THE EFFECT OF DIFFERENT PHYSICAL ACTIVITY INTENSITIES ON COGNITIVE PERFORMANCE RELATED TO ALZHEIMER'S DISEASE

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Abstract

Alzheimer's disease is a neurodegenerative disorder that is characterized by cognitive decline and other pathological hallmarks, such as amyloid-beta and tau pathology, and cholinergic dysfunction. As pharmacological treatment targeting these hallmarks is limited, different lifestyle interventions are proposed, such as diet, physical activity, and social support. This thesis investigates the effect of different intensities of physical activity on cognitive decline associated with Alzheimer's disease. All intensities of physical activity appear to have beneficial effects on cognition compared to a sedentary lifestyle. Analysis of low, moderate, and vigorous physical activity intensities reveal that moderate to vigorous physical activity intensity enhances neuroprotection through a variety of possible mechanisms, including improving cerebral blood flow and synaptic plasticity. Low to moderate physical activity intensity has shown direct effects on cognition. As the studies have limitations in their design, it remains difficult to causally link the intensity of physical activity to the observed changes in cognitive performance. Further research is required for elucidating the mechanism of the effect of different intensities of physical activity on cognitive markers related to Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects cognition and behavior. AD is the most common cause of dementia, accounting for 60-80% of the cases (Alzheimer's Association, 2023). The estimated total global healthcare costs for the treatment of AD patients in 2019 is estimated to be around $305 billion USD, with an estimated 18.6 billion hours of unpaid care by informal caregivers (Wong, 2020). The number of patients is calculated to be around 24 million people worldwide in 2020, expected to increase fourfold by 2050 (Dos Santos Picanto et al., 2018).

AD is characterized by a decline in cognitive abilities and a specific neuropathology in the brain, which is loss of neuronal synapses and pyramidal neurons (Francis et al., 1999). There are multiple hypotheses on the origin of AD, of which most include two key pathological hallmarks; the accumulation of amyloid beta of amyloid-beta (Aβ) protein and neurofibrillary (tau) tangles (NFT). Other features include an inflammatory response in the brain, oxidative stress, and microglial activation (Amelimojarad et al., 2024).

Multiple risk factors have been discovered, such as gender, sustained head injury, age-related changes in the brain, genetic factors, environmental factors, vascular disease, infections, and lifestyle factors (Breijyeh & Karaman, 2020). However, the underlying cause of the associated pathological changes in AD (Aβ, NFTs, synaptic loss) remains elusive, and therefore, no generally accepted hypothesis for AD has been established yet.

Pharmacological treatments have shown limited impact on slowing the disease progression and no pharmacological prevention or cure has been discovered yet. Growing evidence supports that lifestyle interventions may play a crucial role in reducing the risk, as well as delaying the onset of AD (Bhatti et al., 2020). Among lifestyle interventions that have emerged as effective strategies are physical activity (PA) and a healthy diet, which are thought to reduce Aβ accumulation and to positively affect neuroplasticity. These interventions are becoming increasingly recognized to function as a preventative initiative and as a complementary intervention to existing pharmacological treatments (ADEAR, 2023). Rodent models have provided a causal explanation for how physical activity inhibits AD-related cognitive decline via different pathways (Wan et al., 2024; García-Mesa et al., 2011). In humans, however, this direct causality lacks evidence.

Despite extensive research has shown the general benefits of physical activity on AD related pathology development and symptoms, there remains a gap in understanding how different intensities of PA have different effect-mechanisms on AD related symptoms, and in specific, cognitive decline. This review explores how different intensities of PA affect AD-related cognitive decline, and how these findings can be incorporated in AD treatment. To address this question, the possible mechanisms of PA on cognition and health in general will be discussed. The effects on cognitive performance induced by different intensities of PA will be analyzed. Possible mechanisms will be elucidated, providing implications for future research and possible treatment options.

I. Alzheimer's Disease Background

Ia. Pathology of Alzheimer's Disease

AD pathology is mainly characterized by two types of neuropathological changes. The first neuropathological change is the accumulation of neurofibrillary tangles, Aβ plaques, dystrophic neurites, neutrophil threads, and other deposits. The second main neuropathological change is atrophy due to neural, neuropil, and synaptic loss (Figure 1). There are other factors involved that cause neurodegeneration as well, such as injury of cholinergic neurons, oxidative stress, and neuroinflammation (Breijyeh & Karaman, 2020). AD initially damages the neural connections in the entorhinal cortex and hippocampus, which are areas that are involved in memory. At later stages, the disease also affects areas in the cerebral cortex, which are responsible for language, social behavior, and reasoning. Eventually, AD spreads throughout many other areas in the brain, which will result in loss of ability to function independently. Ultimately, the disease is fatal (Scheltens et al., 2021).

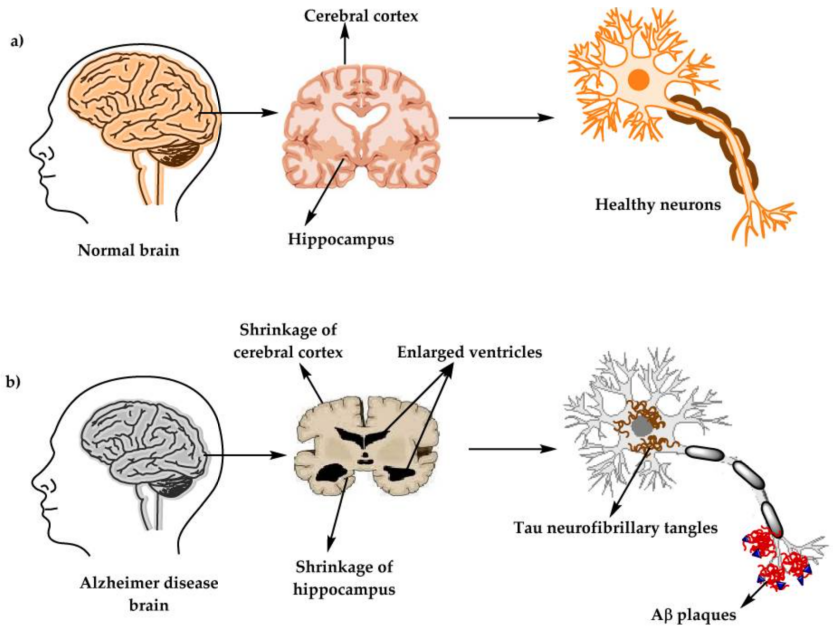

Figure 1: The physiological changes induced by AD. A comparison between the brain and neurons of a (a) healthy brain and a (b) AD brain. AD is characterized by atrophy and accumulation of Aβ plaques and NFTs (Breijyeh & Karaman, 2020).

