Effects of Physical Activity on Cognitive Function in Older Adults with Alzheimer's Disease: A Systematic Review

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3. Abbreviations

5-HT	Serotonin
Aß	Amyloid-ß
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
AD	Alzheimer's Disease
APOE-ε4	Apolipoprotein E epsilon 4 allele
BDNF	Brain-Derived Neurotrophic Factor
BERG	Berg Balance Scale
CAMCOG	Cambridge Cognitive Examination
CBF	Cerebral Blood Flow
CRP	C-reactive Protein
CST	Cognitive Stimulation Therapy
FR	Functional Reach (Test)
GM	Grey Matter
GRAY	Ghent University Research for Ageing Young
HHS	US Department of Health and Human Services
HRR	Heart Rate Reserve
HRV	Heart Rate Variability
IGF-1	Insulin-Like Growth Factor 1
IL-6	Interleukin 6
IL-10	Interleukin 10
LAM	Lymphangioleiomyomatosis
(a)MCI	(Amnestic) Mild Cognitive Impairment
MET	Metabolic Equivalent
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MS	Multiple Sclerosis
NFT	Neurofibrillary Tangles
NS	Not Specified
PA	Physical Activity
PFC	Prefrontal Cortex
PICO(T)	Population, Intervention, Comparison, Outcome (and Time)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
RPE	Rating of Perceived Exertion
T2DM	Type 2 Diabetes Mellitus
TNF(-alpha)	Tumour Necrosis Factor
TUGT	Timed Up and Go Test
VEGF	Vascular Endothelial Growth Factor
VO2max	Maximal Oxygen Consumption
WHO	World Health Organisation
WMD	White Matter Disease

4. Abstract

4.1 English

Introduction: The global rise in Alzheimer's disease, presents a critical health and economic challenge, with cases projected to reach 152 million by 2050. Physical activity shows promise in mitigating cognitive decline in older adults with Alzheimer's Disease, yet current guidelines lack clear, specific recommendations tailored to this population. This master thesis investigates the neurobiological effects of physical activity, with a focus on brain-derived neurotrophic factor and other key factors influencing cognitive function. By specifying effective exercise types and dosages, it aims to refine physical activity guidelines for older adults with Alzheimer's disease, offering evidence-based strategies to enhance cognitive outcomes.

Materials & Methods: A literature search was performed in PubMed, Embase, and Web of Science databases. Most articles were excluded due to no full text, not according to PICO(T), no relevance to the formulated research question, and/or language other than English. The remaining 301 articles were reviewed on title, abstract, study type and content. This resulted in 86 articles being selected. For each article an adequate risk of bias and a level of evidence was assigned.

Results: From 4611 studies screened, 86 met inclusion criteria, mostly RCTs (65.1%) from diverse regions, predominantly published after 2010, with sample sizes from 7 to 691 participants aged 18 to 99. Studies addressed conditions like healthy ageing (59.3%) and Alzheimer's Disease (10.5%), with 65.1% rated as high quality (level 2) and low-to-moderate bias in most RCTs and non-RCTs. Findings show physical activity positively impacts brain structure, noting increased grey matter and reduced atrophy in older adults. Moderate to high-intensity aerobic and resistance exercises most effectively promote BDNF, and IGF-1. While aerobic exercise and yoga effectively reduce inflammation. Tai Chi, aerobic, and resistance exercises reduce oxidative stress.

Conclusion: Evidence highlights physical activity as a key factor in supporting cognitive function and preventing cognitive decline in older adults with Alzheimer's Disease. Different types of physical activity complement each other through overlapping pathways – improving cardiovascular health, releasing neurotrophic factors, strengthening muscles, and reducing inflammation and oxidative stress – each with its own optimal dose. Combined, they provide a holistic strategy to preserve cognitive function, enhance mobility, and lower fall risk in individuals with Alzheimer's disease. These findings underscore the value of multifaceted and personalised physical activity regimens – tailored to individual needs and genetic factors – to optimise both the prevention and management of Alzheimer's Disease.

4.2 Dutch

Introductie: De wereldwijde toename van de ziekte van Alzheimer vormt een belangrijke gezondheid en economische uitdaging, met naar schatting 152 miljoen gevallen tegen 2050. Fysieke activiteit lijkt veel belovend bij het tegengaan van cognitieve achteruitgang bij oudere volwassenen met de ziekte van Alzheimer, de huidige richtlijnen missen echter heldere en specifieke aanbevelingen die op deze doelgroep zijn afgestemd. Deze master thesis onderzoekt de neurobiologische effecten van fysieke activiteit, met de nadruk op *brain-derived neurotrophic factor* en andere cruciale factoren die de cognitieve functie beïnvloeden. Door effectieve oefentypes en doseringen te specificeren, beoogt deze thesis de richtlijnen voor fysieke activiteit bij oudere volwassenen met Alzheimer verder te verfijnen en *evidence-based* strategieën aan te reiken om cognitieve uitkomsten te verbeteren.

Materialen & Methoden: Er werd een literatuurstudie uitgevoerd in de databanken van PubMed, Embase en Web of Science. De meeste artikels werden geëxcludeerd wegens het ontbreken van een volledige tekst, niet aansluiten bij de PICO(T)-criteria, irrelevantie voor de geformuleerde onderzoeksvraag en/of een andere taal dan Engels. De resterende 301 artikels werden geanalyseerd op basis van titel, abstract, studietype en inhoud. Dit resulteerde in 86 geselecteerde artikels. Voor elk artikel werd het risico op *bias* beoordeeld en werd een adequaat *level of evidence* toegekend.

Resultaten: Van de 4611 gescreende studies voldeden er 86 aan de inclusiecriteria, waarvan het merendeel *RCT*s (65.1%) uit diverse regio's, hoofdzakelijk gepubliceerd na 2010 waarbij de steekproefgroottes varieerden van 7 tot 691 deelnemers met leeftijden tussen 18 en 99 jaar. De onderzochte populaties betroffen voornamelijk gezond ouder worden (59.3%) en Alzheimer (10.5%), waarbij 65.1% van de studies als hoge kwaliteit (level 2) werden beoordeeld met een laag tot matig risico op *bias* in de meeste *RCT*s en niet-*RCT*s. De bevindingen laten zien dat fysieke activiteit een positief effect heft op de hersenstructuur, waaronder een toename van grijze stof en een afname van atrofie bij ouderen. Matig tot hoog intensieve aerobe en weerstandsoefeningen stimuleren BDNF en IGF-1 het meeste, terwijl aerobe training en yoga effectief zijn in het verminderen van ontstekingen. Daarnaast blijkt dat Tai Chi, aerobe en weestandsoefeningen de oxidatieve stress verlagen.

Conclusie: De evidentie toont dat fysieke activiteit een sleutelrol speelt bij het ondersteunen van cognitieve functies en het voorkomen van cognitieve achteruitgang bij oudere volwassenen met de ziekte van Alzheimer. Verschillende types van fysieke activiteit vullen elkaar aan via overlappende mechanismen – verbeteren van cardiovasculaire gezondheid, stimuleren van neurotrofe factoren, versterken van spieren en verminderen van ontstekingen en oxidatieve stress – elk met een eigen optimale dosering. Gecombineerd bieden ze een holistische strategie om cognitieve functies te behouden, mobiliteit te verbeteren en het valrisico bij mensen met de ziekte van Alzheimer te verlagen. Deze bevindingen benadrukken het belang van veelzijdige en gepersonaliseerde fysieke activiteit regimes – afgestemd op de individuele behoeften en genetische factoren – om zowel de preventie als het management van Alzheimer te optimaliseren.

5. Introduction

The global population is undergoing a significant demographic shift, with a substantial increase in the older population projected for the coming decades. This demographic change is accompanied by a rise in non-communicable chronic diseases, including Alzheimer's disease (AD). Currently, around 55 million people worldwide are living with dementia, and this number is anticipated to increase to 152 million by 2050, with a particularly steep increase in low and middle-income countries. (1-10) AD, the most common form of dementia, accounts for approximately 60-80% of dementia cases. Its hallmark characteristics are irreversible and progressive cognitive and behavioural decline, often accompanied by various neurological impairments. (2, 11) AD not only significantly impacts individuals and their families but also has a considerable economic toll on global societies. In 2019, the worldwide cost associated with dementia was estimated at more than USD 1.3 trillion. In Europe, about 14.1 million individuals are affected by dementia, with the total annual expenses reaching around €400 billion. Specifically, in Belgium, the "*Expertisecentrum Dementie Vlaanderen*" estimated around 200,000 dementia cases in 2020, with the total projected costs amounting to circa €1.36 billion. The global number of dementia cases is expected to double or even triple by 2050, highlighting the urgent need for developing effective prevention and treatment measures. (1-3, 12-14)

The key determinants of health and longevity (genetics, environment, and behaviour) are interconnected, with each factor influencing the others. This complex interplay between nature and nurture also extends to cognitive health, impacting the development and progression of dementia, including AD. Epigenetic changes, triggered by lifestyle choices or early-life stress, can alter gene expression in ways that increase susceptibility to chronic diseases and multimorbidity. In the context of Alzheimer's, these factors collectively contribute to neurodegeneration, highlighting how lifestyle and environmental influences can interact with genetic predispositions to either mitigate or exacerbate the onset and severity of dementia symptoms. [Figure 1] (2)

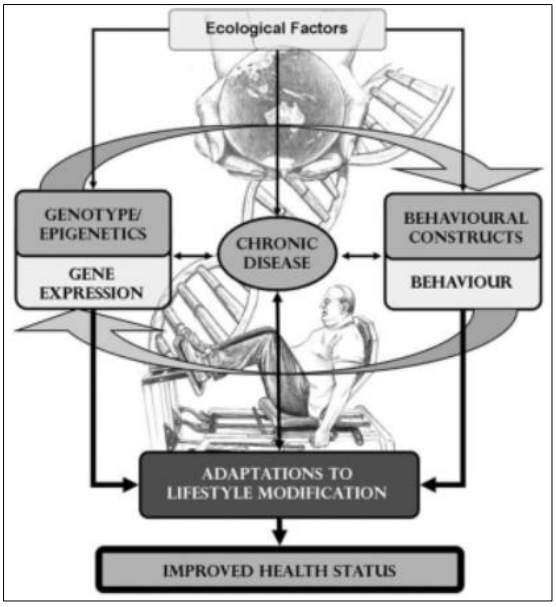


Figure 1: Improving Health Status (2)

One of the primary risk factors for AD is age, and as the global population ages, the prevalence of AD is only expected to increase. (1-3) The process of ageing in humans typically begins around 20-30 years of age, marking the commencement of physiological changes that unfold over time. Normal ageing is associated with global brain atrophy, modifications in brain functional responses, and cognitive decline. This ageing process is not uniform but exhibits heterogeneity influenced by various factors, notably patterns of living, experiences, and behaviours. Among these factors, a crucial determinant of the ageing phenotype is the level of physical activity (PA) and exercise one engages in, or the lack thereof. (1-4, 15) AD is characterised by the progressive loss of neuronal synapses and pyramidal neurons, resulting in cognitive neurodegeneration. Key regions associated with complex brain functions, including the hippocampus and neocortex, are profoundly affected. (4) The hippocampus is a pivotal brain region involved in synaptic plasticity processes and memory formation. (5, 6) The neuropathological hallmarks of AD include the accumulation of senile plaques and the formation of neurofibrillary tangles (NFTs). The immune response plays a crucial role in AD progression, initially aiding the removal of amyloid-ß (Aß), but later contributing to chronic inflammation, further Aß production, hyperphosphorylation of tau, and neuronal damage. This immune dysregulation drives cognitive decline and disease development. (1-6, 16-22)

Neurotrophins, a family of growth factors, play a vital role in regulating various aspects of brain function, including axonal growth, synaptic plasticity, neurotransmission, hippocampal neurogenesis, and long-term potentiation. Among these neurotrophins, Brain-Derived Neurotrophic Factor (BDNF) has garnered substantial attention due to its strong association with exercise and cognitive function. Under normal conditions, the brain synthesises approximately 75% of BDNF. Low levels of BDNF have been identified in the brains of individuals with AD, suggesting that enhancing its production could be a viable strategy to delay disease onset. (1, 3-5, 7, 15, 23)

AD presents as a complex clinical picture characterised by a progressive cognitive decline. This neurodegenerative disorder significantly impairs individuals, affecting not only their memory, but also reasoning and language, and eventually all their physical capabilities. There are typically three stages: early (mild), middle (moderate), and late (severe) marked by an intensification of symptoms. In the beginning, the individual may experience subtle changes that could be easily mistaken for normal ageing. Memory lapses, difficulties in finding the right words, mild confusion and problems with concentration and decision-making are courant symptoms. In the middle stage, these symptoms become more prominent and interfere with daily activities (memory loss and confusion deepen, forgetting personal history and familiar faces, struggling with more complex tasks, mood swings, irritability, changes in sleep patterns and even depression). In the late stage of AD it evolves into severe memory loss, deterioration in communication skills, loss of coherent speech, significant challenges in mobility and an increased risk of infections. This trajectory varies widely among individuals, but it generally evolves from mild forgetfulness to complete dependency. (1-3, 5, 18, 24-26)

The management of AD combines non-pharmacological and pharmacological approaches to improve symptoms and improve quality of life in the absence of a cure. Non-pharmacological strategies, include PA, cognitive stimulation therapy (CST), occupational therapy, diets, social engagement, and caregiver support play crucial roles in comprehensive care. Developing research into immunotherapy and gene therapy holds promise for future disease-modifying treatments. Current pharmacological treatments for AD primarily involve acetylcholinesterase inhibitors, such as Donepezil, Galantamine and Rivastigmine, which provide some cognitive symptom relief but do not address the underlying neurodegeneration. Even with treatment, the cognition of most individuals with dementia tends to worsen further. The available medications can, in the best-case scenario, only slow down the

progression of the disease. However, curing dementia is not possible. Additionally, these medications are known to cause various side effects, which can reduce their effectiveness over the long term. (4, 27, 28)

However, studies in humans have shown that PA can increase peripheral BDNF levels, and in some cases, this increase is associated with cognitive improvements. Moreover, aerobic exercise-induced growth in hippocampal volume is linked to higher serum BDNF levels in cognitively healthy older individuals, and elevated serum BDNF is associated with a reduced risk of AD. (1, 3-5, 7, 15, 23) PA serves as a preventive medicine in the healthy phenotype, while in the non-healthy phenotype, PA tends to be applied far downstream from the initiation of pathological processes and therefore operates as a true therapeutic agent. [Figure 2] While ageing is one of the major risk factors for most chronic diseases, the relationship is bidirectional, as chronic diseases ("geriatric syndromes"), and/or adverse consequences of their treatment may accelerate biological ageing. Next to dementia, frailty (diminished physiological reserve, rendering individuals susceptible to cognitive, social and physical stressors leading to disability and heightened mortality risk) and sarcopenia (gradual age-related decline in muscle mass, strength, and quality affecting physical performance) are among other important conditions which are associated with many adverse outcomes including falls, disability, cognitive decline leading to accelerated ageing and mortality. (2)

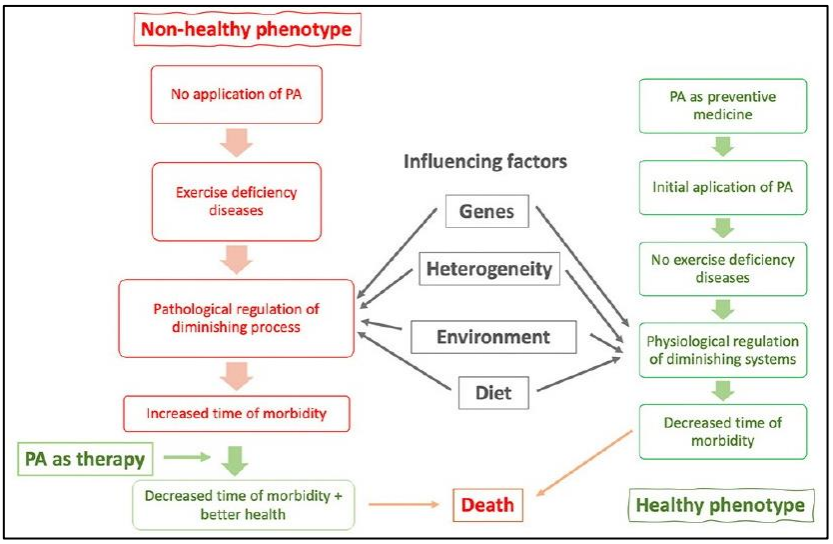


Figure 2: The left-hand side shows the application of PA as a therapeutic agent to pathologies that have developed because of a lack of PA. Reflecting pathological, not physiological changes. The effects of these pathologies can be ameliorated by PA. The right-hand side show the application of PA as preventive medicine and the maintenance of effective but diminishing physiological function. This side is investigated by the science of physiology and ageing. Both sides are in constant decremental change because of the inherent ageing process. The centre shows major effectors of both pathological and physiological processes. (2)

To clarify the term, 'physical activity' encompasses any bodily movement involving skeletal muscles that significantly increases energy expenditure, with a wide range of intensity and duration. On the other hand, 'exercise' falls under the umbrella of PA and refers to planned, structured, and repetitive bodily movements, often undertaken with the explicit intent of enhancing physical fitness components, including aerobic capacity, muscle strength, power, endurance, balance, coordination, and flexibility. (1, 3, 6, 7)

PA has the potential to reduce the risk of AD and delay its onset. It offers a readily accessible, safe, and potentially cost-effective approach to maintain, delay, or enhance brain structure and function throughout one's life. (1-4) The beneficial effects of PA extend beyond the realm of skeletal muscle

and encompass adaptations in various organs, including the brain. Exercise triggers a cascade of cellular and molecular processes within the brain, leading to phenomena such as angiogenesis, neurogenesis, synaptogenesis, and the release of neurotrophic factors. These processes collectively contribute to improved learning, and memory. (4, 5, 7, 9, 15, 29) It also has a positive influence on cognitive flexibility, depressive symptoms, cardiovascular health, sleep patterns, and general wellness. (1, 3, 4) These factors are predictors of ongoing neurodegenerative processes in individuals without dementia. Furthermore, PA could improve cognitive functions and neural pathways in patients with dementia, including those with AD, through the mechanisms of neuroplasticity. This effect was confirmed with Parkinson's Disease patients where aerobic exercise training induced functional changes in brain structures related to motor learning, which aligned with the enhanced behavioural performance. (30) Therefore, PA – more specifically aerobic training – could serve as a valuable non-pharmacological intervention, promoting not only physical fitness but also enhancing motor learning capacity for daily activities through increased plasticity in motor-related structures. Consequently, PA represents a novel and promising area of research in dementia, particularly in AD. Several key factors moderate the relationship between PA and cognitive function, including exercise dose (intensity, duration, frequency, and type of PA), the specific cognitive variables under assessment, and the mode of exercise. (1-5, 7, 31)

