; GluA1: glutamate ionotropic receptor AMPA type subunit 1; GluN2B: glutamate ionotropic receptor NMDA type subunit 2B; GSK-3β: glycogen synthase kinase 3 beta; HIIT: high-intensity interval training; IGF-1: insulin-like growth factor 1; IL: interleukin; IRE1: inositol-requiring enzyme 1; JNK: c-Jun NH2-terminal kinase; MAP2: microtubule-associated protein 2; MAPK : mitogen-activated protein kinase; MDA: methane dicarboxylic aldehyde; MICT: moderate-intensity continuous training; MyHC IIb: the myosin heavy chain IIb isoform; NCAM: neural cell adhesion molecule; NGF: nerve growth factor; NMDA: the N-methyl-D-aspartate; NRF1: nuclear respiratory factor 1; p-: phosphorylation; PC: protein carbonyl; PGC-1α: peroxisome proliferative activated receptor, gamma, coactivator 1 alpha; PI3K: phosphoinositide 3-kinase; PINK1: PTEN-induced kinase 1; PP2B: protein phosphatase 2B; PS1: presenilin 1; PSD95: postsynaptic density protein 95; ROS: reactive oxygen species; sAPPα: soluble amyloid precursor protein α; sAPPβ: soluble amyloid precursor protein β; SIRT1: silent information regulator factor 1; SOD: superoxide dismutase; TNF-α: tumor necrosis factor-α; TrkB: tropomyosin-related kinase B.

Table 2. Clinic trials in AD patients at different stages

Author (Year)	The stage of AD	Exercise types	Effects	Imaging	Biochemical indicators

de Farias J.M., et al. (2021) [68]	AD	Physical exercise training	Improve judgment and problem-solving abilities	-	↑: serum sulfhydryl and nitrite levels; anti-inflammatory cytokine IL-4 ↓: serum carbonyl and DCFH levels; serum catalase activity; neuronal damage marker NSE
Pedrinolla A., et al. (2020) [69]	AD	Moderate-high-intensity aerobic and strength training	Improve peripheral vascular function	↑: blood flow and shear rate	↑: plasma VEGF levels
de Andrade LP., et al.(2013) [39]	AD with mild or moderate dementia	Multimodal exercise	Improve the frontal cognitive function, as well as the postural control and balance	-	-
Satoh M., et al. (2017) [70]	AD with mild and moderate dementia	Physical exercise combined with music vs cognitive stimulation	Improve cognitive function and activities of daily livings, excluding memory	-	-
Sobol N.A., et al. (2016) [26]	Mild AD	Moderate-to-high intensity aerobic exercise	Improve cardiorespiratory fitness, single- and dual-task physical performance, and exercise self-efficacy	-	-
Morris J., et al. (2017) [71]	Mild AD	Aerobic exercise	Improve memory performance and cardiorespiratory fitness	↓: hippocampal atrophy	-
Yang S.Y., et al. (2015) [24]	Mild AD	Aerobic exercise (moderate intensity cycling training)	Improve cognitive function, mental state, and the quality of life	-	↑: plasma Apo-A1 levels
Castellano C.A., et al. (2017) [25]	Mild AD	Aerobic exercise (moderate intensity treadmill walking)	Improve brain energy metabolism	↑: CMRacac, Kacac and dCMRket	-
Cezar NOC., et al. (2021) [72]	Mild-to-moderate AD	Home-based multimodal exercise	Improve muscle strength and function Reduce the risk of falls	-	-
Yu F., et al.	Mild-to-	Aerobic exercise vs light-intensity	Delay the decline in global cognitive	-	-

(2021) [73]	moderate AD	stretching	function		
Ben Ayed I, et al. (2021) [28]	Moderate AD	Aerobic exercises alone or combined with cognitive games	Improve cognitive function	-	-

Apo-A1: apolipoprotein A1; CMRacac: global cerebral metabolic rate of acetoacetate; DCFH: dichlorofuorescein; dCMRket: global cerebral metabolic rate of ketone; Kacac: rate constant for net uptake of acetoacetate; NSE: neuron-specific enolase; VEGF: vascular endothelial-derived growth factor.

4.1. Exercise improves cerebrovascular dysfunction

The coordination between neuronal activity and cerebral blood flow is maintained by a mechanism called neurovascular coupling [74]. The neurovascular unit, consisting of endothelial cells, vascular smooth muscle cells, pericytes, neurons, and glia, controls this coupling [75]. It has been shown that the glutamate-NMDA receptor-neuronal nitric oxide synthase (nNOS) axis is critical for cerebrovascular function, because it triggers soluble guanylate cyclase in nearby arteriolar smooth muscle cells to promote vasodilation [76]. In patients with AD, there is a progressive reduction in cerebral blood flow in affected brain regions, which is closely linked to their cognitive decline [77]. Exercise training can improve peripheral vascular function in AD patients, by increasing Nitric oxide (NO) and vascular endothelial growth factor (VEGF) to cause vasodilation and increased arterial blood flow and shear rate [69].

