Review

Diet and Exercise as Complementary Medicine for the Management of Alzheimer's Disease: A Narrative Review

Amanda N Szabo-Reed * and Mickeal N Key

Posted Date: 30 April 2025

doi: 10.20944/preprints202504.2566.v1

Keywords: Alzheimer's disease; diet; nutrition; exercise; physical activity; brain health; brain function; cognition

 doi:10.20944/preprints202504.2566.v1

Review

Diet and Exercise as Complementary Medicine for the Management of Alzheimer's Disease: A Narrative Review

Amanda Szabo-Reed [1,2,*] and Mickeal N. Key [1,3]

[1] KU Alzheimer's Disease Research Center, Fairway, KS, USA.
[2] Department of Internal Medicine, Division of Physical Activity and Weight Management, University of Kansas Medical Center, Kansas City, KS, USA
[3] Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA
* Correspondence: aszabo@kumc.edu

Abstract: Alzheimer's Disease (AD) is characterized by complex brain alterations leading to progressive cognitive decline and neuropsychiatric disturbances. This paper explores these changes and the potential of diet and exercise as modifiable lifestyle factors to mitigate AD's impact. While some dietary components (e.g., B vitamins, ketogenic diet) and physical activity, particularly aerobic exercise, show promise for improving cognitive function and managing symptoms, evidence for consistent benefits remains limited and requires further investigation. Dietary and exercise research in AD faces significant limitations, including intervention complexity, study design challenges, disease heterogeneity, and difficulties in measuring long-term effects. Addressing these limitations is crucial to fully realize the therapeutic potential of these lifestyle interventions in combating AD.

Keywords: Alzheimer's disease; diet; nutrition; exercise; physical activity; brain health; brain function; cognition

1. Introduction

Alzheimer's Disease (AD), a progressive neurodegenerative disorder, casts a growing shadow on an aging global population in terms of both personal and financial loss.[1] This paper delves into the intricate and multifaceted changes in the brain as AD advances, subsequently exploring the associated cognitive impairments and the promising role of modifiable lifestyle factors, specifically diet and exercise, in mitigating its impact. We first dissect the structural, functional, neurochemical, metabolic, and vascular alterations within the brain that are hallmarks of AD, laying the groundwork for understanding the disease's profound effects on cognition. Following this, we examine the characteristic cognitive decline observed in AD, focusing on early deficits in memory and executive functions and the progression to language and visuospatial impairments. Finally, we turn our attention to the burgeoning evidence highlighting the potential of dietary interventions and physical exercise as powerful tools in managing AD, exploring their effects on brain health, cognitive function, and underlying AD pathology. By synthesizing current research, this paper aims to provide a comprehensive overview of the interplay between brain changes, cognitive decline, and the modifiable lifestyle factors that hold promise for addressing this devastating disease.

2. Changes in The Brain and Cognition Associated with Ad

2.1. Brain Changes Associated with AD

Brain structure. AD involves brain changes like regional atrophy and enlarged ventricles.[2,3] Key hallmarks are senile plaques (beta-amyloid aggregates) and neurofibrillary tangles (tau protein aggregates), which precede neuronal death.[4] Plaques appear first in the neocortex and spread to

 doi:10.20944/preprints202504.2566.v1

other brain regions, including the allocortex, hippocampus, basal ganglia, midbrain, and cerebellum, years before clinical symptoms appear.[5] Tangles emerge later, starting in the transentorhinal region and progressing through the hippocampus and neocortex.[6] Early detection is challenging due to overlapping amyloid and tau pathologies. Advanced imaging, including Magnetic Resonance Imaging (MRI), diffusion tensor imaging, and Positron Emission Tomography (PET) scans using amyloid-specific ligands, aids in identifying micro-structural abnormalities and pathological substances, improving diagnostic capabilities.[7,8] In addition, there is also a correlation between AD neuropathological changes and cognitive impairment, suggesting the severity of cognitive impairment correlates best with the burden of neocortical neurofibrillary tangles.[9]

Synaptic and neurochemical changes. AD is a progressive and synaptic failure disease. Synaptic pathology and mitochondrial oxidative damage are early events in AD progression.[10] Loss of synapses and synaptic damage are the best correlates of cognitive deficits found in AD patients. As the disease progresses, there are significant changes at the synapse.[11] AD progression is associated with reduced spine density, impaired memory, coordination of activities, and reduced signal transmission. Synapse loss is an early event disease process due to soluble amyloid beta, phosphorylated tau accumulation, and increased production of mitochondrially generated free radicals at synapses.[12] The clinical manifestations of AD result from the impairment in these cerebral pathways, among which the basal forebrain cholinergic innervation of cortical areas is the most vulnerable. Consequently, the cholinergic receptors are dysregulated during AD progression and impairment of the cholinergic system is considered an early event in AD, compromising cognition. Additionaly, the dysregulation of receptors for other endogenous neurotransmitters has also been described in patients and different experimental and animal models.[13]

There is evidence of a loss of glutamatergic neurons in AD patients, particularly in the hippocampus's neocortex and the CA1 region. Additionally, the abnormal accumulation of amyloid-beta and tau proteins may lead to astrocytosis and microgliosis.[13] Although the dopaminergic system is not a key player in AD, the loss of dopaminergic neurons has been identified in the AD brain.[14] A recent meta-analysis linking the dopaminergic system and AD has summarized that the level of dopamine and D1 and D2 receptors are decreased in patients with AD. However, the specific role of this neurotransmitter system remains unclear in AD.[15] Overall, early synaptic failure, mitochondrial oxidative damage, and significant changes in multiple neurotransmitter systems, most notably the cholinergic and glutamatergic pathways, leading to cognitive decline are characteristics associated with AD.

Brain function. Normal cognitive function depends on the brain's ability to efficiently process and transmit information within and between specialized structural regions and functional networks. AD is characterized by the breakdown of neuronal connectivity within the brain due to structural changes (i.e., brain atrophy and neuronal dysfunction). Early alteration in brain functional connectivity may be associated with AD pathology.[16] Resting-state functional MRI has shown that as tau spreads through functional connections within the brain, lower functional connectivity to tau epicenters is associated with tau spreading through functional connections in both amyloid-beta-negative and amyloid-beta-positive participants.[17] Also, amyloid-beta-PET in tau epicenters mediated the association of tau spreading and functional connectivity to epicenters, suggesting a partial mediating effect of amyloid-beta deposition in tau epicenters on the local impact of tau spreading on functional connectivity. These findings support that tau spreading through connection is locally associated with disrupted functional connectivity between tau epicenter and non-epicenter regions independent of amyloid-beta pathology. Amyloid-beta, other co-pathologies, and the apolipoprotein E epsilon 4 (APOE4) allele can lead to tau-relative functional disconnection vulnerability.[18] Overall, AD disrupts normal cognitive function by breaking down neuronal connectivity, primarily through tau protein spread that weakens functional connections, often independently of amyloid-beta. However, amyloid-beta and other factors can exacerbate this disconnection.

 doi:10.20944/preprints202504.2566.v1

Metabolic changes. Metabolic dysfunction is an established feature of AD supported by brain glucose hypometabolism that can be observed before the development of many AD symptoms.[19] In addition, individuals with insulin resistance (i.e., type 2 diabetes mellitus, hyperlipidemia, obesity, or other metabolic disease) have an increased risk for the development of AD.[20] This association may partly be due to systemic mitochondrial dysfunction.[21] Mitochondria are essential cellular organelles responsible for the energy production necessary for neuronal function and can become impaired in AD, triggering several cellular consequences.[22] Mitochondrial dysfunction is associated with factors such as oxidative stress, disturbances in energy metabolism, failures in the mitochondrial quality control system, and dysregulation of calcium release. These abnormalities are linked to the neurodegenerative processes driving AD development and progression. Mitochondrial abnormalities are among the earliest detectable changes in AD pathology.[23] The mitochondrial cascade hypothesis suggests that mitochondrial dysfunction and Amyloid-beta pathology are interconnected, forming a vicious cycle that accelerates neurodegeneration.[24] However, this theory does not fully encompass sporadic AD, highlighting the importance of incorporating mitochondrial dysfunction into the broader understanding of the disease.[25] Mitochondrial-focused approaches represent transformative strategies to combat AD, including metabolic modulators, mitophagy enhancers, antioxidants, and advanced therapeutic techniques such as mitochondrial transplantation and gene therapy.[26–35]

Similar to insulin resistance and mitochondria, there is strong evidence for an inflammatory component of AD.[36] Extrinsic factors, such as brain trauma, diet, systemic and local infections, and the gut microbiota, impact the inflammatory element of AD.[37] Intrinsic factors, including microglial phagocytosis, blood-brain barrier function, cellular metabolism, and cell senescence, also play a central role in neuroinflammation in AD.[38] Cells such as astrocytes, oligodendrocytes, lymphocytes, and peripheral myeloid cells and even vascular cells are activated in AD and contribute to the chronic neuroinflammation that causes a leaky blood-brain barrier.[39,40] A contributing role of the dysregulation of the glymphatic system, or the movement of cerebrospinal fluid into the brain to clear metabolic waste, may also contribute to sustained neuronal inflammation.[41] Thus, like mitochondria, new therapeutic approaches based on targeting the inflammatory component of AD are currently being tested in clinical trials.

Vascular changes. As with many other brain changes associated with AD, vascular changes may potentially precede the onset of the hallmark pathophysiological and cognitive symptoms of the disease.[42] Substantial evidence indicates a strong interplay between vascular changes and amyloid pathology in AD.[43] Studies show reduced cerebral blood flow correlating with amyloid accumulation in early AD and gray matter loss in later stages. Vascular health metrics, including cerebral blood flow changes, indicate disease progression, particularly in preclinical populations.[44,45] Age-related vessel deterioration, microvascular abnormalities, and impaired cerebral blood flow, potentially due to amyloid angiopathy and stagnant capillaries, contribute to AD.[46,47] Structural vascular changes, endothelial dysfunction, blood-brain barrier disruption, and neuroinflammation play pivotal roles in neurodegenerative pathways.[47–51] Zlokovic's "two-hit" hypothesis proposes that initial vascular dysfunction (hit 1) leads to reduced cerebral blood flow and breakdown of the blood-brain barrier, impairing amyloid clearance. This increases amyloid accumulation (hit 2), further exacerbating vascular dysfunction.[52] These hits affect the neurovascular unit, including vascular smooth muscle cells, pericytes, astrocytes, and endothelial cells, contributing to dementia progression.[47,51,52] Impaired angioneurins expression further disrupts the neurovascular unit, impacting cerebral blood flow and blood-brain barrier integrity and contributing to neurodegeneration. Improved vascular health may reduce AD progression.[52–54]

2.2. Summary of Pathophysiological Brain Changes Associated with AD

Alzheimer's Disease involves multifaceted brain changes. Structural changes include regional atrophy, enlarged ventricles, and hallmark plaques/tangles that precede neuronal death. Imaging detects these abnormalities.[2] Functional changes associated with AD disruption in neuronal

 doi:10.20944/preprints202504.2566.v1

connectivity, particularly through tau protein spread, lead to functional disconnection. Amyloid-beta and other factors exacerbate this.[16,17] Neurochemical and synaptic changes result in synaptic failure, mitochondrial damage, and neurotransmitter dysfunctions (cholinergic, glutamatergic), which are early events that correlate with cognitive decline.[10] Metabolic changes, including glucose hypometabolism, insulin resistance, and mitochondrial dysfunction, contribute to AD.[21] These factors interact with amyloid and tau pathology.[13] Neuroinflammation, influenced by intrinsic and extrinsic factors, is also crucial.[39] Finally, AD is implicated in cerebrovascular dysfunction, blood-brain barrier disruption, and reduced cerebral perfusion. Vascular changes interact strongly with amyloid pathology, with reduced cerebral blood flow correlating with amyloid accumulation. The "two-hit" hypothesis highlights the interplay between vascular dysfunction and amyloid accumulation.[47,52] In conclusion, AD is a complex neurodegenerative disorder characterized by a confluence of structural, functional, neurochemical, metabolic, and vascular alterations that collectively contribute to progressive cognitive decline.

2.3. Changes in Cognition Associated with AD

Early neuropsychological investigations into AD aimed to define the cognitive profile of patients with mild dementia, revealing a consistent pattern of deficits.[55] A primary finding was a significant impairment in episodic memory, the ability to learn and retain new information.[56] This manifests in everyday challenges like remembering conversations or appointments and laboratory tasks involving learning and recalling stories, word lists, or paired associates.[57] Studies comparing AD patients to healthy older adults demonstrated this striking memory deficit.[58] Furthermore, when compared to other forms of dementia, like frontotemporal dementia or Lewy body dementia, AD patients exhibited a more pronounced difficulty in retaining information over time.[59,60]

Beyond memory, early-stage AD patients also showed substantial impairments in executive functions, which encompass abilities like coordinating multiple tasks and shifting between mental sets.[61] These deficits were observed in both individuals with mild and moderate dementia, with evidence suggesting that executive function decline often precedes language and spatial impairments.[60,62,63] Language function is also affected in AD, with semantic memory, the system for processing and storing word meanings, being particularly vulnerable. This is reflected in difficulties with category fluency, naming objects, and making similarity judgments.[64,65] While some studies have reported deficits in word priming, others have not.[65] Visuospatial function, involving spatial reasoning and visual perception, is generally preserved in very early stages, as evidenced by performance on simple copying tasks.[66,67] However, visuospatial impairments become increasingly common as the disease progresses to moderate stages.[68] It's important to note that while these cognitive changes are typical, AD can present with variations. Some individuals experience a gradual decline in spatial abilities, known as posterior cortical syndrome. In contrast, others primarily exhibit language deficits, which can be challenging to differentiate from primary progressive aphasia, a form of frontotemporal lobar degeneration. These atypical presentations highlight the heterogeneity of AD and underscore the importance of comprehensive neuropsychological assessments.[55] Perception of cognitive decline is heightened in the early stages of AD but diminishes later.[69] Overall, early neuropsychological studies of AD consistently identified core cognitive deficits, notably in episodic memory and executive functions, with language and visuospatial impairments emerging as the disease progresses. However, atypical presentations highlight the disease's variability.

