

2018

# Alzheimer's disease: a review of exercise as a protective function

---

<https://hdl.handle.net/2144/31285>

*"Downloaded from OpenBU. Boston University's institutional repository."*

BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**ALZHEIMER'S DISEASE:  
A REVIEW OF EXERCISE AS A PROTECTIVE FUNCTION**

by

**CAMERON EVAN SCHMUTZ**

B.A., Brigham Young University, 2014

Submitted in partial fulfillment of the  
requirements for the degree of  
Master of Science

2018

© 2018 by  
CAMERON EVAN SCHMUTZ  
All rights reserved

Approved by

First Reader

---

Maria Isabel Dominguez, Ph.D.  
Assistant Professor of Medicine  
Boston University School of Medicine

Second Reader

---

John S.K. Kauwe, Ph.D.  
Assistant Professor of Biology  
Brigham Young University

## **DEDICATION**

I would like to dedicate this work to my enduringly patient and supportive spouse Rachel  
and to my daughter and best friend Adelyn.

## **ACKNOWLEDGMENTS**

I want to thank Dr. Isabel Dominguez for her consistent support, much needed motivation, and great friendship. Her insight and sense of humor was a needed light throughout the last year and a half. I also want to thank Dr. John Kauwe for making time to support this project and many previous endeavors. He has been a fantastic mentor and friend, and I wouldn't be at this point in my education without his influence.

**ALZHEIMER'S DISEASE:  
A REVIEW OF EXERCISE AS A PROTECTIVE FUNCTION  
CAMERON EVAN SCHMUTZ**

**ABSTRACT**

Alzheimer's disease (AD) is the leading cause of dementia accounting for between 60-80% of all dementia related cases. It is the 6<sup>th</sup> leading cause of death in the US and is the only one in the top 10 leading causes of death without a prevention or cure. As the life-expectancy across the world continues to increase, the number of AD cases are expected to likewise increase dramatically.

AD is a multifaceted disease. There is no one pathway or genetic predisposition that researchers can pinpoint as causing disease in all cases. Approximately 5-10% of cases are caused by an inherited genetic mutation, while 90-95% of cases are sporadic with determined underlying mechanism. This makes treatment for disease extremely difficult. In recent years focus has been given to modifiable risk factors to lower risk for AD, including exercise, diet, cardiovascular health, education, and smoking.

This study reviews the possible protective effects of exercise on the development of AD. Randomized control trials (RCTs), longitudinal studies, and meta-analyses and studies in AD mouse models are scrutinized to determine whether there is an association between exercise and lower risk of AD, and to potentially pinpoint the molecular mechanisms behind this protective effect. The majority of studies concur that exercise does lower risk of AD, but the mechanisms still need to be elucidated. Although more research is needed, the results so far have been promising.

## TABLE OF CONTENTS

TITLE.....	i
COPYRIGHT PAGE.....	ii
READER APPROVAL PAGE.....	iii
DEDICATION.....	iv
ACKNOWLEDGMENTS.....	v
ABSTRACT.....	vi
TABLE OF CONTENTS.....	vii
LIST OF TABLES.....	ix
LIST OF FIGURES.....	x
LIST OF ABBREVIATIONS.....	xi
INTRODUCTION.....	1
Symptoms.....	2
Molecular Mechanism of AD Pathology.....	3
Genetics of Alzheimer’s Disease.....	4
Risk Factors.....	5
Modifiable Risk Factors.....	5
CURRENT LITERATURE REVIEW.....	7
Epidemiological Studies.....	8

<i>Randomized Control Trials</i> .....	8
<i>Twin Study</i> .....	15
Preclinical Studies .....	16
<i>App Processing and BACE 1</i> .....	18
<i>BDNF and Ketones</i> .....	23
Neuroinflammation .....	25
<i>AD Studies: exercise and inflammatory gene expression</i> .....	26
<i>Non-AD Studies: exercies and inflammatory gene expression</i> .....	27
<i>AD Models</i> .....	31
Role of Microglia in AD Pathology.....	31
NSAIDs.....	36
DISCUSSIONS AND CONCLUSIONS .....	37
Potential Impact on AD Prevention and Treatment.....	37
Future Directions .....	38
Conclusion .....	40
REFERENCES .....	41
CURRICULUM VITAE.....	48

## LIST OF TABLES

Table	Title	Page
1	Results from 22 RCTs between 1991-2013	9

## LIST OF FIGURES

Figure	Title	Page
1	Healthy brain vs Alzheimer's Diseased brain	2
2	Projected AD Prevention Percentages	7
3	Hypothesized Mechanism of Exercise A $\beta$ Prevention	19
4	Results of Exercise on APP, BACE1, etc.	21
5	Molecular Changes in AD Mouse Model	22
6	Amyloid precursor protein and neural development	24
7	Exercise and Inflammatory Marker Release	29
8	Activated Microglia	34

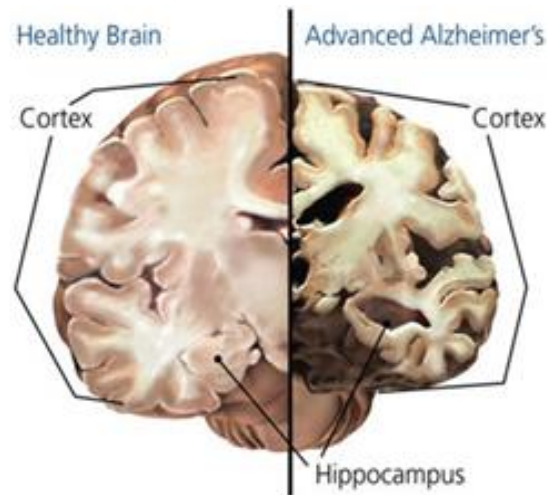
## LIST OF ABBREVIATIONS

A $\beta$ .....	Amyloid Beta
AD.....	Alzheimer's Disease
ADL .....	Activities of Daily Living
APP .....	Amyloid Precursor Protein
BACE1 .....	Beta Secretase 1
BDNF.....	Brain Derived Neurotrophic Factor
CNS.....	Central Nervous System
CRP.....	C-Reactive Protein
FAD.....	Familial Alzheimer's Disease
HDAC .....	Histone Deacetylases
LOAD .....	Late On-Set Alzheimer's Disease
MCI.....	Mild Cognitive Impairment
NSAIDs.....	Nonsteroidal Anti-inflammatory Drugs
RCT.....	Randomized Control Trial
TLR.....	Toll Like Receptor
TNF.....	Tumor Necrosis Factor

## **INTRODUCTION**

Alzheimer's disease (AD) is the leading cause of dementia accounting for between 60-80% of all dementia related cases and affecting more than an estimated 5.5 million people in the United States. It is the 6<sup>th</sup> leading cause of death in the US and currently has no effective treatment or cure. (Alzheimer's Association, n.d.). With the US population increasing in age the incidence of AD is expected to increase dramatically by the year 2050, with close to 16 million people in the US presenting with the disease. It has been estimated that between 2013 and 2050, persons over the age of 60 years old will more than double and that people over the age of 80 is expected to more than triple (Taurmi & Zhang, 2017). In 2017, AD and other dementias are estimated to cost the US \$259 billion and these costs are projected to only increase, rising to a staggering \$1.1 trillion by mid-century (Alzheimer's Association, n.d.). This not only presents as a national health care crisis but also as a national financial crisis.

Considering both the health and cost implications, it is imperative that a cure or effective preventative measure is found for this deleterious disease. Symptoms do not appear until years after initial physiological changes in the brain occur (Alzheimer's Association). Additionally, a definitive diagnosis of AD cannot be determined until an autopsy is performed, which will reveal a preponderance of amyloid plaques and neurofibrillary tangles and reduced volume in the cortex and hippocampus (see Figure 1). Here we review the literature to evaluate the validity of the proposed positive impact of exercise on Alzheimer's Disease.



**Figure 1. Healthy brain vs Alzheimer's Diseased brain.** (Left) View of a normal brain. Cortex and Hippocampus are healthy. (Right) View of a brain with Alzheimer's disease. Cortex and Hippocampus are both shriveled, hallmarks of AD. (Figure from brainfacts.org).

### *Symptoms*

Symptoms of AD do not appear until years after initial molecular and physiological changes in the brain occur, adding to the difficulty of treating the disease. The earliest and most common symptom of AD is a progressive worsening ability to remember and recall new information. The gradual worsening of memory is thought to occur from the destruction of neurons by the buildup of  $A\beta$  plaques and neurofibrillary tangles in the hippocampus--the portion of the brain responsible for forming new memories--as well as neuronal inflammation. Other early symptoms include neurobehavioral symptoms like sleeplessness, delusion, agitation, apathy, depression, impaired communication, confusion, and behavior changes (Alzheimer's Association).

As the disease progresses, it causes the affected individual to lose the ability to perform daily activities on his/her own. The disease gradually deprives a person from

being able to bath, dress, walk, and eventually swallow. Alzheimer's disease progression varies from individual to individual with most people living between 4 and 8 years from initial diagnosis, while others living up to 20. Persons with advanced stages of AD require 24-hour assistance. This around the clock care is physically, emotionally, and financially taxing on caregivers and loved ones.

Adding to the difficulty of treatment, symptoms alone are not enough to diagnose AD. An autopsy is required to give a definitive diagnosis, which will reveal A $\beta$  plaques and neurofibrillary tangles, along with a reduced volume in the cortex and hippocampus (Alzheimer's Association).

#### *Molecular Mechanisms of AD Pathology*

Alzheimer's disease pathology is characterized by the accumulation of inflammation, A $\beta$  plaques, and neurofibrillary tangles in the brain. Most experts agree that AD development is a multifaceted mechanism and cannot be attributed to a single cause. The most common and perhaps most accepted theory in the development of AD is the "amyloid cascade" hypothesis, which asserts that the disease is triggered by an accumulation of A $\beta$  plaques which form in the brain from the improper cleavage of the APP protein. These toxic plaques then initiate several downstream mechanisms that cause neurofibrillary tangles from the aggregation of Tau protein inside neurons and an increasingly toxic level of neuroinflammation (Ebrahimi et al., 2017 & Correia et al., 2011, Alzheimer's Association).

I would add here a paragraph and figure about APP processing, so it is easy to follow the rest of the thesis.

### *Genetics of Alzheimer's Disease*

There are two broad categories of AD, Familial (FAD) or Early Onset and Sporadic or Late Onset (LOAD). FAD represents roughly 5-10% of all AD patients and is characterized by the presence of AD like symptoms before 65 years old, with symptoms showing as early as 30 years of age. FAD is caused by a genetic mutation in the APP, PSEN1, or PSEN2 genes (Ebrahimi et al., 2017). These genes directly cause disease and are considered deterministic. A mutation present in APP or PSEN1 results in 100% of people developing AD, while a mutation in PSEN2 results in approximately 95% of people developing disease (Alzheimer's Association).

Interestingly, since APP is located on chromosome 21, approximately 50% of individuals with Down Syndrome develop AD in their lifetimes. It is hypothesized that the 3<sup>rd</sup> copy of the 21<sup>st</sup> chromosome causes an overabundance or production of APP and thus an overproduction of A $\beta$  oligomers and plaques (Alzheimer's Association).

