International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	THE IMPACT OF REGULAR PHYSICAL ACTIVITY ON DELAYING THE ONSET OF ALZHEIMER'S DISEASE: A REVIEW OF NEUROPROTECTIVE MECHANISMS
DOI	https://doi.org/10.31435/ijitss.1(49).2026.4942
RECEIVED	26 January 2026
ACCEPTED	23 March 2026
PUBLISHED	30 March 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

THE IMPACT OF REGULAR PHYSICAL ACTIVITY ON DELAYING THE ONSET OF ALZHEIMER'S DISEASE: A REVIEW OF NEUROPROTECTIVE MECHANISMS

Luiza Łabuzińska *(Corresponding Author, Email: luizalabuzinska@gmail.com)*
University Clinical Hospital No. 2 of the Medical University of Lodz, Łódź, Poland
ORCID ID: 0009-0004-7404-1662

Laura Magdalena Sikorska
Andrzej Frycz Modrzewski University, Kraków, Poland
ORCID ID: 0009-0009-5326-779X

Paulina Pudło
Medical Student, Faculty of Medicine, Collegium Medicum, University of Rzeszów, Rzeszów, Poland
ORCID ID: 0009-0006-9440-6061

Anna Koman
University Children's Hospital of Cracow (UCH), Kraków, Poland
ORCID ID: 0009-0009-6999-8407

Martyna Bukowiec
Central Clinical Hospital of Medical University of Lodz, Łódź, Poland
ORCID ID: 0009-0007-2901-9230

Karolina Szałata
Jan Mikulicz-Radecki University Clinical Hospital in Wroclaw, Wrocław, Poland
ORCID ID: 0009-0006-0042-0082

Mikołaj Asztabski
Łańcut Medical Centre Ltd., Łańcut, Poland
ORCID ID: 0009-0009-3286-4632

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by memory impairment, cognitive deterioration, and neurobiological changes, notably the accumulation of amyloid-beta (Aβ) and tau pathology. Recent data suggests that consistent physical activity (PA) may delay the onset and progression of Alzheimer's disease (AD) through various neuroprotective mechanisms. This research synthesizes results from 31 contemporary investigations encompassing both human and animal subjects. The focus is on the impact of physical activity on brain-derived neurotrophic factor (BDNF) expression, cerebral blood flow, inflammation reduction, and proteinopathy management. Brain-Derived Neurotrophic Factor (BDNF) is crucial for maintaining synaptic plasticity and promoting neurogenesis in the hippocampus, both of which are significantly compromised in Alzheimer's Disease (AD). PA-induced elevations in BDNF enhance cognitive resilience and neuronal integrity. Furthermore, exercise has been shown to enhance cerebral perfusion, so improving the delivery of oxygen and nutrients while promoting the disposal of waste, including glymphatic flow. The anti-inflammatory effects of PA entail the downregulation of pro-inflammatory cytokines (e.g., IL-6, TNF-α) and the upregulation of anti-inflammatory mediators, which alleviate chronic neuroinflammation commonly seen in Alzheimer's disease. Furthermore, PA appears to reduce oxidative stress by enhancing innate antioxidant systems, including superoxide dismutase and glutathione peroxidase. PA may significantly affect essential pathophysiological features of AD, such as amyloid-beta buildup and tau hyperphosphorylation, by promoting proteostasis and stimulating autophagy. Research from both preclinical and clinical studies repeatedly reveals associations between regular physical activity and improved cognitive function, augmented brain structural integrity, and less neurodegeneration. The data indicate that physical activity serves as a cost-effective, accessible, and non-pharmacological intervention with significant neuroprotective potential to reduce the risk of Alzheimer's disease and delay its development.