NO, a major vasodilator, is generated by the activation of endothelial nitric oxide synthase (eNOS). The decrease in NO in the cerebrovascular endothelium is associated with increased levels of APP and β-site APP-cleaving enzyme 1 (BACE1), resulting in increased production of cytotoxic Aβ1-40 and Aβ1-42 [78, 79]. In addition, endothelial NO plays important roles in regulating synaptic plasticity, mitochondrial biogenesis, and function of neuronal progenitor cells [80], linking cerebrovascular function with cognition. Indeed, eNOS-deficient mice exhibit impaired cognitive performance [81]. In APP/PS1 mice, exercise has been shown to ameliorate cerebrovascular dysfunction by enhancing P2Y2 receptor-mediated eNOS signaling and NO release [51]. Exercise can also alleviate endoplasmic reticulum stress and associated apoptosis by reducing phosphorylated inositol-requiring enzyme 1 (p-IRE1), phosphorylated eukaryotic initiation factor 2 (p-eIF2α) and CCAAT-enhancer-binding protein homologous protein (CHOP), which are all significantly elevated in the brains of AD mice [51].

Pericytes play a critical role in the stabilization of the capillary wall, maintenance of the blood-brain barrier, and regulation of capillary diameter and cerebral blood flow. Pericyte degeneration has been shown to lead to neurovascular uncoupling, reduce oxygen supply to the brain, and cause metabolic

stress [82]. Reduced pericyte number may disrupt BBB properties and result in neuronal dysfunction during AD pathogenesis [83]. A study showed that Aβ can induce pericyte-mediated cerebral capillary blood vessel constriction, resulting in the reduction of cerebral blood flow during the early stage of AD [84]. Therefore, managing dysfunctional neurovascular units may help to slow down neurodegeneration and improve cognitive function in AD patients.

Indeed, twelve-month aerobic exercise in patients with mild cognitive impairment has been shown to improve memory function and blood flow in the hippocampus and anterior cingulate cortex without change in brain volume [85]. Restoring blood supply by exercise can increase brain oxygenation and nutritional supply and benefit cognitive functions. However, another study has shown that sixteen weeks of moderate-to-high-intensity aerobic exercise was insufficient to produce a sustained increase in cerebral blood flow, which may be due to the short intervention time and small sample size [86]. In some cases, there may be improved blood vessel oxygen and nutrition delivery function, rather than an increase in absolute blood volume. This speculation needs to be confirmed bu future studies. Nevertheless, sustained exercise, especially at the early stage of AD, could prevent vascular lesions and dysfunction by maintaining sufficient cerebral perfusion.

4.2. Exercise enhances synaptic plasticity and hippocampal neurogenesis

Synaptic plasticity is fundamental to learning and memory. At the early stage of AD, synaptic dysfunction and loss of the dendritic spines are associated with cognitive decline and other neurological impairments [87]. Aβ can interact with ionic glutamate receptors to reduce synaptic integrity and plasticity, resulting in synaptic loss and neuronal death [88]. There is also a significant increase in synaptic markers in cerebrospinal fluids, such as PSD95, presynaptically localized synaptosomal-associated protein 25 and neurogranin, which may be used as early diagnostic biomarkers [89]. Exercise can reduce Aβ40, Aβ42 and Aβ deposition, resulting in significantly increased synaptic number, as well as the length and thickness of postsynaptic structure in the hippocampal CA1 region [52]. In a rat model of AD, impaired basal synaptic transmission and long-term potentiation in the dentate gyrus can be rescued by four weeks of moderate treadmill exercise, as well as normalized basal levels of phosphorylated CaMKII and PP2B [58]. In 3xTg mice, resistance exercise and running wheel exercise can increase synaptic density and plasticity, resulting in improved cognitive performance [32, 63], through brain fibronectin type III domain-containing protein 5 (FNDC5)-irisin signaling [90]. Therefore, improving synaptic density and plasticity is the key to restoring cognitive function in patients with AD by exercise.