2.4. Behavior, Mood, and Psychiatric Disturbances Associated with AD

AD is characterized by a spectrum of neuropsychiatric disturbances, including depression, anxiety, apathy, agitation/aggression, psychosis, and cognitive decline.[70–73] These symptoms manifest as progressive mood changes, such as increased irritability, sadness, and anhedonia. Behavioral alterations, such as agitation, wandering, and repetitive questioning, are also common. Agitation and aggression often stem from confusion, frustration, or misinterpretation of the

 doi:10.20944/preprints202504.2566.v1

environment. Depression and apathy can further accelerate cognitive decline and diminish quality of life. Notably, sleep disturbances, a common feature of AD, contribute to both cognitive and behavioral deterioration. The shared neurobiological basis of these symptoms across neurodegenerative diseases, including AD and Parkinson's Disease, suggests that similar mechanisms, particularly neurotransmitter dysregulation, underlie these mood and behavioral changes.[72]

2.5. Changes in Sleep and Sleep Deprivation Associated with AD

Sleep disorders are very common in neurodegenerative diseases, including AD, and are a key factor in the quality of life of patients and their families. Growing evidence for the role of sleep disorder in the pathophysiology of AD has resulted in the proposal of a bidirectional relationship, with disordered sleep being both a clinical feature of AD and a risk factor.[74,75] Sleep is essential for brain function, including clearing brain metabolites, conserving energy, and consolidating memory. Sleep deprivation can lead to various negative effects, such as poor concentration, emotional instability, increased pain sensitivity, and metabolic and cardiovascular diseases. Factors contributing to sleep deprivation include environmental changes, mental health issues, and lifestyle choices. Disruption of circadian rhythms, such as through shift work, can also negatively impact cognitive performance and overall health.

Sleep and circadian rhythm disturbances are common in AD patients and can appear early in the disease.[76] Sleep-wake cycles and circadian rhythms are critical in controlling Amyloid-beta levels, as sleep disorders can potentially increase them in the brain.[77] Like Amyloid-beta, tau protein levels are also influenced by sleep-wake cycles and significantly increased by sleep deprivation. Thus, tau plays a critical role in neurodegenerative lesions and cognitive decline in AD, with tau pathology possibly preceding amyloid-beta accumulation.[78] Furthermore, the relationship between tau pathology, amyloid-beta, and sleep disorders highlights the need for further research into their interconnected roles in AD progression.[79]

2.6. Changes in Appetite Associated with AD

Patients with AD sometimes suffer loss of appetite and decrease their body weight.[80,81] Some patients with vascular dementia have pseudobulbar palsy, resulting in difficulty swallowing, and have a high risk of aspiration pneumonia.[82,83] Similarly, patients with Lewy body dementia have difficulty swallowing and loss of appetite[84], while patients with frontotemporal dementia and semantic dementia increase their appetite, prefer sweet and pungent foods, and want to eat the same foods repeatedly.[85,86] However, most studies focused on specific aspects of eating disturbance, such as swallowing and appetite. Few comprehensive studies have included eating habits and food preferences in patients with AD.[87]

2.7. Summary of Changes in Brain and Cognition Associated with AD

AD is a complex neurodegenerative disorder characterized by a confluence of structural, functional, neurochemical, metabolic, and vascular alterations that collectively contribute to progressive cognitive decline.[2] Structurally, AD involves brain atrophy, enlarged ventricles, and the accumulation of amyloid plaques and tau tangles.[8] Functionally, this disrupts neuronal connectivity, primarily through tau protein spread.[2,16–18] Neurochemically, synaptic failure and neurotransmitter dysfunctions are prominent, particularly in cholinergic and glutamatergic systems. Metabolically, glucose hypometabolism, insulin resistance, and mitochondrial dysfunction play significant roles, while neuroinflammation, influenced by both intrinsic and extrinsic factors, further exacerbates the disease.[24] Vascular changes, including reduced cerebral blood flow and blood-brain barrier disruption, interact strongly with amyloid pathology, contributing to the progression of AD.[40,42,48,52,53] These pathological changes manifest in cognitive deficits, notably in episodic memory and executive functions, and are accompanied by behavioral, mood, psychiatric, sleep, and

 doi:10.20944/preprints202504.2566.v1

appetite disturbances. Early neuropsychological investigations consistently identify core cognitive deficits, while neuropsychiatric symptoms such as depression, agitation, and sleep disorders further diminish the quality of life.[2,73] Metabolic dysfunctions such as mitochondrial dysfunction and neuroinflammation are also key components of AD.[24] Changes in appetite and weight are also observed. Overall, AD involves a complex interplay of multifaceted brain changes that lead to progressive cognitive decline.[2]

3. Modifiable Risk Factors in Ad

The 2024 Lancet Commission report highlights 14 modifiable risk factors for the prevention and delay of AD, 7 of which are associated with lifestyle.[88] High low-density lipoprotein (LDL) cholesterol, hypertension, obesity, type 2 diabetes, depression, sedentary lifestyle, and excessive alcohol consumption are all strongly associated with increased AD risk and can be mitigated through diet and exercise. Each of these factors contributes to the neuropathological changes found in AD, including vascular disease, amyloid accumulation, neuroinflammation, energy dysregulation, and neurotransmitter dysfunction. For example, elevated LDL cholesterol has been linked to increased amyloid plaque formation[89], while hypertension compromises cerebral blood flow and contributes to white matter damage.[90] Obesity in midlife is associated with chronic inflammation and insulin resistance, both of which can accelerate neuronal dysfunction.[91]

Type 2 diabetes increases AD risk through mechanisms such as impaired glucose metabolism and increased oxidative stress.[92] Depression is both a potential early sign of and a contributing factor to AD, potentially due to genetics, AD-related biomarkers elevated in depression, and elevated inflammation that causes vascular damage and weakens the blood-brain barrier.[93] A sedentary lifestyle compounds many of these effects by negatively influencing glycemic control[94] and increasing risk factors such as cardiovascular disease, cognitive decline, and depression.[95] Finally, excessive alcohol consumption is connected to systemic inflammation, reduced brain volumes, and disruptions to neurotransmission.[96]

Together, these modifiable risk factors underscore the critical role that diet and regular exercise, which are the focus of this narrative review, play in supporting overall brain health.[97,98] Interventions centered on diet and physical activity not only reduce the prevalence of these conditions but also offer a robust, multi-modal strategy for lowering AD risk, improving AD symptoms, and slowing cognitive decline. Additional information related to these two adjunction and complementary therapies is detailed within.

4. Effects of Diet on Cognition and Brain Health in patients with Ad

Whereas there are a plethora of diets, foods, and natural products that have been investigated for impact on brain health in cognitively intact individuals and the prevention of AD[98], a limited number of these dietary interventions have been implemented in trials for individuals with AD. Recent reviews and meta-analyses have focused on a small subset of individual and multi-ingredient vitamins, minerals, fatty acids, and other natural products explored within the context of placebo-controlled, randomized controlled trials (RCT) that have had positive, albeit mixed effects.[99,100] Conversely, only a few holistic dietary approaches have either changed the dietary pattern in part or completely in trials for individuals with AD.[101–104]

Vitamins & Minerals. Appropriate vitamin and mineral intake is vital for the optimal functioning of the body and the brain. A deficiency in B complex vitamins, for example, can cause elevated levels of homocysteine. Homocysteine has been established as a strong, independent risk factor for Alzheimer's and related dementias.[105] This is due in large part to its role in cardiovascular disease and AD pathology.[106] Accordingly, there has been extensive research examining the effect of B vitamin supplementation in patients with AD. A 2022 systematic review and meta-analysis examined the impact of B vitamin supplementation on the rate of cognitive decline in 6,155 participants across 14 RCTs. The analysis revealed that not only was supplementation associated with

 doi:10.20944/preprints202504.2566.v1

a benefit to cognition versus placebo, but in studies where the placebo group showed cognitive decline, vitamin B supplementation slowed cognitive decline for the intervention group.[107] Vitamin D deficiency is also considered a risk factor for dementia. Along with correcting the deficiency, vitamin D supplementation is also suspected to provide neuroprotection via its antioxidant and anti-inflammatory properties. While cohort studies have found a reduced incidence of AD in individuals taking Vitamin D supplements[108], intervention studies in patients with AD are mixed, with the majority of studies finding no benefit of supplementation on cognition.[109–111] Those studies that have found a benefit often have multiple limitations that make interpretation of results difficult.[112]

Aside from the elevated systemic inflammation associated with age[113], there are many metabolic and cardiovascular risk factors associated with AD that contribute to the inflammatory status of an individual. Therefore, an emphasis has been placed on investigating natural products known to have anti-inflammatory or antioxidant properties. There are several vitamins and minerals with anti-inflamatory and/or antioxidant and have been investigated in RCTs for their ability to reduce AD symptoms and/or slow disease progression. The most promising of these natural products include thiamine, vitamin E, vitamin C, and selenium. A 2022 systematic review concluded that although there was insufficient evidence for the use of vitamin E and C in improving cognition in individuals with AD, thiamine, both alone and with folic acid had a positive impact on cognition.[109] The literature also supports that supplementation with selenium improves cognition in patients with AD.[114]

Omega 3-Fatty Acids. There is a vast literature on the benefits of omega-3 fatty acids in the support of healthy brain aging, due to their role in cell membrane structure, anti-inflammatory activity, and in supporting a healthy vascular system.[115] In observational studies, omega-3 fatty acids are associated with improved cognition[116], but this has not been replicated widely in interventions with patients diagnosed with Alzheimer's disease. In a 2020 systematic review and meta-analysis, 38 moderate-quality RCTs provided evidence that omega-3 fatty acid supplementation (with intervention duration at an average of 20.5 months) had little to no effect on new neurocognitive outcomes or cognitive impairment.[117] A 2022 RCT with a sample size of 163 AD patients and an intervention duration of 24 months found that while omega-3 supplementation did not reduce cognitive, functional, or depressive symptom outcomes, there was improvement in the intervention group on sub-items of the ADAS-cog associated with language ability and visuospatial skills.[118]

Other Natural Products. There are several other plant-derived compounds that have been evaluated for their ability to improve AD symptoms or slow cognitive decline, but few have been implemented in human clinical trials, let alone trials involving AD patients. Curcumin, a polyphenol extracted from tumeric, and the phytobioactive compounds in ginseng, are both considered anti-inflammatory and antioxidant and have been investigated for their neuroprotective benefits in AD populations.[119,120] The benefits, however, have not been verified, as these studies are limited due to methodological issues, and conclusive evidence has yet to be provided.

Multi-ingredient Intervention. Researchers have also considered how multiple vitamins, minerals, and natural products might work synergistically to improve symptoms and disease progression in AD. Although not conducted in AD patients, there is evidence that daily multivitamin-mineral supplementation is effective in improving both general cognition and episodic memory in older adults over a 2-year period.[121] Souvenaid, a supplemental drink designed to improve brain function and cognition, has been investigated for its effectiveness in patients with AD, but a meta-analysis of four studies concluded that there was no evidence to support its ability to slow the progression of AD and mixed evidence of its impact on cognition.[122]

Dietary Interventions. Considering a more ecological approach, researchers have explored how whole diets or dietary patterns might impact symptoms and disease progression in AD. The ketogenic diet has been studied extensively for its ability to shift the body into ketosis, where the use of ketones as a primary energy source has been found to improve brain energy metabolism and

 doi:10.20944/preprints202504.2566.v1

cognition[103]Ketones have also been found to positively affected brain insulin resistance, mitochondrial function, and neurotransmission.[123] In two recent reviews examining a total of 18 RCTs, a ketogenic diet adherence was associated with improved general cognition, mental state, and episodic memory in patients with MCI and AD.[104] Ketones can also be provided by supplementing medium-chain triglycerides (MCT oil). A recent review found that while some studies have reported improvements in brain energy metabolism, more studies are needed to assess their effects on cognition.[124]

Time-restricted eating, such as intermittent fasting, has been investigated for its positive impact on several AD risk factors like cerebrovascular disease and inflammation.[125] This is largely due to its ability to improve insulin sensitivity, which in turn also reduces the risk of type 2 diabetes and obesity. Intermittent fasting also helps the body produce ketones, which is important for minimizing the effect of amyloid beta and improving cognition. Intermittent fasting also improves mitochondrial health and reduce inflammation and oxidative stress, both of which are important for suppring cardiovascular health.**[125]** Although not in AD**,** a small, yet promising 3-year study of 99 patients with mild cognitive impairment, intermittent fasting improved cognitive function, insulin sensitivity, and inflammation.[126]

While not as widely studied in AD patients, the Healthy Diet Index and Mediterranean Diet were examined in the multi-modal lifestyle intervention MIND-AD$_{mini}$. The study included an intervention group that received diet education and a supplemental drink and found a reduced likelihood of declining CDR-SOB scores (Clinical Dementia Rating- Sum of Boxes), but not global CDR scores.[101]

Summary of the Effects of Diet on AD

Research exploring the impact of dietary interventions on AD reveals a disparity between the plethora of investigated options for cognitively healthy individuals and the limited number tested in those with established AD. Reviews and meta-analyses focusing on specific vitamins, minerals, fatty acids, and other natural products in placebo-controlled trials have yielded mixed results.[107,109,112,117,118] Similarly, only a few holistic dietary approaches have been examined. Regarding specific nutrients, B vitamin supplementation appears promising for slowing cognitive decline in AD patients,[107] while the role of vitamin D remains inconclusive despite observational links.[112] Thiamine and selenium have shown some cognitive benefits, whereas vitamins E and C lack sufficient evidence.[109,114] Omega-3 fatty acids, beneficial for general brain health, have demonstrated little overall cognitive improvement in AD, though some language and visuospatial benefits were noted in one study.[117] Other natural products like curcumin[119] and ginseng[120] require more rigorous investigation. Multi-ingredient interventions show some promise in older adults without AD, but specific formulations for AD, like Souvenaid, lack strong evidence.[122] Shifting focus to broader dietary patterns, the ketogenic diet has shown potential for improving cognition and memory in individuals with MCI and AD.[104] Time-restricted eating has also demonstrated cognitive benefits in MCI.[125] While the Healthy Diet Index and Mediterranean Diet were explored in a multimodal study, significant cognitive benefits in AD were not consistently observed.[101] Overall, while certain dietary components and patterns offer potential, more robust research is needed to establish effective dietary interventions for individuals living with AD.