The majority of AD cases are LOAD, accounting for roughly 90-95% of all cases. There are approximately 20 genes that have been implicated in increasing a person's risk for developing disease, the most prevalent being the APOE E4 allele. APOE has 3 alleles: E2, E3, and E4. Inheriting the E4 allele dramatically increases an individual's risk for AD while inheriting the E2 allele decreases risk for AD. Although, the main function of APOE is transporting cholesterol, it also regulates A $\beta$  metabolism (Kanekiyo et al.,

2014). It also exists in AB plaques and can affect the formation and clearance of extracellular A $\beta$  (Honjo et al., 2012 and Strittmatter et al., 1993).

Several other genes have been implicated in increasing risk for disease including: PICALM, CLU, CR1, BIN1, MS4A, CD2AP, EPHA1, ABCA7, SORL1, TREM2, PLD3, HLA-DRB5/HLA0DRB1, PTK2B, SLC24A4-ORING3, DSG2, INPP5D, MEF2C, NME8, ZCWPW1, CELF1, FERMT2, and CASS4 with more being discovered (NIH study, 2013, Karch et al., 2014). Although not deterministic, mutations in these genes do significantly raise the risk of developing AD during a person's lifetime.

### *Risk Factors*

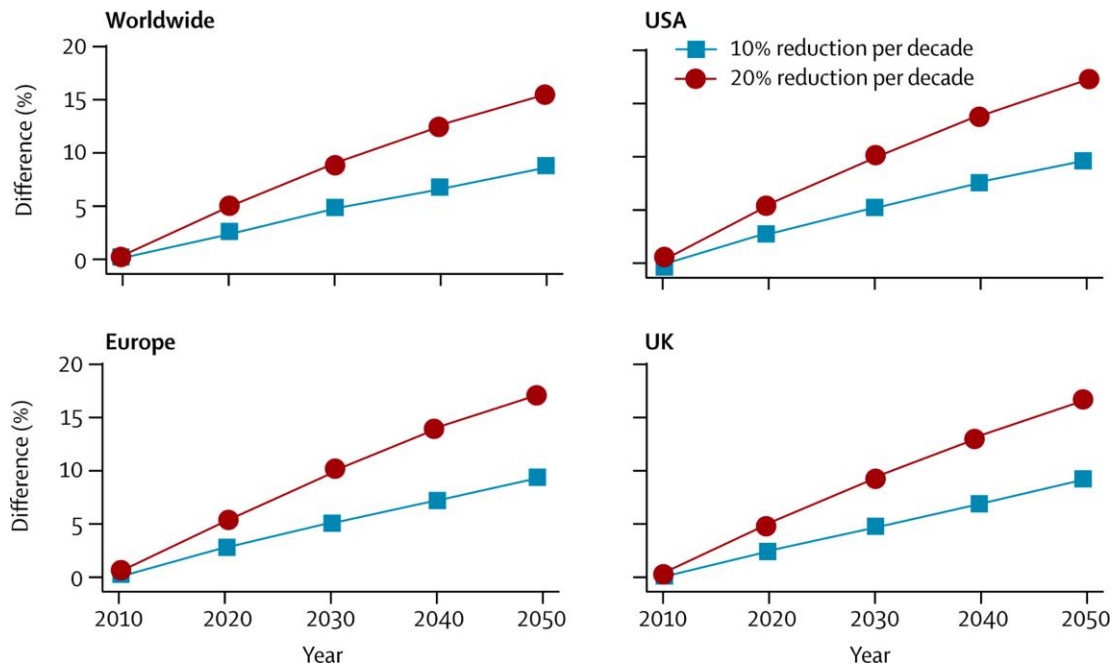
In addition to family history--especially when having a first-degree relative with AD--and the inheritance of the APOE-e4 allele there are other risk factors for disease, including age (Green et al., 2002). Indeed, the single greatest risk factor for developing AD is age. Estimates have shown that 3% of people between the ages of 65-74 have AD, 17% of people between the ages of 75-84 have AD, and 32 to 50% of people over 85 show symptoms of disease (Prince et al., 2013). With the average life expectancy across the globe increasing each year, the number of AD cases are expected to rise dramatically by mid-century and with it, the health care costs for patients suffering with AD.

### *Modifiable Risk Factors*

While age, family history, and genetics cannot be altered, we can potentially modify and control several other risk factors for developing AD. These include, but are

not limited to, education level, exercise, social and cognitive engagement, traumatic brain injuries, cardiovascular health, and depression.

A 2014 population-based analysis by Norton et al., suggests that possibly up to a third of all AD cases can be attributed to modifiable risk factors. The risk factors they identified are diabetes mellitus, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational status. Researches estimated that a 10% reduction in the prevalence of risk factors per decade, by the year 2050, could reduce the number of AD cases by 8.7% in the US alone. And a 20% reduction could reduce the prevalence of AD by up to 16.3% in the US. This is a huge population in the US-- between 0.8 and 1.5 million people--that could possibly avoid the devastation of AD (see Figure 2). They also found that the largest proportion of AD cases in the US could be attributed to physical inactivity.



**Figure 2. Projected AD Prevention Percentages.** Projected percentages of AD cases that could be prevented, with 10% or 20% reduction per decade in the relative prevalence of the seven risk factors. (From Norton et al., 2014)

Therefore, as scientists come closer to developing drugs to treat disease, many scientists are now also studying the possible protective effects of modifiable risk factors. Several recent studies have linked physical activity and AD. Mounting evidence suggests that aerobic exercise could be a viable option in delaying onset of AD and/or alleviating symptoms of disease. The purpose of this review is to examine the impact of exercise on cognition and AD at the epidemiological and molecular level.

## CURRENT LITERATURE REVIEW

Several studies have been published in the last 10 years to determine the benefits exercise has on persons with AD with varying results. The discrepancy in results can be

attributed to the high heterogeneity within and across studies, including exercise type, neuropsychological tests, severity of AD, age, sex, and race. Most agree that exercise offers some improvements in living standards and some forms of cognition (executive function, global cognition, verbal frequency), but to what extent is debated. Additionally, the molecular mechanisms of how exercise provides the cognitive benefits is still unknown. Here we review several of the prevailing hypotheses.

## **Epidemiological Studies**

### *Randomized Control Trials (RCT)*

In 2014, Ohman et al. conducted a systematic review of 22 RCTs from 1991 to 2013 that included 1,699 participants: 1,021 subjects with Mild Cognitive Impairment (MCI) and 678 with dementia (See Table 1). The researchers found that most of the studies done were of poor methodological quality and caution that the results be interpreted with that in mind. The studies also had high levels of heterogeneity between them.

Nevertheless, Ohman et al. concluded that physical exercise had the most cognitive benefit in persons with MCI. These benefits were mainly seen on global cognition, executive function, and attention. They found that the results on persons with dementia were inconclusive and more research needs to be done with high methodological quality. In this regard, Ohman et al. suggests having larger sample sizing,

longer exercise programs, better and longer follow up, and more rigorously defined levels of dementia.

Study	Global cognition	Executive function	Attention	Working memory	Delayed recall	Declarative memory	Communication
<b>Study population with MCI</b>							
Suzuki et al., 2013 [41]	+ <sup>a</sup>			+ <sup>a</sup>	+ <sup>a</sup>		
Nagamatsu et al., 2012, 2013 [42, 43]		+ <sup>b</sup>	+		+		
Varela et al., 2012 [35]	0						
Lam et al., 2011 [32]	+	0	+		0		
Baker et al., 2010 [30]		+	+		0	0	
van Uffelen et al., 2008, 2009 [26, 27]	0	0	+ <sup>c</sup>		+ <sup>d</sup>		
Lautenschlager et al., 2008 [25]	+	0		0	0		
Scherder et al., 2005 [22]		+		0	0		
<b>Study population with dementia</b>							
Vreugdenhil et al., 2012 [36]	+						
Venturelli et al., 2011 [33]	0						
Yágüez et al., 2011 [34]			+	0			
Kemoun et al., 2010 [31]	+						
Steinberg et al., 2009 [28]						0	
Eggermont et al., 2009 [29]		0		0	0	0	
Burgener et al., 2008 [37]	+						
Christofoletti et al., 2008 [38]	0	+ <sup>e</sup>		0	0	0	
Kwak et al., 2008 [24]	+						
Miu et al., 2008 [39]	0						
Stevens and Killeen, 2006 [23]		+					
van de Winckel et al., 2004 [21]	+	+		0		+	
Cott et al., 2002 [20]							0
Friedman and Tappen, 1991 [19]							+

+ = Improvement; 0 = no difference between intervention and control groups.  
<sup>a</sup> Amnesic MCI; <sup>b</sup> reaction time improved in Spatial Memory Test; <sup>c</sup> female; <sup>d</sup> male; <sup>e</sup> group 1.

**Table 1. Results from 22 RCTs between 1991-2013.** Table measures various types of cognition and memory. (From Ohman et al, 2014)

In a 2011 systematic review, Littbrand et al. came to several of similar conclusions as Ohman et al. They identified 10 RCTs that studied the cognitive and physical benefits of walking and exercise in persons with AD and living in residential care facilities. However, even though Littbrand et al. concluded that there may be some physical functionality benefit, they could not come to any conclusions on positive cognitive effects due to poor methodological quality of the studies reviewed. They concur

with Ohman et al. by suggesting new RCTs of higher scientific quality are needed to elucidate any protective or positive cognitive effects of exercise on AD patients.

In another 2014 systematic review and meta-analysis of 6 RCTs, Farina et al. found that there was a possible positive effect on rate of cognitive decline between people with AD and physical exercise. Researchers focused their review on 6 RCT studies (these same studies were among the 22 RCTs in Ohman et al., 2014) that had clear exercise programs, cognitive tests, and only evaluated AD subjects. Although they found evidence for a positive correlation between cognitive decline and exercise, they cautioned that methodological heterogeneity limits their conclusions. They stated that due to the heterogeneity of exercise regimens throughout the 6 studies, it is impossible to determine the optimal type and intensity for cognitive improvement.

Several RCTs have been conducted in the years since the systematic reviews by Ohman et al., Littbrand et al., and Farina et al., most of which have shown a positive protective effect aerobic exercise on neuropsychiatric signs and symptoms, as well as on physical strength and the ability to perform activities of daily living (ADLs). Two studies done by Telenius et al. and Fleiner et al. showed significant reductions in neuropsychiatric signs like depression, apathy, and agitation through aerobic exercise. Neither studies considered cognition or performed any cognitive tests. The studies focused instead on effect exercise has on ADLs and neuropsychiatric improvements. Both studies showed improvement in these two categories with aerobic exercise. The authors of each study suggested more robust sample sizes in further studies.

A 2015 study by Yang SY et al. showed that aerobic exercise was protective against AD. The study brought together 50 volunteers with cognitive impairment between the ages of 50 and 80 years old. The subjects were randomly split evenly into a control group and an exercise group, which consisted of 40-minute exercises 3 times a week for 3 months. Yang SY et al. concluded aerobic exercise can improve cognitive function in persons with mild AD.