Hypotheses of Alzheimer's Disease

Several hypotheses have been proposed as an explanation for the neurodegenerative mechanisms that induce cognitive decline, of which 3 are widely accepted. The *Amyloid Cascade Hypothesis* is a widely accepted theory that proposes that the main cause of cognitive symptoms related to AD is the accumulation of Aβ plaques in the brain. Aβ is the product of the cleavage of amyloid precursor protein (APP), which yields either one of the two isoforms $A\beta_{42}$ or $A\beta_{40}$. $A\beta_{42}$ is known to be more prone to aggregation and is therefore associated with AD. The buildup of Aβ plaques triggers a cascade of inflammatory responses, activation of immune cells (e.g., microglia), synaptic and neuronal injury, hyperphosphorylation of tau, and neuronal dysfunction as well as cell death (Barage & Sonawane, 2015). The *Tau Hypothesis* suggests that tau proteins, which usually function as stabilizers for microtubules in neurons, become hyperphosphorylated, which causes loss of support of microtubule structure (Agarwal et al., 2020). This results in microtubule destabilizing, as well as aggregation of tau into NFTs. NFTs cause loss of function and degeneration of neurons by disrupting the neurons intracellularly (Barghorn et al., 2004). The *Cholinergic Hypothesis* states that the neurotransmitter acetylcholine (ACh), which is involved in learning and memory formation, is reduced, as well as a decline in enzymes that are involved in ACh production and degradation. These lowered levels are linked to memory impairment, which also contributes to the cognitive decline that is observed in AD (Chen., 2022).

Ib. Risk Factors for Alzheimer's Disease

As AD is a complex and multifactorial condition, multiple risk factors contribute to the timing of onset and the development of AD. While the direct cause of AD remains elusive, several risk factors have been identified already in extensive research. Understanding these risk factors may allow better prevention and treatment options (Zhang et al., 2021).

The most prominent risk factor for AD is age, as aging contributes to biological processes, such as a higher oxidative stress, mitochondrial dysfunction, and inflammation. These three processes play a significant role in the development of AD (Hou et al., 2019). Aging accounts for more than 95% of the AD cases (Liu, 2022).

Another risk factor for developing AD is a genetic predisposition. The most common variant is the apolipoprotein E (APOE) gene, and in particular the APOE ε4 allele. Carrying one copy of this allele increases risk by approximately 3 times and homozygotes with two copies have 10-15 times higher risk. Carrying this allele, however, is not causally related to AD development, as other factors also affect the development (Farrer et al., 1997). A genetic variant that does result in AD in almost all cases, are in the presenilin 1 (PSEN1) gene, presenilin 2 (PSEN2) gene, or in the amyloid precursor protein (APP) gene, which are dominantly autosomally inherited. These gene mutations are involved in APP synthesis and proteolysis, which lead to excessive production of Aβ (Perkovic & Pivac, 2019). Aside from these gene mutations, there seems to be another risk factor that is related to genetics, as those who have family members that are diagnosed with AD, also have a higher risk of being diagnosed. This could be due to genetics, as well as to environmental and lifestyle factors that might be adopted (Loy et al., 2014).

Gender is also considered a risk factor, as women have a higher likelihood of developing AD than men, with 60% of the AD patients being female (Mosconi et al., 2021). This might be explained by the drop in estrogen levels after menopause, which is thought to be linked to Aβ accumulation rates (Yue et al., 2005).

There are several lifestyle and environmental factors involved that contribute to the development and progression of AD. These factors include cardiovascular health, which is thought to be essential for maintaining brain health by supplying oxygen to the brain, and diabetes, which is another cardiovascular risk factor that can cause insulin resistance in the brain, which is in turn related to Aβ and tau accumulation, and neuroinflammation (Pugazhenthi et al, 2016).
PA is beneficial for cognitive function and brain plasticity. A sedentary lifestyle is therefore associated with an increased risk of AD. Physical activity has also been demonstrated to reduce Aβ levels, while promoting the release of neurotrophic factors that enhance neuronal health (Iso-Markku et al., 2022; Hillman et al., 2008). Other lifestyle factors include diet, sleep, smoking, alcohol use, and head injury (Stefaniak et al., 2022; Irwin & Vitiello, 2019; Orgeta et al., 2019).

These studies highlight how AD is a multifaceted disorder where both genetic and environmental factors play a role. Whereas certain risk factors are not modifiable (e.g., age and genetics), factors such as diet and physical activity are. Therefore, when designing new preventative strategies for AD, these factors should be further investigated.

Amyloid-Beta & Cognitive Decline

The accumulation of Aβ plaques in the brain is thought to disrupt synaptic transmission and to decrease neuronal plasticity, which both are involved in learning and memory formation. Aβ plaques can also contribute to the dysfunction of mitochondria, and therefore to the overproduction of reactive oxygen species (ROS). This process results in oxidative stress, which is involved in acute and chronic pathologies in the brain, and has been proposed to facilitate the secretion of Aβ (Reddy & Beal, 2008). Both animal and human studies have already shown a direct relationship between Aβ accumulation and the degree of cognitive decline (Poon et al., 2020; ,Mormino & Papp, 2018). Therefore, it is thought that interventions that target Aβ accumulation may reduce its harmful effects and preserve cognition. Such interventions might therefore slow down the progression of AD. However, the relation between Aβ accumulation and cognitive performance is still under debate, and it remains unclear whether Aβ accumulation causes the cognitive symptoms, or is simply a result of AD (Struble et al., 2011).

II. Physical Activity as a Neuroprotective Intervention

IIa. General Benefits of Physical Activity

PA has already been established to have beneficial effects for overall health by improving cardiovascular fitness, musculoskeletal strength, and metabolic regulation (Ruegsegger & Booth, 2018). Aside from systemic effects, exercise has also been discovered to have great neuroprotective effects by enhancing brain plasticity, promoting neurogenesis, and increasing the production of brain-derived neurotrophic factor (BDNF), which promotes synaptic plasticity (Cotman et al., 2007). PA also improves cerebral blood flow, reduces systemic inflammation, and provides more oxygen supply to the brain (Hu et al., 2024).

IIb. Physical Activity-induced Neuroprotection & Cognitive Function

PA in general has extensively been linked to improved cognition by previous studies through a range of mechanisms. PA is a strong gene modulator that induces structural and functional changes in the brain that are related to cognitive function. PA also functions as a neuroprotector against neurodegeneration. It is, however, unclear whether this has to do with epigenetics, better lymphatic mechanisms, or better compensation against attacks. Both experimental and clinical studies have indicated that PA induces both structural and functional changes in the brain (Mandolesi et al., 2018). PA is thought to have neuroprotective effects through a range of biological processes that result in preservation of brain structure and function, a reduction of the risk of neurodegenerative disease, and a decrease in neuroinflammation. One of the primary mechanisms of PA is the enhancement of neuroplasticity, which is the ability of the brain to adapt and reorganize neural networks in response to stimuli. PA induces increased production of BDNF, which is involved in the maintenance and growth of neurons. BDNF can strengthen synaptic connections, which results in enhanced communication between neurons, which facilitates learning and memory (Di Liegro et al., 2019). By promoting neuroplasticity through BDNF, PA facilitates the maintenance of a healthier brain structure, which counteracts the neural degradation that is observed in AD.

Additionally, cerebral blood flow (CBF) is enhanced by PA. CBF supplies oxygen and other nutrients to brain tissues. Improved circulation results in angiogenesis as well, which is the formation of new blood vessels. This particularly occurs in the hippocampus and as the hippocampus is involved in memory and learning, PA counteracts the cognitive decline that is caused by AD as well through this mechanism (Di Liegro et al., 2019).