5. Effects of Exercise on Brain Health and Cognition in Patients with Ad

Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. Exercise, on the other hand, is a subset of physical activity that is planned, structured, and repetitive, intending to improve or maintain physical fitness.[127] Regular endurance and resistance exercise training decreases age-related morbidity and mortality, improves risk factors for chronic disease, and helps maintain independent functioning.[128–130] Physical activity, including exercise, has been recognized as a means of preventing and managing AD.

 doi:10.20944/preprints202504.2566.v1

5.1. Effects of Exercise on AD

Prevention. Growing evidence shows that physical activity and exercise play a significant role in preventing AD.[131] Animal studies indicate that exercise fosters brain health by stimulating neurogenesis[132], enhancing neuronal survival[133], boosting synaptic plasticity[134], and promoting vascularization.[135,136] In healthy older adults, exercise correlates with reduced cerebral amyloid deposition and modulates vascular dementia risk factors.[137–139] Specifically, it decreases inflammatory markers and elevates neuroprotective proteins such as BDNF while also improving glucose metabolism.[140–142] Endurance exercise, widely studied for its cognitive benefits, exhibits positive associations with cognitive function and a reduction in age-related brain volume decline in observational and some randomized trials.[143–145] Resistance training, although less researched, has demonstrated improvements in executive function, memory, and global cognition and offers unique benefits to muscle and bone health.[146–151] Combined aerobic and resistance training appears to be optimal for insulin resistance[152–156] and physical function [152,153,155], although there is a lack of direct comparison studies on cognition.[157] Emerging research highlights the potential cognitive benefits of alternative exercises such as yoga[158,159], Tai Chi[160,161], and high-intensity interval training (HIIT)[162–167], demonstrating improvements in memory, executive function, and brain structure. However, limitations exist, including the absence of a systematic review, the lack of studies testing current public health exercise recommendations, and the unclear role of alternative exercises in conjunction with traditional forms. Further research is needed to fully understand the independent and combined impacts of various exercise modalities on cognitive function and brain health in older adults.

In addition to prevention studies, low levels of physical activity is a risk factor associated with AD at a later age.[168] Findings from population-based cohort studies of older adults who exercise suggest that they are more likely to maintain their cognitive function as they age.[169] The English Longitudinal Study of Ageing (ELSA) suggests that inactive, low, and moderate-to-high active groups had a cumulative incidence of AD of 4.8% (95% CI: 4.4 to 5.4), 0.9% (95% CI:0.8 to 1.1), and 0.2% (95% CI: 0.1 to 0.5), respectively. In adjusted analyses, participants in the low and moderate-to-high active groups had, respectively, 60% and 78% lower risk of developing AD than the inactive group. Survival analyses revealed significant between-group differences in the cumulative incidence of dementia over 15 years based on the physical activity categories. This study suggests that even low levels of physical activity have beneficial effects in preventing AD.[169] A recent meta-analysis revealed a decreased risk of AD (0.86, 95% CI 0.80 to 0.93, n = 128, 261) is associated with physical activity participation. Neither baseline age, follow-up length, nor study quality significantly moderated the associations. Dose-response meta-analyses revealed significant linear, spline, and quadratic trends within estimates for all-cause dementia incidence but only a significant spline trend for AD. This suggests that physical activity is associated with a lower incidence of AD, even in longer follow-ups, supporting physical activity as a modifiable protective lifestyle factor, even after accounting for the effects of reverse causation.[170]

Disease management. A recent meta-analysis of eight cohort and case-control studies examined whether physical exercise could improve, or at least maintain, the physical and functional capacity, cognitive performance, neuropsychiatric symptoms, and quality of life of patients with AD.[171] Six of the eight studies assessed physical function, and five of those reported positive effects of exercise on physical function tasks post-intervention.[172–176] One intervention even noted that, one year post-intervention, all groups showed deterioration. However, this was greater for the control group ($p = .003$) than for the physical exercise group.[172] This suggests a protective effect could, therefore, be attributed to physical exercise. Five of the eight studies assessed cognitive function, and all five reported a positive impact of exercise on cognitive function following the intervention.[173,175–178] Similarly, two of eight studies examined neuropsychiatric symptoms, and both reported positive effects of exercise post-intervention.[176,177] In addition, two of the eight studies examined the quality of life and reported a positive impact of exercise in one, while the other study reported no difference.[173,177] Similarly, a meta-analysis of 16 trials revealed that physical activity (PA)

 doi:10.20944/preprints202504.2566.v1

significantly improved global cognition in AD (SMD = 0.41, $p < 0.01$).[179] Aerobic exercise (SMD = 0.60) was more effective than mixed exercises (SMD = 0.24). Shorter exercise sessions (<45 minutes, SMD=0.66) yielded greater cognitive benefits than longer ones (SMD = 0.27). Moderate to severe AD stages showed larger improvements (SMD = 0.75) compared to mild to moderate stages (SMD = 0.20). The time of the exercise session had a significant impact on cognition ($\beta = -0.0105$, $p = 0.03$). Nine studies within the meta-analysis indicated that PA also significantly improved Activities of Daily Living (ADL) in AD patients (SMD = 0.56, $p < 0.001$). Other factors, such as exercise duration and frequency, did not show significant differences in cognitive outcomes. Together, these studies suggest that participation in physical activity is beneficial for cognitive function, physical outcomes, and overall disease management in individuals with AD.

5.2. Mechanism of Action for the Effect of Exercise on AD Pathology

Brain structure. Studies investigating the relationship between physical activity and brain volume in individuals with AD have yielded mixed results, suggesting a complex interplay between factors. Using tensor-based morphometry imaging, Boyle et al. found that physical activity has a protective effect on brain volume in relation to AD in individuals enrolled in the Cardiovascular Health Study.[180] Higher physical activity levels were correlated with increased overall brain and parietal lobe volume and reduced ventricular dilation, factors often compromised in AD. Conversely, a higher Body Mass Index (BMI) was associated with reduced brain volume, particularly in the frontal, temporal, parietal, and occipital lobes, including the orbitofrontal cortex and anterior cingulate gyrus. Overlapping brain regions, including the orbitofrontal cortex, posterior cingulate gyrus, and posterior hippocampus, are affected by both physical activity and BMI. AD and Mild Cognitive Impairment (MCI) are associated with decreased brain volume, particularly in the frontal lobe and ventricular dilation. While physical activity did not show a direct interaction with AD/MCI diagnosis, BMI did, demonstrating that higher BMI and AD/MCI are associated with reduced brain volume, predominantly in the frontal lobe.[180]. Cross-sectional research also shows a significant positive correlation between cardiorespiratory fitness and parietal and medial temporal volume in AD patients. In contrast, non-demented patients did not exhibit a significant relationship between brain volume and cardiorespiratory fitness globally. In early-stage AD, cardiorespiratory fitness was also associated with regional brain volumes in the medial temporal and parietal cortices, suggesting that maintaining cardiorespiratory fitness may modify AD-related brain atrophy.[181] Very few RCTs have been conducted to evaluate the impact of exercise on brain structure in patients with AD. A recent meta-analysis[182] found three studies evaluating the influence of a physical activity intervention on regional brain volume. Morris and colleagues[183] found that individuals with probable AD enrolled in a 26-week RCT comparing the effects of 150 minutes of aerobic exercise per week versus non-aerobic stretching showed that a change in cardiorespiratory fitness was positively correlated with changes in memory performance and bilateral hippocampal volume. Vidoni et al[184]. on the other hand, it was found that 52 weeks of aerobic exercise also significantly improved cardiorespiratory fitness (11% vs. 1% in the control group); however, there were no differences in change measures of amyloid, brain volume, or cognitive performance compared to control. Similarly, Frederiksen et al. did not find evidence to support the effect of a 16-week aerobic exercise intervention on brain volume changes in patients with AD. Overall, the effect of physical activity on brain volume and structural changes in individuals with AD remains inconclusive.

Brain function. Few studies have investigated the impact of physical activity on brain function in patients with AD. Several studies have investigated the relationship between physical activity level and brain function in individuals at risk for AD, specifically in those carrying the APOE4 allele. The findings suggest that higher cardiorespiratory fitness or reported physical activity is associated with greater brain activity when compared to those with lower cardiorespiratory fitness or physical activity levels.[185,186] In addition, brain imaging (functional MRI) has been used to understand and predict cognitive decline, particularly in relation to AD risk and physical activity. Early cognitive decline can lead to increased brain activity, as measured by the BOLD signal, during episodic

 doi:10.20944/preprints202504.2566.v1

memory tasks, making it challenging to interpret fMRI results accurately.[187] Paradoxically, higher brain activation during these tasks can predict future cognitive decline. Semantic memory, which encompasses general knowledge, is less affected by normal aging but is more susceptible to early AD. Lower brain activation during semantic tasks may indicate a higher risk of cognitive decline. Semantic memory areas overlap with brain regions affected by AD, making it a potentially more reliable marker than episodic memory. Studies show that higher PA is linked to greater brain activation during the famous name task, particularly in individuals with APOE4.[188] This suggests that PA may provide neuroprotection and delay cognitive decline, especially in those at genetic risk. In addition, Woodard et al.[188] demonstrated that even among individuals with the genetic marker for increased Alzheimer's risk, high levels of physical activity resulted in brain scans that resembled those of individuals with low genetic risk. Therefore, while the mechanisms are complex and require further study, evidence suggests that physical activity may modulate brain function in individuals at risk for AD, potentially offering a protective effect, particularly in those with genetic predispositions, such as the APOE4 allele.

Amyloid-β and Tau. Exercise may help regulate the production and clearance of amyloid beta and tau, which are previously discussed hallmarks of AD. A recent systematic review and meta-analysis examining the anti-amyloid effect of regular exercise in animal models suggests that regular aerobic exercise is associated with a decrease in amyloid beta.[189] This reduction of amyloid beta was associated with a decrease in the amyloidogenic pathway and an increase in the non-amyloidogenic pathway. Hence, regular physical exercise has been shown to exhibit an anti-amyloid effect in experimental models of AD, leading to positive alterations in amyloid precursor protein processing through various signaling pathways.[189,190] Similarly, in animal models of tauopathy, exercise has been shown to reduce brain tau phosphorylation.[191,192] However, models are limited.

Research exploring the impact of exercise on Amyloid Beta in humans is still limited. A meta-analysis of eight studies found no overall effect favoring exercise interventions was observed for both negative (SMD95% = 0,286 [-0,131; 0,704]; $p = 0,179$) or positive AD status (SMD95%=0,110 [-0,155; 0,375]; $p = 0,416$).[193] The absence of an overall effect favoring exercise interventions was also found for Amyloid beta peptides (SMD95% = 0,226 [-0,028; 0,480]; $p = 0,081$) and soluble amyloid precursor protein components (SMD95% = -0,038 50 [-0,472; 0,396]; $p = 0,863$) levels. This suggests that exercise interventions do not improve Amyloid beta-related pathology in both healthy individuals and individuals with dementia (SMD95% = 0,157 [-0,059; 0,373]; $p = 0,155$), indicating that the beneficial effects of exercise for AD reported in previous studies are related to other mechanistic effects rather than direct amyloid effects. Similarly, the findings for the effect of exercise on Tau in human patients have also yielded no significant effects, per a meta-analysis including four studies.[194,195]

Neurotrophic Factors. Physical activity stimulates the release of brain-derived neurotrophic factor (BDNF), promoting neuronal growth and survival in mouse models[196,197] and some non-demented older adults.[198,199] However, a meta-analysis by Huang and colleagues included eight studies (7 RCTs and 1 non-RCT) that measured BDNF from blood samples. The results revealed no significant effect on exercise's ability to change BDNF levels in individuals with AD.[194]

Inflammation. Exercise can reduce inflammation in the brain, which is linked to AD progression.[200] A meta-analysis by Huang and colleagues included nine studies (7 RCTs and 2 non-RCTs) evaluated the effects of exercise on inflammatory factors, with eight including Tumor necrosis factor (TNF-α) and six including Interleukin-6 (IL-6).[194] For TNF-α, the meta-analysis indicated an insignificant effect, however, subgroup analyses revealed aerobic exercise had a significant decreasing impact on the level of TNF-α (SMD = −1.21; 95%CI: −2.29, −0.14). The result of the meta-analysis for IL-6 showed that exercise interventions could significantly decrease the level of IL-6, with a pooled SMD of −0.45 (95% CI: −0.72, −0.18) and low heterogeneity (I2 = 17.0%). No significant differences were found for other inflammatory factors including Interleukin-10 or C-reative protein.

