The Effects of Exercise on the Cognitive Function of Patients with Alzheimer’s Disease

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The Effects of Exercise on the Cognitive Function of Patients with Alzheimer’s Disease

Amanda Savitski

Western Michigan University
Abstract

Alzheimer’s disease (AD) is America’s most common neurodegenerative disease affecting over 5.4 million Americans (Fernández et al., 2017). A literature review was completed to assess the possible relation between physical activity and the progression of AD. Articles were collected from various peer-reviewed, published journals using the available databases of Western Michigan University library which included PubMed, ClinicalTrials.gov, and the National Institute of Health (NIH). Keywords used for the database searches included “Alzheimer”, “Alzheimer’s Disease”, “neurodegeneration”, “aging brain”, “exercise”, and “physical activity”. Based upon the literature reviewed, aerobic exercise appears to slow the progression of AD and possibly reverses it slightly in some cases. Neurologically this is observed with β-amyloid plaques and neurofibrillary tangles beginning to breakdown, and hippocampal volume increasing. There are a few instances where neural synapses increase, and neuronal activity improves. As the cause of AD is still predominantly unknown, there are very few treatments and prevention opportunities available at this time, therefore, many people are turning towards non-pharmacological care such as physical exercise.
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Introduction

Affecting over 5.4 million adults, Alzheimer’s Disease (AD) is the most common neurodegenerative disease in America (Fernández et al., 2017). It is primarily characterized by the buildup of β-amyloid plaques and tau proteins creating neurofibrillary tangles in the frontal-temporal regions of the brain (Fernandez et al., 2017). AD is thought to be the result of genetic inheritance, but an official cause has not been discovered. Different forms of the disease may have different onset times (Ryman et al., 2014), but no matter how AD develops in someone’s brain, very few treatments are available to slow the progression once it begins. Even within these treatments, the effectiveness of each depends on the individual. Research is shifting its focus towards preventative medicine, especially regarding AD. One research area that may prove to be promising is the relationship between AD and physical activity.

Alzheimer’s can be diagnosed from a number of factors such as memory loss, performance on verbal or written tests, and/or by diagnostic scans. A Mini-Mental State Examination (MMSE) can test a patient’s mental competence, while an MRI or CT scan may display physical brain abnormalities. AD can be described based on the age of onset being “early” or “late”, and the stage of the disease as “mild”, “moderate” or “severe” (Ryman et al., 2014).

In a healthy human brain, exercise can improve brain plasticity and may “arrest, slow down or even reverse the pathophysiological evolution to Mild Cognitive Impairment (MCI)” (Foster, 2015). Physical exercise appears to lessen the effects of age-related deterioration on three important brain networks. Brain plasticity can be observed in healthy brains which are often creating new synapses while degrading old connections. Often, excess elimination of
synapses is what can lead to cognitive impairments such as AD or other neurodegenerative diseases (Foster, 2015). Another indication of AD is decreased levels of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) circulating in the body which is related to smaller hippocampal volume and a decline in learning and memory. Although levels of VEGF decrease with age, BDNF and VEGF amounts are altered with exercise, and can then have lasting effects on the plasticity and neural connections in the brain (Voss et al., 2013).

Within the brain, many biochemical abnormalities are observed with the progression of AD. The most common identifying factors of the disease are the creation of β-amyloid plaques in the brain, neurodegeneration, and a decrease in hippocampal volume (Gomez-Pinilla & Hillman, 2013). The specifics of how Alzheimer’s is triggered is still a mystery, but there are some genes, such as Apolipoprotein E (APOE), that are considered risk factor genes. Their presence in the genome seems to increase the risk of developing AD (Soto et al., 2015). Often the gene still needs to be triggered by some environmental factor or event for AD to begin.

