The effects of aerobic exercise and physical activity on progression of Alzheimer's disease and mild cognitive impairment

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THE EFFECTS OF AEROBIC EXERCISE AND PHYSICAL ACTIVITY ON PROGRESSION OF ALZHEIMER’S DISEASE AND MILD COGNITIVE IMPAIRMENT

by

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CHAITALI KORGAAONKAR

ABSTRACT
This abstract will provide a brief overview of the following literature review. Alzheimer’s disease (AD) is the most common cause of dementia, and is a rapidly growing public health concern, as an increasing number of the world’s population is living well beyond 65 years of age. Alzheimer’s Disease is a progressive neurodegenerative condition, first presenting with mild memory impairment, and advancing over the course of years to profound memory loss, complete immobility, lack of speech and facial recognition. Currently, only palliative treatments are available to delay the progression of the disease, and lessen the severity of the cognitive impairment. However, until a cure is available, researchers and physicians have turned their attention to alternate therapies, one of the most important being exercise. Research efforts have now turned to examining the relationship between the positive physiological responses to exercise, and attenuation of the classic neurodegenerative patterns in patients with AD. The current study examined the effects of aerobic exercise, strength training and resistance-based exercise, and multimodal exercise (containing both
of the aforementioned exercise modalities) on the physical and mental/cognitive health of patients with mild cognitive impairment (MCI) and AD. Thus far, exercise therapy has proven to be of great potential value as a supplement to pharmacological treatment, as well as a stand-alone prescription for patients with a milder form of cognitive impairment due to the onset of a neurodegenerative condition. The benefits can be grouped into two categories, cognitive and physiological. The effects on cognitive function range from improved memory to increased independence in activities of daily living, and the physiological effects range from improved clearance of amyloid beta plaques in the brain, to reduction of neuroinflammatory processes. The available research on this subject is extensive, covering a variety of exercise modalities at different intensities, and taking into consideration effects on individuals with MCI, early AD, and advanced AD. The general consensus is that continued, long-term adherence to an appropriate exercise routine can delay cognitive decline, and help patients with neurodegenerative diseases to live independently for a longer period of time. The improvements in cognition, memory, immediate recognition, and other related cognitive functions are mostly attributed to the heightened health of the brain tissue and neural circuitry due to exercise. Exercise (mainly aerobic) enhances cerebral blood flow, improves cardiovascular health, reduces the risk for type 2 diabetes mellitus, and has several other important effects that prevent the formation of pathological biomarkers of AD and promote neurogenesis. Atrophy of regions such as the hippocampus, amygdala, and cerebral cortex can be
prevented, and reversed to a certain extent, as a result of long-term exercise therapy. The results of current research could assist physicians and caregivers to provide the appropriate type and intensity of exercise to patients with early, intermediate, and advanced stages of Alzheimer’s disease. Proactive exercise therapy for individuals with a known family history of neurodegenerative disease may help to maintain brain volume, specifically in the hippocampus, and reduce the risk of severe cognitive impairment. Future directions for research include examining the combined effects of pharmacological treatment and exercise therapy, and determining the average amount of time by which exercise delays the progression of early stage cognitive impairment to advanced impairment.

**Key Terms:** aerobic exercise, Alzheimer's disease, amyloid plaque, hippocampus, mild cognitive impairment, neurodegeneration, neurofibrillary tangle
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LIST OF ABBREVIATIONS

$A\beta_{40}$.......................................................... Amyloidogenic amyloid beta (40 amino acids)

$A\beta_{42}$.......................................................... Amyloidogenic amyloid beta (42 amino acids)

AD ........................................................................... Alzheimer’s disease

ADL ........................................................................... Activities of daily living

BDNF ...................................................................... Brain-derived neurotrophic factor

CAA ......................................................................... Cerebral amyloid angiopathy

CSF ......................................................................... Cerebrospinal fluid

FDA ......................................................................... Food and Drug Administration

FTD ......................................................................... Frontotemporal dementia

GDNF ...................................................................... Glial cell line-derived neurotrophic factor

MCI ......................................................................... Mild Cognitive Impairment

NFT ......................................................................... Neurofibrillary tangle

PE ............................................................................ Physical exercise

T2DM ....................................................................... Type 2 diabetes mellitus

IGF-1 ....................................................................... Insulin-like growth factor-1

$\text{VO}_{2}\text{max}$ .......................................................... Peak oxygen consumption rate
INTRODUCTION

The first part of this thesis will briefly discuss the known impacts of Alzheimer’s disease (AD) on cognitive and behavioral functions, significance in a public health context, and the importance of diversifying treatment options for individuals with early-stage diagnosis. Next, the efficacy of a novel approach to mitigating some of the symptoms of Alzheimer’s disease will be discussed through a review and analysis of existing literature. This body of literature focuses on physical exercise interventions, and their impact on multiple parameters used to measure disease progression. Finally, recommendations for further study and future directions for research will be given, as well as opinions regarding clinical applications of the existing research.

A brief overview of Alzheimer’s disease

Alzheimer’s disease is the most common form of dementia, and is currently the sixth leading cause of death in the United States, with over five million Americans currently affected by AD. It is a progressive disease affecting memory, cognition, and behavior, with advancing age being the most significant risk factor (alz.org, 2016). The principal symptoms are decline in short-term memory and fine motor skills, speech difficulties, and impairment in mood regulation. Ultimately, AD patients may become completely immobile, requiring constant care and supervision for activities of daily living (ADL). Early AD is often confused with normal age-related change in cognitive ability, and the differences between the two are essential in early detection.
Table 1. Key differences between Alzheimer's disease and normal age-related change. Early detection and diagnosis is the most important way to slow the progression of disease symptoms. Taken from (alz.org/10signs (n.d.)).

<table>
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<th>Signs of Alzheimer’s/dementia</th>
<th>Typical age-related changes</th>
</tr>
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<td>Poor judgment and decision making</td>
<td>Making a bad decision once in a while</td>
</tr>
<tr>
<td>Inability to manage a budget</td>
<td>Missing a monthly payment</td>
</tr>
<tr>
<td>Losing track of the date or the season</td>
<td>Forgetting which day it is and remembering later</td>
</tr>
<tr>
<td>Difficulty having a conversation</td>
<td>Sometimes forgetting which word to use</td>
</tr>
<tr>
<td>Misplacing things and being unable to retrace steps to find them</td>
<td>Losing things from time to time</td>
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With a growing aging population, AD is becoming a greater concern in the context of public health, as more resources are being used in the care of AD patients in assisted living homes, skilled nursing facilities, hospitals, and in their own homes. Barnes (2015) estimates that over 20% of United States residents are currently over the age of 65 years and approximately 11% of the population
over 65 years of age are diagnosed with AD (alz.org, 2016). This impressive statistic results from major advances in public health, medical care, accessibility, and technology, but also poses a challenge to keep the elderly population in good health. Further, individuals who provide care for family members with AD often face significant physical, emotional, and financial demands. In 2015, over 15 million caregivers of AD patients delivered approximately 18.1 billion hours of unpaid care, and in 2016, the care of patients with AD and other dementias in the United States will cost roughly $236 billion (alz.org, 2016).

Due to the significant impact of AD on individual families and on the health care system, prevention, or delaying the onset of severe symptoms, needs to be at the forefront of research efforts. The FDA has approved several pharmacological treatments to palliate the symptoms of AD. While none of these drugs are curative, they work at various stages of disease progression to alleviate some of the most debilitating symptoms, namely, the decline in cognitive function. However, the effects of these drugs are limited and transient.