Metabolism. Participation is physical activity and exercise is assocaiated with improved metabolic indicators and insulin sensitivity[201] and Mitochondrial function in older adults.[202] Twelve studies (10 RCTs and 2 non-RCTs) measured the effects of exercise interventions on metabolic

 doi:10.20944/preprints202504.2566.v1

indicators, such as insulin, cholesterol, and cortisol.[194] Eight of them included cholesterol markers, such as high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride. The meta-analysis for LDL revealed a significant effect induced by exercise, with a pooled SMD of −0.26 (95% CI: −0.50, −0.01; I2 = 0.0%). In contrast, no significant effects were found on HDL, triglycerides, and total cholesterol. In addition, one study evaluated the effects of exercise interventions on cortisol secretion.[203] Considering the diurnal rhythm of cortisol, Ho et al.[203] collected the salivary samples at five-time points and found that the exercise groups showed a more dynamic diurnal pattern of cortisol secretion compared with the control groups. Current research also shows that exercise promotes mitochondria communication with other organelles in AD neurons, however, the therapeutic potential of exercise is not conclusive.[204,205]

Vascular changes. Pre-clinical and clinical studies suggest that exercise may enhance cerebral blood flow and vascular function, thereby promoting vascular repair in the aging and AD- affected brain.[206] Additionally, gender and APOE status may moderate the cerebrovascular response to exercise in healthy older adults[207] as well as amyloid burden.[208] Unfortunately, limited studies exploring the impact of exercise on cerebrovascular function in patients with AD are available. One small study in 39 patients with AD show that individuals who completed moderate to high-intensity aerobic activity and strength training, increased flow-medicated dilation (+ 3.725%, $p < 0.001$), passive leg movement (+ 99.056 ml/min, $p = 0.004$), the area under the curve (+ 37.359AU, $p = 0.037$) and vascular endothelial growth factor (+ 8.825 pg/ml, $p = 0.004$) after 6 months. In the control group, no difference between pre-and post-treatment was found for any variable. Additionally, an increase in blood flow and shear rate was observed during exercise ($p < 0.05$ for both), but not during the control treatment.[209]

Improved Cognitive Function. Exercise in healthy older adults has been shown to affect cognitive function positively in observational and some randomized trials.[143–151] Regular physical activity can enhance memory, attention, and executive function in individuals with early-stage AD.[210] A recent review by Demurtas et al.[210] found that in patients with AD, physical activity/exercise effectively improved global cognition (SMD = 1.10; 95% CI 0.65–1.64). Thus, this review suggests that physical activity/exercise positively affects several cognitive aspects of AD, but additional RCTs are still needed to confirm this relationship.[210] In addition, Liang et al.[211], in a systematic review of 21 studies also reports improvements in the mini-mental state exam (MMSE) and Alzheimer's Disease Assessment Sclae- Cognition (ADAS-cog) with participation in exercise (MMSE: SMD = 0.46, 95% CI = 0.29 ~ 0.63, $p < 0.01$; ADAS-cog: SMD = −0.23, 95% CI = −0.4 ~−0.06, $p < 0.01$). Regular exercise appears to positively impact various cognitive functions, including memory, attention, and executive function, in healthy older adults and individuals with AD, as indicated by improved scores on cognitive assessments. However, further research is needed to solidify these findings.

Behavioral symptom management. Physical activity is a favorable non-pharmacological means for attenuating the neuropsychiatric symptoms of elderly people with AD.[210] Liang et al.[211] showed that participation in exercise is associated with improvements in neuropsychological symptoms (Neuropsychiatric Inventory Questionnaire, NPI: SMD = −0.3, 95% CI = −0.52 ~−0.08, $p < 0.01$). Similarly, a review of 13 studies by McCartney et al.[212] suggests that exercise is effective in reducing agitation and studies with higher adherence to exercise demonstrated more positive effects on agitation and behaviours that challenge. Additionally, in healthy older adults, exercise has a positive impact on the prevention of the development of circadian rhythm disturbances and stimulates the resynchronization of circadian rhythms. This overall helps to promote restful sleep.[79,213,214] Previous RCTs in older adults show that older adults can successfully improve their sleep quality through exercise.[215] Moderate physical activity has also been found to improve sleep in individuals with AD.[216] Physical activity offers a beneficial non-drug approach for reducing neuropsychiatric symptoms like agitation and improving sleep quality by regulating circadian rhythms in elderly individuals, including those with AD.

 doi:10.20944/preprints202504.2566.v1

5.3. Influence of Exercise Type on AD

Aerobic Exercise, including activities like walking, jogging, swimming, and cycling, have shown promising results in mitigating the effects of AD. A recent meta-analysis of RCTs by Zhang et al.[217] included 15 RCTs. The authors found a significant effect of aerobic exercise on increasing MMSE score in AD patients [weighted mean difference (WMD), 1.50 (95% CI, 0.55 to 2.45), p = 0.002]. Subgroup analyses showed that interventions conducted 30 min per session [WMD, 2.52 (95% CI, 0.84 to 4.20), p = 0.003], less than 150 min per week [WMD, 2.10 (95% CI, 0.84 to 3.37), p = 0.001], and up to three times per week [WMD, 1.68 (95% CI, 0.46 to 2.89), p = 0.007] increased MMSE score significantly. In addition, a worse baseline cognitive status was associated with greater improvement in MMSE scores. Unfortunately, aerobic exercise in humans has not been shown to reduce amyloid accumulation in cognitively normal older adults at risk for AD[44] or individuals with AD.[193] Inter-individual differences in aerobic fitness and cognitive responses to aerobic exercise in older adults with mild-to-moderate dementia due to AD.[218] However, additional research is needed to determine the impact of aerobic exercise on AD prevention and the reduction of pathology and associated symptoms.

Strength training, also known as resistance exercise, is characterized by contractions of specific muscles against external resistance. It has emerged as an essential strategy to improve muscle mass and strength, bone density, overall body composition, as well as functional capacity and balance, thereby attenuating or even reversing sarcopenia and reducing difficulties in task performance.[219,220] It may improve cognitive function and overall physical health, which is essential for maintaining independence in individuals with AD. Overall, fewer RCTs utilizing resistance training have been completed compared to those utilizing aerobic exercise. Vital et al.[221] found in a sample of 34 older adults with AD that there was no significant difference associated with cognition in patients with AD when comparing resistance training and social gathering group activities. However, this is a single study. Additionally, although reviews[222] suggest that resistance training may prevent or ameliorate AD, this relationship has not been fully characterized; therefore, additional research is warranted.

Mind-body exercises, such as Yoga and tai chi, can enhance balance, coordination, and cognitive function in older adults.[223] Unfortunately, no research is currently available on the association between AD symptoms and mind-body exercise. In individuals with MCI, yogic practices can have positive effects on sleep, stress levels, BDNF, serotonin levels, and brain volume. As both *in vitro* and/or *in vivo* studies have shown that sleep, stress levels, and serotonin directly act on amyloid-beta, it is tempting to speculate that yoga and meditation might slow disease progression in AD patients.[224] However, given the lack of RCTs to test this hypothesis, additional research is needed.

6. Exercise and AD Summary

Regular physical activity, particularly structured exercise, is increasingly recognized for its potential in preventing and managing AD. In prevention, exercise in animal models promotes brain health through neurogenesis, neuronal survival, synaptic plasticity, and vascularization.[131,222,225] Studies in healthy older adults link exercise to reduced amyloid deposition, modulation of vascular risk factors, decreased inflammation, and increased neuroprotective proteins like BDNF, alongside improved glucose metabolism.[44,185,189,190,201,208] While endurance training shows cognitive benefits and reduced brain volume decline, resistance training improves executive function, memory, and global cognition.[44,173,176,183,217] Combined aerobic and resistance training appears optimal for metabolic and physical function, and emerging research suggests benefits from yoga, Tai Chi, and HIIT, though more systematic research is needed. Population-based studies indicate that even low physical activity levels are associated with a lower risk of developing AD.[169,226]

In managing existing AD, exercise has shown promise in improving physical and functional capacity, cognitive performance, and neuropsychiatric symptoms, although effects on quality of life are less consistent. Meta-analyses suggest that physical activity significantly improves global

 doi:10.20944/preprints202504.2566.v1

cognition and activities of daily living in AD patients, with aerobic exercise and shorter sessions potentially being more effective.[179,182,211,217,227] Mechanistically, while the impact of exercise on brain structure in AD is still under investigation with mixed results, some studies suggest a protective effect on brain volume and a correlation between cardiorespiratory fitness and brain volume in specific regions.[179,217] Exercise may also modulate brain function, particularly in individuals at genetic risk for AD.[185] While animal studies show exercise can regulate amyloid-beta and tau, human studies have not yet demonstrated a significant direct impact on these AD hallmarks.[10,44,189] However, exercise can influence neurotrophic factors (though not consistently BDNF in AD patients), reduce inflammation (especially TNF-α with aerobic exercise and IL-6), improve metabolic indicators like LDL cholesterol, enhance vascular function, and ultimately lead to improved cognitive function and behavioral symptom management in individuals with AD.[174,199,206] Different types of exercise, such as aerobic, strength training, and mind-body practices, show varying degrees of benefit, warranting further specific investigation.[217,221,222,224]

6.1. Exercise Recommendations for Individuals with AD

Strong evidence exists of a protective effect of regular exercise against AD risk. However, the dose-response association is unclear.[227] Based on current meta-analysis and systematic reviews, aerobic exercise, especially when conducted for 30 minutes per session, less than 150 minutes per week, and up to three times per week, improves cognitive function in AD patients. Additionally, a worse basal cognitive status contributed to more significant improvements in cognitive function.[217,227] Unfortunately, the evidence for other forms of exercise, including resistance training and mind-body exercises, is currently unavailable.

6.2. Diet and Exercise, the Effect of Combined Intervention on AD

Limitations of Available Research

Dietary research on AD is hampered by several inherent limitations. The complexity of nutritional interventions, involving numerous interacting components, contrasts with the simplicity of single-compound drug trials, making it challenging to pinpoint specific beneficial elements. The typically slow progression of AD necessitates lengthy and costly studies to observe meaningful effects, often plagued by difficulties in maintaining participant adherence and high dropout rates. The heterogeneity of AD, with its diverse presentations influenced by individual factors, further complicates the identification of universally effective dietary strategies. Blinding participants and researchers to dietary changes is often impractical, introducing potential bias. Accurately assessing long-term dietary intake remains a methodological challenge, relying on potentially inaccurate recall-based methods. Many current studies suffer from small sample sizes, limiting their statistical power. The timing of intervention relative to the disease stage is critical but often variable across studies. Participant-related factors, such as advanced age, co-existing health conditions, cognitive impairment affecting eating habits, and varying socioeconomic circumstances influencing access to specific foods and support, add further layers of complexity. Finally, the sensitivity of cognitive tests to detect subtle dietary-induced changes and the limited immediate responsiveness of AD biomarkers pose challenges in measuring outcomes. Overcoming these limitations through more rigorous study designs, larger and more diverse cohorts, extended intervention durations, improved assessment methods, and relevant outcome measures is essential to advance our understanding of the role of diet in addressing AD.

Similar to the research on diet, the research on the effects of exercise on brain health and cognition in the context of AD also faces several limitations. While animal studies offer promising insights into the mechanisms by which exercise might prevent AD, including promoting brain health at a cellular level and potentially regulating amyloid and tau, these findings haven't consistently translated to human studies, particularly concerning direct impacts on AD's biological hallmarks. The effects of exercise on brain structure in individuals with AD also remain unclear, with studies

 doi:10.20944/preprints202504.2566.v1

yielding mixed results. Furthermore, the influence of exercise on neurotrophic factors like BDNF in AD patients is not consistently observed. Research on alternative exercise types beyond aerobic and resistance training, such as yoga, Tai Chi, and HIIT, is still emerging and requires more systematic investigation. A lack of direct comparative studies between different exercise modalities and the need for more robust RCTs further limit the current understanding. Establishing optimal exercise parameters and consistently demonstrating improvements in quality of life for AD patients also present ongoing challenges. The complexity of interpreting brain function changes in early AD and the limited research on cerebrovascular function in this population add to the existing limitations. Finally, the potential role of mind-body exercises in managing AD symptoms warrants dedicated future research.[171]

7. Conclusion

In conclusion, this paper has illuminated the intricate cascade of structural, functional, neurochemical, metabolic, and vascular alterations that characterize the AD brain, culminating in a progressive decline in cognitive abilities, particularly episodic memory and executive functions, and often accompanied by behavioral, mood, sleep, and appetite disturbances. Furthermore, it has explored the significant role of modifiable lifestyle factors, specifically diet and exercise, in potentially mitigating the impact of this devastating disease. While research into specific dietary components and holistic dietary patterns offers some promising leads, particularly regarding B vitamins and the ketogenic diet, the evidence for consistent benefits in established AD remains limited and requires further rigorous investigation. Similarly, physical activity, especially aerobic exercise, demonstrates potential in improving cognitive function, managing neuropsychiatric symptoms, and possibly influencing underlying AD pathology. However, the precise mechanisms and optimal exercise parameters are still being elucidated. Despite the encouraging findings, both dietary and exercise research in the context of AD face considerable limitations, including the complexity of interventions, challenges in study design and adherence, the heterogeneity of the disease, and difficulties in accurately measuring long-term effects on both cognition and brain biology. Recognizing and addressing these limitations in future research endeavors is crucial to fully harness the therapeutic potential of these modifiable lifestyle factors in the ongoing fight against AD.

