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Motivational Cognitive Behavioral Therapy for Dementia Prevention: A Pilot Study to Protect the Brain and Memory

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Philadelphia College of Osteopathic Medicine
School of Professional and Applied Psychology
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MOTIVATIONAL COGNITIVE BEHAVIORAL THERAPY FOR DEMENTIA

PREVENTION: A PILOT STUDY TO PROTECT THE BRAIN AND MEMORY

Nicholas Hope
Submitted in Partial Fulfillment of the Requirements for the Degree of
Doctor of Psychology
May 11, 2022

DISSERTATION APPROVAL

This is to certify that the thesis presented to us by ___Nicholas Hope___ on the 11th day of May 2022,

in partial fulfillment of the requirements for the degree of Doctor of Psychology, has been examined and

is acceptable in both scholarship and literary quality.

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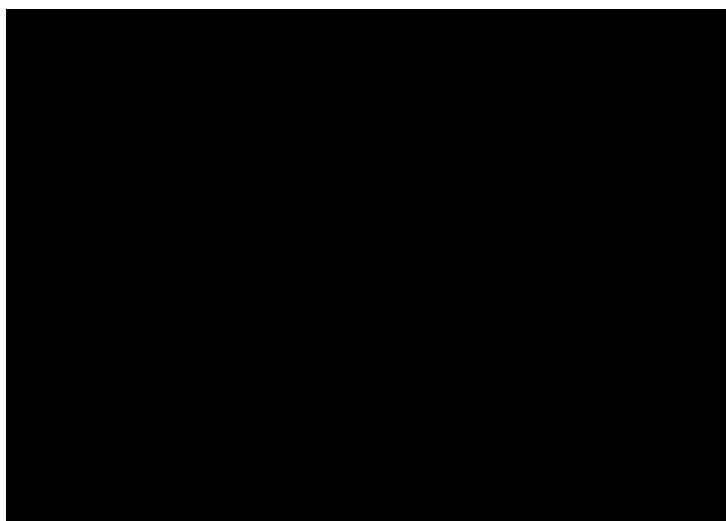
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Abstract

This study sought to explore the efficacy of a manualized group therapy protocol developed for this project combining empirically-supported Cognitive Behavioral Therapy (CBT) and Motivational Interviewing (MI), which we coined as Motivational CBT (MI-CBT), adapted for individuals at a heightened risk of cognitive decline in later adulthood. Specifically, this study investigated changes in cognition, adaptive sleep behavior, diet, exercise, depression, anxiety, and dementia knowledge as well as modifiable lifestyle factors such as Body Mass Index (BMI), hypertension, cholesterol, cigarette smoking, and medical adherence. A group of twenty-five participants ($N = 25$) were recruited in a large Northeastern city from a university-based family medicine practice, psychoeducation group, social media postings, and research recruitment website. A pretest-posttest experimental design was utilized. Individuals were assessed using measures to acquire baseline and outcomes on cognition (Montreal Cognitive Assessment), sleep (Sleep Disorders Symptom Checlist-25), depression (Patient Health Questionnaire-9), anxiety (Penn State Worry Questionnaire), diet (Lent-Hope Diet Questionnaire), exercise (Step-Up mobile application), and dementia knowledge (Dementia Awareness Questionnaire) as well as a medical adherence questionnaire. Fifteen of the original twenty five participants completed posttest measures immediately following the MI-CBT group treatment and the same fifteen of the original twenty five were assessed at three-month follow-up. Statistical analysis using a one-way repeated measures Analysis of Variance (ANOVA) revealed significant improvements in insomnia sleep pathology, diet adherence, dementia knowledge, and BMI. This study provides preliminary evidence for a brief group intervention for medically at-risk individuals for dementia and offers practical suggestions on how to overcome obstacles to effective treatment

CHAPTER 1: INTRODUCTION

Statement of the Problem

Dementia is one of the most dreaded of all diseases (Corner & Bond, 2004). The prospect of losing one's memories earned over a lifetime ignites fear in most people. As the disease progresses, a cascade of neurological changes escalate in the brain, as plaques, consisting of amyloid beta plaques (AB); neurofibrillary tangles, comprised of hyperphosphorilated tau (tau) accumulate; and brain regions slowly atrophy (Budson & Solomon, 2016). Over time, these changes correlate with gradual loss of memory, cognitive decline, personality change, inability to recall once familiar faces, wandering off and becoming lost, and progressively incoherent communication (Budson & Solomon, 2016). Continued decline results in increasing helplessness and dependence on others for even the basic activities of daily living, which may eventually necessitate round the clock care or, in some cases, confinement to a locked dementia unit (Sperling et al., 2011). After continued brain atrophy into the brainstem, the final stage results in death that often comes 3 to 10 years after initial diagnosis, when one loses the ability to swallow, aspirates saliva, and dies of pneumonia, while struggling to breathe (Wattmo et al., 2014). This is a fate that anyone would want to avoid.

Another frightening aspect of Alzheimer's disease is that it is increasing in prevalence, world-wide. According to the Alzheimer's Association (2019), from 2010 to 2017, the incidence rate of Alzheimer's increased 145%, making it the 6th leading cause of death in the United States. Since that time, it is estimated that 5.8 million people are living with dementia and this number is expected to rise to 14 million by 2050 care. Along with the epidemiology and personal health consequences of dementia, the disease has a significant financial toll. In 2019 alone, Alzheimer's disease cost the United States $290 billion. By 2050, that number is expected to rise to $1.1

trillion. These rising costs are also associated with prolonged and more frequent hospital stays, a higher likelihood of comorbid medical conditions, and a higher need for supervised care in the form of organized agencies including, but not limited to, home health care, skilled nursing facilities, rehabilitation hospitals, and adult day care. Finally, the Alzheimer's association estimated, in 2019, 16 million Americans provide unpaid support services to a loved one with dementia. The value of this care is appraised at $234 billion.

As a result of these concerns, researchers are looking at ways of preventing this neurodegeneration before it occurs. There is significant evidence that certain lifestyle characteristics are associated with the cognitive decline found with patients with dementia. There is significant empirical evidence that these lifestyle characteristics can be modified when addressed alone (Peters et al., 2019). However, there is little scientific evidence to support the use of a standardized model that targets such factors in a collaborative way.

Purpose of the Study

The main purpose of the present study is to examine empirical evidence that a brief, manualized intervention to improve lifestyle and increase behavior that has been associated with delay or prevention of onset and progression of the most common manifestations of dementia, both neurological and cognitive (e.g., Ngandu et al., 2015). Given the insidious nature of the disease, with neurological changes often beginning 10 to 20 years prior to recognition of cognitive decline, (Jack et al., 2013) the study will primarily target middle aged individuals, that is, between the ages of 40-60 years. With some exceptions, patients with Alzheimer's disease (AD) typically begin to show traditional symptoms of the disease in their 60's. However, the majority of research suggests that physiological changes that underlie these symptoms occur as early as 20 years prior (Kowall & Budson, 2013). As a result, we aimed to address patients at the

highest risk in the earliest prodromal stages of AD, in order to best intervene prior to symptom manifestation.

The specific interventions in the study were derived from evidence-based cognitive behavioral therapy (CBT) and motivational interviewing, which are empirically shown to have salubrious effects on sleep, exercise, diet, stress (i.e. anxiety and depression), weight management, smoking cessation, health-related behavior. The primary outcome measures of this study were behavioral change and change in cognitive functioning as evidenced by neuropsychological testing. In summary, this study examined the feasibility of a manualized pilot cognitive behavioral and motivational intervention for more comprehensive and long-term research into behavioral modification to delay or prevent the onset of Alzheimer's disease.

Hypotheses

Research Question 1

Will an adapted group MI-CBT treatment change improve cognition in individuals at a heightened risk for dementia?

Hypothesis 1

Following a 7-session group MI-CBT intervention and again at 3 month follow up, participants in the treatment group will show no cognitive decline, operationalized as performance on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). These results will be maintained during a 3-month follow-up.

Research Question 2

Will this adapted group MI-CBT treatment improve sleep quality and sleep pathology in individuals at a heightened risk for dementia?

Hypothesis 2

Following the 7-week group intervention and again at 3-month follow up, participants will report an observed more adaptive sleep behavior, operationalized as improved score on the Sleep Disorder Symptom Checklist- 25 (Klingman, Jungquist, and Perlis, 2016)

Research Question 3

Will this adapted group MI-CBT treatment improve depression scores in individuals at a heightened risk for dementia?

Hypothesis 3

Following the 7 week group MI-CBT intervention, participants in the experimental group will have an observed lower stress score as operationalized as decreased scores on the PHQ-9 (Kroeke et al., 1999).These results will be maintained during a 3-month follow-up.

Research Question 4

Will this adapted group MI-CBT treatment improve anxiety scores in individuals at a heightened risk for dementia?

Hypothesis 4

Following the 7 week group MI-CBT intervention, participants in the experimental group will have an observed lower stress score as operationalized as decreased scores on the PSWQ (Meyer, Miller, Metzger, & Borkovec, 1990). These results will be maintained during a 3-month follow-up.

Research Question 5

Will this adapted group MI-CBT treatment increased understanding and knowledge of dementia in individuals at a heightened risk for dementia?

Hypothesis 5

Following the 7-week MI-CBT group intervention and again at 3-month follow up, participants will show improved knowledge of dementia as operationalized by the Dementia Awareness Questionnaire. These results will be maintained during a 3-month follow-up.

Research Question 6

Will this adapted MI-CBT group treatment increase healthy eating habits in individuals at a heightened risk for dementia?

Hypothesis 6

Following the 7-week group MI-CBT intervention, participants will report an observed greater adherence to the MIND diet (Morris et al., 2015) operationalized as improved rating on a self-report questionnaire regarding the MIND diet. These results will be maintained during a 3-month follow-up.

Research Question 7

Will this adapted group MI-CBT treatment increase daily exercise in individuals at a heightened risk for dementia?

Hypothesis 7

Following the 7-week group MI-CBT intervention, participants will report an observed higher number of steps per day, operationalized as the Step-Up mobile application (Synder, Colvin, & Gammack, 2011). These results will be maintained during a 3-month follow-up.

CHAPTER 2: REVIEW OF LITERATURE

Dementia and Neurodegenerative Disease

Dementia is a general term for a neurodegenerative disorder that results in progressive cognitive decline including memory, language, and executive functioning. A core characteristic of dementia is also its impact on functioning. As the disease progresses, a person has persistent difficulty with tasks of daily living that include, but are not limited to bathing, toileting, grooming, and dressing. Aside from the physiological and functional changes, dementia can have behavioral symptoms as well that include impulsivity, mood swings, paranoia, and major personality changes. Dementia is classified into different groups of more specific diseases that include, but are not limited to, Alzheimer's disease vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. Every form of dementia has its own set of similarities (e.g. impact on functioning) but also a number of differences. However, as the disease progresses to late stages, oftentimes the disease has significant overlaps in symptoms (Kowall & Budson, 2013).

Alzheimer's disease (AD), also referred to as a major neurocognitive disorder in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) is the most common form of dementia, accounting for 60-80% of cases of dementia (Kowall & Budson, 2011; American Psychiatric Association, 2013). Alzheimer's disease is characterized by three major stages with its own set of symptoms which build off of each other as the disease progresses (Kowall & Budson, 2013). The first stage is characterized by significant challenges in short-term memory. This can be characterized by word-finding difficulty, trouble remembering names, forgetting items one has just read, losing and misplacing objects, trouble at work or social functioning, and trouble with planning and organizing. The second stage of AD is typically

characterized by more pronounced memory loss, personality changes, confusion, and loss of functioning. Common symptoms of stage 2 include pronounced memory loss from one's personal history (e.g. address, telephone number, alma mater, etc.), withdraw from social or cognitively taxing situations, issues with present orientation (e.g. where they are), trouble with dressing, urinary or bowel incontinence, changes in sleep patterns, wandering or becoming lost, and paranoia or suspiciousness. The second stage of AD is typically the longest and can last several years. The third and final stage of AD is characterized by the need for round-the-clock care, loss of awareness of experiences or surroundings, loss of basic physical abilities (e.g. walking, taking, swallowing, etc.), difficulty with communication, and a much higher proneness to infections such as pneumonia. Anatomically, this stage shows pronounced shrinkage of the brain including shriveling of the cerebral cortex and hippocampi as well as enlargement of the ventricles. There are also two primary types of AD: early onset (before age 65) and late onset (after age 65), with late onset being the most common form of AD (Budson & Solomon, 2016).

Theories of Alzheimer's Disease

The etiology of AD is complex and, oftentimes contradictory. There are four major theories behind AD, including the cholinergic theory, the isoprenoid theory, tau theory, and amyloid theory. The first, and oldest theory is the cholinergic theory of AD, which states that a deficiency in the excitatory neurotransmitter. Acetylcholine leads to the neuronal death seen in AD and other forms of dementia. When such a deficiency is severe enough, neurons die and are, otherwise unable to properly communicate, leading to the theory that the neuronal and muscle loss associated with AD can be associated with severely deficient levels of acetylcholine (Boller & Forette, 1989).

A second theory of AD revolves around the isoprenoid hypothesis, which states that deficient levels of dolichol and higher levels of ubiquinone in the brain, which play a major role in modifying proteins and regeneration in the brain, can result in neurological decay. These changes can lead to more rapid cognitive decline seen in older adult populations (Cole & Vassar, 2006). Despite the cholinergic and isoprenoid hypotheses garnering a significant amount of discussion and research, the two most current prominent theories of AD are the tau theory of AD and the amyloid theory of AD.

The tau theory of AD posits that an abnormal clustering of mutated phosphorylated tau, a misfolding of the protein tau, causes neurofibrillary tangles (NFT; Wood et al., 1986) These tangles prevent proper oxygen from getting to the cells and, once the cells of have been deprived of oxygen long enough the cells die (Iqbal et al., 2010). This initiates a process that progresses in a cascade-like fashion, slowly killing cells seen in patients with AD and perpetuates a vicious cycle of brain matter loss and decreased neural functioning (Chen & Mobley, 2019). Further support of the tau theory in AD comes in the way that it typically progresses. These tangles typically first destroy cells in the temporal and frontal lobes, commonly associated with memory loss, the most common first symptom of AD (Lu & Wood, 1993). As the tangles become more pronounced, they lead to further cell death throughout the brain (Chen & Mobley, 2019).

More specifically, Braak and Braak (1991) identified six major stages of the progression of these NFTs. The first two stages target the transentorhinal and entorhinal cortices of the medial temporal lobe, with the later parts of stage two affecting the hippocampal CA1 region, temporal cortex, magnocellular forebrain nuclei, and anterior dorsal nucleus of the thalamus as well. In stage three sees damage to the subiculum, amygdala, reuniens nucleus of thalamus, and tuberomammillary nucleus. Stage four builds involves exacerbation of the same areas as well

damage to the claustrum and the initial changes in neocortex. Stage five fully involves the limbic

system. The sixth and final stage manifests as universal neuronal loss, with the sensory and

motor regions beginning to die (Braak & Braak, 1991). It is known that this stage is correlated

with the end stages of AD as the tangles begin to affect areas in the brain stem controlling

breathing, swallowing, and other vital functions (Chen & Mobley, 2019).

However, of all the four models of AD, the most widely-accepted theory in the scientific

community revolves around what is called the amyloid theory of Alzheimer's disease. The

amyloid theory of AD essentially states that the accumulation of amyloid beta in the interstitial

fluid of the brain leads to AD. Amyloid beta is a peptide of 36-43 amino acids and is the product

of Amyloid Precursor Protein (APP). APP is split by beta secretase and gamma secretase to form

oligomers. It is believed that if these oligomers mutate or fold abnormally, they can form

proteins that are toxic to neurons and other vital cells in the brain such as amyloid beta. More

specifically to AD, it is believed that these mutated oligomers allow for excess calcium to flow

into neurons by forming more membrane ion channels for these calcium ions to enter through.

When this influx of calcium in the neurons occurs, homeostasis becomes significantly disrupted

and, as a result, can induce cell death, also known as apoptosis (Neve & Robakis, 1998).

Typically, the body is able to properly dispose of amyloid beta at a rate faster than new

amyloid is produced (Reid et al., 2017). However, when the body is unable to clear out this

amyloid at the same rate it is being produced, they form clumps or amyloid plaques. This plaque

production, along with other inflammatory responses such as cytokine and microglia

accumulation, lead to brain atrophy, which is associated with the cognitive decline seen in AD

and other forms of dementia. It is believed that this accumulation and inflammatory response

antagonize blood flow to the brain. When this chronically occurs, cells are unable to survive

without the nutrients and oxygen that the blood in the capillaries provide, and those cells begin to

die (Reid et al., 2017). It has recently been demonstrated, in a number of observational and

experimental studies, that a number of behavioral health conditions produce neurological

changes in the brain that create the conditions that exacerbate both the tau and amyloid cascades.

These conditions include cardiovascular disease, diabetes, hypertension, chronic sleep

deprivation, sedentary lifestyle, and stress (Ngandu et al., 2018). More on this below.

According to Corrada and colleagues (2010), although there is evidence supporting

many, the direct cause of AD seems to be multifactorial and remains largely unknown, however,

experts agree that the disorder is attributable to a number of risk factors. The most important risk

factor of Alzheimer's disease is age. As one ages, it is common for cognitive abilities begin to

decline and the brain begin to shrink or atrophy. This natural occurrence, however, occurs at

different rates for different people. Nonetheless, it is believed that, eventually, one will develop

some form of dementia if one lives long enough. It is estimated that the risk of dementia doubles

for every 5 years after one turns 65 years of age. There are also a number of age-related

physiological changes to the brain that are associated with AD, including natural atrophy,

inflammation, free radical production, and loss of communication between neurons.

Genetic Implications of Early-Onset Alzheimer's Disease

In addition to age-related causes of AD, genetics also plays a direct and related role

within the disease. Genetic mutations can contribute to both early-onset and late-set AD in

different ways. Early-onset AD, considered to occur when significant symptoms appear before

the age of 65, is typically associated with mutations on chromosomes 1, 14, and 21 (Levy-Lahad

et al., 1995).

Chromosome 1 is the most notable chromosome associated with early-onset AD (Bird et al., 1996). Chromosome is 1 the largest chromosome in the human body, consisting of 249 million nucleotides, or chemical building blocks (8% of the total chromosomal make-up in humans). Chromosome 1 is responsible for the development of presenilin 2 (White, 2007). Presenilin 2 plays a critical role in chemical signaling within a cell's membrane and nucleus; when these signals are properly transmitted, cellular growth and maturation occur (Wolozin et al., 1996). However, when this chemical signaling to the brain is compromised, the cells of the brain cannot develop to their fullest potential (Bird et al., 1996). More specifically, the amino acid asparagine, which lies on position 141 on the amino acid strand (Asn141Ile) is replaced by the amino acid isoleucine (Bird et al., 1996). Mutations in presenilin 2 also replace methionine with the amino acid valine at position 239 (Met239Val) (Sherrington et al., 1996). When these amino acid replacements occur, the production of (APP) is disturbed (Sherrington et al., 1996). APP is an integral membrane protein that is implicated in the regulation of neuroplasticity, synapse formation, antimicrobial activity, and iron export. More notable, APP is also the precursor protein for amyloid beta, which will be discussed further in this review. When APP regulation is disturbed, overproduction of amyloid beta can occur (Thinakaran & Koo, 2008).

Chromosome 14 is another large chromosome, consisting of 107 million DNA blocks (about 3.5% of the total chromosomal make-up in humans). Chromosome 14 is responsible for the development of presenilin 1, a protein that aids in breaking down proteins into peptides. When mutated, abnormal presenilin 1 develops and proteins are not properly broken down as a result. (Boeras et al., 2008). This is particularly pertinent to AD as these abnormal proteins can lead to increased deposits of amyloid in the brain. Additionally, affects the secretase enzyme, which has also been shown to increase production of amyloid beta (DeStrooper et al., 2010).

Chromosome 21 is the final chromosome implicated in early-onset AD. It is the smallest of the chromosomes, comprising. Between 1.5 and 2% of the total chromosomal make-up in humans (Goate et al., 1989). Despite its relatively diminutive size in the human genome, it plays a major role in early-onset AD. With specific regards to AD, chromosome 21 is associated with the development of mutated APP (St. George et al., 1987). As noted above, when this occurs, amyloid beta can clump and bind to brain matter at an easier and more rapid rate (Goate et al., 1989).

Genetic Implications of Late-Onset Alzheimer's Disease

Late-onset AD also has a number of genetic implications as well. Late-onset, defined as dementia diagnosed after the age of 65, not only is much more common than early-onset AD but it also has more pronounced associated genetic factors as well (Koedam et al., 2010). The most commonly cited and well known of these factors is apolipoprotein E (ApoE) found on chromosome 19, of the seven different alleles of ApoE (Liu et al., 2013). Although the majority of the alleles of ApoE have no positive or negative effect on AD risk, 2 major forms of the allele do. Surprisingly, apolipoprotein E2 (ApoE2) plays a minor protective role in AD. One 2019 post-mortem study of over 5,000 patients with AD and a control group without AD found that carriers of the ApoE2 gene had up 90% less incidence of AD compared to the rest of the subjects of the study, showing that the non-AD group had higher incidence of carrying the ApoE2 gene. It is believed at ApoE2 increased grey matter volume in the brain, thus increasing the number of neuronal cell bodies (Feussner et al., 2019).

Another study found that patients with a diagnosis of mild cognitive impairment (MCI; now mild NCD [APA, 2013]) who were carriers of the ApoE2 gene saw decreased progression to full AD compared to non-carriers with MCI (Morgen et al., 2013). Based upon educated

hypotheses, most researchers believe that ApoE2 is unable to bind to LDLR's and, as such, allows for greater and more productive amyloid beta deterioration (Huang et al., 2017).