5.1 Brain Mechanisms to Counter Dementia: The Role of Physical Activity and Exercise

Figure 3 and 4 present possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia. Cognitive reserve plays a pivotal role in protecting individuals from the devastating effects of dementia. It is defined as the concept accounting for the disparity between an individual's clinical symptoms and the extent of neuropathological damage in the brain. This concept can be divided into neurobiological brain reserve (the number of neurons and synapses at a given time), brain maintenance (the neurobiological capital at any time, based on genetics and lifestyle choices, mitigating brain changes and pathological developments), and cognitive reserve (the adaptability of the brain), allowing individuals to maintain cognitive function and everyday functioning despite the presence of brain pathology. (1, 3)

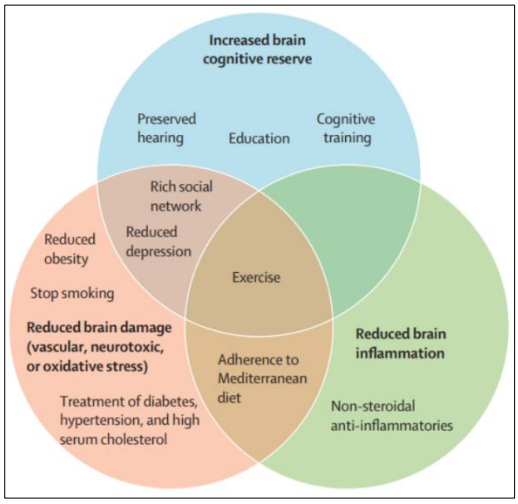


Figure 1: Brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia. (1)

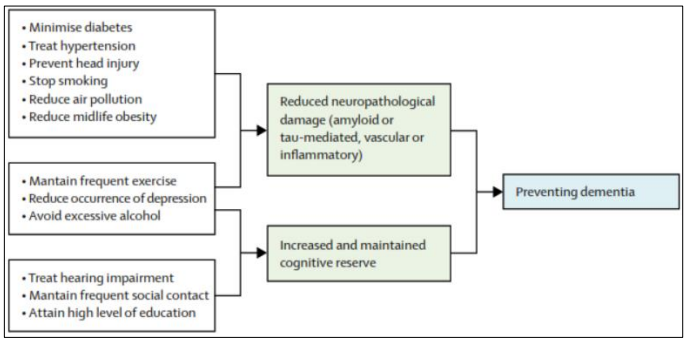


Figure 2: Potentially modifiable risk factors in preventing dementia. (3)

As shown in Figure 3 and Figure 4, exercise plays a vital role in preventing dementia through effects on increased and maintained cognitive reserve, reduced neuropathological damage, and reduced brain inflammation. However, multiple potentially modifiable risk factors have been researched. Early-life factors, such as lower levels of education, can negatively affect cognitive reserve. Additionally, midlife (hearing loss, arterial hypertension, obesity, etc.) and old-age (smoking, depression, physical inactivity, social isolation, diabetes, etc.) risk factors influence the trajectory of age-related cognitive decline and the initiation of neuropathological developments. Socioeconomic factors, such as culture (regarding lifestyle, Mediterranean diet reporting fewer vascular risk factors, reduced plasma glucose and serum insulin concentration, reduced insulin resistance, and reduced oxidative stress and inflammation), poverty, and inequality, significantly impact cognitive reserve. Exercise has emerged as a promising intervention in the prevention of dementia. It offers multiple potential mechanisms of protection: weight management (weight reduction and lowering the risk of diabetes), cardiovascular health (improving cardiovascular function), neurogenesis (enhancing hippocampal neurogenesis, essential for learning and memory), HDL cholesterol (higher levels of HDL cholesterol, possibly protecting against vascular risk and reduce inflammation accompanying Aβ pathology in mild cognitive impairment), and enhancing neurobiological mechanisms (growth factors, inflammation and oxidative stress, neurotransmitters). (1, 3, 5)

5.2 Physical Activity and the Neurobiological Mechanisms for Alzheimer's Disease Prevention

After reaching the third decade of life, the brain experiences a decline in neurogenesis capacity, along with a decrease in the volume of the hippocampus. Simultaneously, ageing is accompanied by the unwelcome companions of neuroinflammation and oxidative stress. These physiological alterations in the brain are closely linked to the decline in cognitive functions, including memory and fluid intelligence, and contribute to the rising prevalence of AD, which accounts for a significant proportion of dementia cases. These alterations in brain structures and functions may commence over two decades before the clinical symptoms of AD become evident. (15)

5.2.1 Exercise Physiology

During PA, the body undergoes various adaptations to enhance endurance and exercise performance [Figure 5]. These adaptations encompass the release of growth factors, including BDNF, insulin-like growth factor-I (IGF-1), and vascular endothelial-derived growth factor (VEGF). BDNF, a key player, promotes glucose utilisation, enhances lipid oxidation, and facilitates tissue repair and remodelling. IGF-1, released from the liver and skeletal muscle, stimulates carbohydrate and lipid metabolism, while VEGF, released from multiple tissues, stimulates vessel growth and tissue repair, thereby enhancing endurance performance. Additionally, lactate, conventionally regarded as a waste product, serves as an alternate energy source for various tissues, including the brain. (1-5, 7, 10, 15)

During PA, interleukin-6 (IL-6) is released from skeletal muscle to promote the breakdown of triglycerides (lipolysis), increase fat oxidation, and boost glucose production. This release also leads to enhanced mitochondrial production and antioxidant enzyme activity in both peripheral tissues and the brain. These effects improve energy efficiency and endurance. Additionally, the brain releases neurotransmitters like dopamine and serotonin (5-HT), which contribute to motor control, learning, and overall exercise capacity. (15)

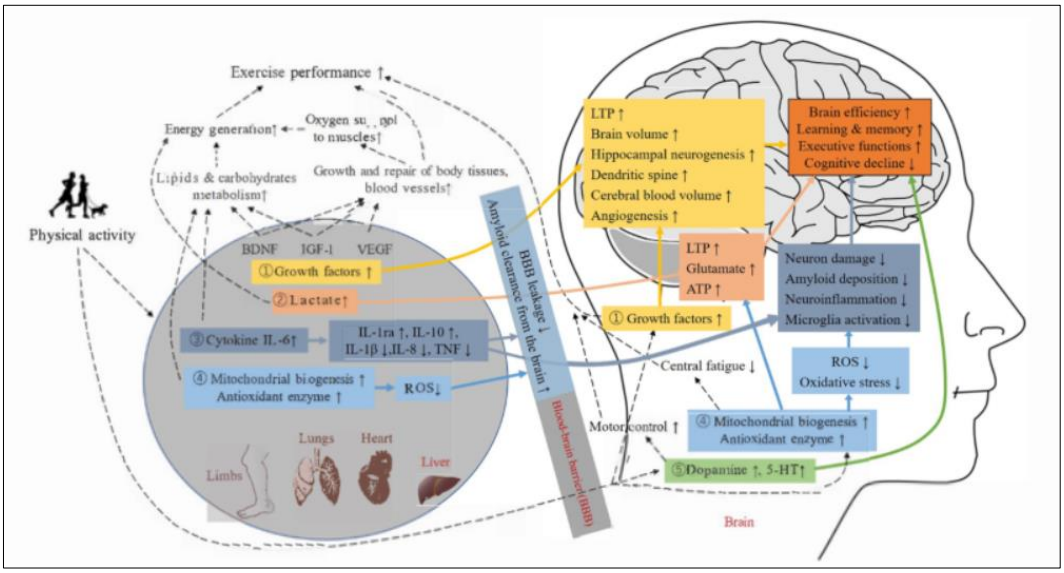


Figure 3: Exercise Physiology and Neurobiological Mechanisms (15)

5.2.2 Neurobiological Mechanisms of Physical Activity for Brain Health

Understanding the neurobiological effects of PA is essential for brain health, as exercise promotes growth factors to support neuron resilience, increases lactate production to fuel neurons, reduces inflammation and oxidative stress linked to ageing and neurodegeneration, and regulates neurotransmitters that enhance mood and cognition, collectively protecting against cognitive decline and dementia. (1, 3-5, 7, 9, 10, 15, 29, 32)

Growth Factors: PA triggers the release of growth factors, such as BDNF, IGF-1, and VEGF, into the bloodstream. These factors can then traverse the brain-blood barrier, facilitating brain health. BDNF is vital for neuron development, survival, and adult neurogenesis in the hippocampus. Adult neurogenesis, in turn, contributes to cognitive flexibility and pattern separation, essential for learning and memory. IGF-1 and VEGF further promote neurogenesis and synaptic growth. (1, 3, 5, 7, 10, 15, 29, 32)

Lactate: Previously viewed as a metabolic waste product, lactate serves as an alternate energy source for the brain. Lactate can cross the blood-brain barrier, providing the brain with an energy substrate. Moreover, lactate contributes to glutamate synthesis, a crucial excitatory neurotransmitter in the brain. (15)

Inflammation and Oxidative Stress: Excessive and chronic inflammation, prevalent in the ageing process, can damage brain tissue and contribute to neurodegenerative diseases like Alzheimer's. PA counteracts chronic inflammation by producing IL-6, which has anti-inflammatory effects. It also aids in the clearance of amyloid from the brain and preserves the integrity of the blood-brain barrier, essential for protecting against external toxins and pathogens. Additionally, PA mitigates oxidative stress by several mechanisms (antioxidant enzyme activity by neutralising harmful reactive oxygen species (ROS), enhanced mitochondrial function, anti-inflammatory effects, improved blood flow through enhancing circulation, hormonal regulation), which plays a significant role in neurodegenerative diseases. (1, 3, 9, 15)

Neurotransmitters: PA leads to the release of neurotransmitters, including dopamine, 5-HT, and norepinephrine. These neurotransmitters influence behaviour, mood, motor control, learning, working memory, and cognitive flexibility, among other functions. Dopamine in the prefrontal cortex (PFC) supports working memory and cognitive flexibility, while dopamine in the hippocampus is critical for long-term memory formation and neurogenesis. (15) PA increases calcium levels in the brain, which, in turn, stimulate dopamine synthesis. Reduced dopaminergic function in AD patients is linked to psychiatric symptoms such as apathy and depression. (4) Serotonin regulates adult neurogenesis in the hippocampus, suggesting a potential link between antidepressants and neurogenesis. (15) Exercise-induced stimulation of both norepinephrine and serotonin has been linked to the up-regulation of BDNF, a fundamental mediator of neuronal survival and plasticity in the hippocampus. (4)

5.3 Physical Activity and the Cardiovascular Benefits

PA has been shown to have a significant impact on metabolite processes. It has been shown to reduce the incidence of “traditional” cardiovascular risk factors (e.g., obesity, diabetes, hypertension). PA leads to a decrease in serum levels of glucose, cholesterol, cortisol, and metabolic syndrome markers. Additionally, exercise promotes an increase in high-density lipoprotein and insulin production. These changes are instrumental in reducing the risk of “traditional” cardiovascular risk factors commonly associated with AD. (4, 6) Regular PA can enhance endothelial

function by activating nitric oxide synthase. This activation results in improved angiogenesis within the brain and the preservation of neuronal plasticity. These mechanisms may collectively help reduce the burden of white matter disease (WMD) in individuals with AD. (4)

5.4 Modes of Exercise and Their Cognitive Impact

The effects of PA and exercise can be categorised into two main groups: physical activities and motor activities. These categories are defined based on the type of energy required for the activity and their impact on cognition. The physical training activities primarily consist of aerobic exercises (e.g. brisk walking, swimming, running, etc.), which involve repetitive and automatic movements that demand high metabolic energy but relatively low neuromuscular effort. Additionally, strength training (lifting weights, working with resistance bands, heavy gardening, hill walking, etc.) is also considered a PA, but requires more neuromuscular effort than aerobic exercises. These activities are important for enhancing various body systems. (1-3, 6, 10, 18, 20, 23, 29, 31, 33)

On the other hand, motor activities encompass balance and coordination exercises, which places high neuromuscular demands on individuals but have relatively low metabolic requirements. These activities involve perceptual and higher-level cognitive processes, including attention. Flexibility exercises, such as those aimed at extending joint range of motion, are also classified as motor activities, although they do not require significant neuromuscular effort. (1-3, 6, 10, 18, 20, 23, 29, 31, 33)

Within each of these categories, specific movement skills and exercises branch out. Examples include yoga, Tai Chi, quiet dances, and certain exergames (movement-based video games). Exergames involve the simultaneous performance of motor or physical activities along with cognitive stimulation, providing a unique avenue for investigating the effects of exercise on cognitive functioning in the context of Alzheimer's disease. All these activities are derived from the basic motor activities but require higher levels of neuromuscular effort compared to simple balance and coordination exercises. Activities like bicycle riding and swimming, while primarily physical (metabolic) in nature, do require neuromuscular effort during the initial skill acquisition phase. However, once individuals master these skills, neuromuscular demands become minimal. (1-3, 7, 10, 17, 18, 29, 31)

Furthermore, a more demanding subcategory that combines physical and motor activities exists, requiring both metabolic and neuromuscular energy. Examples of such activities include tennis, basketball, and energetic dancing, as well as certain exergames. In addition to these specific skills and exercises, there is the concept of dual-task activities. These activities involve a controlled combination of two tasks or activities performed simultaneously, often designed to promote basic motor systems, postural control, or cognitive functioning. Dual-task activities can fall into three categories: motor-cognitive tasks (e.g. standing on one foot while counting backwards by 6 from 100), physical and cognitive activities (e.g. walking briskly on a treadmill while simultaneously performing various tasks displayed on a screen), and two motor tasks (e.g. standing on one foot while engaging in throwing and catching a ball). (6, 7, 17, 18, 29, 31)

5.5 Optimising Exercise Interventions for Enhanced Cognitive Function in Alzheimer's Disease

PA refers to muscle-induced bodily movement that elevates energy expenditure above 1.0/1.5 MET (metabolic equivalent of task). This term encompasses a wide range of activities conducted regularly or irregularly, ranging from unstructured and unplanned movements to specific, planned, and structured forms of physical exercises. Physical exercises, on the other hand, represent a subset of PA and are characterised by their planned and structured nature. (23)

Physical exercises can be further categorised based on temporal characteristics into acute physical exercise (single bout) and chronic physical exercises (repeated bouts). Acute physical exercises are typically referred to as "acute bouts of physical exercise", while chronic physical exercises conducted regularly in a planned, structured, and purposeful manner are termed "physical training". Despite the predominant use of the term "acute exercise" in the field, the nature of the activities studied in existing literature aligns more suitably with the broader concept of 'physical activity' rather than specifically 'exercise.' Hence, employing the term 'physical activity' offers a more conceptually fitting description. (7, 23, 32, 34)

5.5.1 Individualisation: "Responder" vs "Non-responder"

Recognising that individuals respond differently to acute physical exercises and physical training, the concept of "responders" and "non-responders" has emerged [Figure 6]. These terms refer to individuals who exhibit varying degrees of sensitivity to such interventions. This interindividual variability in response may also extend to neurocognitive outcomes. (23, 32)

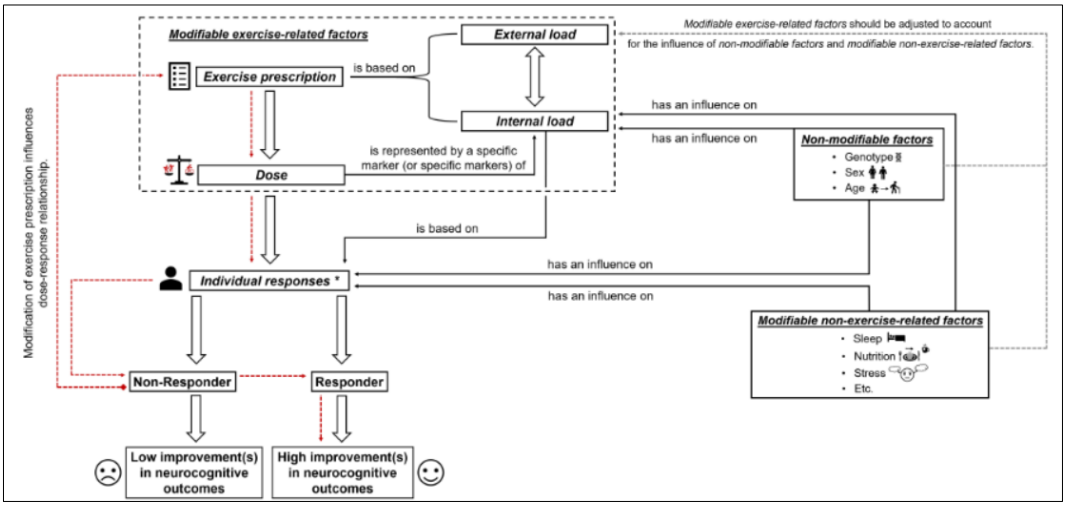


Figure 4: Schematic Illustration of the Possible Influence of Exercise Prescription on Dose, and Individual Responsiveness (responder and non-responder) with the Assumed Extent of Improvements (High Improvements in Neurocognitive Outcomes and Low Improvements in Neurocognitive Outcomes). The Dotted Red Lines Show that by Using an Appropriate Exercise Prescription, Non-Responders Could Be Turned into Responder. (23)

5.5.2 Factors Influencing Response to Physical Exercises

The response to physical exercises and training is influenced by a combination of non-modifiable factors (e.g., sex or genotypes) and modifiable factors (e.g., nutrition, social and cognitive activities, and exercise prescription). Genetics play a significant role in explaining a substantial portion of interindividual heterogeneity in physical and cognitive outcomes. However, lifestyle factors can

potentially mitigate the effects of unfavourable genetics. Individuals with high cardiorespiratory fitness levels but less favourable genetic profiles may perform just as well as those with low cardiorespiratory fitness but favourable genetics. (1-3, 5, 23, 32)

5.5.3 Dosing Physical Exercises for Optimal Impact

The concept of "dose" in exercise-cognition research refers to exercise variables, such as intensity, duration, and type, in acute bouts of physical exercises. In training studies, dose encompasses exercise variables, training frequency, and the application of training principles. It is crucial to determine an appropriate concept of dose, particularly for its role in triggering neurobiological processes and cognitive changes. (2, 6, 7, 10, 17, 23, 32)

