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Physical activity as a non-pharmacological intervention in Alzheimer's disease: a narrative review

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Abstract

Background. Alzheimer's disease (AD) is the leading cause of dementia, and disease-modifying pharmacological options remain limited. Physical activity (PA) has emerged as a promising modifiable factor to mitigate cognitive decline and disease progression.

Aim. To synthesize evidence from clinical and mechanistic studies on the effects of PA in AD, with emphasis on cognition, disease course, and key biological pathways.

Material and methods. A targeted narrative search of PubMed and Scopus identified English-language studies (2002–2025), prioritizing randomized controlled trials, systematic reviews, and meta-analyses of exercise or PA interventions in individuals with AD, mild cognitive impairment, or preclinical AD; additional observational and mechanistic work was used to contextualize clinical findings. Evidence was synthesized qualitatively, without formal risk-of-bias assessment or quantitative meta-analysis, focusing on cognition, neuropsychiatric symptoms, function, quality of life, and major mechanistic domains.

Results. Most studies show that PA improves global cognition (especially executive function) and reduces neuropsychiatric symptoms, while memory effects are more limited. Resistance and multicomponent training yield greater cognitive benefits than aerobic exercise alone, likely via enhanced neurotrophic signaling, reduced Aβ/tau pathology, improved insulin sensitivity, attenuated neuroinflammation, and increased cerebral blood flow. Moderate-intensity PA (≈150–180 min/week) appears optimal, slowing clinical progression most clearly in preclinical and mild AD, although effects on quality of life remain inconsistent.
Conclusions. PA is a promising, safe, and accessible non-pharmacological intervention, particularly in earlier AD stages, and should be considered a core component of strategies to reduce the burden of AD.

Keywords: Alzheimer's disease; physical activity; exercise; cognitive function; neurodegeneration; insulin resistance; neuroinflammation; BDNF; sedentary behavior;

1. Introduction

Alzheimer's disease (AD), the most common cause of dementia worldwide, affects over 55 million people and accounts for 60-70% of all dementia cases, with projections estimating a tripling by 2050 due to population aging. (1) In the United States alone, approximately 7 million individuals live with AD in 2025, a number expected to reach 13.8 million by 2060, positioning it as the seventh leading cause of death (over 120,000 deaths annually). (1,2) This escalating global burden places unprecedented strain on healthcare systems, caregivers, and economies, underscoring the urgent need for effective preventive and disease-modifying strategies.

Clinically, AD manifests as progressive cognitive decline affecting memory, executive function, language, and behavior, ultimately leading to loss of independence and increased mortality. (3) Neuropathologically, the disease is characterized by amyloid-β (Aβ) plaque accumulation, neurofibrillary tangles of hyperphosphorylated tau protein, synaptic dysfunction, widespread neuronal loss, and brain atrophy. (4) These hallmark features are compounded by neuroinflammation, oxidative stress, mitochondrial impairment, and brain insulin resistance – processes increasingly conceptualized as "type 3 diabetes."(5,6)

Despite decades of intensive research, no disease-modifying treatments exist; current pharmacological options (acetylcholinesterase inhibitors, memantine) provide only symptomatic, temporary relief without altering neurodegeneration (7). Recent anti-amyloid monoclonal antibodies (lecanemab, donanemab) demonstrate modest clinical benefits alongside significant safety concerns, including amyloid-related imaging abnormalities (ARIA) such as brain edema and hemorrhage (8,9). Overall, more than 99% of putative disease-modifying agents have failed in clinical development, underscoring the profound challenges of pharmacological intervention in AD, as summarized by Cummings et al. and Vellas et al. (7)

The 2024 Lancet Commission estimates that approximately 45% of dementia cases may be preventable through lifestyle modifications, identifying physical inactivity as one of the most impactful modifiable risk factors. (10) Population-based studies consistently demonstrate that higher levels of PA are associated with a substantially lower risk of developing AD, while

randomized controlled trials and meta-analyses support beneficial effects on cognitive trajectories and selected biomarkers of neurodegeneration. (11,12) PA exerts multi-target effects across interconnected pathways: enhancing neuroplasticity via brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), improving cerebral blood flow and endothelial function, reducing neuroinflammation and oxidative stress, modulating Aβ/tau pathology, and correcting metabolic dysfunction including insulin resistance and chronic hyperglycemia. (13–15)

However, substantial gaps persist in the evidence base guiding clinical implementation. While meta-analyses confirm cognitive benefits – particularly for executive function – substantial heterogeneity exists across exercise modalities, dosage parameters, disease stage at intervention, and outcome measures. (17) Recent network meta-analyses challenge conventional assumptions by indicating that resistance training is often the most effective modality for preserving global cognition in patients with AD and in cognitively healthy older adults, whereas aerobic and mind–body exercises appear to provide domain-specific advantages, particularly for memory and executive functions. (18,19) Taken together with dose–response analyses, these findings suggest that regular, moderate-intensity exercise performed at least 150 minutes per week is a pragmatic target for cognitive benefits, although the optimal protocol likely varies by cognitive domain and population. (17,19)

This narrative review synthesizes evidence between 2015 and 2026 on the biological mechanisms, clinical effects, and optimal parameters of PA across AD stages to provide evidence-based, personalized recommendations for clinical practice and future research.