KEYWORDS

Alzheimer's Disease, Physical Activity, Exercise, Neuroprotection, BDNF, Cognitive Decline, Amyloid-Beta, Tau Protein

CITATION

Luiza Łabuzińska, Laura Magdalena Sikorska, Paulina Pudło, Anna Koman, Martyna Bukowiec, Karolina Szałata, Mikołaj Asztabski. (2026) The Impact of Regular Physical Activity on Delaying the Onset of Alzheimer's Disease: A Review of Neuroprotective Mechanisms. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4942

Methods: A structured search was conducted on the PubMed database using combinations of the following keywords: "Alzheimer's disease", "physical activity", "exercise", "BDNF", "neuroprotection", "amyloid-beta", and "tau protein". Peer-reviewed articles published within the past 10 years were selected, with preference for original research and systematic reviews. Thirty-three studies were selected for inclusion. Data were synthesized qualitatively, focusing on mechanistic insights and clinical relevance.

Introduction

The examination of Alzheimer's disease within populations

Alzheimer's disease constitutes around 60–80% of all dementia cases. The aging population is projected to quadruple the global frequency by 2050, with the most significant increases anticipated in low- and middle-income nations [32]. Presently, more than 6 million individuals in the United States are afflicted with Alzheimer's disease. In the absence of new treatments, this figure is projected to exceed 13 million by 2050 [33]. The disease predominantly impacts individuals over 65; however, approximately 5% of cases are early-onset Alzheimer's dementia, occurring prior to age 65. Advanced age, genetic predisposition (notably the APOE ε4 allele), cardiovascular comorbidities, insufficient physical exercise, and diminished cognitive reserve constitute risk factors for Alzheimer's disease. Alzheimer's disease imposes significant financial burdens on society and the economy, encompassing direct healthcare expenses, informal caregiving, and diminished productivity. Estimates indicate that the amount exceeds hundreds of billions of dollars annually.

Contemporary treatment approaches and their constraints

The majority of currently approved medications for Alzheimer's disease concentrate on alleviating symptoms rather than altering the disease's progression. Physicians frequently prescribe cholinesterase inhibitors, such as donepezil and rivastigmine, along with the NMDA receptor antagonist memantine, to enhance cognitive function; however, these medications provide only temporary benefits and lack enduring efficacy. Several novel pharmaceuticals, such as aducanumab and lecanemab, are monoclonal antibodies that specifically target amyloid-beta. They are ineffective and potentially hazardous, leading to cerebral edema and microhemorrhages [33]. Moreover, these treatments are costly and inaccessible to numerous patients, particularly in resource-limited areas. Current treatments for Alzheimer's disease do not target the several underlying causes, such as inflammation, vascular issues, mitochondrial dysfunction, and protein misfolding.

Due to these constraints, there has been an increased focus on preventive strategies that address modifiable lifestyle factors. Physical activity is crucial as it can significantly alter certain neurobiological processes associated with Alzheimer's disease. Exercise mitigates disease progression by elevating neurotrophin levels, enhancing the integrity of cerebral blood vessels, regulating immunological responses, and facilitating the clearance of proteins. Given the absence of very effective treatments that alter the disease's trajectory, consistent physical activity serves as a pragmatic and comprehensive method to reduce the risk of Alzheimer's disease and postpone cognitive deterioration.

Over 50 million individuals globally suffer from Alzheimer's disease, which remains a significant cause of disability and dependence among the elderly. Pathologically, this indicates that Aβ plaques accumulate extracellularly, tau tangles aggregate intracellularly, synaptic function is impaired, mitochondrial efficacy is

diminished, and neuroinflammation persists. As Alzheimer's disease progresses, cerebral blood flow and neurotrophin levels decline, resulting in neuronal death and exacerbating cognitive impairment [1, 2, 3, 4, 5]. Although pharmacological interventions continue to advance, their efficacy is frequently limited and mostly addresses symptoms. This illustrates the significance of identifying efficient methods to avert these issues.

Recent studies indicate that lifestyle modifications, particularly consistent physical activity, may serve as a therapeutic intervention to postpone the onset of Alzheimer's disease or mitigate its severity. Researchers have demonstrated that exercise can alter various brain health indicators, including elevating neurotrophic factors such as brain-derived neurotrophic factor (BDNF), enhancing cerebral blood flow, reducing oxidative stress, and modifying inflammatory pathways [9, 10, 11, 12]. PA can assist in eliminating misfolded proteins, reducing the accumulation of Aβ, and stabilizing tau phosphorylation [13, 14, 15]. These circuits elucidate the mechanism by which physical activity may mitigate the risk of Alzheimer's disease.