Ohman et al. (2016) performed a RCT that divided participants into two cohorts: a home-based exercise cohort and group-based exercise cohort. Each group exercised twice a week for 1 year and were compared with a control group. They found that after 12 months there was significant executive function improvement in the home-based cohort in comparison with the control group, although the same results were not found between the group-based cohort and the control group. They also found that all groups declined in verbal fluency and in the Mini-Mental State Examination. Ohman et al. concluded that exercise may be slightly beneficial for executive function, but positive correlations were not found for semantic memory or global cognition. Although, enhancements in ADLs were shown.

A study by Yu et al. (2017) corroborates the findings by Ohman et al., also concluding that aerobic exercise may help maintain executive function in persons with dementia. Researchers conducted a 6-month trial of aerobic exercise on community-dwelling adults with mild to moderate AD. They determined that aerobic exercise may offer a positive effect on executive function in individuals with AD but suggest future RCTs be conducted to support their conclusions.

A previous pilot study by Yu et al. (2013) also followed a group of AD patients in community-dwelling for 6 months, during which they did an exercise program. They concluded that aerobic exercise may have beneficial results on executive function as well as depression but saw a downward trend in global cognition. They recommended future, robust RCTs.

Toots et al. primarily looked to measure changes in global cognitive function and executive function in persons with AD. Participants exercised based on the High-Intensity Functional Exercise (which is mostly non-aerobic) for 45 minutes, 5 times per 2-week period over 4 months. Toots et al. used the Mini-Mental State Examination and Alzheimer's Disease Assessment Scale-Cognitive Subscale to assess global cognition. Researchers concluded that the High-Intensity Functional Exercise had no positive effects on global cognition or executive function. They did find, as in previous studies, an increased ability to perform ADLs.

In a separate study by Portugal et al. in 2016, researchers focused on strength training exercises, as opposed to aerobic exercise, and its effect on AD. To investigate this, they performed a somewhat comprehensive review of research done on strength training and AD. They found that strength training has an unclear effect on cortical atrophy and cerebral blood flow and a positive effect on the neurotransmitters IGF-1 and BDNF. They concluded that strength training may be useful in neurogenesis and neuroplasticity.

Hoffmann et al. evaluated approximately 200 persons with mild AD that participated in an aerobic exercise regimen. The research did not find a significant

correlation of exercising and increased cognition. Rather, they discovered a connection with improved neuropsychiatric symptoms that accompany AD, including depression, dysphoria, apathy, irritability, etc.

A 2017 study by Morris et al. found similar results in functional ability and ADLs. They also measured memory, executive function, and depression. They had 76 probable AD patients who participated in 150 minutes of aerobic exercise per week for 26 weeks. Along with improved ADLs, Morris et al. found indirect evidence that improved cardiorespiratory fitness was positively associated with memory performance and bilateral hippocampal volume. Aerobic exercise did not attenuate cognitive AD symptoms, this only occurred when those exercises were met with improved cardiorespiratory fitness.

In summary the RCTs evaluated here provide an inconclusive analyses of the effects aerobic exercise have on the progression and development of AD. Several studies show a possible positive correlation in executive function, neuropsychiatric symptoms, and ADLs but only one of them found a positive correlation in global cognition. There are several possible reasons for these results including varying intensities of exercise, different types of exercise, and poor methodological quality. But perhaps, a prevailing reason could be that AD symptoms were already present when the therapy of exercise was administered. Although evidence suggests exercise to be beneficial in living standards for persons with AD, it seems it can't reverse or slow the major cognitive deficits of disease. It may be necessary for exercise to be administered before onset of symptoms to have a protective role in cognitive function.

### *Meta Analyses*

Several meta analyses have been performed assessing the protective role of exercise on cognition in AD patients. Most of them agree that there is a positive correlation between the two. As discussed previously, additional studies need to be done to corroborate these findings.

The earliest analysis we will discuss here is a 2009 study from Hamer & Chida. They included 16 prospective studies in their analysis with a total of 163,797 non-demented participants at baseline and with 2,731 AD/dementia cases at follow up. Researchers used random effects modelling to allow for heterogeneity between studies. Their results suggest that physical activity reduces the risk for AD by up to 45%. Although, they determined that it is unclear at what time in a person's life exercise is most important for protection against AD, and they were not able to determine an optimal dose of physical activity. Hamer & Chida offered several theories on the mechanisms of how exercise provides its protective effects but did not expound on any of them.

A meta-analysis on RCTs by Groot et al. found that aerobic—not non-aerobic—exercise had positive cognitive results and increased benefit on ADLs in AD patients. Three exercise groups were created: an aerobic group, non-aerobic group, and a group that did both. Researchers also concluded that both high frequency and low frequency exercise interventions promote positive cognitive effects in AD patients. They also suggested that exercise interventions of more than 150 minutes per week did not provide any additional protection or positive effects.

Similarly, a meta-analysis on RCTs by Cai et al. found a positive effect of exercise intervention on cognitive function in AD patients. They concluded that even low to mid-frequency exercise had positive effects, similar to what was concluded by Groot et al.

In comparison, a 2017 study by Guure et al. found a strong association between high physical activity and cognitive maintenance in AD subjects. Researchers employed the Bayesian parametric and nonparametric approaches to control for bias and heterogeneity. They found that high intensity physical activity reduces risk by 38% and moderate exercise by 29%.

In contrast to each of the above meta-analyses, Forbes et al. found no evidence that physical activity improves cognition in persons with dementia. They did not distinguish between types of dementia. They reviewed 17 trials with 1,067 participants. Researchers also did not find any evidence that exercise was beneficial for neuropsychiatric symptoms including depression, although they did find benefit for ADLs. Forbes et al. acknowledges the study had high heterogeneity and cautions the interpretation of results.

### *Twin Study*

A 2008 study by Andel et al. evaluated the role of exercise at midlife and AD in human subjects. This was done by comparing the midlife physical activity of 90 sets of twins, with one twin in each pair experiencing dementia. The level of activity was self-reported in many instances, which proves to be problematic, given that some patients had

dementia. Despite this, when controlled for age, sex, education, smoking, alcohol consumption, diet, BMI and angina, the study concluded that even light exercise in midlife can decrease a person's risk for AD.

Overall, these meta-analyses and twin study conclude that physical exercise lowers the risk of developing AD and aids in maintaining of cognitive function in AD patients. However, in the analysis by Forbes et al. that didn't find this correlation, it was acknowledged several times throughout the study that the high heterogeneity could skew results. Despite this one study the majority of studies suggest that exercise can potentially be a powerful risk reducer in the development of AD. Even when assessing RCTs they found a positive association between exercise and cognitive maintenance. This is compelling evidence that a healthy, exercise filled lifestyle can act as a deterrent for disease. A reasonable future step should be evaluating the right dosage of exercise and time of application that will lead to the greatest results.

### **Preclinical Studies**

Evidence from epidemiological studies suggest that exercise can lower the risk of developing AD and possibly help maintain cognition in persons who are already demented, but the molecular mechanisms still need to be elucidated. It is evident that exercise induces some changes in APP processing to lower the A $\beta$  load, but it is difficult to know exactly how. Preclinical studies in mice also link exercise with AD development/progression and have identified potential genes involved in the response to exercise.

Several studies have also concluded that exercise improves A $\beta$  load, tau phosphorylation, and neuroinflammation although not offering a mechanism or even addressing the regulation of genes. For example, Tapia-Rojas et al. conducted aerobic exercise experiments over 10 weeks with double transgenic APP mouse models. They found that volunteer running (mice are not shocked or otherwise coerced to run) decreased A $\beta$  load and tau phosphorylation, neuroinflammation, and prevented cell loss in the hippocampus, increased neurogenesis in the dentate gyrus, and improved cognitive performance in their AD mouse models. Researchers did not determine if the running has its effect on APP process or A $\beta$  clearance or both, and researchers did not determine the molecular mechanisms behind their findings.

Zhang et al. studied APP/PS1 transgenic AD mouse models and found that aerobic exercise maintains white matter volume and capillaries in white matter. They also found that aerobic exercise improved spatial learning and memory in AD mice.

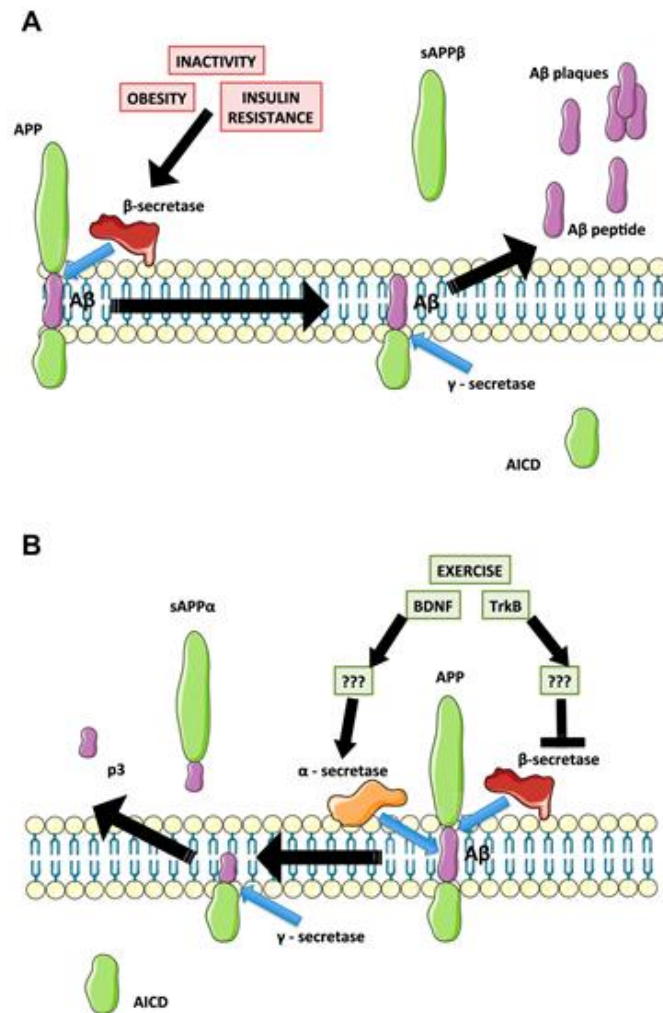
In a systematic review in 2016, Ryan et al. investigated the possible benefits of exercise on neuroinflammation, cognition, and neurogenesis in mouse models of AD. They provide evidence from previous research that neurogenesis in the hippocampus is imperative to adult memory and cognition, and that neuroinflammation reduces neurogenesis in the hippocampus and directly contributes to the development of AD. In a comprehensive study and analysis of previous research done in mouse models, Ryan et al. concludes that aerobic exercise decreases amyloid pathology, increases neurogenesis in the hippocampus, and has potent pro-neurogenic and pro-cognitive effects.

### *APP Processing and BACE 1*

Several studies have pointed to a decrease in Beta Secretase 1 (BACE1)—which is a transmembrane protease that catalyzes the first step in the formation of amyloid beta peptide from APP—as the main factor in the decrease of A $\beta$ , but MacPherson et al, 2017 argues that exercise results in improvements in total adiposity, circulating metabolites, glucose intolerance, and insulin sensitivity which makes it difficult to determine what exactly affects APP processing (PubMed).