Funding: Fellowship support for M.N.K. was provided by the National Institute on Aging of the National Institutes of Health under award number T32AG078114. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abbreviations

Alzheimer's Disease (AD)
Magnetic Resonance Imaging (MRI)
Positron Emission Tomography (PET)
apolipoprotein E epsilon 4 (APOE4)
Low-density lipoprotein (LDL)
Randomized Controlled Trial (RCT)
Clinical Dementia Rating (CDR)
Sum of Boxes (SOB)
Brain-derived Neurotrophic Factor (BDNF)
High-intensity interval training (HIIT)

 doi:10.20944/preprints202504.2566.v1

References

1. Lynch C. World Alzheimer Report 2019: Attitudes to dementia, a global survey. *Alzheimer's & Dementia*. 2020;16(S10):e038255. doi:https://doi.org/10.1002/alz.038255
2. Ávila-Villanueva M, Marcos Dolado A, Gómez-Ramírez J, Fernández-Blázquez M. Brain Structural and Functional Changes in Cognitive Impairment Due to Alzheimer's Disease. *Front Psychol*. 2022;13:886619. doi:10.3389/fpsyg.2022.886619
3. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde". *Clin Anat*. 1995;8(6):429-31. doi:10.1002/ca.980080612
4. Thal DR, Rüb U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology*. Jun 25 2002;58(12):1791-800. doi:10.1212/wnl.58.12.1791
5. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. Aug 30 2012;367(9):795-804. doi:10.1056/NEJMoa1202753
6. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239-59. doi:10.1007/bf00308809
7. Hojjati SH, Feiz F, Ozoria S, Razlighi QR. Topographical Overlapping of the Amyloid-β and Tau Pathologies in the Default Mode Network Predicts Alzheimer's Disease with Higher Specificity. *J Alzheimers Dis*. 2021;83(1):407-421. doi:10.3233/jad-210419
8. Park M, Moon WJ. Structural MR Imaging in the Diagnosis of Alzheimer's Disease and Other Neurodegenerative Dementia: Current Imaging Approach and Future Perspectives. *Korean J Radiol*. Nov-Dec 2016;17(6):827-845. doi:10.3348/kjr.2016.17.6.827
9. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol*. May 2012;71(5):362-81. doi:10.1097/NEN.0b013e31825018f7
10. John A, Reddy PH. Synaptic basis of Alzheimer's disease: Focus on synaptic amyloid beta, P-tau and mitochondria. *Ageing Res Rev*. Jan 2021;65:101208. doi:10.1016/j.arr.2020.101208
11. Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging*. Oct 2006;27(10):1372-84. doi:10.1016/j.neurobiolaging.2005.09.012
12. Kashyap G, Bapat D, Das D, et al. Synapse loss and progress of Alzheimer's disease -A network model. *Sci Rep*. Apr 25 2019;9(1):6555. doi:10.1038/s41598-019-43076-y
13. Gasiorowska A, Wydrych M, Drapich P, et al. The Biology and Pathobiology of Glutamatergic, Cholinergic, and Dopaminergic Signaling in the Aging Brain. Review. *Frontiers in Aging Neuroscience*. 2021-July-13 2021;13doi:10.3389/fnagi.2021.654931
14. Roostaei T, Nazeri A, Felsky D, et al. Genome-wide interaction study of brain beta-amyloid burden and cognitive impairment in Alzheimer's disease. *Mol Psychiatry*. Feb 2017;22(2):287-295. doi:10.1038/mp.2016.35
15. Pan X, Kaminga AC, Wen SW, Wu X, Acheampong K, Liu A. Dopamine and Dopamine Receptors in Alzheimer's Disease: A Systematic Review and Network Meta-Analysis. *Front Aging Neurosci*. 2019;11:175. doi:10.3389/fnagi.2019.00175
16. Al-Ezzi A, Arechavala RJ, Butler R, et al. Disrupted brain functional connectivity as early signature in cognitively healthy individuals with pathological CSF amyloid/tau. *Communications Biology*. 2024/08/23 2024;7(1):1037. doi:10.1038/s42003-024-06673-w
17. Fathian A, Jamali Y, Raoufy MR, et al. The trend of disruption in the functional brain network topology of Alzheimer's disease. *Scientific Reports*. 2022/09/02 2022;12(1):14998. doi:10.1038/s41598-022-18987-y
18. Nabizadeh F, Initiative AsDN. Disruption in functional networks mediated tau spreading in Alzheimer's disease. *Brain Communications*. 2024;6(4)doi:10.1093/braincomms/fcae198
19. Stockhorst U, de Fries D, Steingrueber H-J, Scherbaum WA. Insulin and the CNS: effects on food intake, memory, and endocrine parameters and the role of intranasal insulin administration in humans. *Physiology & behavior*. 2004;83(1):47-54.

 doi:10.20944/preprints202504.2566.v1

20. Terzo S, Amato A, Mulè F. From obesity to Alzheimer's disease through insulin resistance. *Journal of Diabetes and its Complications*. 2021/11/01/ 2021;35(11):108026. doi:https://doi.org/10.1016/j.jdiacomp.2021.108026
21. Neth BJ, Craft S. Insulin Resistance and Alzheimer's Disease: Bioenergetic Linkages. *Front Aging Neurosci*. 2017;9:345. doi:10.3389/fnagi.2017.00345
22. Glover HL, Schreiner A, Dewson G, Tait SW. Mitochondria and cell death. *Nature cell biology*. 2024;26(9):1434-1446.
23. Reiss AB, Gulkarov S, Jacob B, et al. Mitochondria in Alzheimer's disease pathogenesis. *Life*. 2024;14(2):196.
24. Swerdlow RH. The mitochondrial hypothesis: dysfunction, bioenergetic defects, and the metabolic link to Alzheimer's disease. *International review of neurobiology*. 2020;154:207-233.
25. Nasb M, Tao W, Chen N. Alzheimer's disease puzzle: delving into pathogenesis hypotheses. *Aging and Disease*. 2024;15(1):43.
26. Turner RS, Thomas RG, Craft S, et al. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. *Neurology*. Oct 20 2015;85(16):1383-91. doi:10.1212/wnl.0000000000002035
27. Tapia-Monsalves C, Olesen MA, Villavicencio-Tejo F, Quintanilla RA. Cyclosporine A (CsA) prevents synaptic impairment caused by truncated tau by caspase-3. *Mol Cell Neurosci*. Jun 2023;125:103861. doi:10.1016/j.mcn.2023.103861
28. Di Rita A, Maiorino T, Bruqi K, Volpicelli F, Bellenchi GC, Strappazzon F. miR-218 Inhibits Mitochondrial Clearance by Targeting PRKN E3 Ubiquitin Ligase. *Int J Mol Sci*. Jan 5 2020;21(1)doi:10.3390/ijms21010355
29. Arroum T, Hish GA, Burghardt KJ, et al. Mitochondria Transplantation: Rescuing Innate Muscle Bioenergetic Impairment in a Model of Aging and Exercise Intolerance. *J Strength Cond Res*. Jul 1 2024;38(7):1189-1199. doi:10.1519/jsc.0000000000004793
30. Li W, Peng X, Mei X, Dong M, Li Y, Dong H. Multifunctional DNA Tetrahedron for Alzheimer's Disease Mitochondria-Targeted Therapy by MicroRNA Regulation. *ACS Applied Materials & Interfaces*. 2023/05/17 2023;15(19):22977-22984. doi:10.1021/acsami.3c03181
31. Han Y, Chu X, Cui L, et al. Neuronal mitochondria-targeted therapy for Alzheimer's disease by systemic delivery of resveratrol using dual-modified novel biomimetic nanosystems. *Drug Deliv*. Dec 2020;27(1):502-518. doi:10.1080/10717544.2020.1745328
32. McManus MJ, Murphy MP, Franklin JL. The mitochondria-targeted antioxidant MitoQ prevents loss of spatial memory retention and early neuropathology in a transgenic mouse model of Alzheimer's disease. *J Neurosci*. Nov 2 2011;31(44):15703-15. doi:10.1523/jneurosci.0552-11.2011
33. Young ML, Franklin JL. The mitochondria-targeted antioxidant MitoQ inhibits memory loss, neuropathology, and extends lifespan in aged 3xTg-AD mice. *Mol Cell Neurosci*. Dec 2019;101:103409. doi:10.1016/j.mcn.2019.103409
34. Hou Y, Chu X, Park JH, et al. Urolithin A improves Alzheimer's disease cognition and restores mitophagy and lysosomal functions. *Alzheimers Dement*. Jun 2024;20(6):4212-4233. doi:10.1002/alz.13847
35. Ryu D, Mouchiroud L, Andreux PA, et al. Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. *Nature Medicine*. 2016/08/01 2016;22(8):879-888. doi:10.1038/nm.4132
36. Heneka MT, van der Flier WM, Jessen F, et al. Neuroinflammation in Alzheimer disease. *Nature Reviews Immunology*. 2024/12/09 2024;doi:10.1038/s41577-024-01104-7
37. Suresh S, Singh SA, Rushendran R, Vellapandian C, Prajapati B. Alzheimer's disease: the role of extrinsic factors in its development, an investigation of the environmental enigma. *Front Neurol*. 2023;14:1303111. doi:10.3389/fneur.2023.1303111
38. Rim C, You MJ, Nahm M, Kwon MS. Emerging role of senescent microglia in brain aging-related neurodegenerative diseases. *Transl Neurodegener*. Feb 20 2024;13(1):10. doi:10.1186/s40035-024-00402-3
39. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. *Signal Transduction and Targeted Therapy*. 2023/07/12 2023;8(1):267. doi:10.1038/s41392-023-01486-5
40. Ting KK, Coleman P, Kim HJ, et al. Vascular senescence and leak are features of the early breakdown of the blood-brain barrier in Alzheimer's disease models. *Geroscience*. Dec 2023;45(6):3307-3331. doi:10.1007/s11357-023-00927-x

 doi:10.20944/preprints202504.2566.v1

41. Buccellato FR, D'Anca M, Serpente M, Arighi A, Galimberti D. The Role of Glymphatic System in Alzheimer's and Parkinson's Disease Pathogenesis. *Biomedicines*. Sep 13 2022;10(9)doi:10.3390/biomedicines10092261
42. Govindpani K, McNamara LG, Smith NR, et al. Vascular Dysfunction in Alzheimer's Disease: A Prelude to the Pathological Process or a Consequence of It? *J Clin Med*. May 10 2019;8(5)doi:10.3390/jcm8050651
43. Mattsson N, Tosun D, Insel PS, et al. Association of brain amyloid-β with cerebral perfusion and structure in Alzheimer's disease and mild cognitive impairment. *Brain*. 2014;137(5):1550-1561.
44. Vidoni ED, Morris JK, Watts A, et al. Effect of aerobic exercise on amyloid accumulation in preclinical Alzheimer's: A 1-year randomized controlled trial. *PloS one*. 2021;16(1):e0244893.
45. Vidoni ED, Morris JK, Palmer JA, et al. Dementia risk and dynamic response to exercise: A non-randomized clinical trial. *PloS one*. 2022;17(7):e0265860.
46. Sisante JV, Vidoni ED, Kirkendoll K, et al. Blunted cerebrovascular response is associated with elevated beta-amyloid. *J Cereb Blood Flow Metab*. Jan 2019;39(1):89-96. doi:10.1177/0271678x17732449
47. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. *Nat Rev Neurol*. Jan 2020;16(1):30-42. doi:10.1038/s41582-019-0281-2
48. Nelson AR, Sweeney MD, Sagare AP, Zlokovic BV. Neurovascular dysfunction and neurodegeneration in dementia and Alzheimer's disease. *Biochim Biophys Acta*. May 2016;1862(5):887-900. doi:10.1016/j.bbadis.2015.12.016
49. Steinman J, Sun HS, Feng ZP. Microvascular Alterations in Alzheimer's Disease. *Front Cell Neurosci*. 2020;14:618986. doi:10.3389/fncel.2020.618986
50. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*. Jan 21 2015;85(2):296-302. doi:10.1016/j.neuron.2014.12.032
51. Kisler K, Nelson AR, Montagne A, Zlokovic BV. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nat Rev Neurosci*. Jul 2017;18(7):419-434. doi:10.1038/nrn.2017.48
52. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci*. Nov 3 2011;12(12):723-38. doi:10.1038/nrn3114
53. Zacchigna S, Lambrechts D, Carmeliet P. Neurovascular signalling defects in neurodegeneration. *Nat Rev Neurosci*. Mar 2008;9(3):169-81. doi:10.1038/nrn2336
54. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature*. May 19 2011;473(7347):298-307. doi:10.1038/nature10144
55. Albert MS. Changes in cognition. *Neurobiol Aging*. Dec 2011;32 Suppl 1(0 1):S58-63. doi:10.1016/j.neurobiolaging.2011.09.010
56. Wilson RS, Bacon LD, Fox JH, Kaszniak AW. Primary memory and secondary memory in dementia of the Alzheimer type. *J Clin Neuropsychol*. Dec 1983;5(4):337-44. doi:10.1080/01688638308401181
57. Petersen RC, Smith GE, Ivnik RJ, Kokmen E, Tangalos EG. Memory function in very early Alzheimer's disease. *Neurology*. May 1994;44(5):867-72. doi:10.1212/wnl.44.5.867
58. Spaan PEJ, W. RJG, and Jonker C. Alzheimer's Disease Versus Normal Ageing: A Review of the Efficiency of Clinical and Experimental Memory Measures. *Journal of Clinical and Experimental Neuropsychology*. 2003/04/01 2003;25(2):216-233. doi:10.1076/jcen.25.2.216.13638
59. Stopford CL, Thompson JC, Neary D, Richardson AM, Snowden JS. Working memory, attention, and executive function in Alzheimer's disease and frontotemporal dementia. *Cortex*. 2012;48(4):429-446.
60. Ferman TJ, E. SG, F. BB, et al. Neuropsychological Differentiation of Dementia with Lewy Bodies from Normal Aging and Alzheimer's Disease. *The Clinical Neuropsychologist*. 2006/12/01 2006;20(4):623-636. doi:10.1080/13854040500376831
61. Baudic S, Dalla Barba G, Thibaudet MC, Smagghe A, Remy P, Traykov L. Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Archives of clinical neuropsychology*. 2006;21(1):15-21.
62. Kirova A-M, Bays RB, Lagalwar S. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *BioMed research international*. 2015;2015(1):748212.