PA also plays a role in reducing neuroinflammation and oxidative stress, which both are factors that contribute to neurodegenerative diseases. Chronic inflammation and oxidative stress result in cell damage and death. PA migates these effects, which are typical hallmarks of AD, and by altering immune responses and reducing cytokine production, which are pro-inflammatory proteins (El Assar et al., 2022). By activating neuroprotective mechanisms, cognition can be partly preserved in AD patients (Liu et al., 2023). PA contributes to neuroprotection through a variety of mechanisms, and combined they support cognitive ability and lower the risk and progression of AD.

III. Physical Activity Intensity & Cognition

IIIa. Definition of Physical Activity Intensities

To analyze and compare different studies, the PA intensities were determined based on the classification of CDC and concluded in table 1 (CDC, link).

Low-Intensity Physical Activity (LPA)	Moderate-Intensity Physical Activity (MPA)	Vigorous-Intensity Physical Activity (VPA)
Slow-paced, minimal exertion	Sustained activity	High exertion, intermittent or sustained
Slow-paced walking, stretching, household activities, mild strength training	Brisk walking, light jogging, cycling at a steady pace, swimming at a moderate speed	Running, swimming laps, cycling at high speed, high-intensity interval training (HIIT)
< 3 METs	3-6 METs	> 6 METs
< 50% of maximum heart rate (bron)	50-70% of maximum heart rate (bron)	70-85% of maximum heart rate (bron)
Aerobic	Aerobic	Aerobic and anaerobic

Table 1: Classification of different intensities of PA based on data from CDC (link). The intensities are provided with a description, examples of activities, MET scores, heart rate, and type of activity.

IIIb. Physical Activity Intensities & Cognition

Different intensities of PA affect health via various mechanisms with different health effects as a result. LPA can improve metabolic health, enhance circulation, and have beneficial effects on mental health and cognition. MPA, specifically, improves cardiovascular health and aerobic capacity. However, VPA has shown to be most beneficial in general for health improvements (Samitz et al., 2011). The effect of different PA intensities on cognition specifically, and especially in the context of AD, remains to be discovered.

In patients with mild cognitive impairment (MCI), PA in general has beneficial effects on cognition. Different intensities of a PA intervention were compared, and revealed that MPA and VPA display similar effects on the cognitive state of these individuals (Yu et al., 2022). Therefore, it remains unknown whether and how different intensities affect cognitive performance in AD patients.

Ornish et al. (2024) have investigated the effects of intensive lifestyle changes on the progression of MCI due to AD and plasma Aβ42/40 ratio. The study consists of 51 individuals (mean age = 73.5 y) that were diagnosed with mild AD or MCI. During a 20 week period, the intervention group started an intensive, multidomain lifestyle intervention compared to the control group, which received usual care. The intervention entailed changes in diet, adjusted PA, stress management, group support, and supplements. The PA intervention consisted of an aerobic exercise scheme of walking at least 30 minutes per day and performing mild strength exercises 3 times per week, which aligns with LPA in table 1. Cognitive and biomarker assessment was performed after the 20 week intervention. The intervention group showed an improvement in cognitive performance on the cognitive tests, whereas the control group scored worse. Between-group analysis reveals a significant difference in the following cognitive tests; CGIC ($p = 0.001$), CDR-SB ($p = 0.032$), and CDR-Global ($p = 0.037$), and an almost significant difference in ADAS-Cog ($p = 0.053$). These findings indicate an improvement in cognition due to the multidomain intervention.

Plasma Aβ42/40 ratio increased in the intervention group but decreased in the control group after the intervention ($p = 0.003$, two-tailed), and is significantly correlated with lifestyle ($p = 0.011$, correlation = 0.306). These results indicate that the intensive lifestyle intervention is associated with an increase in cognitive performance, as well as a lowered plasma Aβ42/40 ratio. In the control group, the cognitive

decline progresses further, and the plasma Aβ42/40 ratio increases, which is an indicator of AD progression (Doecke et al., 2020).

An observational study by Desai et al., (2022) provides more insight into how different intensity levels of PA are related to cognitive decline in individuals with elevated neurofilament light chain (NfL) levels. NfL is a biomarker of axonal damage. High NfL levels are associated with cognitive decline in AD (Giacomucci et al., 2022). The test group consists of 1158 older adults (mean age = 77.4 y) with either high NfL levels (> 25 pg/ml) or low NfL levels (≤ 25 pg/ml). Based on self-reported PA, the individuals are classified at 3 different PA intensity levels; low (no PA), medium (< 150 min/week), and high (≥ 150 min/week). The PA activity includes aerobic training in a variety of disciplines, such as uptempo walking, running, gardening, dancing, bicycle riding, and swimming. This intensity aligns with MPA in table 1.
For individuals with elevated NfL levels, PA is associated with a slower rate of cognitive decline, with a 12% slower rate for medium PA, and 36% slower rate for high PA compared to the low PA group. High PA is specifically associated with better episodic memory ($p = 0.03$) and perceptual speed ($p = 0.06$). These results indicate that for individuals with biomarker scores that indicate axonal damage, medium and high activity levels are associated with a decrease in cognitive decline, which can be linked to AD. This study is merely an observational study, and therefore, no causal relation between MPA and cognitive performance can be concluded.

Yu et al. (2021) have investigated a lifestyle intervention as well, with aerobic exercise as an isolated factor over the timespan of 6 months. The test group included 96 patients (mean age = 77.4 y) diagnosed with mild-to-moderate AD. The intervention consisted of cycling at a moderate intensity for 20-50 minutes at 50-70% of maximum heart rate for 3x per week, which corresponds to MPA in table 1, and the control group performed low intensity stretching instead, which corresponds to LPA in table 1. Cognitive performance was assessed through ADAS-Cog and MMSE examination. Right after the 6-month intervention, the ADAS-Cog score revealed a smaller within-group decrease than the natural expected ($p = 0.001$), which indicates a slower cognitive decline. However, the 12-month difference analysis did not show significant differences between the intervention group and the control group ($p = 0.386$). The rate of change of ADAS-Cog score over 12 months was smaller in the intervention group (0.192) than the control group (0.200) but is not statistically significant. These results indicate that the intervention results in slower cognitive impairment right after the intervention, but these results do not last for a prolonged period after the intervention. This could be due to a lack of statistical power, or due to PA not having long-lasting cognitive effects.

Gaitán et al. (2021) investigated a test group of 25 cognitively healthy individuals (mean age = 63.9 y) who are considered AD risk patients, due to either a genetic predisposition, or a familial background. The individuals were selected on an inactive lifestyle at baseline (PA < 150 min/per week). The intervention consisted of 26 weeks of aerobic treadmill exercise at 60-75% of the maximum heart rate for 3x per week. The control group continued with usual PA levels. The PA intensity of the intervention corresponds to MPA to VPA in table 1. After the 26-week intervention, cognitive performance was assessed with MMSE, CVLT, and D-KEFS, which are comprised of different subsets. The intervention resulted in improved cognitive function, and in particular, executive function ($p < 0.005$) and episodic memory ($p = 0.005$). VO_2peak was measured for assessing cardiorespiratory fitness, which had significantly increased in the intervention group ($p = 0.018$), but not in the control group ($p = 0.557$). A previous study from Gaitan et al. (2019) has revealed a correlation between increase in VO_2peak and change in D-KEFS ($p = 0.032$). Biomarker analysis reveals significantly increased Cathepsin B (CTSB) level ($p = 0.009$), decreased brain-derived neurotrophic factor (BDNF) level ($p = 0.003$), and increased

sphingolipid and phospholipid levels ($p < 0.001$). A correlation was discovered between change in plasma CTSB level and change in CVLT outcomes ($p < 0.05$). No other correlation between biomarker and cognitive outcomes were found. These results indicate that CTSB can be used as a marker for cognitive changes (CVLT) for middle-aged adults at risk for AD. As the intervention has positive effects on executive function and episodic memory, this intensity of PA could be further analyzed to investigate whether it can be implemented in AD treatment.