2. Biological Mechanisms of Physical Activity in Alzheimer's Disease

2.1 Metabolic regulation (insulin resistance, "type 3 diabetes")

Chronic hyperglycemia and brain insulin resistance represent central pathological mechanisms linking metabolic dysfunction to AD progression (5,6). Conceptualized as "type 3 diabetes", AD features impaired neuronal insulin signaling that disrupts glucose transport (reduced GLUT4 translocation), energy metabolism, and protective neurotrophic pathways, thereby rendering neurons more vulnerable to Aβ/tau toxicity, oxidative stress, and apoptosis (16,17). Epidemiological data confirm these relationships: type 2 diabetes increases AD risk by approximately 50–100%, while even prediabetic elevations in blood glucose are associated with accelerated cognitive decline(18).

PA counteracts these metabolic deficits through both insulin-dependent and insulin-independent mechanisms(19). Acutely, muscle contraction enhances GLUT4-mediated glucose uptake independent of insulin, reducing postprandial hyperglycemia and chronic glycemic burden(14). Chronically, exercise improves peripheral and central insulin sensitivity via upregulation of PI3K/Akt signaling, reducing hyperphosphorylation of insulin receptor substrate-1 (IRS-1) at serine residues – a key convergence point between diabetes and AD pathology(20). These adaptations decrease the formation of advanced glycation end-products (AGEs) and mitigate AGE–RAGE-mediated neuroinflammation (21).

In AD-specific contexts, exercise helps restore brain bioenergetics and modulates insulin-degrading enzyme (IDE) activity(22). Because IDE, which is competitively inhibited by insulin, degrades both insulin and Aβ, exercise-induced improvements in insulin homeostasis can enhance Aβ clearance while also reducing tau hyperphosphorylation via GSK-3β inhibition(23,24). Randomized controlled trials further demonstrate that resistance training yields superior glycemic control compared with aerobic exercise, with significant

reductions in HbA1c and fasting glucose among older adults with cognitive impairment(25). Collectively, these findings indicate that PA directly targets core metabolic abnormalities increasingly conceptualized as “type 3 diabetes” in AD, thereby acting on an upstream driver of neurodegeneration. By restoring insulin sensitivity and reducing chronic glycemic stress, exercise may create a more favorable bioenergetic environment in which other neuroprotective mechanisms can operate. The main biological pathways through which PA may exert neuroprotective effects in AD are summarized in Table 2.

2.2 Neuroplasticity and Neurotrophic Support (BDNF, IGF-1, hippocampus volume)

PA exerts profound effects on brain plasticity through upregulation of neurotrophic factors that are critical for neuronal survival and synaptic integrity(13,26). Exercise consistently increases levels of brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), promoting hippocampal neurogenesis, dendritic spine formation, and synaptogenesis(27). Resistance training has been associated with increased circulating BDNF levels and other neuroprotective factors in older adults, although most evidence comes from non-AD or mixed cognitive-impairment populations(28–30). Network meta-analysis indicates that resistance training is the most promising strategy to slow global cognitive decline in AD (25). Aerobic exercise has been shown to increase hippocampal volume by approximately 2% over 12 months (compared with about 1% atrophy in controls), an effect that correlates with improvements in spatial memory(31). Multicomponent training engages both neurotrophic and cognitive networks, enhancing default mode network connectivity and strengthening frontoparietal executive networks(32).

Taken together, these data show that PA not only slows structural brain decline, but actively promotes neuroplastic remodeling in regions that are critically involved in learning and memory. Neurotrophic upregulation therefore represents a key pathway through which exercise can counterbalance synaptic loss and hippocampal atrophy in AD.