Adult hippocampal neurogenesis is important in maintaining learning and memory functions

throughout life. Alterations in hippocampal neurogenesis occur at the early stage of AD, even before neurofibrillary tangles or Aβ plaques appear in the dentate gyrus [91]. Interestingly, inducing hippocampal neurogenesis alone by drugs or genetic modification yields marginal cognition benefits in 5×FAD mice; however, additional exercise can improve cognition, along with reduced Aβ deposition and increased BDNF, FNDC5, and synapses. It is likely that exercise improves the local environment and enables the benefit of hippocampal neurogenesis [92]. In fact, exercise alone, regardless of running wheel or treadmill exercise, has been shown to increase hippocampal neurogenesis and ameliorate cognitive function in several mouse models of AD, including Aβ1-42 induced AD, 3xTg, and APP/PS1 mice [20, 49, 56]. Exercise can also increase brain BDNF levels, promote APP proteolysis, and reduce toxic Aβ peptides [93], which help to create a healthy hippocampal microenvironment for neurogenesis [53]. Therefore, hippocampal neurogenesis can be the goal for developing effective therapeutic strategies for AD patients.

4.3. Exercise modulates glial functions

Microglia are the innate immune cells in the brain and the first responders to pathological changes. Early microglial activation promotes Aβ clearance and is neuroprotective. As the disease progresses, these activated microglia produce a large number of pro-inflammatory cytokines IL-1β and TNF-α, which inhibit microglial Aβ-binding receptors (eg. scavenger receptor A and CD36) and Aβ-degradation enzymes (eg. insulysin and neprilysin) to decrease its phagocytic capacity and exacerbate Aβ accumulation [94]. In addition, oligomeric Aβ induces endoplasmic reticulum stress and Ca^{2+} release, leading to GSK-3β mediated tau phosphorylation and neurofibrillary tangles and subsequently, neurodegeneration [95].

Growing evidence suggests that exercise exerts neuroprotective effects by inhibiting microglial activities and related neuroinflammation in AD brain. In APP/PS1 mice, twelve weeks of treadmill exercise can preserve hippocampal cognitive function and suppress Aβ deposits at an early stage of AD, possibly by modulating microglia-mediated neuroinflammation and oxidative stress [54]. Treadmill exercise promoted the transition of microglia from the pro-inflammatory (neurotoxic) phenotype to the anti-inflammatory (neuroprotective) phenotype, with increased anti-inflammatory cytokine TGF-β and decreased pro-inflammatory cytokines IL-1β and TNF-α [54]. Similar effects of treadmill exercise on microglial phenotype change were also observed in streptozotocin-induced AD rats, with increased anti-inflammatory cytokines IL-4 and IL-10 [60]. In Aβ1-42 induced AD mice, treadmill exercise attenuates the pre-inflammatory responses in the hippocampus by modulating MAPK signaling [56]. Resistance exercise also inhibited neuroinflammation in the frontal cortex of 3xTg AD mice [32]. In older people with mild cognitive impairment, both aerobic

exercise and resistance exercise can reduce serum TNF-α levels [96]. All these indicate that exercise can mitigate neuroinflammation by inhibiting microglial activities and promoting microglia polarization to an anti-inflammatory phenotype.

Astrocytes are supporting cells. They assist in neuronal metabolism and synaptic transmission, maintain blood-brain barrier integrity, and finely tune neuroinflammation with microglia. Astrocytes may also be neuroprotective by phagocytosis of Aβ deposits and dystrophic neurites [97, 98]. Astrocyte dysfunction due to the deletion of glial fibrillary acid protein (GFAP) and vimentin genes led to increased Aβ plaques and related dystrophic neurites in the APP/ PS1 mice [99]. Similar to microglia, astrocytes have pro-inflammatory and anti-inflammatory phenotypes [100]. Microglia-derived IL-1α, TNF-α, and complement component 1 subcomponent q (C1q) can convert astrocytes to a neurotoxic phenotype, losing their primary supporting functions [101]. Astrocytes may represent a significant source of Aβ during neuroinflammation in AD, as amyloidogenic APP synthesis in astrocytes can be increased by the presence of pro-inflammatory cytokines (TNF-α and IFN-γ), as well as Aβ oligomers and fibrils [102].

Both aerobic exercise and resistance exercise can reduce astrocyte activation in the brain of AD mice [20, 32, 49, 56]. In 5xFAD mice, six months of voluntary exercise can remodel the astrocytes to reverse cognitive impairment. Morphological analysis indicates that voluntary exercise induces a significant increase in the primary branch number, branch length and soma size of plaque-associated astrocytes without changing the distance between the astrocytes and Aβ plaques, with increased astrocytic BDNF and postsynaptic protein PSD95 levels [64]. Astrocytic water channel aquaporin 4 (AQP4) is normally located in the perivascular astrocytic end-feet ensheathing the brain vasculature, which facilitates the clearance of Aβ and the loss of perivascular AQP4, also known as AQP4 depolarization, promotes Aβ plaque formation [103, 104]. In aged mice, six weeks of voluntary exercise promotes glymphatic clearance of Aβ and attenuates neuroinflammation, by increasing AQP4 expression and polarization and restoring perivascular localization of AQP4 [66].