In the past three to five years, research has expanded to include alternate therapies and one that shows promise is physical exercise as a potential preventive measure. It has been hypothesized that physical exercise that may delay the onset of the more severe symptoms of AD and may improve many of the parameters (cognitive function, performance on ADLs, memory recall, and histopathological markers such as Aβ deposition and presence of NFTs) that are used to measure disease progression.
Neuropathological changes in Alzheimer's disease

The hallmark neuropathological signs of AD are protein deposits in the brains that include senile plaques and neurofibrillary tangles (Hardy & Allsop, 1991). The extracellular plaques are made up of amyloid fibrils surrounded by a ring of dystrophic neurites, as well as reactive microglia and astrocytes. Cleavage of the amyloid precursor protein (APP) by β-secretase and γ-secretase yields amyloidogenic Aβ, which is 40 or 42 amino acids in length. Cleavage of the protein by α-secretase does not yield the amyloidogenic version. The APP gene is located on chromosome 21, and a substitution mutation in the 642\textsuperscript{nd} position gives rise to the disease in familial cases inherited through an autosomal dominant pattern. A mutation in the 618\textsuperscript{th} position results in cerebral amyloid angiopathy and increased risk of cerebral hemorrhage (Hardy & Allsop, 1991). However, genetic mutations make up very few cases of AD as compared to the sporadic occurrences. Intact APP plays a role in cell-cell adhesion, and aberrant cleavage patterns induce the formation of amyloidogenic Aβ (Hardy & Allsop, 1991).

While diffusely staining plaques are common in the cognitively intact elderly, plaques with dense cores are found in patients with AD (Serrano-Pozo, Frosch, Masliah & Hyman, 2011). The best evidence of Aβ-induced neurotoxicity is the presence of dystrophic neurites surrounding the dense core of the plaque. Dendrites and axons can become elongated, distorted, or bulbous (Su, Cummings & Cotman, 1993). Cytoskeletal abnormalities make these neurons
prime candidates for immunoreactive staining techniques. Amyloid plaques accumulate mainly in the isocortex, but their spread is not as predictable as that of NFTs. The plaques tend to spread to the allocortex, basal ganglia, nuclei of the brainstem, and the cerebellum. Similar to NFTs, association areas are affected more severely than primary sensory, motor, and visual areas. (Serrano-Pozo, Frosch, Masliah & Hyman, 2011).

There are two staging systems for amyloid deposition. The first system progresses through (A) amyloid deposits found in basal portions of the frontal, temporal, and occipital lobes, (B) all isocortical association areas affected with only mild hippocampal involvement, and (C) deposition of amyloid in primary isocortical areas and sometimes in the molecular layer of the cerebellum and subcortical nuclei like the striatum, thalamus, hypothalamus, subthalamic nucleus, and red nucleus (Braak & Braak, 1991). The second staging system consists of (1) isocortical deposition, (2) additional allocortical deposits in the entorhinal cortex, hippocampal formation, amygdala, insular, and cingulated cortices, (3) involvement of subcortical nuclei including striatum, basal forebrain cholinergic nuclei, thalamus, hypothalamus, and white matter, (4) involvement of brainstem structures, and (5) amyloid deposits accumulating in the pons and the molecular layer of the cerebellum (Thal, Rub, Orantes & Braak, 2002).

In addition to accumulating in the brain parenchyma, amyloid plaques also build up in the walls of the cerebral vasculature, specifically in the interstitium between the smooth muscle cells of the tunica media layer. This is called
cerebral amyloid angiopathy (CAA), and can also occur in the absence of AD. However, it is very common in AD patients, with about 80% of AD patients presenting with CAA at autopsy (Serrano-Pozo, Frosch, Masliah & Hyman, 2011). The same stains can be used to visualize amyloid plaques in the brain parenchyma and in CAA (Congo red, Thioflavin-S, or immunohistochemical stain with antibodies against Aβ). The staging system for CAA starts with grade 0, or absence of staining; grade 1, congophilic rim around otherwise normal-appearing vessel; grade 2, complete replacement of tunica media with congophilic material; grade 3, cracking of more than 50% of the vessel circumference, giving a “vessel within a vessel” appearance; and grade 4, fibrinoid necrosis of the vessel wall with additional amyloid deposit in the surrounding Neuropil (Serrano-Pozo, Frosch, Masliah & Hyman, 2011).

CAA typically affects cortical capillaries, small arterioles, and middle-sized arteries, with little involvement of venules, veins, and white matter arteries. Posterior parietal and occipital vasculature is affected more severely than the frontal and temporal lobes, but the cause for this is unknown. In the parietal and occipital lobes, the leptomeningeal arteries are affected more than the cortical arteries. Severity of CAA in a particular region of the cortex is scored from zero to four, with a score of zero corresponding to no staining of vasculature, and a score of four corresponding to widespread circumferential staining in leptomeningeal and cortical vessels, and additional perivascular amyloid deposition (Serrano-Pozo, Frosch, Masliah & Hyman, 2011).
The dystrophic neurites surrounding amyloid plaques in the brain parenchyma contain paired helical filaments, which make up the intracellular neurofibrillary tangles (NFTs) consisting of the hyperphosphorylated tau protein that is associated with microtubules. Neuropil threads, structures that commonly accompany Neuropil threads, are the breakdown products of dendrites and axons containing NFTs. The hyperphosphorylation of tau is mediated by the neurotoxic properties of Aβ, such as disturbance in calcium homeostasis (Hardy & Allsop, 1991).

There are three morphological stages recognized for NFTs. The first is the pre-NFT or diffuse NFT stage that is visualized as diffuse tau staining or otherwise normal-looking neurons. Dendrites are intact, and the nucleus is centered. The second stage is the mature or fibrillar intraneuronal NFT with cytoplasmic filamentous aggregates of tau that push the nucleus off to one side of the soma. The proximal portion of the axon, and all dendrites, appear distorted. The third stage is extraneuronal ghost NFTs resulting from death of neurons with tangles. The nucleus is absent and the cytoplasm stains prominently (Braak, Braak & Mandelkow, 1994, Augustinack, Schneider, Mandelkow & Hyman, 2002, Su, Cummings & Cotman, 1993). NFTs first appear in the allocortex of the medial temporal lobe and spread to the associative isocortex. The tangles then accumulate in limbic structures such as the hippocampus, amygdala, thalamus, and claustrum. Finally, NFTs spread to all
isocortical areas, with associative areas most severely affected (Serrano-Pozo, Frosch, Masliah & Hyman, 2011).

**Figure 1. Pathological lesions seen in Alzheimer's disease.** (A) Plaque in the frontal cortex stained by H&E. (B) Tangle in a hippocampal pyramidal neuron stained by H&E. (C) Plaque and a tangle, both highlighted by the silver stain. (D) Immunohistochemistry stain against the Aβ plaque. (E) Immunohistochemistry stain against the tau tangles. (F) A cortical Lewy body stained by H&E, (panel F not from an AD patient). Taken from Serrano-Pozo, Frosch, Masliah & Hyman (2011).

**Common pharmacological treatments for the symptoms of Alzheimer's**

Currently, all pharmacological treatments for AD are palliative and only treat the symptoms (Table 2). There are no existing drugs that can cure the disease completely. Therefore, disease progression can be slowed, but not halted. The most widely used treatments are the acetylcholinesterase inhibitors
donepezil, rivastigmine, and galantamine (Campos et al., 2016). Figure 2 shows the mechanism of action of the cholinesterase inhibitors, specifically at cholinergic neurons that innervate the hippocampus. Cholinergic neurons are typically lost in the progression of AD (Kim, Moon & Han, 2013), and acetylcholine synthesis is therefore diminished. A lack of cholinergic neurons has been found to contribute to cognitive deficits in AD patients (Shinotoh et al., 2000).

**Table 2. Common treatment options for Alzheimer’s disease.** Adapted from (http://www.alz.org/alzheimers_disease_standard_prescriptions.asp#memantine (n.d.)).

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Approved For</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Aricept</td>
<td>All stages</td>
<td>Nausea, vomiting, loss of appetite and increased frequency of bowel movements</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Razadyne</td>
<td>Mild to moderate</td>
<td>Nausea, vomiting, loss of appetite, and increased frequency of bowel movements</td>
</tr>
<tr>
<td>Memantine</td>
<td>Namenda</td>
<td>Moderate to severe</td>
<td>Headache, constipation, confusion and dizziness</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon</td>
<td>Mild to moderate</td>
<td>Nausea, vomiting, loss of appetite, and increased frequency of bowel movements</td>
</tr>
<tr>
<td>Memantine + donepezil</td>
<td>Namzaric</td>
<td>Moderate to severe</td>
<td>Headache, diarrhea, dizziness, loss of appetite, vomiting, nausea, and bruising</td>
</tr>
</tbody>
</table>
Figure 2. Acetylcholinesterase inhibitor: mode of action. Adapted from Campos et al. (2016).