2.3 Modulation of Aβ and Tau pathology

Exercise also influences the core pathological hallmarks of AD, Aβ and tau, by enhancing protein clearance and reducing their production. In animal models, chronic exercise reduces Aβ burden by approximately 30–50%, an effect partly mediated by increased expression of Aβ-degrading enzymes such as neprilysin and insulin-degrading enzyme (IDE) (13). In humans, higher cardiorespiratory fitness has been associated with more favorable CSF Aβ42/40 ratios and lower cortical amyloid deposition on Pittsburgh Compound B (PiB) PET imaging(33). Exercise may further facilitate Aβ removal by upregulating Aβ-degrading enzymes and by modulating low-density lipoprotein receptor-related protein-1 (LRP-1)–dependent clearance pathways at the blood–brain barrier and in peripheral organs, as suggested by mechanistic studies on Aβ clearance and lifestyle-related regulation of LRP-1. (34,35)

Tau pathology may also benefit from exercise through inhibition of glycogen synthase kinase-3β (GSK-3β) via IGF-1/PI3K signaling and activation of phosphatases, thereby reducing neurofibrillary tangle formation (23,24). Thus, PA appears to influence both the production and clearance of Aβ and tau, acting on the very proteins that define the neuropathological core of AD. While human evidence remains more limited than animal data, the convergence of biomarker and imaging findings supports a biologically plausible disease-modifying potential of exercise at the molecular level.

2.4 Anti-inflammatory and Antioxidant Effects

Chronic neuroinflammation is a central driver of AD progression, characterized by sustained microglial activation, astrocytic reactivity, and elevated pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6, which together contribute to synaptic dysfunction and neuronal loss (36). Experimental and clinical data increasingly indicate that physical exercise can modulate these processes at multiple levels, acting on both peripheral immune signaling and central glial responses (37). In animal models of AD, regular aerobic or combined training attenuates microglial and astroglial activation, reduces expression of pro-inflammatory cytokines and NLRP3 inflammasome components, and shifts glia toward a more neuroprotective phenotype, changes that parallel improvements in cognition and reductions in amyloid and tau pathology (36,37). Human studies, although fewer and more heterogeneous, suggest that exercise interventions in older adults with cognitive impairment can lower systemic inflammatory markers and may blunt central neuroinflammatory signaling, supporting the translational relevance of these preclinical findings(37). Collectively, this evidence supports the view that suppression and reprogramming of maladaptive neuroinflammation constitutes a key mechanism through which PA may confer neuroprotection and slow disease progression in AD (36,37).

2.5 Cerebrovascular and White Matter Protection

Exercise improves cerebral blood flow (CBF), vascular health, and white matter integrity – vascular factors that account for a substantial proportion of dementia risk(38). Aerobic training has been associated with increased CBF, including in hippocampal and frontal regions, in older adults, providing a potential haemodynamic substrate for cognitive benefits(38,39). In a 12-month randomized controlled trial in older women, resistance training attenuated progression of white matter lesions compared with a non-exercise control group, suggesting that strength training may contribute to structural preservation of cerebral white matter(40). Aerobic exercise programmes have also been shown to improve white matter microstructure, with increases in fractional anisotropy in major association tracts that correlate with better executive function and processing speed(39). Although specific data on cerebral autoregulation in AD are limited, studies in older adults indicate that regular exercise can improve dynamic cerebral autoregulation and reduce vascular pulsatility, changes that are expected to mitigate microvascular damage and small-vessel disease burden(38). Together, these cerebrovascular and white matter effects position PA as a key intervention at the intersection of neurodegenerative and vascular pathways, providing a structural and haemodynamic substrate for the cognitive improvements observed in clinical trials.

Table. 1. Biological mechanisms underlying the protective effects of physical activity in Alzheimer's disease

Mechanism	Pathophysiological process in AD	Effect of PA	Clinical relevance	Key supporting studies
Glucose metabolism / insulin resistance	Hyperglycemia, insulin resistance ("type 3 diabetes"), neuronal dysfunction	Improved insulin sensitivity, reduced blood glucose levels	Reduced risk of AD, slower disease progression	(6,14,41)

Mechanism	Pathophysiological process in AD	Effect of PA	Clinical relevance	Key supporting studies
Neuroinflammation	Chronic microglial activation, increased pro-inflammatory cytokines	Reduction of pro-inflammatory cytokines, modulation of immune response	Neuroprotection, reduced neuronal damage	(13,36,37)
Amyloid-β accumulation	Plaque deposition and amyloid-related neurotoxicity	Reduced amyloid accumulation and enhanced clearance	Potential slowing of disease progression	(34,35,42)
Tau pathology	Neurofibrillary tangles, cytoskeletal disruption, neuronal dysfunction	Potential modulation of tau phosphorylation	Improved neuronal stability	(20,24)
BDNF and neuroplasticity	Reduced synaptic plasticity and neurogenesis, neuronal loss	Increased BDNF levels, enhanced neurogenesis and synaptic plasticity	Improved cognition and memory	(15,31)
Cerebral blood flow	Reduced cerebral perfusion, vascular dysfunction	Improved cerebral circulation and oxygen delivery	Better cognitive function	(38,39,43)
Brain structure (hippocampus)	Hippocampal atrophy and volume loss	Increased hippocampal volume, reduced rate of atrophy	Preservation of memory function	(31,44)
Genetic modulation	Genetic susceptibility (e.g. APOE-related pathways)	Modulation of gene expression and risk pathways by PA	Attenuation of the impact of genetic risk	(45)
Sedentary behavior (negative mechanism)	Reduced neuronal activation, increased neurodegeneration with inactivity	Replacement of sedentary time with movement improves outcomes	Independent reduction in dementia risk	(46)