The above evidence indicates that exercise can mitigate neuroinflammation by regulating both microglia and astrocyte functions to improve cognitive function in AD models and patients. Therefore, exercise represents a promising option in the early management of AD.

4.4. Exercise induces neurotrophic factors

BDNF is one of the most important growth factors in the brain for its roles in neuronal survival,

neurite outgrowth and synaptic plasticity. It is highly expressed in the hippocampus, cerebral cortex, and basal forebrain, all involved in learning, memory, and cognitive contemplation. BDNF exerts its effects through interacting with tropomyosin-related kinase B (TrkB) receptors and subsequently activating various signaling pathways, including MAPK, phosphoinositide 3-kinase (PI3K) and phospholipase C-γ (PLCγ) pathways [105]. BDNF can also reduce Aβ levels by enhancing the α-secretase activity and shifting APP towards the non-amyloidogenic pathway [93, 106]. Decreased BDNF levels may lead to synapse loss and cognitive dysfunction [107]. It has shown that reduced brain BDNF occurs in the early stage of AD and is associated with cognitive impairment [108]. As the condition progresses, AD patients also show decreased BDNF levels in the serum [109]. Exercise can improve cognitive function by enhancing the expression of BDNF. In APP/PS1 transgenic mice, treadmill exercise can enhance BDNF expression in the hippocampus, associated with hippocampal neurogenesis and spatial memory improvement [53, 61]. In D-galactose and aluminium chloride induced AD rats, voluntary, involuntary and forced exercises can equally reverse behavioral impairment by increasing hippocampal neurotrophic factors, such as nerve growth factor and BDNF, [67]. A meta-analysis shows that acute and chronic exercises in AD patients can ameliorate cognitive impairment with increased blood BDNF levels, which may be used as a biomarker for evaluating the effect of exercise among AD patients [110].

Insulin-like growth factor 1 (IGF-1) is an important neurotrophic factor that modulates neuronal excitability, metabolism, growth, and differentiation [111, 112]. During the progression of AD, IGF-1 levels in the blood and cerebrospinal fluid are reduced, which may serve as a potential biomarker for predicting cognitive deterioration [113]. Moreover, low baseline levels of serum IGF-1 are associated with faster cognitive decline in AD patients [114]. Exercise can significantly increase IGF-1 levels in the blood, and boost brain uptake of circulating IGF-1 [115]. A study in experimental neurodegenerative mice confirms that subcutaneous administration of anti-IGF-1 antibodies can block the circulating IGF-1 entering the brain, diminishing exercise-induced neuronal protection. This suggests that circulating IGF-1 is indispensable for exercise-induced neuroprotection [116]. Another study has found that intracarotid injection of IGF-1 can mimic the effect of exercise to increase BDNF in the hippocampus, indicating that IGF-1 may be an upstream regulator of BDNF [115]. In individuals with mild cognitive impairment, acute aerobic exercise can increase serum levels of both IGF-1 and BDNF, while acute resistance exercise can only increase serum IGF-1 levels, indicating different working mechanisms of these two types of exercise [37].

Irisin is a myokine released by the proteolysis of FNDC5 in the skeletal muscle after exercise [117]. Irisin can cross the blood-brain barrier and induce the expression of BDNF in the hippocampus to

improve neuronal function [118], by activating the peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α)/FNDC5 pathway [119]. Irisin can also promote hippocampal cell proliferation through STAT3 signaling [120], and reduce oxidative stress-induced neuronal damage through activating Akt and ERK1/2 signaling pathways [121]. FNDC5 is also expressed in the hippocampus, and its levels in the hippocampus and cerebrospinal fluid are reduced in AD patients and a rat model of AD [90]. Knockdown of brain FNDC5/irisin can weaken the neuroprotective effect of exercise on synaptic plasticity and memory retention in AD mice [90]. On the other hand, the administration of exogenous irisin is effective in ameliorating both cognitive deficit and neuropathology in the APP/PS1 and 5xFAD mice [122]. Thus, irisin may represent a new treatment option for managing cognitive decline in patients with AD.