This review aims to synthesize and critically assess the evidence from clinical and experimental studies regarding the impact of regular physical activity on the progression of Alzheimer's disease via neuroprotective mechanisms. This study examines the molecular, vascular, immunological, and metabolic pathways influenced by exercise to provide a comprehensive and current understanding of how physical activity may aid in the prevention of Alzheimer's disease [16, 17, 18, 19, 20].

The Role of BDNF in Alzheimer's Disease

Brain-derived neurotrophic factor (BDNF) is a crucial neurotrophin that supports the survival, growth, and health of neurons in the central nervous system. Synaptic plasticity, learning, and memory are significantly impacted by Alzheimer's disease (AD). Brain-derived neurotrophic factor (BDNF) primarily functions by binding to the tropomyosin receptor kinase B (TrkB), initiating intracellular signaling cascades, including the PI3K/Akt, MAPK/ERK, and PLCγ pathways. These pathways facilitate neuronal survival, promote dendritic growth, and enhance synaptic connections over time (LTP) [1, 2, 3]. Individuals with Alzheimer's disease exhibit significantly reduced BDNF levels in impacted brain regions, such as the hippocampus and cortex. This correlates with the severity of the disease and cognitive impairments [4, 5, 6]. Decreased BDNF signaling exacerbates synaptic loss, accelerates neuronal degeneration, and diminishes cognitive reserve, rendering it a critical diagnostic and therapeutic target.

Numerous studies have shown that exercise significantly enhances the expression of BDNF in both animal models and humans. Elevated BDNF levels resulting from exercise are associated with enhanced neurogenesis in the hippocampus, increased synaptic formation, and improved cognitive performance [6, 7, 9]. In rat models of Alzheimer's disease, voluntary wheel running and treadmill training elevate BDNF mRNA and protein concentrations in the hippocampus. This enhances cognition and reduces amyloid pathology [10, 11, 14]. In elderly individuals, elevated blood levels of BDNF are associated with enhanced executive function, reduced cognitive decline, and a decelerated transition from moderate cognitive impairment (MCI) to Alzheimer's disease (AD) [15, 20, 23]. BDNF is crucial as it regulates proteostasis by promoting autophagy and reducing the accumulation of Aβ, hence enhancing neuronal protection.

Genetic variations also alter BDNF signaling. The Val66Met polymorphism influences the activity-dependent release of BDNF, resulting in Met carriers exhibiting reduced BDNF release and less plasticity, but still deriving benefits from exercise therapy [20, 28]. Individuals possessing the APOE ε4 allele, which increases their likelihood of developing Alzheimer's disease, typically exhibit reduced baseline levels of BDNF. Nevertheless, they exhibit significant elevations in BDNF levels subsequent to adherence to regular exercise regimens [3, 6, 15]. The data indicate that exercise can diminish genetic susceptibility by enhancing BDNF activity.

Brain-Derived Neurotrophic Factor (BDNF) is crucial in the neuroprotective benefits of physical exercise. Its influence on neuronal resilience, plasticity, and protein clearance renders it a crucial element in the battle against Alzheimer's disease. Lifestyle modifications that enhance BDNF expression, like as regular exercise, may assist individuals, particularly those at elevated risk, in preserving cognitive function and mitigating neurodegeneration.

PA diminishes pro-inflammatory cytokines such as TNF-α and IL-6 while elevating anti-inflammatory molecules including IL-10 and adiponectin. This mitigates persistent neuroinflammation and glial activation [9, 10, 23, 30]. It enhances the body's capacity to combat free radicals by increasing the amounts of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, which reduce reactive oxygen species and lipid peroxidation [18, 27, 31]. Moreover, consistent physical activity regulates proteostasis pathways, thereby diminishing the amyloidogenic processing of APP, accelerating the clearance of Aβ via neprilysin and insulin-degrading enzyme, and stabilizing tau by inhibiting kinases such as GSK-3β [11, 12, 13, 26, 28].