Table. 1. presents the key biological mechanisms through which PA is proposed to exert neuroprotective effects in AD. It integrates metabolic, vascular, inflammatory, and neurobiological pathways, including improved glucose metabolism and insulin sensitivity, attenuation of neuroinflammation, reduced amyloid-β and tau-related pathology, enhancement of BDNF-mediated neuroplasticity, and preservation of hippocampal structure. The table also underscores the potential of PA to modulate genetic susceptibility and counteract the

detrimental impact of sedentary behavior. Collectively, these mechanisms provide a coherent pathophysiological rationale for the beneficial clinical effects of exercise and support its inclusion as a core component of comprehensive prevention and management strategies for AD.

3. Clinical Effects of Physical Activity in Alzheimer's Disease

3.1. Cognitive outcomes

Meta-analyses of randomized controlled trials consistently demonstrate cognitive benefits from PA in AD and related dementias, with the most robust effects typically observed for global cognition and executive function (47). Groot et al.'s meta-analysis of 18 randomized controlled trials in patients with dementia (n≈800) reported a moderate overall effect of PA on cognitive function (SMD 0.42, 95% CI 0.23–0.62), with similar benefits in those with AD (SMD 0.38, 95% CI 0.09–0.66) and in mixed AD/non-AD dementia samples (SMD 0.47, 95% CI 0.14–0.80) (48). A recent network meta-analysis in AD suggests a hierarchy of exercise modalities, with resistance training showing the highest probability of being the most effective approach for global cognition, multicomponent exercise performing best for executive function, and purely aerobic training generally ranking lower, although still beneficial compared with usual care (25). Dose–response analyses across older adults with and without cognitive impairment indicate that moderate weekly volumes of exercise are associated with the most consistent cognitive gains, whereas very low doses tend to produce only small effects and higher doses do not clearly add further benefit(48). Taken together, these findings support the use of regular, structured PA as a clinically relevant strategy to preserve cognition in AD, while also highlighting that optimal modality and dosage likely vary across individuals and disease stages(25,47,48).

3.2 Neuropsychiatric Symptoms and Behavioral Effects

Neuropsychiatric symptoms are common in AD and related dementias, and several trials suggest that PA can help alleviate this burden. A meta-analysis by Groot et al. reported that exercise interventions in people with dementia not only improve global cognition but also show favourable, though more modest, effects on behavioural and psychological symptoms, particularly when programs are supervised and multicomponent (47). A recent systematic review of exercise programs in community-dwelling individuals with dementia similarly found consistent small-to-moderate improvements in neuropsychiatric symptoms and activities of daily living, with better outcomes in interventions that combined aerobic, strength, and balance components and were delivered regularly over several months (49). In studies that included both cognitive and affective outcomes, such as those summarized by Jia et al., improvements in mood and behavioural symptoms often paralleled gains in cognitive performance, suggesting that exercise may act on shared pathways influencing motivation, engagement, and overall quality of life, even though effect sizes vary across trials and symptom domains (50).

3.3 Functional Capacity and Quality of Life (QoL)

PA appears to preserve functional independence in individuals with AD, often to a greater extent than would be expected based on cognitive changes alone(47). In a meta-analysis of

randomized controlled trials in dementia, Groot et al. reported small-to-moderate improvements in activities of daily living, particularly in multicomponent programs combining resistance, balance, and endurance training(47). Consistently, the six-month Body & Brain multicomponent intervention by Borges-Machado et al. attenuated functional decline and helped maintain or slightly improve ADL and QoL-AD scores compared with usual care in people with major neurocognitive disorder (51).
Evidence on QoL is more heterogeneous: shorter aerobic interventions, such as the nine-week continuous versus interval training trial by Enette et al., improved aerobic fitness and walking capacity and suggested modest QoL benefits despite minimal cognitive change (15). At a broader level, Dauwan et al.'s transdiagnostic meta-analysis across chronic brain disorders, including AD, showed a medium effect of exercise on QoL and a large effect on depressive symptoms, indicating that mood and psychological well-being are particularly responsive to PA and likely mediate much of the QoL gain in dementia (52). Overall, these findings suggest that exercise-related QoL improvements in AD are real but modest and are driven more by mood, functional capacity, and social engagement than by cognition alone.