5.5.4 Using Markers of Internal Load as Dose Proxies

Markers of internal load, such as heart rate variability (HRV) and peripheral blood lactate levels, have been proposed as proxies for dose (Figure 6). HRV considers individual fitness levels and daily readiness, making it a promising marker for individualising and adjusting exercise prescription. Peripheral blood lactate levels are also relevant as they can cross the blood-brain barrier and provide energy to the brain. Peripheral blood lactate levels have been associated with peripheral serum BDNF levels, a key neurotrophic factor linked to neuroplasticity and cognitive enhancement. This suggests that markers of internal load related to neurotrophic molecules may be valuable for individualising exercise prescription. (23, 32)

5.5.5 Individualising Exercise Prescriptions

To achieve individualisation in physical exercises and training, exercise prescription should be adjusted based on markers of internal and external load (Figure 6). This approach can minimise the interindividual heterogeneity in dose and, subsequently, neurocognitive outcomes. External load encompasses various elements such as climatic conditions, equipment, and ground conditions, all of which impact the work completed by individuals independently of their internal characteristics. Traditional exercise prescriptions often rely on relative percentages of maximum values for exercise intensity. However, this approach can lead to significant interindividual variability in dose and subsequently impact neurocognitive outcomes. To enhance the effectiveness of exercise-cognition interventions, it is imperative to strike a balance between external and internal load considerations, thereby optimising exercise prescriptions and reducing interindividual heterogeneity in outcomes. (23, 32)

5.6 Global Recommendations on Physical Activity for Public Health

5.6.1 WHO Guidelines for Adults (18–64 years)

For adults (18 – 64 years old), the guidelines emphasise the importance of both aerobic and muscle-strengthening PA. The evidence suggests that substantial health benefits can be achieved with weekly volumes of 150–300 minutes of moderate-intensity aerobic activity or 75–150 minutes of vigorous-intensity aerobic activity, or an equivalent combination of moderate to vigorous aerobic physical activity. In addition to aerobic activity, muscle-strengthening activities involving major muscle groups on two or more days per week should be included. Furthermore, accumulating PA in

shorter bouts is now acknowledged, reflecting new evidence that highlights the value of the overall volume of PA, regardless of the length of individual bouts. Health benefits can still be realised with PA levels below these recommendations. (12)

5.6.2 WHO Guidelines for Older Adults (65 years and above)

The guidelines, stated above, extend to older adults, and the evidence related to PA and sedentary behaviour in this age group aligns with those for younger adults. However, additional health-related outcomes are considered due to their relevance to older adults: falls, fall-related injuries, physical function, frailty, and osteoporosis. (2, 6, 12)

High-certainty evidence reveals a dose-response relationship between the volume of aerobic PA and the risk of physical functional limitations in older adults. Furthermore, balance and functional exercises are shown to reduce the incidence of falls, while engaging in a variety of physical activities can enhance several aspects of physical function. Moderate-certainty evidence indicates that the risk of fall-related injury may be reduced through multicomponent PA, encompassing balance, strength, endurance, gait, and physical function training. Therefore, the guidelines recommend that older adults engage in diverse multicomponent physical activities at a moderate or greater intensity on three or more days each week to enhance functional capacity and prevent falls. The US Department of Health and Human Services (HHS) suggests a combination of multicomponent exercises, including balance training, muscle-strengthening activities (at least twice a week), and moderate-intensity aerobic exercises for 30 to 45 minutes per session, at least three to five times per week, to enhance functional ability in older adults with frailty. (2, 6, 12)

Despite the established benefits of exercise, current guidelines often go unmet, particularly among older adults. Failure to meet these recommendations has significant consequences, contributing to a substantial number of deaths globally each year. (2, 6, 12)

5.7 From Theory to Practice

With AD's growing prevalence and its societal impact, identifying effective prevention and intervention strategies are extremely urgent. This master thesis delves into the neuro-imaging and neurobiological effects of PA, specifically focusing on the role of BDNF and other essential growth factors, which are key to understanding PA's impact on cognition. These neurobiological mechanisms, including BDNF's influence on neuroplasticity and cerebral health, offer insights into how PA might counteract AD's pathophysiology. Currently, there is limited knowledge regarding precise dose factors of PA and its cognitive effects on AD. This master thesis aims to refine the parameters of PA – such as duration, intensity, and frequency – to maximise cognitive benefits, moving beyond broad recommendations to identify precise, evidence-based guidelines for AD prevention and management.

6. Materials and Methods

6.1 Research Question and PICO

The primary research question of this master thesis, presented as a systematic review, is stated as: "Does physical activity have a significant positive effect on cognitive function in patients with Alzheimer's disease?"

Additional sub-questions were stated as follows:

- What are the (neuro)biological mechanisms mediating the effects of PA on cognitive function?
- How does dose and type of physical activity affect cognitive function?
- Which physical exercise has the most effect?

The PICO(T) model was used to frame the research question in terms of population, intervention, comparison, outcome, and type of study. The PICO(T) framework is as follows:

- Population: patients (> 65 years old) diagnosed with Alzheimer's disease (including cognitive impairment)
    - Sixty-five years is old is highlighted by Van Den Noortgate et al. (GRAY Whitepaper) as a key threshold because age-related health conditions, such as multimorbidity, frailty, and cognitive decline, become more prevalent and pronounced from this age onward, making it a crucial focus for geriatric healthcare interventions and research. (35)
    - Due to limited studies on specific PA parameters in AD, broader populations were included to synthesise patterns and refine evidence-based guidelines for AD prevention and management.
- Intervention: physical activity (different in duration, intensity, frequency, nature of activity)
- Comparison: distinctly different durations/intensities/frequencies/types of physical activity or absence of physical activity
- Outcome: improvement in cognitive function, improved brain structure and function, reduced risk of developing Alzheimer's disease, reduced inflammation, and oxidative stress
- Type of study: variable; RCTs, prospective, and cross-sectional studies have been included.

6.2 Article Selection Process

6.2.1 Eligibility Criteria

Studies were included if met the following criteria:

- RCTs, prospective, and cross-sectional studies.
- Commentaries, editorials, and other publication types were excluded.
- Published in peer-reviewed and English language journals.
- Articles published after 1995.
- Examined (non)-healthy (older, age groups equal or above 65 years old) adults with and without Alzheimer's Disease and mild cognitive impairment (MCI)
- Examined a direct association between PA and cognition on biological, physiological, and neurobiological mechanisms.

6.2.2 Information sources and search

For this master thesis, the literature search was performed using PubMed, Embase, and Web of Science. The search was conducted on 22 October 2023 by the author MH. The search strategy was constructed based on the PICO framework (see above). For each term used in the search strategy a selection of appropriate MeSH descriptors was made, as well as synonyms and text words to include the most relevant articles. Also, possible minor writing errors were taken into consideration while building the search strategy. All studies were first screened based on title and abstract and, subsequently, the selected full-text publications were systematically reviewed. Consequently, all relevant information from eligible studies was collected. The following data were extracted from the eligible studies: publication year, country, number of participants, age, population, type of study, type of PA, variables researched, intensity, frequency, duration, results, statistical significance.

6.2.3 Risk of Bias in Individual Studies

A specific screening checklist was set up in combination with the analysis of Levels of Evidence, ROBINS-I tool, and Cochrane Risk of Bias Tool (Table 1)

Levels of Evidence

- Level 1: Systematic review or meta-analyses
- 2: Randomised Controlled Trials (RCT)
- 3: Cohort studies
- 4: Case-control studies
- 5: Cross-sectional studies
- 6: Expert opinion, case-reports, etc.

ROBINS-I Tool (assessing the risk of bias in non-randomised studies):

- Each of seven domains (D1 through D7) received an individual score. These scores were synthesised to generate an overall risk-of-bias rating (Table 1). The domains are:
    - D1: Bias due to confounding (confounding bias)
    - D2: Bias due to selection of participants (selection bias)
    - D3: bias in classification of interventions (information bias)
    - D4: Bias due to deviations from intended interventions (performance bias)
    - D5: bias due to missing data (attrition bias)
    - D6: bias in measurement of outcomes (detection bias)
    - D7: bias in selection of the reported result (reporting bias)

Cochrane Risk of Bias Tool (assessing the risk of bias in randomised controlled trials (RCTs)):

- Each of seven domains (D1 through D6) received an individual score. These scores were synthesised to generate an overall risk-of-bias rating (Table 1). The domains are:
    - D1: Random sequence generation (selection bias)
    - D2: Allocation concealment (selection bias)
    - D3: Blinding of participants and personnel (performance bias)
    - D4: Blinding of outcome assessment (detection bias)
    - D5: Incomplete outcome data (attrition bias)
    - D6: Selective reporting (reporting bias)

Table 1: Summary of characteristics (first author, year, country, number of participants, age, population, type of study, level of evidence, and evaluation of risk of bias).

Category	First Author	Year	Country	Number of Participants	Age	Population	Type of Study	Level of Evidence	ROBINS-I TOOL	Cochrane Risk of Bias Tool
BRAIN STRUCTURE	Floel et al. (36)	2010	Germany	75	50 – 78	Healthy	Cross-sectional	5	**Moderate-Serious**	
	Rovio et al. (37)	2010	Finland & Sweden	75	71.6	AD, MCI & Healthy	Prospective	3	**Moderate**	
	Erickson et al. (38)	2010	USA	299	78	Healthy	Prospective			
	Rosano et al. (39)	2010	USA	30	80.8		RCT	2		**Low-Moderate**
	Ruschweyh et al. (40)	2011	Germany	62	50 – 72		RCT			
	Smith et al. (41)	2011	USA	68	65 – 85		Cross-sectional	5	**Moderate-Serious**	
	Ho et al. (42)	2011	USA	226	77.9		Cross-sectional			
	Gow et al. (43)	2012	UK	691	72.2	NS	Prospective	3	**Moderate**	
	Smith et al. (44)	2014	USA	97	65 – 89	Healthy	Prospective			
AEROBIC PA and the Effects on AD (all RCT's)	Kemoun et al. (45)	2010	France	31	81.8 ± 5.3	AD	RCT	2		**Low-Moderate**
	Venturelli et al. (46)	2011	Italy	21	84 ± 5					
	Vreughdenhil et al. (47)	2012	Australia	40	74.1					
	Arcoverde et al. (48)	2014	Brazil	20	79	AD + mixed				
	Holthoff et al. (49)	2015	Germany	30	72.4 ± 4.3	AD (mild to moderate)				
	Hoffmann et al. (50)	2016	Denmark	200	70.5	Mild AD				
	Kim et al. (51)	2016	Japan & Republic of Korea	33	81.5 ± 6.6	AD (moderate to severe)				
AEROBIC										
AEROBIC	Wallace et al. (52)	1999	Australia Denmark UK Sweden Italy	17	18 - 40	Healthy	Prospective	3	**Moderate**	
	Edwards et al. (53)	2004	USA	18	63 ± 9	Coronary Artery Disease				
	Linke et al. (54)	2005	Germany	35	55 ± 2	Chronic Heart Failure	RCT	2		**Low-Moderate**
	Gordon et al. (55)	2008	Jamaica Cuba	231	64.0	T2DM				
	Gomes et al. (56)	2008	Brazil	48	49.4 ± 2.3	Metabolic Syndrome	Prospective	3	**Moderate**	
	Griffin et al. (57)	2011	Ireland Australia	47	22 ± 2	Healthy				
	Tartibian et al. (58)	2011	Iran	79	58 - 78		RCT	2		**Low-Moderate**
	Scott et al. (59)	2011	UK	10	28 ± 4					
	Luk et al. (60)	2012	Hong Kong PR China	64	67.1 ± 8.4	Coronary Artery Disease				
	Arikawa et al. (61)	2013	USA	319	25.4 ± 3.5	Healthy				
	Wanderley et al. (62)	2013	Portugal	50	68 ± 5.5					
	Wahl et al. (63)	2014	Germany	12	24.7 ± 3.4		Prospective	3	**Moderate**	
	Wadley et al. (64)	2014	UK	19	56 ± 10	Rheumatoid Arthritis	RCT	2		**Low-Moderate**
	Mitranun et al. (65)	2014	Thailand	43	50 - 70	T2DM				
	Nikseresht et al. (66)	2014	Iran	34	34 - 46	Healthy, obesity				
	Jeon et al. (67)	2017	Republic of Korea	40	14 - 17	Healthy				
	Eizadi et al. (68)	2018	Iran	30	30 - 40	Obesity				

	Paolucci et al. (69)	2018	Canada	61	21 ± 2	Healthy	RCT	2		Low-Moderate
	Hashimoto et al. (70)	2018	Japan Denmark	14	24 ± 1.0		Prospective	3	Moderate	
	Tsai et al. (71)	2018	Taiwan Slovakia	66	60 - 80	Amnestic Mild Cognitive Impairment (aMCI)	RCT	2		Low-Moderate
	Park et al. (72)	2019	South Korea	41	76.6 ± 6.0	Healthy	Prospective	3	Moderate	
	Kujach et al. (73)	2020	Poland Japan South Korea	36	20 - 23		RCT	2		Low-Moderate
	Behrendt et al. (74)	2021	Germany	38	58 - 71					
	Weaver et al. (75)	2021	UK	24	23 ± 5					
	Yamamoto et al. (76)	2022	Japan	7	43 - 69					
	Eken et al. (77)	2022	Turkey	36	18 - 26					
	Ando et al. (78)	2022	Japan UK	19	22.5 ± 2.3					
RESISTANCE										
	Vincent et al. (79)	2002	USA	62	60 – 83	Healthy	RCT	2		Low-Moderate
	Lagally et al. (80)	2002	USA	20	24.6 ± 3.8		Cross-sectional	5	Moderate-Serious	
	Benson et al. (81)	2006	USA & Canada	13	25.2 ± 0.3					
	Cassilhas et al. (82)	2007	Brazil	62	65 – 75	Sedentary, healthy	RCT	2		Low-Moderate
	de Souza Vale et al. (83)	2009	Brazil	35	> 60	Healthy	Prospective	3	Moderate	
	Yarrow et al. (84)	2010	USA	20	21.9 ± 0.8					
	Philips et al. (85)	2010	USA	35	72.1 ± 6.1					
	Bobeuf et al. (86)	2011	Canada	57	65.6 ± 3.8		RCT	2		Low-Moderate
	Philips et al. (87)	2012	USA	23	65.6 ± 2.6	Obesity	Prospective	3	Moderate	
	Coelho et al. (88)	2012	Brazil	48	71.5 ± 4.4	Healthy				
	Hasani-Ranjbar et al. (89)	2012	Iran	34	20 – 30		RCT	2		Low-Moderate
	Wanderley et al. (62)	2013	Portugal	50	68 ± 5.5					
	Karabulut et al. (90)	2013	USA	36	56.8 ± 0.6					
	Azizbeigi et al. (91)	2013	Iran	20	18 – 26	NS				
	Watanabe et al. (92)	2014	Japan	18	60 – 77	Healthy				
	Tsai et al. (93)	2014	Taiwan	60	20 – 29					
	Beck et al. (94)	2014	USA	58	18 – 35					
	Forti et al. (95)	2014	Belgium	40	62 – 72		Prospective	3	Moderate	
	Strandberg et al. (96)	2015	Sweden	55	65 - 70		RCT	2		Low-Moderate
	Kjolhede et al. (97)	2016	Denmark	35	18 - 60	MS	Prospective	3	Moderate	
	Ribeiro et al. (98)	2017	Portugal	38	18 – 30	Healthy				
	Tsai et al. (71)	2018	Taiwan & Slovakia	66	60 – 80	aMCI	RCT	2		Low-Moderate
	Alikhani et al. (99)	2019	Iran	44	18 – 25 55 – 65	Healthy				
	Dora et al. (100)	2021	Japan	20	21					
	Arazi et al. (101)	2021	Iran	30	59 - 63					
NEUROMUSCULAR										
EXERGAMES	Anderson-Hanley et al. (102)	2012	USA	63	58 – 99	Healthy	RCT	2		Low-Moderate
	Silvi et al. (103)	2022	Indonesia	13	26 – 37		Prospective	3	Moderate	

	Henrique et al. (104)	2023	Brazil	20	64.05		RCT	2		**Low-Moderate**
DANCE	De Angelis et al. (105)	1998	Italy	30	23.6		Cross-sectional	5	**Moderate-Serious**	
	Müller et al. (106)	2017	Germany	22	63 – 80		RCT	2		**Low-Moderate**
	Rehfeld et al. (107)	2018	Germany	38	63 – 80					
	Wharton et al. (108)	2021	USA	34	59.7	High-risk group for developing AD				
TAI CHI	Irwin et al. (109)	2012	USA	83	59 – 86	Breast cancer survivors	RCT	2		**Low-Moderate**
	Mendoza-Nunez et al. (110)	2014	Mexico	49	60 – 74	Metabolic Syndrome	Prospective	3	**Moderate**	
	Campo et al. (111)	2015	USA	54	55 – 84	Breast cancer survivors	RCT	2		**Low-Moderate**
	Sungkarat et al. (112)	2018	Thailand	60	67.9	aMCI				
	Mendoza-Nunez et al. (113)	2018	Mexico	85	60 – 74	Metabolic Syndrome	Prospective	3	**Moderate**	
	Solianik et al. (114)	2021	Lithuania	30	60 – 78	Sedentary, healthy	RCT	2		**Low-Moderate**
YOGA	Lee et al. (115)	2014	Republic of Korea	25	41.9 ± 8.9	Chronic Low Back Pain	Prospective	3	**Moderate**	
	Kiecolt-Glaser et al. (116)	2014	USA	181	27 – 76	Breast Cancer Survivor	RCT	2		**Low-Moderate**
	Harkess et al. (117)	2016	Australia	28	41.21	Sedentary				
	Shete et al. (118)	2017	India	37	41.5 ± 5.2	T2DM				
	Li et al. (119)	2020	China	24	39.8 ± 8.5	Lymphangioleiomyomatosis (LAM)	Prospective	3	**Moderate**	
	Nugent et al. (120)	2021	USA	84	45.2 ± 12.7	Depression	RCT	2		**Low-Moderate**
	Viswanathan et al. (121)	2021	India	300	30 – 65	T2DM				

7. Results

7.1 Study characteristics

Of the 4611 studies identified through literature search, 301 references met the inclusion criteria, based on title and abstract. After reviewing the full text articles, 86 articles were included. A full report of the selection process can be found in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) diagram [Figure 7]. (36-121)

The study designs were as follows: fifty-six studies (65.1%) were RCT's, twenty-four studies (27.9%) were prospective, and six studies (7%) were cross-sectional. Furthermore, twenty-one studies (24.4%) were (partially) conducted in the USA, seven studies (8.1%) in Germany, seven studies in Japan, six studies (7%) in Iran, six studies in the UK, six studies in Brazil, five studies (5.8%) in South Korea, four studies (4.6%) in Denmark, four studies (4.6%) in Australia, three studies (3.5%) in Canada, three studies in Italy, three studies in Sweden, three studies in Taiwan, three studies in Portugal, two studies (2.3%) in India, two studies in Slovakia, two studies in China, two studies in Mexico, two studies in Thailand, one study (1.2%) in Belgium, one in Turkey, one in Poland, one in France, one in Ireland, one in Cuba, one in Jamaica, and one in Lithuania.