Many studies have been completed to compare the effect of exercise on the progression of AD. The studies have utilized different types of exercise including aerobic, strength, and alternative exercises such as yoga and tai chi (Mooventhan & Nivethitha, 2017). These various exercise categories have different levels of effectiveness in AD patients with aerobic exercise presenting positive results most frequently. Exercise has been shown to affect hippocampal volume, increased APOE stabilization, and increased brain mitochondrial fitness or efficiency as well as increased BDNF, VEGF, and insulin-like growth factor type 1 (IGF-1) levels (Bernardo et al., 2016; Foster, 2015).
Animal studies have also been done to test the efficacy of exercise for slowing disease progression. The question is, do animal studies produce valid data or are they a distraction? There have been conflicting views, but overall, they have produced similar results to human trials. With animal studies, there are more factors to consider than in humans because of the innate differences in their genome, and how the experiment is completed. For example, in animal studies, the Alzheimer’s gene is purposely introduced into the body and triggered. This could lead to some discrepancies when comparing to human trials, however it is still more ethical to begin with animal trials before testing on humans.

There are many factors to consider in relation to the treatment of neurodegenerative diseases including the cause of the disease, the method of action behind the disease, and how the body reacts to such treatments. Because much is still unknown about AD, pharmacological treatments have been difficult to formulate. Therefore, the purpose of this literature review is to present research related to the effectiveness of different types of exercise on slowing the progression of Alzheimer’s Disease. Additionally, there will be a discussion on current clinical trials, as well as, a proposed future study.

Methodology

Published and Peer-reviewed articles were collected from many sources, mainly the Western Michigan University library databases. Online journal databases such as PubMed, Medline, ClinicalTrials.gov, and National Institute of Health (NIH) were the primary sources for much of the literature found. The specific search terms included “Alzheimer”, “Alzheimer’s Disease”, “neurodegeneration”, “aging brain”, “exercise”, “physical activity” and varying combinations of these key words. Therefore, we will review Alzheimer’s Disease, it’s definition,
diagnosis, how it’s affected by exercise, exercise as a treatment, and current and future treatments/studies.

**What is Alzheimer’s Disease?**

AD is a type of dementia determined by neurofibrillary tangles and amyloid plaques building up in the brain. This buildup leads to neurodegeneration and inevitably, loss of memory and cognitive function. In the absence of disease, any frequently used or overlearned abilities are considered “crystallized intelligence” and typically remain stable or may slightly improve with normal aging. Types of memory that are in this category include vocabulary, and spatial perception. On the other hand, the ability to problem solve and think reasonably under varying circumstances fall under “fluid intelligence”. Chains of thought that fall under “fluid intelligence” include executive functions, processing speed, attention, and declarative memory. These “fluid intelligence” activities tend to decline with healthy aging, however, the deterioration does not typically impact their ability to complete everyday tasks or activities (Tyndall et al., 2018, p. 216). AD and other neurodegenerative diseases promote the decline in memory and general cognitive ability even after everyday tasks become impossible.

In the absence of AD, many elderly individuals experience amyloid deposition in their brain. According to research conducted by Aizenstein et al. (2008), about 50% of people over 65 years old have some level of amyloid deposition in their brain, but half of these people do not show symptoms. It was shown that about 21% of the people studied who have amyloid deposits are not cognitively impaired. Therefore, it cannot be deduced just because there are amyloid plaques in the brain, that a patient will have a decrease in cognitive functioning (2008). Cognitive decline is based on observed symptoms and previously the only way to detect amyloid
plaques was during an autopsy, however, PET scans can now show images of the affected areas of patients in vivo.

APOE is the most commonly studied genetic variant relating to late onset Alzheimer’s disease (LOAD). The ε4 allele on APOE seems to increase the risk of developing LOAD the most and is a frequent topic of study of the APOE gene. The chance of developing LOAD increases two and a half times for carriers of the ε4 allele, while having two copies of the ε4 allele increases the risk 16 times (Tyndall et al., 2018). This demonstrates a strong relation between the presence of the allele and the onset of AD. Early onset AD, on the other hand, appears to relate more with genetic variants (Tyndall et al., 2018). Variants specifically in the APP, PSEN1, and PSEN2 genes have been associated with mostly early onset AD, but also some late onset familial and sporadic cases have shown some variation in APP, PSEN1, and PSEN2.