In contrast to these protective factors associated with ApoE2, the most prominent biomarker of AD is the apolipoprotein E4 (ApoE4) gene. It is believed that ApoE4 causes disturbance in function of microglia in the brain (Blacker et al., 1997). Microglia, the immune cells of the human brain, remove amyloid beta though phagocytosis and also play a critical role in anti-inflammatory regulation of the brain. When these microglia become compromised, they leave the brain more susceptible to attack from both external and internal damage (i.e. amyloid beta accumulation and clumping into amyloid plaques; Paasila et al., 2019). A 2019 study by Safieh, Michaelson, and Korczynfound that patients with the ApoE4 gene had higher inflammatory responses in human microglia and decreased phagocytosis of toxic bodily material. ApoE4 is also much more common than ApoE2 in that 50% of patients with AD are ApoE4 carriers (Ungar et al., 2014).

In addition to the medical and biological pathologies that contribute to AD noted above, the bacterial pathogen chlamydia pneumoniae is another major consideration to take when understanding Alzheimer's etiology and pathology. Balin and colleagues (2018) posits that this intracellular bacterium related to the respiratory system is tied to several respiratory-like infections such as pneumonia in addition to non-respiratory diseases such as atherosclerosis, inflammatory arthritis, multiple sclerosis. However, it is believed that chlamydia pneumoniae has a strong tie to late-onset Alzheimer's disease as well.

These hypotheses are support by a number of confirmatory studies as well. For example, a 1998 study by Balin and colleagues found that 90% of brains studied post-mortem had a significant concentration of chlamydia pneumoniae while less than 5% of post-mortem control

brains had it. Of the infected experimental brains, the highest concentration of chlamydia

pneumoniae remained in the temporal, parietal and pre-frontal cortices as well as the

hippocampus (Balin et al., 1998). In a separate confirmatory study which followed up from Balin

and colleagues' research in 1998, Gerard and colleagues (2006) found a concentration of

chlamydia pneumoniae in 80% of brain samples of late-onset AD while only finding a

concentration of chlamydia pneumoniae in 11% of control brains. Importantly, chlamydia

pneumoniae has a strong connection to ApoE4 and its relation to AD etiology. More specifically,

post mortem studies have shown that individuals with the ApoE-4 allele and confirmed late-

onset AD have had higher concentrations of chlamydia pneumoniae in their brains compared to

non-ApoE-4 carrying individuals (Gerard et al., 2005). Finally, chlamydia pneumoniae has been

shown to play a role in neuroinflammation, another critical component of AD pathology. It is

believed that chlamydia pneumoniae leads to infection involved in neuropatholgenesis which

subsequently leads to the production of proinflammatory cytokines and reactive oxygen species

(Balin et al., 1998; Gérard et al., 2006).

Modifiable Risk Factors of Alzheimer's Disease

Alzheimer's disease has a number of known risk factors. Some risk factors are more

known, such as genetics, while others are less known, have only recently come to light but, are

more modifiable. There is also significant evidence that changes to such risk factors can play a

key role in the prolongation of brain health over the lifetime and can delay or prevent the

biological, behavioral, and mental effects of AD. More specifically, diet, exercise, cognitive

stimulation, proper sleep, medical adherence, and stress reduction have all been shown to have

significant positive effects on brain health and long-term well-being.

Sleep

It is not surprising that poor sleep is associated with a number of significant health conditions such as heart disease, high blood pressure, diabetes, and weight gain (Meid et al., 2017). It also has a significant impact on mental health and plays a role in depression, anxiety, trauma-related disorders, obsessive-compulsive disorder, substance use disorders, bipolar disorder, psychosis, and dementia (Tarokh et al., 2016). As a result, it is not surprising that sleep plays a critical role in productivity and brain health.

Physiologically, sleep plays a critical role in restoring, recovering, and replenishing the brain from stress of the waking hours. Without this, the brain is unable to perform to its fullest ability because it has lost its ability to properly recover. Sleep deprivation and virtually every sleep disorder is associated with a number of cognitive issues begin to arise that include deficits in attention, working memory, reward processing, stimulus processing, and memory processing (Kolb & Whitshaw, 2015). All of the issues are also key features of cognitive decline and AD in older populations as well, which is consistent with research demonstrating a strong association between sleep disturbance and AD (Dickson & Weller, 2011).

Attention is a key executive function domain that can be significantly impacted by insufficient sleep. For example, results of functional magnetic resonance imaging (fMRI) studies find reduced signaling of the dorsolateral prefrontal cortex and intraparietal sulcus on attentional tasks in sleep deprived patients (Chee et al., 2011). Poor sleep has also shown a reduced activity on the extra striate visual cortex during visuospatial attention tasks (Chee et al., 2010). One study found that sleep deprived patients had reductions in top down signaling of the frontoparietal cortex, extra-striate cortex, and thalamus (Chee et al., 2008). Practically speaking, these deficits are shown to be significant with attending to target stimuli while ignoring outside stimuli and

top-down attention, such as orienting to a situation, indicating increased distractibility (Krause et al., 2017). Sleep deprivation also has a profound effect on sustained attention. Neuroimaging has found that there are continued reductions in in activity of the dorsolateral prefrontal cortex and intraparietal sulcus during tasks of sustained attention (Krause et al., 2017; Soares, 2019).

The default mode network, which is tied to wakeful inattention (e.g. daydreaming), is also implicated in the attentional effects of sleep deprivation (Krause et al., 2017). Neuroimaging studies found the continued activation of the midline anterior and posterior cortical regions of the default mode network during attentional tasks, suggesting deficits in acute and sustained attention in patients who have been experiencing sleep deprivation (Drummond et al., 2005). Another study utilizing fMRI on sleep deprived patients found significant selective reductions in default mode network functional connectivity and default mode network anticorrelated network (ACN), supporting the hypothesis that sleep deprivation reduces functional connectivity between neural networks (Havas et al., 2012). There also appear to be differences in rested and sleep deprived persons in the salience-detection network. This network is part of the fronto-insular cortex and is responsible for detecting and filtering important stimuli (Legrain et al., 2011). Findings indicate that sleep deprivation reduces activity in the brain during attentional tasks (Ma et al., 2015). Research has also found that reduced activity in the fronto-insular cortex is also associated with worse performance on tasks of attention to new and salient stimuli (Gumenyuk et al., 2011) as well as following moving targets (Gazes et al. 2012).

In addition to attention and working memory, reward and pleasure processing are impacted by sleep as well. This can have both short- and long-term effect on behavioral activation, motivation, and sustained effort. Specifically, it is known that sleep affects dopamine signaling and is highly correlated with prolonged disturbed sleep (Krause et al, 2017). Dopamine

production and regulation is also associated with lack of sleep and wakefulness (Perogamvros &

Schwartz, 2012). Additionally, when looking at stimulant drugs (e.g., amphetamines), one of the

primary activation systems that takes place is one that increase dopamine transmission and

arousal (Krause et al., 2017). When catecholamines, such as dopamine, are depleted, there is

often an increase in sleep behavior and decrease in vigilance (McCann et al., 1993). This effect

has been supported through neurodiagnostic studies as well. For example, positron emission

tomography (PET) reveals that chronic sleep deprivation leads to decreased activity of the D2

and D3 dopamine receptors in the dorsal and ventral striatum, which is associated with not only

decreased performance on reward processing-related tasks but also attention and working

memory (Volkow et al., 2012). Decreased D2 and D3 receptor activity is also inversely related to

adenosine productivity (Krause et al., 2017). Adenosine is a purine nucleoside base that

accumulates during periods of wakefulness and induces somnolence. Adensoine is critical as it

acts allosterically to decrease affinity for dopamine to bind to D2 and D3 receptors. When this

occurs D2 and D3 receptor internalization occurs as well as the reduction of dopamine that is

bound to D2 and D3 receptors. This complex process results in impaired cognitive functioning,

reduced productivity, and increased sleepiness (Elmenhorst et al., 2007).

Volkow and colleagues (2012) determined that variations in sleep affect the sensitivity

and availability of dopamine receptors in the basal ganglia leading to generalized hypo-

metabolism of the basal ganglia (Hershey & Chad, 1992). Sleep deprivation has also been shown

to increase activity in the ventral striatum, insula, and medial prefrontal cortex (Mullin et al.,

2013; Venkatraman et al., 2007). These areas of the brain are closely associated with affect,

value setting, empathy, and viscerosensory functioning (Mullin et al., 2013; Venkatraman et al.,

2007). When these areas show increased activity, an individual is more inclined to make risky

and impulsive decisions as a result of faulty value setting (Libedinsky et al., 2011). This theory is supported by neuroimaging studies. FMRI studies have found that signals in the medial prefrontal cortex, orbitofrontal cortex (OFC), and anterior insula cortex do not change between situational risk and reward fluctuations in sleep deprived individuals. This lack of discriminability suggests that the brain is less capable adapt to changing stimuli as quickly as with sufficient sleep, resulting in more impulsive and short-term reward-driven decisions (Olson et al., 2016).

The prefrontal cortex is not the only affected neural area associated with reward and pleasure processing. Studies have found that striatal and amygdala activation increases following sleep deprivation as well. These same studies found faulty discriminatory signaling of stimulus valence (i.e. pleasurable vs non-pleasurable) in the anterior insula, medial prefrontal cortex (mPFC) and OFC areas of the brain (Gujar et al., 2011).

Taken altogether, reward processing and decision making plays a critical role in impulse control as it allows a person to weigh risks and rewards of a certain action and make a contrived decision on a course of action to take. Sleep is a major factor in this concept (Franken et al., 2008). For example, the go/no-go task is a common neuropsychological assessment used to measure cognitive control and impulsivity. Following sleep deprivation, participants had a significantly lower response time and significantly higher number of errors, suggesting that loss of sleep was associated with slower processing speed and poorer impulse control (Demos et al., 2016; Anderson & Platten, 2011). Another study found that, in participants who were sleep deprived, low-effort rewards elicit even greater reward-related brain activity than high-effort rewards, suggesting the reduced ability to effectively process costs and rewards (Menz et al., 2012). The Balloon Analogue Risk Task (BART) is another common assessment used to

measure impulsivity. Acheson and colleagues determined that sleep deprived participants displayed more impulsive tendencies following chronic partial sleep deprivation (Acheson et al., 2007; Rossa et al., 2014). Studies on the BART also indicate that there are gender differences in performance on impulse control tasks (Acheson et al., 2007). For example, total sleep deprivation did not result in any change in performance on the BART in men, while there were clinically significant changes in performance in women (Demos et al., 2016).

Much like sleep deprivation affects incentive and reward processing, it also affects aversive stimulus processing. Sleep deprivation is correlated with weakened emotional regulation and emotional processing (Krause et al., 2017). Yoo and colleagues (2007) conducted a study that observed sleep deprivation lead to as much as 60% increases in amygdala activity when presented with negative stimuli. It also found decreased connectivity between the amygdala and the medial-prefrontal cortex (Yoo et al., 2007). Another study that built on Yoo's study found that rapid presentation of negative stimuli elicited the same hyperactivity in the amygdala, suggesting such heightened limbic reactivity was reactive and uncontrolled (Montomura et al., 2013). This supports the notion that this sort of amygdala reactivity along with disrupted peripheral autonomic nervous system feedback of visceral body information, can lead to challenges with emotional expression as well, a symptom common of patients with AD (Yoo et al., 2007).

In addition, to amygdala reactivity, sleep deprivation also effects processing of anticipated emotional challenge. For example, Goldstein and colleagues (2013), found that patients who had been sleep deprived had increased reactivity in the amygdala, anterior insula, and anterior cingulate cortex as well as the peripheral autonomic nervous system, similar to that of anxiety, another common manifestation of emotional disturbance.

Goldstein and colleagues have also found that sleep-rested individuals perform better in tasks of emotional detection and reading while sleep deprived patients have more restricted and generalized response to various emotional stimuli (Goldstein et al., 2014). For example, a 2010 study by Van Der Helm, Gujar, and Walker found that sleep deprived patients had a slower reaction time and lower performance on tasks of emotion identification. Similarly, it has been shown that patients with impaired sleep tend to rate neutral faces more negatively than participants with sufficient sleep (Daniela et al., 2010). Interestingly, however, sleep deprived patients also have been shown to inaccurately rate salient positive stimuli (i.e. faces) as negative or threatening (Goldstein-Piekarski et al., 2015). These findings are also supported on a biological level (Simon et al., 2015). Functional MRI imaging shows generalized increases in amygdala as well as viscerosensory regions of the anterior insula and anterior cingulate cortices (Alfarra et al., 2015). On a cellular level, it is found that REM sleep allows for overnight reduction in noradrenergic tone, leading to proper levels of noradrenaline. However, when sleep is disrupted, this hypernoradrenergic response, the amygdala and the viscerosensory cortical regions can become innervated by excess noradrenaline, leading to a more generalized emotional response (Siegel & Rogawski, 1988; Goldstein & Walker, 2014).

Hippocampal and memory processing is a critical area of brain functioning that is impacted by sleep, including in animal studies. McDermot and colleagues (2003) examined the anatomical and physiological impact of sleep disturbance on rodents. Following a period of sleep disruption, the rodents had decreased strengthening of the synapses in the brain (Long-Term Potentiation or LTP) and a more rapid decay of brain matter when LTP was achieved (McDermot et al., 2003). More specifically, the metabolic product adenosine – the sleep inducing neuropeptide-builds up during wakeful hours and is removed during sleep.

Consequently, sleep disturbance allows for excess build-up of this adenosine which leads to

cAMP, AMPA, and NMDA receptor signaling, all of which are critical for health LPT, become

disrupted (Abel et al., 2013). Fernandes and colleagues (2015) found that sleep disturbance is

associated with decreased neurogenesis and impaired synthesis in vital brain areas for memory

such as the hippocampus, all of which are associated with AD.

        Much like rodents, humans exhibit neurological changes as a result of sleep disturbance.

Drummond and colleagues (2000) conducted a study of 13 healthy human brains and found that

sleep disturbance was associated with significant challenges in encoding and learning in the

medial temporal lobe, specifically the hippocampus. Interestingly, neuroimaging has found that

deprivation and/or enhancement of certain stages of sleep also has an impact on memory (Krause

et al., 2017). A 2009 study by Van Der Werf and colleagues used selective deprivation of non-

rapid eye movement (NREM) sleep to assess for encoding and learning in the hippocampus.

Following this selective deprivation, the researchers found slower learning and lower encoding

activity in the hippocampus, suggesting that stages of sleep also play a critical role. Additionally,

it has been shown that enhancement of NREM has a neurotropic benefit to hippocampal strength

as well. Antonenko and colleagues (2013) found that transcranial stimulation of 37 participants

to induce NREM sleep lead to better learning and encoding in the hippocampus. Finally, NREM

has been found to have a direct connection with AD and other forms of dementia (Krause et al.,

2017). Older adults, both cognitively healthy and impaired, show decreased NREM sleep, with

patients with AD having more pronounced NREM deficits (Mander et al., 2016)

        Sleep disturbance does not have a negative impact on the hippocampus alone, but rather

interconnected networks of cortical regions essential for memory (Krause et al., 2017). The

dorsolateral prefrontal cortex and the posterior parietal cortices have both been shown to be

associated with poorer performance on memory encoding tasks with sleep deprivation (Chiuah et al., 2009). In the visual domain, the fusiform cortex of the occipital lobe becomes more impaired following sleep deprivation, leading to decreased top-down, visual processing (Poe & Chee, 2017).

Taken altogether, the implications of sleep deprivation on the human brain ties into the brain's allostatic load, the cumulative effect on the body due to stress and trauma (McEwen, 2006). This is problematic because, proinflammatory cytosines become triggered from increased allostatic load, leading to increased sympathetic response, which should be reserved for life-- threatening stimuli (Bierhaus et al., 2003). When this occurs, it is believed that the structural integrity of the brain is compromised, most notably the prefrontal cortex, hippocampus, and amygdala, and the memory and emotional deficits seen with sleep deprivation occur (McEwen, 2004). Such symptoms are also similar with AD (McEwen, 2006).

So far, it has been noted in this literature review that sleep impairment has an impact on various levels of functioning. However, there is considerable evidence that directly links impaired sleep with AD and other forms of dementia (Shi et al, 2018). For example, a 2013 prospective population-based cohort study of 737 non-clinical members of the community examined the relation between sleep fragmentation and disturbed sleep on the risk of dementia. Over a six-year time period, participants reported sleep patterns and were administered a battery of neuropsychological tests. Follow-up at 6 years indicated that participants with higher sleep fragmentation were at a higher risk of AD ($HR = 1.22$, 95% CI [1.03,1.44], $P = 0.02$); these persons also had a 1.5 fold risk of AD compared to participants with reported healthy sleep patterns, suggesting that abnormal and disturbed sleep is associated with a 50% higher risk of AD (Lim et al., 2013).

Another study from 2015 examined the relation between self-reported sleep disturbance and risk of dementia at ages 50 and 70 years old. During follow-up, participants who had initially self-reported significant sleep disturbance had an increased risk of developing non-Alzheimer's types of dementia by 33% and 51% specifically to AD. Not surprisingly, the researchers also found that sleep-disturbed participants who were older (age 70 and above) had the highest risk of non-Alzheimer's types of dementia with a 114% risk and AD with a 192% risk (Benedict et al., 2015). Finally, a 2013 secondary analysis from the Survey of Health, Ageing, and Retirement in Europe (SHARE) examined the relationship between sleep, dementia, and subsequent mortality. Utilizing the Sleep Disturbance Index (SDI), the researchers found that those who had a heightened score on the SDI had a higher risk of developing AD or another form of dementia, with an additional heightened risk of mortality. These findings lead the researchers to conclude that sleep plays a critical role in AD and dementia manifestation as well as mortality and could suggest that sleep disturbance may be one of the first symptoms of AD and is a significant risk factor (Sterniczuk et al., 2013).

Not surprisingly, insomnia is often used interchangeably with sleep disturbance. A retrospective study of 321 participants studied the relation between insomnia and incidence of AD. The participants were all cognitively healthy at baseline and then grouped into normal-AD or normal-normal groups at a 6.8-7.9 year follow-up depending on their AD status. Of the participants who progressed to AD, those who also had insomnia at baseline had a significantly higher risk of AD at the end of the study in comparison to those without insomnia ($OR = 2.39$, 95% CI). These results lead researchers to conclude that sleep disturbance associated with insomnia was positively correlated with risk of AD (Osorio et al., 2011). Another retrospective study of insomnia took medical data of 179,738 male veterans and conducted follow-up studies

over a 7-year period. Following this post-testing period, it was found that veterans who had a diagnosis of insomnia were 27% more at risk of developing dementia in comparison to well-rested participants ($RR = 1.27$, 95% confidence interval: 1.20%-1.34%), suggesting that chronic sleep disturbance associated with insomnia had a direct relation to incidence of dementia later in life (Yaffe et al., 2015). Finally, a 2018 population-based case-control study examined the relation between primary insomnia and dementia. Of the 310,449 participants used, the patients who were classified as having primary insomnia had a 2.14 fold increased risk of dementia in comparison to the non-primary insomnia group. Interestingly, the researchers also found that dementia occurred at an earlier rate in younger patients with primary insomnia compared to non-primary insomnia patients, further supporting the relation between insomnia and subsequent risk of dementia (Hung et al., 2018).

Conversely, improved sleep was shown to have a neurotropic effect that can delay the onset of cognitive decline seen in AD and other forms of dementia (Kivipelto et al., 2013). A 2017 study by Dissel and colleagues examined the role of sleep in the progression of amyloid and tau build up in flies. To enhance sleep, flies were administered the GABA-A agonist 4, 5, 6, 7-tetrahydroisoxazolo-[5, 4-c] pyridine-3-ol (THIP). Using aversive Phototaxic Suppression (APS) and courtship conditioning, scientists were able to test memory in the specimens. Biological data was also examined using analysis of synaptic protein discs, which is essential in memory retention. The study found that enhancing sleep in specimens lead to restoration of short term and long term memory as well as fully restored digoxin levels. Finally, researchers found that sleep induction helped restore cAMP signaling, a signaling mechanism critical to cellular communication and memory. Taken altogether, the researchers concluded that increasing

sleep was associated with decreased expression of toxic peptides that are associated with the

progression of Alzheimer's disease in humans.

In support of these results and suggesting generalizability to humans, Lucy and

colleagues (2019) examined the role of non-REM sleep on cognitive functioning. By examining

brain imaging, cerebrospinal fluid, and cognitive performance task results, researchers were able

to analyze the relationships between the three variables. Results indicated that non-REM sleep

had an inverse relationship with Alzheimer's pathology, specifically with regards to incidence

and tau pathology in the brain. This led researchers to conclude that decreased non-REM sleep

could help discriminate risk for tau pathology and cognitive impairment either before or at the

beginning stages of AD (Lucey et al., 2019).

Exercise

Exercise is another critical lifestyle activity that has a monumental impact on the human

brain. Exercise has been shown to reduce insulin resistance, reduce inflammation, and promote

neurotrophins, all of which play key roles in reducing AD risk (Godman, 2018). Brain derived

neurotropic factor (BDNF) is one of the neurotrophins that exercise promotes and is a core

characteristic of brain health that is commonly considered in discussions about AD and other

forms of dementia. BDNF is protein encoded by the BDNF gene that promotes neuronal growth,

differentiation, neuroplasticity, and survival (Cotman & Engesser-Cesar, 2002). Although it can

be found in other areas, it is primarily concentrated in the hippocampus, basal forebrain, and

cortex, the areas of the brain also heavily implicated in in both normal memory function and AD

(Yamada et al., 2003). BDNF also plays a critical role in neurogenesis, the production and

growth of new neurons, even in adults (Pencea et al., 2001). Studies in mice also suggest that

BDNF plays a critical role in prenatal normal cell development as evidenced by mice born

without the ability to produce BDNF having nervous system deficits and dying soon after birth (Ernfors, 1995).