3.4 Disease progression slowing

Moderate evidence suggests that PA may slow clinical progression in AD, although long-term (>12–24 months) randomized controlled trials remain scarce(53). A meta-analysis of randomized trials in individuals with AD and mild cognitive impairment reported that exercise interventions produced moderate improvements in global cognition, with effect sizes for MMSE and related measures in the range of Hedges' g 0.4–0.6, indicating attenuation rather than abolition of cognitive decline(54). Across available 6–12-month trials, exercise groups typically show smaller declines in global cognition than control groups, corresponding to between-group differences of roughly 1–2 MMSE points over one year, particularly when interventions are initiated in earlier disease stages(53,54). These estimates should be interpreted cautiously given the limited number of long-term RCTs and the heterogeneity of exercise protocols and study populations(53).

3.5 Disease Stage-Specific Effects

Observational evidence indicates that higher levels of PA are associated with a substantially lower incidence of all-cause dementia and AD in mid- to late life, supporting exercise as a modifiable preventive factor rather than a purely symptomatic intervention(11). Multidomain lifestyle trials initiated at prodromal stages, such as the FINGER study in individuals with increased dementia risk, suggest that combining PA with dietary counseling, cognitive training, and vascular risk management can help preserve global cognition over several years, although absolute effect sizes remain modest (55). Across randomized and quasi-experimental exercise studies in people with mild to moderate cognitive impairment or dementia, multicomponent training appears particularly suitable for adaptation across early Clinical Dementia Rating stages by simultaneously targeting mobility, balance, and executive demands, which supports its preferential use when the primary clinical goal is to maintain function and delay disability rather than reverse established deficits.

4. Optimal Exercise Protocols for Alzheimer's Disease

4.1 Clinical Effects of Different Physical Activity Modalities in AD and MCI

PA appears to exert multidimensional benefits across the AD continuum, with converging evidence from observational, randomized, and comparative studies. Higher levels of total daily PA are associated with a substantially lower risk of incident AD and slower cognitive decline in community-dwelling older adults, independent of traditional risk factors and even in individuals without structured exercise habits (12). In patients with mild to moderate AD, a 9- week randomized trial showed that both continuous and interval aerobic training improved aerobic fitness and cognitive performance, with parallel increases in plasma brain-derived neurotrophic factor (BDNF), underscoring a plausible neurotrophic mechanism linking exercise to cognitive gains (15). Network meta-analysis of exercise interventions in AD further indicates that structured resistance training and multicomponent programs (combining aerobic, strength, and balance elements) produce the most consistent improvements in global cognition and executive function, whereas purely aerobic protocols tend to yield smaller but still meaningful effects (25). In individuals with mild cognitive impairment, controlled aerobic exercise trials demonstrate improvements in executive function and processing speed beyond those observed in non-exercising controls, supporting the use of aerobic training as an early-stage intervention (33). Multicomponent physical exercise programs in people with dementia have additionally been shown to reduce neuropsychiatric symptoms and improve or stabilize QoL, suggesting that combining different exercise modalities may maximize both cognitive and psychosocial outcomes in this population (51).

Table 2. Types of physical activity and their clinical effects in Alzheimer's disease

Type of PA	Main clinical effects	Predominant cognitive domains	Additional benefits / clinical notes	Key supporting studies
Aerobic exercise	Improvement in global cognition; enhancement of cerebral blood flow	Global cognition, attention	Cardiovascular fitness; reduction of neuroinflammation; good feasibility	(15,33,56)
Resistance training	Slowing of cognitive decline; significant improvement in memory	Memory (strongest effect), global cognition	Improved insulin sensitivity; increased muscle strength; fall risk reduction	(25,29,40)
Power / high-velocity resistance training	Improvement in executive function and processing speed	Executive functions	Better neuromuscular coordination; improved reaction time	(57)
Multicomponent training (aerobic	Most comprehensive improvement across	Global cognition,	Better QoL; reduction of neuropsychiatric	(51,52)

Type of PA	Main clinical effects	Predominant cognitive domains	Additional benefits / clinical notes	Key supporting studies
+ resistance + balance/coordination)	cognitive, functional, and psychological outcomes	executive function	symptoms; improved ADL; high ecological validity	
Nordic walking / functional outdoor activity	Improvement in global cognition and everyday functioning	Global cognition	Enhanced mobility; accessible, low-cost, high adherence in mild–moderate AD	(58)
Continuous aerobic training	Improvement in cognition and physical capacity	Global cognition	Cardiovascular adaptation; suitable for structured rehabilitation programs	(15)
Interval aerobic training	Stronger effect on neuroplasticity markers (e.g. BDNF) with cognitive gains	Memory, executive function	Pronounced increase in BDNF; potentially greater neurobiological impact	(15)
General daily PA (non-exercise movement, lifestyle PA)	Reduced risk of incident AD; slower cognitive decline	Global cognition	Primary prevention; feasible at population level; integrated into daily routine	(12)

Table 2. PA interventions in AD differ in their cognitive and functional profiles, with resistance training showing the strongest effect on memory, multicomponent programs providing the broadest benefits across domains, and aerobic exercise primarily supporting global cognition and cardiovascular mechanisms. These data suggest that exercise prescription should be individualized, taking into account both the targeted cognitive domain and the patient's functional status.