From the 86 studies included, two studies (2.3%) were published before 2000, nine studies (10.5%) were published between 2000 and 2009, and seventy-five studies (87.2%) were published after 2010. Additionally, from the 86 studies included, fifty-six studies (65.1%) had a sample size below 50, twenty-two studies (25.6%) between 51 and 100, seven studies (8.1%) between 101 and 500, and one study (1.2%) above 500 participants. The sample size varied from 7 to 691 participants. The age range of study participants varied from 18 to 99 years of age. More specifically, the participants were above 65 years of age regarding the RCTs and their respective aerobic interventions assessing their impact on cognition for the AD group.

From the 86 studies included, the population group was healthy in fifty-one studies (59.3%), had AD in nine studies (10.5%), diabetes mellitus type 2 in four studies (4.7%), metabolic syndrome in three studies (3.5%), (amnestic) mild cognitive impairment in three studies (3.5%), obesity in three studies (3.5%), survived breast cancer in three studies (3.5%), coronary artery disease in two studies (2.3%), not specified in two studies (2.3%), high-risk group in developing AD in one study (1.2%), rheumatoid arthritis in one, Multiple Sclerosis in one, chronic heart failure in one, chronic low back pain in one, LAM in one, and depression in one.

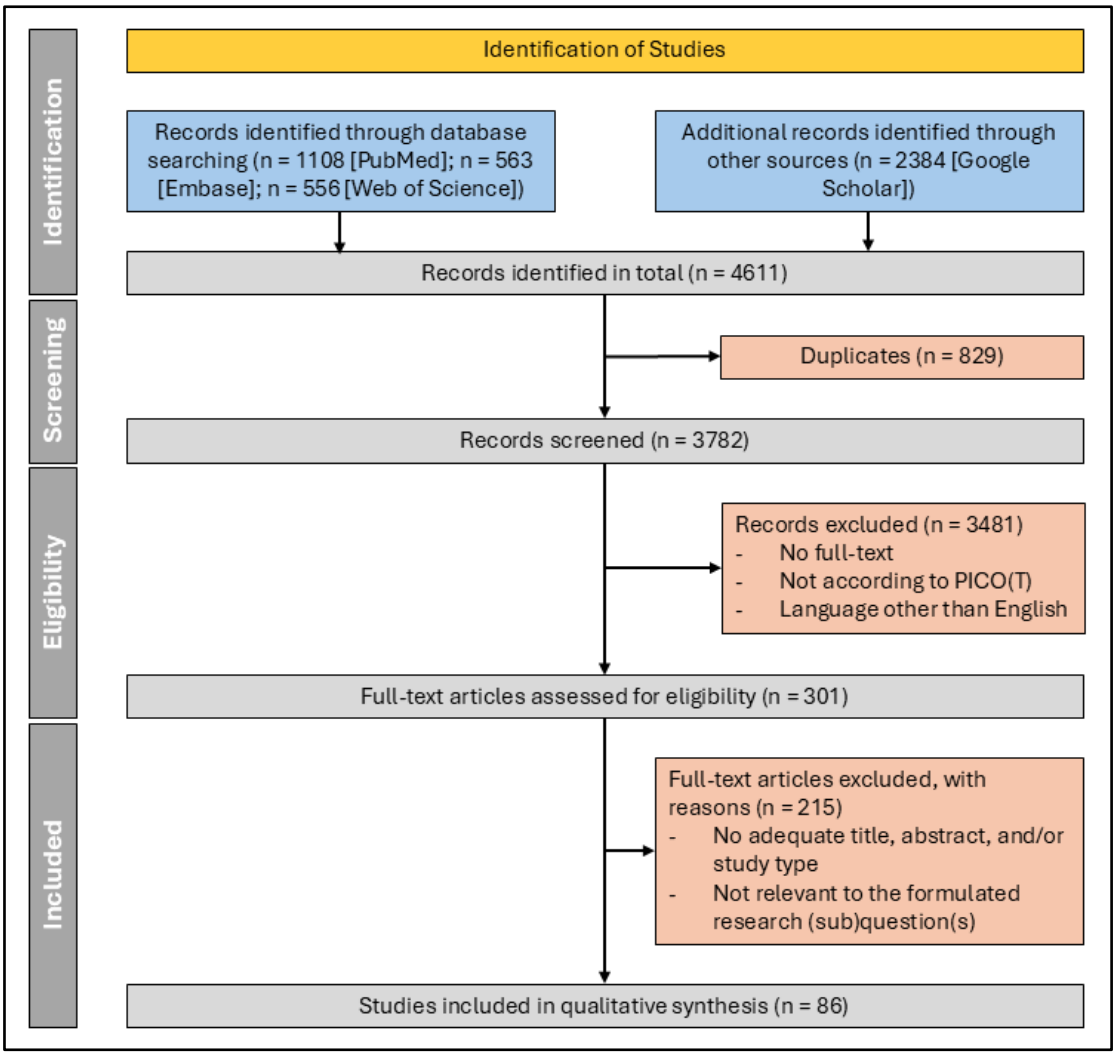


Figure 5: Article selection process

7.2 Risk of bias

The level of evidence was determined for each article to evaluate the findings within a hierarchy of evidence quality. Overall, the studies were of good quality: fifty-six studies (65.1%) were level 2, twenty-four studies (27.9%) were level 3, and six studies (7%) were level 5. Additionally, both the ROBINS-I tool for non-randomized studies and the Cochrane Risk of Bias tool for randomized controlled trials were used. Regarding the ROBINS-I tool (thirty articles): twenty-four studies (80%) had a moderate risk of bias, another six studies (20%) had moderate-serious risk. Regarding the Cochrane Risk of Bias tool: fifty-six studies (100%) had a low-to-moderate risk.

7.3 Effects of PA on Brain Structure

Nine studies (two RCTs, four prospective, three cross-sectional; Table 2) (36-44) investigated the impact of PA on brain structure, brain volume, cognition, and the potential protective effects against AD in older adults, including those with healthy cognition, and MCI. Across these studies, all but two noted a positive association between PA and increased grey matter (GM) volume. (36-38, 40, 42-44)

Furthermore, Gow et al. (prospective) stated a decrease in brain atrophy and white matter integrity issues with increased PA. (43) Erickson et al. (prospective) reported that walking longer distances was significantly associated with higher GM in frontal, occipital, temporal, and entorhinal regions, as well as the hippocampus, over a period of nine years. (38) In contrast, Rosano et al. (RCT) and Smith et al. (cross-sectional) reported no significant relationship between PA and GM volume. However, both studies indicated that PA positively influenced cognitive performance and brain function, with Smith et al. emphasising improvements in semantic memory and functional outcomes, particularly in individuals at higher risk for AD (apoE-4 carriers). (39, 41)

7.4 Effects of PA on AD

Seven RCTs (Table 3) (45-51) evaluated the influence of PA (aerobic exercise) on cognitive function in patients with AD. Across these studies, PA interventions consistently resulted in cognitive improvements.

Vreugdenhil et al. (RCT) (47) specifically highlighted that low intensity PA led to significant enhancements in cognitive outcomes (particularly MMSE, Timed Up and Go, and Sit-to-Stand tests). Moderate intensity PA was assessed in four studies, which also reported improvements in cognitive performance and functional capacity (MMSE, CAMCOG, and functional measures like BERG, FR, and TUGT). (45, 46, 48, 50)

However, Hoffmann et al. (RCT) stated that while moderate intensity PA did not yield significant improvements in cognitive function, high intensity PA did result in notable cognitive gains. The PA interventions ranged in frequency and duration, from two sessions per week to daily, with session lengths varying 30 minutes to 1 hour over a span of 12 weeks to 6 months. (50)

7.5 Effects of Aerobic Exercise on Neurobiological Mechanisms

A total of twenty-seven studies (twenty RCTs, seven prospective; Table 4) (52-78) examined the effects of aerobic physical activity on neurobiological mechanisms. Nine studies (seven RCTs, two prospective) reported significant changes in BDNF levels, with exercise intensities ranging from low to high, conducted in single sessions to two times per week, over durations of 20 minutes to 12 weeks. (57, 67, 71-77) However, Hashimoto et al. (prospective) and Ando et al. (RCT) found no significant changes, while Eken et al. (RCT) reported significant increases only for high-intensity exercise. (70, 77, 78)

Six studies (7 RCTs, 2 prospective) reported significant increases in IGF-1 levels, though Jeon et al. (RCT) reported no changes for low-intensity exercise. Weaver et al. (RCT) reported a significant reduction in IGF-1 levels post-exercise, while Griffin et al. (prospective) and Ando et al. (RCT) did not find significant changes. (52, 57, 67, 71, 73-76, 78)

Four studies (three RCTs, one prospective) found significant increases in VEGF levels, particularly for high-intensity training ranging from single sessions to three times per week. However, Tsai et al. (RCT) and Park et al. (prospective)(low-to-moderate intensity, single sessions of 20 – 30 mins) did not find significant changes, and Eken et al. (RCT) observed significance only for high-intensity exercises. (63, 71-73, 75, 77)

Two RCTs and one prospective study analysed that lactate levels consistently increased with exercise intensity across studies. (59, 70, 75)

Five RCTs reported significant reductions in inflammatory markers such as IL-6, Tumour Necrosis Factor (TNF(-alpha)), and Interleukin 10 (IL-10), across varying intensities (single sessions to three times per week, 90 minutes to 8 months). However, Scott et al. (RCT) and Nikseresht et al. (RCT) found no changes for TNF-alpha and IL-10. (54, 58, 59, 62, 66, 68, 69)

Six studies (four RCTs, two prospective) reported significant reductions in oxidative stress markers, particularly for moderate to high-intensity exercise, performed daily to five times per week over periods of 8 weeks to 12 months. Luk et al. (RCT) and Mitranum et al. (RCT) reported no significant changes. (53-56, 60, 61, 64, 65)

7.6 Effects of Resistance Exercise on Neurobiological Mechanisms

A total of twenty-five (fifteen RCTs, eight prospective, two cross-sectional; Table 5) (62, 71, 79-101) studies investigated the effects of resistance exercise on neurobiological mechanisms. Three studies (one RCT, two prospective) reported significant increases in BDNF levels following moderate to high-intensity resistance training, with interventions ranging from three times per week over 5 to 10 weeks. (84, 88, 101) In contrast, two other studies (one RCT, one prospective) found no significant changes in BDNF levels. (93, 95)

Six studies (five RCTs, one prospective) highlighted significant increases in IGF-1 levels with low to high-intensity protocols, which were conducted as single sessions or up to three times per week over periods of 30 minutes to 24 weeks. (71, 82, 83, 89, 93, 101) However, one study by Karabulut et al. (RCT) did not find significant changes in IGF-1 levels.

VEGF levels were reported to significantly increase by Ribeiro et al. (prospective), particularly for intensities of 60% to 80% 1RM, while Tsai et al. (RCT) did not observe any significant changes in VEGF levels across similar intensity levels.

Lactate was found to significantly increase following resistance training in three studies (one RCT, two cross-sectional) (30 to 90% 1RM), indicating higher metabolic activity. (80, 81, 92) Additionally, four studies (four RCTs) demonstrated a significant reduction in oxidative stress, with both low- to high-intensity resistance exercises leading to decreased oxidative markers. (79, 91, 94, 100) However, Bobeuf et al. (RCT) reported no significant changes.

Regarding inflammatory markers, six studies reported no significant changes in IL-6, TNF-alpha, or other inflammatory markers. (62, 85, 90, 96, 97, 99) However, Philips et al. and Forti et al. found a significant reduction in TNF-alpha, IL-6 levels, and C-reactive protein (CRP) levels.

7.7 Effects of Neuromuscular Exercise on Neurobiological Mechanisms

A total of twenty studies (fourteen RCTs, five prospective, one cross-sectional; Table 6) (102-121) explored the effects of neuromuscular physical activity on neurobiological mechanisms. This included three studies (two RCTs, one prospective) on exergames (102-104), four studies (three RCTs, one cross-sectional) on dance (105-108), six studies (four RCTs, two prospective) on Tai Chi (109-114), and another seven studies (five RCTs, two prospective) on yoga (115-121). These studies assessed various variables with differing intensities and frequencies of PA. However, some studies did not specify all variables, highlighting inconsistencies in the reported parameters across the research.

7.7.1 Exergames

Three studies (two RCTs, one prospective) explored the impact of exergames on neurobiological mechanisms, particularly focusing on BDNF, inflammatory markers (IL-6, IL-10, TNF-alpha), and cognitive performance. All studies reported significant changes in BDNF levels following exergame interventions, underlining enhanced neuroplasticity. (102-104)

Additionally, Silvi et al. (prospective) confirmed increased lactate levels with high-intensity sessions lasting 38 minutes, conducted three times a week. While Henrique et al. (RCT) found significant increases in IL-10 and TNF-alpha (though IL-6 levels remained unchanged) during twice weekly sessions over six weeks. Cognitive improvements were observed across the studies, as measured by tests such as the Montreal Cognitive Assessment (MoCA). (102-104)

7.7.2 Dance

Four studies (three RCTs, one cross-sectional) investigated the effects of dance on neurobiological markers and cognitive functions. Rehfield et al. (RCT) reported significant increases in BDNF levels after 6 months (returning to baseline after 18 months), particularly following dance interventions conducted at a frequency of two times per week, with session durations of 90 minutes. De Angelis et al. (cross-sectional) found that both low- and high-intensity dance sessions significantly increased lactate levels. Müller et al. (RCT) noted region-specific brain volume increases and improvements in verbal memory. Whereas Rehfield et al. reported increases in brain volume, particularly in regions associated with attention and spatial memory. Finally, Wharton et al. (RCT) found that tango dancing significantly improved TNF-alpha levels and overall balance. (105-108)

7.7.3 Tai Chi

A total of six studies (four RCTs, two prospective) investigated the effects of Tai Chi on neurobiological markers and cognitive functions. Two RCTs reported significant increases in BDNF levels following moderate-intensity Tai Chi interventions, performed two to three times per week over periods ranging from 10 weeks to 6 months. Despite these findings, most studies did not observe significant changes in anti-inflammatory markers such as IL-6, IL-10, or TNF-alpha. However, Mendoza-Nunez et al. (prospective) demonstrated significant improvements in total antioxidant status and oxidative stress scores with moderate-intensity Tai Chi performed five times per week, with each session lasting around 50 to 60 minutes. (109-114)

7.7.4 Yoga

Seven studies (five RCTs, two prospective) investigated the effects of yoga on neurobiological markers and cognitive functions. (115-121) Four RCTs reported a significant decrease in IL-6 and TNF-alpha levels following yoga interventions. These interventions typically involved hour-long sessions conducted two to six times per week for a minimum duration of 12 weeks. (116-118, 121)

In contrast, Nugent et al. (RCT) found no significant reductions inflammatory markers despite similar session frequencies and duration. Additionally, Li et al. (prospective) observed no significant changes in VEGF levels after 24 weeks of yoga practice. However, Lee et al. (prospective) demonstrated a significant increase in BDNF levels, with yoga sessions performed three times per week for 12 weeks.

8. Discussion

Worldwide, the older population is growing due to the global rise in life expectancy. This future shift emphasises the growing challenge of cognitive decline, deterioration in brain health associated with ageing, which impacts individuals' autonomy and quality of life. The role of PA in maintaining and enhancing brain health has become more pronounced. Research increasingly supports that engaging in PA positively affects both the structure and function of the brain, offering potential protective benefits against cognitive decline and AD. As AD advances, neurons shrink and lose synaptic connections, leading to significant neuronal loss and brain atrophy, erasing the ability to form new memories. The evidence suggests that PA can improve cognitive function in elderly individuals, potentially preventing or delaying AD and cognitive deterioration through mechanisms independent of its effects on cardiovascular risk factors such as hypertension, diabetes, hypercholesterolemia, and obesity. PA's impact on brain health extends to enhancing mitochondrial biogenesis and antioxidant enzyme activity, facilitating amyloid clearance from the brain, and slowing down amyloid-related cognitive decline and GM volume loss. Despite these long-standing findings, research on specific types and dose of PA and their advantages on cognition remain in its infancy. (1-10, 12, 122)

The purpose of this systematic review was to explore the neurostructural and the neurobiological effects of PA in AD. Given the limited research on the specific parameters of PA – such as types, and dose (duration, intensity, and frequency) – in relation to AD, this review examined these factors across a broader range of populations. By drawing on findings from diverse groups, this review aims to synthesise relevant patterns and provide more refined evidence-based guidelines for the prevention and management of AD.

8.1 Physical Activity and Cognitive Function in Alzheimer's Disease

The primary research question (“Does physical activity have a significant positive effect on cognitive function in patients with Alzheimer’s disease?”) was specifically examined with a focus on the relationship between brain structure and physical activity in Alzheimer’s disease, as well as the impact of aerobic PA on cognitive function in this population.