ACh= acetylcholine; cAMP= cyclic adenosine monophosphate; CoA= coenzyme A; M= muscarinic receptors; N= nicotinic receptors; PI= phosphoinositols.
Another common treatment option is Memantine, an uncompetitive, moderate-affinity NMDA receptor antagonist (Campos et al., 2016). The drug works based on a voltage-dependent mechanism, such that signal induction is blocked when glutamate levels are high. When glutamate levels are high, depolarization frequency at the postsynaptic membrane increases, and the magnesium ion that blocks the NMDA under basal conditions is displaced. Blocking the signal prevents pathological calcium influx and oxidative stress in postsynaptic neurons, while physiological levels of signal transmission can still occur (Francis, 2009, Danysz, Parsons, Mobius, Stoffler & Quack, 2000, Parsons & Gilling, 2007). Memantine essentially decreases extraneous “noise” associated with erratic firing and transmission of signals (Francis, 2009).

While cholinesterase inhibitors are beneficial for patients with mild to moderate AD, memantine is the treatment of choice for patients with moderate to severe AD (Campos et al., 2016). Combination therapy with one cholinesterase inhibitor along with memantine is another treatment option; however, the efficacy and advantage over therapy with just one drug remains inconclusive for patients with moderate to severe AD (Campos et al., 2016). Table 2 gives a brief summary of the most common treatment options for AD. The multitude of side effects from drug therapy makes exercise an appealing alternative for many patients and their caregivers.
Importance of exercise in Alzheimer’s patients

The cognitive and behavioral decline in AD has a great impact on cardiorespiratory fitness, which is often a measure of physical fitness that can be improved with exercise. This is defined as a measure of the ability of the heart to provide the body with oxygenated blood (Yu et al., 2011). With decreased cardiorespiratory fitness, there is an increased chance of death at an early age, particularly in patients with AD who display neurological and psychological symptoms that serve as barriers to promoting physical fitness and adhering to an exercise regimen.

Figure 3. Cardiovascular health and relation to neuronal death. Decreased cardiorespiratory fitness is almost always seen in patients with cardiovascular disease. Both hypertension and hypotension can lead to neuronal death, through
lack of blood flow and waste product buildup, as well as Aβ accumulation; hypertension may also damage neurons via high pressure flow. Figure adapted from Barnes (2015).

Boyle et al. (2015) also found an inverse relationship between body mass index (BMI) and specific brain volumes, as well as a positive correlation between physical activity levels, and whole brain and parietal lobe volume. In patients with higher BMI, frontal and occipital lobes in particular had significantly smaller regional volumes. Physical activity is clearly a major contributor to good physical health, specifically in preserving the brain anatomy as it pertains to patients with neurodegenerative diseases. Higher BMI’s can place strain on the cardiovascular system, and prevent adequate blood flow from reaching the brain, thus increasing the risk of neuronal death and neurodegeneration, as shown in Figure 4.

Figures 4, 5, and 6 show the extent of correlation between BMI, physical activity, AD or MCI diagnosis and brain volume. Almost the entire brain volume is associated with BMI, and smaller portions, specifically the parietal lobe, with physical activity alone. Boyle et al. (2015) found well-defined regions (orbitofrontal cortex, posterior cingulate gyrus, and posterior hippocampus) that were associated with both BMI and physical activity. Weight loss due to aerobic exercise and other forms of physical activity can have a great impact on reducing brain atrophy and preventing volume loss in specific regions of the brain that are also affected by neurodegenerative diseases. Figure 6, from a study by Boyle et al. (2015) maps out such brain regions.
Figure 4. Correlation of brain volume with BMI and physical activity, brain location #1. The top panel shows regions of the brain where volume is associated independently with BMI. The center panel shows regions of the brain where volume is associated independently with physical activity. The bottom panel shows regions of the brain where volume is associated significantly with both high BMI and low physical activity. Figure taken from Boyle et al. (2015).

Early research on effects of exercise in AD patients focused on the feasibility of an exercise program for patients with moderate to severe AD, and determining whether cardiorespiratory fitness changed as a result of aerobic exercise. Yu et al. (2011) determined that aerobic exercise such as cycling indoors was a feasible way to improve cardiorespiratory fitness, and showed that with adequate guidance, patients with AD would be able to adhere to such a
program. It is recommended that patients with dementia be placed in physical exercise (PE) programs in order to maintain cardiovascular and respiratory health in spite of declining cognitive function (Ashlskog, Geda, Graff-Radford & Petersen, 2011).

![Figure 5. Correlation of brain volume with BMI and physical activity, brain location #2. MRI layout follows same pattern as that described for Figure 3, simply examining different brain regions. Figure taken from Boyle et al. (2015).](image)

Additionally, ADLs often require strength in the lower extremities, and with lack of use, muscle atrophy and weakness perpetuate the inability of AD patients to walk, bathe, climb stairs, and stand independently. Assessment of ability to
perform ADLs is a key factor in diagnosing dementia, and helps mark the progression of many neurodegenerative diseases, including AD (Nascimento et al., 2014). With weakness of the extremities, older adults, especially those with AD, are not motivated to exercise, and remain sedentary for longer hours in the day, thus perpetuating the disease progression (Yu, Savik, Wyman, & Bronas, 2011, Nascimento et al., 2014). While aerobic exercise proved to increase cardiorespiratory fitness, no significant changes were found in lower extremity strength, indicating that strength training should also be a focus of research in AD patients (Yu, Savik, Wyman & Bronas, 2011). This study also informed the idea that various exercise modalities need to be explored, as they improve different measures of health and ability to function independently.
Figure 6. Correlation of brain volume with BMI and diagnosis of AD or MCI. The top panel shows brain regions where volume is significantly correlated with BMI. The center panel shows brain regions where volume is significantly correlated with positive diagnosis of AD or MCI. The bottom panel shows brain regions where volume is significantly correlated with both BMI and positive AD or MCI diagnosis. Figure taken from Boyle et al. (2015).

Feasibility and safety of exercise in patients with AD

One of the main barriers to promoting exercise in the AD patient population, in addition to exercise program adherence, is concern for the safety of the patient. Without proper balance while using machines, and measures taken to ensure security of exercise equipment, there is a great potential for falls
and other injuries. However, even mild exercise has the same level of effect on cognitive function as moderate exercise, in patients with mild cognitive impairment (MCI), which is known as the defining line between normal aging and dementia (Varela, Ayán, Cancela & Martín, 2011). Therefore, even simple exercises such as walking or light cycling are advantageous, and heavy cycling or running exercises are not necessary for positive impacts on health.

**Physiological parameters improved by exercise**

Early small-scale studies that demonstrated the potential success of aerobic exercise interventions in improving physical fitness in patients with AD opened up possibilities for exercise improving certain parameters more directly related to the clinical course of AD. By enhancing blood flow through the brain vasculature, neurotrophins such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) that help to improve neuronal plasticity and memory, are up-regulated (Radak et al., 2010, Baker et al., 2010). BDNF gene expression is up-regulated by physical activity, and is one of the principal determinants of neuronal size and growth (Neeper, Gomez-Pinilla, Choi & Cotman, 1996). Additionally, exercise can enhance oxidative stress repair mechanisms, thus reducing the chance of free-radical accumulation, which is seen even before the characteristic amyloid plaques of AD (Radak et al., 2010, García-Mesa et al., 2011). Aerobic exercise can also decrease circulating levels of the Aβ biomarker for AD (Baker et al., 2010).
Diabetes and pre-diabetes have been consistently proven as risk factors for cognitive decline (Ravona-Springer et al., 2010), MCI (Roberts et al., 2008), and dementia (Schnaider et al., 2004). Clearance of blood glucose, which has also been shown to improve with exercise, is a significant factor in cognitive impairment and dementias, as unregulated glucose and insulin levels can have adverse impacts on the brain tissue (Baker et al., 2010). Regulation of blood glucose levels dictates the efficiency with which numerous metabolic processes occur, and also has a direct effect on the metabolism of other fuel sources. Promoting exercise in the AD patient population may also work to prevent simultaneous diseases such as type 2 diabetes mellitus and associated hyperinsulinemia, resulting in further dysregulation of blood glucose. Patients with late stages of AD are less likely to be able to manage their own medication regimen, and would also be at a higher risk of brain damage or death due to an uncontrolled hyper- or hypo-glycemic episode.