4.2 Dose-Response Relationship

Evidence from dose–response analyses suggests that moderate total volumes of PA, in the range of approximately 150 minutes per week of moderate-intensity exercise, are associated with the most consistent cognitive benefits in older adults with cognitive impairment, including dementia(48). In the meta-regression by Sanders et al., moderate weekly volumes generally produced small-to-moderate improvements in global cognition, whereas lower doses were associated with only small effects and higher doses did not show a clear additional

advantage(48). Complementary findings from randomized trials in patients with dementia indicate that longer sessions and sufficiently high weekly doses are needed to elicit meaningful gains in both cognition and physical function, supporting the notion that there is a minimal effective "threshold" of exercise exposure(29). Overall, exercising two to three times per week at moderate intensity appears to balance adherence and physiological adaptation, although robust data supporting the superiority of higher frequencies or more complex periodization schemes in AD are still lacking(29,48).

4.3 Intensity Prescriptions

Current evidence does not support a single optimal intensity threshold for all patients with dementia, but available trials and exercise science guidelines converge on the use of moderate-intensity protocols as a pragmatic and well-tolerated target. In a 9-week combined aerobic and strength training program in patients with dementia, Bossers et al. used moderate-intensity cycling and resistance exercises and observed improvements in both cognitive and motor function without excess adverse events or poor tolerance, supporting the feasibility of this intensity range in clinical populations(56). Network meta-analysis in AD indicates that resistance and multicomponent training are particularly effective for cognition, and most included trials prescribed exercises at moderate to moderately high relative loads (for example, multiple sets of 8–12 repetitions at self-reported moderate effort), rather than very low or maximal intensities(25). Concept papers on exercise for dementia prevention further recommend flexible, individualized prescriptions centred on moderate intensity—often operationalized as a Borg rating of perceived exertion around 12–14 or a comfortable but somewhat challenging pace—which can be adjusted according to comorbidities, baseline fitness, and disease stage(59). Collectively, these data support the use of moderate-intensity aerobic and resistance exercise as the default starting point in AD, with progression or reduction in intensity guided by tolerance, safety, and clinical response rather than fixed numerical targets.

4.4 Disease Stage-Specific Recommendations

These stage-oriented recommendations synthesize patterns from cohort studies, randomized controlled trials, and meta-analyses on PA in older adults with MCI and AD. They are intended as a pragmatic framework rather than prescriptive rules. Observational data suggest that higher total daily PA is associated with reduced risk of incident AD and slower cognitive decline in preclinical and MCI populations, particularly when activity levels approximate or exceed 150 minutes per week of moderate-intensity movement (e.g. brisk walking, household tasks)(12). Randomized trials in MCI and mild AD indicate that aerobic and resistance training at moderate intensity can improve executive function and global cognition, while multicomponent programs tend to provide additional benefits for balance, mobility, and neuropsychiatric symptoms (15,25,33,51). In moderate AD, exercise effects shift toward preservation of function and mobility, with multicomponent protocols showing the most consistent impact on ADL and fall risk in available studies. In severe AD, the evidence base is sparse, but small trials and clinical experience support the use of seated or assisted low-intensity activity to maintain comfort, circulation, and basic mobility, with safety and caregiver burden as primary constraints. Overall, intensity and volume should be individualized, with moderate-intensity, supervised exercise as a reasonable default starting point that can be scaled up or down according to tolerance and clinical response

Table 3. Pragmatic Stage-Specific Exercise Recommendations in Alzheimer's Disease

AD stage	Primary goal	Preferred modality*	Typical weekly volume**	Expected impact (approximate)
Preclinical / MCI	Risk reduction / delay onset	Multicomponent (aerobic + strength + balance)	~150 min/week moderate intensity	Small–to- moderate improvement in cognition; lower risk of progression (12,33)
Mild AD (MMSE 20–26)	Cognitive support	Resistance or multicomponent	~120–150 min/week moderate intensity	Moderate benefit on global cognition and executive function (15,25,33,51)
Moderate AD (MMSE 10–20)	Functional independence / ADL	Multicomponent with emphasis on balance/strength	~90–120 min/week, tailored	Small–to- moderate improvement or stabilization in ADL and mobility; modest cognitive benefit (47,51)
Severe AD (MMSE <10)	Safety, mobility, comfort	Seated or assisted low- intensity exercise	~60–90 min/week in short bouts	Small gains in mobility and comfort; maintenance of posture and circulation; focus on safety and caregiver feasibility

* "Preferred modality" reflects patterns observed across trials and meta-analyses rather than a rigid prescription; individual comorbidities, preferences, and resources should guide final choice.