BACE1 is the rate-limiting step in the production of  $\beta$ -amyloid and can be considered a biomarker for early AD detection. Therefore, it should also be looked at as a potential therapeutic target. In an AD brain, there are no changes in BACE1 mRNA, however BACE1 enzymatic activity is upregulated. Interestingly, in aerobic exercise studies, it has been shown that BACE1 expression levels and activity are downregulated in the brain. Studies have also shown that when administered BACE1 inhibitors, rat models do not develop  $\beta$ -amyloid plaques.

MacPherson asserts that modifiable risk factors like inactivity, obesity, and insulin resistance may be partly to blame for the increase in BACE1 activity. MacPherson found that a single bout of exercise decreases BACE1 activity by inducing BDNF to exert a positive downstream effect on  $\alpha$ -secretase and inducing TrkB to exert a prohibitive downstream effect on BACE1, thereby decreasing total A $\beta$  load (See Figure 3). However, the exact mechanism remains unknown.



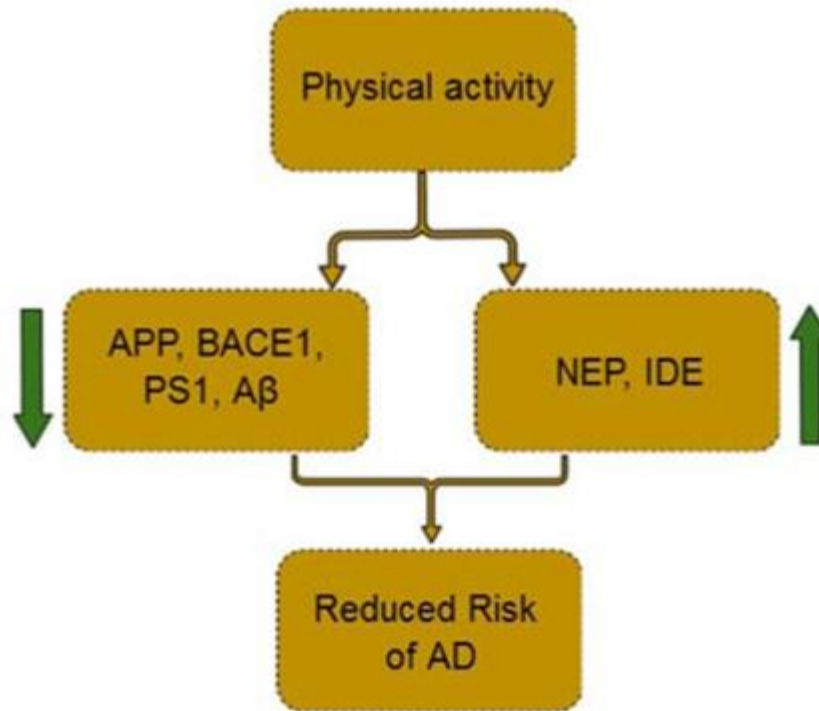
**Figure 3. Hypothesized Mechanism of Exercise  $A\beta$  Prevention** Hypothesized mechanism that exercise has on preventing  $A\beta$  build up. (From MacPherson et al, 2017)

Similarly, Kang et al. found that aerobic (treadmill) exercise prevented memory impairment from PSEN2 in a mouse model and reduced  $A\beta$  deposition through the inhibition of BACE1 activity or levels of expression. They showed that PSEN2 mice who exercised had lower  $A\beta$  deposition and less cognitive impairment, as well as lower levels of BACE1 and its product, C-99, in the hippocampus. Results also showed downregulation in several other genes included in inflammation and apoptosis. They concluded that aerobic exercise is protective against AD because it downregulates

BACE1 expression, ER stress, and inflammation, and not only inhibits A $\beta$  production but removes existing A $\beta$  plaques.

Cho et al. drew the same conclusions as the above-mentioned studies. They also found that BACE1 expression and its end-product were significantly reduced with aerobic (treadmill) exercise in a triple transgenic AD mouse model when compared to the same mouse model without exercise. They also showed reversal of memory loss and AD-like symptoms, lower A $\beta$  and hyper-phosphorylated tau, and increased in BDNF. Dao et al. found that running protects BDNF, calmodulin, and calcineurin expression, as well as prevents impairment in the dentate gyrus and signaling pathways.

In a separate systematic review by Ebrahimi et al., researchers proposed that physical exercise exerts its effects by lowering APP, PSEN1, A $\beta$  load, and BACE1, which is part of a duo of enzymes, including  $\gamma$ -secretase, that cleaves APP to generate A $\beta$ , and by increasing neprilysin (NEP) and insulin degrading enzyme (IDE), which work together to determine and lower A $\beta$  concentration (See Figure 4). The authors do not suggest a mechanism for how these genes are upregulated.

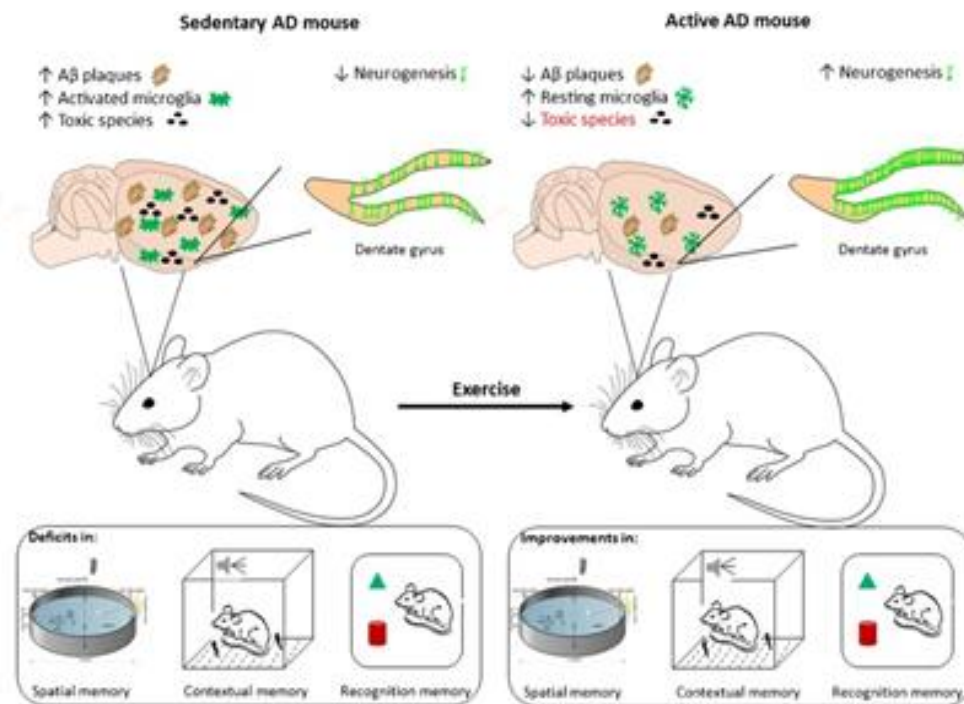


**Figure 4. Results of Exercise on APP, BACE1, etc.** Figure showing the results of physical activity on APP, BACE1, PSEN1, A $\beta$ , NEP, and IDE and their subsequent influence on risk of developing AD. (From Ebrahimi et al. 2017.)

The same review highlights recent evidence that exercise may inhibit the deleterious memory deficits caused by PS2 mutations, may inhibit activation of  $\beta$ -secretase, and may reduce A $\beta$ 42 deposition in the hippocampus (Ebrahimi et al., 2017). Physical activity has also recently been shown to be especially helpful in persons who have the APOE  $\epsilon$ 4 allele. Several studies suggest that physical exercise is just as effective or more in persons with APOE  $\epsilon$ 4 than non-carriers (Ebrahimi et al., 2017).

In contrast, Adlard et al. did not find a relationship between physical activity and a change in levels of BACE1, NEP, or IDE. Although, researchers did show a decrease in the overall A $\beta$  burden.

Overall, AD mouse models seem to almost collectively agree that aerobic (treadmill) running offers protective effects in the development of AD (See Figure 5). Despite the remaining questions on the exact molecular mechanisms induced by aerobic exercise, several of the above studies agree that exercise causes a reduction in A $\beta$  load, tau pathology is ameliorated, neuroinflammation is decreased, BDNF is increased, neurogenesis is increased especially in the dentate gyrus, and so is cognitive performance.



**Figure 5. Molecular Changes in AD Mouse Model.** Compares the molecular changes that occur in the brain of a Sedentary AD Mouse and Active AD Mouse. (From Ryan et al. 2016)

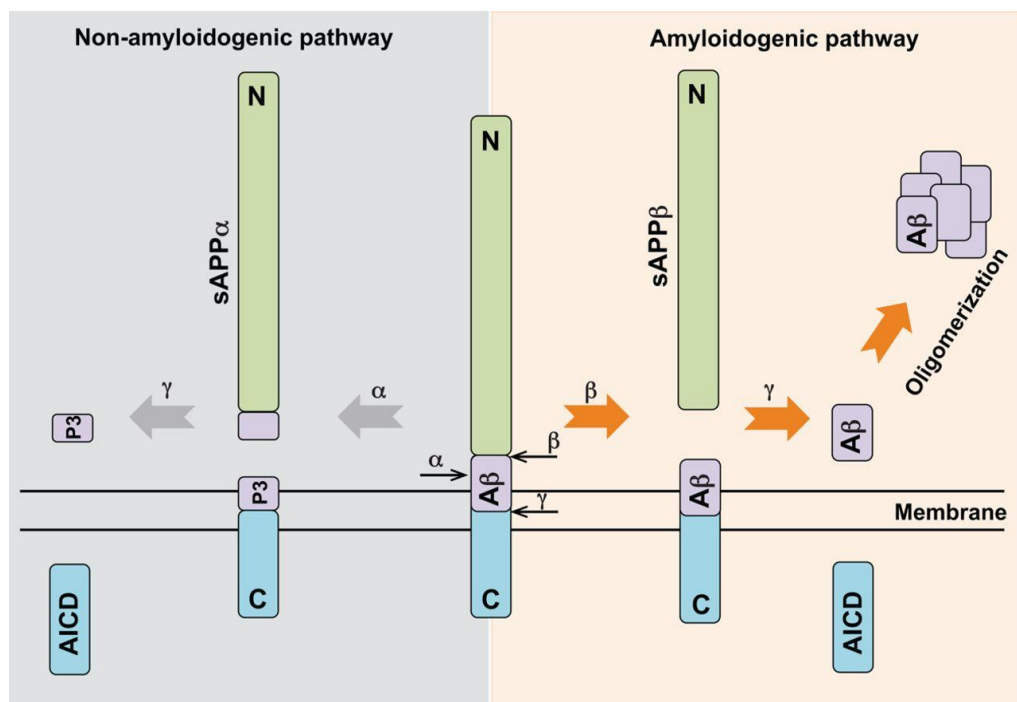
### *BDNF & Ketones*

In recent years, Brain Derived Neurotrophic Factor (BDNF) has received attention for its possible protective role in AD pathology. BDNF aids in and enhances neurogenesis (both in proliferation and on survival), synapse formation, learning & memory, and neuronal stress resistance (Nigam et al., 2017, BDNF, Binder and Scharfman, 2004). Additionally, it has been observed that BDNF protein is rapidly and significantly increased in the hippocampus during contextual learning, and that blocking BDNF impairs spatial learning (Binder and Sharfman, 2004). Other studies have also demonstrated an upregulation of BDNF in dorsal root ganglion cells as well as hippocampal and cortical neurons during exercise (Huang and Reichardt, 2001). Reduction in BDNF mRNA in the hippocampus has been shown in Alzheimer's disease specimens (Ferrer et al., 1999; Phillips et al., 1991, Murer et al., 2001).