The hippocampus, a structure associated with memory and learning, is known to progressively degenerate in AD (Jack et al., 2010), and MRI studies show that with exercise, blood flow to the hippocampus increases significantly. Increased blood flow may counteract some of the degenerative processes, and allow a slower progression of AD (Ashlskog, Geda, Graff-Radford & Petersen, 2011). Various exercise modalities have been found to affect this parameter in different ways. In addition to deterioration of the hippocampus, there is a disproportionately large decrease in frontal, parietal, and temporal lobe volumes,
which are associated with a broad array of cognitive processes (Park, Polk, Mikels, Taylor & Marshuetz, 2001). Deposition of amyloid plaques in both the hippocampus and the amygdala is pronounced in patients with MCI and AD (Haroutunian et al., 1998, Markesbery et al., 2006), although the hippocampus has received more attention in research.

In many neurodegenerative diseases, sleep disturbances coexist with other symptoms, and while the exact cause is unknown, deterioration of the hypothalamus and brain stem do affect sleep-wake cycles (Nascimento et al., 2014). Sleep is often a time of restorative processes in the brain, and sleep disturbance prevents the appropriate metabolic processes from taking place in the brain tissue. Exercise may improve sleep quality by slowing the progression of neurodegenerative diseases (Nascimento et al., 2014). Although there is currently no consensus on the best type of PE for Alzheimer’s patients, studies have clearly outlined the multiple benefits of various exercise programs (Paillard, Rolland & de Souto Barreto, 2015).

In a broad context, chronic aerobic exercise has been found to improve synaptic connections in the brain and improve plasticity (van Praag, Christie, Sejnowski & Gage, 1999, Anderson et al., 2000), due to growth of capillaries in the brain (Black, Isaacs, Anderson, Alcantara & Greenough, 1990), increased length and number of dendritic connections between neurons (Cotman & Berchtold, 2002), and increased cell number in the hippocampus (van Praag, Christie, Sejnowski & Gage, 1999). All of these effects have significant
implications in the progression of AD, and the ability to manipulate such variables is advantageous in the treatment of patients with AD.

This thesis will explore the direct and indirect benefits of aerobic exercise and strength training exercise for AD patients. The effects of various exercise modalities on mild cognitive impairment (MCI), a clinical prodrome to dementias such as AD will also be discussed.
**Specific Aims**

The specific aims of this thesis include:

1. Examination of the effects of aerobic exercise and strength training exercise on psychological parameters used to monitor AD progression.
2. Examination of the effects of aerobic exercise and strength training exercise on physiological biomarkers for AD.
3. Conclude whether or not exercise will help patients with AD.
4. Provide recommendations for clinicians regarding how to prescribe exercise for patients with AD.
LITERATURE REVIEW

Studies investigating the neurological and cognitive symptoms of AD

This section will explore the effects of various exercise modalities on the cognitive function of patients with AD and MCI. Cognitive function includes abilities such as memory recall, attention, and executive function, to name a few. Although many of the improvements in cognitive function are a result of physiological changes in the neural tissue, increased cerebral blood flow, and increase in metabolic rate, they will be outlined separately in this section.

Baker et al. (2010) found that six months of aerobic exercise improved executive function, divided attention, cognitive flexibility, and working memory in a patient sample with glucose intolerance and risk of cognitive impairment. Aerobic exercise resulted in improved glucose handling, and led to improvements in the factors listed above, suggesting that the body’s ability to metabolize glucose efficiently affects the health and function of neural tissue, leading to cognitive function enhancement. These findings not only prove that exercise can improve cognitive function, but also underline the interaction between physiological (i.e. glucose metabolism) and cognition-related (i.e. attention, executive function, memory) benefits of aerobic exercise.

Suzuki et al. (2013) performed a study, recruiting participants with MCI, ages 65 years and older, to complete a multimodal six-month exercise program, including aerobic exercise, strength training, postural balance training, and dual-task training. Using the Alzheimer’s Disease Assessment Scale- cognitive
subscale (ADAS-cog), Mini-Mental State Examination (MMSE), and the Wechsler Memory Scale (WMS), participants were evaluated for significant changes resulting from the exercise regimen, compared to a non-exercise control group. Based on the scores for MMSE evaluation, participants with amnestic MCI (MCI with memory impairment) showed significant improvement compared to the control group. The ADAS-cog and WMS scores showed improvement over six months for all MCI exercise participants, compared to the control group. The MMSE is typically used to evaluate overall cognitive function, while the ADAS-cog and WMS are given as more specific tests for memory and executive function. These tests give a quantitative measure of the effects of exercise on cognitive function, and prove that a multimodal six-month program can benefit early stage AD patients, as well as patients with MCI who are at risk for AD (Suzuki et al., 2013).

Smith et al. (2013) conducted a study to determine whether patients with MCI who underwent a 12-week walking exercise program (mild aerobic exercise), four days a week (30 minutes per session), showed improvement in semantic memory fMRI activation, compared to cognitively normal, age-matched adults aged 60 to 88 years. Exercise intensity increased throughout the study up to 50-60% heart rate reserve. In this study, MCI was defined by multiple parameters; the patient had to have concern for his/her changes in memory and cognition, the patient had to be impaired in one or more cognitive domains, the patient had to be able to perform ADLs independently, and the patient could not
be demented (Smith et al., 2013). The fMRI task consisted of 30 celebrity/famous names, and 30 names out of a phone book. Participants were later asked to match names with either the famous or non-famous list. Although the participants with MCI did not experience a significant improvement in the recall and matching task, the fMRI showed a decreased volume of tissue activated (based on blood flow) post-exercise, in the MCI group and in the cognitively normal group (Smith et al., 2013). It may seem paradoxical that the activated tissue volume decreased after exercise, but Smith et al. (2011) suggest that this result entails more efficient neuronal processing, while greater levels of tissue activation can be stressful (Park & Reuter-Lorenz, 2009), and lead to greater brain amyloid accumulation, and MCI progression to AD. Smith et al. (2013) suggest that even mild exercise improved brain plasticity, resulting in a reduced neural workload, which was conveyed in the fMRI results. Reducing stresses on the neuronal circuitry is beneficial in delaying the progression from MCI to AD, and can delay symptom progression in patients who adhere to a regular exercise regimen, as in the abovementioned study.

Arcoverde et al. (2014) implemented a four-month, controlled treadmill exercise regimen for patients diagnosed with AD. A total of 32 treadmill exercise sessions were performed at 60% VO$_{2\text{max}}$. Cognitive function was assessed using the Cambridge Cognitive Examination (CAMCOG), which includes the Clock Drawing Test (executive function) and the verbal fluency test (executive, semantic memory and language functions). Additional tests included the Rey
Auditory Verbal Learning Test for learning and verbal memory evaluation, and the Digit Span test to assess immediate memory and attention. Finally, the Trail Making Test was used to evaluate executive function, and the Stroop test evaluated selective attention, mental flexibility, and inhibitory control. The results of the intervention showed a significant improvement in the exercise group compared to the non-exercise control group based on the CAMCOG scores; the control group scores actually declined (Arcoverde et al., 2014). However, exercise did not correlate with a reduction in scores for the Digit Span and Rey Auditory Verbal Learning tests. This study shows that while moderate aerobic exercise can improve global cognitive functioning, executive function, semantic memory, and verbal/language skills were not improved.