The aggregation of tau proteins, which are considered another hallmark of AD, are encoded by the MAPT gene. Studies completed regarding this hypothesis have conflicting results but reveal the relation of MAPT variants increasing risk for AD, particularly in people who are not carriers of the APOE ε4 allele. In one study, researchers identified 36 different Mendelian variants in 11 genes, including APP, PSEN1, PSEN2, and MAPT, that can affect the chance of developing AD. It was also observed that genetic variants similar to those may cause early onset AD and relate with other neurodegenerative diseases including Parkinson’s disease (PD), Amyotrophic lateral sclerosis (ALS), and Frontotemporal lobar degeneration (FTD) (Fernández et al., 2017).

However, there is still a lot that we don’t know about the cause or causes of AD, and there could still be many factors that lead to its onset that are yet to be discovered.
Physical exercise and the brain

Though there is no cure for AD, research has been conducted to find either preventative methods or treatment options to slow the progression. One potential treatment may be increasing physical activity. We know that healthy brains are positively affected by physical activity. After every workout, the brain’s dopamine, serotonin, and noradrenaline levels are higher than normal. This can improve mood, but also increase attention span, focus, and eventually memory (Suzuki, 2017).

Aerobic Exercise

Exercise has been shown to influence brain plasticity in a variety of ways. In one study, healthy sedentary individuals between the ages of 55 and 80 years old were randomly divided into either the aerobic (walking) group or the non-aerobic, flexibility, toning, and balance (FTB) group. It was noted that the FTB group was possibly altering the results by testing the social aspect of group exercise along with FTB exercises, while the walking group tested brain function as a direct result of aerobic activity (Voss et al., 2013). In the walking group, it was recommended that participants walk in their target heart rate zone each week with a five-minute warm up and cool down surrounding the activity. In the FTB group, the four different exercises were changed every three weeks, always including toning exercises, yoga sequences, balance practice, and an exercise of their choice, along with warm up and cool down periods. The first week they focused on learning the exercise, while during weeks three and four, they increased the intensity by adding more weights or repetitions. There were positive relationships shown between BDNF and IGF-1 serum levels, hippocampal volume, and aerobic exercise, however, these were not significant in the FTB group (Voss et al., 2013). Because of the more social and
team-like atmosphere of the FTB group, we cannot determine that any outcomes are from exercise alone. The comparison eventually demonstrated the plasticity of the brain in healthy adults, however, it is impossible to know if the increase in social interaction of the FTB group had any significant effect on brain plasticity along with the type of exercise.

Aerobic exercise affects the function of the brain by influencing BDNF, IGF-1, and VEGF levels. Increases in BDNF can also be associated with greater hippocampal volume leading to an increase in cognitive ability (Voss et al., 2013). The details are still unclear about how this works on a molecular level. Without dementia, adults already lose 1-2% of their hippocampal volume per year. The most atrophied areas after the age of 30 are the prefrontal, neostriatal, and hippocampal regions. Degradation of these sections first, causes memory to be the first cognitive ability to wane (Tyndall et al., 2018). Because BDNF, IGF-1, and VEGF function most apparently in the lateral and temporal lobes, they often play a major role in minimizing cognitive decline as well (Voss et al., 2013). The temporal lobes are involved with processing sensory input and associating senses and emotion with memories. These areas are the main regions of interest when finding ways to combat AD, and because BDNF, IGF-1, and VEGF appear to increase growth and survival of specific subtypes of neurons, this neurogenesis could reduce the effects of AD (Bernardo et al., 2016).

Aerobic exercise is associated with increases in gray and white matter in both healthy older adults as well as those with dementia. This increase is primarily in the temporal, hippocampal and prefrontal regions. This further illustrates the plasticity of the brain in response to exercise (Tyndall et al., 2018). Because the brain demonstrates plasticity or remodeling, aerobic exercise may be a path to positively alter brain function. Braskie et al. (2014) investigated 82 individuals at least 65 years old from the Cardiovascular Health Study (observing
coronary heart disease and stroke in the older population) who had neurological and neuropsychological exams that appeared “cognitively intact at baseline”. Of these individuals, 43 remained cognitively intact for the study while 39 developed AD before the final MRI was completed. The researcher found that lower physical activity intensity strongly related both with those who developed AD before the MRI and those who had lower brain volume after 9 years, while controlling for other factors affecting brain atrophy including age, sex, diagnosis of AD, and BMI (Braskie et al., 2014). In this study, they also noticed the year-nine reported physical activity values were not significantly related to brain volume. However, this could be from inaccurate reporting of physical activity from the AD patients. Another possibility for this contradiction is that long term effects of exercise are more effective at increasing brain volume than the immediate effects of exercise (Braskie et al., 2014).