Sobol et al. (2018) have investigated the relation between change in fitness and change in cognition and neuropsychiatric symptoms after a 16 week intervention of supervised aerobic exercise for 30 minutes at 70-80% of the maximum heart rate for 3x a week, which could consist of bicycle, cross-trainer, or treadmill exercise. The control group received usual care. The test group consisted of 55 patients (mean age = 69.2) diagnosed with mild AD. After the 16-week intervention SDMT testing was used for assessing cognitive performance, NPI testing for neuropsychiatric symptoms, and VO_2peak for cardiorespiratory fitness. The cognitive test solely did not show significant results between intervention and baseline. However, between-group analysis between baseline and the 16-week intervention revealed a higher absolute VO_2peak in the intervention group ($p = 0.001$), as well as a larger increase in VO_2peak ($p = 0.003$). With combined data of the control and the intervention group, associations were found between change in VO_2peak and change in SDMT ($rho = 0.36$, $p = 0.01$), and between change in VO_2peak and change in NPI ($rho = -0.41$, $p = 0.042$). These results indicate that the intervention results in a larger increase of VO_2peak and a higher absolute VO_2peak. Change in VO_2peak is correlated with change in cognition and change in neuropsychiatric symptoms.

Physical Activity Intensity & Alzheimer's Disease Biomarkers

$A\beta_{42/40}$ ratio: A lower Aβ42/40 ratio is linked to increased plaque deposition and AD progression. $A\beta_{42}$ is more prone to aggregate and is therefore associated with AD (Doecke et al., 2020).
NfL: NfL is a protein that is released when axons are damaged. Elevated NfL levels are associated with AD as it is a sign of neurodegeneration (Giacomucci et al., 2022).
CTSB: An enzyme that is involved in protein degradation. Elevated CTSB levels are associated with AD, as it improves memory deficit and reduces Aβ (Hook et al., 2023).
Sphingolipids and phospholipids: Lipid molecules that are involved in maintaining structural integrity of the cell, signal transduction and neuroprotection. High sphingolipid and phospholipid levels are associated with AD (Wang et al., 2024; Kosicek & Hecimovic, 2013).
BDNF: A protein that is involved in neuronal growth. A reduced BDNF level is associated with later stages of AD. In early AD stages, an increase in BDNF is observed as a compensatory mechanism (Ng et al., 2021).

Study	Test Group	PA intensity	Cognitive Outcomes	Biomarker Outcomes	Main Result	Limitations
Ornish et al. (2024)	N = 51 Mean age = 73.5y Specifics: early AD / MCI	LPA: 30 min/day walking, mild strength	↑ Cognitive function[1]	↑ Plasma Aβ42/40 ratio.	Correlation between lifestyle and both cognitive function and plasma Aβ42/40 ratio	Multidomain intervention; no isolated PA. Small sample size
Desai et al. (2022)	N = 1158 Mean age = 77.4y Specifics: different PA levels and NfL levels	MPA: ≥ 150 min/week aerobic PA	↓ cognitive decline[2] (particularly in elevated NfL individuals)	-	PA is linked to slower cognitive decline, particularly in high NfL group.	Self-reported PA levels. Observational study
Yu et al. (2021)	N = 1158 Mean age = 77.4y Specifics: AD patients	MPA: Cycling 3x/week for 20-50 min.	↑ Cognitive function[3]	-	Moderate exercise slows cognitive decline (6-month result)	No biomarker measures. Small sample size, no superior effects. Pilot study
Gaitán et al. (2021)	N = 25 Mean age = 63.9y Specifics: AD risk group	MPA / VPA: Treadmill 3x/week	Correlation between ↑ CTSB and ↑ executive function & ↑ episodic memory	↑ CTSB, ↓BDNF	Improved cognitive markers. Enhanced CTSB. Decreased BDNF	Small sample size, only specific to biomarkers CTSB, BDNF
Sobol et al. (2018)	N = 55 Mean age = 69.2y Specifics: mild AD	MPA / VPA: aerobic exercise 3x/week at 70-80% max HR.	Association ↑ VO_{2peak} & ↑ neuropsychiatric state[4]. Association between changes in VO_{2peak} and ↑ cognition[5].	↑ VO2peak.	Improved cardiorespiratory fitness (associated with cognitive and neuropsychiatric improvements)	No biomarker measures. Small sample. Mixed effect social interaction.

Table 2: A summary of the main characteristics and findings of the 5 papers. The 5 papers that are used for comparison are categorized, in ascending order from lowest PA intensity to most vigorous PA intensity. Characteristics about the study set up and results are summarized in the table, containing test group characteristics (number, age, AD status, other selected criteria), PA intensity according to table 2, cognitive outcomes, biomarker outcomes (if mentioned), main result, and limitations for the (contextual) interpretation of these studies (Ornish et al., 2024; Yu et al., 2021; Desai et al., 2022; Gaitán et al., 2021; Sobol et al., 2018).

[1] In CGIC, CDR-SB, CDR Global. Almost significant in ADAS-Cog.

[2] Particularly in individuals with elevated NfL.

[3] In ADAS-Cog at 6 months. No differences between 6-12 months

[4] NPI test

[5] SDMT test

IV. Discussion & Implications

The study of Ornish et al. (2024) focuses on a low-intensity PA intervention in combination with a broader range of lifestyle interventions, including diet, social engagement, and supplements. This multi-domain intervention causes significant improvement of the cognitive condition of the patients that underwent the intervention, compared to the control group. Therefore, the intervention appears to be effective in treating AD-related cognitive decline. However, it is not possible to analyze how the LPA as an isolated factor has contributed to these results. It is possible to hypothesize, based on these results, with which mechanism LPA could affect the results, but the direct link remains elusive. For clinical implications, the study is of great scientific significance, as the multi-domain can be incorporated into standard AD treatment. For examining what the effects of LPA specifically is on cognitive decline related to AD, this study does not suffice. The significant correlation between plasma Aβ42/40 ratio and cognitive function is supported by literature, as increased plasma Aβ42/40 ratio is proposed to be a biomarker for amyloid clearance, which is thought to be related to cognitive performance (Stevens et al., 2022). However, the relation between Aβ and cognitive impairment is not established in other literature (Aizenstein et al., 2008; Pan et al., 2022).