In murine models, physical activity reinstated cognitive function and enhanced learning by elevating BDNF levels in the hippocampus, reducing oxidative stress, and normalizing mitochondrial function and synaptic protein expression [14, 18, 20, 27]. Cognitive assessments indicated that physical activity mitigates the advancement from moderate cognitive impairment (MCI) to Alzheimer's disease (AD), enhances executive function, and aids memory retention [15, 19, 21, 25, 29, 30, 31]. These data indicate that regular exercise safeguards the brain through its influence on biochemical, structural, vascular, and immunological pathways critical to the progression of Alzheimer's disease.

The differential impacts of aerobic and resistance training on the progression of Alzheimer's disease

The nature of physical activity significantly influences the strength and specificity of neuroprotective advantages in Alzheimer's disease. Aerobic and resistance training have both been shown to be beneficial, albeit through distinct mechanisms.

Walking, cycling, and swimming are forms of aerobic exercise that enhance hippocampus volume, increase cerebral blood circulation, and elevate BDNF levels, so facilitating memory and learning. Aerobic exercises significantly enhance neurovascular coupling, facilitate angiogenesis, and accelerate the clearance of metabolic waste, including Aβ peptides [8, 10, 13, 28]. Longitudinal studies on humans indicate that consistent aerobic exercise may prevent cerebral atrophy, particularly in regions predisposed to Alzheimer's disease, such as the precuneus and posterior cingulate cortex [22, 29].

Conversely, resistance exercise, such as weight lifting or utilizing resistance bands, has been associated with enhancements in executive function, working memory, and functional connectivity, particularly in older adults with moderate cognitive impairment (MCI) [15, 25, 30]. Resistance exercise appears to enhance outcomes by elevating insulin-like growth factor 1 (IGF-1), improving mitochondrial function, and augmenting the synthesis of synaptic proteins [3, 24]. Resistance training may significantly impact anti-inflammatory mechanisms and glucose metabolism, both of which are disrupted in Alzheimer's disease [23, 27].

Combined training programs incorporating both aerobic and strength exercises may be more effective in addressing the vascular and metabolic aspects of neurodegeneration. Research on animals indicates that these therapies are more effective in combination than individually in enhancing learning, memory, and synaptic plasticity [20, 27]. Research indicates that including both forms of exercise into a training regimen can enhance cognitive function in an additive or perhaps multiplicative manner [19, 21, 31].

Aerobic and resistance exercises both confer benefits; however, aerobic training may more significantly enhance hippocampal health and cerebral blood vessels, whereas resistance training may more effectively improve executive function and metabolic resilience. Experts believe that tailored exercise regimens, which consider an individual's cognitive profile, physical state, and genetic predisposition (such as the APOE ε4 allele), will be the most efficacious in decelerating the advancement of Alzheimer's disease [6, 15, 24].

The impact of exercise intensity, age, and genetic variables on neuroprotective outcomes

The intensity of physical activity is crucial for obtaining neuroprotective advantages. High-intensity interval training (HIIT) elevates BDNF and IGF-1 levels more rapidly and markedly than moderate-intensity continuous training (MICT). HIIT is a superior method for enhancing synaptic plasticity and neurogenesis. Conversely, prolonged moderate-intensity exercise induces cumulative alterations in blood vessels and sustained anti-inflammatory benefits while minimizing oxidative damage. A balance between intensity and safety is crucial for individual tolerance, particularly for the elderly.

Age significantly influences the efficacy of neuroprotection following physical activity. Individuals under 65 exhibit more pronounced baseline neurotrophin upregulation and angiogenic responses, whilst those over 65 may require extended treatment durations to achieve comparable enhancements in BDNF and cerebral perfusion [5, 7, 14]. Commencing exercise later in life persists in mitigating cognitive decline and maintaining hippocampal function, demonstrating advantages throughout life and across various stages of disease [19, 21, 25].

Genetic variables, particularly the presence of APOE ε4, influence the efficacy of exercise. Individuals possessing the APOE ε4 allele exhibited reduced baseline BDNF levels and elevated amyloid levels. Intensive exercise regimens significantly elevate BDNF levels and diminish Aβ deposition in this group, hence mitigating genetic risk disparities [3, 6, 15]. The BDNF Val66Met polymorphism alters the brain's response to exercise. Individuals possessing the Met variation have reduced BDNF release yet nevertheless derive cognitive advantages from physical exercise [20, 28]. Customizing pharmacological agents for Parkinson's disease according to genetic profiles may yield optimal neuroprotective advantages.