4.5. Exercise improves mitochondrial integrity

Maintaining mitochondrial structural and functional integrity is critical to upholding cellular energy and metabolic equilibrium. When mitochondria are damaged, it leads to energy supply deficiency, intracellular calcium imbalance, and oxidative stress, all of which aggravate tau hyperphosphorylation and Aβ accumulation, resulting in synaptic dysfunction, cognitive decline and memory loss [123]. Exercise-induced lactate can increase brain mitochondrial biogenesis-associated factors (such as PGC-1α; nuclear respiratory factor 1 and 2; mitochondrial transcription factor A) and mitochondrial DNA copy numbers, and improve mitochondrial dynamics in hippocampal neurons [36, 49]. In 6-month-old APP/PS1 mice, exercise has also been shown to improve mitophagy machinery, which can promote mitochondrial renewal and mitochondrial function through the silent information regulator factor-1 / forkhead transcription factors 1/3 (FOXO1/3) -phosphatase and tensin homolog-induced putative kinase 1 (PINK1) / Parkin pathway [55, 124]. High-intensity interval exercise and moderate-intensity continuous exercise can also improve hippocampus mitochondrial morphology and reduce mitochondrial fragmentation and hippocampal Aβ burden in APP/PS1 mice [62]. Exercise can also increase the repair capacity of oxidative stress-induced damage to mitochondrial DNA and mitochondrial ATP production, leading to increased synaptic plasticity and synaptic density in the hippocampus and cerebral cortex of APP/PS1 mice [125]. This suggests mitochondrial integrity and function play a key role in synaptic plasticity in AD brains.

4.6. Exercise affects epigenetic regulation

Epigenetic regulation is a key mechanism in neural response and adaptation to external

environmental stimuli. There are mainly three epigenetic mechanisms, DNA methylation, histone modification, and non-coding RNAs, e.g., microRNAs. A study found that Aβ can increase the DNA methylation of neprilysin (an enzyme responsible for Aβ degradation) and further suppress its mRNA expression and protein levels [126]. Moreover, the frontal lobe of the AD brain had lower DNA methylation levels at the APOE CpG island and exhibited increased mRNA expression of otal APOE, which is the most significant hereditary risk factor for late-onset AD [127]. It has been confirmed that the methyl-CpG binding protein 2 (MeCP2) - mediated dysregulation of the epigenome in the striatum is linked to impaired cognitive functions and abnormal neuronal activity in AD mice, which can be rescued by knocking down striatal MeCP2 [128]. A possible protective role of mild cognitive impairment by exercise is supported by the changes in genome-wide DNA methylation patterns [129]. This suggests that exercise can alter epigenetic regulations associated with cognitive function.

Histone acetylation has also been shown to play a significant role in regulating synaptic plasticity and memory processes [130]. Histone acetylation is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). It has been shown that some HATs, such as CREB-binding protein (CBP) and its homolog p300, are significantly decreased in the frontal cortex and hippocampus of AD brains, associated with learning and memory deficits [131, 132]; while treadmill exercise can increase global HAT activity in the cortex and hippocampus of rodents [133, 134]. HDACs play an important role in memory formation and synaptic plasticity. HDAC2 is increased in AD brains which is associated with memory impairments by reducing the histone acetylation of genes important for learning and memory. Reducing HDAC2 can restore brian structure and synaptic plasticity and diminish neurodegeneration-associated cognitive decline [135]. Exercise can reduce several HDACs, such as HDAC2, HDAC3 and HDAC5, to increase histone acetylation, in line with the improvement in memory performance [136, 137] .

MicroRNAs have been increasingly recognized to play a key role in neural development and synaptic plasticity, and their dysregulation has also been linked to the development and progression of AD [138]. For example, miR-155 is over-expressed in the brain of 3xTg AD mice, which is associated with activation of astrocytes and microglia, and increased expression of inflammatory factors, such as IL-6 and IFN-β [139]. Several studies have confirmed that exercise can modulate miRNA expression in its effect on cognitive function. Voluntary running wheel exercise has been shown to suppress over-expressed miR-132 in the hippocampus of SAMP8 mice with improved cognitive function [140]. MiR-137 is downregulated in both the hippocampus and cerebral cortex of APP/PS1 mice, resulting in tau hyperphosphorylation [141]; while voluntary wheel running can upregulate miR-137 expression and improve the memory function in mice [142]. MiR-15b is reduced

in brains from AD models and patients, associated with increased expression of BACE-1 [143]. Chronic aerobic exercise can upregulate miR-15b expression in the hippocampus of SAMP8 mice and reduce BACE-1 levels to decrease Aβ accumulation in the brain [65]. Exercise can also regulate other miRNAs, including miR-124, miR-146a and miR-148b, and their mechanisms of action in neurodegeneration and cognitive functions require future studies [144].

4.7. Sex differences in exercise-induced cognitive changes

There are sex differences in the effects of exercise on cognitive functional outcomes. In streptozocin-induced AD rats, treadmill exercise decreases depression-related behaviours in female rats, while reduces anhedonia-like behaviour in male rats [145]. However, treadmill exercise only increased BDNF levels in the hippocampus and IL-10 levels in the prefrontal cortex in female rats, suggesting sex-difference in working mechanims [145]. Another study found the total white matter volume and myelinated fibers were significantly lower in the female AD mice than in the male counterparts [146]. However, running exercise was more effective in delaying the decline in spatial learning and memory functions and attenuating the changes in the myelinated fibers in female AD mice than in male AD mice [146]. Sex differences in neuroplasticity and neurotrophic factors may mediate the difference in the efficacy of exercise on improving cognition in AD models [147], suggesting individualized exercise protocols are needed for male and female patients.