Research shows that BDNF increases with exercise throughout the brain and especially in the dentate gyrus, but the exact mechanism remains elusive (Dao et al., 2015). In a recent study Sleiman et al. discovered  $\beta$ -hydroxybutyrate --a ketone body created in the liver-- which upregulates BDNF expression in the brain. They proposed that D- $\beta$ -hydroxybutyrate is induced by exercise and accumulates in the hippocampus where it acts as an inhibitor of class I histone deacetylases (HDACs) to specifically induce BDNF expression. HDACs are a class of enzymes that remove acetyl groups from an  $\epsilon$ -N-acetyl lysine amino acid on a histone, allowing the histones to wrap the DNA more tightly. In a 4-week trial of voluntary exercise, the BDNF promoter I and II

expression in the hippocampus increased significantly in AD and non-AD mice, as well as mature BDNF protein levels.

Recent evidence suggests that increased BDNF levels lead to less A $\beta$  and A $\beta$  Plaques and may have a direct effect on APP processing and A $\beta$  build up through the upregulation of  $\alpha$ -secretase. APP is cleaved by three enzymes:  $\alpha$ ,  $\beta$ , and  $\gamma$  secretase.  $\beta$  and  $\gamma$  secretase increase levels of A $\beta$  40 and 42, which results in the amyloidogenic pathway of AD (Heneka et al., 2015). In contrast  $\alpha$  secretase cleaves APP and prevents A $\beta$  generation and leads to the non-amyloidogenic pathways (Nigam et al., 2017) (See Figure 6).



**Figure 6. Amyloid precursor protein and neural development.** (From Nicholas and Hassan 2014)

Nigam et al. and MacPherson determined that BDNF increases  $\alpha$ -secretase and lowers soluble A $\beta$  in the hippocampus of transgenic AD mice. They hypothesized that exercise can shift the processing of APP to the non-amyloidogenic pathway by increasing BDNF levels, which will increase  $\alpha$ -secretase.

Although BDNF acts on A $\beta$ , it has no known effect on tau proteins. Jiao et al. studied the relationship between BDNF and the hyperphosphorylation of tau detected in AD and found none. It has been shown that aerobic exercise does protect against tau pathogenesis, but this could be due to several factors (Gratuze et al., 2017). They did however find that BDNF protected against tau-related neurodegeneration. Interestingly, their research led them to discover that BDNF can alleviate behavior deficits and prevent neuronal loss, synaptic degeneration, and neurogenesis impairment without affecting tau hyperphosphorylation.

While research into BDNF has uncovered possible therapeutic targets, there is still much to be done in terms of research and testing. Increases in BDNF in vivo have not shown strong enough evidence to reverse disease, most probably because it has never been administered at early stages. More research should be done on this topic.

### **Neuroinflammation**

The “amyloid cascade” hypothesis has long been considered the most accepted theory in AD pathology. Neuroinflammation was thought to be a “late-stage event” in AD, with the activation of innate immune system through glial cells and proinflammatory markers responding to the buildup of A $\beta$  (Balducci and Forloni, 2018, Heneka et al.,

2015). The studies suggest that the neuroinflammation is often in response to the AB buildup (Balducci and Forloni, 2018).

Increasingly more evidence shows that innate immune system activation actively contributes to AD pathogenesis, rather than arising as a bystander reaction to amyloid build up (Sarius and Heneka, 2017, Heneka et al., 2015). For example, a recent study by Sarius and Heneka, 2017 even found that inflammation and microglial activation occur before the onset of AD and may be a driving force in AD pathology. Although this finding needs to be further researched, it adds to the compelling narrative of the intimate relationship between neuroinflammation and the development or forwarding of AD.

With an ever-growing body of research showing the relationship between AD and neuroinflammation, it becomes apparent that exercise may be valuable in the attenuation of AD symptoms through its anti-inflammatory effects.

#### *AD studies: exercise and inflammatory gene expression*

AD mice models and patients show an upregulation of several inflammatory genes including: HLA-DRB5/DRB1, INPP5D, MEF2C, CR1, TREM2, Tumor Necrosis Factor Alpha (TNF- $\alpha$ ), IL-6, CD33, TYROBP, C-Reactive Protein (CRP), IL-1 $\beta$  and MSA4A (Jones et al., 2015, Vanltallie, 2017, Dansokho and Heneka, 2017, Karch et al., 2014 See Dansokho et al. for more). These genes are thought to contribute to the neuroinflammation that exists in demented brains, although how much each gene contributes, and their mechanisms have not been fully elucidated.

When compared with inflammatory genes that are downregulated during exercise, there seems to be a compelling overlap between several genes, namely between TNF- $\alpha$ , IL-6, IL-1 $\beta$ , & CRP (Sloan et al., 2007, Ryan et al., 2016, Kohut et al., 2006, Lakka et al., 2005, Flynn et al., 2007, Kasapis and Thompson, 2005, Kang et al., 2013). If aerobic exercise can neutralize the inflammatory genes and cytokines that are upregulated in AD and arrest or at least lower neuroinflammation, it may be an effective way to ameliorate the symptoms and pathologies of the disease. The evidence supporting this hypothesis is scant, in part because studies scrutinizing this theory are few and results from these studies are inconclusive. Only a very few studies have investigated how aerobic exercise affects the inflammatory markers in the CNS and fewer have been done when evaluating AD cases.

Despite this, there have been many studies that explore how exercise exerts an anti-inflammatory response throughout the body regarding other diseases like cardiovascular disease. Based on these studies there may be exciting parallels to what can occur in the CNS and they may still enlighten us on the possible effects of exercise on inflammation in the demented brain.

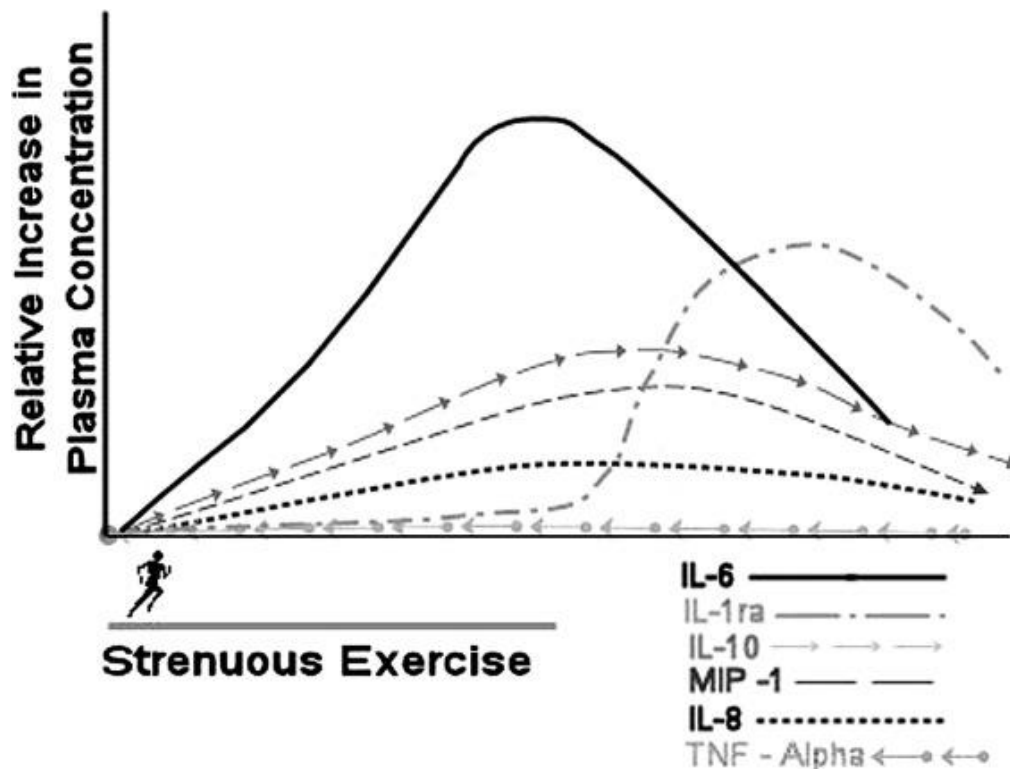
#### *Non-AD Studies: exercise and inflammatory gene expression*

Exercise has been shown time and again to reduce CRP, TNF-alpha, IL-6, IL-1 $\beta$ , and other inflammatory markers throughout the body. In 2005, Lakka et al., determined through a 20-week exercise program that aerobic exercise lowers levels of CRP in sedentary adults with high levels of CRP. Researchers took parents (age 65 or younger)

and their children (age 17 or older) and subjected them to an exercise regimen. The results of reduced CRP were consistent across the board. Sloan et al., Flynn et al., Kasapis and Thompson, Kohut et al., and Petersen and Pedersen all came to similar conclusions.

Sloan et al. studied young sedentary adults aged 20-45 years old. They broke up their subjects into two groups, a moderate-intensity exercise group and a high-intensity exercise group. They found that only the high-intensity exercise group led to a decrease in TNF-alpha and CRP release. In a review study, Flynn et al. argued that although more research is needed, the majority of studies agree that physical activity and physically fit people have lower levels of IL-6, TNF-alpha, CRP, and IL-1 $\beta$ .

In a separate systematic review, Kasapis and Thompson found that strenuous exercise produced a short term inflammatory response during an Acute Phase Response (APR) to the physical exertion (See Figure 7). They showed that pro-inflammatory cytokines (IL-6 and IL-1) increase, while TNF-alpha stays relatively the same. There was also an increase of anti-inflammatory markers, namely IL-8, IL-10 and macrophage inflammatory proteins 1 (MIP-1).



**Figure 7. Exercise and Inflammatory Marker Release.** Shows effect of strenuous exercise on the release of inflammatory markers. (From Kasapis and Thompson 2005)

In contrast, they found that regular physical activity was inversely related to inflammatory marker concentration. They suggest that physical activity needs to be consistent to produce the anti-inflammatory response, citing a study by Wannamethee et al. that showed when active men stopped exercising their CRP levels increased to those found in sedentary men who remained inactive, showing that CRP levels, and the anti-inflammatory response, need constant upkeep.

Interestingly, Kohut et al. found that not only does aerobic exercise reduce levels of IL6, TNF-alpha, IL-18, and CRP, these reductions also correlated with improvement in depression, optimism, and a sense of coherence. These psychosocial results may be due

to several aspects and results of exercise. Further research is needed to determine the exact mechanisms.

Petersen and Pedersen suggest that chronic-low grade inflammation occurs as people age, with aged people showing increased levels of TNF-alpha, IL-6, and CRP. They implicated adipose tissue as the major producer of TNF-alpha, which also increases IL-6, IL-1, and CRP. They showed that IL-6 is released from muscles during exercise and directly mimics the levels of TNF-alpha and, in contrast to the above studies, suggest that IL-6 has important anti-inflammatory effects. It causes these effects by inhibiting TNF-alpha and IL-1 and through increasing production of IL-1ra and IL-10, both anti-inflammatory cytokines. Despite these differences, the conclusion is the same, that exercise can be used to ameliorate systemic inflammation.