The study of Desai et al. (2022) does isolate PA as a separate factor to investigate the effect of different PA levels on cognition, both in individuals with low and high NfL levels. A limitation of this study is that the study is an observational study that links self-reported PA levels to cognitive decline. Therefore, the causality between PA level and cognitive outcomes cannot be established. Various genetic and environmental factors, which are not accounted for, can alter the cognitive outcomes, as these factors are not manipulated with an intervention in the research. Environment and NfL levels can have a reciprocal effect on each other, and the environmental factors that affect NfL levels, can be the same factors that affect PA level of the individuals (Koini et al., 2022). Therefore, there might be a skew in the representability of the test group. Self-reporting has also been observed not to be reliable in patients with mild vascular cognitive impairment, which makes it questionable whether patients with mild cognitive decline related to AD are able to (Verdelho et al., 2022). If reliability of self-reporting decreases with a heavier cognitive decline, this might skew the outcomes of the research. For examining how different intensities affect AD-related cognitive decline, the study is not adequate, as it lacks a manipulated factor in the research, and the scored PA level (low / medium / high) only provides insight about duration and frequency, not the specific intensity. Therefore, for understanding the disease and its possible treatments, it is of significance to observe how PA levels affect cognition, especially in individuals with elevated NfL levels, but it does not provide causal explanation.

Yu et al. (2021) compared an MPA intervention to an LPA intervention, which did reveal within-group differences right after the intervention compared to the baseline, but not between-group differences. The effect was diminished after 6 months after the intervention. The study does account for a social effect, by having similar interventions for the control group and the experimental group, whereas the results of the other studies could be affected by the positive influence of a social effect as well (Ren et al., 2023). The only factor that differs between these two groups is the intensity of PA. This allows for very precise testing for the effect of different PA intensities. The study does not include biomarker measures, which makes it more difficult to back up findings, or to elucidate certain associations. This study design could be improved by including more cognitive and biomarker measures.

Gaitán et al. (2021) use a moderate-to-vigorous intensity PA intervention of treadmill exercise for 3x per week for 6 months. This allows for examination of a longer intervention period, which might yield more reliable results than a shorter intervention period. This study measures cognitive function, as well as specific AD-related biomarkers, such as CTSB, sphingolipids, and phospholipids. These measures

allow for investigating the mechanism behind the observed neuroprotection related to the PA. The cognitive testing uses multiple tests, with different cognitive domains, which yields specific results, as general cognitive performance did not show significant results, but certain domains did. As the study has a sample size of only 25 subjects, the study does not have a great statistical power, and therefore, the results would be more reliable if the procedure was to be repeated with a larger sample size. The cognitive domain-specific findings can be implemented in treatment, especially when the symptoms regard that specific domain.
Sobol et al. (2018) used a moderate-to-vigorous intensity PA intervention as well, consisting of aerobic activity for 3x a week, for a period of 16 weeks. The study uses VO_2peak as an objective measure of PA intensity, which has as a benefit that this study is easily comparable to other studies that also use VO_2peak as an objective measure, which could evade the problem that different studies in the field use different measures for intensity. The only cognitive performance measure was the SDMT test, which mainly tests for cognitive processing speed, which is a component of a healthy functioning cognition. However, other factors, such as memory processing and executive functions, are involved as well and can be separately assessed (Harvey, 2019). This would provide a more complete image of AD-related cognitive impairment and possible improvements that result from an intervention. The conclusive statement that the combined data of the control and the intervention group resulted in associations between change in VO_2peak and change in SDMT and NPI, could be misinterpreted. It seems that a general association between VO_2peak and the other measures is established. However, separate analysis reveals that this association is only present in the control group ($rho = 0.74$, $p < 0.0001$), but not in the intervention group ($rho = 0.23$, $p = 0.26$). Therefore, the VO_2peak measure could be useful for predicting cognitive performance at baseline, but not after an intervention.

When comparing the duration of the experiment, it is noticeable that the durations vary a lot between the studies. Desai et al. (2022) perform a one-time measurement without any manipulated parameters, and Sobol et al. (2018), Ornish et al. (2024), and Gaitán et al. (2021) perform both measurement at baseline, and at the end of the intervention at week 16, week 20, and week 26 respectively. Yu et al. (2021) performs measurement at baseline, month 3, 6, 9, and 12. The study of Yu et al. is an example of how outcome measures differ at different time points, which makes it difficult to compare studies. The studies could be improved by adding multiple time points for measuring. This would result in more comparable studies and would increase the reliance of the studies as well.

Future research should aim for more standardized procedures. Standardized testing would allow for more easily comparable results. This is necessary for comparing different intensities of PA on cognitive measures. When comparing current literature, many different measures are used to categorize PA intensity, such as percentage of the maximum heart rate, duration, frequency, and type of activity. It would be more straightforward if there was a more generally used scale of different intensities, which includes all of these measures. Future research can also benefit from standard testing for various biomarkers that are related to either cognitive decline related to AD or to PA intensity. Examples of biomarkers are AD hallmarks, such as $A\beta_{42}$, $A\beta_{40,}$ and phosphorylated tau, as well as metabolic products, such as lipids, and biomarkers that indicate the effect of PA, such as blood pressure, increase in maximum heart rate, and increase in VO_2peak (Gunes et al., 2022). Desai et al. have demonstrated that it is possible that there is no significant general cognitive effect, while there is a significant effect on a specific cognitive domain. Therefore, future research would provide more reliable results if the cognitive assessment tests multiple cognitive domains separately as well. Some cognitive domains are more associated with certain AD pathologies than others (Digma et al., 2019). This would yield more precise results and could improve the field by providing more insights in specific mechanisms or specific brain regions that are affected by AD and by the PA intervention.

For future research, as study design with multiple test groups would be beneficial gain more insight into how different intensities of PA affect cognition related to AD. There would be 4 test groups: control group (no PA), LPA group, MPA group, VPA group. The test group would consist of individuals with similar background in lifestyle, genetics (i.e., no specific predisposition), and AD status (e.g., MCI). During an intervention period of 25 weeks, the control group receives no PA intervention but continues regular treatment. The other 3 groups undergo an intervention corresponding to the specific intensity level. Different cognitive domains are tested, and multiple biomarkers are measured, as previously proposed. This would allow for more precise determination of which protective mechanisms are involved and will result in more easily comparable results. This study design provides more insight in how the specific PA intensities affect the cognitive and biomarker measures that are associated with AD. Biomarkers and cognition will be measured every 5 weeks up to 25 weeks after the intervention, which will provide a more complete picture of how these measures progress over the time of the intervention and the period after. These measurements in the context of the timeframe of the intervention will provide insights into whether PA can be a long-acting intervention as a supplement for treating AD-related cognitive decline.

Gaining more understanding in how different PA intensities counteract AD-related cognitive decline will subsequently allow for more suitable treatment options. After more extensive research, healthcare professionals might be able to offer personalized interventions for recently diagnosed AD patients.

V. Conclusion

In this review, the effect of different intensities of PA on cognitive decline associated with AD was investigated. Findings indicate that PA is an effective intervention to either target AD-related cognitive decline in patients with MCI, or to prevent cognitive decline in AD risk patients. As most findings are co-influenced by other factors, such as a multifactorial intervention or social effects, no direct conclusion on the effects of different types of PA intensity can be drawn. These findings indicate that PA can function as a supplemental treatment to pharmacological treatment, as these findings show promising effects. However, to obtain more knowledge on the mechanisms behind these effects, and on which intensity is most effective, further research is required. Future research would benefit from more standardized biomarker testing and multi domain cognitive testing for more striking results. Ultimately, these findings suggest that PA could play a significant role in the prevention and delay of AD-related cognitive symptoms, which would result in less burden for society.