BDNF also appears to play a critical role in conjunction with other major bodily functions such as synaptic transmission, N-methyl-D-aspartate (NDMA) synaptic activity, synapse stability, GABAergic signaling, synaptogenesis, and dendritogenesis, all of which are critical to memory formation and retention (Cotman & Engesser-Cesar, 2002). Finally, it is believed that BDNF is so heavily influenced by exercise because the visual, physical, and cognitive nature of exercise tasks leads to more synaptic communication and neuronal activity, Moreover, exercise improves the depth and quality of sleep, further increasing the likelihood of BDNF production, which occurs mainly during SWS (Zhong et al., 2009). By increasing activity to the brain, increased blood blow and neuronal activity activates centers of the brain and strengthens cognition over time (O'Connor & Youngstedt, 1995). Additionally, these same mechanisms that aid in cognitive health over time are also useful in promoting sleep; more specifically, BDNF and overall neural activity are shown to aid in more efficient and effective utilization of the hypothalamus, one of the sleep centers of the brain p (Morgan et al., 2015). Overall, exercise is shown to provide environmental enrichment to the brain and BDNF, which in return leads to further cognitive strengthening; more specifically, environmental enrichment has also been associated with synaptogenesis, dendridogenesis, and neurogenesis (Zhong et al., 2009).

Exercise has been shown to have a positive influence on BDNF in both animal and human studies. For example, a Neeper and colleagues (1996) examined how treadmill exercise in rats affected BDNF and mRNA levels. Following 7-day trial period, the rats displayed significantly higher levels of BDNF and mRNA proteins in the hippocampus, caudal neocortex,

and retrosplenial cortex (Neeper et al, 1996). Another study found that exercise was related to

progressively increased up-regulation of BDNF following a 28- day exercise program in rodents.

These results led researchers of this study to conclude that BDNF, and subsequently brain

plasticity, is strongly influenced by exercise (Molteni et al., 2002). Finally, another study looked

at exercise's influence on BDNF as well as sedentary lifestyles in rodents. Following an induced

spinal cord injury, half of the rats were prescribed to an exercise group while the other half was

prescribed to an SCI control group. Following intervention, both groups were compared to a

group of rats with no spinal cord injury. Following a 7-week trial period, the exercise group had

more improved allodynia and restored normal sensation. They also had no significant changes in

their BDNF compared to the non-SCI control. In comparisons, the sedentary group had more

pronounced allodynia, decreased sensation, and lower levels of BDNF, further supporting that

exercise plays a critical role in the maintenance of BDNF in the brain (Hutchinson et al., 2004).

Studies on BDNF have also be conducted with humans, although literature is less

extensive. Ferris, Williams, and Chen (2007) followed 15 participants and subscribed them to an

exercise regimen. Following their program, their n enzyme-linked immunosorbent assay

(ELISA) levels and Stroop test scores were compared. During a post-test evaluation, the

researchers found improved cognitive performance and higher BDNF levels. They also found

that the level of BDNF was correlated with the intensity of the exercise that was prescribed,

leading researchers to conclude that there is a positive relationship between both exercise and the

intensity of exercise and BDNF and cognitive performance (Ferris, Williams, & Chen, 2007).

A 2016 meta-analysis of 29 studies, spanning across 910 participants found that exercise

was associated with significantly higher peripheral blood levels of BDNF both immediately

following exercise and at rest. They also compared aerobic and resistance training and found that

aerobic exercise showed higher improvement in BDNF level and that results were long lasting

(Dinoff et al., 2016). Another 2015 meta-analysis of 29 studies and 1111 participants examined

the relationship between exercise and BDNF. The researchers found that exercise following just

one session was associated with higher levels of BDNF. Following a regimented exercise routine

over a period of several days, the effect of exercise on BDNF level also increased. Additionally,

supporting the results of the 2016 meta-analysis, the researchers also found improved resting

BDNF in participants who exercised compared to those who had not (Szuhany et al., 2015). This

is further supported by a 2018 meta-analysis of 55 studies that found similar results and had the

same conclusions (Dinoff et al., 2018).

     In addition to the changes that exercise provides the brain on a chemical level, exercise

has also been shown to have a positive impact the brain on an anatomical level. Research on the

cerebellum and motor cortex demonstrate how exercise influences the brain's anatomy. Rodent

studies have shown that prescribed 30 day exercise regimens of physical activity (i.e. running on

a wheel or navigating mazes) was associated with a higher concentration of synapses in the

purkinje cells and more dense capillaries in the areas surrounding the cerebellum and motor

cortex, brain loci associated with motor functioning (Black et al., 1990; Kleim et al., 2002;

Swain et al., 2003).

     The most compelling anatomical evidence of the benefits of exercise on the brain is in the

hippocampus, which is also one of the primary brain areas implicated in AD. For example, wheel

running has been shown to be correlated with increased volume of the hippocampus, number of

neurons in the hippocampus, and cerebral blood flow to the hippocampus in rats (van Praag et

al., 1999; Pereira et al., 2007). Such findings have also been shown to an extent in a small

number of middle-aged human participants in a 2007 exercise study on cerebral blood volume

(Pereira et al., 2007). More specific to human subjects, scientists have compared maximal oxygen uptake (VO2) scores to hippocampal size in humans. VO2 Max is the maximum rate that the body can use oxygen while it is engaged in some type of strenuous work; as one exercises, their VO2 Max increases and, as such, the body can utilize more oxygen with continued regular exercise (Oh et al., 2016). Studies have shown that higher VO2 max scores are correlated with higher hippocampal volume, ranging from 2-16%, in both children and adult subjects (Chaddock et al., 2010; Erickson et al., 2009; Erickson et al., 2011).

The changes to neuroanatomy associated with exercise also occur on a more micro-level. For instance, exercise has been shown to be correlated with higher concentrations of grey matter in the brain. A 2018 study of 261 older adults found that adults with a more physically active lifestyle (e.g., exercise, chores, walking) had higher concentrations of grey matter in their bran in comparison to more sedentary older adults (Rush University Medical Center, 2018). This is particularly relevant as AD has been shown to decrease grey matter density.

In addition to grey matter, white matter volume is also associated by exercise. For instance, Colcombe and colleagues (2004) examined white matter concentration using Voxel-based morphometrytechnology to compare brains of participants in an exercise group and a control group. Following 6 months of exercise, the experimental group had increased white matter concentrations in the frontal region of the brain in comparison to the control group (Colcombe et al., 2004). Another study in 2010 used diffuse tensor imaging (DTI) to study white matter integrity among elderly patients in a 1-year fitness program. Following 1 year of exercise, the experimenters found that VO2 Max scores were correlated with better white matter integrity in the frontal and temporal lobes (Heo & Kramer, 2010).

Default Mode Network, discussed in the sleep section, has also been shown to be impacted by exercise. More specifically, a 2010 study found a positive correlation between VO2 score and functional connections in the default mode network, most notably the posterior cingulate gyrus and the middle frontal gyrus; such connectivity has also been shown to be correlated with improved executive functioning and spatial memory, two areas also implicated in AD (Voss et al., 2010). Glia are also impacted by exercise (Thomas et al., 2012). These cells play a crucial role in the metabolic support of neurons, regulate efficacy of synapses, and can communicate between neurons using calcium ion signaling (Zhang & Haydon, 2005). As such, it was hypothesized that exercise would have an impact on the glia in a positive way. A 1994 study on rats assessed for the impact of exercise on glia and neurons following a motor learning and exercise regimen. Following the experiment, the researchers found high glial volume per Purkinje cell as well as an increase in overall molecular volume in the motor learning group, suggesting that exercise and motor learning can increase glial, astrocytic, and synaptic mass (Anderson et al., 1994).

Finally, in addition to both macro and mico-level neuroanatomical changes, exercise is also implicated in various biochemical mechanisms within the brain that promote brain health and resilience Although BDNF is the most commonly cited factor, vascular endothelial growth factor (VEGF) is another mechanism that is critical in brain health. VEGF and helps endothelial cells lining the wall of the blood vessels to multiply (Bloor, 2005). VEGF is also critical in producing new neural progenitor cells, aiding in the process of angiogenesis. Studies have shown that exercise increases VEGF, with some of specifically focusing on the elderly population (Thomas et al., 2012). For instance, Park and colleagues (2010) found that following 12 weeks of treadmill training lead to, in the exercise group, significant increases in VEGF and other

important factors, such as increase oxygen uptake per weight, carotid artery Longitudinal

Displacement; and decreases in body fat mass, diastolic blood pressure, systolic blood pressure,

Total Cholesterol, and LDL-C in comparison to the control group (Park et al., 2010). A similar

study from Sandri and colleagues (2005) determined that, following a 4 week exercise trial, those

in the exercise group had as much as a 103% increase in their VEGF in comparison to the control

group, which did not see any change in VEGF.

Angiogenesis, the proliferation of new blood vessels, is another biochemical process

implicated by exercise (Thomas et al., 2012). For example, a 2017 found that rats prescribed to a

7-week exercise group had increased levels of HCAR1, which is critical to blood supply to the

brain and VEGF both increase compared to a sedentary group (Morland et al., 2017). A 2019

systemic analysis of exercise and angiogenesis found similar results, indicating that exercise can

lead to higher concentrations of blood cells and overall cerebral blood volume (Bloor, 2019).

Finally, neurogenesis, the development of nerves and nerve tissue such as neurons, is a

critical focus of AD research. It also has serious implications with its relation to exercise

(Thomas et al., 2012). Neurogenesis in the hippocampus and dentate gyrus, two critical areas

implicated in AD and dementia, has been shown to increase following exercise. For example, a

1999 study of 34 female mice who were put into an exercise or control group found that the

exercise group had higher concentrations of neurons in the hippocampus in comparison to the

control group (van Praag et al., 1999). Another area that is heavily implicated by exercise and

dementia is the dentate gyrus, which is part of the hippocampal formation. A 2007 study used a

small group of human subjects to assess for neurons and cerebral blood volume in the dentate

gyrus following an exercise program. The researchers concluded that exercise was positively

correlated with increased cerebral blood flow and, as such, was inferred to have increased exercise-induced neurogenesis in the dentate gyrus (Periera et al., 2007).

The beneficial effects of exercise on the brain have been directly observed in regards to AD and dementia-related research as well. A 2004 meta-analysis by Heyn and colleagues examined the effect of exercise training on elderly persons with cognitive impairments and dementia. The analysis analyzed 30 randomized control studies, consisting of a total of 2020 participants over the age of 65. The meta-analysis found over 30 trials, with significant effect sizes for strength training, physical fitness, functional performance, cognitive performance, and behavior. Such findings indicate that a large number of studies support the notion that increased physical activity is a protective factor against further decline in functional status among patients with dementia as well as other important health benefits. However, some research has found contradictory results.

Exercise has also been shown to be a protective factor against dementia developing in the first place. A 2018 study by Hacket and colleagues looked to examine the relationship between walking speed and subsequent risk of cognitive decline and dementia. The study, which ran from 2002-2015, examined walking speed using timed distance walking and cognition using tests for memory, time orientation, verbal fluency, and processing speed. During the second half of the study (2006-2015), researchers used physician-diagnosed dementia documentation and the Informant Questionnaire on Cognitive Decline in the Elderly to assess for incidence of dementia. The researchers found that the individuals who had developed dementia were rated lower on walking speed and cognition at the beginning of the study. The researchers concluded that walking speed has a significant impact or is at least associated with on cognitive decline and dementia. As such, the authors suggest that exercise regimens focused on increasing walking

speed could be a protective factor in delaying or preventing the onset of dementia. Won and

colleagues (2019) examined brain activation during semantic memory tests following exercise.

fMRI results indicated significantly higher activation in the middle frontal, inferior temporal,

middle temporal, and fusiform gyri, as well as the bilateral hippocampus, all areas highly

associated with memory and executive functioning, following only one session of cardiovascular

exercise (Won et al., 2019).

A 2018 study of 494 individuals with dementia investigated the role that aerobic and

resistance exercise plays in the progression of the disease. Following 12 months of intervention,

the exercise group, which consisted of an aerobic and strength based conditioning regimen, did

not perform significantly different on the Alzheimer's Disease Assessment Scale-Cognitive

Subscale (ADAS) compared to the control group. The researchers proposed that such findings

could be suggestive that implementing an exercise regimen earlier on could be more effective at

controlling for cognitive impairment and that, once dementia is diagnosed, it may be too late for

such an intervention to be implemented (Lamb et al., 2018). This ties into the concept of

cognitive reserve. Cognitive reserve is essentially the theory that humans are able to compensate

for decline by engaging in cognitively rich activities early in life, building "reserve." Although

evidence of cognitive reserve has been inconclusive within patients with pre-existing dementia,

the overwhelming majority of researchers do agree that addressing exercise long before AD

symptom onset can play a critical role in delay or managing the disease later on. Cognitive

reserve will be discussed in depth later on.

A 44 year, longitudinal study published in 2015 examined if cardiovascular exercise

decreased the incidence of dementia in women in middle age (38-60 years old; Horder et al.,

2018). The study, which consisted of 1462 women who were randomly assigned to stepwise-

increased maximal ergometer cycling test to evaluate cardiovascular fitness or control group, examined patients' cognitive performance at the 6, 12, 24, 32, 37, and 41-year marks. Over the 44-year span of the study, the adjusted hazard ratio for the control group was 1.41 compared to the high cardiovascular fitness group whose ratio was .12. Such findings are indicative that cardiovascular fitness during midlife was associated with a decreased risk of subsequent dementia.

Another study, conducted in 2006, aimed to assess for a negative relationship between exercise and the incidence of dementia. The study consisted of over 1,700 participants over the age of 65, with no diagnosis of any cognitive impairment. Participants were examined for exercise frequency, cognitive function level, physical functioning, depression, lifestyle stressors, and comorbid medical conditions; and then re-assessed during a 6-year follow-up. The results found that the participants who exercised 3 days per week or more, had an incidence of dementia of 13 per every 1000 people, compared to the participants who exercised less than 3 days per week who had an incidence of dementia of 19 per every 1000 people. The researchers concluded that regular exercise can play a significant role in the prevention of dementia and a more sedentary lifestyle could be a contributing risk factor to the onset of dementia (Larson et al., 2006).

Andel and colleagues (2008) conducted a twin study that examined the role of physical exercise during midlife and the risk of dementia in later adulthood. A case control analysis of 264 cases with dementia and 2870 controls including 90 pairs of twins examined how much physical exercise each participant was getting using a Likert-style questionnaire and incidence of dementia. The results indicated that light and regular exercise was associated with lower risk of dementia in comparison to those who did not exercise regularly. When looking at twins

specifically, twins who reported higher levels of exercise had lower incidence of dementia compared to their co-twin. Such findings imply that physical exercise not only has an impact on dementia prevention in biologically different individuals but also in biologically similar individuals.

Another meta-analysis conducted in 2011 consisting of 29 randomized control trials found that regular exercise in middle aged individuals was associated with better performance on tests of memory, attention, processing speed, and executive functioning. The meta-analysis also noted a specific study which found improved cortical connectivity and activation in a 6-month exercise group compared to a control group on fMRI imaging (Ahlskog et al., 2011).

Although the majority of research into exercise and dementia primarily focuses on cardiovascular exercise, other forms of physical activity have also been shown to be beneficial to preventing cognitive decline in older age. A 2019 study examined the relationship resistance training exercise and cognitive impairment in female rats. The study, which injected intraventricular lipopolysaccharide into the dentate gyrus to induce cognitive impairment, separated rats into a ladder climbing resistance regime (weights tied to their tails as an analogue to weight-resistance exercise) and a sedentary control group ($n = 14$). After a 6-week experimental trial, the rats who were in the exercise arm of the trial had decreased spatial learning deficits and increased dentate gyrus plasticity compared to the sedentary arm of the trial. Such results indicate that resistance training can have a significant impact on slowing and decreasing cognitive decline in the brains of mammals, even in the presence of neurological stressors (Kelty et al., 2019).

A 2012 randomized control trial also examined the role of resistance training on cognitive health, with a specific focus in its implications of older adults with MCI and its

progression to full-blown dementia. Following a 26-week trial, the resistance training group had significantly better performances on both the Stroop test and associative memory tests. On a biological level, the resistance training group also had functional changes in the right lingual, occipital-fusiform gyrus, and right frontal pole regions of the cortex via fMRI analysis. Finally, there was a positive correlation between hemodynamic activity in the right lingual gyrus and associative memory performance. All such findings led researchers to conclude that resistance training can and does play a critical role in anatomical changes and performance improvements in areas affected by AD and dementia (Nagamatsu et al., 2012).

Interestingly, dancing is another alternative form of exercise that has shown significant promise in delay and prevention of AD and dementia. A 2019 pilot study examined the role of dance and quality of life in patients with mild, moderate, and severe forms of dementia (Choo et al., 2019). Following a 10 session dance protocol, statistically significant increases in quality of life were shown among all three groups.

Cognitively, a 2010 study aimed to examine the role of dance on posture and balance parameters, reaction times, motor behavior, tactile and cognitive performance in 62 elderly patients, assigning them to either a dance-based group or a non-dance control group (Kattenstroh et al., 2010). Following the experimental period, the dance group had statistically significant better performances on all domains. Another multi-trial experiment in 2015 found improved minimum foot clearance variability and cognitive performance in a dual-task situation in elderly participants who were part of a 6-month dance program, in comparison to a non-dance control group (Hamacher et al., 2015). A 2012 systemic review of 10 studies examining the role of dance in elderly patients found that those involved in a dancing group had improved social interaction, quality of life, motor ability, and physical strength and flexibility as well as

decreased problem behaviors (Guzman-Garcia et al., 2013). Another literature review conducted

in 2017 found increased cognitive, physical, and emotional wellness as well as increased social

engagement in patients with dementia following dance-related exercise (Klimova et al., 2017). It

should be noted that, in addition to exercise, the robust impact of dance, in addition to exercise,

is that dance also involves a huge social component. More on the effect of social interaction,

below

  A third alternative form of exercise that has gained attention over the years has been Tai

Chi. Tai Chi, low impact, slow motion exercise, which originated in China, and intends to

integrate the mind and body through movement, breathing, and mindfulness. Thai chi has been

clinically proven to aid in balance, flexibility, strength, and cardiovascular health (Jahnke et al.,

2010). It has also been shown to lower blood pressure and decrease risk of diabetes (Thornton et

al., 2004; Tsang et al., 2007). In addition to these positive attributes, tai chi has now begun to

show that it can aid in cognitive health. For example, a Mortimer and colleagues (2012) assigned

120 participants to 4 potential groups (tai chi, walking, social interaction, and no intervention)

and compared their brain imaging for brain volume changes as well as performances of

neuropsychological testing. Following a 40-week trial period, the tai chi and social interactions

groups had significant increases in brain volume, as confirmed by MRI imaging. The researchers

also found improved performance on the Mattis Dementia Rating Scale, Trails A and B,

Auditory Verbal Learning Test, and Animal Naming test among the tai chi group compared to

the other groups, suggesting that tai chi can be an effective form of exercise that improves

cognitive health (Mortimer et al., 2012). Another study from 2014 examined the impact of tai chi

and mahjong on the cognitive health of 110 elderly Chinese participants with some degree of

cognitive impairment (Mini Mental Status Exam score between 10 and 24). Over a 12-week

period, the mahjong and tai chi groups both had variable effects in their performances on the

MMSE. Compared to the control group (no intervention), the mahjong and tai chi groups both

had sustained their cognitive functioning while the control group declined cognitively over a 9-

month follow-up period, suggesting that social and physical stimulation can delay cognitive

decline in older adults, even in the stages of a neurodegenerative process (Cheng et al., 2014).

Finally, a 2014 meta-analysis of 22 studies that examined the relation between tai chi and

cognition found that tai chi aided in preserving cognitive health, with the most significant areas

being in executive functioning (Wayne et al., 2014).

Stress

Stress is another area that has a significant impact on the pathophysiology of AD and

dementia. Although stress can be defined in many ways, for the purposes of this study, stress will

be operationalized as depression, anxiety, or unspecified stressors such as work, family, or

health-related stressors, all of which play a significant role in brain health and cognition.

Depression has significant negative impact on the brain in multiple ways (Palazidou,

2012). Anatomically, it has been shown that depression is associated with atrophy and actually

seems to shrink the brain. More specifically, areas that are implicated in AD have been shown to

suffer the greatest impact. Imaging has also shown reduced cerebral blood flow and poorer

glucose metabolism in the prefrontal cortex in comparison to health patients (Drevets, 1998). For

instance, depressed patients tend to have significantly lower brain volume in the anterior

cingulate, orbitofrontal cortex, putamen, and the caudate of the prefrontal cortex (Koolschijn et

al., 2009). Finally, depression has been associated with reduced cell count in neuronal and glial

density in the orbitofrontal and dorsolateral prefrontal cortex (Raikowska et al., 1999).

The amygdala, often thought to be a guiding force in emotion, is also implicated by depression and plays a key role in emotional learning and memory, chemical responses to stress, and cortical arousal (Palazidou, 2012). A 2008 meta-analysis by Hamilton, Siemer, and Gotlib found that depressed patients had a reduced overall amygdala size than their healthy counterparts.