In a separate study, Kohman et al. investigated the effects that exercise may have on microglia activity, finding that the hippocampus, and microglia in the hippocampus, are particularly responsive to exercise. They discovered that aerobic exercise can alter the activation of microglia in the hippocampus, which in turn, changes the cytokines and inflammatory genes used by the microglia.

These studies show a pronounced anti-inflammatory response of exercise in people of all ages. The evidence of exercise directly modifying microglia and the release of inflammatory cytokines and markers is compelling. It is also interesting to note that several of the studies found regular, long-term exercise being the most beneficial in promoting the anti-inflammatory effect when studying other diseases. A potential parallel can be drawn when comparing these data with that found in the reduction in AD risk in

people who exercise throughout their lives. Perhaps the reduced risk in AD in people that exercise is due in part to the lowering of inflammation systemically and in the CNS.

### *AD Models*

Exercise downregulate pro-inflammatory markers, and also upregulates anti-inflammatory markers. In a Tg2576 AD mouse model sedentary mice were found to overexpress the pro-inflammatory IL-1 $\beta$  and TNF-alpha more so than wild type mice. In addition, aerobic exercise lowered expression of IL-1 $\beta$  and TNF-alpha to levels similar with that of wild type mice (Stranahan et al., 2012). Ryan et al. focused on the inflammation of the hippocampus and the results of exercise in this tissue. They found that AD models show decreases in hippocampal IL-1 $\beta$  and TNF-alpha, as well as increases in CXCL1 and CXCL12 which are neuroprotective chemokines. They further suggest that exercise may have direct effects on microglia activity in the hippocampus.

### **Role of Microglia in AD Pathology**

Microglia has been shown to have a higher density in the hippocampus than other parts of the brain (Kohman et al.). In studying the regulation of unfolded protein response (UPR) Kang et al. found that treadmill running in a 3xTg mutant mouse model of AD showed a decrease in TNF-alpha and IL-1alpha, possibly through modification of the UPR.

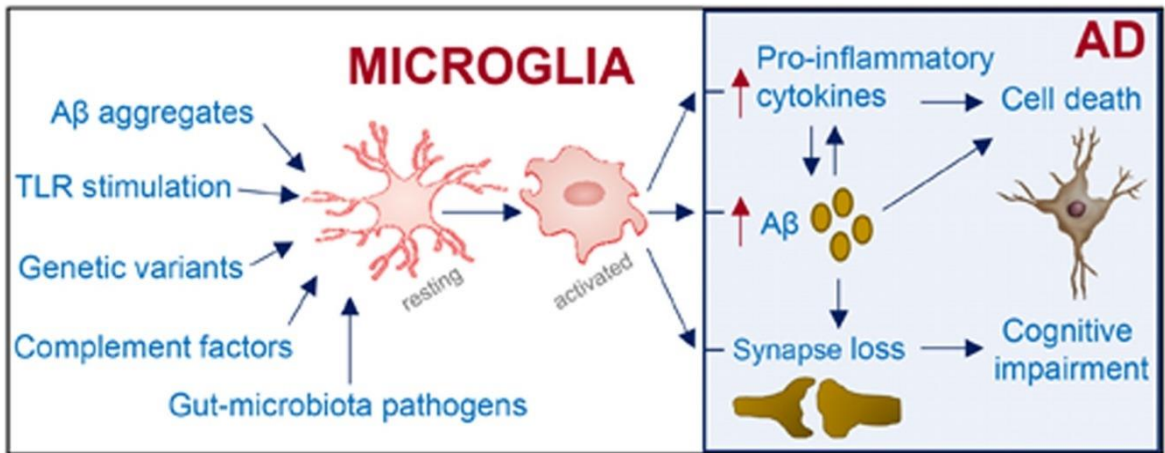
Interestingly, AD models show evidence that exercise extends its anti-inflammatory affect into the CNS and quite possibly through modification of microglia.

These studies show a marked decrease in pro-inflammatory cytokines, especially TNF-alpha, IL-1, and CRP. It has been shown that activated microglia are responsible for releasing TNF-alpha and IL-1 in the CNS (Su et al., 2016 & Balducci & Forloni, 2018). In this light, the hypothesis the ant-inflammatory effects from exercise are due to the modification of microglia is appealing. Microglia are the resident immune cells of the brain and the first line of defense in response to pathogens. They recognize exogenous and endogenous CNS insults and are vital to a healthy brain environment, while comprising between 10-15% of all CNS cells (Solito and Satre, 2012 & Balducci and Forloni, 2018). Once thought to primarily be phagocytic cells, recent discovery has shown microglia have a variety of functions including phagocytosis of synaptic structures, active remodeling of presynaptic environment, and the release of soluble factors in the mature and aging brain. Microglia also act as critical mediators in the modulation of neurogenesis (Su et al., 2016).

Microglia exist in two major states: resting and activated. In the resting state, microglia are on a continuous patrol of the neuronal environment. They contribute to tissue homeostasis, release neurotrophic factors, and survey the activity of synapses to ensure regular processing of new memories (Balducci and Forloni, 2018, Sarius and Heneka, 2017, and Chitnis & Weiner, 2017). They express a collection of innate immune receptors including Toll-like receptors (TLRs), scavenger receptors, and receptors for advanced glycosylation end products. These respond to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs).

TLRs have been scrutinized in recent years for their role in AD. They are a family of pattern recognition receptors expressed on microglia (Balducci & Forloni, 2018). It has been shown that several types of TLRs are associated with AD, mainly due to their phagocytic and inflammatory response when recognizing and responding to AB oligomers and plaques and other misfolded proteins (Dansokho and Heneka, 2017, Heneka, 2017). Activation of these TLRs is what leads to the release of proinflammatory cytokines like TNF-alpha, IL-6, and IL-1B (Su et al., 2016 & Balducci & Forloni, 2018). Disrupting and/or blocking the downstream cascade of TLRs has been shown to improve the clearance of AB and shift microglial cells to an anti-inflammatory phenotype (Heneka et al., 2015 and Dansokho & Heneka, 2017).

When encountering pathogens through TLRs, microglia can transform into the activated state. In the active state, microglia increase in number, undergo phenotypic changes, and changes in secretory mediator and proliferative response (Balducci and Forloni, 2018 & Sarius and Heneka, 2017). They express and release a number of inflammatory markers including CD36, CD14, CD11c, MHC-11, iNOS, IL-1 $\beta$ , IL-6, TNF-alpha, IL-8, macrophage inflammatory protein-1alpha and marks of the M1 phenotype (Sarius and Heneka, 2017 & Solito and Satre, 2012, Dansokho & Heneka, 2017). This induces an inflammatory response which resolves the insult. It is also this inflammatory response, when it becomes chronic and over exaggerated, that exacerbates the symptoms of AD (See Figure 8).



**Figure 8. Activated Microglia.** Shows the possible negative results of activated microglia. (From Balducci and Forloni, 2018)

Neuroinflammation acts as a double-edged sword when it comes to AD. In the early stages of AD and during an acute inflammatory response, neuroinflammation may play a protective function in the development of AD. It can help defend the brain and CNS and aid in the removal of cell debris and toxic factors, with one of its primary beneficial function being the removal of amyloid through microglia (Balducci and Forloni, 2018).

Yet, chronic inflammation has been implicated as a driving force behind AD and studies have shown inflammation playing a key role in AD through neuronal damage, increased Aβ generation, increased phosphorylation of tau, and cognitive impairment (Solito and Satre, 2012 & Sarius and Heneka, 2017). Inflammation and Aβ generation may even create a positive feedback mechanism, where inflammation increases Aβ generation through increasing the transcription of BACE1 and Aβ generation increasing the inflammatory response (Solito and Satre, 2012, Heneka et al., 2015). It has also been

shown that stimulation of the immune system by AB deposits and proinflammatory cytokines impairs the ability of microglia to clear AB. Additionally, the activation of the immune system may reduce microglial capacity to produce neurotrophic factors (Heneka et al. 2015).

There are many theories into why and how microglia maintain their chronic activation. One intriguing hypothesis is that the microglia develop a gene-expression pattern that is unlike the gene-expression shown by the microglia that resided in the brain before being activated. Over time, the new microglia could maintain this expression pattern and sustain a chronic neuroinflammation in AD (Heneka et al., 2015).

Another theory is that when microglia become activated in AD, they surround the neurons with AB build up until they can remove the insult. It is when they cannot remove the buildup that they slip into chronic inflammation. The microglia stay surrounded around the neuron, continuously attacking it and releasing pro-inflammatory cytokines, essentially killing the neuron and promoting the neurodegenerative process (Balducci and Forloni, 2018).

Despite not knowing the exact process of maintaining the chronic inflammatory state of microglia, the evidence points to microglia playing an integral part in AD. With the additional evidence that exercise possibly alters microglial activation, it stands to reason that exercise may attribute its lowering of AD risk to microglial modification. Certainly, more studies need to be done to assess this hypothesis, but the current evidence looks promising. Microglia may very well be the key to preventing and/or reversing AD.

## **NSAIDs**

It is reasonable to believe that if inflammation is a driving force behind AD, then taking Nonsteroidal Anti-inflammatory Drugs (NSAIDs) may alleviate symptoms (Heneka et al., 2015). Although compelling, the research and evidence is awash with disagreement. A 2002 study by Lindsay et al. followed 4,088 people over a 5-year period and found that the use of NSAIDs reduced the risk of Alzheimer's disease by 35%. Although they did not discuss the mechanism for why, one can assume these results are due in part from the anti-inflammatory effect of the drugs. In a separate study in 2017 by McGeer et al. they hypothesized that NSAIDs may be effective as a preventative treatment, only if they are started well before the onset of clinical symptoms. Several other studies have shown that NSAIDs do not offer any protective function in the development of AD (Miguel-Alvarez et al., 2015 & Wang et al., 2015). Further studies and experiments are needed to determine if altering the dosage, time of dosage in a person's lifetime, and type of NSAID would have differing results.

Even if treatment with NSAIDs became a viable option, taking them over a prolonged time period would still present with adverse health risks. There are several common side-effects of these drugs, including heart attack, stroke, gastrointestinal pain, stomach ulcers, headaches, dizziness, liver and kidney problems, and high blood pressure.

## **DISCUSSIONS AND CONCLUSIONS**

### **Potential Impact on AD Prevention & Treatment**

As discussed at the beginning of this review, the societal impact of AD is enormous. Millions of people are suffering with the disease throughout the US and the world, with that number only projected to increase dramatically in the coming years. Along with this health care crisis, billions and soon to be trillions of dollars are being and will be spent to provide adequate care for people diagnosed with AD. The disease does not just destroy the lives of the people who have it, it hinders and dismantles the lives of the loved ones who are drained emotionally, physically and financially as caregivers.