Alternative Exercise

Other types of exercise focusing on mindfulness, tai chi, and the practice of yoga have also been observed with regards to neurological disorders. Combining mind therapy with physical motion can produce some interesting results with neurotransmitters and hormones in the brain. In patients with dementia in long term care facilities, practicing yoga three times a week for 12 weeks has reduced depression states and problem behaviors while increasing overall mental health. With increased availability of alternative medicine practices, treatments such as yoga have made an appearance with a nice balance of physical exercise and mental relaxation. There is a shortage of evidence-based research on the effects of alternative exercise practices on neurological conditions, but a study was completed with a Sit ‘N Fit chair yoga class to test for different brain growth factors with AD. After 8 weeks of the chair yoga program, the researchers noticed an improvement in the Six-Minute Walk Test, Gait Speed Test, and Berg Balance Scale
Score. There were also increased levels of nerve growth factor (NGF) which protects basal forebrain neurons that are otherwise affected in people with AD. After just 20 minutes of yoga chanting, the NGF levels were significantly elevated, demonstrating the relationship between yoga and increasing brain function (Mooventhan & Nivethitha, 2017).

There is a current study still recruiting participants that tests the combined treatment of yoga practice and taking 800mg curcumin twice a day. However, the participants cannot begin with any type of dementia and must have an MMSE > 24. The thought behind this was that curcumin is isolated from turmeric and has been discovered to “inhibit several potential disease pathways” (“Curcumin and Yoga Therapy for Those at Risk for Alzheimer’s Disease,” n.d.). Paired up with yoga, which could initiate brain plasticity and growth, together they could potentially prevent Alzheimer’s and other dementias before they begin.

There are still many factors to exercise in addition to the physical activity that could be beneficial to patients with AD or other dementias. Exercising outdoors or having increased exposure to sunlight can increase vitamin D production which can then increase bone density, inevitably protecting AD patients if or when they fall. Physical activity can increase cognitive reserve to prevent delirium in patients with dementia or AD. Many forms of exercise also have a social component that can influence the human brain and cognition which could slow the progression of AD. A lack of social interaction and involvement is something that appears to relate with an increased risk of dementia for many older people who live alone, but very little research has been completed on the direct relationship between social networks and AD. In nursing homes, one intervention promoting social involvement demonstrated more successful management of “transient agitation behavior” in people who had dementia compared to those who didn’t have social intervention (Nelson & Tabet, 2015).
Physical exercise for patients with AD

It has been supported by many studies that exercise does slow the decline in cognitive ability for patients with AD. The specifics of how physical exercise works on a molecular level to protect the brain is still undergoing research, but exercise is considered a recommended “preventive and therapeutic non-pharmacological strategy” in helping people with neurodegenerative diseases (Bernardo et al., 2016). Bernardo et al. also contrasts the adaptations of brain matter after physical exercise to the contractile effects on skeletal muscles, saying that the brain is associated with more of the systemic changes due to physical exercise. In mouse models, a decrease in amyloid plaques and tau proteins were observed following exercise training. This signifies that physical activity could help regulate the basic mechanisms that lead to AD. The health of brain mitochondria appears to be tied to increased BDNF levels, specifically with regards to improved glucose transport, increasing responsiveness of certain enzymes, and preventing apoptosis of neural tissue. This directly impacts neurodegeneration and highlights that an “acute bout of aerobic exercise seems to be sufficient to increase BDNF plasma levels in patients with AD” (Bernardo et al., 2016).