However, one of the most impacted areas of the brain in both AD and depression is the hippocampus. It has been widely shown that depression is associated with lower volume of the hippocampus (MacMaster & Kusumakar, 2004; Hastings et al., 2004; Czeh & Lucassen, 2007). Depression has also been shown to have implications on overall brain functioning. For example, depressed patients perform significantly worse on hippocampus-dependent verbal memory tests compared to non-depressed participants (MacQueen et al., 2003). Interestingly, these symptoms tend to predate any structural changes to the hippocampus, suggesting performance related deficits begin to emerge before any structural deficits (Videbech & Ravenkilde, 2004). Despite these findings, there is also hope that such structural changes can be reversed (Palazidou, 2012). It has been shown that patients who are in remission from depression tend to have higher brain volume in comparison to non-remitted patients, suggesting that some of the structural change seen can be reversed through behavioral and/or medical intervention (Frodl et al., 2004).

In addition to the bidirectional anatomical changes associated with depression and the brain, depression can also impact the brain on a chemical level. For instance, depression has been shown to be correlated with increased levels of proinflammatory which are associated with serotonin depletion, activation of the hypothalamic pituitary adrenal (HPA) axis (stress response), and glucocorticoid resistance, all of which are tied with the symptoms of depression (Palazidou, 2012). Additionally, these cytokines elicit inflammatory responses in the brain that

mimic sickness behavior, such as fatigue, nausea, and fever (Sankowski et al., 2015). In more

extreme cases, confusion, hallucinations, and personality changes can also occur, that are

consistent with severe depression and even psychotic features (APA, 2013; Sankowski et al.,

2015). When chronically exposed to such an inflammatory response, the brain can become

damaged, oftentimes mimicking damage associated with AD (Palazidou, 2012).

Alterations in BDNF is another chemical response implicated in both depression and AD

(Yu & Chen, 2011). There is strong correlational is evidence supported by the facts that there are

lower levels of BDNF in the hippocampus and PFC in depressed patients and also an increase in

BDNF in patients taking anti-depressants and other forms of therapy. Additionally, the

neurotransmitter serotonin is one of the most prevalent chemicals in the brain that is implicated

in depression. It is widely understood that depression is correlated with lower levels of serotonin

and, conversely the mechanism of action for many anti-depressants is to increase the action of

serotonin, either by inhibiting reuptake or preventing depletion (Palazidou, 2012). However,

lower levels of serotonin are now being shown to be implicated with cognitive decline and AD.

This is evidenced by a 2017 neuroimaging study which utilized MRI and PET scanning to

compare the number serotonin transporters (SERT) in patients with MCI and healthy controls in

addition to using neuropsychological testing. The MCI population demonstrated lower levels of

SERT as well as worse performance on the MMSE, California Verbal Learning Test-3(CVLT-3),

and Clinical Dementia Rating Scale. This is also relevant as SERT interacts with other

neurotransmitters such as glutamate, norepinephrine, dopamine, and acetylcholine, all of which

are also implicated in AD and other forms of dementia (Splete, 2017).

Furthermore, it has been shown that depression also has a direct impact on AD and

dementia. Almeida, Hankey, Yeap, Golledge, and Flicker conducted a study in 2018 that

examined the causal relationship between depression and risk of dementia. The 14 year

longitudinal study examined nearly 5,000 cognitively healthy men. During the follow-up period,

at a total of 38% of men developed dementia. When comparing men with a history or current

episode of dementia to depression-free men, the depressed group had a hazard ratio of 1.3,

indicating a 30% increased risk. The authors also found the use of antidepressant medication to

have no effect on dementia progression or protection (Almeida et al., 2018). These results

indicate that depression has a positive correlation with dementia risk and that pharmacological

treatment may not be entirely effective. As a result of these findings, it is hypothesized that

individuals undergoing psychotherapy in conjunction with anti-depressant use may see better

outcomes regarding onset and risk of dementia.

Additionally, Barnes and colleagues (2012) conducted a retrospective cohort study to

examine the etiologic risk factors of depression on dementia. The longitudinal study examined

depression at midlife and late life. The participants were separated into 4 groups: no depression,

midlife depression, late life depression, and both times depressed. Of the 27.5% of participants

with some form of depression (groups 2-4), 22.5% were subsequently diagnosed with dementia

at follow-up (Barnes et al., 2012). The authors also found that midlife-depression only had a HR

of 1.19 (approximately 20% higher than the non-depressed group), late-life depression had a HR

of 1.72 (72% higher compared to the non-depressed group), and both had the highest risk with an

HR of 1.77 (nearly 80% higher than the non-depressed group). These findings further support the

relationship between depression and dementia.

Richard and colleagues (2013) examined 2,160 men and women 65 years and older to

assess for a relationship between depression and dementia, with a specific focus on progression

of mild cognitive impairment to dementia. The results found that adults with comorbid

depression had an increased prevalence of MCI and dementia (OR = 1.4 and 2.2, respectively, 95% CI), as compared to participants without depression. Additionally, they found that the risk of incident dementia was also increased in this population (*HR* = 1.7, 95 % CI: [1.2–2.3]). Finally, people with comorbid MCI and depression had the highest risk of subsequent dementia with a HR of 2.0. These results support the hypothesis that depression is positively correlated with cognitive decline and that the risk is positively associated with severity of cognitive impairment.

Similar results have also been found in twin studies. A two-part twin study by Brommelhoff and colleagues (2009) examined whether there was a relationship between depression and risk of dementia and, if there was, was the age of the first episode predictive of further risk. A review of hospital discharge registries, medical history, and medical records in patients aged 65 and older found that individuals with a recent registry-identified depression, per medical documentation, had over 3 times a greater risk of dementia. Surprisingly, they also found that registry-identified depression earlier in life did not have a significant relationship with dementia risk. They also found that each 1-year increase in time between depression onset and dementia onset was associated with over an 8% decrease in dementia risk. These findings led to the conclusion that depression is associated with increased risk of depression but that early onset of depressive symptoms negatively associated or may not be associated with risk, especially as compared to depressed patients later in life.

Finally, Byers and colleagues (2012) investigated the relationship between dysthymia (APA, 2000) and depression on the risk of dementia in military veterans. 281,540 cognitively healthy veterans were assessed for depression at baseline and then examined for depression and cognitive functioning at a 1 and 10-year follow-up. The results indicated that participants with

depression had over twice the likelihood of developing dementia (*HR* = 2.18, 95% CI [2.08, 2.28]) compared to non-depressed participants. Patients with dysthymia also had nearly twice the likelihood of developing dementia compared to the control group (*HR* = 1.96, 95% CI [1.71, 2.25]). The authors also found depression and dysthymia to have a higher risk of death (*HR* = 1.47 and 1.41, 95% CI [1.31, 1.53]) (Byers et al., 2012). These results indicate that depression and dysthymia can have a significant impact on cognitive functioning.

Chronic stress and anxiety are also often interlinked, with both having a significant impact on the brain and cognition. Much like depression, anxiety and stress can alter the brain's neuroanatomy and lead to issues with cognition and processing. Much like with depression, stress and anxiety have a profound impact on hippocampal functioning (Bremner, 2006). Chronic stress has been shown to be associated with dendritic atrophy in the hippocampal region as well as hippocampal synapses and mossy fiber terminals (Sousa et al., 2000). Stress also impedes proliferation and neurogenesis in the hippocampus (Tanapat et al., 2001). The impact of hippocampal functioning is also seen quantitatively. A 1994 animal study of 344 rats found that stress was associated with worsened performance in tasks of spatial and working memory (Arbel et al., 1994). A similar study in 1994 also found stress to be correlated with reduced performance on spatial memory tasks. Interestingly, it also found that, with proper treatment, operationalized as psychotherapy and/or medication treatment, these spatial memory deficits and dendritic atrophy could be reversed, suggesting that proper treatment could be beneficial (Luine et al., 1994). This is further supported in a 2000 study in which medication treatment of anxiety was found to be associated with increased neurogenesis in the hippocampus in rats (Malber et al., 2000).

In addition to the hippocampus, anxiety and stress also have a profound impact on areas such as the amygdala, prefrontal cortex, and overall brain volume (Bremner, 2006). For example, chronic stress can lead to increases in bed nucleus of stria terminalis (Vyas et al., 2003) and arborization of neurons in the amygdala (Vyas et al., 2002). Chronic stress has also shown to reduce dendritic branching in the medial prefrontal dopaminergic system of the prefrontal cortex (Radley et al., 2004). Finally, stress and anxiety have also been shown to decrease the volume of the brain overall (Knutson et al., 2001). A 2001 study of 87 healthy individuals compared MRI's of patients with neuroticism scores, associated with negative emotion and impulsivity, as measured by the Revised NEO Personality Inventory (Knutson et al., 2001; McCrae & Costa, 1978). When controlling for age and sex, the researchers found a negative relationship between neuroticism score and brain volume, suggesting that emotional stress can is negatively associated with overall volume of the brain (Knutson et al., 2001).

In addition to the anatomical and chemical impact of stress and anxiety on the brain, it can also impact cognitive performance. For example, as has been demonstrated in numerous studies, Vytal and colleagues (2013) examined the role that anxiety can play in performance on spatial and working memory tasks. Following completion of the study, researchers found that induced anxiety was correlated with worsened performance on both visual and spatial working memory tasks. Additionally, they found that low to medium difficulty verbal tasks were more impacted by anxiety, while spatial memory saw no difference in task difficulty (Vytal et al., 2013). Another study conducted in 2006 found that participants with more intense anxiety had worse performances on spatial working memory tasks, compared to non-anxious controls (Shackman et al., 2006). Additionally, Singh and colleagues (2015) examined 91 undergraduate students to assess if anxiety affected visual attention Results supported the initial hypothesis that

higher levels of trait anxiety were associated with poorer performance on tests of visual attention and vigilance (Singh et al., 2015).

More specifically, there is evidence that anxiety and stress have direct links to AD and other dementias. Gallacher and colleagues (2009) conducted a prospective study to examine if there was a relationship between anxiety and the risk of dementia. A total of 1,481 men ages 48-67 were given a baseline anxiety scale and then administered cognitive testing 17 years later during a follow-up. During follow-up, patients with a reported history of anxiety at baseline had an increased risk for both mild cognitive impairment and dementia later in life (*OR* = 2.31 and 2.37, respectively, 95% CI [0.98, 5.71]) and had significantly poorer performance on the learning memory subtest of the Cambridge Cognitive Examination of Elderly.

Additionally, 1,082 twins in Sweden were the subject of a 2017 study that examined cognitively healthy subjects, who were assessed for anxiety at baseline and followed over a 28-year period. The researchers found that subjects with an overall heightened anxiety score had a significantly higher risk of dementia compared to non-anxious individuals (Petkus et al., 2018). In addition to the general findings of anxiety, subjects that endorsed the highest anxiety had the highest risk of dementia, with a 48% higher risk compared to the non-anxious control group. (Petkus et al., 2017). Finally, a 2011 longitudinal cohort study by Wilson and colleagues examined the relationship between stress and anxiety and the development of cognitive impairment. The study consisted of 785 cognitively healthy adults who were administered self-report measures measuring neuroticism and then administered cognitive testing at follow-up. In the event the participant died, an autopsy was performed to study brain anatomy. At follow-up, the researchers found that participants with higher levels of anxiety and vulnerability to stress had an increased risk of cognitive decline associated with dementia (Wilson et al., 2011). More

specifically, subjects more prone to anxiety and stress had decreased performances on measures

of working memory, and perceptual speed. Researchers also examined autopsy reports of

patients who had died during the length of the study and found overall higher levels of

deterioration of brain matter, specifically the hippocampus, in anxious participants. Such

findings indicate that stress and anxiety in adulthood are associated with an increased risk of

cognitive decline later in life (Wilson et al., 2011). Overall, the researchers concluded that

anxiety is indeed associated with increased risk of dementia.

Diet

According to Brennan and colleagues it has long been understood that one's diet can have

significant implications for physical, mental, and cognitive health, both positively and

negatively. Foods that are high in vitamins and other nutrients are associated with better

physical, psychological, behavioral, and cognitive outcomes, whereas foods rich in in salt, sugar,

and other preservatives have been shown to problematic in all of these domains. Unfortunately,

the Standard American Diet, or Western Pattern Diet, among others, are most commonly

associated with the latter. The standard American diet is characterized by high intakes of red

meat, preservatives, processed and fried foods, butter, high-fat dairy, refined grains, complex

carbohydrates, and sugar (Grotto & Zied, 2010).

Aspects of the standard American diet are linked to neuroanatomical changes that are

likely connected with AD and cognitive decline. For example, a 2012 cell culture experiment

examined the role of dietary fat in the aggregation of amyloid. The researchers found increased

amyloidogenic APP and amyloid beta protein as well as decreased non-amyloidogenic APP

(Grimm et al., 2012). A 2018 dietary study of rats found that 3 months of high fat food

consumption was associated with weaker integrity of the blood brain barrier. They also found

significant elevations in cortical and hippocampal glial acidic fibrillary protein and Fluoro Jade-C staining, which are associated with degeneration and inflammation in the brain (Takechi et al., 2017). Another study from 2006 found that rats who were exposed to a high fat diet over 4 months had a 40% increase in amyloid beta levels (Oksman et al., 2006). On a more macro-anatomical level, high sugar consumption has been shown to reduce neurogenesis and BDNF in the hippocampus (van der Borght et al., 2011; Molteni et al., 2002)

Although its physical implications are well-documented, the standard American diet also has significant cognitive implications that both mirror and increase the risk for AD and other cognitive impairments. For example, the same dietary study with rats (Takechi et al., 2018) also found that diets of high fat were associated with worse performance on the Morris Water Maze, a test of memory. Kalmijn and colleagues (2004) conducted another study of 1,613 participants compared items of the food-frequency questionnaire and performance scores on tests of memory, psychomotor speed, cognitive flexibility, and overall cognition. When adjusted for age, sex, education, smoking, alcohol consumption, and energy intake, the lowest performing group (bottom 10%) also had a higher intake of saturated fats and cholesterol. Additionally, participants who had higher consumption of omega 3's and polyunsaturated fatty acids (PUFA) had overall better performances on cognitive testing (Kalmijn et al., 2004).

More specifically, poor diet has also been connected to AD and general cognitive decline for some time. A review of literature from 2014 found an increase beta-amyloid protein levels in mice's brains who had a diet of high saturated and trans fats (Morris & Tangney, 2014). These results have also been consistent in human studies. Kalmijn and colleagues (1997) examined the association between fat intake and the risk of dementia. The study had 5,386 non-demented individuals who were assessed using food-frequency questionnaire and clinical examination.

After a 2 year follow-up, researchers examined relations between diet and change in cognitive status compared to baseline. The researchers found that higher rates of consumption of total fat, saturated fat, and cholesterol were all associated with increased rates of dementia in their sample. The study also found that regular consumption of fish high in n-3 polyunsaturated fatty acids were associated with lower rates of dementia. The results suggest that diets associated with high cardiovascular risk (i.e. high fat/high cholesterol diets) are associated with higher incidence of dementia while diets rich in n-3 polyunsaturated fatty acids were associated with lower rates of dementia (Kalmijn et al., 1997). Another study examined dietary patterns of 815 cognitively healthy elderly patients and compared any subsequent incidence of dementia. Following a mean follow-up period of 3.9 years, the researchers found a positive correlation between high fat intake and risk of dementia. Interestingly, they found that higher consumptions of omega-6 polyunsaturated fat, monounsaturated fat, and vegetable fat were negatively correlated with incidence of AD and dementia, suggesting that certain fats can be protective against cognitive decline (Morris et al., 2003).

The connection between a healthier diet and slowing of cognitive decline has also been well established for some time. Gateu and colleagues (2007) examined 8,085 men and women over the age of 65 with no diagnosis of dementia. The researchers also separated participants on whether or not they carried the ApoE4 gene to examine the role of genetics in diet and dementia progression. The study found that decreased risk of dementia was associated with daily consumption of fruits and vegetables, omega 3 among both ApoE4 carriers and noncarriers. Noncarriers also had a reduced risk of dementia when they included weekly consumption of fish in their diets. Non-carriers were also shown to be at a heightened risk of dementia, compared to ApoE4 carriers, if their diet consisted of high levels of omega 6 oils that were not compensated

by omega 3 oils. These findings are suggestive that consumption of fruits, vegetables, fish, and omega-3 rich oils are all considered protective factors that can reduce the risk of dementia.

Of the many beneficial aspects of the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, it has been shown to reduce oxidative stress and inflammation, the accumulation of free radicals in the brain that can cause damage to the brain cells. The primary hypothesis to these conclusions is that the antioxidants in berries and the vitamin E in olive oil, green leafy vegetables and nuts can serve as a protective factor against oxidative stress (Gómez-Pinilla, 2008). Additionally, the omega-3 fatty acids found in fatty fish is associated with decrease inflammation in the brain (Devassy et al., 2016). Fito and colleagues evaluated 372 patients at a high cardiovascular risk following 3 months of either a low fat diet, traditional Mediterranean diet (TMD) with nuts, or TMD with olive oil, for any changes in oxidative stress. Following a 3 month experimental period, both TMD groups should a significantly lower level of oxidative stress, as measured by low-density lipoprotein (LDL) levels, while the low fat group did not display any significant change (Fito et al., 2007). A similar study from 2004 investigated how the TMD affected inflammation and coagulation in over 3,000 healthy adults over a 1-year period (Chrysohoou et al., 2004). Following 1 year, the patients with the highest adherence to the TMD had 20% lower C-Reaction Protein (CRP) levels, 17% lower interleukin (IL)-6 (IL6) levels, 15% lower homocysteine levels, 14% lower white blood cell counts, and 6% lower fibrinogen levels compared to those participants with the least amount of adherence to the TMD (Chrysohoou et al., 2004).

The DASH diet has also seen similarly positive results. Lopes and colleagues prescribed the DASH diet to 12 overweight patients over a 4-week period and then compared their results to a control group. A pre- and post-test analysis of Ferric-reducing activity of plasma (FRAP) and

plasma F2-isoprostanes revealed that patients prescribed the DASH diet had significantly

increased FRAP and F2-isoprostanes, suggesting that the DASH diet can raise antioxidant

capacity, lower blood pressure, and reduce oxidative stress (Lopes et al., 2003). Finally, a 2008

longitudinal study of 88,517 nurses over a 24-year period assessed for adherence to the DASH

diet and incidence of myocardial infarction, coronary heart disease death, and stroke. The results

indicated that women who had the highest adherence to the DASH diet had the lowest incidence

of these conditions (Fung et al., 2008). Additionally, however, they also found that the DASH

diet was correlated with lower plasma levels of C-reactive protein and IL6, indicating, an overall

lower cardiovascular risk among patients as well as decreased neuro-inflammatory responses in

the brain (Fung et al., 2008; Bermudez et al., 2002). Because the MIND diet is a hybrid of the

two diets, it is hypothesized that the MIND diet will have similar or better results.

Recently the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)

diet has begun to emerge as a protective dietary intervention for AD and other cognitive

deterioration. The MIND diet, which is a hybrid of more popular and widely-accepted

Mediterranean and DASH diets, consists of food items like green leafy vegetables (6 servings

per week), other vegetables (at least 1 serving per day), berries (at least 2 servings per week),

nuts (at least 5 servings per week), olive oil used as the main cooking oil, whole grains (at least 3

servings per day), fish (at least 1 serving per week), beans (at least 4 servings per week), poultry

(at least 2 servings per week), and wine in moderation (no more than 1 glass per day). In addition

to foods that should be targeted, the MIND diet also discourages excessive consumption other

types of foods as well. Butter/margarine (less than 1 tablespoon per day), cheese (less than 1

serving per week), red meat (no more than 3 servings per week), fried foods (less than once per

week), and pastries/sugary foods (no more than 4 times per week) should all be limited according

to the MIND diet doctrine (Morris et al., 2015).

Specific to AD, it is hypothesized that the MIND diet can be protective against amyloid beta. The basis for this hypothesis is that the vitamins and antioxidants found in the foods that comprise the MIND diet are also associated with decreased amyloid beta accumulation in the brain (Obulesu et al., 2011). Coinciding with this notion is the fact that the MIND diet also discourages consumption of saturated fats and trans fats, which is shown to be associated with increased amyloid beta accumulation in the brain (Morris & Tangney, 2014).

The MIND diet is also quickly accruing a significant body of empirical support as well. Morris and colleagues (2014) examined the effects of the MIND diet compared to the DASH and Mediterranean diet. 915 participants who were part of the Rush Memory and Aging Project participated in the study in which cognitive testing was performed after a prolonged period (average 4.8 years). The researchers found that all three diets had positive association with delayed cognitive decline. However, the MIND diet had the slowest rate of cognitive decline. These results led researchers to conclude that the specifically tailored aspects of the MIND diet have more profound effect on cognitive decline, in comparison to diets not specifically tailored to brain health. Morris and colleagues (2015) conducted a study of 960 individuals who had been experiencing memory issues for an average of 4.5 years studied the impact of the MIND diet on the progression of cognitive decline. Findings indicated that the MIND diet was negatively associated with cognitive decline compared to a control group across domains of episodic memory, working memory, semantic memory, visuospatial ability, and perceptual speed. These results suggest that tailoring diet to other protective factors in dementia prevention can delay the onset of significant cognitive decline.