Progressive memory loss, one of the hallmark features of AD, may be delayed via adrenergic agonist administration, which specifically improves emotional memory (O’Carroll, Drysdale, Cahill, Shajahan & Ebmeier, 1999, Cahill & Alkire, 2003). Exercise has proven to endogenously induce noradrenergic activation and emotional memory (McIntyre, Hatfield & McGaugh, 2002, Segal & Cahill, 2009). Segal, Cotman & Cahill (2012) note that pharmacological administration of noradrenergic agonists could have adverse consequences in the elderly, so exercise is a preferred alternate method of activating the system. Endogenous norepinephrine production can be measured as salivary alpha-amylase (sAA) (Segal & Cahill, 2009). In a study by Segal, Cotman & Cahill (2012), patients with amnestic MCI (MCI with memory deficit) were recruited to
determine the effects of aerobic cycling exercise (at 70% VO$_{2\text{max}}$) on stimulation of memory consolidation through activation of the noradrenergic system (measured via sAA production). Using scores on image recall tests and comparing these with sAA values before and after exercise, it was concluded that the exercise group experienced a significant (2-fold) improvement in recall tasks compared to control groups. While the study focused only on the effects of acute exercise on memory recall, chronic exercise may show even greater benefits in memory consolidation through activation of the noradrenergic system. In applying these principles to MCI patients, progression to AD can be delayed (Segal, Cotman & Cahill, 2012).

Depending on the type and severity of the dementia, loss of balance is commonly associated with MCI and early AD (Allan, Ballard, Burn & Kenny, 2005, Pettersson, Olsson & Wahlund, 2005, Morgan et al., 2007). Inability to maintain balance results in frequent falls, and the inability to perform ADLs independently (Sherrington et al., 2008). Task-specific exercises may be most beneficial in people with Alzheimer’s disease, since “motor skill transfer” (Toots et al., 2016), the ability to use acquired skills in new contexts, is impaired or lacking (Dick, Hsieh, Dick-Muehlke, Davis & Cotman, 2000, Dick, Hsieh, Bricker & Dick-Muehlke, 2003).

Toots et al. (2016) studied the effects of exercise on improvement in independent performance of ADLs in patients with Alzheimer’s dementia and non-Alzheimer’s dementia. The exercises came from the high-intensity functional
exercise (HIFE) program developed by Littbrand et al. (2006), and were implemented for a four-month period, with five sessions held in each two-week time frame. These exercises mimicked the use of muscles in ADLs such as standing, rising from a chair, and walking. Balance exercises were implemented as part of the intervention, to improve postural stability, according to original protocol by Littbrand et al. (2006).

Toots et al. (2016) found that independence in ADLs worsened in both AD dementia and non-AD dementia groups. However, balance improved at the four-month checkpoint, and then declined at the seven-month checkpoint. The decline in balance was most likely due to discontinuation of the exercise after study completion. Overall, participants with non-AD dementia experienced better outcomes than the AD dementia group, and participants who started with a higher baseline cognitive level benefited more from the intervention. The AD dementia participants did not experience a significant any improvement in ADL, potentially due to difficulties in motor learning that are a symptom of AD (van Halteren-van Tilborg, Scherder & Hulstijn, 2007). The motor skill impairment is not as pronounced in non-AD dementias such as vascular dementia, underlining the added challenges to improving quality of life for patients with AD. This intervention did not include any aerobic exercise component, which has had the most positive effects on cognition and memory thus far, but has not been tested for its ability to improve independent performance on ADLs or balance-related tasks.
A study by Holthoff et al. (2015) found that a home-based, 12-week intervention of passive, motor assisted, or active resistive leg training and changes in direction on a movement trainer resulted in a significant improvement in independent performance on ADLs in patients diagnosed with AD. At a three-month follow-up visit, however, the exercise group had returned to baseline performance on ADL (same as that prior to the beginning of the intervention period). This points to the need for continuity of exercise in order to have long-term benefit in terms of independence in ADLs. The study by Toots et al. (2016) did not use any motorized equipment to augment the training exercises, which resulted in a decline in ADLs over time, as is expected with normal AD progression. Additionally, Holthoff et al. (2015) implemented the exercise regimen in the homes of the participants, allowing for familiarity of surroundings to facilitate the participants’ ability to transfer learned leg movements to ADLs. The study by Toots et al. (2016) was conducted in specified exercise facilities, where the surroundings were not familiar to participants. The impairment of “motor skill transfer” in AD patients, as outlined by Toots et al. (2016), was thus underlined by the results of these two studies concerning ADLs, by failure to improve ADL performance (Toots et al., 2016) and success in improving ADL performance (Holthoff et al., 2015).

The previously mentioned study by Arcoverde et al. (2014) also examined the effects of moderate-intensity treadmill exercises on static and dynamic balance (using tasks that mimicked ADLs), mobility, lower limb strength, and
cardiac rhythms. For all functional capacity tests, the exercise group improved significantly, while the control group declined. However, the authors did not discuss transferability to real-life and independent performance on ADLs.

Lu et al. (2016) used a novel intervention type, called momentum-based dumbbell training, to assess changes in cognitive function in a sample of patients with AD aged 65 years and older, with MMSE scores of 24 or higher. The exercises involved arm movements while holding and spinning dumbbells in various positions, and focused more on the aspect of strength training. After a 12-week intervention period (exercise sessions three times per week), the training group had significantly improved scores on the ADAS-cog subscale compared to the control group, indicating enhanced global cognitive function. Scores for the Trail Making Test (for executive function) and Digit Span Test (for immediate memory and attention) also showed similar improvements in the training group compared to the control group (Lu et al., 2016). This intervention was the first of its kind, and demonstrated the advantages of momentum-based strength training for patients with AD-related cognitive deficits. Lu et al. (2016) did not provide a mechanism by which such exercises improve cognitive measures, but positioning and movement of the dumbbells may improve spatiotemporal orientation, selective attention, and executive control. The current body of literature on strength training and its effects on cognitive function in AD is vastly underdeveloped compared to the literature on aerobic exercise, but the clear benefits outlined by Lu et al. (2016) give more credibility and push for future
strength training studies.

**Studies concerning physiological effects of exercise and biomarkers of AD**

Proper glucose handling is essential for the energy demands of the body (especially the brain), and for ensuring the efficiency of metabolic processes. Without the ability to regulate blood glucose, there is an obvious increase in the risk of type 2 diabetes mellitus (T2DM), and also a related increased risk of cognitive impairment and AD (Baker et al., 2010). The most common intervention for T2DM patients is exercise; metabolic disturbances can be reduced in this way, and glucose tolerance also improves. Ravona-Springer et al. (2012) demonstrate that in non-diabetic elderly subjects with early stages of cognitive decline, MMSE scores decreased significantly with increasing HbA1c levels (1.37 MMSE points per unit HbA1c). Yaffe, Blackwell, Whitmer, Krueger & Barrett (2006) demonstrate that for every 1% increase in HbA1c levels, the likelihood of developing MCI and/or dementia increases significantly. Furthermore, high HbA1c levels have been correlated with increased risk of cardiovascular disease (Park, Barrett-Connor, Wingard, Shan & Edelstein, 1996), which diminishes pumping of blood to all vital organs, including the brain, particularly in the hippocampus (Mattson, Guthrie & Kater, 1989, Cervos-Navarro & Diemer, 1991). Chronically elevated HbA1c levels lead to chronic vascular pathology, which results in cognitive decline (Schneider & Bennett, 2010, Duckrow, Beard & Brennan, 1987) and may cause MCI to develop into proper dementia.
Baker et al. (2010) examined the effects of aerobic exercise in older adults with glucose intolerance, on executive control processes. Insulin sensitivity, plasma cortisol, BDNF, insulin-like growth factor-1 (IGF-1), and Aβ 1-40 and 1-42 were also measured.