8.1.1 Effects of Physical Activity on Brain Structure

To investigate the effects of PA on brain structure, a combination of RCTs, prospective studies, and cross-sectional studies was analysed, providing valuable insights while acknowledging variability in study design strength and reliability (Table 1). Neuroimaging research has further clarified the cognitive benefits of PA in older adults, revealing specific brain changes associated with various exercise modalities and durations (Table 2). Increased PA is generally associated with decreased age-related losses in cortical volume, increased grey and white matter volume, and increased hippocampal volume. It has been stated that PA initiates increased cerebral blood flow (CBF) in the hippocampal dentate gyrus, suggesting a potential mechanism for enhanced neurogenesis. (32, 36-44, 123)

Mostly observational research (limiting the ability to establish causal relationships with high confidence) indicated a positive impact of PA on brain structure, particularly in the frontal and temporal regions, including the hippocampus. However, Rosano and Smith et al. reported an

apparent increase in overall cognitive and memory performance, although no effect of PA on total brain volume, and GM or atrophy was observed by neuroimaging. (36-44)

Hippocampal atrophy is a recognised biomarker for AD and has been associated with cognitive and memory dysfunction. Evidence suggests that PA may attenuate the age-related decline in hippocampal volume. Erickson et al. has shown that walking greater distances is associated with larger hippocampal and GM volumes, which in turn reduces the risk of cognitive impairment. More specifically, aerobic exercise has been connected to increased volumes in the anterior hippocampus and is predictive of increased brain volumes in the frontal, occipital, entorhinal, and hippocampal regions, alongside improvements in spatial memory. However, as stated by Smith et al., the protective effect of PA on hippocampal volume appears to be more pronounced in individuals carrying the APOE-ε4 genotype, emphasising the potential relevance of genetic factors in the role of PA for brain health. (36-44)

8.1.2 Effects of Aerobic Physical Activity on Alzheimer's Disease

For assessing the impact of aerobic PA on cognitive function in AD patients, only high-quality RCTs with a low-to-moderate risk of bias (Table 1) were included, ensuring a robust and reliable evidence. This evidence strongly suggests that aerobic PA (low to high intensity) results in cognitive improvements in patients with AD. Although the optimal duration, intensity, and frequency of PA for maximising benefits to hippocampal volume are not fully defined, the overall evidence underscores the importance of regular PA in the prevention and management of AD. (45-51)

The relationship between PA and the prevention of AD is complex and influenced by multiple factors. However, baseline performance significantly influences the impact of PA, with individuals exhibiting poorer performance at pretest demonstrating the greatest opportunity for improvement. Suggesting that the effects of PA might vary depending on the initial cognitive state and physical state of the individual, with those at atypical levels of baseline performance (either poorer or superior) showing higher or lower sensitivity to the effects of PA. The cognitive reserve hypothesis further supports that PA across the lifespan contributes to the maintenance of cognitive function in older adults. Changes in PA patterns (e.g. retirement, lifestyle transitions, changes in caregiving responsibilities, technological changes, economic or social barriers, etc.), can influence the overall impact of PA on AD risk, with varying effects based on the physical demands of one's occupation and socioeconomic status. (1-3, 5, 18, 45-51)

The interaction between PA and genetic factors (for example APOE-ε4 allele) play crucial roles in AD risk modulation. The APOE-ε4 allele, known for its disruptive effects on lipid homeostasis and amyloid precursor protein function, among other things, poses an increased risk for AD. Interestingly, PA appears to offer more pronounced benefits to APOE-ε4 allele carriers compared to non-carriers. This may be due to the allele's impact on lipid metabolism and brain amyloid clearance, suggesting that PA can mitigate some of these adverse effects. However, the relationship between PA, AD risk, and APOE-ε4 carriership remains complex, with studies showing varying levels of protection offered by PA based on APOE genotype and the timing of PA engagement in life. (22, 29, 41, 45-51, 123)

8.2 Neurobiological Effects of Aerobic, Resistance, and Neuromuscular Physical Activity

Regarding the sub-question: "What are the (neuro)biological mechanisms mediating the effects of PA on cognitive function?", primarily RCTs and prospective studies were included, with fewer cross-

sectional designs (Table 1). This resulted in a diverse and methodologically robust collection of evidence, minimising the overall risk of bias (low-to-moderate) and allowing a high level of evidence.

The neurotrophic factors like BDNF, IGF-1, and VEGF are crucial for the development, survival, and differentiation of neurons and are upregulated by PA. This upregulation not only stimulates the production of these neurotrophic factors, also promotes neurogenesis and synaptic plasticity, enhancing the integration of new neurons into neural networks, particularly under cognitively demanding conditions. From a neurobiological perspective, moderate to high-intensity aerobic exercise is more effective than low intensity exercise in enhancing neurobiological mechanisms. This is largely due to its ability to increase levels of BDNF, VEGF, and lactate levels while reducing inflammation markers and oxidative stress, manifesting its superior role in combating ageing-related cognitive decline. Although the effects of low intensity aerobic PA are less pronounced, these exercises can also offer cognitive and brain health advantages. Low to high intensity resistance exercises have shown to have the greatest impact on IGF-1, lactate levels and oxidative stress with advantages increasing as intensity rises. While this does not indicate that resistance training is more superior than other types of PA, it suggests that resistance exercises have particularly pronounced effects on these neurobiological pathways, specifically more so than aerobic PA regarding these pathways. Exergames, dance, Tai Chi, and yoga have also been shown to increase BDNF levels across varying intensities. Particularly, Tai Chi significantly reduced oxidative stress (by increasing antioxidant markers and decreasing pro-oxidant markers), while yoga reduced inflammation markers. (52-121)

In summary, the most beneficiary physical activities appear to be moderate to high-intensity aerobic exercise and low to high-intensity strength exercise, which primarily promote the release of growth factors. Low to high-intensity aerobic exercise and yoga are particularly effective in reducing inflammation. Moderate to high-intensity aerobic exercise, low to high-intensity resistance, and Tai Chi are the primary activities that decrease oxidative stress. The practice of Tai Chi involves agility, mobility, and the learning new movement patterns, which impact cognitive function through unique neurophysiological pathways. Additionally, Tai Chi's meditative and relaxation aspects can reduce anxiety and depression, affecting stress-related pathways linked to cognitive decline. (52-121)

8.3 The Importance of Dose and type of Physical Activity

Addressing the sub-question: “How does dose and type of physical activity affect cognitive function?”, predominantly RCTs and prospective studies were included, with fewer cross-sectional designs (Table 1). Allowing a wide-ranging and well-founded evidence collection and supporting a high level of evidence.

The research highlights the critical role of optimising the duration and frequency of PA to improve cognitive function. The duration of exercise is inherently linked to its intensity, with higher intensities allowing for shorter durations. However, a minimum duration is essential to trigger cognitive benefits. The above findings suggest that aerobic exercise sessions of 20-30 minutes are most effective for enhancing neurobiological pathways, while shorter sessions show limited effects. Resistance exercise sessions can yield benefits with sessions lasting 12-30 minutes, but longer durations may be counterproductive. Neuromuscular exercises are typically performed for 30-60 minutes per session. To better understand post-exercise cognitive effects, researchers should transparently report the total duration of cognitive assessments and their timing after physical activity. This would help clarify study differences and account for factors like participant fatigue, which may influence the persistence of cognitive benefits after exercise. In terms of frequency, aerobic and neuromuscular exercises show more lasting cognitive benefits when done three times a

week. Resistance training is generally ineffective if performed less frequently than three times a week. Overall, interventions scheduled up to three times weekly lead to more significant cognitive improvements than less frequent sessions. (1, 3, 7, 9, 10, 18, 20, 29, 32-34, 52-121, 123)

However, the literature shows inconsistencies in defining "intensity" (for a detailed discussion of how the neurobiological effect of intensity varies across different forms of physical activity, see Section 8.2) across studies, with measures ranging from heart rate reserve (HRR), maximal oxygen consumption (VO2max), and maximal heart rate to intervention duration. This lack of standardisation highlights the need for a unified system, especially for research on PA's cognitive benefits in older adults with AD. The American College of Sports Medicine (2018) recommends using the HRR method, which considers the range between resting and maximal heart rate, offering a more personalised approach that adjusts for individual cardiac profiles. Conventional methods also face criticism for not distinguishing between aerobic and anaerobic contributions to exercise intensity, which might be better captured by setting intensity relative to the anaerobic threshold. On the other hand, psychological measures, such as the Borg and OMNI Rating of Perceived Exertion (RPE) scales, add another layer by accounting for perceived effort. (32, 123)

8.4 Multicomponent Physical Activity for Older Adults with Alzheimer's Disease

Exploring the sub-question: "Which physical exercise has the most effect?", a broad range of high-quality RCTs and prospective studies (Table 1) were thoroughly analysed. This systematic approach resulted in the development of a comprehensive, evidence-based PA program for older adults with AD which should include aerobic, resistance, and neuromuscular training. Each type of exercise offers unique benefits, supporting both cognitive and physical health through different pathways. When combined, these exercises provide a holistic approach that enhances cognitive function, improves mobility, and reduces fall risk. (2, 32, 52-121, 124) Below are practical guidelines for each type of PA, offering starting points and progressive steps tailored for older adults with AD. These recommendations are drawn from the systematic review of research conducted in this master's thesis and have been specifically tailored for older adults with AD. Although many of the studies reviewed focused on a variety of populations or individuals with other health conditions, key insights have been adapted to create practical guidelines for older adults with AD.

8.4.1 Aerobic Physical Activity (2, 32, 52-78)

Aerobic exercise promotes cardiovascular health, preserves aerobic capacity, and supports cognitive function by increasing blood flow and stimulating neurotrophic factor production.

Recommended guidelines:

Initial Phase: Early in the program, especially if the participant has basic mobility and stable cardiovascular health.

Activities: Walking-based aerobic exercises (short and supervised walks, treadmill walking at a slow speed, Nordic walking with poles, etc.), seated aerobic exercises (seated marching, seated arm exercises, seated step taps, seated pedalling, seated dancing, etc.), chair-assisted side steps, standing marching in place, side-to-side steps, toe and heel walking, etc.

Frequency and Duration: Start with short sessions, around 10-15 minutes, twice a week, at a low to moderate intensity where participants can comfortably hold a conversation.

Progression: Gradually increase sessions to 20-30 minutes, three times per week. Increase intensity slowly, allowing participants to feel "comfortably challenged."

8.4.2 Resistance Physical Activity (2, 32, 62, 71, 79-101)

Resistance exercises are crucial for building muscle strength, preventing sarcopenia, and enhancing mobility. They are typically performed at low to moderate intensity and can include simple movements with body weight or light resistance equipment.

Recommended guidelines:

Initial Phase: Early in the program, often combined with aerobic exercises, if the participant has adequate muscle control and can perform basic movements with ease.

Activities: Seated resistance exercises (seated leg lifts, seated knee extensions, seated marching with resistance bands, seated arm curls with light weights or resistance bands, seated shoulder press, seated side leg lifts, seated rows, seated grip strength exercises, etc.), assisted or supported resistance exercises (chair-assisted sit-to-stand, wall push-ups, countertop or chair squats, standing heel raises with support, etc.), etc.

Frequency and Duration: Start with two sessions per week, performing 8-10 repetitions of each exercise.

Progression: Gradually increase the resistance (using slightly heavier bands or weights) and aim for 2 sets per exercise. Emphasise control and form over speed.

8.4.3 Neuromuscular Physical Activity (2, 32, 102-121)

Balance and coordination exercises are essential for reducing fall risk and enhancing motor control, which is particularly valuable for individuals with AD. Neuromuscular exercises focus on stability and coordination through functional movements.

Recommended guidelines:

Initial Phase: Once the participant demonstrates basic balance abilities and can stand with minimal support. If balance is limited, aerobic and resistance exercises should be prioritised until balance improves.

Activities: Exergames, dance, Tai Chi, yoga, seated neuromuscular activities (seated weight shifts, seated heel and toe taps, seated arm and leg coordination, seated Tai Chi/yoga/dancing, seated drawing with feet, etc.), assisted weight shifting, standing heel-toe-balance, balloon volleyball, mirror movements, hand clapping patterns, obstacle course walking, walking on a compliant surface such as foam mattresses, etc.

Frequency and Duration: Start with two sessions per week for about 20-30 minutes.

Progression: Gradually extend sessions to 30-60 minutes. As participants become more comfortable, gradually reduce reliance on hand support and introduce more challenging postures or movements, such as backward walking or side stepping.

8.4.4 Dual-Task Training (15, 31)

Dual-task exercises involve performing two activities simultaneously, combining cognitive demands with physical or motor tasks. These activities simulate real-life scenarios that require multitasking, supporting cognitive resilience. Real-life scenarios often require multitasking and divided attention, which can be especially challenging in older adults when attentional capacities may be limited, yet dual-task training has shown potential in maintaining or enhancing cognitive efficiency, often providing greater benefits than single-task exercises. Consistent evidence suggested that combining physical/motor and cognitive training may have the potential to maintain or enhance cognitive efficiency during ageing and may surpass the benefits of single-task activities.

Recommended guidelines:

Initial Phase: Once the participant demonstrates comfort with at least one of the primary activities, dual-task exercises require a higher level of focus and neuro-muscular coordination.

Activities: Walking while naming items in a category (e.g., colours, animals), or counting steps while alternating stepping directions.

Frequency and Duration: Start with one session per week, around 15 minutes. Dual-task training can be easily integrated into other exercise sessions.

Progression: Gradually increase to two sessions per week, adjusting the cognitive demands by incorporating more complex tasks or memory exercises, such as recalling information while walking or balancing.

8.4.5 Implementation Strategy (2, 15, 31, 32, 52-121)

An individualised (considering factors like risk level, medical history, musculoskeletal limitations, functional ability, tolerance, and personal preferences) structured yet flexible approach allows older adults with AD to progress at their own pace, ensuring each exercise component is introduced according to individual physical and cognitive capabilities. By gradually adjusting dose and combining multiple types of PA, this type of implementation strategy supports both cognitive and physical well-being, enhancing quality of life in a safe and supportive environment.

8.5 The Additional Complexities of Introducing Physical Activity to Older Adults with Alzheimer's Disease

PA can enhance the well-being of older adults with AD by improving mood, cognitive function, and daily functioning. However, cognitive decline and comorbidities complicate the adoption of exercise routines, requiring strategies that evolve over time.

As AD advances, remembering instructions or following routines can become increasingly difficult, and resistance to unfamiliar activities can arise. Additional comorbid conditions like cardiovascular/respiratory/renal disease, arthritis or osteoporosis may further affect the intensity or type of feasible exercise. Practical factors — finances, transportation, and accessible facilities — further shape whether a program can be sustained long term.

Within this framework, general practitioners play a vital role by coordinating through identifying exercise needs, ensuring safety, and adjusting recommendations alongside (necessary) pharmacological treatments. Collaboration with physical therapists, as well as mental health professionals, supports a holistic approach. Additionally, caregivers provide day-to-day supervision, encouragement, and adaptation of exercises to meet changing abilities.

In Belgium, *Bewegen op Verwijzing* ("Exercise on Prescription") highlights how structured, subsidised support can mitigate many of these challenges. General practitioners refer patients to specialised coaches who tailor exercise plans to the individuals' medical status and personal goals. By leveraging local networks and reducing costs, the program promotes safe, socially engaging, and sustainable PA for people living with and without AD.

8.6 Strengths and Limitations

The main strengths are that the included research (numerous randomised controlled trials with low-to-moderate risk of bias) consistently shows that different forms of PA (aerobic, resistance, and neuromuscular) have varying positive impacts. These benefits extend across multiple domains, including overall cognitive function, executive function, processing speed, motor-cognitive integration, and functional independence. (2, 17, 123, 124)

The limitations are that isolating the effects of PA is challenging because of other influencing factors such as diet, environmental conditions, sleep patterns (including fragmented sleep and daytime napping or other circadian disruptions), mental health conditions like depression, and social support. A key challenge is the considerable variations in how PA is measured: studies differ in the type of PA (aerobic, resistance, neuromuscular, mixed), the intensity, frequency and duration of each exercise session, and the overall quality of the measurements. (1-3, 15, 22, 32, 123, 125, 126) An additional limitation is the differences in genetics, baseline fitness levels, and potentially insufficient training

stimulus can all affect how individuals respond to PA. (1-3, 15, 22, 32, 123, 125) An additional drawback is the variability in cognitive assessment tools, many being traditional clinical tests (e.g., MMSE) that lack the sensitivity and ability to assess multiple cognitive domains. Effective PA interventions require well-designed, repeatable measures (e.g., MoCA, ADAS-Cog, etc.) which minimise familiarity and compensatory strategies. (2, 17, 123, 124)

9. Conclusion

Neuroimaging research has advanced our understanding of the positive impact PA can have on cognitive function in older adults and show that higher levels of PA preserve or increase cortical, grey/white matter, and hippocampal volumes - all critical structures for cognitive performance. The findings significantly show that aerobic PA, at both low and high intensities, leads to cognitive improvements in individuals with AD.

More specifically, moderate to high-intensity aerobic exercise and low to high-intensity resistance training most effectively stimulate growth factors, while lower-intensity aerobic activities and yoga reduce inflammation. Moderate to high-intensity aerobic and resistance exercises, and Tai Chi mitigate oxidative stress. The optimal dose generally involves 20–30 minutes of aerobic exercise and 12–30 minutes of resistance training per session, with longer sessions sometimes limiting benefits. Neuromuscular exercises like Tai Chi, yoga, and balance training typically last 30–60 minutes, and scheduling any of these activities three times a week yields the most sustained cognitive gains. However, inconsistencies in defining exercise intensity highlight the need for standardised measures to accurately compare and interpret findings.

Different types of PA complement each other through multiple, overlapping pathways – improving cardiovascular health, releasing neurotrophic factors, strengthening muscles, and reducing inflammation. Combined, they provide a holistic strategy to preserve cognitive function, enhance mobility, and lower fall risk in individuals with AD. These findings underscore the value of multifaceted personalised PA regimens – tailored to individual needs and genetic factors – to optimise both the prevention and management of AD, while also emphasising the need for further research to refine and standardise these approaches.