Another prospective study by Morris and colleagues examined the role that the MIND

diet plays in the reduction of cognitive decline compared to the DASH and Mediterranean diet.
The study consisted of 923 participants, ranging in age from 58 to 98 years of age, who were
assessed over a 4.5-year period (3 tertiles; Morris et al., 2015b). Results indicated that, although
all three diets were associated with reduction in cognitive decline, the MIND diet had the earliest
effects (tertile 1) results compared to the DASH and Mediterranean diets (tertile 3; Morris et al.,
2015b). The researchers concluded that adherence to all three diets aided in the reduction of risk
of developing Alzheimer's, however, the MIND diet saw the earliest and most robust results and
the lowest need for strict adherence, all of which have important implications for both positive
outcome and reducing attrition in real-world clinical practice.

      Finally, a third study by Morris and colleagues then evaluated dietary patterns of 923
older adults over an over an average period of 4.5 years. During follow-up, the researchers found
that the participants with the most compliance had a 53% decreased risk for dementia when
accounting for age, sex, education, ApoE-4, total energy intake, physical activity and
participation in cognitively stimulating activities. They also found, although they were effective,
the DASH and Mediterranean diets had lower risk ratios for AD compared to the MIND diet,
suggesting that the MIND diet was the most effective diet in their study at preventing cognitive
decline (Morris et al., 2015c).

      Another, larger study of over 16,000 women, aged 70 and over, examined the association
between adherence to the MIND diet and cognitive decline in aging. Over a 14 year period,
researchers kept track of diet adherence using the Food Frequency Questionnaire. Over a 6-year
period following diet tracking, researchers administered the Telephone Interview for Cognitive
Status (TICS) to track cognitive status over time. The results indicated that greater adherence to
the MIND diet was associated with greater verbal memory in comparison to those who had not

adhered to the MIND diet. These findings are suggestive that long-term adherence to the MIND

diet is associated with reduced deficits in verbal memory (Berendsen et al., 2018).

Cognitive Stimulation and Cognitive Reserve

A more recent movement has begun to gain empirical support in the field of AD and

dementia research that focuses on the role of cognitively stimulating activity as a protective

factor against cognitive decline. This concept is the basis of cognitive reserve theory. This theory

states that the brain has the ability to compensate and find alternate ways of fulfilling any deficits

that it may be experiencing (Stern, 2012). There are two primary forms of cognitive reserve:

active and passive. Passive reserve, or brain reserve, refers to the physical characteristics of the

brain that may make it more resilient to neurodegeneration such as size, neuron concentration,

and blood flow. Common ways of measuring passive reserve include brain imaging to assess for

brain volume, head circumference, synaptic count, or dendritic branching (Stern, 2006).

Active reserve, on the other hand, refers to the brain's ability to overcome damage by

using compensation or different brain processes to retain the ability to function well. The

primary measures of active reserve include anecdotal data focusing on socioeconomic status,

educational history, and degree of literacy as well as more formal cognitive assessments such as

intelligence testing and neuropsychological assessment (Stern, 2006). The main focus of AD-

related research, including this study, is on active cognitive reserve because it is a mutable

variable and, therefore, amenable to treatment.

Contributing to the complexity of cognitive reserve are the multiple variables that can

influence it. A common focus of cognitive reserve research is in education levels and, to a lesser

extent, intellectual stimulation at work. It is believed that continued education and occupational

stimulation pushes the brain to continue working and, thus, build more reserve within the brain

over time. This hypothesis has been well supported in the literature as well. For example, Carret and colleagues (2010) aimed to compare performance on memory tests of a high education group and low education group. A total of 1,022 cognitively and physically healthy elderly patients were administered a battery of neuropsychological tests. Following evaluation and analysis, the researchers found that the participants with higher educational and occupational attainment, operationalized as more than 12 years of education or mentally intensive work, performed significantly better on tasks of controlled processes and conceptualization ability compared to participants with lower educational and occupational attainment. In addition, the researchers also found that participants who were engaged in tasks demanding attention generally performed better on the neuropsychological evaluation, supporting the hypothesis that increased cognitive stimulation can be a protective factor against cognitive decline.

Another retrospective review of patients 65 and older obtained from National Alzheimer's Coordinating Center Minimum and Neuropathology Data Sets examined the relationship between education and incidence of dementia. The researchers found that, of the 4,548 patients that were examined, there was an inverse relationship between education, defined as 12 years of education or greater, and incidence of dementia. These results support the hypothesis that patients with the physiological markers of AD, such as amyloid accumulation or brain matter loss, are less likely to present functional markers of AD if they have higher educational attainment (Roe et al., 2007). A third and final study supporting the educational component of cognitive reserve theory was conducted by meta-analysis of observational studies looking at dementia, AD or vascular dementia (VaD) and education over a 31-year period. The meta-analysis, which consisted of 133 studies spanning over a total 437,477 participants, found that education was inversely correlated with risk of dementia. A qualitative analysis of the data also

found that higher education served as a protective factor against developing dementia and, of the

patients who did develop dementia, had a later age of onset of symptoms (Meng & D'Arcy,

2012). The findings from all three of the above studies provide empirical support that continued

education and stimulation can play a critical role in preserving brain functioning.

Bilingualism is a common area of focus in cognitive reserve literature because of its

potential to be studied at many points in life. One example of bilingualism and cognitive reserve

comes from a 2012 study which compared the white matter integrity and grey matter volume

patterns of 40 participants using MRI and diffusion tensor imaging (DTI). The researchers found

that the bilingual participants had lower anisotropy and/or higher radial diffusivity in the inferior

longitudinal fasciculus/inferior fronto-occipital fasciculus bilaterally, the fornix, and multiple

portions of the corpus callosum compared to the monolingual group, suggesting that knowing

two languages can increase the neurological substrates associated with cognitive reserve (Gold et

al., 2013).

Craik, Bialystok, and Freedman (2010) conducted a retrospective study involving patients

diagnosed with AD and examined their background information including their language profile

(bilingual vs monolingual). Following analysis, the researchers found that the bilingual patients

were diagnosed with AD 4.3 years later than the monolingual patients. They also found that the

bilingual patients' first reported instances of cognitive decline occurred 5.1 years later than the

monolingual group, suggesting having multiple languages was associated with delay the onset of

noticeable cognitive decline.

A third and final bilingual study hypothesized that patients who were bilingual and

diagnosed with AD would have more atrophy than a monolingual patient with AD in the same

stage. The basis of this hypothesis is that, because of their cognitive reserve that they could

function at an equivalent level with less brain matter. Utilizing CT scan analysis, the researchers found that bilingual patients had significantly greater amounts of neuro-atrophy than the monolingual group, suggesting that CR associated with bilingual knowledge allowed for better functioning despite the fact that there was even more neuropathology in the bilingual group (Schweizer et al., 2012).

Scarmeas and colleagues examined the role that involvement in leisure activities plays in the etiology or delay of AD. Over a 7-year period, a total 1,772 participants were monitored for their activity level as well as incidence of dementia retrospectively (Scarmeas et al., 2001). During follow-up, researchers found that high participation in leisure activities, such as reading, exercise, or playing games, significantly decreased the risk of developing dementia ($RR = 0.62$, 95% CI [0.46, 0.83]) compared to those who did not participate in leisure activities (Scarmeas et al., 2001). A third study of 469 elderly patients and examined involvement in leisure activities. Over a median of 5.1 years, patients who participated in activities such as reading, playing board games, playing musical instruments, and dancing had a significantly lower risk of dementia compared to non-active patients ($RR = 0.93$, 95% CI [0.90, 0.97]), most notably in measures of memory decline (Verghese et al., 2003). A final study investigated 6,634 elderly Chinese patients for psychosocial risk factors associated dementia. Over a 10-year follow-up period, with two assessment intervals, the researchers found that low educational level, low cognitive function, low occupational status, lack of social interaction or leisure activities, and poor well-being were all associated worse scores on the Mini-Mental State Examination and Activities of Daily Living (He et al., 2000).

A final area that has been shown to enhance cognitive reserve is social interaction. For example, a 2006 study examined data from 2,513 Asian-American patients who were part of

Honolulu Heart Program and the Honolulu-Asia Aging Study from 1965 and analyzed incidence

of dementia starting in 1991 (Saczynski et al., 2006). Using a Cox proportional hazards models,

the researchers found that increased social isolation later in life was associated with a higher risk

of dementia (HR = 2.34, 95% CI [1.18, 4.65]). Another 2000 study examined 1,203 cognitively

healthy elderly Swedish patients over a 3-year period and compared incidence of dementia in

socially engaged vs. socially isolated participants. When adjusted for outside variables, those

with a poor or limited social network had an increased risk of dementia as high as 60% compared

to the socially engaged group (Fratiglioni et al., 2000).

Helmer and colleagues (1999) recruited 3,675 participants from the Personnes Agées

QUID (PAQUID) cohort and examined the role that marital status can play in the incidence of

AD and dementia. The participants were broken up into four groups: widowed, never married,

divorced or separated, and married or cohabitating (Helmer et al., 1999). During a 5-year follow-

up study, researchers found that the never married group had the highest risk of AD and

dementia (RR = 2.68, p = p<0.001), while the married and cohabiting group had the lowest

incidence of AD and other dementias (RR = 1.91, p = 0.018) Another study followed 2,040

French elderly participants over 3 years and assessed for their social engagement and leisure

activity. After 3 years, researchers analyzed any instances of dementia and found that

participants who engaged in activities such as traveling, odd jobs, knitting, and gardening with

other people had a significantly lower incidence of dementia compared to non-engaged

participants, supporting the hypothesis of both social engagement and leisure activity as a

protective factor in dementia prognosis (Fabrigoule et al., 1995). A final study from Wang and

colleagues analyzed data from the Kungsholmen Project and examined participants' activity 6.4

years before their dementia diagnosis. When controlling for outside factors such as race, gender,

ApoE status, and SES, the researchers found that participants who were actively engaged in

mental, social, and productive activity had a significantly lower risk of developing dementia (*RR*

= 0.54, 0.58, and 0.58, respectively, 95% CI [0.34, 0.91]), further asserting that social

engagement and leisure activities play a positive role in log-term cognitive health (Wang et al.,

2002).

One negative aspect of the above contributing factors, education and bilingual language

development, is that not all people have the same opportunities for education and language

development, creating a consideration for equal opportunity, improving the education system and

social justice. However, other cognitively stimulating activities have also been shown to enhance

cognitive reserve that virtually anybody can participate in. For example, a 2002 study examined

over 800 Catholic nuns and priests and followed them over an average of 4.5 years. During that

time, they monitored their level of cognitive activity and the incidence of dementia. During

follow-up researchers found that the more cognitively active participants had a 33% reduction in

risk of developing AD. More specifically, a 1-point increase in cognitive activity,

operationalized by self-report data involving their daily activities, was associated in increases in

global cognition by 47%, working memory by 60%, and perceptual speed by 30% (Wilson et al.,

2002).

Other Medical and Lifestyle Risk Factors and Comorbidities

In addition to the above factors, a number of other comorbid medical and lifestyle factors

have also been shown to have an impact on the risk of dementia. For instance, smoking has been

shown to have a number of health implications associated with risk. In addition to its ties with

lung cancer, stoke, cardiovascular and other diseases, smoking also has neuroanatomical

implications as well. Smoking has been linked to thinning of the prefrontal cortex, a traditional

marker for cognitive decline (Karma et al., 2015) as well as reduced acetylcholine receptors (Brunzell et al., 2015), and overall brain volume atrophy (Durazzo et al., 2017).

With the aforementioned neurological sequelae, is not surprising that smoking has also been linked to cognitive decline. For example, Luchsinger and colleagues (2015) examined the role of smoking and cognition in nondemented elderly patients. The cohort of 791 elderly patients without any cognitive impairment were administered neuropsychological testing over a 5-year period. Researchers then analyzed neuropsychological testing results and compared them to current smokers, past smokers, and non-smokers. The results indicated that current smokers had the most rapid decline in memory performance in comparison to past smokers and non-smokers. In a finding with significant implications for AD, they also found that smokers had an increased risk of developing AD despite their ApoE4 status. The authors concluded that current smokers performed worse on cognitive tasks and had more rapid decline in memory-based performance in comparison to past smoker and nonsmoker populations. The authors also concluded that current smoking habits play a significant role in cognitive decline and the role of ApoE4 can also contribute to the current behavioral risk factors such as cardiovascular management and diet adherence.

In another study, Galanis, Petrovitch, Launer, Harris, Foley, and White (1997) examined if there were any associations between a smoking history and later cognitive impairment, with 3,429 Japanese Americans who were administered the Cognitive Abilities Screening Instrument (CASI) and assessed for smoking habit at each arm of the study (at 1,2, and 3-year marks). The researchers found that nonsmokers and past smokers, including those that had quit during the study, had significantly better CASI scores in comparison to participants who had smoked regularly during the exam period. The results led researchers to conclude that there is a

significant, positive correlation between smoking in middle age and the incidence of dementia and cognitive decline later in life, especially when the smoking is persistent. Furthermore, they concluded that stopping smoking can improve cognitive performance, although long-term smoking produces prolonged effects on cognition.

Finally, a third study screened 17,610 elderly persons over the age of 65 for dementia and later assessed at 2.3 years to examine any cognitive decline over that time. At each year mark, nonsmokers had the smallest decline in MMSE performance in comparison to past smoker and current smoker populations. The researchers also found that cognitive decline associated with smoking was remarkable for both men and women and persons with and without a family history of dementia, suggesting that smoking cigarettes plays a major role in the development of dementia, regardless of genetic/familial risk. The researchers also found that the amount one smoked had a positive correlation with cognitive decline (Ott et al., 2004).

In addition to general cognitive decline, smoking has also been linked to subsequent risk of AD and other dementias. Rusanen and colleagues (2011) examined the correlation between tobacco smoking and the prevalence of dementia. The study of 21,123 participants first assessed heath behavior, including smoking habits, over a 7-year period and then followed the incidence of dementia in the population over another 14-year period. The results indicated that over 25% of the study participants were diagnosed with either Alzheimer's disease or vascular dementia at some point during the follow-up period. The incidence of dementia in the smoking population was significantly higher in comparison to the nonsmoking population by an adjusted hazard ratio of 2.14, 2.57, and 2.78 (other dementia, vascular dementia, Alzheimer's, respectively). The researchers concluded that heavy smoking in midlife increased one's risk of developing dementia by over 100%. Starr, Deary, Fox, and Whally (2007) investigated the role of smoking on IQ

performance by comparing scores early in life and again at 66-years-old. The study of 298

participants analyzed performance on memory and information processing, two major areas

affected by dementia. The results found that lifelong nonsmokers scored 4.9 and 2.6 points

higher on memory and information processing tests, respectively than current smokers, when

adjusting for age-related cognitive changes. The results also found that former smokers also

performed better (3.5 and 1.9 points higher, respectively) than current smokers, further

suggesting that current smoking habits play a significant role in cognitive decline and that

stopping smoking in mid-life can have a further protective influence later in life (Starr et al.,

2007).

A 2010 analysis of biracial patients in Chicago examined the relation between smoking

tobacco and the incidence of dementia. The results indicated that individuals who regularly

smoked tobacco had a significantly higher risk of developing dementia compared to the non-

smoking population. Supporting earlier results, the researchers found that quitting smoking in

mid-life had the same relative rate of dementia diagnosis in comparison to lifelong non-smokers,

suggesting that smoking cessation may also be a protective factor. Finally, researchers found that

smokers with the ApoE4 gene had significantly higher incidence of dementia diagnosis in

comparison to ApoE4 carriers who had not smoked. These findings suggest that tobacco

smoking exacerbates the risk of developing dementia when paired with a pre-existing risk factor

(Cataldo et al., 2010).

Another study from 1999 utilized longitudinal data to examine the relationship between

current and former cigarette smoking and dementia. They also looked at the role of the ApoE4

gene on dementia risk in comparison to members of the smoking population. The results

indicated that a relative risk score of dementia was lowest in the former smoker group ($RR = 0.7$,

95% CI [0.5, 1.1]) while in comparison to the current smoking group (*RR* = 1.9, 95% CI [1.2,

3.0]). When looking at genetic components, the researchers found that current smokers with the

ApoE 4 allele had the highest risk of dementia (*RR* = 2.1, 95% CI [2.1, 3.7]) in comparison to

any other group including the current smoking group with the allele (*RR* = 1.4, CI [0.6, 3.3]).

These results indicate that smoking increases the risk of dementia and that smoking cessation

during mid-life can decrease one's risk of dementia significantly, independent of and,

surprisingly, in excess of gene status (Merchant et al., 1999).

Finally, Juan, Zhou, Li, Wang, Gao, and Chen (2004) conducted a prospective study that

examined the relation between dementia and smoking. The study of 2,820 participants ages 60

and over were administered were assessed for dementia using the MMSE (Mini-Mental State

Examination) and DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders) criteria

for dementia and were classified based on their smoking status (current smoker, past smoker, and

non-smoker). A proportional hazards regression analysis found that current smokers had a

significantly higher rate of dementia prevalence in relation to AD and vascular dementia (*RR* =

2.72; RR = 1.98, respectively, 95% CI [1.53, 5.42]) compared to the non-smoking population

and former smoking population. The study also compared the rate of dementia among smokers

based on the amount that they smoke and found that heavy smokers had a significantly higher

risk of dementia in comparison to the combined medium smoker and light smoker groups (*RR* =

2.56 and 3.03, respectively, 95% CI [1.25, 5.52]), suggesting that not only does smoking serve as

a risk factor of dementia but also the amount that one smokes (Juan et al., 2004).

Diabetes, Hypoglycemia, and Insulin-Resistance

Type 2 diabetes and hypoglycemia are two other risk factors that have been implicated in

the risk of AD and dementia. These conditions have been shown to be correlated with damage to

intracranial blood vessels and reduction in white matter (Havenon et al., 2019). Brain imaging

studies have also shown patients with diabetes have reduced activation in the left inferior frontal

gyrus as well as the left middle frontal gyrus and superior frontal gyrus (Zhang et al., 2014).

There is also significant evidence that both diabetes and hypoglycemia are strongly

associated with cognitive decline and dementia. For instance, a 2017 study by Davis and

colleagues examined the relation between type 2 diabetes and the incidence of dementia,

compared non-diabetic patients. The study of 1,291 patients with diabetes and 5,159 patients

without diabetes examined incidence of dementia over a 13.8 year period and found that patients

with type 2 diabetes had a 1.5% higher incidence of dementia diagnosis compared to non-

diabetic patients (Davis et al., 2017). The researchers also found that the age of diagnosis and

age of death associated with dementia were both lower in the diabetic population compared to

the nondiabetic population (1.7 years and 2.3 years respectively). These results led researchers to

conclude that type 2 diabetes increased the risk that one develops dementia, is diagnosed earlier,

and subsequently succumbs to the disease more rapidly compared to those without diabetes.

These results were further supported by a 2017 study of 102 diabetic patients and 101

nondiabetic patients, examining conversion rates from MCI to dementia over a period of 2 years'

time. The results indicated that diabetic patients had a conversion rate of 57.4% compared to

non-diabetic patients who had a conversion rate of 42.6%. These results lead the authors to

conclude that type 2 diabetes is an independent risk factor for more rapid progression of

cognitive decline from mild cognitive impairment to dementia (Ciudin et al., 2017).

Anna and colleagues (2016) examined which cognitive domains are earliest affected in

patients with diabetes. A cohort of 2,305 cognitively intact participants were administered

neuropsychological testing and examined for diabetic status as well as other vascular diseases

and risk factors. Of that sample, 196 of them had diabetes (75% with uncontrolled diabetes) and

571 had prediabetes. Linear regression analysis found that diabetic patients had lower

performances on processing speed, category fluency, primary memory, and digit span forward.

These performances were even further impaired in the uncontrolled diabetic group. They also

found poorer results in participants who were diabetic and non-ApoE4 carriers. These findings

led researchers to conclude that diabetes begins to influence multiple domains earlier in

comparison to other domains and non-diabetic populations.

A similar study in 2019 conducted by Albai, Frandes, Timar, Roman, and Timar further

examined the role of type 2 diabetes and the risk associated with developing dementia both from

an initial MCI diagnosis and no previous diagnosis of cognitive impairment. A total of 207

individuals with type 2 diabetes were administered the MMSE to evaluate for cognitive

functioning. Of the 20 patients, 43% of individuals were subsequently diagnosed with MCI after

a 3 year period. Further analysis led researchers to conclude that duration of diabetes was

positively correlated with of risk of developing dementia. They also found that patients with

MCI had higher body fat, glucose levels, low-density lipoprotein cholesterol levels; and the

presence of cardiovascular disease compared to the non-MCI group. Such results have led

researchers to further conclude that type2 diabetes patients in the early to late stages of MCI are

more likely to develop dementia compared to a non type2 diabetic population. Finally,

researchers urge glycemic control and diabetes management to prevent such the rapid decline

seen in their study.

These results are consistent on an international level as well. Smolina, Wotton, and

Goldacre (2015) conducted a retrospective study of patients who had been hospitalized in

England from 1998 to 2011. A total of 343,062 people with type 1 diabetes and 1,855,141

people with type 2 diabetes were compared to a nondiabetic control population and analyzed

regarding their subsequent risk for developing dementia. The results indicated that both type 1

diabetes and type 2 diabetes had a higher risk ratio for dementia in comparison to the

nondiabetic population (RR = 1.65 and 1.37 respectively, 95% CI [1.35, 1.68]). They also

found that earlier age of admission (age 30-39) led to higher risk rate of dementia compared to

those hospitalized at a later age (ages 40-49 and >/=80; RR = 7.1, 4.4, and 1.16, for the

respective three groups, 95% CI [1.11, 10.6]). These results led researchers to conclude that

there is a significant relationship between diabetes (both type 1 and type 2) and a diagnosis of

dementia as well as the age of hospitalization and the diagnosis of dementia.