A six-month treadmill exercise program by Baker et al. (2010) (4 days/week) improved glucose handling and cardiorespiratory fitness, decreased adiposity and plasma triglyceride levels, and also decreased plasma LDL. Levels of AD biomarker Aβ 1-42 (amyloidogenic Aβ peptides) were variable throughout the course of the six months, but trended downward overall (Baker et al., 2010). According to Moore et al. (2016), Aβ 40 and Aβ 42 show dose-dependent decreases in the cortex and hippocampus, with heavy exercise being more beneficial than mild exercise, and mild exercise being more beneficial than sedentary behavior. This is attributed to improved regulation of glucose; impaired regulation alters Aβ metabolism (via degradative enzymes) and results in higher frequency of amyloidogenic Aβ formation via enzymatic cleavage by β and/or γ secretase (Moore et al., 2016). Aβ degradation enzymes, particularly neprilysin, also increased in a dose-dependent manner with mild and heavy exercise, as did molecular chaperone proteins (particularly HSP70, but also ApoE, ApoJ, and A2M) that facilitated folding of Aβ degradative enzymes (Moore et al., 2016). A decrease in soluble cortical Aβ is a positive outcome of exercise in early AD patients (Adlard, Perreau, Pop & Cotman, 2005, Um et al., 2011).
Cortisol and BDNF increased for the control group and decreased for the aerobic exercise group, but these values were not statistically significant in the study (Baker et al., 2010). However, Suzuki et al. (2013) found that baseline high serum BDNF levels do have a beneficial effect on general cognitive function of MCI patients; therefore, while the actual changes in BDNF may be inconsistent, the effects of higher serum BDNF are not. Erickson et al. (2011) found that over the course of one year, moderate-intensity aerobic exercise did not result in greater changes in serum BDNF compared to control groups. However, the same study found that in individual participants with greater changes in serum BDNF, anterior hippocampal volume increased to a greater extent than in participants who did not experience the same amount of change in BDNF. The anterior hippocampus is significant in spatial memory (Moser, Moser, Forrest, Andersen & Morris, 1995), and shows greater age-related atrophy than the posterior hippocampus (Raji, Lopez, Kuller, Carmichael & Becker, 2009). Erickson et al. (2011) postulate that areas such as the posterior hippocampus that do not degenerate with age, may also be less capable of growth at a later age. Thus, the anterior hippocampus is amenable to BDNF-mediated growth in old age, as demonstrated by the study conducted by Erickson et al. (2011).

IGF-1 was not altered by physical activity (Baker et al., 2010). A study by Yu, Savik, Wyman, and Bronas (2011) with comparable duration and frequency of aerobic exercise in a small sample of patients with AD using a stationary cycle showed a significant improvement in cardiorespiratory fitness. Vidoni, Honea,
Billinger, Swerdlow & Burns (2012) demonstrated that the improved cardiorespiratory fitness significantly slowed brain atrophy and cognitive decline in Alzheimer’s patients over the course of two years.

Sleep disturbance is yet another problem associated with neurodegenerative diseases, including AD, although the exact cause of sleep disturbance is unknown (Nascimento et al., 2014). In a study by Nascimento et al. (2014), participants with AD who were on regular pharmacological treatment were recruited to determine the effects of a multimodal exercise program on sleep disturbances. Exercises included a warm up, muscular resistance exercises, balance and motor coordination activities, and aerobic exercise. Significant reductions in sleep disturbance were observed in the patient sample over the course of the six month program (Nascimento et al., 2014). Furthermore, performance on ADLs also improved with the multimodal exercise program, according to Nascimento et al. (2014), which could be partially attributed to decrease in whole brain cortex atrophy in exercising participants compared to a control group over a period of six months (Suzuki et al., 2013).

A study by Colcombe et al. (2006) compared changes in regional brain volumes using high-resolution MRI, between an intervention group that participated in six months of cardiovascular exercise, and a control group that participated in non-aerobic stretching exercises. All participants were 59 years of age or older, and cognitive function was evaluated using the MMSE survey. The exercise group started the program at an intensity of 40-50% heart rate reserve,
and completed the program at an intensity of 60-70% heart rate reserve. Using the MRI scans, maps of the grey and white matter were created, and compared pre- and post-intervention. The exercise group showed a greater increase in brain volume of grey matter areas compared to the control group in the left superior temporal lobe (ISTL), anterior cingulate cortex (ACC)/supplementary motor area (SMA), and right inferior frontal gyrus (rIFG). Additionally, the anterior white matter tracts (AWM) also showed significant increases in volume in the exercise group compared to the control group (Colcombe et al. 2006). The greatest percentage of changes in brain volume occurred in the frontal lobes of the brain, where higher order attention control and memory processes take place (West, 1996 and Duncan & Owen, 2000, Gunning-Dixon & Raz, 2003). There was also an increase in temporal lobe volume, which is significant in the context of AD dementia given that the temporal lobe mediates long-term memory, which is disrupted in AD (Colcombe et al., 2006). The risk for future volume loss was also significantly lower in the same brain regions that experienced increases in volume due to physical activity. An additional finding of this study was that the peak oxygen uptake (VO$_{2peak}$) increased significantly by 16.3% in the exercise group, while the control participants showed a non-significant 5.3% change (Colcombe et al., 2006). This suggests increased oxygen delivery and blood flow to the brain, facilitating increased brain volumes. Increased cardiorespiratory fitness in patients with early AD has been shown to preserve brain volume, and
reduce atrophic processes (Burns et al., 2008), thus slowing disease progression.

**Figure 7. Increases in brain volumes due to aerobic exercise.** Regions of the brain showing significant increases in volume in participants who were in the aerobic exercise group, compared to those in the non-exercise control group. Blue regions show grey matter areas, and yellow regions show white matter areas. Image taken from Colcombe et al. (2006).

A study by ten Brinke et al. (2015) also reported significant increases in left and right hippocampal volume in aerobic training groups, compared to control groups (no exercise) and resistance training groups. It should be noted that this study only recruited women of 70-80 years who had probable MCI; the diagnosis was not confirmed by specific criteria as in other studies. However, with multiple studies reporting increases in hippocampal volume due to exercise, increased blood flow, decrease in inflammatory cytokines leading to neuronal atrophy, and reduced beta amyloid deposition in the hippocampus all have clear neuroprotective effects on this important brain region.
Lin et al. (2015) found that in APP/PS1 transgenic mouse models, dendritic arborization improved significantly due to exercise in both the hippocampus, specifically in CA1 and CA3 neurons, and in the amygdala. This is typically regulated by BDNF signaling pathways (Lin et al., 2012). According to the same study, transgenic mice experienced complete restoration of the synaptic connections in the amygdala, as visualized by fluorescent dye injection into the cytoplasm of individual neurons, which could be at least partially attributed to increased levels of BDNF found in the amygdala after a ten-week treadmill exercise regimen. Lin et al. (2015) showed that BDNF levels increased in the amygdalas of both transgenic and wild type mice, suggesting neuroprotective (in wild type) and palliative (in transgenic) effects of exercise. The exercise condition significantly reduced the amount of Aβ40 and Aβ42 in the amygdala and hippocampus, although the baseline levels in the amygdala were highest in the transgenic sedentary (control group) mice (Lin et al., 2015). In the same study, low-density lipoprotein receptor-related protein (LRP1) levels increased significantly in the hippocampus and amygdala, facilitating better Aβ clearance in both regions.

In addition to atrophy of certain brain regions, brain inflammation is also prevalent in neurodegenerative diseases (Amor, Puentes, Baker & van der Valk, 2010, McGeer & McGeer, 2010, Faria et al., 2014). Specifically in AD, pro-inflammatory and anti-inflammatory cytokines are elevated (Brosseron, Krauthausen, Kummer & Heneka, 2014), resulting in further neurodegeneration.
This occurs due to activation of astrocytes by pro-inflammatory cytokines, resulting in the release of more inflammatory cytokines, nitric oxide, and reactive oxygen species, all of which accumulate in the neural tissue and cause nerve damage (decreased conduction velocity, neuronal shrinkage, and apoptosis) (McGeer & McGeer, 2010). Physical activity has been known to decrease inflammation in the brain (Souza et al., 2013), and accordingly, Nascimento et al. (2014) found that in MCI patients, six months of aerobic exercise (three times per week) at 60-80% of heart rate reserve significantly decreased serum levels of pro-inflammatory cytokines TNF-α and IL-6. The reduction in pro-inflammatory cytokines may serve to depress the rate of neurodegeneration, deriving from the strong correlation between inflammation and brain atrophy. However, there appears to be a time-dependent effect of exercise on inflammatory cytokines. A study by Elahi et al. (2016) found that short term treadmill exercise (five days per week for three weeks) resulted in increased neuroinflammation, through increases in pro-inflammatory cytokines IL-1β and IL-18. This is due to oxidative stress resulting in increased levels of insoluble hyperphosphorylated tau and NFTs, further provoking inflammatory processes. Short term exercise, therefore, should be avoided, and patients with AD who are started on an aerobic exercise regimen should be evaluated for ability to continue exercise over a period of six months to one year, optimally.