10. Bibliography

1. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. The lancet. 2017;390(10113):2673-734.
2. Izquierdo M, Merchant R, Morley J, Anker S, Aprahamian I, Arai H, et al. International exercise recommendations in older adults (ICFSR): expert consensus guidelines. The journal of nutrition, health & aging. 2021;25(7):824-53.
3. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet. 2020;396(10248):413-46.
4. Veronese N, Solmi M, Basso C, Smith L, Soysal P. Role of physical activity in ameliorating neuropsychiatric symptoms in Alzheimer disease: a narrative review. International journal of geriatric psychiatry. 2019;34(9):1316-25.
5. De la Rosa A, Olaso-Gonzalez G, Arc-Chagnaud C, Millan F, Salvador-Pascual A, García-Lucerga C, et al. Physical exercise in the prevention and treatment of Alzheimer's disease. Journal of sport and health science. 2020;9(5):394-404.
6. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. British journal of sports medicine. 2020;54(24):1451-62.
7. Erickson KI, Hillman C, Stillman CM, Ballard RM, Bloodgood B, Conroy DE, et al. Physical activity, cognition, and brain outcomes: a review of the 2018 physical activity guidelines. Medicine and science in sports and exercise. 2019;51(6):1242.
8. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. Neurobiology of aging. 2014;35:S20-S8.
9. Erickson KI, Weinstein AM, Lopez OL. Physical activity, brain plasticity, and Alzheimer's disease. Archives of medical research. 2012;43(8):615-21.
10. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. British journal of sports medicine. 2018;52(3):154-60.
11. Association As. 2019 Alzheimer's disease facts and figures. Alzheimer's & dementia. 2019;15(3):321-87.
12. Organization WH. WHO guidelines on physical activity and sedentary behavior: at a glance Geneva: World Health Organization, 2020; 24 p. URL: https://www who int/pub lications/i/item/9789240014886 (15 May 2022).
13. Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. World Alzheimer Report 2016. Improving healthcare for people living with dementia: Coverage, Quality and costs now and in the future: Alzheimer's Disease International; 2016.
14. Prevalentie. Expertisecentrum Dementie Vlaanderen. 2024.
15. Chen C, Nakagawa S. Physical activity for cognitive health promotion: an overview of the underlying neurobiological mechanisms. Ageing Research Reviews. 2023:101868.
16. Beckett MW, Ardern CI, Rotondi MA. A meta-analysis of prospective studies on the role of physical activity and the prevention of Alzheimer's disease in older adults. BMC geriatrics. 2015;15(1):1-7.
17. Du Z, Li Y, Li J, Zhou C, Li F, Yang X. Physical activity can improve cognition in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Clinical interventions in aging. 2018:1593-603.
18. López-Ortiz S, Lista S, Valenzuela PL, Pinto-Fraga J, Carmona R, Caraci F, et al. Effects of physical activity and exercise interventions on Alzheimer's disease: An umbrella review of existing meta-analyses. Journal of neurology. 2023;270(2):711-25.

19. Müller S, Preische O, Sohrabi HR, Gräber S, Jucker M, Ringman JM, et al. Relationship between physical activity, cognition, and Alzheimer pathology in autosomal dominant Alzheimer's disease. Alzheimer's & Dementia. 2018;14(11):1427-37.
20. Panza GA, Taylor BA, MacDonald HV, Johnson BT, Zaleski AL, Livingston J, et al. Can exercise improve cognitive symptoms of Alzheimer's disease? Journal of the American Geriatrics Society. 2018;66(3):487-95.
21. Phillips C, Akif Baktir M, Das D, Lin B, Salehi A. The link between physical activity and cognitive dysfunction in Alzheimer disease. Physical Therapy. 2015;95(7):1046-60.
22. Stephen R, Hongisto K, Solomon A, Lönnroos E. Physical activity and Alzheimer's disease: a systematic review. The Journals of Gerontology: Series A. 2017;72(6):733-9.
23. Herold F, Müller P, Gronwald T, Müller NG. Dose–response matters!–a perspective on the exercise prescription in exercise–cognition research. Frontiers in psychology. 2019;10:2338.
24. Feldman H, Woodward M. The staging and assessment of moderate to severe Alzheimer disease. Neurology. 2005;65(6_suppl_3):S10-S7.
25. It K, KNOW W. What is Alzheimer's disease. N Engl] Med. 1986;314:964-73.
26. Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? European archives of psychiatry and clinical neuroscience. 1999;249:S14-S22.
27. Pisani S, Mueller C, Huntley J, Aarsland D, Kempton MJ. A meta-analysis of randomised controlled trials of physical activity in people with Alzheimer's disease and mild cognitive impairment with a comparison to donepezil. International Journal of Geriatric Psychiatry. 2021;36(10):1471-87.
28. Epperly T, Dunay MA, Boice JL. Alzheimer disease: pharmacologic and nonpharmacologic therapies for cognitive and functional symptoms. American family physician. 2017;95(12):771-8.
29. Domingos C, Pêgo J, Santos N. Effects of physical activity on brain function and structure in older adults: a systematic review. Behavioural Brain Research. 2021;402:113061.
30. Duchesne C, Gheysen F, Boré A, Albouy G, Nadeau A, Robillard M, et al. Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals. NeuroImage: Clinical. 2016;12:559-69.
31. Netz Y. Is there a preferred mode of exercise for cognition enhancement in older age?—a narrative review. Frontiers in medicine. 2019;6:57.
32. Pontifex MB, McGowan AL, Chandler MC, Gwizdala KL, Parks AC, Fenn K, Kamijo K. A primer on investigating the after effects of acute bouts of physical activity on cognition. Psychology of Sport and Exercise. 2019;40:1-22.
33. Jia R-x, Liang J-h, Xu Y, Wang Y-q. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. BMC geriatrics. 2019;19:1-14.
34. Ludyga S, Gerber M, Pühse U, Looser VN, Kamijo K. Systematic review and meta-analysis investigating moderators of long-term effects of exercise on cognition in healthy individuals. Nature human behaviour. 2020;4(6):603-12.
35. Van Den Noortgate N, Petrovic M, Bulterijs S, Rietzschel E, Cardon G, Stegen S. Gezond Verouderen: Waar kunnen we.
36. Flöel A, Ruscheweyh R, Krüger K, Willemer C, Winter B, Völker K, et al. Physical activity and memory functions: are neurotrophins and cerebral gray matter volume the missing link? Neuroimage. 2010;49(3):2756-63.
37. Rovio S, Spulber G, Nieminen LJ, Niskanen E, Winblad B, Tuomilehto J, et al. The effect of midlife physical activity on structural brain changes in the elderly. Neurobiology of aging. 2010;31(11):1927-36.
38. Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman A, et al. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. Neurology. 2010;75(16):1415-22.

39. Rosano C, Venkatraman VK, Guralnik J, Newman AB, Glynn NW, Launer L, et al. Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2010;65(6):639-47.
40. Ruscheweyh R, Willemer C, Krüger K, Duning T, Warnecke T, Sommer J, et al. Physical activity and memory functions: an interventional study. Neurobiology of aging. 2011;32(7):1304-19.
41. Smith JC, Nielson KA, Woodard JL, Seidenberg M, Durgerian S, Antuono P, et al. Interactive effects of physical activity and APOE-ε4 on BOLD semantic memory activation in healthy elders. Neuroimage. 2011;54(1):635-44.
42. Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, et al. The effects of physical activity, education, and body mass index on the aging brain. Human brain mapping. 2011;32(9):1371-82.
43. Gow AJ, Bastin ME, Muñoz Maniega S, Valdés Hernández MC, Morris Z, Murray C, et al. Neuroprotective lifestyles and the aging brain: activity, atrophy, and white matter integrity. Neurology. 2012;79(17):1802-8.
44. Smith JC, Nielson KA, Woodard JL, Seidenberg M, Durgerian S, Hazlett KE, et al. Physical activity reduces hippocampal atrophy in elders at genetic risk for Alzheimer's disease. Frontiers in aging neuroscience. 2014;6:61.
45. Kemoun G, Thibaud M, Roumagne N, Carette P, Albinet C, Toussaint L, et al. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dementia and geriatric cognitive disorders. 2010;29(2):109-14.
46. Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. American Journal of Alzheimer's Disease & Other Dementias®. 2011;26(5):381-8.
47. Vreugdenhil A, Cannell J, Davies A, Razay G. A community-based exercise programme to improve functional ability in people with Alzheimer's disease: A randomized controlled trial. Scandinavian journal of caring sciences. 2012;26(1):12-9.
48. Arcoverde C, Deslandes A, Moraes H, Almeida C, Araujo NBd, Vasques PE, et al. Treadmill training as an augmentation treatment for Alzheimer's disease: a pilot randomized controlled study. Arquivos de neuro-psiquiatria. 2014;72:190-6.
49. Holthoff VA, Marschner K, Scharf M, Steding J, Meyer S, Koch R, Donix M. Effects of physical activity training in patients with Alzheimer's dementia: results of a pilot RCT study. PloS one. 2015;10(4):e0121478.
50. Hoffmann K, Sobol NA, Frederiksen KS, Beyer N, Vogel A, Vestergaard K, et al. Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: a randomized controlled trial. Journal of Alzheimer's Disease. 2016;50(2):443-53.
51. Kim M-J, Han C-W, Min K-Y, Cho C-Y, Lee C-W, Ogawa Y, et al. Physical exercise with multicomponent cognitive intervention for older adults with Alzheimer's disease: a 6-month randomized controlled trial. Dementia and geriatric cognitive disorders extra. 2016;6(2):222-32.
52. Wallace JD, Cuneo RC, Baxter R, Ørskov H, Keay N, Pentecost C, et al. Responses of the growth hormone (GH) and insulin-like growth factor axis to exercise, GH administration, and GH withdrawal in trained adult males: a potential test for GH abuse in sport. The Journal of Clinical Endocrinology & Metabolism. 1999;84(10):3591-601.
53. Edwards DG, Schofield RS, Lennon SL, Pierce GL, Nichols WW, Braith RW. Effect of exercise training on endothelial function in men with coronary artery disease. The American journal of cardiology. 2004;93(5):617-20.
54. Linke A, Adams V, Schulze PC, Erbs S, Gielen S, Fiehn E, et al. Antioxidative effects of exercise training in patients with chronic heart failure: increase in radical scavenger enzyme activity in skeletal muscle. Circulation. 2005;111(14):1763-70.
55. Gordon LA, Morrison EY, McGrowder DA, Young R, Fraser YTP, Zamora EM, et al. Effect of exercise therapy on lipid profile and oxidative stress indicators in patients with type 2 diabetes. BMC complementary and alternative medicine. 2008;8:1-10.

56. Gomes VA, Casella-Filho A, Chagas AC, Tanus-Santos JE. Enhanced concentrations of relevant markers of nitric oxide formation after exercise training in patients with metabolic syndrome. Nitric Oxide. 2008;19(4):345-50.
57. Griffin ÉW, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly ÁM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. Physiology & behavior. 2011;104(5):934-41.
58. Tartibian B, Hajizadeh Maleki B, Kanaley J, Sadeghi K. Long-term aerobic exercise and omega-3 supplementation modulate osteoporosis through inflammatory mechanisms in post-menopausal women: a randomized, repeated measures study. Nutrition & metabolism. 2011;8:1-13.
59. Scott J, Sale C, Greeves JP, Casey A, Dutton J, Fraser WD. Effect of exercise intensity on the cytokine response to an acute bout of running. Medicine and science in sports and exercise. 2011;43(12):2297-306.
60. Luk T-H, Dai Y-L, Siu C-W, Yiu K-H, Chan H-T, Lee SW, et al. Effect of exercise training on vascular endothelial function in patients with stable coronary artery disease: a randomized controlled trial. European journal of preventive cardiology. 2012;19(4):830-9.
61. Arikawa AY, Thomas W, Gross M, Smith A, Phipps WR, Kurzer MS, Schmitz KH. Aerobic training reduces systemic oxidative stress in young women with elevated levels of F2-isoprostanes. Contemporary clinical trials. 2013;34(2):212-7.
62. Wanderley FA, Moreira A, Sokhatska O, Palmares C, Moreira P, Sandercock G, et al. Differential responses of adiposity, inflammation and autonomic function to aerobic versus resistance training in older adults. Experimental gerontology. 2013;48(3):326-33.
63. Wahl P, Jansen F, Achtzehn S, Schmitz T, Bloch W, Mester J, Werner N. Effects of high intensity training and high volume training on endothelial microparticles and angiogenic growth factors. PloS one. 2014;9(4):e96024.
64. Wadley AJ, van Zanten JJV, Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Kitas GD, Aldred S. Three months of moderate-intensity exercise reduced plasma 3-nitrotyrosine in rheumatoid arthritis patients. European journal of applied physiology. 2014;114:1483-92.
65. Mitranun W, Deerochanawong C, Tanaka H, Suksom D. Continuous vs interval training on glycemic control and macro-and microvascular reactivity in type 2 diabetic patients. Scandinavian journal of medicine & science in sports. 2014;24(2):e69-e76.
66. Nikseresht M, Agha-Alinejad H, Azarbayjani MA, Ebrahim K. Effects of nonlinear resistance and aerobic interval training on cytokines and insulin resistance in sedentary men who are obese. The Journal of Strength & Conditioning Research. 2014;28(9):2560-8.
67. Jeon YK, Ha CH. The effect of exercise intensity on brain derived neurotrophic factor and memory in adolescents. Environmental health and preventive medicine. 2017;22:1-6.
68. Eizadi M, Laleh B, Khorshidi D. The effect of aerobic training with difference durations on serum il-10 in middle-aged obese females. Acta Endocrinologica (Bucharest). 2018;14(4):563.
69. Paolucci EM, Loukov D, Bowdish DM, Heisz JJ. Exercise reduces depression and inflammation but intensity matters. Biological psychology. 2018;133:79-84.
70. Hashimoto T, Tsukamoto H, Takenaka S, Olesen ND, Petersen LG, Sørensen H, et al. Maintained exercise-enhanced brain executive function related to cerebral lactate metabolism in men. The FASEB Journal. 2018;32(3):1417-27.
71. Tsai C-L, Ukropec J, Ukropcová B, Pai M-C. An acute bout of aerobic or strength exercise specifically modifies circulating exerkine levels and neurocognitive functions in elderly individuals with mild cognitive impairment. NeuroImage: Clinical. 2018;17:272-84.
72. Park S-A, Lee A-Y, Park H-G, Lee W-L. Benefits of gardening activities for cognitive function according to measurement of brain nerve growth factor levels. International journal of environmental research and public health. 2019;16(5):760.
73. Kujach S, Olek RA, Byun K, Suwabe K, Sitek EJ, Ziemann E, et al. Acute sprint interval exercise increases both cognitive functions and peripheral neurotrophic factors in humans: the possible involvement of lactate. Frontiers in neuroscience. 2020;13:490460.

74. Behrendt T, Kirschnick F, Kröger L, Beileke P, Rezepin M, Brigadski T, et al. Comparison of the effects of open vs. closed skill exercise on the acute and chronic BDNF, IGF-1 and IL-6 response in older healthy adults. BMC neuroscience. 2021;22:1-19.
75. Weaver SR, Skinner BD, Furlong R, Lucas RA, Rendeiro C, McGettrick HM, Lucas SJ. Cerebral hemodynamic and neurotrophic factor responses are dependent on the type of exercise. Frontiers in physiology. 2021;11:609935.
76. Yamamoto T, Tanoue Y, Uehara Y, Higaki Y, Tanaka H, Narazaki K. Intermittent Exercise at Lactate Threshold Induces Lower Acute Stress than Its Continuous Counterpart in Middle-to-Older Aged Men. International Journal of Environmental Research and Public Health. 2022;19(12):7503.
77. Eken Ö, Kafkas ME. Effects of low and high intensity interval training exercises on VO2max and components of neuromuscular and vascular system in male volunteers. Journal of Musculoskeletal & Neuronal Interactions. 2022;22(3):352.
78. Ando S, Komiyama T, Tanoue Y, Sudo M, Costello JT, Uehara Y, Higaki Y. Cognitive improvement after aerobic and resistance exercise is not associated with peripheral biomarkers. Frontiers in Behavioral Neuroscience. 2022;16:853150.
79. Vincent KR, Vincent HK, Braith RW, Lennon SL, Lowenthal DT. Resistance exercise training attenuates exercise-induced lipid peroxidation in the elderly. European journal of applied physiology. 2002;87:416-23.
80. Lagally KM, Robertson RJ, Gallagher KI, Goss FL, Jakicic JM, Lephart SM, et al. Perceived exertion, electromyography, and blood lactate during acute bouts of resistance exercise. Medicine & Science in Sports & Exercise. 2002;34(3):552-9.
81. Benson C, Docherty D, Brandenburg J. Acute neuromuscular responses to resistance training performed at different loads. Journal of Science and Medicine in Sport. 2006;9(1-2):135-42.
82. Cassilhas RC, Viana VA, Grassmann V, Santos RT, Santos RF, Tufik S, Mello MT. The impact of resistance exercise on the cognitive function of the elderly. Medicine & Science in Sports & Exercise. 2007;39(8):1401-7.
83. de Souza Vale RG, de Oliveira RD, Pernambuco CS, da Silva Novaes J, de Andrade AdFD. Effects of muscle strength and aerobic training on basal serum levels of IGF-1 and cortisol in elderly women. Archives of gerontology and geriatrics. 2009;49(3):343-7.
84. Yarrow JF, White LJ, McCoy SC, Borst SE. Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). Neuroscience letters. 2010;479(2):161-5.
85. Phillips MD, Flynn MG, McFarlin BK, Stewart LK, Timmerman KL. Resistance training at eight-repetition maximum reduces the inflammatory milieu in elderly women. Medicine and science in sports and exercise. 2010;42(2):314-25.
86. Bobeuf F, Labonte M, Dionne I, Khalil A. Combined effect of antioxidant supplementation and resistance training on oxidative stress markers, muscle and body composition in an elderly population. The journal of nutrition, health & aging. 2011;15:883-9.
87. Phillips MD, Patrizi RM, Cheek DJ, Wooten JS, Barbee JJ, Mitchell JB. Resistance training reduces subclinical inflammation in obese, postmenopausal women. Medicine & Science in Sports & Exercise. 2012;44(11):2099-110.
88. Coelho F, Pereira D, Lustosa L, Silva J, Dias J, Dias R, et al. Physical therapy intervention (PTI) increases plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly women. Archives of gerontology and geriatrics. 2012;54(3):415-20.
89. Hasani-Ranjbar S, Soleymani Far E, Heshmat R, Rajabi H, Kosari H. Time course responses of serum GH, insulin, IGF-1, IGFBP1, and IGFBP3 concentrations after heavy resistance exercise in trained and untrained men. Endocrine. 2012;41:144-51.
90. Karabulut M, Sherk VD, Bemben DA, Bemben MG. Inflammation marker, damage marker and anabolic hormone responses to resistance training with vascular restriction in older males. Clinical physiology and functional imaging. 2013;33(5):393-9.