5. Conclusions and Future Perspectives

Exercise has demonstrated a great capacity to enhance cognitive performance across various life stages, encompassing both youth and later years, as well as within particular populations with cognitive impairments. This phenomenon is supported by a body of evidence ranging from moderate to robust [148]. Both cognitive-aerobic training and a solitary aerobic training regime exhibited effectiveness in enhancing executive function among the elderly with mild dementia [149].

Exercise rehabilitation stands as an exceptionally promising and multifaceted domain that merits comprehensive investigation in the realm of future research initiatives. Its potential implications extend far beyond the confines of research, holding significant promise for integration into routine care for individuals grappling with AD. By harnessing exercise as a therapeutic tool, healthcare practitioners can potentially enhance the quality of life and cognitive function in AD patients (Figure 3).

This paradigm shift opens avenues for personalized care plans, where exercise becomes not only a

physical activity but also a tailored intervention. It has the potential to serve as a predictive biomarker, offering insights into an individual's potential response to exercise-based interventions. These biomarkers could guide healthcare professionals in designing exercise regimens that are precisely aligned with a patient's unique needs and capabilities. This approach holds the potential to optimize the therapeutic benefits of exercise, promoting both physical and cognitive well-being in AD patients.

Furthermore, more research on the intricate mechanisms underlying the cognitive benefits of exercise is needed to unveil novel biomarkers. These biomarkers, which may encompass neurochemical, neuroimaging, or even epigenetic markers, could offer crucial insights into the underlying molecular and physiological changes brought about by exercise. Importantly, these mechanistic biomarkers might also serve as viable targets for the development of new drugs aimed at slowing down the progression of AD or even preventing its onset.

Incorporating exercise rehabilitation into routine care for AD patients necessitates a collaborative effort among healthcare providers, researchers, and policymakers. Such integration would require tailored exercise protocols that consider the varying degrees of cognitive impairment and physical abilities present in different AD patients. Additionally, establishing standardized guidelines and protocols for the assessment of exercise-induced biomarkers can facilitate their consistent use across clinical settings, aiding in treatment planning and decision-making.

Taken together, exercise is a cost-effective intervention to improve the physical and cognitive fitness of AD patients. Different forms of exercise exert positive effects through different mechanisms of action. The prospects of exercise rehabilitation in the context of AD research and clinical practice are undeniably promising.

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Declaration of interests

The authors have no competing interests to declare.

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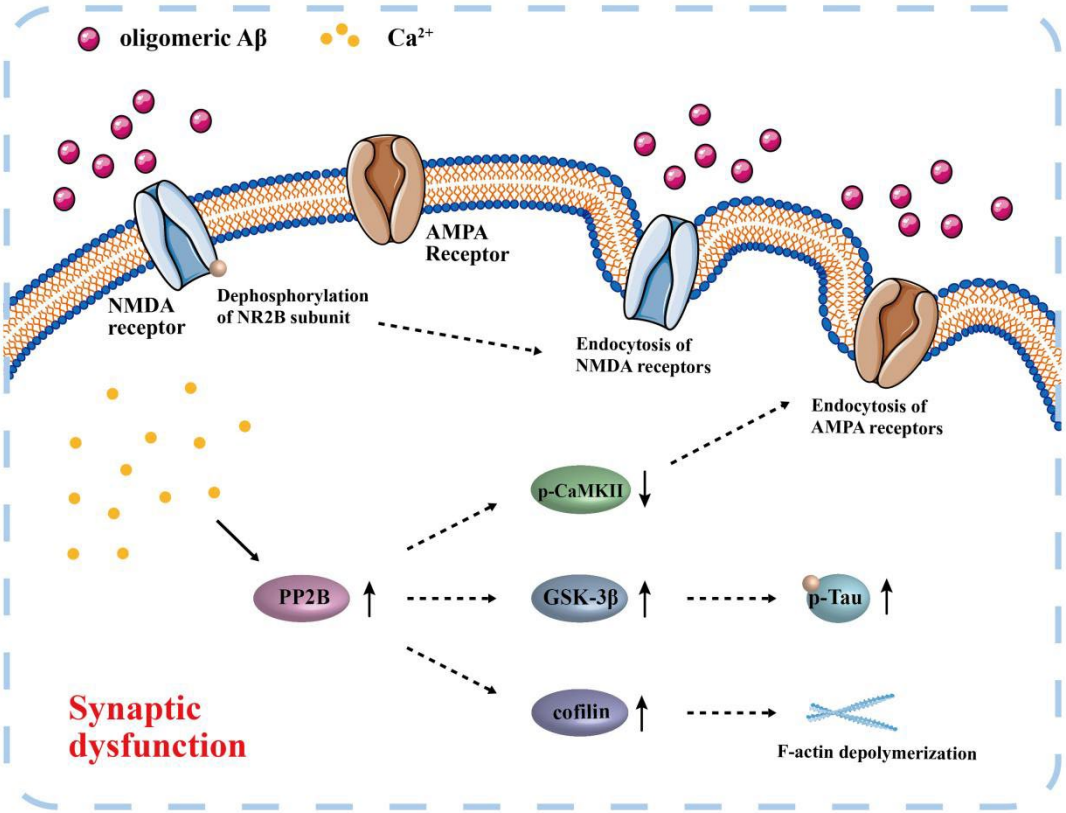