VI. References

Amelimojarad M, Amelimojarad M, Cui X. The emerging role of brain neuroinflammatory responses in Alzheimer's disease. Front Aging Neurosci. 2024 Jul 3;16:1391517. doi: 10.3389/fnagi.2024.1391517. PMID: 39021707; PMCID: PMC11253199.

Agarwal M, Alam MR, Haider MK, Malik MZ, Kim DK. Alzheimer's Disease: An Overview of Major Hypotheses and Therapeutic Options in Nanotechnology. Nanomaterials (Basel). 2020 Dec 29;11(1):59. doi: 10.3390/nano11010059. PMID: 33383712; PMCID: PMC7823376.

Aizenstein HJ, Nebes RD, Saxton JA, et al. Frequent Amyloid Deposition Without Significant Cognitive Impairment Among the Elderly. Arch Neurol. 2008;65(11):1509–1517. doi:10.1001/archneur.65.11.1509

Barage SH, Sonawane KD. Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. Neuropeptides. 2015 Aug;52:1-18. doi: 10.1016/j.npep.2015.06.008. Epub 2015 Jul 2. PMID: 26149638.

Barghorn S, Davies P, Mandelkow E. Tau paired helical filaments from Alzheimer's disease brain and assembled in vitro are based on beta-structure in the core domain. Biochemistry. 2004 Feb 17;43(6):1694-703. doi: 10.1021/bi0357006. PMID: 14769047.

Bhatti GK, Reddy AP, Reddy PH, Bhatti JS. Lifestyle Modifications and Nutritional Interventions in Aging-Associated Cognitive Decline and Alzheimer's Disease. Front Aging Neurosci. 2020 Jan 10;11:369. doi: 10.3389/fnagi.2019.00369. PMID: 31998117; PMCID: PMC6966236.

Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec 8;25(24):5789. doi: 10.3390/molecules25245789. PMID: 33302541; PMCID: PMC7764106.

CDC. “How to Measure Physical Activity Intensity.” Physical Activity Basics, 24 May 2024, www.cdc.gov/physical-activity-basics/measuring/index.html.

Chen ZR, Huang JB, Yang SL, Hong FF. Role of Cholinergic Signaling in Alzheimer's Disease. Molecules. 2022 Mar 10;27(6):1816. doi: 10.3390/molecules27061816. PMID: 35335180; PMCID: PMC8949236.

Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 2007 Sep;30(9):464-72. doi: 10.1016/j.tins.2007.06.011. Epub 2007 Aug 31. Erratum in: Trends Neurosci. 2007 Oct;30(10):489. PMID: 17765329.

Desai P, Dhana K, DeCarli C, Wilson RS, McAninch EA, Evans DA, Rajan KB. Examination of Neurofilament Light Chain Serum Concentrations, Physical Activity, and Cognitive Decline in Older Adults. JAMA Netw Open. 2022 Mar 1;5(3):e223596. doi: 10.1001/jamanetworkopen.2022.3596. PMID: 35315915; PMCID: PMC8941360.

Di Liegro CM, Schiera G, Proia P, Di Liegro I. Physical Activity and Brain Health. Genes (Basel). 2019 Sep 17;10(9):720. doi: 10.3390/genes10090720. PMID: 31533339; PMCID: PMC6770965.

Digma, L.A., Madsen, J.R., Reas, E.T. et al. Tau and atrophy: domain-specific relationships with cognition. Alz Res Therapy 11, 65 (2019). https://doi.org/10.1186/s13195-019-0518-8

Doecke, James D., et al. “Total Aβ42/Aβ40Ratio in Plasma Predicts Amyloid-PET Status, Independent of Clinical AD Diagnosis.” Neurology, vol. 94, no. 15, 16 Mar. 2020, pp. e1580–e1591, https://doi.org/10.1212/wnl.0000000000009240.

Dos Santos Picanco LC, Ozela PF, de Fatima de Brito Brito M, Pinheiro AA, Padilha EC, Braga FS, de Paula da Silva CHT, Dos Santos CBR, Rosa JMC, da Silva Hage-Melim LI. Alzheimer's Disease: A Review from the Pathophysiology to Diagnosis, New Perspectives for Pharmacological Treatment. Curr Med Chem. 2018;25(26):3141-3159. doi: 10.2174/0929867323666161213101126. PMID: 30191777.

El Assar M, Álvarez-Bustos A, Sosa P, Angulo J, Rodríguez-Mañas L. Effect of Physical Activity/Exercise on Oxidative Stress and Inflammation in Muscle and Vascular Aging. Int J Mol Sci. 2022 Aug 5;23(15):8713. doi: 10.3390/ijms23158713. PMID: 35955849; PMCID: PMC9369066.

Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997 Oct 22-29;278(16):1349-56. PMID: 9343467.

Gaitán JM, Boots EA, Dougherty RJ, Oh JM, Ma Y, Edwards DF, Christian BT, Cook DB, Okonkwo OC. Brain Glucose Metabolism, Cognition, and Cardiorespiratory Fitness Following Exercise Training in Adults at Risk for Alzheimer's Disease. Brain Plast. 2019 Dec 26;5(1):83-95. doi: 10.3233/BPL-190093. PMID: 31970062; PMCID: PMC6971821.

Gaitán JM, Moon HY, Stremlau M, Dubal DB, Cook DB, Okonkwo OC, van Praag H. Effects of Aerobic Exercise Training on Systemic Biomarkers and Cognition in Late Middle-Aged Adults at Risk for Alzheimer's Disease. Front Endocrinol (Lausanne). 2021 May 20;12:660181. doi: 10.3389/fendo.2021.660181. PMID: 34093436; PMCID: PMC8173166.

García-Mesa Y, López-Ramos JC, Giménez-Llort L, Revilla S, Guerra R, Gruart A, Laferla FM, Cristòfol R, Delgado-García JM, Sanfeliu C. Physical exercise protects against Alzheimer's disease in 3xTg-AD mice. J Alzheimers Dis. 2011;24(3):421-54. doi: 10.3233/JAD-2011-101635. PMID: 21297257.

Giacomucci G, Mazzeo S, Bagnoli S, Ingannato A, Leccese D, Berti V, Padiglioni S, Galdo G, Ferrari C, Sorbi S, Bessi V, Nacmias B. Plasma neurofilament light chain as a biomarker of Alzheimer's disease in Subjective Cognitive Decline and Mild Cognitive Impairment. J Neurol. 2022 Aug;269(8):4270-4280. doi: 10.1007/s00415-022-11055-5. Epub 2022 Mar 14. PMID: 35288777; PMCID: PMC9293849.

Gunes S, Aizawa Y, Sugashi T, Sugimoto M, Rodrigues PP. Biomarkers for Alzheimer's Disease in the Current State: A Narrative Review. Int J Mol Sci. 2022 Apr 29;23(9):4962. doi: 10.3390/ijms23094962. PMID: 35563350; PMCID: PMC9102515.