Müller et al., (2018) conducted a study that focused on a rare form of AD called autosomal dominant Alzheimer’s disease (ADAD) which was shown to be strongly affected by physical activity. ADAD affects β-amyloid processing and leads to a buildup of β-amyloid plaques. The World Health Organization (WHO) and American College of Sports Medicine’s guidelines were tested regarding 150 minutes of physical activity each week having “beneficial effects on global cognition, cognitive decline, functional status, and AD biomarkers in the brain and cerebrospinal fluid (CSF)” (Müller et al., 2018). The Clinical Dementia Rating (CDR) and MMSE were the scales used to test memory function in this case. The CDR tests six areas
including memory, orientation, judgement and problem-solving, community affairs, home and hobbies, and personal care. This final score, called the Sum of Boxes (SOB) score ranges from 0 to 3, with 3 signifying severe dementia and 0 marking no dementia. Over 12 months, participants reported their leisure-time activity (including swimming, walking, jogging, cycling, or tennis) with 156 staying at or above the 150-minute recommendation per week and 68 participants getting less than the guidelines suggested. In people with the mutation for ADAD, the MMSE scores were higher in those who completed more regular physical activity. However, in this study, among those who do not have the mutation, the MMSE score was not significantly different between those who were more physically active. The CDR-SOB results for people with the mutation also showed that a lower score (minor impairment) is associated with higher levels of physical activity compared to a stronger impairment associated with less activity (Müller et al., 2018).

Animal studies

Animal studies have been done with rats and mice to test the hypothesis of exercise slowing the progression of AD. However, it has been questioned: are animal studies actually valid or a distraction? Popular mouse models are testing familial AD because that is what can be controlled and triggered by altering the genetic code (LaFerla & Green, 2012). Most of the human population with AD however, has sporadic AD meaning that it started with age and a trigger, not necessarily because of a directly inherited gene sequence. For the rest of the AD population suffering from familial AD, it is similar to the mouse model.

In a mouse model study, Soto et al., (2015) concluded that aerobic exercise from midlife to old age had a part in preventing neurovascular decline from old age along with increasing
synaptic plasticity. In the absence of the APOE gene, however, this relationship did not exist between exercise and neurovascular decline. This demonstrates the association between APOE and neurodegeneration. Physical exercise in humans increases the cerebral blood flow, neurogenesis, hippocampal volume, and angiogenesis, and improves memory (Soto et al., 2015).

Enhancing neurogenesis in rats with AD was the goal for one experiment completed by Kim et al., (2014). This study consisted of four groups: a control group without exercise, a control group with exercise, an Aβ$_{25-35}$ injection only group, and Aβ$_{25-35}$ injection and exercise group. The Aβ$_{25-35}$ injection is what was used to simulate the effects of AD on the brain. To test their initial memory, the rats were placed in a light chamber for 60 seconds before a guillotine door opened to reveal a dark chamber. The time was recorded to see how long before the rats entered the dark chamber, and this was called “latency”. Immediately after entry, a guillotine door closed behind the mouse and an electric shock of 75V was delivered to the floor grids for three seconds. Five seconds after the shock ended, they were moved back to their home cages. Twenty-four hours later, the latency to move into the dark chamber was measured again up to a maximum of 600 seconds. This time there was no shock in the dark chamber. It appeared the rats with the injection had a shorter latency period, which relates to a short-term memory impairment. This would signify that the Aβ$_{25-35}$ injection does represent some deficits in short term memory, similar to AD (Kim et al., 2014).

The rats were anesthetized immediately after the latency testing, and their brains were analyzed for BDNF expression, apical dendritic length, and neurogenesis in the hippocampus, among other analyses. The researchers showed that the cells that were actively participating in neurogenesis were decreased upon Aβ$_{25-35}$ injection, but increased again with treadmill exercise in both the injection group and the control group (Kim et al., 2014). This provides us with
Evidence that exercise does increase neurogenesis, both with AD and without the disease. In either case, exercise increases neuronal growth even after being delayed or halted by a neurodegenerative disease.