Figure 1. Schematic diagram of oligomeric Aβ-induced synaptic damage

The oligomeric Aβ triggers a series of toxic events in the synapse, including the overstimulation of NMDA receptors, elevated neuronal calcium influx, increased calcium-dependent activation of calcineurin/PP2B and its downstream signalings, including cofilin, GSK-3β and CaMKII. This results in F-actin depolymerization, tau-hyperphosphorylation and endocytosis of AMPA receptors. The oligomeric Aβ can also induce the endocytosis of NMDA receptors, mediated by dephosphorylation of NMDA receptor subunit NR2B. These events eventually lead to synaptic dysfunction. AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CaMKII: calcium/calmodulin-dependent protein kinase II; GSK-3β: glycogen synthase kinase 3 beta; NMDA: N-methyl-D-aspartate; p-: phosphorylation; PP2B: protein phosphatase 2B.

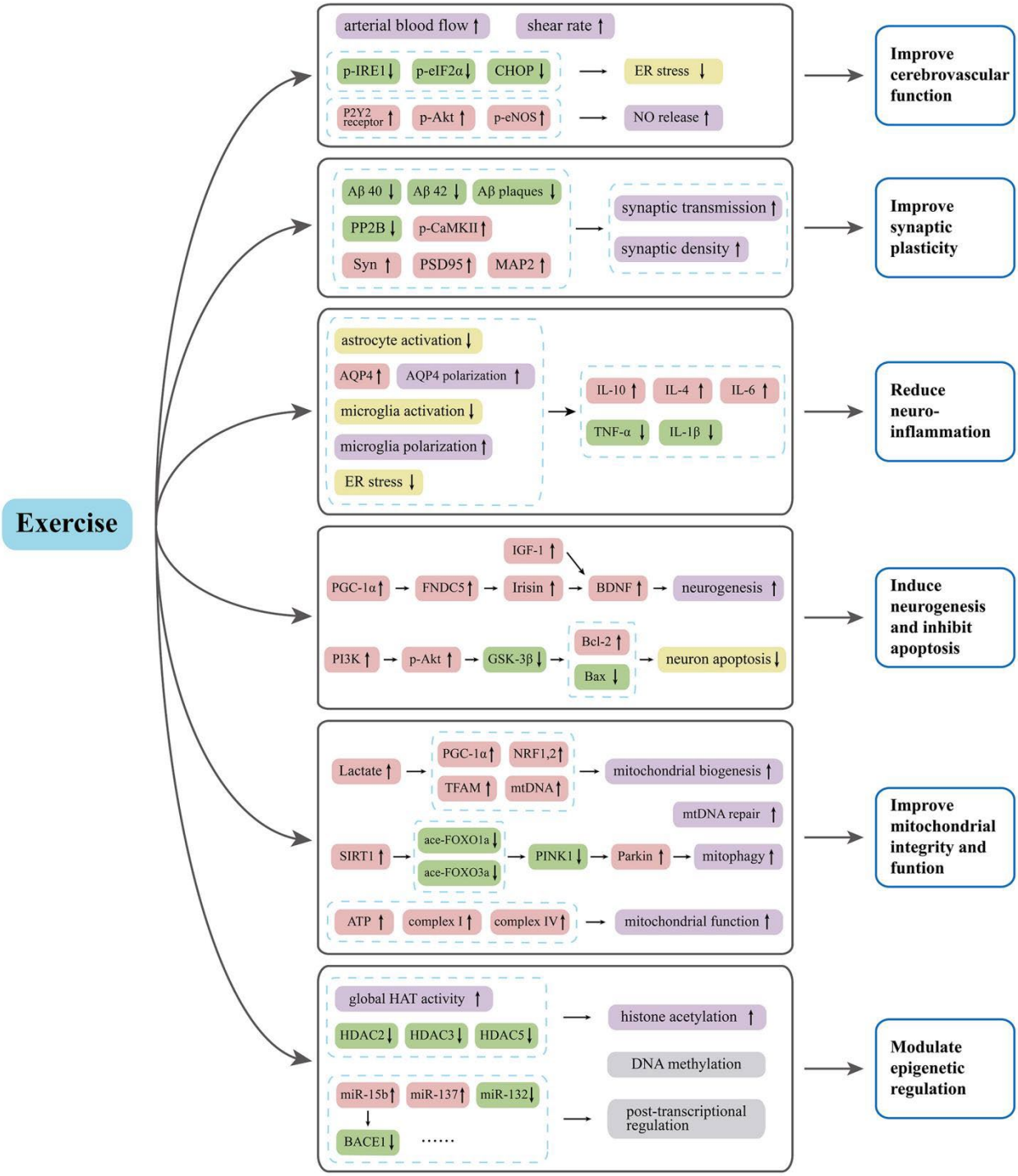

Figure 2. Proposed mechanisms of how exercise affects AD pathology

ace-FOXO1a: acetylated forkhead box O1a; ace-FOXO3a: acetylated forkhead box O3a; Akt: serine/threonine kinase; AQP4: aquaporin 4; BACE1: beta-site amyloid precursor protein cleaving enzyme 1; Bax: Bcl-2-associated X; Bcl-2: B cell leukemia/lymphoma 2; BDNF: brain derived neurotrophic factor; CaMKII: calcium/calmodulin-dependent protein kinase II; CHOP: CCAAT/enhancer-binding protein homologous protein; eIF2α: eukaryotic initiation factor 2α; eNOS: endothelial nitric-oxide synthase; ER: endoplasmic reticulum; GSK-3β: glycogen synthase