As part of the adaptive immune response, B and T cells are able to enter the central nervous system from the periphery to invoke immune (inflammatory)
responses, while phagocytic microglial cells within the central nervous system contribute most to the innate neuroinflammatory response (Ryan & Nolan, 2016). Amyloid plaque and NFT deposition is the major stimulus for inflammation in relation to AD pathology (Elahi et al., 2016). When chronically activated, microglia have adverse effects on neurons, but other studies have demonstrated a role specifically in hippocampal regeneration and neuroprotection upon acute bouts of activation (Czeh, Gressens & Kaindl, 2011). Microglia, similar to peripheral tissue macrophages, have been categorized into two possible polarities in vitro (not yet confirmed in vivo), M1, the pro-inflammatory subtype, and M2, the alternatively activated/anti-inflammatory subtype. The cytokine milieu in the CSF primarily affects the polarity that is achieved by the microglia (Orihuela, McPherson & Harry, 2016). However, as shown by Sierra et al. (2010) and Sierra et al. (2014), in the absence of inflammation, microglia provide trophic support for newly forming cells, and facilitate apoptosis of nascent cells that do not make synaptic connections with existing cells. Currently, the only feasible way to predict neurogenesis in human brains is through performance on memory tasks. Aerobic exercise, in rodent models, has been shown to promote neurogenesis in the hippocampus (Brown et al., 2003), and also reduces pro-inflammatory cytokine levels (Nascimento et al., 2014), demonstrating the increased anti-inflammatory M2 microglial response, which may be beneficial in providing support for growing neurons in the hippocampus, and facilitating neuronal death if synaptic circuits fail to form (Ryan & Nolan, 2016). With a
decrease in neuroinflammation, neurogenesis can occur in limited areas, improving performance on memory tasks in both rodent and human models (Ryan & Nolan, 2016).
DISCUSSION

There is clear evidence supporting the advantages of both aerobic and strength-training exercises in improving psychological parameters used to measure the progression of AD. Mild, moderate, and intensive aerobic exercises all have beneficial effects on various cognitive functions. An overwhelming majority of studies implementing exercise interventions demonstrated that a duration of four to six months was an adequate length of time to produce positive results. Aerobic exercise has multiple effects including improvements in executive function, divided attention, cognitive flexibility, working memory, attention, brain plasticity, global cognitive function, semantic memory, recall tasks, adrenergic stimulation, balance, and lower limb strength (Suzuki et al., 2013, Smith et al., 2013, Arcoverde et al., 2014, Segal, Cotman & Cahill, 2012, Lu et al., 2016). However, independent performance on ADLs did not improve unless the exercise was performed at the home of the participant (Toots et al., 2016, Holthoff et al., 2015). However, even when the intervention was implemented at home, improvements in performance on ADLs were transient, returning to baseline after a few months without exercise (Holthoff et al., 2015). These findings suggest that exercise should be a continued and long-term component of the treatment course for patients with MCI and AD, in order for the effects to last. In the studies referred to in this thesis, language and verbal function did not improve as a result of moderate aerobic exercise over the course of four months (Arcoverde et al., 2014), but more research needs to be done to
examine the effects of high intensity exercise and interventions of longer duration.

Strength training mimicking body movements similar to those performed in ADLs improved balance transiently, with a return to baseline several months after the end of the intervention. The use of motorized devices in aiding body movements had a greater impact on the ability to perform ADLs, than did studies using a passive approach without the motor-assist (Toots et al., 2016, Holthoff et al., 2015). Additionally, home-based strength training interventions were more successful in improving ADL performance, as motor skill transfer is impaired in patients with AD. Fewer studies have focused on the effects on strength training, and more research needs to be done to determine both the feasibility and efficacy of strength training on cognitive function and psychological health for patients with MCI and patients with AD. To the author’s best knowledge, no studies have yet determined the effect of strength training exercise on the progression of MCI to early AD.

Aerobic exercise has many advantageous physiological effects for individuals with MCI and AD. Patients with cognitive impairments are at increased risk of certain comorbidities, many of which can be prevented with regular exercise. Aerobic exercise of any intensity improves cardiorespiratory fitness, and decreases the risk of developing cardiovascular disease. Additionally, glucose handling is significantly improved with exercise, thus decreasing the risk for T2DM (Baker et al., 2010).
Aerobic exercise of moderate to high intensity most importantly reduces Aβ$_{40}$ and Aβ$_{42}$ deposition in the cortex and hippocampus in human subjects, and in mouse models, decreases deposition in the hippocampus and amygdala (Lin et al., 2015). Long-term aerobic exercise can reduce inflammatory cytokines in the CSF, increase Aβ degradative enzymes, and increase grey matter volumes by preventing atrophy through increased blood flow to the brain tissue (Moore et al., 2016). Short-term exercise over a period of three weeks in mouse models was proven to increase oxidative stress and neuroinflammation (Nascimento et al., 2014, Elahi et al., 2016); studies in humans will be necessary to validate this finding and determine if short bouts of exercise could in fact be harmful.

In mouse models, aerobic exercise increased hippocampal neurogenesis, but this finding has yet to be corroborated in human subjects (Ryan & Nolan, 2016). If proven true in humans, many cognitive functions associated with the hippocampus could be restored or improved, and hippocampal volume maintained (ten Brinke et al., 2015). In addition to neurogenesis and increased volume, reduced Aβ and NFT deposition in the hippocampus proves that aerobic exercise has a tremendous neuroprotective effect on this brain region that is adversely affected in AD.

There are still many gaps in the literature regarding the ways in which various types of exercise affect patients with MCI and AD, as well as the progression of MCI to AD. The current literature lacks consistency in reporting the VO$_{2\text{max}}$ achieved during physical activity, as a measure of aerobic exercise.
intensity. The categories “mild”, “moderate”, and “heavy” are thus difficult to quantify. While these values have been defined in literature specific to exercise science research, they need to be adapted to elderly patients with neurodegenerative disorders. In strength training, intensity is more difficult to quantify, and very few studies report physiological effects of strength training or resistance-related exercises in patients with MCI or AD.

Another limitation in this field of research is the inability to easily and directly observe changes occurring in the human brain. Mouse models are sacrificed post-intervention, and changes in neuronal growth and volume can be quantified. However, in human subjects, observations regarding changes to the brain anatomy are often inferred based on cognitive functioning tests that are targeted to a particular area of the brain, or tests mimicking physiological events that cause the release of specific neurotransmitters. Thus, we are limited primarily to imaging techniques when studying anatomical changes; imaging techniques also have inherent limitations. Post-mortem examination of human subjects may occur well after the intervention has ended, and would not provide an accurate indication of the effects of the exercise program.

Many studies, when describing participants, do not specify whether the subjects are using pharmacological treatments at the time of the intervention, or if they have ever used them prior to the time of the intervention. The interaction of drug therapy with an exercise program may have different effects than just exercise alone, and such possibilities need to be considered when synthesizing
information from multiple studies. Analysis of this body of research with regards to coinciding pharmacological treatment must be completed with caution.

Existing studies that recruited participants with MCI rarely, if ever, completed follow-up examinations to determine whether those individuals progressed to AD, and if progression was delayed at all by the exercise treatment. This information would be useful when prescribing exercise therapy as a preventive measure for patients with early signs of cognitive impairment and MCI. One final point regarding improvements that need to be made in this field of research is regarding the duration of exercise intervention. A vast majority of studies implement exercise studies for four to six months. Very few extend study time to the span of one year or longer; therefore, long-term exercise effects cannot be determined. Participants with MCI or AD who are physically able to exercise consistently over the course of several years should be recruited to participate in future studies, so that both feasibility and efficacy can be determined.
CONCLUSION

Future research should focus on three main points for improvement: (a) exercise intensity should always be reported either through VO_{2max} or heart rate reserve; (b) participants taking drug therapy during the exercise intervention should be distinguished so that results can be analyzed separately for such patients; (c) studies that recruit patients with MCI should follow up after a certain time period, or at given time intervals to determine if progression to AD can be prevented, or if progression is at least delayed as a result of exercise.