_Treatments_

Some medications are available along with some therapy programs to treat AD. However, there is no reliable treatment available to cure Alzheimer’s, just to slow the progression. These also don’t work in everyone. Many researchers now believe to find an effective treatment to AD, it’s important that treatment begins in the early pre-symptomatic stages of the disease (Ryman et al., 2014). This becomes difficult because the primary way to diagnose AD is by the observation of symptoms in the affected individual. There are physical and cognitive therapy programs including a new trial called EXERT. Beginning in June 2016 and hoping to collect results in June 2020, this trial is currently in progress. Enrolled are people between the ages of 65 and 89 years old with inclusion criteria consisting of an MMSE score of 24+ for more than a high school education, and MMSE 22+ for people with at least some college. More criteria include a CDR of 0.5, a caregiver or partner with at least weekly contact, sedentary or underactive individuals, willing and able to travel to the YMCA 4 days/week for 18 months, and a modified Hachinski score of 4 or lower. The participants are randomly assigned to the aerobic exercise group or the stretching-balance-range of motion group. The aerobic group exercises at 70-80% of maximum heart rate for 30 min, with 10 minutes added for warm up and an extra 5 minutes for cool down 4 times a week for 12 months. The stretching and balance group will do the same time segments, but at 35% max heart rate or below (“Exercise in Adults with Mild Memory Problems (EXERT),” n.d.). It will be interesting to see what the results will show once this study is complete.
The current first line pharmacological treatment of Alzheimer’s includes acetylcholinesterase inhibitors. By inhibiting acetylcholinesterase, we increase the amount of acetylcholine that is available for use in the body. It doesn’t function by treating the disease itself, but merely attempts to treat symptoms such as functional ability, behavior, and cognition (Knowles, 2006). This helps the patients feel more comfortable with functioning in their everyday life. The most common treatment option is the acetylcholinesterase inhibitor Aricept (donepezil) which is effective for mild to moderate AD. Other medications that fall into this same category for mild to moderate symptoms include Razadyne (galantamine) and Exelon (rivastigmine). As AD progresses to become more severe, preferred medications work on regulation of glutamate. When too much glutamate is present, brain cell death proceeds. Namenda (memantine) is an N-methyl D-aspartate (NMDA) antagonist that can be used in combination with Aricept in a combined form known as Namzaric (“How Is Alzheimer’s Disease Treated?,” n.d.).

Like many diseases, people prefer to pair up a pharmacological treatment with a lifestyle modification. As observed by many research studies that have been completed or are currently in progress, physical activity may aid in slowing the progression of AD or as a primary preventative treatment.

Future

The future of AD treatment is still foggy as we do not clearly understand the causes of the disease. Using cholinesterase inhibitors and targeting NMDA antagonists are the two main methods that we have available for pharmacological treatment of AD. Other main characteristics for Alzheimer’s are neurodegeneration causing a decrease in hippocampal volume, decrease in
BDNF, and creation of neurofibrillary tangles and β-amyloid plaques. One of the ways that we know to increase neurogenesis, hippocampal volume, and BDNF levels are with physical exercise.

There are many studies currently in progress testing the relationship between exercise and AD. A table outlining some of these tests can be found in Appendix A. The study titled “Effects of Aerobic Exercise for Treating Alzheimer’s Disease (FIT-AD)” by Fang Yu, PhD, measures cognition and hippocampal volume every 3 months. The intervention is 20-50 minutes of cycling or range-of-motion exercises, 3 times a week, for a year (“Effects of Aerobic Exercise for Treating Alzheimer’s Disease” n.d.). Another study, on the other hand, led by Jeff Burns, MD, of University of Kansas Medical Center, examines how quantity of exercise may affect AD. Here, there are three exercise groups, each with increasing amounts of exercise for the week. One group exercises 75 minutes over 3 days, the second group exercises 150 minutes over 3-5 days, and the last group exercises 225 minutes over 4-5 days (“Dose Response Study of Aerobic Exercise in Older Adults” n.d.). One more ongoing test compares different exercise intensities with groups performing activities at 70% max heart rate (HR) compared to alternating 60% max HR and 80% HR (“Alzheimer’s Disease and Physiological, Cognitive Function and BDNF Levels of Plasma Adaptation After Exercise Training” n.d.). Once all these results are organized, it will be interesting to compare their outcomes to determine a beneficial activity regimen.