Harvey PD. Domains of cognition and their assessment. Dialogues Clin Neurosci. 2019 Sep;21(3):227-237. doi: 10.31887/DCNS.2019.21.3/pharvey. PMID: 31749647; PMCID: PMC6829170.

Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci. 2008 Jan;9(1):58-65. doi: 10.1038/nrn2298. PMID: 18094706.

Hook G, Kindy M, Hook V. Cathepsin B Deficiency Improves Memory Deficits and Reduces Amyloid-β in hAβPP Mouse Models Representing the Major Sporadic Alzheimer's Disease Condition. J Alzheimers Dis. 2023;93(1):33-46. doi: 10.3233/JAD-221005. PMID: 36970896; PMCID: PMC10185432.

Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, Bohr VA. Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol. 2019 Oct;15(10):565-581. doi: 10.1038/s41582-019-0244-7. Epub 2019 Sep 9. PMID: 31501588.

Hu J, Huang B, Chen K. The impact of physical exercise on neuroinflammation mechanism in Alzheimer's disease. Front Aging Neurosci. 2024 Aug 21;16:1444716. doi: 10.3389/fnagi.2024.1444716. PMID: 39233828; PMCID: PMC11371602.

Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. Lancet Neurol. 2019 Mar;18(3):296-306. doi: 10.1016/S1474-4422(18)30450-2. Epub 2019 Jan 17. PMID: 30661858.

Iso-Markku P, Kujala UM, Knittle K, Polet J, Vuoksimaa E, Waller K. Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case-control studies. Br J Sports Med. 2022 Jun;56(12):701-709. doi: 10.1136/bjsports-2021-104981. Epub 2022 Mar 17. PMID: 35301183; PMCID: PMC9163715.

Koini M, Pirpamer L, Hofer E, Buchmann A, Pinter D, Ropele S, Enzinger C, Benkert P, Leppert D, Kuhle J, Schmidt R, Khalil M. Factors influencing serum neurofilament light chain levels in normal aging. Aging (Albany NY). 2021 Dec 18;13(24):25729-25738. doi: 10.18632/aging.203790. Epub 2021 Dec 18. PMID: 34923481; PMCID: PMC8751593.

Kosicek M, Hecimovic S. Phospholipids and Alzheimer's disease: alterations, mechanisms and potential biomarkers. Int J Mol Sci. 2013 Jan 10;14(1):1310-22. doi: 10.3390/ijms14011310. PMID: 23306153; PMCID: PMC3565322.

Liu J, van Beusekom H, Bu XL, Chen G, Henrique Rosado de Castro P, Chen X, Chen X, Clarkson AN, Farr TD, Fu Y, Jia J, Jolkkonen J, Kim WS, Korhonen P, Li S, Liang Y, Liu GH, Liu G, Liu YH, Malm T, Mao X, Oliveira JM, Modo MM, Ramos-Cabrer P, Ruscher K, Song W, Wang J, Wang X, Wang Y, Wu H, Xiong L, Yang Y, Ye K, Yu JT, Zhou XF, Zille M, Masters CL, Walczak P, Boltze J, Ji X, Wang YJ. Preserving cognitive function in patients with Alzheimer's disease: The Alzheimer's disease neuroprotection research initiative (ADNRI). Neuroprotection. 2023 Dec;1(2):84-98. doi: 10.1002/nep3.23. Epub 2023 Sep 21. PMID: 38223913; PMCID: PMC10783281.

Liu RM. Aging, Cellular Senescence, and Alzheimer's Disease. Int J Mol Sci. 2022 Feb 11;23(4):1989. doi: 10.3390/ijms23041989. PMID: 35216123; PMCID: PMC8874507.

Loy CT, Schofield PR, Turner AM, Kwok JB. Genetics of dementia. Lancet. 2014 Mar 1;383(9919):828-40. doi: 10.1016/S0140-6736(13)60630-3. Epub 2013 Aug 6. PMID: 23927914.

Mandolesi L, Polverino A, Montuori S, Foti F, Ferraioli G, Sorrentino P, Sorrentino G. Effects of Physical Exercise on Cognitive Functioning and Wellbeing: Biological and Psychological Benefits. Front Psychol. 2018 Apr 27;9:509. doi: 10.3389/fpsyg.2018.00509. PMID: 29755380; PMCID: PMC5934999.

Mormino EC, Papp KV. Amyloid Accumulation and Cognitive Decline in Clinically Normal Older Individuals: Implications for Aging and Early Alzheimer's Disease. J Alzheimers Dis. 2018;64(s1):S633-S646. doi: 10.3233/JAD-179928. PMID: 29782318; PMCID: PMC6387885.

Mosconi, L., Berti, V., Dyke, J. et al. Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. Sci Rep 11, 10867 (2021). https://doi.org/10.1038/s41598-021-90084-y

National Institute on Aging. “What Do We Know about Diet and Prevention of Alzheimer’s Disease?” National Institute on Aging, 20 Nov. 2023, www.nia.nih.gov/health/alzheimers-and-dementia/what-do-we-know-about-diet-and-prevention-alzheimers-disease.

Ng TKS, Coughlan C, Heyn PC, Tagawa A, Carollo JJ, Kua EH, Mahendran R. Increased plasma brain-derived neurotrophic factor (BDNF) as a potential biomarker for and compensatory mechanism in mild cognitive impairment: a case-control study. Aging (Albany NY). 2021 Oct 15;13(19):22666-22689. doi: 10.18632/aging.203598. Epub 2021 Oct 15. PMID: 34607976; PMCID: PMC8544315.

Nikolac Perkovic M, Pivac N. Genetic Markers of Alzheimer's Disease. Adv Exp Med Biol. 2019;1192:27-52. doi: 10.1007/978-981-32-9721-0_3. PMID: 31705489.

Orgeta V, Mukadam N, Sommerlad A, Livingston G. The Lancet Commission on Dementia Prevention, Intervention, and Care: a call for action. Ir J Psychol Med. 2019 Jun;36(2):85-88. doi: 10.1017/ipm.2018.4. PMID: 31187723.

Ornish D, Madison C, Kivipelto M, Kemp C, McCulloch CE, Galasko D, Artz J, Rentz D, Lin J, Norman K, Ornish A, Tranter S, DeLamarter N, Wingers N, Richling C, Kaddurah-Daouk R, Knight R, McDonald D, Patel L, Verdin E, E Tanzi R, Arnold SE. Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial. Alzheimers Res Ther. 2024 Jun 7;16(1):122. doi: 10.1186/s13195-024-01482-z. PMID: 38849944; PMCID: PMC11157928.

Pérez-Grijalba V, Romero J, Pesini P, Sarasa L, Monleón I, San-José I, Arbizu J, Martínez-Lage P, Munuera J, Ruiz A, Tárraga L, Boada M, Sarasa M. Plasma Aβ42/40 Ratio Detects Early Stages of Alzheimer's Disease and Correlates with CSF and Neuroimaging Biomarkers in the AB255 Study. J Prev Alzheimers Dis. 2019;6(1):34-41. doi: 10.14283/jpad.2018.41. PMID: 30569084.