With the current research, physicians can still make informed decisions regarding exercise prescriptions for patients with early stages of cognitive impairment. For patients with MCI, moderate to high intensity aerobic exercise can be prescribed to improve brain plasticity and prevent brain atrophy, while improving glucose utilization and cardiovascular health. For patients with mild AD, at-home, multimodal exercise therapy of moderate intensity can improve independent performance on ADLs, and decrease Aβ deposition in important brain regions like the hippocampus, cortex, and amygdala. Additionally, when exercise is a continued part of preventive therapy, inflammatory and degenerative processes in the brain can be slowed and delayed. For patients with moderate to severe AD, the tolerated intensity of exercise will vary, and physicians prescribe exercise only in supervised settings. Strength training or resistance exercises that mimic the movements of ADLs will help provide functional skills and prevent inactivity due to inability to stand up, walk, bathe,
and move around the home. Patients who can tolerate aerobic exercise should be started on a supervised, graded increase in treadmill or cycling exercises.

The applications of exercise science are promising in the field of neurodegenerative disease. The benefits are multiple and widespread, across physiological and psychological arenas. The research on this subject so far has built a solid foundation, proving useful for clinical applications, but further research needs to be done in order to make well-informed and specific exercise prescriptions for patients as a supplement to pharmacological treatments. Exercise may also be prescribed for patients with MCI or early stage AD to avoid or delay the use of medications. As researchers work towards a pharmacological cure for neurodegenerative diseases such as Alzheimer’s disease, exercise therapy shows great promise in improving quality of life for the elderly population until a cure is found.
APPENDIX A

The following index for establishing a patient’s level of independence in activities of daily living was created by Katz, Ford, Moskowitz, Jackson & Jaffe (1963). It is commonly used in the clinic and other health care settings to determine independence. This index can be further utilized to determine the type of exercises an individual should be targeting in order to best improve mobility and independence.

<table>
<thead>
<tr>
<th>Activities</th>
<th>Independence (1 Point)</th>
<th>Dependence (0 Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO supervision, direction or personal assistance.</td>
<td>WITH supervision, direction, personal assistance or total care.</td>
</tr>
<tr>
<td>BATHING Points: Thursday</td>
<td>(1 POINT) Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.</td>
<td>(0 POINTS) Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.</td>
</tr>
<tr>
<td>DRESSING Points: Friday</td>
<td>(1 POINT) Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.</td>
<td>(0 POINTS) Needs help with dressing self or needs to be completely dressed.</td>
</tr>
<tr>
<td>TOILETING Points: Saturday</td>
<td>(1 POINT) Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.</td>
<td>(0 POINTS) Needs help transferring to the toilet, cleaning self or uses bedpan or commode.</td>
</tr>
<tr>
<td>TRANSFERRING Points: Sunday</td>
<td>(1 POINT) Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable</td>
<td>(0 POINTS) Needs help in moving from bed to chair or requires a complete transfer.</td>
</tr>
<tr>
<td>CONTINENCE Points: Monday</td>
<td>(1 POINT) Exercises complete self control over urination and defecation.</td>
<td>(0 POINTS) Is partially or totally incontinent of bowel or bladder</td>
</tr>
<tr>
<td>FEEDING Points: Tuesday</td>
<td>(1 POINT) Gets food from plate into mouth without help. Preparation of food may be done by another person.</td>
<td>(0 POINTS) Needs partial or total help with feeding or requires parenteral feeding.</td>
</tr>
</tbody>
</table>

**TOTAL POINTS:** ______  SCORING: 6 = High (patient independent) 0 = Low (patient very dependent)
Another scoring scale that is commonly used to determine independence in activities of daily living has been established by Lawton & Brody (1969).

### APPENDIX B

<table>
<thead>
<tr>
<th>Patient Name: ___________________</th>
<th>Date: ________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID #: ___________________</td>
<td></td>
</tr>
</tbody>
</table>

#### LAWTON - BRODY

**INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (I.A.D.L.)**

<table>
<thead>
<tr>
<th>Item Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Ability to Use Telephone</td>
<td></td>
</tr>
<tr>
<td>1. Operates telephone on own initiative—looks up and dials numbers, etc.</td>
<td>1</td>
</tr>
<tr>
<td>2. Dials a few well-known numbers</td>
<td>1</td>
</tr>
<tr>
<td>3. Answers telephone but does not dial</td>
<td>1</td>
</tr>
<tr>
<td>4. Does not use telephone at all</td>
<td>0</td>
</tr>
<tr>
<td>E. Laundry</td>
<td></td>
</tr>
<tr>
<td>1. Does personal laundry completely</td>
<td>1</td>
</tr>
<tr>
<td>2. Launders small items—rises stockings, etc.</td>
<td>1</td>
</tr>
<tr>
<td>3. All laundry must be done by others</td>
<td>0</td>
</tr>
<tr>
<td>B. Shopping</td>
<td></td>
</tr>
<tr>
<td>1. Takes care of all shopping needs independently</td>
<td>1</td>
</tr>
<tr>
<td>2. Shops independently for small purchases</td>
<td>0</td>
</tr>
<tr>
<td>3. Needs to be accompanied on any shopping trip</td>
<td>0</td>
</tr>
<tr>
<td>4. Completely unable to shop</td>
<td>0</td>
</tr>
<tr>
<td>F. Mode of Transportation</td>
<td></td>
</tr>
<tr>
<td>1. Travels independently on public transportation or drives own car</td>
<td>1</td>
</tr>
<tr>
<td>2. Arranges own travel via taxi, but does not otherwise use public transportation</td>
<td>1</td>
</tr>
<tr>
<td>3. Travels on public transportation when accompanied by another</td>
<td>1</td>
</tr>
<tr>
<td>4. Travel limited to taxi or automobile with assistance of another</td>
<td>0</td>
</tr>
<tr>
<td>5. Does not travel at all</td>
<td>0</td>
</tr>
<tr>
<td>C. Food Preparation</td>
<td></td>
</tr>
<tr>
<td>1. Plans, prepares and serves adequate meals independently</td>
<td>1</td>
</tr>
<tr>
<td>2. Prepares adequate meals if supplied with ingredients</td>
<td>0</td>
</tr>
<tr>
<td>3. Heats, serves and prepares meals, or prepares meals, or prepares meals but does not maintain adequate diet</td>
<td>0</td>
</tr>
<tr>
<td>4. Needs to have meals prepared and served</td>
<td>0</td>
</tr>
<tr>
<td>G. Responsibility for Own Medications</td>
<td></td>
</tr>
<tr>
<td>1. Is responsible for taking medication in correct dosages at correct time</td>
<td>1</td>
</tr>
<tr>
<td>2. Takes responsibility if medication is prepared in advance in separate dosage</td>
<td>0</td>
</tr>
<tr>
<td>3. Is not capable of dispensing own medication</td>
<td>0</td>
</tr>
<tr>
<td>D. Housekeeping</td>
<td></td>
</tr>
<tr>
<td>1. Maintains house alone or with occasional assistance (e.g. &quot;heavy work domestic help&quot;)</td>
<td>1</td>
</tr>
<tr>
<td>2. Performs light daily tasks such as dish washing, bed making</td>
<td>1</td>
</tr>
<tr>
<td>3. Performs light daily tasks but cannot maintain acceptable level of cleanliness</td>
<td>1</td>
</tr>
<tr>
<td>4. Needs help with all home maintenance tasks</td>
<td>1</td>
</tr>
<tr>
<td>5. Does not participate in any housekeeping tasks</td>
<td>0</td>
</tr>
<tr>
<td>H. Ability to Handle Finances</td>
<td></td>
</tr>
<tr>
<td>1. Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank), collects and keeps track of income</td>
<td>1</td>
</tr>
<tr>
<td>2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.</td>
<td>0</td>
</tr>
<tr>
<td>3. Incapable of handling money</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Total score</th>
</tr>
</thead>
</table>

*A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women and 0 through 5 for men to avoid potential gender bias.*


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Lin, T.-W., Shih, Y.-H., Chen, S.-J., Lien, C.-H., Chang, C.-Y., Huang, T.-Y., …


Sierra, A., Encinas, J. M., Deudero, J. J. P., Chancey, J. H., Enikolopov, G.,


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*Mentor, University of Connecticut, Asiantation Mentoring Program, Storrs, CT*  
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*Dancer, University of Connecticut, Husky Bhangra, Storrs, CT*  
[August 2011-August 2013]