Unfortunately, I could not run my own research study because of the population I wanted to work with, but I have plans for how I would run a study relating exercise to the progression of Alzheimer’s.
Proposed Study

**Subjects:** Previously sedentary people will be recruited who all have been diagnosed with Alzheimer’s for at least a month and are over 60 years old. Levels of decline will be determined with CDR and should be between 0.5 and 2. All subjects will be in an assisted living facility to control for environmental factors that might affect the results.

**Methods:** A PET scan and MMSE score will be completed and recorded before the study begins to determine amyloid plaque buildup and to collect baseline hippocampal volume. Subjects will be randomly assigned to one of three groups aerobic exercise, yoga, or control group. The aerobic group will complete cycling exercise, at 60% of maximum heart rate for 3, 10-minute periods with 5-minute rest between each workout, giving a 2:1 work to rest ratio. This exercise program will be conducted 3 days per week. The yoga group will meet 3 days per week and complete 10 minutes of yoga poses followed by 5 minutes of rest for a total of 30 minutes of yoga poses. The control group will meet 3 days per week for 40 minutes at which time they will watch a predetermined video. The groups will proceed with this plan for 16 weeks. PET scans and MMSEs will be completed before and after the study to look for changes in hippocampal volume and amyloid plaques. Statistical analysis will be conducted using a two-way analysis of variance (group by test) with a priori level of significance set at p<0.05. Post-hoc analysis will be done using Tukey Honest Significant Difference Test.

**Conclusion**

Past research has seemed to indicate that there is promise in the use of exercise as a means to treat AD. Aerobic exercise seems to have a greater influence than strength and flexibility exercises, however, any physical activity is better than adopting a sedentary lifestyle.
If a patient is past the point where they can exercise aerobically, it would still be valuable to get them up and participating in flexibility training, yoga, or strength exercises. Group exercise also includes socialization that can also play a role in how AD progresses in individuals. Because the brain has the characteristic of plasticity and it has been shown that exercise can increase plastic changes in the brain, it makes sense that physical activity should be something that people do throughout their lives to improve, maintain, and slow degeneration of cognitive function.
References


Alzheimer’s Disease and physiological, cognitive function and BDNF levels of plasma adaptation after exercise training - ClinicalTrials.gov. (n.d.). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02968875