** Volumes are approximate ranges commonly used in studies; many trials report benefits with 2–3 supervised sessions per week of 30–60 minutes, adjusted for tolerance and disease severity.

5. Discussion

The present review supports the view that PA should be regarded as an important non-pharmacological strategy in AD, with effects that extend well beyond general health promotion. The available evidence suggests that exercise influences disease risk and progression through a complex interplay of metabolic, vascular, inflammatory, neurotrophic, and epigenetic mechanisms. In particular, disturbances in glucose metabolism—especially

chronic hyperglycemia and insulin resistance—appear to be deeply implicated in AD pathophysiology, reinforcing the concept that neurodegeneration and metabolic dysfunction are tightly interconnected rather than merely coexisting phenomena. The idea of AD as a "type 3 diabetes" has been discussed for years and remains relevant because it captures the observation that impaired brain insulin signaling may contribute to neuronal vulnerability, synaptic dysfunction, and accumulation of classical AD pathological markers, including amyloid-β and hyperphosphorylated tau.

From a mechanistic perspective, chronic hyperglycemia may exert neurotoxic effects through several converging pathways. Increased oxidative stress, mitochondrial dysfunction, and formation of advanced glycation end products (AGEs) can all promote neuronal injury and accelerate synaptic impairment. In parallel, insulin resistance within the central nervous system may reduce synaptic plasticity and alter neuronal metabolism, thereby facilitating amyloidogenic processing and tau pathology. These mechanisms are clinically meaningful because epidemiological studies consistently show that type 2 diabetes mellitus is associated with an increased risk of cognitive decline and dementia, while even mild elevations in glucose levels below the diabetic threshold may also confer risk. Taken together, these data support the notion that metabolic dysfunction is not simply a comorbidity of AD, but may represent one of the upstream drivers of disease expression and progression.

PA appears to counteract several of these pathological processes simultaneously. Regular exercise improves insulin sensitivity and enhances glucose uptake in skeletal muscle through both insulin-dependent and insulin-independent pathways, including GLUT4 translocation. This metabolic effect reduces chronic glycemic exposure and may lessen the systemic burden of hyperglycemia-related stress. Importantly, the benefits of exercise are not limited to peripheral metabolism. Exercise-induced improvements in glucose homeostasis are linked to increased expression of brain-derived neurotrophic factor (BDNF), enhanced synaptic plasticity, and better cognitive performance, suggesting that metabolic regulation may act as an upstream mechanism connecting PA with neuroprotection. In this sense, exercise may help preserve neuronal function not only by lowering metabolic risk, but also by supporting adaptive signaling pathways essential for learning and memory.

The neuroprotective value of PA is further supported by evidence indicating favorable effects on vascular and inflammatory pathways. Exercise improves endothelial function, promotes cerebral perfusion, and reduces chronic low-grade inflammation, thereby mitigating some of the vascular and metabolic consequences of hyperglycemia on the brain. These effects are particularly relevant in AD, where cerebrovascular dysfunction, impaired nutrient delivery, and inflammatory activation contribute to disease progression. The 2024 Lancet Commission report on dementia prevention, intervention, and care emphasized that a substantial proportion of dementia cases may be attributable to modifiable risk factors, including physical inactivity, obesity, and diabetes.(10) This public health perspective is important because it frames physical activity not merely as a supportive measure, but as a potentially powerful preventive tool in a disease for which disease-modifying pharmacological options remain limited.

The clinical literature also suggests that PA may improve cognition, particularly memory and executive functioning, although findings are not fully consistent across studies. (25,47,48,54) This variability likely reflects differences in exercise type, intensity, duration, supervision, baseline disease severity, and outcome measures. Resistance training, multicomponent exercise programs, and aerobic interventions may all be beneficial, but they do not appear to exert identical effects across cognitive domains. Resistance training may be especially effective for global cognition and memory, whereas multicomponent programs may offer broader benefits in executive function, attention, and cognitive flexibility. Aerobic exercise

remains important because of its strong cardiometabolic profile and its association with BDNF-mediated neuroplasticity. The lack of a universally superior modality suggests that exercise prescription in AD should be individualized rather than standardized in a rigid manner.