With an estimated 33% of all AD cases being caused by modifiable risk factors, the possible prevention and treatment of AD with aerobic exercise could be massive. Additionally, if inflammation is the driving force behind AD, the administration of NSAIDs or some other anti-inflammatory drug could be a relatively safe, cost efficient way to treat disease. Drug side effects, primarily gastrointestinal issues, liver and kidney problems, and high blood pressure, would have to be taken into consideration. If researchers can determine the adequate dose of exercise needed and the optimal time of administration to stave off disease, it could be an almost risk free and cost-free prevention that could potentially save millions of lives, trillions of dollars, and the emotional well-being of millions more who live with and care for relatives and friends who struggle with disease.

## **Future Directions**

The research is almost unanimous in its support of physical activity playing a protective and preventive role in the development of AD. The evidence is consistent across all types of studies and all subjects including human and animal. Despite this, there are still several vital questions that need to be answered for scientists to create a viable treatment centering around exercise.

First, when is the best time in a person's life to engage in physical exercise so to provide the greatest amount of protection against AD? Is it in middle to late age when scientists believe AB plaques are beginning to form or some other time? Most researchers agree that treatments for AD have not been effective due to the administration time being too late in disease development. Determining the opportune age for treatment may be the key to unlocking the greatest cognitive benefits seen with exercise in AD patients.

Second, what is the optimal dosage and best type of exercise to create the positive effects. Research points to aerobic exercise offering more benefits than weight or strength training alone, but this has not been confirmed. Additionally, the dosage has not been set. Scientists do not know how often, how long, or at what intensity exercise should be for the greatest protective results.

Third, what is the mechanism behind the protective cognitive function of exercise? Several potential mechanisms have been elucidated including those involving HDACs, BDNF, BACE1, and alterations of microglia. Understanding which mechanism

will allow scientists to not only manipulate the pathway through exercise, but also through pharmaceutical efforts.

Future studies should include more robust and meticulous RCTs with the above-mentioned questions at the center of the study. Previous RCTs have been criticized for their lack of attention to detail and relatively small sample size, which confounded their results. These studies often lacked homogeneity in their subjects with dementia, with patients in all stages of AD and other types of dementia, contributing to uncertain results. Unfortunately, short-term RCTs may not be powerful enough to conclusively answer the question of what age in a person's life is physical exercise most beneficial against AD. A longitudinal study would need to be administered to track progression over lengthy periods of time, potentially decades. Although long-term follow up and tracking is needed to fully consider the protective functions of exercise against AD, it is not entirely practical when a solution for AD is needed now.

Considering the time sensitive nature of finding a treatment, this review proposes that future RCTs focus on the molecular mechanisms of neuroinflammation in AD by measuring levels of pro- and anti-inflammatory cytokines in the blood and microglial activation in the brain at baseline and after aerobic exercise in individuals with dementia and those without symptoms. Microglial activation can be measured using a radiotracer and positron emission tomography (PET) in living human brains (Sandiego et al., 2015). It would also be important to have meticulously detailed exercise programs and cognitive tests. A recommendation on the best cognitive tests to administer is not given here, but these tests should be powerful enough to detect changes in executive function, global

cognition, and verbal frequency. Additionally, AD patients should be screened more heavily prior to participation in the RCTs and grouped by severity of disease. If inflammation is indeed a key player in the cognitive decline shown in AD patients, the mechanisms of how exercise manipulates neuroinflammation should be elucidated.

## **CONCLUSION**

With no cure, the increasing human lifespan, and the accompanying projected increase in AD cases, the world is in desperate need of a powerful Alzheimer's disease deterrent. Recent evidence suggests that physical exercise has the potential to be that needed protector. Whether those protective effects occur from exercise's anti-inflammatory abilities and alterations of microglia activity or its ability to change levels of BDNF and BACE1, exercise has shown real promise in being a cost-effective, almost risk-free avenue to lowering a person's risk of developing AD and in alleviating the symptoms of millions who have it.

## REFERENCES

- Adlard, P. A., Perreau, V. M., Pop, V., & Cotman, C. W. (2005). Voluntary Exercise Decreases Amyloid Load in a Transgenic Model of Alzheimers Disease. *Journal of Neuroscience*, 25(17), 4217-4221. doi:10.1523/jneurosci.0496-05.2005
- Alzheimer's Association. (2018). Alzheimer's Disease Facts and Figures. *Alzheimer's and Dementia*, 14(3), 367-429. doi:10.1016/j.jalz.2018.02.001
- Balducci, C., & Forloni, G. (2018). Novel targets in Alzheimer's disease: A special focus on microglia. *Pharmacological Research*. doi:10.1016/j.phrs.2018.01.017
- Cai, H., Li, G., Hua, S., Liu, Y., & Chen, L. (2017). Effect of exercise on cognitive function in chronic disease patients: A meta-analysis and systematic review of randomized controlled trials. *Clinical Interventions in Aging*, 12, 773-783. doi:10.2147/cia.s135700
- Calle, M. C., & Fernandez, M. L. (2010). Effects of resistance training on the inflammatory response. *Nutrition Research and Practice*, 4(4), 259-269. doi:10.4162/nrp.2010.4.4.259
- Chitnis, T., & Weiner, H. L. (2017). CNS inflammation and neurodegeneration. *Journal of Clinical Investigation*, 127(10), 3577-3587. doi:10.1172/jci90609
- Cho, J., Shin, M., Kim, D., Lee, I., Kim, S., & Kang, H. (2015). Treadmill Running Reverses Cognitive Declines due to Alzheimer Disease. *Medicine & Science in Sports & Exercise*, 47(9), 1814-1824. doi:10.1249/mss.0000000000000612
- Coelho, F. G., Vital, T. M., et al. (2014). Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *Journal of Alzheimer's Disease*, 39(1), 401-408.
- Coulson, Elizabeth J, and Perry F Bartlett. "An Exercise Path to Preventing Alzheimer's Disease." *Journal of Neurochemistry*, 2017, p. 286., onlinelibrary-wiley-com.ezproxy.bu.edu/doi/full/10.1111/jnc.14038.
- Cunningham, C. (2013). Microglia and neurodegeneration: The role of systemic inflammation. *Glia*, 61(1), 71-90. doi:10.1002/glia.22350
- Dansokho, C., & Heneka, M. T. (2017). Neuroinflammatory responses in Alzheimer's disease. *Journal of Neural Transmission*. doi:10.1007/s00702-017-1831-7
- Dao, A. T., Zagaar, M. A., & Alkadhi, K. A. (2015). Moderate Treadmill Exercise Protects Synaptic Plasticity of the Dentate Gyrus and Related Signaling Cascade in a Rat

- Model of Alzheimer's Disease. *Molecular Neurobiology*, 52(3), 1067-1076. Retrieved from <https://doi-org.ezproxy.bu.edu/10.1007/s12035-014-8916-1>.
- Dong, Y., Lagarde, J., Xicota, L., et al. (2018). Neutrophil hyperactivation correlates with Alzheimer's disease progression. *Annals of Neurology*, 83(2), 387-405. doi:10.1002/ana.25159
- Ebrahimi, K., Majdi, A., Baghaiee, B et al. (2017). Physical activity and beta-amyloid pathology in Alzheimer's disease: A sound mind in a sound body. *EXCLI Journal*, 16, 959-972. Retrieved from <https://www-ncbi-nlm-nih-gov.ezproxy.bu.edu/pmc/articles/PMC5579405/>.
- Fang, Y., Nelson, N. W., & Savik, K. (2013). Affecting cognition and quality of life via aerobic exercise in Alzheimer's disease. *Western Journal of Nursing Research*, 35(1), 24-38. Retrieved from <https://www-ncbi-nlm-nih-gov.ezproxy.bu.edu/pmc/articles/PMC5696626/>.
- Fang, Y., Vock, D. M., & Barclay, T. R. (2017). Executive function: Responses to aerobic exercise in Alzheimer's disease. *Geriatric Nursing*. Retrieved from <https://www-ncbi-nlm-nih-gov.ezproxy.bu.edu/pubmed/29031520>.
- Farina, N., Rusted, J., & Tabet, N. (2014). The effect of exercise interventions on cognitive outcome in Alzheimers disease: A systematic review. *International Psychogeriatrics*, 26(1), 9-18. doi:10.1017/s1041610213001385
- Fleiner, T., Dauth, H., Gersie, M., Zijlstra, W., & Haussermann, P. (2017). Structured physical exercise improves neuropsychiatric symptoms in acute dementia care: A hospital-based RCT. *Alzheimers Research & Therapy*, 9(1). doi:10.1186/s13195-017-0289-z
- Flynn, M. G., McFarlin, B. K., & Markofski, M. M. (2007). The Anti-Inflammatory Actions of Exercise Training. *American Journal of Lifestyle Medicine*, 1(3), 220-235. doi:10.1177/1559827607300283
- Forbes, D., Forbes, S. C., Blake, C. M., Thiessen, E. J., & Forbes, S. (2015). Exercise programs for people with dementia. *Cochrane Database of Systematic Reviews*, (4). doi:10.1002/14651858.cd006489.pub4
- Gratuze, M., Julien, J., Morin, F., Marette, A., & Planel, E. (2017). Differential effects of voluntary treadmill exercise and caloric restriction on tau pathogenesis in a mouse model of Alzheimers disease-like tau pathology fed with Western diet. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 79, 452-461. doi:10.1016/j.pnpbp.2017.08.001

- Groot, C., Hooghiemstra, A., Raijmakers, P., et al. (2016). The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing Research Reviews*, 25, 13-23. doi:10.1016/j.arr.2015.11.005
- Guure, C. B., Ibrahim, N. A., Adam, M. B., & Said, S. M. (2017). Impact of Physical Activity on Cognitive Decline, Dementia, and Its Subtypes: Meta-Analysis of Prospective Studies. *BioMed Research International*, 2017, 1-13. doi:10.1155/2017/9016924
- Hamer, M., & Chida, Y. (2009). Physical activity and risk of neurodegenerative disease: A systematic review of prospective evidence. *Psychological Medicine*, 39(01), 3-11. doi:10.1017/s0033291708003681
- Heneka, M. T., Golenbock, D. T., & Latz, E. (2015). Innate immunity in Alzheimer's disease. *Nature Immunology*, 16(3), 229-236. doi:10.1038/ni.3102.
- Honjo, K., Black, S. E., & Verhoeff, N. P. (2012). Alzheimer's disease, cerebrovascular disease, and the  $\beta$ -amyloid cascade. *Canadian Journal of Neurological Sciences*, 39(6), 712-28. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/23227576>.
- Jiao, S. S., Shen, L. L., Zhu, C., et al. (2016). Brain-derived neurotrophic factor protects against tau-related neurodegeneration of Alzheimer's disease. *Translational Psychiatry*, 6(10). doi:10.1038/tp.2016.186
- Jones, L., Lamber, J. C., Wang, L. S., & Choi, S. H. (2015). Convergent genetic and expression data implicate immunity in Alzheimer's disease. *Alzheimer's and Dementia*, 11(6), 658-671. doi:10.1016/j.jalz.2014.05.1757.
- Kanekiyo, Takahisa, Huaxi Xu, and Guojun Bu. (2014). ApoE and A $\beta$  in Alzheimer's Disease: Accidental Encounters or Partners?" *Neuron*, 81(4), 740-54. doi:10.1016/j.neuron.2014.01.045.
- Kang, E., Kwon, I., Koo, J., et al. (2013). Treadmill exercise represses neuronal cell death and inflammation during A $\beta$ -induced ER stress by regulating unfolded protein response in aged presenilin 2 mutant mice. *Apoptosis*, 18(11), 1332-1347. doi:10.1007/s10495-013-0884-9
- Karch, C., Cruchaga, C., & Goate, A. (2014). Alzheimer's Disease Genetics: From the Bench to the Clinic. *Neuron*, 83(1), 11-26. doi:10.1016/j.neuron.2014.05.041
- Kasapis, C., & Thompson, P. D. (2005). The Effects of Physical Activity on Serum C-Reactive Protein and Inflammatory Markers. *Journal of the American College of Cardiology*, 45(10), 1563-1569. doi:10.1016/j.jacc.2004.12.077