Results

Numerous studies indicate that aerobic and resistance exercises significantly elevate BDNF levels, hence enhancing synaptic plasticity and neurogenesis, particularly in the hippocampus [4, 5, 6, 16, 17]. Brain-derived neurotrophic factor (BDNF) and other neurotrophins, including insulin-like growth factor 1 (IGF-1), promote neuronal survival, enhance dendritic complexity, and facilitate long-term potentiation. This contributes to the development of cognitive reserve and offers protection against Alzheimer's disease [1, 3, 20, 24]. Functional MRI studies indicate that individuals who engage in physical activity exhibit increased cerebral blood flow, enhanced cortical thickness, and improved interconnectivity among brain regions. This is particularly applicable to regions of the brain that are predisposed to Alzheimer's disease, such as the default mode network and hippocampus [7, 8, 22]. Exercise induces angiogenesis and enhances endothelial function, facilitating the transport of oxygen and nutrients while eliminating waste via glymphatic channels [2, 10, 13, 28].

Robust data from both animal and human studies indicates that physical activity safeguards the brain in individuals with Alzheimer's disease. BDNF upregulation is a fundamental step that facilitates neuronal survival and the generation of new neurons. Both BDNF and IGF-1 elevate with physical activity, and collectively they enhance synaptic plasticity and long-term potentiation, particularly in the hippocampus and cortex, regions more susceptible to Alzheimer's disease. Aerobic exercise enhances cerebral blood flow, hence augmenting oxygen delivery, nutrition supply, and metabolic clearance. This aids in maintaining equilibrium within neural networks. The vascular advantages encompass an increased capillary density, the formation of new blood vessels, and the synthesis of endothelial nitric oxide, all of which are crucial for maintaining a healthy neurovascular system [1, 3, 7, 20].

The anti-inflammatory properties of PA mitigate the progression of neuroinflammation, hence accelerating neurodegeneration. Exercise decreases the concentrations of pro-inflammatory cytokines in the bloodstream, including IL-6, TNF-α, and CRP, while elevating the levels of IL-10 and other anti-inflammatory mediators. This aids in reestablishing the body's immunological equilibrium and prevents microglia from becoming excessively active [9, 10, 23]. Furthermore, PA enhances the body's capacity to combat free radicals, thereby safeguarding lipids, proteins, and DNA from damage frequently associated with the onset of AD. The overexpression of antioxidant enzymes and enhanced mitochondrial activity contribute to antioxidant effects [18, 27, 31].

Exercise inhibits the aggregation of Aβ and tau, potentially via enhancing autophagy, accelerating lysosomal breakdown, and reducing the activity of kinases such as GSK-3β associated with tau phosphorylation. These proteostatic systems maintain the integrity of neuronal structure and function. Moderate-intensity aerobic exercise and resistance training confer cognitive advantages, albeit individuals may require tailored regimens based on age, initial fitness level, comorbidities, and genetic variables such as APOE-ε4. Neuroimaging studies indicate that individuals who engage in physical activity maintain their hippocampal volume, cortical thickness, and functional connectivity, which are associated with improved cognitive results [8, 22, 25, 30].

These data demonstrate the significance of physical activity as a multifaceted intervention addressing several cellular mechanisms associated with Alzheimer's disease. PA significantly influences neurotrophic signaling, vascular integrity, immunological responses, redox equilibrium, and proteostasis. This indicates that it may assist in delaying or halting the onset of Alzheimer's disease.

Conclusions

Consistent physical activity is an effective method to postpone the onset of Alzheimer's disease without pharmacological intervention. The neuroprotective mechanisms encompass elevated BDNF levels, enhanced cerebral blood flow, reduced inflammation, and diminished accumulation of deleterious proteins. Incorporating exercise into standard health regimens may alleviate the increasing burden of Alzheimer's disease.