 doi:10.20944/preprints202504.2566.v1

63. Storandt M. Cognitive Deficits in the Early Stages of Alzheimer's Disease. *Current Directions in Psychological Science*. 2008;17(3):198-202. doi:10.1111/j.1467-8721.2008.00574.x
64. Almor A, Kempler D, MacDonald MC, Andersen ES, Tyler LK. Why do Alzheimer patients have difficulty with pronouns? Working memory, semantics, and reference in comprehension and production in Alzheimer's disease. *Brain and language*. 1999;67(3):202-227.
65. Altmann LJ, McClung JS. Effects of semantic impairment on language use in Alzheimer's disease. *Semin Speech Lang*. Feb 2008;29(1):18-31. doi:10.1055/s-2008-1061622
66. Karrasch M, Sinervä E, Grönholm P, Rinne J, Laine M. CERAD test performances in amnestic mild cognitive impairment and Alzheimer's disease. *Acta Neurol Scand*. Mar 2005;111(3):172-9. doi:10.1111/j.1600-0404.2005.00380.x
67. Rouleau I, Salmon DP, Butters N, Kennedy C, McGuire K. Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. *Brain Cogn*. Jan 1992;18(1):70-87. doi:10.1016/0278-2626(92)90112-y
68. Rouleau I, Salmon DP, Butters N. Longitudinal analysis of clock drawing in Alzheimer's disease patients. *Brain Cogn*. Jun 1996;31(1):17-34. doi:10.1006/brcg.1996.0022
69. Cacciamani F, Houot M, Gagliardi G, et al. Awareness of Cognitive Decline in Patients With Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Front Aging Neurosci*. 2021;13:697234. doi:10.3389/fnagi.2021.697234
70. Cloak N, Al Khalili Y. Behavioral and psychological symptoms in dementia. 2019;
71. Heilman KM, Nadeau SE. Emotional and Neuropsychiatric Disorders Associated with Alzheimer's Disease. *Neurotherapeutics*. 2022/01/01/ 2022;19(1):99-116. doi:https://doi.org/10.1007/s13311-021-01172-w
72. Cerejeira J, Lagarto L, Mukaetova-Ladinska E. Behavioral and Psychological Symptoms of Dementia. Review. *Frontiers in Neurology*. 2012-May-07 2012;3doi:10.3389/fneur.2012.00073
73. Kwon C-Y, Lee B. Prevalence of Behavioral and Psychological Symptoms of Dementia in Community-Dwelling Dementia Patients: A Systematic Review. Systematic Review. *Frontiers in Psychiatry*. 2021-October-21 2021;12doi:10.3389/fpsyt.2021.741059
74. Villa C, Ferini-Strambi L, Combi R. The synergistic relationship between Alzheimer's disease and sleep disorders: an update. *Journal of Alzheimer's Disease*. 2015;46(3):571-580.
75. Guarnieri B, Sorbi S. Sleep and cognitive decline: a strong bidirectional relationship. It is time for specific recommendations on routine assessment and the management of sleep disorders in patients with mild cognitive impairment and dementia. *European neurology*. 2015;74(1-2):43-48.
76. Rechtschaffen A. Current perspectives on the function of sleep. *Perspectives in biology and medicine*. 1998;41(3):359-390.
77. Ju Y-ES, Ooms SJ, Sutphen C, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain*. 2017;140(8):2104-2111.
78. Barthélemy NR, Liu H, Lu W, Kotzbauer PT, Bateman RJ, Lucey BP. Sleep deprivation affects tau phosphorylation in human cerebrospinal fluid. *Annals of neurology*. 2020;87(5):700-709.
79. Xiong X, Hu T, Yin Z, Zhang Y, Chen F, Lei P. Research advances in the study of sleep disorders, circadian rhythm disturbances and Alzheimer's disease. Review. *Frontiers in Aging Neuroscience*. 2022-August-17 2022;14doi:10.3389/fnagi.2022.944283
80. Grundman M, Corey-Bloom J, Jernigan T, Archibald S, Thal L. Low body weight in Alzheimer's disease is associated with mesial temporal cortex atrophy. *Neurology*. 1996;46(6):1585-1591.
81. Hu X, Okamura N, Arai H, et al. Neuroanatomical correlates of low body weight in Alzheimer's disease: a PET study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2002;26(7-8):1285-1289.
82. Edahiro A, Hirano H, Yamada R, Chiba Y, Watanabe Y. Comparative study of eating behavior in elderly patients with Alzheimer's disease and vascular dementia: a first report.-Comparison of disturbed eating behavior. *Nihon Ronen Igakkai zasshi Japanese Journal of Geriatrics*. 2013;50(5):651-660.
83. Enomoto R, Kikutani T, Suzuki A, Inaba S. Relationship between eating dysfunction and life span and mortality in institutionalized elderly people. *Nihon Ronen Igakkai zasshi Japanese Journal of Geriatrics*. 2007;44(1):95-101.

 doi:10.20944/preprints202504.2566.v1

84. Shinagawa S, Ikeda M, Nestor P, et al. Characteristics of abnormal eating behaviours in frontotemporal lobar degeneration: a cross-cultural survey. *Journal of Neurology, Neurosurgery & Psychiatry*. 2009;80(12):1413-1414.
85. Bozeat S, Gregory CA, Ralph MAL, Hodges JR. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *Journal of Neurology, Neurosurgery & Psychiatry*. 2000;69(2):178-186.
86. Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges J. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 2002;73(4):371-376.
87. Kai K, Hashimoto M, Amano K, Tanaka H, Fukuhara R, Ikeda M. Relationship between eating disturbance and dementia severity in patients with Alzheimer's disease. *PLoS One*. 2015;10(8):e0133666. doi:10.1371/journal.pone.0133666
88. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. Aug 10 2024;404(10452):572-628. doi:10.1016/s0140-6736(24)01296-0
89. Reed B, Villeneuve S, Mack W, DeCarli C, Chui HC, Jagust W. Associations between serum cholesterol levels and cerebral amyloidosis. *JAMA Neurol*. Feb 2014;71(2):195-200. doi:10.1001/jamaneurol.2013.5390
90. Iadecola C, Yaffe K, Biller J, et al. Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. *Hypertension*. Dec 2016;68(6):e67-e94. doi:10.1161/hyp.0000000000000053
91. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat Rev Neurol*. Mar 2018;14(3):168-181. doi:10.1038/nrneurol.2017.185
92. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol*. Oct 2018;14(10):591-604. doi:10.1038/s41574-018-0048-7
93. Huang YY, Gan YH, Yang L, Cheng W, Yu JT. Depression in Alzheimer's Disease: Epidemiology, Mechanisms, and Treatment. *Biol Psychiatry*. Jun 1 2024;95(11):992-1005. doi:10.1016/j.biopsych.2023.10.008
94. Wheeler MJ, Dempsey PC, Grace MS, et al. Sedentary behavior as a risk factor for cognitive decline? A focus on the influence of glycemic control in brain health. *Alzheimers Dement (N Y)*. Sep 2017;3(3):291-300. doi:10.1016/j.trci.2017.04.001
95. Cunningham C, R OS, Caserotti P, Tully MA. Consequences of physical inactivity in older adults: A systematic review of reviews and meta-analyses. *Scand J Med Sci Sports*. May 2020;30(5):816-827. doi:10.1111/sms.13616
96. Topiwala A, Ebmeier KP. Effects of drinking on late-life brain and cognition. *Evid Based Ment Health*. Feb 2018;21(1):12-15. doi:10.1136/eb-2017-102820
97. Baranowski BJ, Marko DM, Fenech RK, Yang AJT, MacPherson REK. Healthy brain, healthy life: a review of diet and exercise interventions to promote brain health and reduce Alzheimer's disease risk. *Applied Physiology, Nutrition, and Metabolism*. 2020;45(10):1055-1065. doi:10.1139/apnm-2019-0910 %M 32717151
98. Key MN, Szabo-Reed AN. Impact of Diet and Exercise Interventions on Cognition and Brain Health in Older Adults: A Narrative Review. *Nutrients*. 2023;15(11):2495.
99. He Q, Bennett AN, Zhang C, Zhang JY, Tong S, Chan KHK. Nutritional interventions for preventing cognitive decline in patients with mild cognitive impairment and Alzheimer's disease: A comprehensive network meta-analysis and Mendelian Randomization study. *Clin Nutr ESPEN*. Mar 25 2025;67:555-566. doi:10.1016/j.clnesp.2025.03.040
100. Testad I, Kajander M, Froiland CT, Corbett A, Gjestsen MT, Anderson JG. Nutritional Interventions for Persons With Early-Stage Dementia or Alzheimer's Disease: An Integrative Review. *Res Gerontol Nurs*. Sep 1 2019;12(5):259-268. doi:10.3928/19404921-20190813-02
101. Thunborg C, Wang R, Rosenberg A, et al. Integrating a multimodal lifestyle intervention with medical food in prodromal Alzheimer's disease: the MIND-AD(mini) randomized controlled trial. *Alzheimers Res Ther*. May 30 2024;16(1):118. doi:10.1186/s13195-024-01468-x
102. Healy E. Impact of the MIND Diet on Cognition in Individuals with Dementia. *J Alzheimers Dis*. 2023;96(3):967-977. doi:10.3233/jad-230651

 doi:10.20944/preprints202504.2566.v1

103. Rong L, Peng Y, Shen Q, Chen K, Fang B, Li W. Effects of ketogenic diet on cognitive function of patients with Alzheimer's disease: a systematic review and meta-analysis. *J Nutr Health Aging*. Aug 2024;28(8):100306. doi:10.1016/j.jnha.2024.100306
104. Grammatikopoulou MG, Goulis DG, Gkiouras K, et al. To Keto or Not to Keto? A Systematic Review of Randomized Controlled Trials Assessing the Effects of Ketogenic Therapy on Alzheimer Disease. *Adv Nutr*. Nov 16 2020;11(6):1583-1602. doi:10.1093/advances/nmaa073
105. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med*. Feb 14 2002;346(7):476-83. doi:10.1056/NEJMoa011613
106. Seshadri S. Elevated plasma homocysteine levels: risk factor or risk marker for the development of dementia and Alzheimer's disease? *J Alzheimers Dis*. Aug 2006;9(4):393-8. doi:10.3233/jad-2006-9404
107. Wang Z, Zhu W, Xing Y, Jia J, Tang Y. B vitamins and prevention of cognitive decline and incident dementia: a systematic review and meta-analysis. *Nutr Rev*. Mar 10 2022;80(4):931-949. doi:10.1093/nutrit/nuab057
108. Chen LJ, Sha S, Stocker H, Brenner H, Schöttker B. The associations of serum vitamin D status and vitamin D supplements use with all-cause dementia, Alzheimer's disease, and vascular dementia: a UK Biobank based prospective cohort study. *Am J Clin Nutr*. Apr 2024;119(4):1052-1064. doi:10.1016/j.ajcnut.2024.01.020
109. Gil Martínez V, Avedillo Salas A, Santander Ballestín S. Vitamin Supplementation and Dementia: A Systematic Review. *Nutrients*. Feb 28 2022;14(5)doi:10.3390/nu14051033
110. Kouba BR, Camargo A, Rodrigues ALS. Neuroinflammation in Alzheimer's disease: potential beneficial effects of vitamin D. *Metab Brain Dis*. Mar 2023;38(3):819-829. doi:10.1007/s11011-023-01188-5
111. Shea MK, Xuan AY, Booth SL. Vitamin D, Alzheimer's disease and related dementia. *Adv Food Nutr Res*. 2024;109:185-219. doi:10.1016/bs.afnr.2023.12.003
112. Littlejohns TJK, K; Henley, W.E.; Kuźma, E.; Llewellyn, D.J. Vitamin D and Dementia. *Journal of Prevention of Alzheimer's Disease*. 2015;3(1):43-52.
113. Raz N, Daugherty AM. Pathways to Brain Aging and Their Modifiers: Free-Radical-Induced Energetic and Neural Decline in Senescence (FRIENDS) Model - A Mini-Review. *Gerontology*. 2018;64(1):49-57. doi:10.1159/000479508
114. Cardoso BR, Roberts BR, Malpas CB, et al. Supranutritional Sodium Selenate Supplementation Delivers Selenium to the Central Nervous System: Results from a Randomized Controlled Pilot Trial in Alzheimer's Disease. *Neurotherapeutics*. Jan 2019;16(1):192-202. doi:10.1007/s13311-018-0662-z
115. Huhn S, Kharabian Masouleh S, Stumvoll M, Villringer A, Witte AV. Components of a Mediterranean diet and their impact on cognitive functions in aging. *Front Aging Neurosci*. 2015;7:132. doi:10.3389/fnagi.2015.00132
116. Wu S, Ding Y, Wu F, Li R, Hou J, Mao P. Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: a meta-analysis. *Neurosci Biobehav Rev*. Jan 2015;48:1-9. doi:10.1016/j.neubiorev.2014.11.008
117. Brainard JS, Jimoh OF, Deane KHO, et al. Omega-3, Omega-6, and Polyunsaturated Fat for Cognition: Systematic Review and Meta-analysis of Randomized Trials. *J Am Med Dir Assoc*. Oct 2020;21(10):1439-1450.e21. doi:10.1016/j.jamda.2020.02.022
118. Lin PY, Cheng C, Satyanarayanan SK, et al. Omega-3 fatty acids and blood-based biomarkers in Alzheimer's disease and mild cognitive impairment: A randomized placebo-controlled trial. *Brain Behav Immun*. Jan 2022;99:289-298. doi:10.1016/j.bbi.2021.10.014
119. Voulgaropoulou SD, van Amelsvoort T, Prickaerts J, Vingerhoets C. The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. *Brain Res*. Dec 15 2019;1725:146476. doi:10.1016/j.brainres.2019.146476
120. Zeng M, Zhang K, Yang J, et al. Effects of Ginseng on Cognitive Function: A Systematic Review and Meta-Analysis. *Phytother Res*. Dec 2024;38(12):6023-6034. doi:10.1002/ptr.8359
121. Vyas CM, Manson JE, Sesso HD, et al. Effect of multivitamin-mineral supplementation versus placebo on cognitive function: results from the clinic subcohort of the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) randomized clinical trial and meta-analysis of 3 cognitive studies within COSMOS. *Am J Clin Nutr*. Mar 2024;119(3):692-701. doi:10.1016/j.ajcnut.2023.12.011