- Kohman, R. A., Bhattacharya, T. K., Wojcik, E., & Rhodes, J. S. (2013). Exercise reduces activation of microglia isolated from hippocampus and brain of aged mice. *Journal of Neuroinflammation*, *10*(1). doi:10.1186/1742-2094-10-114
- Kohut, M., Mccann, D., Russell, D., et al. (2006). Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of  $\beta$ -blockers, BMI, and psychosocial factors in older adults. *Brain, Behavior, and Immunity*, *20*(3), 201-209. doi:10.1016/j.bbi.2005.12.002
- Lakka, T. A., Lakka, H., Rankinen, et al. (2005). Effect of exercise training on plasma levels of C-reactive protein in healthy adults: The HERITAGE Family Study. *European Heart Journal*, *26*(19), 2018-2025. doi:10.1093/eurheartj/ehi394
- Littbrand, H., Stenvall, M., & Rosendahl, E. (2011). Applicability and Effects of Physical Exercise on Physical and Cognitive Functions and Activities of Daily Living Among People With Dementia. *American Journal of Physical Medicine & Rehabilitation*, *90*(6), 495-518. doi:10.1097/phm.0b013e318214de26
- Macpherson, R. E. (2017). Filling the void: A role for exercise-induced BDNF and brain amyloid precursor protein processing. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *313*(5). Retrieved from [https://www-physiology-org.ezproxy.bu.edu/doi/abs/10.1152/ajpregu.00255.2017?url\\_ver=Z39.88-2003&rfr\\_id=ori:rid:crossref.org&rfr\\_dat=cr\\_pub=pubmed](https://www-physiology-org.ezproxy.bu.edu/doi/abs/10.1152/ajpregu.00255.2017?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub=pubmed).
- Mcgeer, P. L., Guo, J. P., Lee, M., Kennedy, K., & Mcgeer, E. G. (2018). Alzheimer's Disease Can Be Spared by Nonsteroidal Anti-Inflammatory Drugs. *Journal of Alzheimers Disease*, *62*(3), 1219-1222. doi:10.3233/jad-170706
- Miguel-Álvarez, M., Santos-Lozano, A., Sanchis-Gomar, F., Fiuza-Luces, C., Pareja-Galeano, H., Garatachea, N., & Lucia, A. (2015). Non-Steroidal Anti-Inflammatory Drugs as a Treatment for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Treatment Effect. *Drugs & Aging*, *32*(2), 139-147. doi:10.1007/s40266-015-0239-z
- Morris, J. K., Vidoni, E. D., & Johnson, D. K. (2017). Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. *PLoS One*, *12*(2). Retrieved from <https://www-ncbi-nlm-nih-gov.ezproxy.bu.edu/pmc/articles/PMC5302785/>.
- (n.d.). Retrieved March 22, 2018, from <http://www.alzrisk.org/riskfactordoc.aspx?rfid=7>
- (n.d.). Retrieved March 22, 2018, from [https://www.alz.org/documents\\_custom/2017-facts-and-figures.pdf](https://www.alz.org/documents_custom/2017-facts-and-figures.pdf)
- (n.d.). Retrieved March 22, 2018, from <https://www.m.alz.org>

Nigam, S. M., Xu, S., Kritikou, J. S., Marosi, K., Brodin, L., & Mattson, M. P. (2017). Exercise and BDNF reduce A $\beta$  production by enhancing  $\alpha$ -secretase processing of APP. *Journal of Neurochemistry*, 142(2), 286-296. doi:10.1111/jnc.14034

Noroozian, M., Shakiba, A., & Iran-Nejad, S. (2014). The impact of illiteracy on the assessment of cognition and dementia: A critical issue in the developing countries. *International Psychogeriatrics*, 26(12), 2051-2060. doi:10.1017/s1041610214001707

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimers disease: An analysis of population-based data. *The Lancet Neurology*, 13(8), 788-794. doi:10.1016/s1474-4422(14)70136-x

Ohman, H., Savikko, N., & Strandberg, T. E. (2016). Effects of Exercise on Cognition: The Finnish Alzheimer Disease Exercise Trial: A Randomized, Controlled Trial. *Journal of American Geriatrics Society*, 64(4), 731-738. Retrieved from <https://www.ncbi.nlm.nih.gov.ezproxy.bu.edu/pubmed/27037872>.

Öhman, H., Savikko, N., Strandberg, T. E., & Pitkälä, K. H. (2014). Effect of Physical Exercise on Cognitive Performance in Older Adults with Mild Cognitive Impairment or Dementia: A Systematic Review. *Dementia and Geriatric Cognitive Disorders*, 38(5-6), 347-365. doi:10.1159/000365388

Petersen, A. M., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology*, 98(4), 1154-1162. Retrieved from [https://www-physiology-org.ezproxy.bu.edu/doi/abs/10.1152/jappphysiol.00164.2004?url\\_ver=Z39.88-2003&rfr\\_id=ori:rid:crossref.org&rfr\\_dat=cr\\_pub=pubmed](https://www-physiology-org.ezproxy.bu.edu/doi/abs/10.1152/jappphysiol.00164.2004?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub=pubmed).

Ryan, S. M., & Kelly, Á M. (2016). Exercise as a pro-cognitive, pro-neurogenic and anti-inflammatory intervention in transgenic mouse models of Alzheimer's disease. *Ageing Research Reviews*, 27, 77-92. doi:10.1016/j.arr.2016.03.007

Ryan, S. M., & Nolan, Y. M. (2016). Neuroinflammation negatively affects adult hippocampal neurogenesis and cognition: Can exercise compensate? *Neuroscience & Biobehavioral Reviews*, 61, 121-131. doi:10.1016/j.neubiorev.2015.12.004

Salter, M. W., & Stevens, B. (2017). Microglia emerge as central players in brain disease. *Nature Medicine*, 23(9), 1018-1027. doi:10.1038/nm.4397

Sandiego, C. M., Gallezot, J., Pittman, B., et al. (2015). Imaging robust microglial activation after lipopolysaccharide administration in humans with PET. *Proceedings of the National Academy of Sciences*, 112(40), 12468-12473. doi:10.1073/pnas.1511003112

Sarlus, H., & Heneka, M. T. (2017). Microglia in Alzheimer's disease. *Journal of Clinical Investigation*,*127*(9),3240-3249. doi:10.1172/JCI90606.

Sharp, E. S., & Gatz, M. (2011). Relationship Between Education and Dementia. *Alzheimer Disease & Associated Disorders*,*25*(4), 289-304. doi:10.1097/wad.0b013e318211c83c

Sloan, R. P., Shapiro, P. A., & Demeersman, R. E. (2007). Aerobic exercise attenuates inducible TNF production in humans. *Journal of Applied Physiology*,*103*(3),1007-1011. Retrieved from [https://www.ncbi.nlm.nih.gov.ezproxy.bu.edu/pubmed/?term=Aerobic exercise attenuates inducible TNF production in humans](https://www.ncbi.nlm.nih.gov.ezproxy.bu.edu/pubmed/?term=Aerobic+exercise+attenuates+inducible+TNF+production+in+humans).

Solito, E., & Sastre, M. (2012). Microglia Function in Alzheimer's Disease. *Frontiers in Pharmacology*,*3*. doi:10.3389/fphar.2012.00014

Stein, A. M., Munive, V., Fernandez, A. M., Nuñez, A., & Aleman, I. T. (2017). Acute exercise does not modify brain activity and memory performance in APP/PS1 mice. *Plos One*,*12*(5). doi:10.1371/journal.pone.0178247

Stranahan, A. M., Martin, B., & Maudsley, S. (2012). Anti-Inflammatory Effects of Physical Activity in Relationship to Improved Cognitive Status in Humans and Mouse Models of Alzheimer's Disease. *Current Alzheimer Research*,*9*(1), 86-92. doi:10.2174/156720512799015019

Su, P., Zhang, J., Wang, D., Zhao, F., Cao, Z., Aschner, M., & Luo, W. (2016). The role of autophagy in modulation of neuroinflammation in microglia. *Neuroscience*,*319*, 155-167. doi:10.1016/j.neuroscience.2016.01.035

Tapia-Arancibia, L., Aliaga, E., Silhol, M., & Arancibia, S. (2008). New insights into brain BDNF function in normal aging and Alzheimer disease. *Brain Research Reviews*,*59*(1), 201-220. doi:10.1016/j.brainresrev.2008.07.007

Tapia-Rojas, C., Aranguiz, F., Varela-Nallar, L., & Inestrosa, N. C. (2015). Voluntary Running Attenuates Memory Loss, Decreases Neuropathological Changes and Induces Neurogenesis in a Mouse Model of Alzheimers Disease. *Brain Pathology*,*26*(1), 62-74. doi:10.1111/bpa.12255

Tarumi, T., & Zhang, R. (2017). Cerebral blood flow in normal aging adults: Cardiovascular determinants, clinical implications, and aerobic fitness. *Journal of Neurochemistry*. doi:10.1111/jnc.14234

Telenius, E. W., Engedal, K., & Bergland, A. (2015). Effect of a High-Intensity Exercise Program on Physical Function and Mental Health in Nursing Home Residents with

Dementia: An Assessor Blinded Randomized Controlled Trial. *Plos One*,10(5). doi:10.1371/journal.pone.0126102

Toots, A., Littbrand, H., Boström, G., et al. (2017). Effects of Exercise on Cognitive Function in Older People with Dementia: A Randomized Controlled Trial. *Journal of Alzheimers Disease*,60(1), 323-332. doi:10.3233/jad-170014

Wang, J., Tan, L., & Wang, H. F. (2015). Anti-inflammatory drugs and risk of Alzheimer's disease: An updated systematic review and meta-analysis. *Journal of Alzheimer's Disease*,44(2), 385-396. doi:10.3233/JAD-141506.

Woods, J. A., Wilund, K. R., Martin, S. A., & Kistler, B. M. (2012). Exercise, Inflammation and Aging. *Aging and Disease*,3(1), 130-140. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3320801/>.

Zhang, B., Gaiteri, C., Bodea, L. G., & Wang, Z. (2013). Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell*,153(3), 707-720. doi:10.1016/j.cell.2013.03.030.

Zhang, Y., Chao, F., Zhou, C., et al. (2017). Effects of exercise on capillaries in the white matter of transgenic AD mice. *Oncotarget*,8(39). doi:10.18632/oncotarget.19505

## CURRICULUM VITAE