91. Azizbeigi K, Azarbayjani MA, Peeri M, Agha-Alinejad H, Stannard S. The effect of progressive resistance training on oxidative stress and antioxidant enzyme activity in erythrocytes in untrained men. International journal of sport nutrition and exercise metabolism. 2013;23(3):230-8.
92. Watanabe Y, Madarame H, Ogasawara R, Nakazato K, Ishii N. Effect of very low-intensity resistance training with slow movement on muscle size and strength in healthy older adults. Clinical physiology and functional imaging. 2014;34(6):463-70.
93. Tsai C-L, Wang C-H, Pan C-Y, Chen F-C, Huang T-H, Chou F-Y. Executive function and endocrinological responses to acute resistance exercise. Frontiers in behavioral neuroscience. 2014;8:262.
94. Beck DT, Martin JS, Casey DP, Braith RW. Exercise training improves endothelial function in resistance arteries of young prehypertensives. Journal of human hypertension. 2014;28(5):303-9.
95. Forti LN, Njemini R, Beyer I, Eelbode E, Meeusen R, Mets T, Bautmans I. Strength training reduces circulating interleukin-6 but not brain-derived neurotrophic factor in community-dwelling elderly individuals. Age. 2014;36:1-11.
96. Strandberg E, Edholm P, Ponsot E, Wåhlin-Larsson B, Hellmén E, Nilsson A, et al. Influence of combined resistance training and healthy diet on muscle mass in healthy elderly women: a randomized controlled trial. Journal of applied physiology. 2015;119(8):918-25.
97. Kjølhede T, Dalgas U, Gade AB, Bjerre M, Stenager E, Petersen T, Vissing K. Acute and chronic cytokine responses to resistance exercise and training in people with multiple sclerosis. Scandinavian journal of medicine & science in sports. 2016;26(7):824-34.
98. Ribeiro F, Ribeiro IP, Gonçalves AC, Alves AJ, Melo E, Fernandes R, et al. Effects of resistance exercise on endothelial progenitor cell mobilization in women. Scientific Reports. 2017;7(1):17880.
99. Alikhani S, Sheikholeslami-Vatani D. Oxidative stress and anti-oxidant responses to regular resistance training in young and older adult women. Geriatrics & Gerontology International. 2019;19(5):419-22.
100. Dora K, Suga T, Tomoo K, Sugimoto T, Mok E, Tsukamoto H, et al. Effect of very low-intensity resistance exercise with slow movement and tonic force generation on post-exercise inhibitory control. Heliyon. 2021;7(2).
101. Arazi H, Babaei P, Moghimi M, Asadi A. Acute effects of strength and endurance exercise on serum BDNF and IGF-1 levels in older men. BMC geriatrics. 2021;21:1-8.
102. Anderson-Hanley C, Arciero PJ, Brickman AM, Nimon JP, Okuma N, Westen SC, et al. Exergaming and older adult cognition: a cluster randomized clinical trial. American journal of preventive medicine. 2012;42(2):109-19.
103. Silvi F, Andriana RAM, Wardhani IL, Prawitri YD, Narasinta I, Melaniani S. The effect of boxing exergame on blood lactate and VO2max in non-athlete healthy young men. Bali Medical Journal. 2022;11(2):827-31.
104. Henrique PPB, Perez FMP, Dorneles G, Peres A, Korb A, Elsner V, De Marchi ACB. Exergame and/or conventional training-induced neuroplasticity and cognitive improvement by engaging epigenetic and inflammatory modulation in elderly women: A randomized clinical trial. Physiology & Behavior. 2023;258:113996.
105. De Angelis M, Vinciguerra G, Gasbarri A, Pacitti C. Oxygen uptake, heart rate and blood lactate concentration during a normal training session of an aerobic dance class. European journal of applied physiology and occupational physiology. 1998;78:121-7.
106. Müller P, Rehfeld K, Schmicker M, Hökelmann A, Dordevic M, Lessmann V, et al. Evolution of neuroplasticity in response to physical activity in old age: the case for dancing. Frontiers in aging neuroscience. 2017;9:56.
107. Rehfeld K, Lüders A, Hökelmann A, Lessmann V, Kaufmann J, Brigadski T, et al. Dance training is superior to repetitive physical exercise in inducing brain plasticity in the elderly. PloS one. 2018;13(7):e0196636.
108. Wharton W, Jeong L, Ni L, Bay AA, Shin RJ, McCullough LE, et al. A Pilot randomized clinical trial of adapted tango to improve cognition and psychosocial function in African American women

with family history of Alzheimer's disease (ACT trial). Cerebral Circulation-Cognition and Behavior. 2021;2:100018.
109. Irwin MR, Olmstead R. Mitigating cellular inflammation in older adults: a randomized controlled trial of Tai Chi Chih. The American Journal of Geriatric Psychiatry. 2012;20(9):764-72.
110. Mendoza-Núñez VM, Hernández-Monjaraz B, Santiago-Osorio E, Betancourt-Rule JM, Ruiz-Ramos M. Tai Chi exercise increases SOD activity and total antioxidant status in saliva and is linked to an improvement of periodontal disease in the elderly. Oxidative medicine and cellular longevity. 2014;2014.
111. Campo RA, Light KC, O'Connor K, Nakamura Y, Lipschitz D, LaStayo PC, et al. Blood pressure, salivary cortisol, and inflammatory cytokine outcomes in senior female cancer survivors enrolled in a tai chi chih randomized controlled trial. Journal of Cancer Survivorship. 2015;9:115-25.
112. Sungkarat S, Boripuntakul S, Kumfu S, Lord SR, Chattipakorn N. Tai Chi improves cognition and plasma BDNF in older adults with mild cognitive impairment: a randomized controlled trial. Neurorehabilitation and neural repair. 2018;32(2):142-9.
113. Mendoza-Núñez VM, Arista-Ugalde TL, Rosado-Pérez J, Ruiz-Ramos M, Santiago-Osorio E. Hypoglycemic and antioxidant effect of Tai chi exercise training in older adults with metabolic syndrome. Clinical Interventions in Aging. 2018:523-31.
114. Solianik R, Mickevičienė D, Žlibinaitė L, Čekanauskaitė A. Tai chi improves psychoemotional state, cognition, and motor learning in older adults during the COVID-19 pandemic. Experimental Gerontology. 2021;150:111363.
115. Lee M, Moon W, Kim J. Effect of yoga on pain, brain-derived neurotrophic factor, and serotonin in premenopausal women with chronic low back pain. Evidence-Based Complementary and Alternative Medicine. 2014;2014.
116. Kiecolt-Glaser JK, Bennett JM, Andridge R, Peng J, Shapiro CL, Malarkey WB, et al. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. Journal of Clinical oncology. 2014;32(10):1040.
117. Harkess K, Ryan J, Delfabbro PH, Cohen-Woods S. Preliminary indications of the effect of a brief yoga intervention on markers of inflammation and DNA methylation in chronically stressed women. Translational psychiatry. 2016;6(11):e965-e.
118. Shete SU, Verma A, Kulkarni DD, Bhogal RS. Effect of yoga training on inflammatory cytokines and C-reactive protein in employees of small-scale industries. Journal of education and health promotion. 2017;6(1):76.
119. Li X, Xu W, Zhang L, Zu Y, Li Y, Yang Y, et al. Effects of yoga on exercise capacity in patients with lymphangioleiomyomatosis: a nonrandomized controlled study. Orphanet Journal of Rare Diseases. 2020;15:1-8.
120. Nugent NR, Brick L, Armey MF, Tyrka AR, Ridout KK, Uebelacker LA. Benefits of yoga on il-6: Findings from a randomized controlled trial of yoga for depression. Behavioral Medicine. 2021;47(1):21-30.
121. Viswanathan V, Sivakumar S, Prathiba AS, Devarajan A, George L, Kumpatla S. Effect of yoga intervention on biochemical, oxidative stress markers, inflammatory markers and sleep quality among subjects with type 2 diabetes in South India: Results from the SATYAM project. diabetes research and clinical practice. 2021;172:108644.
122. Arcoverde C, Deslandes A, Rangel A, Rangel A, Pavão R, Nigri F, et al. Role of physical activity on the maintenance of cognition and activities of daily living in elderly with Alzheimer's disease. Arquivos de neuro-psiquiatria. 2008;66:323-7.
123. Paillard T, Rolland Y, de Souto Barreto P. Protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: a narrative review. Journal of clinical neurology. 2015;11(3):212-9.
124. Karssemeijer EE, Aaronson JJ, Bossers WW, Smits TT, Kessels RR. Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: A meta-analysis. Ageing research reviews. 2017;40:75-83.

125. Rolland Y, van Kan GA, Vellas B. Physical activity and Alzheimer's disease: from prevention to therapeutic perspectives. Journal of the American Medical Directors Association. 2008;9(6):390-405.
126. Varma VR, Watts A. Daily physical activity patterns during the early stage of Alzheimer's disease. Journal of Alzheimer's Disease. 2017;55(2):659-67.

11. Addendum

Table 2: Summary of studies reporting the effects of PA on brain structure in older adults (healthy cognition, MCI and AD), analysis by MRI.

First Author	Year	Design	Variable of Interest	N	Mean age (SD) in years unless otherwise noted	Cognitive Screening	PA Assessment	Findings
Floel et al. (36)	2010	Cross-Sectional	PA, brain volume, and cognition	75	60.5 (6.9)	MMSE AVLT	Freiburg Questionnaire of physical activity	PA is associated with increased gray matter volume in frontal cortext and better memory encoding
Rovio et al. (37)	2010	Prospective	PA and brain volume	75	Active: 73 (3.5) & Sedentary: 72.1 (4.4)	NS	NS	Increased PA in mid-life is associated with increased gray matter volume in late-life
Erickson et al. (38)	2010	Prospective	PA and brain volume	299	78 (3.65)	3MSE TICS DSST IQCODE CES-D 10-item DQ	GM Volume	Greater walking distances were associated with greater GM in the frontal, occipital and temporal regions including the entorhinal cortex and hippocampus 9 years later. Walking relatively long distances (72 blocks) was necessary to detect differences in GM 9 years later.
Rosano et al. (39)	2010	RCT	PA and brain function	27	Successful ageing group: 81.45 (2.77) & PA group: 80.8 (3.95)	NS	NS	PA was not associated with total brain volume or atrophy. Increased PA is associated with increased cognitive performance and related brain function as measured by fMRI.
Ruschweyh et al. (40)	2011	RCT	PA, brain volume, and cognition	62	60.2 (6.6)	NS	NS	Increased PA is associated with increased memory performance, gray matter volume, and BDNF levels, regardless of intensity manipulation.
Smith et al. (41)	2011	Cross-sectional	PA and cognition	68	Age range: 65 – 85	MMSE DRS-2 RAVLT GDS	SBAS	PA was not associated with gray matter volume. Increased PA is associated with increased semantic memory performance and brain function in those at risk for AD (apoE-4 carriers), as measured by fMRI.
Ho et al. (42)	2011	Cross-sectional	PA and brain volume	226	77.9 (3.6)	3MSE	MLTPAQ	Increased PA is associated with increased brain volume, controlling for education and age. Effect was eliminated when including Body Mass Index in the model.
Gow et al. (43)	2012	Prospective	PA and brain volume	691	72.7 (0.7)	NS	NS	Increased PA is associated with increased grey and white matter, as well as decreased atrophy and white matter issues
Smith et al. (44)	2014	Prospective	GM and WM Volume	97	74.4 (5.2)	MMSE DRS-2 GDS	SBAS	Hippocampal volume decreased by 3% in the High Risk/Low PA group. Similar PA effects were not observed in the thalamus, caudate, amygdala, caudal middle frontal gyrus, pre-central gyrus, total GM, or cortical WM volumes.

MMSE: Mini-Mental State Examination; AVLT: Auditory Verbal Learning Test; 3MSE: Modified Mini-Mental State Examination; TICS: Telephone Interview for Cognitive Status; DSST: Digit Symbol Substitution Test; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; CES-D 10-item: Centre for Epidemiologic Studies Depression Scale (10-item version); DQ: Dementia Questionnaire; DRS-2: Dementia Rating Scale, 2nd Edition; GDS: Geriatric Depression Scale; NS: Not Specified.

Table 3: Summary of RCT's reporting the effects of aerobic PA on older adults with Alzheimer's Disease.

First Author	Year	Variable	Intensity	Frequency	Duration	Results	Significance (P-value)
Kemoun et al. (45)	2010	Cognitive Function	Moderate	3 sessions per week	1-hour session over 15 weeks	Control group (Pre): 28.34 ± 7.11 Control group (Post): 23.23 ± 8.37 Intervention group (Pre): 26.81 ± 6.42 Intervention group (Post): 30.38 ± 7.66	P < 0.01
Venturelli et al. (46)	2011	MMSE	Moderate	4 times a week	30 minutes each session	Walking: significant improvement in 6MWT (20%) and ADLs (23%) Control group: significant decline in MMSE (47%) compared to slower decline in WG (13%)	P < 0.001
Vreughdenhil et al. (47)	2012	MMSE, Timed Up and Go, Sit-to-Stand	Low	Daily	30 mins	Significant improvements	MMSE: p = 0.001 Timed Up and Go: p = 0.004 Sit-to-Stand: p < 0.001
Arcoverde et al. (48)	2014	MMSE, CAMCOG, BERG, FR, TUGT	Moderate (60% VO2max)	2 times a week	30 mins/session	Improvement in cognition (MMSE, CAMCOG) and functional capacity (BERG, FR, TUGT)	P < 0.05
Holthoff et al. (49)	2015	Cognitive Function	Moderate	3 times a week	30 mins/session for 12 weeks	Improvement in ADL, cognitive function (MMSE, semantic word fluency), reaction time, hand-eye quickness and attention, neuropsychiatric symptoms, and caregiver burden.	P < 0.05
Hoffmann et al. (50)	2016	Cognitive Performance	Moderate to High	3 times a week	60 minutes per session	Moderate: no significant improvement in cognitive function High: significant improvement	Moderate: P > 0.05 High: P = 0.028
Kim et al. (51)	2016	MMSE, ADAS-Cog, CDT	NS	5 times a week	60 mins per session for 6 months	ADAS-Cog: significant improvement in cognitive function MMSE and CDT: no significant changes	ADAS-Cog: P = 0.03 MMSE and CDT: P = 0.98 and P = 0.17

MMSE: Mini-Mental State Examination; CAMCOG: Cambridge Cognitive Examination; BERG: Berg Balance Scale; FR: Functional Reach Test; TUGT: Timed Up and Go Test; ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale; CDT: Clock Drawing Test; VO2max: Maximal Oxygen Consumption; NS: Not Specified.

Table 4: Summary of studies reporting the effects of PA (Aerobic) on neurobiological mechanisms.

First Author	Year	Variable	Intensity	Frequency	Duration	Results	Significance (P-value)
Wallace et al. (52)	1999	IGF-1	Submaximal (65% of VO2max workload)	NS	30 mins of cycling	Increased transiently	P = 0.001
Edwards et al. (53)	2004	Oxidative stress	Moderate	3 times per week	12 months	Decreased oxidative stress indicated by lower levels of plasma 8-isoprostane-F2	P < 0.05
		Antioxidant defenses				Increased plasma superoxide dismutase (SOD) activity, no change in plasma glutathione peroxidase activity	P < 0.05
Linke et al. (54)	2005	TNF-alpha	Aerobic exercise; 70% of peak VO2	Daily 20 mins	6 months	Baseline (control group): 1.86 ± 0.38 After 6 months (control group) : 2.29 ± 0.60 Baseline (training group): 1.71 ± 0.39 After 6 months (training group) : 0.92 ± 0.19	P < 0.05 vs baseline and control group
		Gluthatione Peroxidase				Baseline (control group): 35.5 ± 3.3 Baseline (training group): 35.3 ± 4.3 After 6 months (training group) : 49.9 ± 3.5	P < 0.05 vs baseline and control group
Gordon et al. (55)	2008	Malondialdehyde	Aerobic exercise	Daily	24 weeks	Decreased by 18.1%	P < 0.0001
Gomes et al. (56)	2008	TBA-RS	Aerobic individualised training program	NS	NS	Control group: lower compared to Metabolic Syndrome group Pre-exercise Metabolic Syndrome group: higher Post-exercise Metabolic Syndrome group: significantly reduced	P < 0.05 for Metabolic Syndrome group post-exercise vs pre-exercise
Griffin et al. (57)	2011	BDNF	High			Increased BDNF concentration post-exercise	P = 0.0126
		IGF-1				No change	/
Tartibian et al. (58)	2011	TNF-alpha and IL-6	65% HRmax	3 times a week	24 weeks	Decrease in inflammatory markers	P < 0.05
Scott et al. (59)	2011	IL-6	Low (55% VO2max), Moderate (65% VO2max) and High (75% VO2max)	Single session	60 mins	High > Moderate > Low	High vs Low/Moderate: p < 0.001 (at end exercise and 30mins after exercise)
		TNF-alpha				No significant effect of exercise intensity	
		Lactate				Low: increased Moderate: increased High: significantly increased	High > Moderate > Low (significantly increased across intensities)
Luk et al. (60)	2012	SOD, 8-isoprostane	Moderate	3 times per week	8 weeks	No significant changes	Not significant
Arikawa et al. (61)	2013	Plasma free F2-isoprostanes	HRmax increasing every 4 weeks to reach 80-85% of HRmax	30 minutes, 5 times per week	4 months	Significant reduction in highest quartile of baseline plasma F2-isoprostanes within exercise group (-20.2 ± 2.5) vs control (-7.4 ± 2.5)	P < 0.001
Wanderley et al. (62)	2013	IL-6, TNF-alpha and IL-10	Aerobic training (70-80% HRR)	3 times per week	8 months	Decrease	P = 0.02
Wahl et al. (63)	2014	VEGF	HIT (high-intensity training): 90-95% PPO	1 session	3 mins active recovery and 4x30 secs all-out efforts with 7:30mins active recovery	Increased immediately post-exercise, returning to baseline after 30 mins	P < 0.01
Wadley et al. (64)	2014	Plasma 3-nitrotyrosine	70% VO2max	3 times per week for 30-40 mins	3 months	Decreased from 2.18 ± 1.78 to 1.10 ± 0.93	P = 0.027
Mitranun et al. (65)	2014	Malondialdehyde, Glutathione Peroxidase				No significant change	No significant change
Nikseresht et al. (66)	2014	IL-10	Aerobic interval training	NS	12 weeks	No significant change	NS
		TNF-alpha					
Jeon et al. (67)	2017	BDNF	Low/Moderate/High/None			Low: no significant change Moderate: significant increase High: significant increase None (stretching): no significant change	Moderate: p < 0.05 High: p < 0.01
		IGF-1				Low: no significant change Moderate: no significant increase High: significant increase None (stretching): significant change	High: p < 0.05 None: p < 0.05