 doi:10.20944/preprints202504.2566.v1

122. Shim Y, Yoon B, Na S, Lim EY, Hong YJ, Yang DW. A systematic review and meta-analysis of the clinical effects of Souvenaid in patients with Alzheimer's disease. *Asia Pac J Clin Nutr*. 2021;30(1):30-41. doi:10.6133/apjcn.202103_30(1).0005
123. Chung JY, Kim OY, Song J. Role of ketone bodies in diabetes-induced dementia: sirtuins, insulin resistance, synaptic plasticity, mitochondrial dysfunction, and neurotransmitter. *Nutr Rev*. Mar 10 2022;80(4):774-785. doi:10.1093/nutrit/nuab118
124. Castro CB, Dias CB, Hillebrandt H, et al. Medium-chain fatty acids for the prevention or treatment of Alzheimer's disease: a systematic review and meta-analysis. *Nutr Rev*. Aug 10 2023;81(9):1144-1162. doi:10.1093/nutrit/nuac104
125. Elias A, Padinjakara N, Lautenschlager NT. Effects of intermittent fasting on cognitive health and Alzheimer's disease. *Nutr Rev*. Aug 10 2023;81(9):1225-1233. doi:10.1093/nutrit/nuad021
126. Ooi TC, Meramat A, Rajab NF, et al. Intermittent Fasting Enhanced the Cognitive Function in Older Adults with Mild Cognitive Impairment by Inducing Biochemical and Metabolic changes: A 3-Year Progressive Study. *Nutrients*. Aug 30 2020;12(9)doi:10.3390/nu12092644
127. Corbin CB, Pangrazi RP, Franks BD. Definitions: Health, fitness, and physical activity. *President's Council on Physical Fitness and Sports Research Digest*. 2000;
128. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical Fitness as a Predictor of Mortality among Healthy, Middle-Aged Norwegian Men. *The New England Journal of Medicine*. 1993;328(8):533-537.
129. Laukkanen JA, Lakka TA, Rauramaa R, et al. Cardiovascular Fitness as a Predictor of Mortality in Men. *Archives of internal medicine*. 2001;161(6):825-831. doi:10.1001/archinte.161.6.825
130. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc*. Jul 2009;41(7):1510-30. doi:10.1249/MSS.0b013e3181a0c95c
131. De la Rosa A, Olaso-Gonzalez G, Arc-Chagnaud C, et al. Physical exercise in the prevention and treatment of Alzheimer's disease. *Journal of Sport and Health Science*. 2020/09/01/ 2020;9(5):394-404. doi:https://doi.org/10.1016/j.jshs.2020.01.004
132. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences of the United States of America*. 1999;96(23):13427-13431.
133. Barde YA. Neurotrophins: a family of proteins supporting the survival of neurons. *ProgClin Biol Res*. 1994;390:45-56.
134. Lu B, Chow A. Neurotrophins and hippocampal synaptic transmission and plasticity. *J Neurosci Res*. 1999;58(1):76-87.
135. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc Natl Acad Sci U S A*. Jul 1990;87(14):5568-72.
136. Isaacs KR, Anderson BJ, Alcantara AA, Black JE, Greenough WT. Exercise and the brain: angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. *Journal Of Cerebral Blood Flow And Metabolism: Official Journal Of The International Society Of Cerebral Blood Flow And Metabolism*. 1992;12(1):110-119.
137. Liang KY, Mintun MA, Fagan AM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol*. Sep 2010;68(3):311-8. doi:10.1002/ana.22096
138. Brown BM, Peiffer JJ, Martins RN. Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease? *Molecular Psychiatry*. 2013/08/01 2013;18(8):864-874. doi:10.1038/mp.2012.162
139. Head D, Bugg JM, Goate AM, et al. Exercise Engagement as a Moderator of the Effects of APOE Genotype on Amyloid Deposition. *Arch Neurol*. May 2012;69(5):636-43. doi:10.1001/archneurol.2011.845
140. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology*. Sep 2002;13(5):561-8. doi:10.1097/01.EDE.0000023965.92535.C0

 doi:10.20944/preprints202504.2566.v1

141. Nichol K, Deeny SP, Seif J, Camaclang K, Cotman CW. Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. *Alzheimers Dement*. Jul 2009;5(4):287-94. doi:10.1016/j.jalz.2009.02.006
142. García-Mesa Y, López-Ramos JC, Giménez-Llort L, et al. 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
143. Colcombe SJ, Erickson KI, Raz N, et al. Aerobic Fitness Reduces Brain Tissue Loss in Aging Humans. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2003;58(2):M176-M180.
144. Burns JM, Mayo MS, Anderson HS, Smith H, Donnelly JE. Cardiorespiratory Fitness in Early-Stage Alzheimer's Disease. . *Alzheimer Dis Assoc Disord*. 2008;22(1):39-46.
145. Honea RA, Thomas GP, Harsha A, et al. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer's Disease. *Alzheimer Dis Assoc Disord*. 2009;*In Press*
146. Borst SE, De Hoyos DV, Garzarella L, et al. Effects of resistance training on insulin-like growth factor-I and IGF binding proteins. *Med Sci Sports Exerc*. Apr 2001;33(4):648-53.
147. Liu CJ, Latham NK. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database Syst Rev*. Jul 8 2009;2009(3):Cd002759. doi:10.1002/14651858.CD002759.pub2
148. Liu-Ambrose T, Donaldson MG, Ahamed Y, et al. Otago home-based strength and balance retraining improves executive functioning in older fallers: a randomized controlled trial. *J Am Geriatr Soc*. Oct 2008;56(10):1821-30. doi:10.1111/j.1532-5415.2008.01931.x
149. Suzuki T, Shimada H, Makizako H, et al. Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: a randomized controlled trial. *BMC Neurol*. Oct 31 2012;12:128. doi:10.1186/1471-2377-12-128
150. Fiatarone Singh MA, Gates N, Saigal N, et al. The Study of Mental and Resistance Training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *J Am Med Dir Assoc*. Dec 2014;15(12):873-80. doi:10.1016/j.jamda.2014.09.010
151. Tarazona-Santabalbina FJ, Gómez-Cabrera MC, Pérez-Ros P, et al. A Multicomponent Exercise Intervention that Reverses Frailty and Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail Elderly: A Randomized Clinical Trial. *J Am Med Dir Assoc*. May 1 2016;17(5):426-33. doi:10.1016/j.jamda.2016.01.019
152. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *Jama*. Nov 24 2010;304(20):2253-62. doi:10.1001/jama.2010.1710
153. Davidson LE, Hudson R, Kilpatrick K, et al. Effects of exercise modality on insulin resistance and functional limitation in older adults: a randomized controlled trial. *Archives of internal medicine*. Jan 26 2009;169(2):122-31. doi:169/2/122 [pii]10.1001/archinternmed.2008.558
154. Donges CE, Duffield R, Guelfi KJ, Smith GC, Adams DR, Edge JA. Comparative effects of single-mode vs. duration-matched concurrent exercise training on body composition, low-grade inflammation, and glucose regulation in sedentary, overweight, middle-aged men. *Appl Physiol Nutr Metab*. Jul 2013;38(7):779-88. doi:10.1139/apnm-2012-0443
155. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med*. Sep 18 2007;147(6):357-69. doi:10.7326/0003-4819-147-6-200709180-00005
156. Sillanpää E, Häkkinen A, Punnonen K, Häkkinen K, Laaksonen DE. Effects of strength and endurance training on metabolic risk factors in healthy 40-65-year-old men. *Scand J Med Sci Sports*. Dec 2009;19(6):885-95. doi:10.1111/j.1600-0838.2008.00849.x
157. Szabo-Reed A, Clutton J, White S, et al. COMbined Exercise Trial (COMET) to improve cognition in older adults: Rationale and methods. *Contemporary Clinical Trials*. 2022/07/01/ 2022;118:106805. doi:https://doi.org/10.1016/j.cct.2022.106805
158. Bhattacharyya KK, Andel R, Small BJ. Effects of yoga-related mind-body therapies on cognitive function in older adults: A systematic review with meta-analysis. *Archives of Gerontology and Geriatrics*. 2021/03/01/ 2021;93:104319. doi:https://doi.org/10.1016/j.archger.2020.104319

 doi:10.20944/preprints202504.2566.v1

159. Gothe NP, Khan I, Hayes J, Erlenbach E, Damoiseaux JS. Yoga Effects on Brain Health: A Systematic Review of the Current Literature. *Brain Plast*. Dec 26 2019;5(1):105-122. doi:10.3233/bpl-190084
160. Liu F, Chen X, Nie P, et al. Can Tai Chi Improve Cognitive Function? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *The Journal of Alternative and Complementary Medicine*. 2021;27(12):1070-1083. doi:10.1089/acm.2021.0084
161. Howe L, Yasser S, Eric A, Hao L. Brain Structural Response and Neurobehavior Changes in the Elderly after Tai Chi Practice - A Literature Review. *Traditional and Integrative Medicine*. 01/11 2023;0(0)
162. Leahy AA, Mavilidi MF, Smith JJ, et al. Review of high-intensity interval training for cognitive and mental health in youth. *Medicine & Science in Sports & Exercise*. 2020;52(10):2224-2234.
163. Jiménez-Maldonado A, Rentería I, García-Suárez PC, Moncada-Jiménez J, Freire-Royes LF. The Impact of High-Intensity Interval Training on Brain Derived Neurotrophic Factor in Brain: A Mini-Review. Mini Review. *Frontiers in Neuroscience*. 2018-November-14 2018;12doi:10.3389/fnins.2018.00839
164. Hugues N, Pellegrino C, Rivera C, Berton E, Pin-Barre C, Laurin J. Is High-Intensity Interval Training Suitable to Promote Neuroplasticity and Cognitive Functions after Stroke? *International Journal of Molecular Sciences*. 2021;22(6):3003.
165. Mekari S, Neyedli HF, Fraser S, et al. High-Intensity Interval Training Improves Cognitive Flexibility in Older Adults. *Brain Sciences*. 2020;10(11):796.
166. Seldeen KL, Lasky G, Leiker MM, Pang M, Personius KE, Troen BR. High Intensity Interval Training Improves Physical Performance and Frailty in Aged Mice. *The Journals of Gerontology: Series A*. 2017;73(4):429-437. doi:10.1093/gerona/glx120
167. Seldeen KL, Redae YZ, Thiyagarajan R, Berman RN, Leiker MM, Troen BR. High intensity interval training improves physical performance in aged female mice: A comparison of mouse frailty assessment tools. *Mechanisms of Ageing and Development*. 2019/06/01/ 2019;180:49-62. doi:https://doi.org/10.1016/j.mad.2019.04.001
168. Cass SP. Alzheimer's Disease and Exercise: A Literature Review. *Current Sports Medicine Reports*. 2017;16(1):19-22. doi:10.1249/jsr.0000000000000332
169. Feter N, Mielke GI, Leite JS, Brown WJ, Coombes JS, Rombaldi AJ. Physical activity in later life and risk of dementia: Findings from a population-based cohort study. *Experimental Gerontology*. 2021/01/01/ 2021;143:111145. doi:https://doi.org/10.1016/j.exger.2020.111145
170. 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. *British Journal of Sports Medicine*. 2022;56(12):701. doi:10.1136/bjsports-2021-104981
171. Cámara-Calmaestra R, Martínez-Amat A, Aibar-Almazán A, Hita-Contreras F, de Miguel Hernando N, Achalandabaso-Ochoa A. Effectiveness of Physical Exercise on Alzheimer's disease. A Systematic Review. *The Journal of Prevention of Alzheimer's Disease*. 2022/10/01/ 2022;9(4):601-616. doi:https://doi.org/10.14283/jpad.2022.57
172. Pitkälä KH, Pöysti MM, Laakkonen M-L, et al. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. *JAMA internal medicine*. 2013;173(10):894-901.
173. Enette L, Vogel T, Merle S, et al. Effect of 9 weeks continuous vs. interval aerobic training on plasma BDNF levels, aerobic fitness, cognitive capacity and quality of life among seniors with mild to moderate Alzheimer's disease: a randomized controlled trial. *European Review of Aging and Physical Activity*. 2020;17:1-16.
174. Pedrinolla A, Venturelli M, Fonte C, et al. Exercise training improves vascular function in patients with Alzheimer's disease. *European Journal of Applied Physiology*. 2020;120:2233-2245.
175. 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):381-388.
176. Sobol NA, Hoffmann K, Frederiksen KS, et al. Effect of aerobic exercise on physical performance in patients with Alzheimer's disease. *Alzheimer's & Dementia*. 2016;12(12):1207-1215.
177. Hoffmann K, Sobol NA, Frederiksen KS, 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):443-453.