Furthermore, exercise has additional advantages beyond mere health maintenance. Physical activity may decelerate the progression of mild cognitive impairment or early Alzheimer's disease symptoms and enhance quality of life by preserving brain volume, augmenting executive function, and stabilizing memory performance. Neuroimaging, biomarker assessment, and behavioral evaluations collectively indicate these functional enhancements.

Physical activity is a scalable and efficacious component of public health initiatives targeting neurodegeneration, as it is accessible, cost-effective, and exerts diverse effects on the body. Future research must concentrate on enhancing exercise prescriptions tailored to individual risk profiles by utilizing genetic,

physiological, and behavioral aspects to achieve optimal outcomes. Investing substantial effort in advocating for physical activity in clinical and community environments could significantly postpone the onset of Alzheimer's disease and mitigate its social and economic repercussions.

Promoting regular exercise among individuals constitutes a cost-effective and easily implementable public health policy, significantly benefiting the elderly population. With the increasing prevalence of Alzheimer's disease globally, exercise serves as an effective means to enhance cognitive resilience, improve quality of life, and address long-term healthcare requirements.

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no external funding.

Conflicts of Interests: The authors declare no conflict of interest.

REFERENCES

1. Cutuli, D., Decandia, D., Giacovazzo, G., & Coccurello, R. (2023). Physical exercise as disease-modifying alternative against Alzheimer's disease: A gut-muscle-brain partnership. *International Journal of Molecular Sciences, 24*(19), 14686. https://doi.org/10.3390/ijms241914686
2. Khemka, S., Reddy, A., Garcia, R. I., Jacobs, M., Reddy, R. P., Roghani, A. K., Pattoor, V., Basu, T., Sehar, U., & Reddy, P. H. (2023). Role of diet and exercise in aging, Alzheimer's disease, and other chronic diseases. *Ageing Research Reviews, 91*, 102091. https://doi.org/10.1016/j.arr.2023.102091
3. López-Ortiz, S., Pinto-Fraga, J., Valenzuela, P. L., Martín-Hernández, J., Seisdedos, M. M., García-López, O., Toschi, N., Di Giuliano, F., Garaci, F., Mercuri, N. B., Nisticò, R., Emanuele, E., Lista, S., Lucia, A., & Santos-Lozano, A. (2021). Physical exercise and Alzheimer's disease: Effects on pathophysiological molecular pathways of the disease. *International Journal of Molecular Sciences, 22*(6), 2897. https://doi.org/10.3390/ijms22062897
4. Radić, B., Blažeković, A., Duraković, D., Jurišić-Kvesić, A., Bilić, E., & Borovečki, F. (2021). Could mental and physical exercise alleviate Alzheimer's disease? *Psychiatria Danubina, 33*(Suppl. 4), 1267–1273.
5. Autio, J., Stenbäck, V., Gagnon, D. D., Leppäluoto, J., & Herzig, K.-H. (2020). (Neuro) peptides, physical activity, and cognition. *Journal of Clinical Medicine, 9*(8), 2592. https://doi.org/10.3390/jcm9082592