## Appendix A

### Current ClinicalTrials.gov Studies

<table>
<thead>
<tr>
<th>Research Study/Location</th>
<th>Subjects</th>
<th>Exercise mode</th>
<th>Variables</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects of Aerobic Exercise for Treating Alzheimer’s Disease (FIT-AD):</strong> (Fang Yu, PhD) University of Minnesota -Clinical and Translational Science Institute</td>
<td>66yo+ with probable or possible AD. 15 ≤ MMSE score ≤ 26. CDR Score 0.5-2 Community dwelling Stable on AD drugs &gt;1 month</td>
<td>Cycling</td>
<td>Independent: 20-50 min 3X/wk of cycling or range of motion exercises. Dependent: Cognition measured after 3, 6, 9, and 12 months with the Alzheimer’s Disease Assessment Scale- Cognitive Subscale. Hippocampal volume measured with an MRI.</td>
<td>Results not posted yet.</td>
</tr>
<tr>
<td><strong>Benefits of Exercise in Alzheimer’s Disease:</strong> (Carmela Tartaglia, MD) University Health Network, Toronto</td>
<td>60-95yo with probable AD. CDR &lt; 2 10-25 on Montreal Cognitive Assessment Presence of respective caregiver</td>
<td>Personalized outpatient exercise program</td>
<td>Independent: A personalized exercise regimen is made for each participant in the exercise group. The other group did not deviate from normal activity levels. Dependent: Behavioral Symptoms measured on the Montreal Cognitive Assessment and volume loss via MRI</td>
<td>Results not posted yet.</td>
</tr>
<tr>
<td><strong>Effect of Physical Exercise on Alzheimer Patients:</strong> (Steen G Hasselbalch) Copenhagen University Hospital, Rigshospitalet</td>
<td>50-90yo MMSE score 20+. Mild to moderate AD. Imaging consistent with AD Home-dwelling with caregiver available At least 7 years of schooling Stable on anti-dementia or mood stabilizing drugs for ≥ 3 months</td>
<td>Patient choice of stationary bike, treadmill, or cross-trainer</td>
<td>Intervention: Supervised 1 hr 3X/wk moderate aerobic exercise for 16 weeks. Control group: receiving usual care. Dependent: Complete blood sampling to measure biomarkers. A subgroup will also get an MRI, PiB-PET and lumbar puncture to check for changes in structure and β-amyloid accumulation.</td>
<td>Results not posted yet.</td>
</tr>
<tr>
<td>Physical Exercise as an Additional Treatment for Alzheimer Disease: (Jerson Laks) Universidade Federal do Rio de Janeiro, Brazil</td>
<td>AD diagnosis</td>
<td>30 min 2X/week on treadmill at moderate intensity</td>
<td>Independent: The exercise group will treadmill at 60% VO2max for 30 min 2X/wk. Dependent: Measured cognitive function with CAMCOG, Trail Making Test A, Digit Span, Stroop Test, Rey auditory-verbal learning test and Clock test. Physical evaluation will be with the BERG balance scale, Sit-to-stand, functional reach test, and the “time to up and go” test. Results not posted yet.</td>
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<tr>
<td><strong>Dose Response Study of Aerobic Exercise in Older Adults: (Jeff Burns, MD) University of Kansas Medical Center</strong></td>
<td>65yo+ Sedentary individuals Community dwelling with caregiver CDR score 0. No dementia Stable medications ≥ 30 days</td>
<td>0, 75, 150 or 225 minutes of exercise/week</td>
<td>Control: maintain current physical activity Exercise 1: (50% group) 75 minutes spread over 3 days. Exercise 2: (100% group) 150 minutes spread over 3-5 days. Exercise 3: (150% group) 225 minutes spread over 4-5 days. After 26 weeks, they tested visuospatial processing, VO2max, and a 9-item physical performance test. Some of these outcomes displayed strong relationships while others did not. Visuospatial Processing improved with any level of exercise, Maximal Oxygen Consumption and Simple Attention both improved directly with more exercise. Physical Performance Tests and Set Maintenance &amp; Shifting showed no correlation with exercise. Verbal memory tended to decrease with more exercise. The Reasoning outcome showed no exercise is best.</td>
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<td><strong>Alzheimer's Disease and Physiological, Cognitive Function and BDNF Levels of Plasma Adaptation After Exercise Training (MARAE): (Jean-Luc Ms Fanon, Doctor) University Hospital Center of Martinique</strong></td>
<td>60yo+ Alzheimer’s Disease patients Score of 15+ on MMSE Not regularly biking Ability to pedal</td>
<td>Endurance training at 70% of maximal heart rate 2X/week Interval training with 4 min at 60% and 4 min at 80% of maximal heart rate. Control: therapeutic</td>
<td>Independent: 20 participants will cycle at 70% max heart rate (HR) 2X/wk. 20 will do interval training with 4-minute base (60%HR) and 1 minute peak (80%HR) 2X/wk. Control group had 9 therapeutic meetings. Dependent: The experimental group’s maximum aerobic power, Results not posted yet.</td>
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<td>Tai Chi 6-Form Sports Apparatus With Alzheimer's Disease: (Alice May-Kuen Wong) Chang Gung Memorial Hospital</td>
<td>59-92yo Mild and moderate AD patients</td>
<td>12 week Tai chi 6 form with music rhythm 12 week computer based cognitive training games 12 week Physico-Mental rehabilitation Wii.</td>
<td>Year 1: 12 weeks of Tai Chi 6-form along with music rhythm. Year 2: 12 weeks of computer-based cognitive training games. Year 3: 12 weeks of Physico-Mental rehabilitation Wii. Measure balance outcomes.</td>
<td>Results not posted yet.</td>
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Education meetings

endurance, heart rate, prehension strength, MMSE, REY’s test, and BDNF plasma levels were examined one month into the study and one month after intervention ended.