Another clinically relevant issue is that improvements in cognitive performance do not always translate into measurable gains in QoL. This does not necessarily indicate treatment failure; rather, it reflects the fact that QoL in AD is influenced by multiple determinants, including mood, social engagement, caregiver support, physical independence, and environmental adaptation. Consequently, even when cognitive outcomes are modest, exercise may still yield meaningful benefits by preserving mobility, reducing apathy, improving sleep, and supporting autonomy. For this reason, PA should be considered within a broader biopsychosocial framework rather than evaluated solely through cognitive test scores.

Emerging evidence also suggests that PA may modify the relationship between genetic risk and AD-related brain changes. High-dimensional mediation analyses indicate that exercise can partially mediate the association between genetic predisposition and brain atrophy, implying that lifestyle may buffer, at least to some extent, the structural consequences of inherited vulnerability. This finding is conceptually important because it challenges the view of AD risk as fixed and deterministic. Instead, it supports the more clinically useful idea that disease expression is modifiable, and that PA may act as an epigenetic and neurobiological regulator of resilience. In parallel, experimental and translational studies have shown that exercise can influence DNA methylation, histone modifications, and non-coding RNA expression, particularly in pathways related to neurotrophins, synaptic plasticity, and amyloid processing. These mechanisms may help explain why regular exercise is increasingly viewed as a biologically active intervention rather than simply a healthy habit.

The present review is also aligned with broader epidemiological evidence showing that higher PA levels are associated with a lower risk of cognitive decline and dementia at the population level. Although the magnitude of protection in observational studies may be modest and susceptible to residual confounding, the consistency of the direction of effect across cohorts strengthens the argument for lifestyle-based prevention. In addition, physical inactivity often clusters with other modifiable risk factors, including obesity, hypertension, diabetes, and social isolation, meaning that exercise may exert indirect benefits by improving overall cardiometabolic and psychosocial health. From this perspective, PA is best understood as a multidimensional intervention with potential effects on several of the major pathways implicated in dementia.

Despite these encouraging findings, the current evidence base has important limitations. Many studies are characterized by small sample sizes, short follow-up periods, and heterogeneous intervention protocols. (25,47,48,54) This makes it difficult to define the optimal frequency, intensity, and duration of exercise for individuals with AD at different disease stages. These estimates should be interpreted cautiously given the limited number of long- term randomized controlled trials and the considerable heterogeneity in exercise protocols, disease stages, and outcome measures. Moreover, some trials use broad cognitive outcomes that may not capture domain-specific benefits, while others lack biomarker-based endpoints that could clarify mechanisms. (8–10) Future research should therefore prioritize standardized randomized controlled trials with longer follow-up, careful monitoring of adherence, and multimodal outcome assessment, including cognition, function, mood, metabolic markers, inflammatory biomarkers, and neuroimaging.(10,11)

In summary, the current body of evidence indicates that PA influences AD through intertwined metabolic, vascular, neurotrophic, inflammatory, and epigenetic pathways. By

improving insulin sensitivity, reducing hyperglycemia-related neurotoxicity, enhancing cerebral perfusion, and supporting neuroplasticity, exercise may contribute to both prevention and disease management.(5,6,10,16–20,22–24) Although it should not be viewed as a substitute for medical care, PA represents a low-cost, accessible, and biologically plausible intervention with the potential to reduce the burden of AD, particularly when introduced early and tailored to the individual's functional capacity. (5,7–12) In the absence of highly effective disease-modifying therapies, regular PA deserves a central place in comprehensive strategies for dementia prevention and care.

6. Conclusions

PA appears to be one of the most promising currently available non-pharmacological strategies in AD, with potential benefits that extend across metabolic, vascular, inflammatory, and neurobiological domains. The accumulated evidence suggests that regular exercise may help reduce disease risk and slow progression by improving insulin sensitivity, attenuating hyperglycemia-related neurotoxicity, enhancing cerebral perfusion, reducing neuroinflammation, and supporting neuroplasticity through neurotrophic mechanisms.

Although the magnitude of benefit varies across studies, the overall direction of the evidence is remarkably consistent: PA is consistently associated with better cognitive outcomes, greater functional independence, and improved brain resilience, particularly when introduced early and adapted to the patient's clinical status. Its effects are likely to be multimodal rather than attributable to a single pathway, which may partly explain its relevance across different stages of the disease.

In the absence of highly effective disease-modifying therapies, PA should be considered a foundational component of comprehensive AD prevention and management. As a low-cost, accessible, and biologically plausible intervention, it offers a meaningful opportunity to reduce the burden of dementia at both the individual and population levels. However, these conclusions should be interpreted in light of the predominantly short-term trials and heterogeneity of exercise protocols, underscoring the need for more standardized, long-duration studies.

Disclosure

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