6. Cutuli, D., Decandia, D., Giacovazzo, G., & Coccurello, R. (2023). Physical exercise as disease-modifying alternative against Alzheimer's disease: A gut-muscle-brain partnership. *International Journal of Molecular Sciences, 24*(19), 14686. https://doi.org/10.3390/ijms241914686
7. Gaitán, J. M., Moon, H. Y., Stremlau, M., Dubal, D. B., Cook, D. B., Okonkwo, O. C., & van Praag, H. (2021). Effects of aerobic exercise training on systemic biomarkers and cognition in late middle-aged adults at risk for Alzheimer's disease. *Frontiers in Endocrinology, 12*, 660181. https://doi.org/10.3389/fendo.2021.660181
8. Quan, H., Koltai, E., Suzuki, K., Aguiar, A. S., Jr., Pinho, R., Boldogh, I., Berkes, I., & Radak, Z. (2020). Exercise, redox system and neurodegenerative diseases. *Biochimica et Biophysica Acta - Molecular Basis of Disease, 1866*(10), 165778. https://doi.org/10.1016/j.bbadis.2020.165778
9. Belaya, I., Kucháriková, N., Górová, V., Kysenius, K., Hare, D. J., Crouch, P. J., Malm, T., Atalay, M., White, A. R., Liddell, J. R., & Kanninen, K. M. (2021). Regular physical exercise modulates iron homeostasis in the 5xFAD mouse model of Alzheimer's disease. *International Journal of Molecular Sciences, 22*(16), 8715. https://doi.org/10.3390/ijms22168715
10. Zhao, R. (2024). Exercise mimetics: A novel strategy to combat neuroinflammation and Alzheimer's disease. *Journal of Neuroinflammation, 21*(1), 40. https://doi.org/10.1186/s12974-024-03031-9
11. Pape, S. E., Baksh, R. A., Startin, C., Hamburg, S., Hithersay, R., & Strydom, A. (2021). The association between physical activity and CAMDEX-DS changes prior to the onset of Alzheimer's disease in Down syndrome. *Journal of Clinical Medicine, 10*(9), 1882. https://doi.org/10.3390/jcm10091882
12. Ren, J., & Xiao, H. (2023). Exercise intervention for Alzheimer's disease: Unraveling neurobiological mechanisms and assessing effects. *Life, 13*(12), 2285. https://doi.org/10.3390/life13122285
13. Pinho, R. A., Muller, A. P., Marqueze, L. F., Radak, Z., & Arida, R. M. (2024). Physical exercise-mediated neuroprotective mechanisms in Parkinson's disease, Alzheimer's disease, and epilepsy. *Brazilian Journal of Medical and Biological Research, 57*, e14094. https://doi.org/10.1590/1414-431X2024e14094
14. Devanand, D. P., Masurkar, A. V., & Wisniewski, T. (2023). Vigorous, regular physical exercise may slow disease progression in Alzheimer's disease. *Alzheimer's & Dementia, 19*(4), 1592–1597. https://doi.org/10.1002/alz.12946
15. Xu, L., Liu, R., Qin, Y., & Wang, T. (2023). Brain metabolism in Alzheimer's disease: Biological mechanisms of exercise. *Translational Neurodegeneration, 12*(1), 33. https://doi.org/10.1186/s40035-023-00364-y
16. Ribarič, S. (2022). Physical exercise, a potential non-pharmacological intervention for attenuating neuroinflammation and cognitive decline in Alzheimer's disease patients. *International Journal of Molecular Sciences, 23*(6), 3245. https://doi.org/10.3390/ijms23063245