   In a 2016 study of 1193 elderly Mexican patients, Salinas Hiriart, Acosta, Sosa, and

Prince examined the relationship between diabetes and dementia in the Mexican population over

a 3-year period. At the end of the study, the researchers found that type 2 diabetic patients had

nearly twice the risk of developing dementia with a risk ratio of 1.9. They also found that

diabetes was often underdiagnosed in their population and those that had not been diagnosed

with diabetes before the study were at a higher risk of developing dementia than those diagnosed

after leading to the conclusion that accurate detection and diagnosis of dementia is another key

factor in reducing risk (Salinas et al., 2016).

   Finally, hypoglycemia, a common co-occurring condition with diabetes in which the

blood does not get enough glucose, is implicated with cognitive decline. For example, Lee and

colleagues examined 2,001 patients with diabetes over a 15-year period and assessed for

hypoglycemia, cognitive functioning, and brain volume utilizing MRI data. During follow-up,

the researchers found that patients with chronic hypoglycemia had a higher incidence of

dementia and smaller total brain volume in comparison to non-hypoglycemic patients. Such

results indicate that diabetes is associated with increased risk of dementia and certain risk

factors can be identified and better managed (Lee et al., 2018). Hypoglycemia was further the

target of investigation in a 2016 prospective study of 4,540 Korean patients over the age of 60.

During a 5-year period, health information was assessed for a relation between hypoglycemia

and cognitive decline or dementia. Of the type 2 diabetes population examined, 118 patients

had at least one hypoglycemia-related event requiring hospitalization. Of all the participants,

the incidence of dementia was 7.5 cases per 1,000 people. The researchers found that patients

who had experienced a hypoglycemia related hospitalization had a significantly (HR = 2.689,

95% CI [1.080, 6.694], P = 0.0335) higher rate of dementia compared to the non-

hypoglycemic population. They also found that increased number of hypoglycemic-related

events had an even higher positive correlation with the incidence of dementia. These results

lead researchers to conclude that hypoglycemia was an additional risk factor for dementia in

type 2 diabetes (Chin et al., 2016).

Lastly, Mehta, Mehta, and Goodwin (2019) conducted a retrospective longitudinal cohort

study to examine the relation between hypoglycemia and the risk of dementia later in life. They

examined 53,055 elderly patients from the time of their initial diabetes diagnosis over a 9-year

period. Over that period, 3,018 patients experienced a hypoglycemic-related episode requiring

medical attention. The overall incidence of dementia in the sample was 12.7 per 1.000 people.

However, after adjusting for confounding variables, the researchers found that participants that

had at least 1 hypoglycemic episode were at a 27% higher risk of subsequently developing

dementia. An analysis of hazard ratios of the number of hypoglycemic episodes also found an

increased risk of dementia when comparing 2 or more hypoglycemic episodes to 1 hypoglycemic

episode *(HR = 1.5 and 1.26 respectively, 95% confidence interval = 1.03% -2.08%)*. These

results further support the poor diabetes management and hypoglycemia are associated with an increased risk of dementia later in life and those risks increase as hypoglycemic episodes also increase.

In conjunction with diabetes, insulin resistance is a critical aspect of many diabetic patients. Insulin resistance occurs when the cell of the body do not respond to insulin as well and have difficulty metabolizing glucose in the blood; when this occurs, the pancreas has more difficulty compensating for cell's reduced response to insulin, diabetes or prediabetes can occur (Zeitler & Nadeau, 2019). This is particularly relevant to the current study as insulin resistance has significant implications in cognitive health and risk of dementia. Another study in 2011 assessed 50 women, 50-65 years of age, using homeostatic assessment of insulin resistance (HOMA-IR) and MRI to examine relations between insulin resistance and cognitive functioning and brain structure. The researchers found that women with endorsed insulin resistance had smaller right and total hippocampal volume. They also found that women with endorsed insulin resistance had worse cognitive performance on measures of verbal and non-verbal memory (Rasgon et al., 2011). Another study by van Himbergen and colleagues examined the relationship between adiponectin and subsequent risk of dementia. Adiponectin, for reference, is a protein hormone that aids in the metabolism of glucose. Adiponectin is also a major factor in insulin resistance. The study of 541 women (average age of 76 years) were followed over a 13 year period. During the follow-up evaluation, the researchers found that those with higher levels of adiponectin had a higher incidence of both dementia and AD compared with women with lower levels of adiponectin (HR = 1.29 and 1.33 respectively 95% CI [1.00, 1.76], P = 0.054% and 0.050%) (Himbergen et al., 2012). Both of these studies implicate insulin resistance in the risk and etiology of both AD and other forms of dementia.

Hypertension

Hypertension is a third risk factor and medical comorbidity that is empirically tied to cognitive decline and dementia risk later in life. Corrada and colleagues (2017) examined the relationship between age of onset of hypertension and the incidence of dementia. In the study 559 adults were assessed every 6 months for a 10-year period. After the 10-year follow-up, the researchers found that hypertension age of onset was negatively correlated with dementia onset, meaning that as age of onset of hypertension increased, dementia risk decreased. Another study by Wysocki and colleagues (2014) investigated the relationship between hypertension and risk of dementia and determined that, of the 224 older participants in the study, patients diagnosed with hypertension had significantly poorer performance and more rapid decline on the MMSE, compared to patients without hypertension. These results indicated that hypertensive individuals have an increased risk of cognitive decline later in life. It also opens up discussion into the role that controlling hypertension plays in protecting the brain from atrophy and decline. Finally, a Gottesman and colleagues (2014) examined the role of mid-life hypertension, defined as hypertension occurring between 48 and 67 years of age, and the risk of cognitive decline later in life. A total of 13,476 middle aged black and white adults participated in the study which examined hypertensive status and cognitive status over a 20-year period. At 20-year follow-up, the participants with midlife hypertension had a higher rate of dementia compared to non-hypertensive patients operationalized by decline in global cognition ($z = -0.085$ and 0.005 respectively). They also found that borderline hypertensive patients were at a higher risk than non-hypertensive patients. Finally, the researchers found that patients who poorly managed their hypertension had worse global cognition compared to the better managed hypertensive group ($z = -0.050, -0.079$ respectively). All of these results further indicate that hypertension is associated

with an increased risk of dementia later in life.

Interaction of Medical Risk Factors and Lifestyle

Interestingly, there is also empirical evidence to suggest a complex interplay between some of these lifestyle and medical factors and AD and other dementias. Lunchsinger and colleagues (2005) examined the role of vascular risk factors in relation to the incidence of dementia. The researchers analyzed 4 different domains of vascular risk: diabetes, smoking, hypertension, and heart disease. Over a 5.5-year period, 1,138 individuals without a dementia diagnosis were followed and examined for the above four risk factors. After 5.5 years, all four risk factors were positively correlated with the incidence of dementia when individually analyzed. The two risk factors with the highest risk ratio of dementia were smoking and diabetes (RR = 2.0 and 2.4, respectively, 95% CI [1.3, 3.2]). The researchers also found that individually having more risk factors were associated with a higher risk of developing dementia (RR =3.14, 95% CI). These results led researchers to conclude that all four vascular risk factors were associated with an increased risk of dementia, with diabetes and smoking being the most prominent. They also concluded that risk of dementia increases as the number of risk factors increase, leading researchers to advocate for better management of controllable lifestyle factors that contribute to vascular disease (Luchsinger et al., 2005).

Current Preventative Treatment Research

Fortunately, a number of studies already exist that lay the groundwork for the current study. Cornerstone studies such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability study (FINGER; Ngandu et al., 2015) and) has shown that combined behavioral intervention can have significant cognitive impacts in the domains of neurodegeneration delay/prevention. The U.S. Study to Protect Brain Health Through Lifestyle

Intervention to Reduce Risk (U.S. POINTER) is currently attempting to replicate these findings. These two research groups, in conjunction with six other centers, are working together in a world-wide consortium known as World-Wide FINGERS (WW-FINGERS) to combine efforts and collect data on lifestyle and medication interventions to delay and hopefully prevent cognitive decline (Rosenberg et al., 2020).

The FINGER study was a groundbreaking project conducted from 2013 to 2018 that followed individuals at heightened risk of dementia and enacted a 2 year intervention program. The study of 1,260 individuals, ages 60-77 years, were obtained from a previous population-based survey and were randomized evenly (1:1 ratio) into an experimental group and control group, consisting of general health advice. It was also noted that there was no significant demographic differences between groups including sociodemographic, vascular, or lifestyle characteristics, although there were slightly more women recruited than men (53.3% to 46.7%). Of the participants in the sample, 66% had a history of hypertension, 50% reported high systolic blood pressure, 54% had high cholesterol, 30% met the criteria for obesity, and 29% got less than 2 days of exercise per week. Cognitively, the mean score of participants on the MMSE in the experimental and control was 26.7. A total of 1,190 participants completed the study, with an even distribution of retention in the control and experimental group. The primary goal was to examine changes in neuropsychological testing performance, incidence of dementia, disability, use of health resources, depression, medical management, and neuroimaging. More specifically, the experimental group saw 83% higher scores on tests of executive functioning and 150% higher scores on tests of processing speed in comparison to the control group (Ngandu et al., 2015). They also found that the control group had a higher risk of decline in overall cognition, executive functioning, and processing speed ($OR = 1.31$, 95% CI [0.44, 1.31]) compared to the

experimental group (Ngandu et al., 2015). Of additional importance was that these results were

not exclusive to any sociodemographic group and had a universal benefit regardless of

cardiovascular risk status. In addition to cognitive outcome measures, secondary measures of

behavioral change were also significant (Rosenberg et al., 2018). More specifically, self-reported

adherence in the experimental group showed behavioral improvement in nutrition adherence

(100%), physical exercise (90%), cognitive training (85%), maintenance of vascular risk factors

(87%), with the majority of participants (72%) acknowledging adherence on all domains

(Ngandu et al., 2015). These results provide empirical evidence that behavioral intervention,

addressing modifiable risk factors can yield significant cognitive protection across time and, as

such, should be examined further in future research.

The U.S. POINTER study is an ongoing research project that is currently attempting to

replicate the findings of the FINGER study in the U.S. population. This study is aimed at

understanding the role that lifestyle modification can play in decreasing the risk of cognitive

decline into later adulthood. With the study expected to conclude in 2023, researchers expect to

find studies similar to that of the FINGER study and provide further insight into the role of

behavioral modification on the risk of dementia (Alzheimer's Association, ND).

In addition to the FINGER and U.S. POINTER studies, a number of other studies in the

WW-FINGERS consortium are addressing critical aspects of dementia prevention by replicating

and expanding on the FINGER study. For example, the Australian-Multidomain Approach to

Reduce Dementia Risk by Protecting Brain Health with Lifestyle Intervention (AU-ARROW)

study is a two-year multi-domain study that is working in conjunction with the U.S. POINTER

study, applying the same interventions and hypotheses in the Australian population (Rosenberg

et al., 2019). The Multimodal Interventions to Delay Dementia and Disability in Rural China

(MIND-CHINA) study is another collaborative project, specifically aimed at addressing multi-domain intervention for cognitive decline specifically in 3,500 members of the rural communities in China. It will consist of two different arms. The first arm of the study focuses on specifically targeting hypertension, diabetes, and high cholesterol, whereas the second arm is targeting smoking, physical exercise, social and mental stimulation, and improving diet (Kivipelto et al., 2018).

The Singapore Intervention Study to Prevent Cognitive Impairment and Disability (SINGER) initiative aims to replicate the results of the FINGER study with a specific focus on culturally appropriate norms and diversity within dementia research (Chen et al., 2017). Another interesting aspect of this study is that it is spanning over the course of 6 months rather than 2 years, thus abbreviating the treatment to a shorter, more manageable format. Another study considering issues of culturally appropriate norms of the FINGER study is the Goiz Zaindu: A FINGER-Adapted Multidomain Lifestyle Intervention to Prevent Dementia in the Basque Country (GOIZ-ZAINDU) study. This one-year multi-domain study is attempting to implement the interventions of the FINGER study in the Basque population in Spain and assess the feasibility of further research within this population. Specifically, the researchers of the GOIZ-ZAINDU study will be addressing issue of vascular risk factors, diet, nutritional compliance, and physical exercise in conjunction with a cognitive training program (Tainta et al., 2019).

The Multimodal Preventive Trial for Alzheimer's Disease (MIND-ADmini) is another interesting study which is based on the FINGER study. Unlike many studies in this consortium, the participants of this study are in the prodromal stages of AD and, as such, will allow researchers to gain insight into the effectiveness of such interventions can have on already present symptoms such as under-baseline memory loss. This study will also provide data from

participants in multiple countries including Finland, France, Germany, and Sweden, furthering these studies' generalizability (University of Eastern Finland, 2018).

Another unique study that is part of the WW-FINGERS consortium is the Maximizing Technology and Methodology for Internet Prevention of Cognitive Decline: the Maintain Your Brain (MYB) trial in Australia (Hefernan et al., 2019). This study is following 6,236 participants and implementing similar interventions from the MIND-ADmini studying an online, internet-based format, providing insight into the efficacy of remote intervention for dementia prevention. In addition to its unique design, it also has a number of publications supporting it methodology as well. For example, a 2020 study by Lancaster and colleagues aimed at utilizing the Research Food Diary app as a method of tracking dietary patterns among adults ages 55-75. The researchers found that the app was an accurate tool for tracking intake of protein, calcium, vitamin B12, zinc, and dairy food servings compared to traditional self-report tools and dietician administered interviews, indicating that the use of applications among older adults can be a useful tool for tracking dietary intake (Lancaster et al., 2020). The researchers are also utilizing behavioral modification in conjunction with a brain training system to enhance cognitive stimulation (Walton et al., 2019). Finally, a 2018 study examined the reliability and validity of online administration of the Mediterranean Diet and Culinary Index (MediCul) "among adult participants. The researchers found that the MediCul program had strong validity and reliability in comparison to other more validated measures of adherence to diet among older adults. (Radd-Vagenas et al., 2018). These results are particularly relevant as it shows that older adults can successfully implement technology into diet tracking.

Motivational Interviewing

A core component of evidence-based dementia prevention strategies is that the focus is,

mainly on modifiable variables, involving behavior related to health and lifestyle. Equally

important is how these behaviors will be changed. Health and lifestyle behaviors are conditioned,

long-term habits. It is not surprising that habits are difficult to break, especially when many of

these habits (e.g. poor diet and lack of exercise) are longstanding. Because of these barriers to

change, clinicians and researchers alike are in need of tools that will motive others to enact such

changes to their lives (Hubley & Dimidjian, 2008).

Motivational interviewing (MI) is one widely-accepted model that has achieved status of

evidence based proactive (EBP) for ameliorating many habitual behaviors and mental health

disorders, including substance use disorders, depression, and anxiety (Miller, 2013).

In support of its clinical utility, MI has accrued substantial empirical evidence. For

example, a 2018 meta-analysis by Magill and colleagues (2018) aimed to assess the efficacy of

motivational interviewing among various patient populations. The review, which consisted of 58

reports, describing 36 primary studies, found that MI-skilled therapists elicited more client

change talk as well as sustain talk, whereas therapists not skilled in MI elicited lower change and

less sustain talk among patients. Another meta-analysis from 2017 investigated 144 studies

examining MI among patients with substance use disorders. The review found that MI was most

effective at decreasing or eliminating alcohol and tobacco use compared to education and

traditional talk therapy. The review also found that, overall, MI was an effective tool for other

forms a substance use such as cannabis, methamphetamine, and opioid use. Finally, the review

found that MI was useful at treating addictive behaviors such as gambling (DiClemente et al.,

2017).

In addition to its overall utility in treating substance misuse, motivational interviewing

has been shown to be effective for a number of various mental health conditions. For example,

MI has been used has been to assist patients with depression. This was evidenced by a 2016

study of primary care patients with major depressive disorder. Participants were assigned to

either a standard care group or a motivational interviewing group. At a 36-week follow-up,

patients in the MI group had significantly reduced depression and remission rates evidenced by

the PHQ-9 compared to the TAU control group (Keeley et al., 2016). Patients with anxiety have

also benefitted from MI. One of the best examples of its effectiveness among patients with

anxiety comes from a 2018 meta-analysis of 12 studies, which examined how MI contributes to

outcomes among patients with anxiety disorders. The review found that every study examined

showed that MI, in conjunction with cognitive behavioral therapy, had the best outcomes when

examining overall anxiety reduction. They also found that there was no difference among groups

on retention rates and no difference among types of anxiety disorders. These findings suggest

that MI can be an effective tool across multiple forms of anxiety and that there is an additive,

synergistic effect of adding CBT to MI (Marker & Norton, 2018).

     MI will be a core tenant of the intervention of the current study. MI is a counseling style

aimed at helping clients identify and increase the salience of their own, unique motivation, with

the ultimate goal of allowing them to change their behaviors in the direction of their own

specific, adaptive aspirations.

     All of these concepts can be characterized by what Miller and Rollnick (2013) describe as

the "Spirit of Motivational Interviewing." The spirit of MI is a way of being that is the building

block of all interventions and conversations that take place in MI. It consists of four major

elements that include collaboration, evoking the client's ideas of change, emphasizing autonomy,

and practicing compassion. Collaboration is important as it build rapport with the client and

allows the clinician to take on the client's point of view. By doing so, the clinician and client are

able to better explore the client's thoughts and actions. Evoking the client's ideas of change is

another crucial aspect of MI as it allows the clinician to draw out any thoughts that may aid in

the client discovering their own reasons and determination to change. Autonomy is a third key

feature that is characterized by acknowledging the power of change being in the client's hands

and relies on the client to make their own independent choices regarding their actions. Finally,

compassion is the fourth key feature that is characterized by genuinely promoting the well-being

of the client the clinician is working with. Effective compassion involves understanding one's

experiences, values, and motivations without judgement and using them to help the client

achieve their goals. All four features are critical to MI and, as such, encompass the spirit of the

practice (Miller & Rollnick, 2013).

One of the major tools used in motivational interviewing that will be utilized in the

current study is the Values Card Sort exercise. The Values Card Sort exercise is an intervention

that allows a client to explore their most pertinent values that underlie their motivation. The

exercise has clients classify 83 different values as very important, important, or not important to

them. After they classify all the cards, they are then instructed to select the ten most important

values to them from the list they have just made. Finally, clients are then asked to rank their ten

cards in ascending order by importance. This exercise allows clients to materialize their values

and explore a wide range of motivations that can play a major role in their behavior. By

identifying these major values, clinicians are able to use this data to help motivate clients to

change their behavior long-term (Miller et al., 2001).

Behavioral is accomplished by addressing any ambivalence the client has and helping

them to tip the scale in the direction of change. MI is a direct, goal-oriented technique that sets

clear and achievable goals for the client to attain. As such, MI has five major principles which

will ultimately guide the intervention of this study. The five principles include Express empathy

through reflective listening, develop discrepancy between clients' goals or values and their

current behavior, avoid argument and direct confrontation, adjust to client resistance rather than

opposing it directly, and support self-efficacy and optimism.

According to Miller and Rollnick (2013), the first principle of MI is to express empathy.

Empathy is a critical tool to convey understanding and building a therapeutic alliance. Although

empathy can be accomplished through multiple methods, a common way of building empathy is

through reflective listening, clarification, and summarizing. It has also been shown that empathy

is a critical part of achieving positive treatment outcomes (Simper et al., 2020).

The second principle or MI is to Rolling with Resistance. Resistance is anything that the

client does that interferes with the therapeutic alliance and the client's ability to achieve their

goals. Goal-interfering behavior can include language that is consistent with the maladaptive

behavior, or "sustain talk" such as arguing, interrupting, denying and ignoring (Miller &

Rollnick, 2013). Resistance is decreased through the use of non-confrontational methods

(Hubley & Dimidjian, 2008). MI advocates accepting client statements of resistance rather than

confronting them directly, with the goal of promoting language about healthy change or "change

talk". Increasing the frequency and intensity of change talk is a crucial goal in MI because such

verbalizations predict actual, adaptive behavior change (Amrhein et al., 2003).

The third principle of MI is to develop discrepancy (Miller & Rollnick, 2013). This

critical stage has the clinician elicit an inner-argument within the client outlining their values and

goals. The clinician and client collaboratively explore how these values and goals are not

congruent with their presenting behaviors and guides them through this thought process. A major

way this is accomplished is by outlining the pros and cons of the problem behavior and

differentially responding to emphasize discrepancies identified by the client (Hubley & Dimidjian, 2008). For example, someone may note that they value their health but engage in poor dietary behaviors. Having a clinician point out these discrepancies can play a critical role in helping these patients obtain a greater level of self-awareness. This will become increasingly relevant to the present study and modifying lifestyle factors diet to risk of dementia.

The fourth principle of MI is to support self-efficacy (Miller & Rollnick, 2013). The major tenant of this principle is to instill within the client the belief that they can succeed. This principle sets out to increase the client's perception of their skills, resources, and abilities that they may access to achieve their desired goal. The fifth and final principle of MI is to avoid argumentation (Miller & Rollnick, 2013). This principle stipulates that, although it may be tempting at times, the clinician should avoid arguing with the client. It is feared that arguing with the client could lead to withdraw and decrease rapport that is critical to the treatment's success or create psychological reactance and further increase sustain talk (Hubley & Dimidjian, 2008). Rather, the clinician should take a supportive and strength-based approach, develop discrepancy and resolve discrepancy in the direction of adaptive change. This is done through respectful reflection and clarification of the client's values, goals, and thoughts, instead of and explicit challenge (Miller & Rollnick, 2013).