 doi:10.20944/preprints202504.2566.v1

178. 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):12-19.
179. Zhou S, Chen S, Liu X, Zhang Y, Zhao M, Li W. Physical Activity Improves Cognition and Activities of Daily Living in Adults with Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *International Journal of Environmental Research and Public Health*. 2022;19(3):1216.
180. Boyle CP, Raji CA, Erickson KI, et al. Physical activity, body mass index, and brain atrophy in Alzheimer's disease. *Neurobiology of Aging*. 2015/01/01/ 2015;36:S194-S202. doi:https://doi.org/10.1016/j.neurobiolaging.2014.05.036
181. Honea RA, Thomas GP, Harsha A, et al. Cardiorespiratory Fitness and Preserved Medial Temporal Lobe Volume in Alzheimer Disease. *Alzheimer Disease & Associated Disorders*. 2009;23(3):188-197. doi:10.1097/WAD.0b013e31819cb8a2
182. Kress GT, Popa ES, Merrill DA, Bramen JE, Siddarth P. The impact of physical exercise on hippocampal atrophy in mild cognitive impairment and Alzheimer's disease: a meta-analysis. *NeuroReport*. 2024;35(8):529-535. doi:10.1097/wnr.0000000000002037
183. Morris JK, Vidoni ED, Johnson DK, et al. Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. *PLOS ONE*. 2017;12(2):e0170547. doi:10.1371/journal.pone.0170547
184. Vidoni ED, Morris JK, Watts A, et al. Effect of aerobic exercise on amyloid accumulation in preclinical Alzheimer's: A 1-year randomized controlled trial. *PLoS One*. 2021;16(1):e0244893. doi:10.1371/journal.pone.0244893
185. Deeny SP, Winchester J, Nichol K, et al. Cardiovascular fitness is associated with altered cortical glucose metabolism during working memory in ε4 carriers. *Alzheimer's & Dementia*. 2012;8(4):352-356. doi:https://doi.org/10.1016/j.jalz.2011.04.010
186. Deeny SP, Poeppel D, Zimmerman JB, et al. Exercise, APOE, and working memory: MEG and behavioral evidence for benefit of exercise in epsilon4 carriers. *Biological Psychology*. 2008/05/01/ 2008;78(2):179-187. doi:https://doi.org/10.1016/j.biopsycho.2008.02.007
187. Sugarman MA, Woodard JL, Nielson KA, et al. Functional magnetic resonance imaging of semantic memory as a presymptomatic biomarker of Alzheimer's disease risk. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*. 2012;1822(3):442-456.
188. Woodard JL, Seidenberg M, Nielson KA, et al. Prediction of cognitive decline in healthy older adults using fMRI. *Journal of Alzheimer's Disease*. 2010;21(3):871-885.
189. Vasconcelos-Filho FSL, da Rocha Oliveira LC, de Freitas TBC, et al. Effect of involuntary chronic physical exercise on beta-amyloid protein in experimental models of Alzheimer's disease: Systematic review and meta-analysis. *Experimental Gerontology*. 2021/10/01/ 2021;153:111502. doi:https://doi.org/10.1016/j.exger.2021.111502
190. Tan Z-X, Dong F, Wu L-Y, Feng Y-S, Zhang F. The Beneficial Role of Exercise on Treating Alzheimer's Disease by Inhibiting β-Amyloid Peptide. *Molecular Neurobiology*. 2021/11/01 2021;58(11):5890-5906. doi:10.1007/s12035-021-02514-7
191. Elahi M, Motoi Y, Matsumoto S-E, Hasan Z, Ishiguro K, Hattori N. Short-term treadmill exercise increased tau insolubility and neuroinflammation in tauopathy model mice. *Neuroscience letters*. 2016;610:207-212.
192. Andrade-Guerrero J, Rodríguez-Arellano P, Barron-Leon N, et al. Advancing Alzheimer's Therapeutics: Exploring the Impact of Physical Exercise in Animal Models and Patients. *Cells*. 2023;12(21):2531.
193. Pucci IM, Aguiar AF, Pucci RM, Casonatto J, Borghi SM. Systematic review and meta-analysis of randomized controlled trials on the effects of exercise interventions on amyloid beta levels in humans. *Experimental Brain Research*. 2024/05/01 2024;242(5):1011-1024. doi:10.1007/s00221-024-06821-y
194. Huang X, Zhao X, Li B, et al. Biomarkers for evaluating the effects of exercise interventions in patients with MCI or dementia: A systematic review and meta-analysis. *Experimental Gerontology*. 2021/08/01/ 2021;151:111424. doi:https://doi.org/10.1016/j.exger.2021.111424
195. Frederiksen KS, Gjerum L, Waldemar G, Hasselbalch SG, Burns J. Effects of Physical Exercise on Alzheimer's Disease Biomarkers: A Systematic Review of Intervention Studies. *Journal of Alzheimer's Disease*. 2018;61(1):359-372. doi:10.3233/jad-170567

 doi:10.20944/preprints202504.2566.v1

196. Gómez-Pinilla F, Ying Z, Roy RR, Molteni R, Edgerton VR. Voluntary Exercise Induces a BDNF-Mediated Mechanism That Promotes Neuroplasticity. *Journal of Neurophysiology*. 2002;88(5):2187-2195. doi:10.1152/jn.00152.2002
197. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience*. 2004;20(10):2580-2590. doi:https://doi.org/10.1111/j.1460-9568.2004.03720.x
198. Ribeiro D, Petrigna L, Pereira FC, Muscella A, Bianco A, Tavares P. The Impact of Physical Exercise on the Circulating Levels of BDNF and NT 4/5: A Review. *International Journal of Molecular Sciences*. 2021;22(16):8814.
199. Titus J, Bray NW, Kamkar N, et al. The role of physical exercise in modulating peripheral inflammatory and neurotrophic biomarkers in older adults: A systematic review and meta-analysis. *Mechanisms of Ageing and Development*. 2021/03/01/ 2021;194:111431. doi:https://doi.org/10.1016/j.mad.2021.111431
200. Ayari S, Abellard A, Carayol M, Guedj E, Gavarry O. A systematic review of exercise modalities that reduce pro-inflammatory cytokines in humans and animals' models with mild cognitive impairment or dementia. *Experimental Gerontology*. 2023;175:112141.
201. Zhou Y, Wu W, Zou Y, et al. Benefits of different combinations of aerobic and resistance exercise for improving plasma glucose and lipid metabolism and sleep quality among elderly patients with metabolic syndrome: a randomized controlled trial. *Endocrine journal*. 2022;69(7):819-830.
202. O'Reilly CL, Miller BF, Lewis TL. Exercise and mitochondrial remodeling to prevent age-related neurodegeneration. *Journal of Applied Physiology*. 2023;134(1):181-189. doi:10.1152/japplphysiol.00611.2022
203. Ho RT, Fong TC, Chan WC, et al. Psychophysiological effects of dance movement therapy and physical exercise on older adults with mild dementia: a randomized controlled trial. *The Journals of Gerontology: Series B*. 2020;75(3):560-570.
204. Feng L, Li B, Yong SS, Wen X, Tian Z. The emerging role of exercise in Alzheimer's disease: Focus on mitochondrial function. *Ageing Research Reviews*. 2024/11/01/ 2024;101:102486. doi:https://doi.org/10.1016/j.arr.2024.102486
205. Brisendine MH, Drake JC. Early-stage Alzheimer's disease: are skeletal muscle and exercise the key? *Journal of Applied Physiology*. 2023;134(3):515-520. doi:10.1152/japplphysiol.00659.2022
206. Alves L, Hashiguchi D, Loss CM, van Praag H, Longo BM. Vascular dysfunction in Alzheimer's disease: Exploring the potential of aerobic and resistance exercises as therapeutic strategies. *Journal of Alzheimer's Disease*. 0(0):13872877251321118. doi:10.1177/13872877251321118
207. Palmer JA, Kaufman CS, Vidoni ED, et al. Sex Differences in Resilience and Resistance to Brain Pathology and Dysfunction Moderated by Cerebrovascular Response to Exercise and Genetic Risk for Alzheimer's Disease. *Journal of Alzheimer's Disease*. 2022;90(2):535-542. doi:10.3233/jad-220359
208. Liu Y, Perdomo SJ, Ward J, et al. Vascular Health is Associated with Amyloid-β in Cognitively Normal Older Adults. *Journal of Alzheimer's Disease*. 2019;70(2):467-475. doi:10.3233/jad-181268
209. Pedrinolla A, Venturelli M, Fonte C, et al. Exercise training improves vascular function in patients with Alzheimer's disease. *European Journal of Applied Physiology*. 2020/10/01 2020;120(10):2233-2245. doi:10.1007/s00421-020-04447-w
210. Demurtas J, Schoene D, Torbahn G, et al. Physical Activity and Exercise in Mild Cognitive Impairment and Dementia: An Umbrella Review of Intervention and Observational Studies. *Journal of the American Medical Directors Association*. 2020;21(10):1415-1422.e6. doi:10.1016/j.jamda.2020.08.031
211. Liang Y-J, Su Q-W, Sheng Z-R, et al. Effectiveness of Physical Activity Interventions on Cognition, Neuropsychiatric Symptoms, and Quality of Life of Alzheimer's Disease: An Update of a Systematic Review and Meta-Analysis. Systematic Review. *Frontiers in Aging Neuroscience*. 2022-March-02 2022;14doi:10.3389/fnagi.2022.830824
212. McCartney A, J. C, B. RS, and Hoe J. The effectiveness of structured physical activity on agitation in people with dementia: a rapid review. *Aging & Mental Health*. 2024/08/02 2024;28(8):1067-1077. doi:10.1080/13607863.2024.2345129
213. Driver HS, Taylor SR. Exercise and sleep. *Sleep Medicine Reviews*. 2000/08/01/ 2000;4(4):387-402. doi:https://doi.org/10.1053/smrv.2000.0110

 doi:10.20944/preprints202504.2566.v1

214. Uchida S, Shioda K, Morita Y, Kubota C, Ganeko M, Takeda N. Exercise Effects on Sleep Physiology. Mini Review. *Frontiers in Neurology*. 2012-April-02 2012;3doi:10.3389/fneur.2012.00048
215. King AC, Oman RF, Brassington GS, Bliwise DL, Haskell WL. Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. *Jama*. Jan 1 1997;277(1):32-7.
216. Jøranson N, Olsen C, Calogiuri G, Ihlebæk C, Pedersen I. Effects on sleep from group activity with a robotic seal for nursing home residents with dementia: a cluster randomized controlled trial. *International Psychogeriatrics*. 2021;33(10):1045-1056. doi:10.1017/S1041610220001787
217. Zhang S, Zhen K, Su Q, Chen Y, Lv Y, Yu L. The Effect of Aerobic Exercise on Cognitive Function in People with Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *International Journal of Environmental Research and Public Health*. 2022;19(23):15700.
218. Yu F, Salisbury D, Mathiason MA. Inter-individual differences in the responses to aerobic exercise in Alzheimer's disease: Findings from the FIT-AD trial. *Journal of Sport and Health Science*. 2021/01/01/ 2021;10(1):65-72. doi:https://doi.org/10.1016/j.jshs.2020.05.007
219. Smith C, Woessner MN, Sim M, Levinger I. Sarcopenia definition: Does it really matter? Implications for resistance training. *Ageing Research Reviews*. 2022/06/01/ 2022;78:101617. doi:https://doi.org/10.1016/j.arr.2022.101617
220. Lopez P, Pinto RS, Radaelli R, et al. Benefits of resistance training in physically frail elderly: a systematic review. *Aging Clinical and Experimental Research*. 2018/08/01 2018;30(8):889-899. doi:10.1007/s40520-017-0863-z
221. Vital TM, Hernández SSS, Pedroso RV, et al. Effects of weight training on cognitive functions in elderly with Alzheimer's disease. *Dement Neuropsychol*. Oct-Dec 2012;6(4):253-259. doi:10.1590/s1980-57642012dn06040009
222. Sepúlveda-Lara A, Sepúlveda P, Marzuca-Nassr GN. Resistance Exercise Training as a New Trend in Alzheimer's Disease Research: From Molecular Mechanisms to Prevention. *International Journal of Molecular Sciences*. 2024;25(13):7084.
223. Ye M, Wang L, Xiong J, Zheng G. The effect of mind–body exercise on memory in older adults: a systematic review and meta-analysis. *Aging Clinical and Experimental Research*. 2021/05/01 2021;33(5):1163-1173. doi:10.1007/s40520-020-01557-5
224. Hüttenrauch M, Castro-Obregón S. How mind-body therapies might reduce pathological features of Alzheimer's disease. *Neural Regeneration Research*. 2022;17(8):1757-1758. doi:10.4103/1673-5374.332146
225. Smith PJ. Pathways of Prevention: A Scoping Review of Dietary and Exercise Interventions for Neurocognition. *Brain Plast*. Dec 26 2019;5(1):3-38. doi:10.3233/bpl-190083
226. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement*. Jun 2015;11(6):718-26. doi:10.1016/j.jalz.2015.05.016
227. López-Ortiz S, Lista S, Valenzuela PL, et al. Effects of physical activity and exercise interventions on Alzheimer's disease: an umbrella review of existing meta-analyses. *Journal of Neurology*. 2023/02/01 2023;270(2):711-725. doi:10.1007/s00415-022-11454-8