17. Clemente-Suárez, V. J., Rubio-Zarapuz, A., Belinchón-deMiguel, P., Beltrán-Velasco, A. I., Martín-Rodríguez, A., & Tornero-Aguilera, J. F. (2024). Impact of physical activity on cellular metabolism across both neurodegenerative and general neurological conditions: A narrative review. *Cells, 13*(23), 1940. https://doi.org/10.3390/cells13231940
18. Ruiz-González, D., Hernández-Martínez, A., Valenzuela, P. L., Morales, J. S., & Soriano-Maldonado, A. (2021). Effects of physical exercise on plasma brain-derived neurotrophic factor in neurodegenerative disorders: A systematic review and meta-analysis of randomized controlled trials. *Neuroscience & Biobehavioral Reviews, 128*, 394–405. https://doi.org/10.1016/j.neubiorev.2021.05.025
19. Cantón-Suárez, A., Sánchez-Valdeón, L., Bello-Corral, L., Cuevas, M. J., & Estébanez, B. (2024). Understanding the molecular impact of physical exercise on Alzheimer's disease. *International Journal of Molecular Sciences, 25*(24), 13576. https://doi.org/10.3390/ijms252413576
20. Stojanovic, M., Jin, Y., Fagan, A. M., Benzinger, T. L., Hassenstab, J., Cruchaga, C., Morris, J. C., & Head, D. (2020). Physical exercise and longitudinal trajectories in Alzheimer disease biomarkers and cognitive functioning. *Alzheimer Disease & Associated Disorders, 34*(3), 212–219. https://doi.org/10.1097/WAD.0000000000000385
21. Sanchez-Martinez, J., Solis-Urra, P., Olivares-Arancibia, J., & Plaza-Diaz, J. (2024). Physical exercise and mechanism related to Alzheimer's disease: Is gut-brain axis involved? *Brain Sciences, 14*(10), 974. https://doi.org/10.3390/brainsci14100974
22. Bagit, A., Hayward, G. C., & MacPherson, R. E. K. (2021). Exercise and estrogen: Common pathways in Alzheimer's disease pathology. *American Journal of Physiology-Endocrinology and Metabolism, 321*(1), E164–E168. https://doi.org/10.1152/ajpendo.00008.2021
23. Jaberi, S., & Fahnestock, M. (2023). Mechanisms of the beneficial effects of exercise on brain-derived neurotrophic factor expression in Alzheimer's disease. *Biomolecules, 13*(11), 1577. https://doi.org/10.3390/biom13111577
24. Mahalakshmi, B., Maurya, N., Lee, S. D., & Bharath Kumar, V. (2020). Possible neuroprotective mechanisms of physical exercise in neurodegeneration. *International Journal of Molecular Sciences, 21*(16), 5895. https://doi.org/10.3390/ijms21165895
25. Arciero, P. J., Grasso, P., Anderson-Hanley, C., & Zimmerman, E. (2023). Editorial: How does exercise modify the course of Alzheimer's disease? *Frontiers in Aging Neuroscience, 15*, 1127747. https://doi.org/10.3389/fnagi.2023.1127747
26. Baranowski, B. J., Mohammad, A., Finch, M. S., Brown, A., Dhaliwal, R., Marko, D. M., LeBlanc, P. J., McCormick, C. M., Fajardo, V. A., & MacPherson, R. E. K. (2023). Exercise training and BDNF injections alter amyloid precursor protein (APP) processing enzymes and improve cognition. *Journal of Applied Physiology, 135*(1), 121–135. https://doi.org/10.1152/japplphysiol.00114.2023
27. Baranowski, B. J., Marko, D. M., Fenech, R. K., Yang, A. J. T., & MacPherson, R. E. K. (2020). Healthy brain, healthy life: A review of diet and exercise interventions to promote brain health and reduce Alzheimer's disease risk. *Applied Physiology, Nutrition, and Metabolism, 45*(10), 1055–1065. https://doi.org/10.1139/apnm-2019-0910
28. Zhao, N., Xia, J., & Xu, B. (2021). Physical exercise may exert its therapeutic influence on Alzheimer's disease through the reversal of mitochondrial dysfunction via SIRT1-FOXO1/3-PINK1-Parkin-mediated mitophagy. *Journal of Sport and Health Science, 10*(1), 1–3. https://doi.org/10.1016/j.jshs.2020.08.009
29. Barros-Aragão, F. G. Q., Januszkiewicz, E., Hunter, T., Lyra e Silva, N. M., & De Felice, F. G. (2025). Physical activity in Alzheimer's disease prevention: Sex differences and the roles of BDNF and irisin. *Frontiers in Neuroendocrinology, 77*, 101189. https://doi.org/10.1016/j.yfrne.2025.101189
30. Jodeiri Farshbaf, M., & Alviña, K. (2021). Multiple roles in neuroprotection for the exercise derived myokine irisin. *Frontiers in Aging Neuroscience, 13*, 649929. https://doi.org/10.3389/fnagi.2021.649929
31. Qi, J. Y., Yang, L. K., Wang, X. S., Wang, M., Li, X. B., Feng, B., Wu, Y. M., Zhang, K., & Liu, S. B. (2022). Irisin: A promising treatment for neurodegenerative diseases. *Neuroscience, 498*, 289–299. https://doi.org/10.1016/j.neuroscience.2022.07.018
32. Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., Cummings, J., & van der Flier, W. M. (2021). Alzheimer's disease. *The Lancet, 397*(10284), 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4
33. Breijyeh, Z., & Karaman, R. (2020). Comprehensive review on Alzheimer's disease: Causes and treatment. *Molecules, 25*(24), 5789. https://doi.org/10.3390/molecules25245789