Open questions, affirmation, reflective listening, and summary reflections (OARS) is a critical aspect of MI that is defined as a combination of techniques and skills that aid in the motivational interviewing approach and help build rapport, assess a client's needs, and individualize a client's treatment plan (Evenden, 2018). These techniques are culturally sensitive and client-centered (Miller & Rollnick, 2013).

In MI terms, the goal of the OARS skills is to elicit change talk, which predicts actual

behavior change. One skill that is often utilized in MI is using open-ended questions. Open-ended questions are inquires that require elaborated responses and cannot be answered with simple, one-word responses such as "yes," "no," or "maybe." By utilizing these types of questions, a client is more inclined to elaborate and provide more useful information for both their own reflection and the clinician to guide change talk (Evenden, 2018).

Another skill associated with MI is the use of affirmations. Affirmations communication of something positive about the client and gives credit or acknowledgement in a genuine and non-condescending manner (Evenden, 2018). For example a patient who is struggling to find the motivation to exercise, may be responsive to the acknowledgement of things they have tried already and may be more motivated to continue to work on their goals instead of giving up.

A third skill used in MI is the use of reflections. Reflections are statements made to the client mirroring back to them the content, process, or emotion in their communication (Evenden, 2018). A reflection is always a statement, rather than a Socratic question and, as such, the inflection at the end of a reflection drops off (Miller & Rollnick, 2013). When using MI, the clinician wants the majority of their communication to be in the form of reflections and not questions (Evenden, 2018). This contrasts somewhat with traditional CBT, which tends to be a bit more Socratic (J. Beck, 2013).

A fourth skill utilized in MI is summarizing, which in essence, is a long reflection (Evenden, 2018). Summaries can be used to make a transition in a session, to end a session, to bring together content in a single theme, or just to review what the client has said (Miller & Rollnick, 2013).

Although eliciting change talk may be considered a specific skill, all of the aforementioned skills are intended to elicit such. Change talk is achieved through the above and

a number of other sub-skills such as exploring the problem, looking backward, looking forward, considering importance, looking at the discrepancy between values and behavior, pro and con listing, and looking at extreme scenarios. Nonetheless, all of these skills have the intention of developing the mental framework for the client to increase change talk and, ultimately, change their behavior in the direction of their most cherished values and desirable goals (Evenden, 2018; Miller & Rollnick, 2013).

Motivational interviewing has been shown to enhance mood and behavior in behavioral healthcare populations. For example, Kulsum and colleagues (2016) conducted a study of 461 patients that examined the effect of MI on mood and behavior following stroke. During follow-up, the researchers found that MI was associated with better mood, quality of life, adjustment, and resource use. They also found that the MI group was more compliant with treatment and had a higher rate of follow-up evaluation attendance than the control group. Another study by Ponsford and colleagues studied a sample of 75 patients with a mild-severe traumatic brain injury to assess the efficacy of MI. Following a 9-week intervention program, participants in an MI and CBT group had significantly better scores on anxiety and depression, in comparison to the CBT only and the waitlist control group. The MI and CBT group also performed better on the stress and depression scales. Finally, at a 30-week follow-up, the MI and CBT group had overall better psychosocial functioning compared to the other two groups, suggesting that motivational intervening can be a useful tool when work with patients with traumatic brain injury and, once again demonstrating the synergistic and enduring benefits of combining CBT and MI (Ponsford et al., 2016).

Finally, MI has been effective at eliciting behavioral change related to a number of variables in the present study. The most commonly studied behavior related to the current study

is physical activity. For example, Arkkukangas and colleagues (2018) examined the role of MI and exercise among older adults. The study followed 114 older adults over a 52-week period and assigned them to either a MI group or a no treatment control group. The researchers found that MI was associated with increased physical activity and, also, that a better baseline of physical activity was a predictor of better outcomes, suggesting that MI is a useful tool at increasing exercise among this vulnerable group but that pre-treatment behavior should be a consideration.

Another study examined how MI can be implemented to increase both exercise and leisure time among adults. The study of 31 patients occurred over a 15-month period also examined hypertension in addition to changes in exercise. Following 15 months of the MI intervention, the researchers found that the participants had increased levels of physical and leisure activity, improved systolic and diastolic blood pressure, heart rate, and BMI (Sjöling et al., 2011). Finally, Fatemah and colleagues (2018) examined the impact of diet and motivational interviewing on obesity among 96 participants. Following an 8 week intervention period, the researchers found that MI was associated with improved blood pressure, decreased BMI and waist circumference, and improved diet adherence in comparison to the control group.

Cognitive Behavioral Therapy in Primary Care

Cognitive Behavioral Therapy (CBT), is a theoretical orientation in psychology that focuses on the inter-relations between thoughts, behaviors, and emotions which allows patients to become more aware of inaccurate or negative thinking that can be impacting their psychological well-being (Beck, 2012). One of the most important aspects of CBT, however, is its level of empirically based support to treatment of a variety of conditions such as depression, anxiety, post-traumatic stress disorder, sleep disorders, and eating disorders. More importantly, with regards to the current study, CBT is also effective at eliciting change in specific behaviors

known to be implicated in AD and cognitive decline (Leahy, 2017).

The most commonly cited use for CBT revolves its use with stress, more specifically depression and anxiety. Gould, Coulson, and Howard conducted a meta-analysis to assess the efficacy of CBT for depression in older adults. The analysis yielded a total of 23 studies, all of which found CBT to be the most effective tool at treating depression compared to a treatment-as-usual and waitlist control group. They also found the same patterns of results over a 6-month follow-up period as well, suggesting long-term treatment effects. Similar results have also been displayed with anxiety. Gould, Coulson, and Howard (2012) also conducted a meta-analysis of twelve different studies of anxiety among patients 65 years of age and older. The researchers observed similar results, suggesting that CBT was more effective at treating anxiety in comparison to a treatment-as-usual and waitlist control group. They also found CBT to be the most effective form of therapy in comparison to an active control group at 6-month follow-up, suggesting further long-term effects (Gould, Coulson, & Howard, 2012b).

Cognitive behavioral therapy for insomnia (CBT-I) helps identify and replace thoughts that impede one's ability to get sustained and fulfilling sleep. CBT-I has also been shown to be tremendously effective with addressing poor sleep patterns and behaviors. This is particularly relevant as sleep is one of the major outcome variables of the current study. One meta-analysis by Mitchell and colleagues (2012) reviewed 5 different CBT-I studies and assessed for their efficacy among sleep deprived patients. The researchers found that 3 of the 5 studies concluded that CBT-I was a more effective treatment for disordered sleep than benzodiazepines. They also found that CBT-I had significantly better long-term outcomes among sleep-deprived patients in studies ranging from 6-24 months. More specifically, the CBT-I was associated with improvements of 30 to 45 minutes in sleep latency and 30 to 60 minutes in total sleep time.

In addition to its empirical evidence for specific diagnoses, CBT is effective at increasing exercise. One of the most pertinent studies examined CBT and its role of promoting exercise in older adults (average age 64.5); over a 3 month intervention period, participants in the cognitive behavioral intervention group showed increases in exercise, exercise tolerance, health status, and self-efficacy compared to the non-treatment control group (Atkins, 1984). A more recent study from by Brawley, Rejesky, and Lutes (2000) prescribed 60 older adults to either a waitlist control group or group-mediated cognitive behavioral therapy to increase physical activity and compared their exercise patterns during a 9-month follow-up. At the follow-up evaluation, the CBT group had higher frequency of weekly physical activity, had higher aerobic power, and higher self-reported quality of life in comparison to the waitlist control group (Brawley, Rejesky, & Lutes, 2000). A final pilot study examined the effects of CBT on exercise among older adults and compared them to a non-treatment control group; at the 6-month follow-up, the participants in the CBT group had increased frequency of self-reported exercise behavior in comparison to the control group (Schneider et al., 2004).

Diet adherence and weight loss has been another area that CBT has been shown to be effective. For example, a 2008 study examined whether or not CBT was an effective tool at improving body composition, diet, and physical activity in 47 overweight individuals. Following a 10 week intervention period and 10 week follow-up period, the CBT group, in comparison to a waitlist control, showed decreased soft drink consumption, waist circumference, BMI, overall weight, and abdominal fat (Tsiros et al., 2008). There is also some research regarding CBT's efficacy at adapting to specific diets, such as the Mediterranean diet. Corbalan and colleagues aimed to assess the utility of CBT for treatment of obesity and determine obstacles related to weight loss, with a specific focus on adherence to the Mediterranean diet. The study, which

consisted of 1,406 obese patients, ages 20-65 years of age, were prescribed to a 34-week CBT group focused on diet and weight loss. Following the treatment program, participants in the experimental group saw an average 7.7kg reduction in weight. Additionally, 89% of CBT participants reported adherence to the Mediterranean diet. The researchers also found that the most common barriers to weight loss and diet adherence were low motivation and stress-induced eating (Corbalan et al., 2009). This is particularly relevant as motivational interviewing may be a useful tool at addressing these barriers in our proposed study.

Finally, medical adherence and compliance is a final area that has evidence to CBT's beneficial effects. One example of this is hypertension. Eisenberg and colleagues conducted a meta-analysis of studies examining the role of CBT in hypertension management. Of the 26 studies utilized, including a combined total of 1,264 participants, the researchers found CBT, on average decreased systolic and diastolic blood pressure by 2.8 mm compared to the placebo control groups which only saw a 1.3 mm change, suggesting that CBT can be an effective tool at managing hypertension (Eisenberg et al., 1993). Similar results have been seen in diabetic patients. One 2014 study aimed to assess for the efficacy of CBT with regards to adherence and depression among patients with type-2 diabetes. A total of 87 participants were randomized to either a treatment-as-usual control group or the experimental CBT group, which spanned 9-11 sessions. At a 4-month follow-up, the CBT group displayed a 20.7% increase in oral medication adherence, 30.2% increase in self-monitoring of blood glucose, a 6.22 point decrease in the Montgomery-Asberg Depression Rating Scale, a 0.74 point decrease on Clinical Global Impression, and a 0.72 unit decrease in A1C. Similar results were also seen a 4, 8, and 12-month follow-up (Safren et al., 2014). Finally, it has been long understood that CBT can aid in smoking cessation. For example, a 2010 study examined the effectiveness of CBT with regards to

smoking cessation among African Americans. A total of 154 African Americans (average age of 44 years) were randomly assigned to either a CBT group or an educational control group. Following a 2-week intervention period, the point prevalence abstinence of the CBT group was 24% greater than the control group immediately after intervention, 14% greater at the 3-month follow up, and 17% greater at the 6-month follow-up (Webb et al., 2010). These results build on previous evidence to show that CBT is an effective tool at aiding in smoking cessation. Overall, these results provide further support to demonstrate that CBT is an effective tool at eliciting behavioral change necessary to be successful in our present study.

One of the primary goals of this study is to incorporate the behavioral changes seen in the FINGER study into evidence-based treatments such as CBT and MI. All of the behaviors seen in the FINGER study and other studies from the WW-FINGERS program have evidence to suggest CBT and MI are effective tools at eliciting these changes long-term. As such, it is critical to explore these skills in depth, in conjunction with the standard behavioral implications we intend to target in our treatment.

CHAPTER 3: METHODS

Study Design and Study Justification

This study employed a mixed method design. A quantitative, experimental study using a pretest, posttest, follow-up study design was utilized to assess the efficacy of the MI-CBT protocol for a group of individuals with a heightened risk for dementia and the aforementioned hypotheses were investigated. Later, a qualitative analysis analyzed relevant cognitive and behavioral factors in treatment and outcomes.

Participants

Participants were recruited through Research Match, social media posting, a medical college-based family medicine clinic in a large Northeastern city, and flyers marketing a study to preserve memory and promote brain health. Participants who scored a six or higher on the CAIDE Dementia Risk scale were contacted to participate in the study. A total of 25 participants were recruited and consented to participate.

Inclusion and Exclusion Criteria

Participants were eligible to participate in the study if they were 40-60 years of age and fluent in English. The age range for recruitment was chosen due to the research indicating that the physiological changes to the brain associated with AD begin to occur during middle age (ages 40-60 years). Participants must have scored at least a 6 on the CAIDE Dementia Risk scale, consistent with the FINGER study. Given the telehealth format of the program, participants also needed access to a device (e.g. computer or smart phone) with reliable internet access. Participants also needed to be under the care of a primary care provider and provided contact information for their provider in the event of any adverse medical effects related to the study.

Participants were excluded if they had a documented diagnosis in the medical record or

by self-report of an intellectual disability, attention-deficit/ hyperactivity disorder (ADHD,

autism spectrum disorder, any form of dementia or mild cognitive impairment, psychosis, active

substance use, or a terminal medical condition that required the individual to receive ongoing

medical treatment (APA, 2013). Participants were also be excluded if they were taking any

medications with the specific purpose of improving memory including but not limited to Aricept,

Exelon, and Razadyne, and memantine. They were also be excluded if they had received any

form of neuropsychological testing within one year of pretest data collection, to reduce the

probability of practice effects on study measures.

Measures

The Montreal Cognitive Assessment

The MoCA is a brief cognitive screening tool used in a majority of healthcare settings to

obtain an initial cognitive profile of a patient. The MoCA is a 30-point test that can be

administered either electronically or via paper-and-pencil administration and assesses for

functioning in the cognitive domains of attention and concentration, executive functions,

memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation

(Julayanont et al., 2013). All of these cognitive domains are critical areas of dementia prevention

and can be a good indicator of risk of cognitive decline (Lichtenberger et al., 2000). The memory

domain is assessed via a short-term list learning task and assessed for immediate and delayed

recall. The visuospatial domain is assessed by having the patient draw a clock at a set time as

well as a 3-dimensional object. Attention, concentration, and working memory are assessed

using a target tapping/sustained attention task, a serial subtraction test, and an abbreviated

version of the digit span forward and backwards test. The language domain is measured through

a confrontational object naming test as well as a sentence repetition test and semantic fluency task. Orientation is measured by asking the client about the date and the city. Finally, executive functioning is measured by a combination of tasks on cognitive shifting through an abbreviated version of the Trails B test, phonemic fluency, and a two-item verbal abstraction task. Coinciding with these domains, abstract thinking is measured by an abbreviated version of the similarities test (Nasreddine et al., 2005).

Scoring of the MoCA is convenient. The MoCA is scored on a 30-point scale based on the weight of each item tested. A score of 26 or higher constitutes normal cognitive functioning in most cases. Individuals with mild cognitive impairment had an average score of 22.1 while patients with AD had an average score of 16.2. Level of education is also a major consideration in the MoCA as individuals with a high school diploma or higher typically score higher on the MoCA. As a result of these inconsistencies, the new version of the MoCA has test administrators give participants an extra point if they have less than 12 years of education (Nasreddine et al., 2005). Finally, the MoCA has been shown to be adapted to a remote/telehealth format. This is especially important with regards to the current study as the entire study was conducted virtually due to the COVID-19 pandemic.

The MoCA is a psychometrically validated measure. For example, a 2012 comparison study of the MoCA and MMSE found that the MoCA was significantly better at differentiating patients with vascular dementia compared to the MMSE (AUC (MoCA full version) = .950; 95% CI = [.868, .988], AUC (MMSE) = .860; 95% CI [.754, .932]) (Freitas et al., 2012). An additional study of cardiovascular patients with mild cognitive impairment found a 100% sensitivity rate at diagnosing amnestic MCI and 83.3% for multiple-domain MCI, with specificity rates between 50 and 52% (McLennan et al., 2010). Another study found fair to good

concurrent and predictive validity between the MoCA and Stroke Impact Scale, suggesting

strong psychometric validation of the measure (Wu et al., 2019).

The Sleep Disorders Symptom Checklist-25

The Sleep Disorders Symptom Checklist-25 (SDS-CL-25) is a 25-item, self-report

screening questionnaire used to assess sleep patterns and the presence of sleep disorders in adults

(Klingman et al., 2017). The 25 items of the SDS-CL-25 are based on the DSM-5 criteria for 13

different sleep disorders. These disorders include advanced sleep phase syndrome, delayed sleep

phase syndrome, obstructive sleep apnea, restless legs syndrome/periodic limb movement

disorder, narcolepsy nightmare disorder, night terror disorder, REM sleep behavior disorder,

sleep-related temporomandibular joint movement, sleep insufficiency disorder, shiftwork sleep

disorder, unspecified excessive daytime sleepiness, and fatigue. These disorders are grouped into

major categories of insomnia, circadian rhythm disorders, narcolepsy, sleep apnea, parasomnias,

restless leg syndrome, and sleep wake disorders. There is additional significance of the ninth

item of the measure which specifically probes into its functional impact on the respondent and

allows the test administrator to understand the level of distress exhibited by the subject.

The SDS-CL-25 consists of 15 items on a 5-point Likert scale ranging from 1 (strongly

disagree) to 5 (strongly agree) (Klingman et al., 2017). Symptoms that occur more than three

times per week are generally considered positive for sleep pathology, whereas symptoms that

occur less than three times per week are generally considered negative (Seewald et al., 2020).

The measure also assesses for other relevant sleep-related variables, including age, gender,

height, weight, work characteristics, bed partner(s), and general nightly sleeping patterns.

Finally, the SDS-CL-25 is parsimonious and logistically useful, taking approximately 3-5

minutes to administer (Klingman et al., 2017). The SDS-CL-25 has also been validated in a 2017

study by (Klingman et al., 2017), which found sensitivity and specificity rates of sleep disorders

to range between 0.64 to 0.88.

The Lent-Hope Diet Questionnaire

Diet data was operationalized utilizing the Lent-Hope diet Questionnaire. This

questionnaire was developed for this study by Dr. Michelle Lent alongside Nicholas Hope, the

responsible investigator (RI). Dr. Lent is a board-certified clinical psychologist who specializes

in feeding and eating disorders, behavioral treatment of binge eating, and cognitive behavioral

therapy. The intention of the measure is to assess for adherence to the MIND diet, which was the

core focus of the diet portion of the study. Participants of this study were given a self-report,

Likert-type instrument documenting how much they believe they have consumed the foods and

nutrients consistent with the MIND diet; and how much they believe they had avoided foods that

the MIND diet discourages. Scores ranged from 15 (least adherence) to 75 (most adherence).

Step-Up Mobile Application

Exercise was operationalized as the number of steps walked on a daily basis. Walking is a

relevant way of operationalizing exercise as it has sufficient evidence to its efficacy, it is easily

accessible, and can be easily tracked using different forms of instrumentation such as pedometers

and mobile applications. Walking is one of the most commonly cited sources of cardiovascular

exercise (Hacket et al., 2018). Walking data was quantified by using a mobile phone application

called StepUp. StepUp uses a phone's built-in fitness tracker to count one's steps while in the

participant's hand, bag, or pocket. Step-Up is compatible with all Apple and Android

smartphones. It is particularly useful as it allows participants to share their data with others. In

the case of the current study, participants were asked for permission to share their step data with

the responsible investigator. Baseline data began during the first week of treatment and then

collected weekly at the beginning of each group. Step data was then collected at the post-test

data collection and three-month follow-up.

Patient Health Questionnaire

The Patient Health Questionnaire (PHQ-9) is a 9-item questionnaire that screens for

presence and severity of depression. The items are based directly on the diagnostic criteria for

major depressive disorder (MDD) in the Diagnostic and Statistical Manual of Mental Disorders

5th edition (DSM-5) (American Psychological Association, 2013). More specifically, the PHQ-9

assesses for apathy, feelings of sadness, sleep disturbance, fatigue, appetite disturbance, and low

self-esteem, trouble with concentration, psychomotor retardation, and suicidal ideation. The 9-

item measure utilizes a 3-point Likert scale ranging from 0 (*not at all*) to 3 (*nearly every day*). It

follows up with an unweighted question addressing the impact of the symptoms listed in the

questionnaire and how it impacts their daily functioning. Scoring of the PHQ-9 ranges from a

minimum score of 0 to a maximum score of 27. Any score under 5 indicates absence of clinical

depression. A score of 5-9 indicates minimal, symptoms which may be addressed through

support and education. A score of 10-14 indicates some mild depression or dysthymia, which

typically is further addressed by support and education as well as potentially psychotherapy and

medication. A score of 15-19 indicates moderate depression which should be addressed by a

professional in the form of psychotherapy and/or medication. Finally, a score of 20 or greater

indicates severe depression and should be addressed by a professional in the form of

psychotherapy and/or medication (Kroenke & Spitzer, 2002).

The PHQ-9 has been psychometrically validated through a number of reliability and

validity studies. A validation study by Kroenke and colleagues (2001) found that the PHQ-9 had

a sensitivity and specificity of 88%. This same study found high internal consistency with

Cronbach alphas of .86 and .89. Another study in 2020, which compared the PHQ-9 to the

Hamilton Depression Scale (HAMD-17), found the PHQ-9 had strong construct validity

compared to the HAMD-17 ($r = 0.610$, $p < 0.001$). Intra-class correlation was also strong

between measures (0.594 (95% confidence interval, 0.456–0.704, P < 0.001; Cronbach's α =

0.892). The study also found strong test-retest reliability with a correlation coefficient of 0.737

(Sun et al., 2020).

Penn State Worry Questionnaire

To measure anxiety, the study utilizes the Penn State Worry Questionnaire (PSWQ). The

PSWQ is a 16 item self-report measure aimed at detecting worrisome thoughts and behaviors

related to anxiety. The measure utilizes a 5-point Likert scale ranging from "not very typical of

me" to "very typical of me." Although the measure does not have specific sub-scales, the PSWQ

specifically assesses the excessiveness, generality, and uncontrollable dimensions of worry and

fear. Scoring of the PSWQ ranges from a minimum score of 16 to a maximum score of 80. When

scoring, a value of 1-5 is assigned to a response. To control for response bias, some of the items

are reverse scored (Meyer et al., 1990).