kinase 3 beta; IGF-1: insulin-like growth factor 1; IL: interleukin; IRE1: inositol-requiring enzyme 1; MAP2: microtubule-associated protein 2; NRF1,2: nuclear respiratory factor 1 and 2; p-: phosphorylation; PGC-1α: peroxisome proliferative activated receptor, gamma, coactivator 1 alpha; PI3K: phosphoinositide 3-kinase; PINK1: PTEN-induced kinase 1; PP2B: protein phosphatase 2B; PSD95: postsynaptic density protein 95; Syn: synapsin; TNF-α: tumor necrosis factor-α.

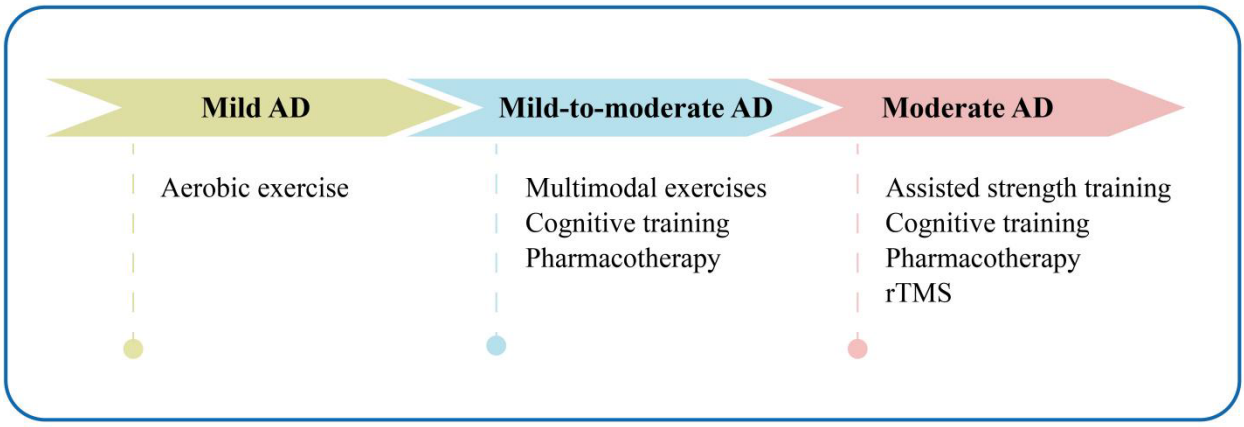

Figure 3. Proposed therapeutic regimen for AD patients at different stages

Exercise is beneficial for AD patients at different stages. Mild AD patients can engage in aerobic exercise to maintain cognitive function, while mild to moderate AD patients can combine pharmacotherapy, cognitive training and multimodal exercises, including aerobic exercise and stretching training, to prevent a rapid decline in cognitive function and enhance muscle strength. For moderate AD patients, especially those unsuitable for voluntary aerobic exercise, strength training can be performed with the help of trained carers or personal trainers to prevent muscle atrophy. In addition, repeated transcranial magnetic stimulation (rTMS) can improve cognitive function and psychobehavioral symptoms in AD patients with dementia.