Pan FF, Huang Q, Wang Y, Wang YF, Guan YH, Xie F, Guo QH. Non-linear Character of Plasma Amyloid Beta Over the Course of Cognitive Decline in Alzheimer's Continuum. Front Aging Neurosci. 2022 Mar 23;14:832700. doi: 10.3389/fnagi.2022.832700. PMID: 35401142; PMCID: PMC8984285.

Poon CH, Wang Y, Fung ML, Zhang C, Lim LW. Rodent Models of Amyloid-Beta Feature of Alzheimer's Disease: Development and Potential Treatment Implications. Aging Dis. 2020 Oct 1;11(5):1235-1259. doi: 10.14336/AD.2019.1026. PMID: 33014535; PMCID: PMC7505263.

Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta Mol Basis Dis. 2017 May;1863(5):1037-1045. doi: 10.1016/j.bbadis.2016.04.017. Epub 2016 May 6. PMID: 27156888; PMCID: PMC5344771.

Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. Trends Mol Med. 2008 Feb;14(2):45-53. doi: 10.1016/j.molmed.2007.12.002. Epub 2008 Jan 22. PMID: 18218341; PMCID: PMC3107703.

Ren Y, Savadlou A, Park S, Siska P, Epp JR, Sargin D. The impact of loneliness and social isolation on the development of cognitive decline and Alzheimer's Disease. Front Neuroendocrinol. 2023 Apr;69:101061. doi: 10.1016/j.yfrne.2023.101061. Epub 2023 Feb 8. PMID: 36758770.

Ruegsegger GN, Booth FW. Health Benefits of Exercise. Cold Spring Harb Perspect Med. 2018 Jul 2;8(7):a029694. doi: 10.1101/cshperspect.a029694. PMID: 28507196; PMCID: PMC6027933.

Samitz, G., Egger, M., Zwahlen, M. Domains of physical activity and all-cause mortality: systematic review and dose–response meta-analysis of cohort studies, International Journal of Epidemiology, Volume 40, Issue 5, October 2011, Pages 1382–1400, https://doi.org/10.1093/ije/dyr112

Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM. Alzheimer's disease. Lancet. 2021 Apr 24;397(10284):1577-1590. doi: 10.1016/S0140-6736(20)32205-4. Epub 2021 Mar 2. PMID: 33667416; PMCID: PMC8354300.

Sobol NA, Dall CH, Høgh P, Hoffmann K, Frederiksen KS, Vogel A, Siersma V, Waldemar G, Hasselbalch SG, Beyer N. Change in Fitness and the Relation to Change in Cognition and Neuropsychiatric Symptoms After Aerobic Exercise in Patients with Mild Alzheimer's Disease. J Alzheimers Dis. 2018;65(1):137-145. doi: 10.3233/JAD-180253. PMID: 30040719; PMCID: PMC6087450.

Stefaniak O, Dobrzyńska M, Drzymała-Czyż S, Przysławski J. Diet in the Prevention of Alzheimer's Disease: Current Knowledge and Future Research Requirements. Nutrients. 2022 Oct 30;14(21):4564. doi: 10.3390/nu14214564. PMID: 36364826; PMCID: PMC9656789.

Stevens DA, Workman CI, Kuwabara H, Butters MA, Savonenko A, Nassery N, Gould N, Kraut M, Joo JH, Kilgore J, Kamath V, Holt DP, Dannals RF, Nandi A, Onyike CU, Smith GS. Regional amyloid correlates of cognitive performance in ageing and mild cognitive impairment. Brain Commun. 2022 Feb 7;4(1):fcac016. doi: 10.1093/braincomms/fcac016. PMID: 35233522; PMCID: PMC8882008.

Struble RG, Ala T, Patrylo PR, Brewer GJ, Yan XX. Is brain amyloid production a cause or a result of dementia of the Alzheimer's type? J Alzheimers Dis. 2010;22(2):393-9. doi: 10.3233/JAD-2010-100846. PMID: 20847431; PMCID: PMC3079347.

Verdelho A, Correia M, Ferro JM, Madureira S, Vilela P, Rodrigues M, Borges M, Oliveira V, Santos AC, Gonçalves-Pereira M, Santa-Clara H. Physical Activity Self-Report Is Not Reliable Among Subjects with Mild Vascular Cognitive Impairment: The AFIVASC Study. J Alzheimers Dis. 2022;87(1):405-414. doi: 10.3233/JAD-215381. PMID: 35275531.

Wan, Changjian, et al. “Long-Term Voluntary Running Improves Cognitive Ability in Developing Mice by Modulating the Cholinergic System, Antioxidant Ability, and BDNF/PI3K/Akt/CREB Pathway.” Neuroscience Letters, vol. 836, 1 July 2024, pp. 137872–137872, https://doi.org/10.1016/j.neulet.2024.137872.

Wang X, Li H, Sheng Y, He B, Liu Z, Li W, Yu S, Wang J, Zhang Y, Chen J, Qin L, Meng X. The function of sphingolipids in different pathogenesis of Alzheimer's disease: A comprehensive review. Biomed Pharmacother. 2024 Feb;171:116071. doi: 10.1016/j.biopha.2023.116071. Epub 2024 Jan 6. PMID: 38183741.

Wong W. Economic burden of Alzheimer disease and managed care considerations. Am J Manag Care. 2020 Aug;26(8 Suppl):S177-S183. doi: 10.37765/ajmc.2020.88482. PMID: 32840331.

Yu DJ, Yu AP, Bernal JDK, Fong DY, Chan DKC, Cheng CP, Siu PM. Effects of exercise intensity and frequency on improving cognitive performance in middle-aged and older adults with mild cognitive impairment: A pilot randomized controlled trial on the minimum physical activity recommendation from WHO. Front Physiol. 2022 Sep 19;13:1021428. doi: 10.3389/fphys.2022.1021428. PMID: 36200056; PMCID: PMC9527311.

Yu F, Vock DM, Zhang L, Salisbury D, Nelson NW, Chow LS, Smith G, Barclay TR, Dysken M, Wyman JF. Cognitive Effects of Aerobic Exercise in Alzheimer's Disease: A Pilot Randomized Controlled Trial. J Alzheimers Dis. 2021;80(1):233-244. doi: 10.3233/JAD-201100. PMID: 33523004; PMCID: PMC8075384.

Yue X, Lu M, Lancaster T, Cao P, Honda S, Staufenbiel M, Harada N, Zhong Z, Shen Y, Li R. Brain estrogen deficiency accelerates Abeta plaque formation in an Alzheimer's disease animal model. Proc Natl Acad Sci U S A. 2005 Dec 27;102(52):19198-203. doi: 10.1073/pnas.0505203102. Epub 2005 Dec 19. PMID: 16365303; PMCID: PMC1323154.

Zhang XX, Tian Y, Wang ZT, Ma YH, Tan L, Yu JT. The Epidemiology of Alzheimer's Disease Modifiable Risk Factors and Prevention. J Prev Alzheimers Dis. 2021;8(3):313-321. doi: 10.14283/jpad.2021.15. PMID: 34101789.

2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023 Apr;19(4):1598-1695. doi: 10.1002/alz.13016. Epub 2023 Mar 14. PMID: 36918389.