Eizadi et al. (68)	2018	IL-10	60-75% of HRmax	3 times per week	12 weeks	Pre-training: 14.79 ± 3.04 Mid-training (6 weeks): 17.36 ± 2.72 Post-training (12 weeks): 17.79 ± 3	Mid vs Pre : p = 0.001 Post vs Pre : p = 0.002 Mid vs Post : p = 0.361
Paolucci et al. (69)	2018	TNF-alpha	HIT (high-intensity interval training) and MCT (moderate continuous training)	3 times per week	6 weeks	HIT: increased relative to MCT Decreased relative to CON	MCT vs CON: decrease TNF-alpha (p < 0.05)
		IL-6				HIT: increased relative to MCT and CON	P < 0.05
Hashimoto et al. (70)	2018	BDNF	High-intensity interval exercise (HIIE) (80-90% Wmax interspersed with 50-60% Wmax)	Two sessions	28 mins each	Increased after both HIIEs	No significant difference between first and second HIIE
		Lactate				Increased after first HIIE, attenuated increase after the second HIIE	P < 0.05 for increase after first HIIE
Tsai et al. (71)	2018	BDNF	Moderate (65-75% HRR)	Single session	30 mins	Significantly increased	P < 0.05
		IGF-1				Significantly increased	P < 0.05
		VEGF				Tended to increase	p-value approaches significance
Park et al. (72)	2019	BDNF	Low-to-Moderate	Single session	20 mins	Pre-intervention: 53.75 ± 21.49 Post-intervention : 58.26 ± 23.40	P = 0.038
		VEGF				Pre-intervention: 338.69 ± 171.64 Post-intervention : 325.83 ± 145.98	P = 0.126
Kujach et al. (73)	2020	BDNF	All-out cycling exercise (>100% VO2max)	Single session	5 mins warm-up + six 30s sprints with 4.5mins rest	Significant increase immediately post-exercise and at 1 hour post-exercise	P < 0.01 (immediately and at 1 hour post)
		IGF-1				Significant increase immediately post-exercise; returned to near baseline at 1-hour post-exercise	P < 0.01 (immediately post)
		VEGF				Significant increase immediately post-exercise and sustained at 1 hour post-exercise	P < 0.05 (immediately and at 1 hour post)
Behrendt et al. (74)	2021	BDNF	OSE (Badminton) CSE (bicycling)			Acute effect : increased Chronic effect : increased in OSE, unchanged in CSE	Significant for OSE (p < 0.05)
		IGF-1				Acute effect: increased Chronic effect: decreased	Acute effect: p < 0.05 Chronic effect: p < 0.05
Weaver et al. (75)	2021	BDNF	Supramaximal	Single session	SIT (4 intervals of 30 secs)	Significantly increased	P < 0.001
		IGF-1				Significant reduction post-exercise	P = 0.017
		VEGF				Significant elevation post-exercise	P < 0.001
		Lactate				>5-fold greater in SIT	P = 0.002
Yamamoto et al. (76)	2022	BDNF	Lactate threshold (Moderate)	NS	Continuous Exercise (CE): continuous 20-minutes bout of cycling	Increased at E50% and E100% vs CON	Significant interaction (p < 0.01); increase in CE at E50% and E100% (p < 0.05)
		IGF-1				Increased at E50% vs CON	Significant interaction (p < 0.05); increase in CE at E50% (p < 0.05)
Eken et al. (77)	2022	BDNF	LIIT (57-64% HRmax) and HIIT (85-90% HRmax)	2 times per week	4 weeks	LIIT: increased HIIT: significantly increased	P < 0.05
		VEGF				LIIT: increased HIIT: significantly increased	P < 0.05
Ando et al. (78)	2022	BDNF, IGF-1, Lactate	40% peak oxygen uptake (light)		30 mins	No significant association with changes in peripheral biomarkers (all p > 0.05)	/

TBA-RS: Thiobarbituric Acid Reactive Substances; BDNF: Brain-Derived Neurotrophic Factor; IGF-1: Insulin-like Growth Factor 1; TNF-alpha: Tumour Necrosis Factor Alpha; IL-6: Interleukin 6; SOD: Superoxide Dismutase; 8-isoprostane: 8-iso-Prostaglandin F2α; IL-10: Interleukin 10; VEGF: Vascular Endothelial Growth Factor; VO2max: Maximal Oxygen Consumption; HRmax: Maximum Heart Rate; HRR: Heart Rate Reserve; LIIT: Low-Intensity Interval Training; MIIT: Moderate-Intensity Interval Training; HIIT: High-Intensity Interval Training; OSE: Overground Self-paced Exercise; CSE: Cycle-based Self-paced Exercise; HIIE: High-Intensity Intermittent Exercise; CE: Continuous Exercise: E50%: Exercise at 50% Intensity; NS: Not Specified.

Table 5: Summary of studies reporting the effects of PA (Strength) on neurobiological mechanisms.

First Author	Year	Variable	Intensity	Frequency	Duration	Results	Significance (P-value)
Vincent et al. (79)	2002	Oxidative stress	Low (50% 1RM), High (80% 1RM)	3 times per week	6 months	Lower oxidative stress in Low (14%) and High (18%) exercise	P < 0.05
Lagally et al. (80)	2002	Lactate	30%, 60% and 90% 1RM	1 session	NS	30%: 1.01 to 2.53 60%: 1.12 to 2.96 90%: 1.07 to 3.70	P < 0.04
Benson et al. (81)	2006	Lactate	90-100% 10RM	NS	NS	1.34 vs 2.92 (100% 10RM) 1.74 vs 2.76 (90% 10RM)	P < 0.05 (both protocols)
Cassilhas et al. (82)	2007	IGF-1	50% of 1RM for moderate, 80% of 1RM for High	3 times per week	24 weeks	Increased IGF-1 levels for moderate and high intensity physical activity	P = 0.02 (Moderate vs control) P < 0.001 (High vs control)
de Souza Vale et al. (83)	2009	IGF-1	High (75-85% 1RM)	3 times per week (2 sets of 8-10 reps)	12 weeks	Pre: 116.35 ± 36.87 Post: NS	P < 0.05
Yarrow et al. (84)	2010	BDNF	2 protocols (52.5% to 75% 1RM; 40% to 120% 1RM)	3 times per week (min. 48 hours rest between sessions)[circa 60mins]	5 weeks	+98% greater change post-intervention compared to baseline	P < 0.05
Philips et al. (85)	2010	Inflammation markers (IL-6, IL-1A, TNF-alpha)	Moderate to High (8RM)	3 times per week	10 weeks	Decrease in TNF-alpha by 37% Stimulated production of IL-6 and IL-1A, and TNF-alpha reduced at all time points (pre-, post-, and 2 hours post-exercise)	NS
Bobeuf et al. (86)	2011	Malondialdehyde	Resistance training (various)	NS	NS	NS	NS
Philips et al. (87)	2012	Inflammation markers (CRP, Leptin and TNF-alpha)	Moderate to High (8RM)	3 times per week	12 weeks	CRP: decreased 33% Leptin: decreased 18% TNF-alpha: decreased 29%	Resistance training reduced circulating CRP, Leptin, and TNF-alpha
Coelho et al. (88)	2012	BDNF	Progressive, starting at 50% 1RM, increasing to 75% 1RM	3 times per week	60 minutes per session (10 weeks)	Increased BDNF levels after physical therapy intervention	P < 0.001
Hasani-Ranjbar et al. (89)	2012	IGF-1	70-80% 1RM	Single session	60 mins	Pre-exercise 306.80 ± 73.93 Post-exercise 331.10 ± 79.61 After 5 hours: 260.10 ± 80.73 After 8 hours: 224.50 ± 85.27	P < 0.05 at (5- and 8-hours after exercise)
Wanderley et al. (62)	2013	Inflammatory biomarkers	Resistance training	NS	NS	No significant change	No significant change
Karabulut et al. (90)	2013	IL-6	High (80% 1RM) and low (20% 1RM)	3 times per week	6 weeks	Pre: 7.0 ± 0.8 (High) Post: 7.9 ± 1.5 (High) Pre: 14.0 ± 4.8 (Low) Post: 13.5 ± 4.7 (Low)	No significant change
		IGF-1				Pre: 322.3 ± 20.2 (High) Post: 337.2 ± 21.4 (High) Pre: 381.4 ± 23.9 (Low) Post: 399.1 ± 15.2 (Low)	No significant change
Azizbeigi et al. (91)	2013	Superoxide Dismutase	50-80% E1RM	3 times per week	8 weeks	Pre: 1323 ± 212.52 Post: 1449.9 ± 173.8	P = 0.014 (significant increase in SOD activity, suggesting enhanced anti-oxidant defence)
		Malondialdehyde				Pre: 5.39 ± 1.7 Post: 3.67 ± 0.7	P = 0.03 (significant decrease in MDA levels, indicating reduced lipid peroxidation and oxidative stress)
Watanabe et al. (92)	2014	Lactate	30% 1RM (Low intensity)	2 times per week	12 weeks	Increased significantly after exercise; higher than CON	P < 0.05
Tsai et al. (93)	2014	IGF-1	Moderate and High	Single session	30 mins	Increased post-exercise, decreased 20 mins post-exercise	P < 0.001 (High vs control) P = 0.01 (Moderate vs control)

Beck et al. (94)	2014	Oxidative stress	Moderate	3 times per week	8 weeks	Post: reduced by 43%	P < 0.05
Forti et al. (95)	2014	BDNF	Progressive strength training	NS	12 weeks	Unchanged	No significant change
		IL-6				Decreased	P = 0.001 (significant reduction)
Strandberg et al. (96)	2015	IL-6	50-85% 1RM	2 times per week	24 weeks	No significant changes	No significant changes
Kjolhede et al. (97)	2016	Inflammation markers (IL-10, TNF-alpha)	NS, but progressive resistance training	2 times per week	24 weeks	No significant changes	No significant changes
Ribeiro et al. (98)	2017	VEGF	60%, 70% and 80% 1RM	Single session	Circa 30 mins	60%: 52.0 ± 6.5 to 61.2 ± 7.4 70%: Significant increase immediately, 6h and 24h post-exercise compared to baseline 80%: 52.4 ± 8.9 to significant increase, highest at 6h and 24h post-exercise	60%: p = 0.039 70%: p < 0.001 (compared to 60% at 6h post-exercise) 80%: p < 0.001
Tsai et al. (71)	2018	BDNF	75% 1RM	Single session	30 mins	Not significantly changed	No significant change
		IGF-1				Increased post-exercise; returned to baseline after cognitive task	P < 0.001
		VEGF				Not significantly changed	No significant change
Alikhani et al. (99)	2019	TNF-alpha	75% 1RM	3 times per week	12 weeks	Post: decrease (not significant)	P > 0.05
Dora et al. (100)	2021	Malondialdehyde	30% 1RM	2 times per week	12 mins	Significant decrease	P < 0.0001
Arazi et al. (101)	2021	BDNF	65-70% of 1RM			Pre-exercise: 3.58 ± 1.05 Post-exercise: 4.16 ± 1.82	P = 0.003
		IGF-1				Pre-exercise: 134.4 ± 21.6 Post-exercise: 139.5 ± 20	P = 0.03

IGF-1: Insulin-like Growth Factor 1; BDNF: Brain-Derived Neurotrophic Factor; IL-6: Interleukin 6; IL-1A: Interleukin 1A; TNF-alpha: Tumour Necrosis Factor Alpha; CRP: C-reactive protein; IL-10: Interleukin 10; VEGF: Vascular Endothelial Growth Factor; RM: Repetition Maximum; CON: Control condition/group; SOD: Superoxide Dismutase; NS: Not Specified.

Table 6: Summary of studies reporting the effects of PA (Neuromuscular) on neurobiological mechanisms.

Type	First Author	Year	Variable	Intensity	Frequency	Duration	Results	Significance (P-value)
Exergames	Anderson-Hanley et al. (102)	2012	BDNF	NS	NS	NS	Significant increase in BDNF levels	p = 0.05 (suggests enhanced neuroplasticity among cybercyclists)
			Executive function				Significant improvement in executive function	P = 0.002
	Silvi et al. (103)	2022	Lactate	High	3 times a week	38 minutes (incl. warm-up, core training, and cooling down) per session for one month	Pre: 2.03 Post: 3.0	P = 0.001
	Henrique et al. (104)	2023	BDNF	Exergames (NS)	2 times per week	6 weeks (12 sessions)	Increased after first session compared to baseline	P < 0.05
			IL-6, IL-10 and TNF-alpha				IL-6 : No significant change IL10 and TNF-alpha increased in Exergaming	IL-10: p = 0.002 TNF-alpha: p = 0.001
			Cognitive Performance (MoCA Score)				Significant improvement observed	P < 0.05
Dance	De Angelis et al. (105)	1998	Lactate	Low and High	3 times per week	55 mins per session	Increase in lactate concentration	P < 0.001
	Müller et al. (106)	2017	BDNF	NS	NS	NS	Increased after 6 months Returned to baseline after 18 months	NS
			Gray matter volume change				Increase in left precentral gyrus after 6 months Increase in right parahippocampal gyrus after 18 months	NS (increase in specific brain regions involved in motor control memory)
			Neuropsychological tests				Improved verbal memory after 18 months	NS (significant improvements in attention and verbal memory)
	Rehfeld et al. (107)	2018	BDNF	Dance training requiring constant learning of new choreographies	2 times per week	90 mins per session	Increase after training	P = 0.046
			Brain volume changes				Larger increases in cingulate cortex, insula, corpus callosum, sensorimotor cortex	NS (showed larger volume increases in more brain areas)
			Cognitive functions				Improvement in attention and spatial memory	NS
	Wharton et al. (108)	2021	TNF-alpha	Tango (dance type)	2 times per week	90 mins, 20 lessons, 12 weeks	Pre: 10.71 ± 4.67 Post: 10.51 ± 4.54	P = 0.011
			30s Chair Stand				Pre: 12.67 ± 4.59 Post: 12.75 ± 4.3	P = 0.018
			Fullerton Advanced Balance Scale				Pre: 32.83 ± 4.72 Post: 33.3 ± 6.06	P = 0.023
Tai Chi	Irwin et al. (109)	2012	IL-6	Moderate	3 times per week	16 weeks	Decrease in those with high baseline levels	P = 0.07 (trend)
			Psychological outcomes				Decreases correlated with IL-6 decrease	P < 0.05
	Mendoza-Nunez et al. (110)	2014	Total Antioxidant Status	Moderate	5 times per week	60 mins	Baseline: 0.53 ± 0.33 At 6 months: 0.70 ±0.35	P < 0.01
			Superoxide Dismutase				Baseline: 1.62 ± 0.83 At 6 months: 2.79 ± 1.6	P < 0.001
			IL-6				Baseline: 18.66 ± 7.25 At 6 months: 4.76 ± 1.93	P = 0.09
	Campo et al. (111)	2015	Inflammatory markers (IL-6, TNF-alpha, IL-10)	Moderate	3 times per week	12 weeks	No significant change	No significant change
	Sungkarat et al. (112)	2018	BDNF	Moderate	3 times per week	6 months	Increased from 162.3 to 314.4	P < 0.05
			TNF-alpha				No significant change	NS
			IL-10				No significant change	NS
			Logical Memory Delayed Recall				Improved	P < 0.05
			Trail Making Test B-A				Improved	P < 0.05

	Mendoza-Nunez et al. (113)	2018	Total antioxidant status	Moderate	5 times per week	50 mins per session, 6 months	Increase	P < 0.05
			Oxidative stress score				Decrease	P < 0.05
			IL-8				Decrease	P < 0.01
	Solianik et al. (114)	2021	BDNF	Moderate	2 times per week	10 weeks	Increased	P < 0.001
			Psycho-emotional state				Stress decreased, depression symptoms decreased	Perceived stress: p < 0.001 Depression: p < 0.042
			Cognitive performance				Improved mental switching, inhibitory control, and visuospatial processing	P < 0.05 (for areas specified)
			Motor Learning				Reaction time decreased	P = 0.028
Yoga	Lee et al. (115)	2014	BDNF	Yoga (not explicitly defined)	3 times per week	12 weeks	Baseline: 23973.6 ± 6996.6 Post (at 12 weeks): 31395.9 ± 7962.7	P < 0.01
	Kiecolt-Glaser et al. (116)	2014	IL-6	Yoga (not explicitly defined)	NS	12 weeks	Decreased after 3 months	P = 0.027
			TNF-alpha					
	Harkess et al. (117)	2016	IL-6	Yoga (moderate)	2 times per week (hour-long sessions)	8 weeks	IL-6: decreased	P = 0.073 [Many cytokine samples were below detection limit, indicating low inflammation levels in this non-clinical population]
	Shete et al. (118)	2017	IL-6	Yoga (not explicitly defined)	1 hour a day, 6 days a week	12 weeks	Baseline: 1.9 Post (after 3 months): 1.3	P < 0.001
			TNF-alpha				Baseline: 34.0 Post (after 3 months): 27.1	P < 0.001
	Li et al. (119)	2020	VEGF	Yoga (not explicitly defined)	- Single session (Yoga class) [90 mins per session] - No fewer than 2 home sessions per week [15 mins per session]	24 weeks	Baseline: 2957 ± 2915 After 24 weeks: 2079 ± 1149	No significant change
	Nugent et al. (120)	2021	IL-6	Yoga (not explicitly defined)	Weekly classes (80 mins each, including pranayama and meditation)	10 weeks	Baseline: 2.82 ± 2.04 After 3 weeks: 2.96 ± 2.79 After 10 weeks: 1.95 ± 1.67	No significant decrease
			TNF-alpha				Baseline: 3.17 ± 2.18 After 3 weeks: 3.62 ± 3.11 After 10 weeks: 3.43 ± 2.32	No significant change
	Viswanathan et al. (121)	2021	IL-6	Yoga (not explicitly defined)	50 mins a day, 5 times per week	12 weeks	Pre: 22.6 Post: 13.3	P = 0.02
			TNF-alpha				Pre: 13.8 Post: 10.8	P = 0.01
			Adiponectin				Pre: increased Post: significant increase	P = 0.03
			TBARS				Pre: decreased Post: significant reduction	P < 0.001
			PTGIS				Pre: 8.3 Post: 9.5	P = 0.02
			Sleep Quality (PSQI score)				Total score improved (post-exercise)	P < 0.005

BDNF: Brain-Derived Neurotrophic Factor; IL-6: Interleukin 6; IL-10: Interleukin 10; TNF-alpha: Tumour Necrosis Factor Alpha; ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive Scale; IL-8: Interleukin 8; VEGF: Vascular Endothelial Growth Factor; TBA-RS: Thiobarbituric Acid Reactive Substances; PTGIS: Prostaglandin-I Synthase; PSQI: Pittsburgh Sleep Quality Index; NS: Not Specified.