The PSWQ is also psychometrically sound. Meyer and colleagues (1990) found the

PSWQ demonstrated strong test-retest reliability among college students ($r = 0.92$; Meyer et al.,

1990). It was also been shown to have high convergent validity with other anxiety measures; for

example in comparison to The Worry Domains Questionnaire, the PSWQ had a convergent

validity score of ($r = .67$; Tallis et al., 1992); similar results were observed on the student worry

scale ($r = .59$; Davey et al., 1992). The PSWQ has also shown high discriminant validity as

evidenced by comparison studies of the State Trait Anxiety Inventory Meyer et al., 1990;

Spielberger et al., 1983) and the Beck Depression Inventory (Beck et al., 1961; Meyer et al.,

1990).

Medical Adherence Questionnaire

The medical adherence questionnaire is a single measure that assess for five separate domains as per self-report: hypertension, cholesterol, smoking, body weight, and medical follow-up. Hypertension was operationalized by self-report of current blood pressure readings as wither above or at/below 140 mmHg. Cholesterol was operationalized by self-report of current level of cholesterol as greater or equal to/less than 6.5 mmol/L. Smoking was measured by self-report measure on a smoking log that outlines the number of cigarettes smoked per week each week (McFall, 1970). Body weight was operationalized as BMI. As such, changes in body weight were measured by comparing BMI of the patient pre-test to and post-test and, then again, at follow up. BMI was assessed by the responsible investigator by asking the participant for their current weight and height. BMI was then be calculated remotely by the responsible investigator. Medical follow-up was operationalized by self-report of whether or not they had follow-up on any referrals made to them throughout the treatment (yes, no, or NA).

Dementia Awareness Questionnaire

The Dementia Awareness Questionnaire was developed by Heger and colleagues (2019) to assess for dementia literacy and knowledge about preventative factors associated with cognitive decline into later adulthood. The test developers based the literacy questions off of the British Social Attitudes (BSA) study on dementia from the UK (Marcinkiewicz & Reid, 2015), while the remaining items were based off of the "Lifestyle for Brain Health" (LIBRA) score. This questionnaire consists of 31 items, not including two follow-up items specific to their study; scores could range from -34 to 34. The questionnaire is set up in a Likert-scale system that measures an individual's agreement to a statement ranging from "strongly disagree" to "strongly

agree" And is a relatively quick measure to administer, averaging an administration time of approximately 5 minutes (Heger et al., 2019). This questionnaire also has embedded validity measures related to use of painkillers, having children, ambient noise, and personal hygiene. These questions indicate response bias, for example, simply endorsing "strongly agree" to every item and boosting their score blindly.

Procedure

Upon PCOM IRB approval, individuals were recruited from a university-based family medicine practice and psychoeducational group both located in the Northeastern United States, as well as an online recruitment flyer posted on social media, and ResearchMatch. Participants were screened via online questionnaire screening for all inclusion and exclusion criteria as well as the CAIDE Dementia Risk Scale. Individuals who did not meet criteria for the study were thanked for their time and directed to the Alzheimer's Association website for further resources. Individuals who met criteria for recruitment during the initial screening questionnaire were contacted via phone by the RI to discuss their interest in participating in a 7-week psychoeducation group aimed at preserving brain health and memory into later adulthood. Interested participants were verbally read the informed consent procedure to assure proper comprehension the information being provided, by the RI. Following successful informed consent, participants were invited to be evaluated on the measures of the study (outlined above) and participate in the group.

During the initial online pre-test assessment, the participants were read the informed consent again and digitally recorded that they had agreed to participate. They were provided a unique four-character code so that we could de-identify data. The master list of participant names and unique codes were stored by the RI on a password protected computer, encrypted, and kept

separate from study data. The participants were then administered the MoCA, SDS-CL-25, PHQ-9, PSWQ, Lent-Hope Diet Questionnaire, Dementia Awareness Questionnaire, and Medical Adherence Questionnaire. Participants were then provided with details related to the first treatment session as well as instructions related to use of Zoom and the Step-Up mobile application.

Upon completion of all pre-test requirements, participants began attending weekly group Motivational Cognitive Behavioral Therapy (seven sessions of 90 minutes each) administered by the RI, a doctoral student, under the supervision of the principal investigator (PI), a licensed psychologist. Due to limitations in available participants, no control group was utilized. However, the study design allowed for baseline data to be used as a control.

The Motivational CBT protocol utilized in the study contained seven 90 minute sessions that were delivered once per-week over a 7-week period. In the 7 days between each group session, text, phone, and/or communication was utilized to further motivate and reinforce healthy behavior change; no data was collected during these correspondences. Assessment and treatment sessions were conducted over Zoom, in compliance with public safety guidelines related of the COVID-19 pandemic. At the beginning of each group session, participants were sent an individual link with electronic forms of the Step-Up data input and Lent-Hope Diet Questionnaire that they submitted privately.

Motivational CBT Manual (Synopsis)

Session 1. The first session consisted of orientation to the study. Participants were provided psychoeducation on the impact of lifestyle factors that contribute to health and long-term optimal aging. It was explained to the participants that their score on the initial recruitment evaluation suggests that there are areas that may put them more at risk of dementia and that

purpose of the study in order to educate participants on the treatment and between session

homework/action plans. During the first session, the RI lead participants in the Personal Values

Card Sort procedure (Miller et al., 2001) to assess for and highlight underlying motivations for

improvement, which was used throughout the course of treatment and to help patients identify

optimally desirable health-related goals. Of note, the Values Card Sort is not a formal assessment

but rather a therapy exercise to allow clients to explore their own values and motivations. The

Values Card Sort served as a discussion point to a larger conversation about the participant's

motivations. In the final part of the first session, participants outlined and ranked the

individualized goals in order on which they hoped to work and achieve. A homework/action plan

for the session included self-monitoring exercise for the week and were given resources for

participants to track their steps as a proxy for cardiovascular fitness.

Each group session began with a mood check and assessed behavior change over the last

week. Participants reviewed their self-monitoring of their goals and were asked to reflect on any

change to their ability to enact behavior change, compared to the week before. Each week,

participants noted if they reached their goals and, if they did, what they did to reach them

(Miller, 2013). If they did not meet their goals for the week, we discussed obstacles, including

practical obstacles (time, money, equipment, etc.) or task-interfering cognitions so that the group

could collaboratively problem solve ways to remove those obstacles. Another core component of

each session was goal-setting; in each session participants committed to weekly goals which they

wrote down to further increase private cognitive commitment to their goals. Patients were also

encouraged to consider sharing their goals with others, to increase public commitment and the

likelihood that they would change their behavior in a way that was consistent with their values,

goals, and health.

In each session, we intended to maximize the use of imagery and collaboration by using a multi-method approach, which consisted of multimedia visual aids, high-impact videos, group discussion, interactive activities, and personal reflection. This interactive approach was utilized to maximize learning and collaboration and in turn lead to higher motivation and episodic memory encoding of session information.

Session 2. The second session consisted of the initial mood check as noted above. The group facilitator and participants reviewed the week's action plan and discussed the impact of self-monitoring had on their cognitions and behavior. The group then collaboratively worked together to address ways of increasing self-efficacy and goal attainment for the coming week. The RI then provided psychoeducation and interactive exercises further detailing the impact of exercise on brain health, emphasizing the research on neurological benefits of exercise (e.g., an increase in BDNF) and potential risks of a more sedentary lifestyle (Rosenberg et al., 2018). To increase cognitive dissonance and promote exercise, participants considered how lack of exercise increased the risk of dementia. The group discussed different types of exercise and collaboratively set specific goals for walking exercise for the following weeks (Rosenberg et al., 2018). The RI then used MI-CBT skills to relate how their most cherished values, discussed in the first session, impact their motivation and actions, which lead to goal attainment, specifically, protecting brain health and memory.

Because the next session focused on sleep, participants were given a sleep log (Maich et al., 2018) and asked to log the number of hours they slept per night for their weekly action plan, to be discussed during the next class in conjunction with previous tasks to self-monitor their steps per week on the App to promote increased exercise and prevent behavioral relapse.

Session 3. The third session, consisted of a mood check and review of the week's action plan focusing on the sleep diary, which they completed in the previous week to objectively assess nightly sleep patterns. Group members collaborated and shared obstacles that impacted their sleep as well as problem-solving strategies to address those barriers. The RI then provided collaborative psychoeducation on sleep and brain health (Krause et al., 2017), while also reviewing their sleep log for the week. Participants were taught the biopsychosocial benefits of sleep and costs of sleep deprivation, specific to its effect on tau, amyloid beta, and cellular autophagy, as well as general principles of sleep hygiene, stimulus control, and different CBT-I strategies to increase sleep (Perlis et al., 2008). To increase cognitive dissonance and promote sleep hygiene, and did a cost-benefit analysis of the short-term benefits of poor sleep behavior (e.g., more productivity) and the long-term negative health effects (e.g., risk of dementia). An action plan related to sleep goals was discussed and planned for the coming week.

Specific skills related to motivational interviewing focused on core values and how the implications of sleep impact their brain health and memory, along with how participants can empower themselves to change, with values and goals in mind. In order to build on their current progress, participants were encouraged to maintain their sleep and step-monitoring as, which has been shown to aid in behavioral change. As part of their action plan for the coming week, participants were asked to self-monitor their diet by using a food diary provided by the RI (Swendeman et al., 2018). This was done to reinforce all behaviors that they were currently working on in an effort to build their self-efficacy and follow-through with their specific goals related to exercise, sleep, and diet.

Session 4. During session 4, participants worked together with the RI to address issues that had arisen in the previous week, including how to balance multiple goals within a week.

Participants also discussed their weekly action plan related to diet tracking and processed what it was like increasing awareness of their exercise, sleep, and now, diet. Participants participated in psychoeducation on healthy eating principles and tied it into how it affects brain health long-term, with a focus on detailed information on the MIND diet and how each factor of the diet contributes to their brain health (Morris et al., 2015). For example, participants were informed how sugar impacts oxidative stress on the brain as well as how it slows the brain's metabolism of nutrients. The RI worked with participants on properly self-monitoring their diet, setting goals, and addressing obstacles to those goals in the session (Beck, 2011). Following proper education on diet, we also discussed how risk factors for dementia such as hypertension and obesity, can be reduced by diet and enacting behavioral interventions like self-monitoring blood pressure using at-home methods, medication adherence, regular follow-up with medical professionals, stimulus control, and especially, exercise and meal planning (Pondenejadan et al., 2013). These discussions lead to a process-oriented reflection of how diet is directly tied to each participants' core values and goals. The RI discussed how unhealthy habits are directly in contrast with those values and worked alongside the group to develop greater congruence between values and behavior. The action plan for the following week included self-monitoring mood, utilizing a self-report form (Beck, 2012), in conjunction with continuing self-monitoring and adaptive modification of sleep, diet, and exercise in an effort to improve relapse prevention and ultimate outcome.

Session 5. Session 5 consisted of a more detailed process-oriented approach that provided members to review their action plan from the prior week, while also building self-efficacy regarding the behaviors that would lead each individual to achieving their long-term goals. Participants also discussed their weekly action plan related to mood tracking and processed what

it was like increasing awareness of their exercise, sleep, diet, and now, mood. In addition to problem-solving barriers to success and verbally reinforcing members' progress, we once again focused on the interconnectedness of values, behaviors, and goals. The RI provided psychoeducation about stress (Williams et al., 2012), including operationalized definitions of stress including depression and anxiety (American Psychological Association, 2013). They were told how these symptoms can manifest as common symptoms of stress in men and women (Beck, 2011; Beck et al., 2005). Participants then collaboratively engaged in immersive group psychoeducation discussing the impacts of stress on brain health and its relation to other medical complications (Yaribeygi et al., 2017). For example, participants were reminded of the role that oxidative stress plays in cell death and noted how biological factors discussed in the psychoeducation portion directly related to brain health. We then discussed ways of addressing each common form of stress and offered coping skills for different types of stressors that the participants endorsed in the session (Beck, 2011; Beck et al., 2005). We discussed negative thoughts patterns as well as developed a behavioral activation plan for the next week. Behavioral activation is an evidence-based core tenant of CBT that aims to increase the exposure to positively rewarding experiences; thereby improving mood, proximity to health-related goals, and self-efficacy. When this is accomplished, research shows that individuals are more likely to follow-through with those behaviors in the future and further reinforce their own mood (Beck, 2011; Beck et al., 2005; Miller & Rollnick, 2013). Further action plans for the next week focused on self-monitoring their mood, diet, weekly steps, and hours of sleep using the tools provided to them in previous sessions in order to facilitate relapse prevention.

      Session 6. In session 6, the RI lead a process-oriented discussion over how participants believed they had changed over the course of the treatment arm and how they planned to make

more adaptive changes for each of the specific domains of behavior addressed in treatment (Beck, 2011; Rollnick et al., 2008; Miller, 2013). Participants discussed any remaining goals they have not yet accomplished and worked together to identify and address potential obstacles (Beck et al., 2005; Miller, 2013). The last part of the sixth lesson was spent preparing for wrap-up by discussing relapse prevention and ways that participants can remain motivated in the long-term following treatment. We concluded the sixth session by discussing the final session and documenting the strategies on coping cards or smart phones, which led to their success, for future use to retain and further improve adaptive lifestyle behavior. Participants agreed that it would be helpful to review these coping cards/notes on a regular basis in light of their values and goals of maintaining brain health and memory.

Session 7. Following assessment in week 7, the RI engaged in cognitive rehearsal of desirable behavior to maintain progress and addressed ways of continuing to improve beyond the end of the seven-week treatment (Beck, 2011; O'Donohue & Fisher, 2008). Participants discussed how to continue progress through the 3-month period and beyond. We collaboratively fine-tuned documented strategies on coping cards or smart phones, which led to their success, for future use. The final part of the seventh session was spent obtaining constructive feedback from participants regarding ways to improve the protocol moving forward and thanking them for their time.

After the last session of Motivational Cognitive Behavioral Therapy (week 7), study participants were contacted by the RI to be scheduled for a time to meet via Zoom, where post-test data was collected on all measures. Participants were then contacted 3 months after the termination of treatment (week 7) for the final virtual assessment session with either the RI where three-month follow-up data was collected on all measures. Subsequent to the three-month

follow-up, participants were be entered into a randomized computer drawing which chose the

five winning participants who received a $50 Visa gift card.

CHAPTER 4: RESULTS

Demographic Analyses

A total of 25 subjects were recruited and consented to participate in the study. Of the 25 subjects who consented, 21 participants completed the pre-treatment assessment data collection. Of the 21 participants who completed pre-test data collection, 15 completed post-test data collection and the three-month follow-up. Participants ranged in age from 44-59, with a mean age of 54. The sample consisted of seventeen females (81%) and four males (19%). Most identified as Caucasian ($n = 16$; 76%), followed by African American ($n = 4$; 19%), and then non-white Hispanic ($n = 1$; 5%). Nearly half of the group participants (47%) attended all seven sessions with 27% attending three to four sessions, and another 27% attending two or fewer sessions. The average number of sessions attended was 4.7. Reasons for inconsistent attendance are reviewed in the discussion section.

Table 1.1

Demographic Characteristics of Participants (N = 21)

Variable	n	%
Gender		
Male	4	19%
Female	17	81%
Ethnicity		
Caucasian	16	76%
African American	4	19%
Hispanic	1	5%
Age		
40-45	1	5%
46-50	2	10%
51-55	7	33%
56-59	11	52%

Table 1.2

Session Attendance Statistics (N = 21)

Session Number	n	%
1	11	73%
2	10	67%
3	8	53%
4	6	40%
5	10	67%
6	6	40%
7	10	67%
Total (Average)	8.71	58.14%

Statistical Analyses

To evaluate the hypotheses in this study, a within subjects, repeated measures analysis of variance (ANOVA) was utilized. The one-way repeated measures ANOVA consisted of three different levels of the independent variable (time) which, for purposes of this study, were the three different time points (pre-test, post-test, and 3-month follow-up; Field, 2018). The dependent variables for each of the ANOVAs conducted were the various measures outlined in the seven hypotheses (MoCA, Lent-Hope Diet Questionnaire, Step-Up application data, medical adherence questionnaire, SDS-CL-25, PHQ-9, PSWQ, and Dementia Awareness Questionnaire.

Hypothesis I Analysis

First, it was hypothesized that there would be no change in cognitive functioning over the course of the seven-week intervention period or after the three-month follow-up phase. Cognitive

functioning was operationalized as scores on the MoCA. An overall score summary and

comparison of means and standard deviations are shown in Table 3. Mauchly's Test of sphericity

is not significant, indicating the assumption of homogeneity is supported. A repeated measures

ANVOA determined that, although it was approaching significance, MoCA score did not

significantly change between time points (but approached significance), $F(2, 28) = 3.296$, $p =$

.052, and the first hypothesis was confirmed.

Table 2

Descriptive Statistics of MoCA Scores

	Mean	Standard Deviation	N
Pretest	27.40	1.844	15
Posttest	28.13	1.995	15
3 Month Follow-Up	28.87	1.187	15

Hypothesis II Analysis

Second, it was hypothesized that there would be decreased sleep pathology among

participants following the seven-week intervention and at the 3 month follow-up. Sleep

pathology was operationalized using the SDS-CL-25 which divided disorders down based off of

six different sleep pathologies. Table 3 displays descriptive statistics of responses to items 3-6 on

the SDS-CL-25 between pretest, posttest, and follow-up. Because Mauchly's test of Sphericity

was significant, sphericity could not be assumed and a Greenhouse Geisser correction was

performed. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that

insomnia pathology scores differed statistically significantly between time points, $F(1.422,$

19.905), $p = .003$. Post hoc analysis with a Tukey adjustment revealed that insomnia pathology

scores statistically significantly decreased from pretest to posttest (2.333) (95% CI, [0.663,

4.004)], $p = 0.006$), and from pretest to 3 month follow-up (1.933) (95% CI [0.087, 3.780]), $p =$

.039), but not from posttest to 3 month follow-up (-.400) (95% CI [-1.349, 0.549]), $p = .812$).

Analysis of effect size utilizing partial eta square revealed a large effect size (.410) and the null

hypothesis was rejected.

Regarding sleep apnea, because Mauchly's test of Sphericity was significant, sphericity

could not be assumed and a Greenhouse Geisser correction was performed. A repeated measures

ANOVA with a Greenhouse-Geisser correction determined that sleep apnea scores did not

statistically significantly change between time points $F(3.600, 15.534) = 2.011, p = .177$.

Regarding restless leg syndrome, Mauchly's test of Sphericity was not significant and sphericity

was assumed. However, a repeated measures ANOVA determined that RLS scores did not

statistically significantly change between time points $F(2, 28) = 0.723, p = .494$. Similar

findings were observed with restless leg syndrome, circadian rhythm disorders, narcolepsy, and

parasomnias.

Table 3.1

Descriptive Statistics of Insomnia Scores

	Mean	Standard Deviation	N
Pretest	4.400	3.757	15
Posttest	2.067	2.963	15
3 Month Follow-Up	2.467	4.051	15

Table 3.2

Descriptive Statistics of Restless Leg Syndrome Scores

	Mean	Standard Deviation	N
Pretest	1.80	2.731	15
Posttest	1.400	1.993	15
3 Month Follow-Up	1.667	2.498	15

Table 3.3

Descriptive Statistics of Sleep Apnea Scores

	Mean	Standard Deviation	N
Pretest	2.600	3.089	15
Posttest	2.000	3.644	15
3 Month Follow-Up	2.00	3.723	15

Hypothesis III Analysis

Third, it was hypothesized that there would there would be an improvement in depression scores following the completion of the seven-week intervention period as well as the 3 month follow-up. Depression was operationalized using the PHQ-9. As shown in Table 4, scores on the PHQ-9 changed from 4.8 to 3.73. Because Mauchly's test of Sphericity was significant, sphericity could not be assumed and a Greenhouse Geisser correction was performed. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that depression

scores did not statistically significantly change between time points $F(1.110, 15.534) = 2.515$, p = .131. As a result, the null hypothesis was not rejected.

Table 4

Descriptive Statistics of PHQ-9 Scores

	Mean	Standard Deviation	N
Pretest	4.80	3.895	15
Posttest	3.93	4.415	15
3 Month Follow-Up	3.73	4.667	15

Hypothesis IV Analysis

Next, it was hypothesized that there would be an improvement in anxiety scores following the treatment program at post-test and 3 month follow-up. Anxiety was operationalized using the PSWQ. Because Mauchly's test of Sphericity was significant, sphericity could not be assumed and a Greenhouse Geisser correction was performed. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that anxiety scores did not statistically significantly change between time points $F(1.163, 16.287) = 2.475$, $p = .132$. As a result, the null hypothesis was not rejected.

Table 5

Descriptive Statistics of PSWQ Scores

	Mean	Standard Deviation	N
Pretest	47.93	12.355	15
Posttest	44.27	11.285	15
3 Month Follow-Up	44.00	11.650	15

Hypothesis V Analysis

It was hypothesized that participants would increase their knowledge and awareness of dementia following the seven-week intervention and maintain that knowledge at the 3 month follow-up. Dementia knowledge was operationalized using the Dementia Awareness Questionnaire. Descriptive statistics are shown in Table 6 demonstrating that the mean score from the pretest to posttest increased from 9.2 to 27.00; the mean score from posttest to 3 month follow-up increased from 27.00 to 28.87. Because Mauchly's test of Sphericity was significant, sphericity could not be assumed and a Greenhouse Geisser correction was performed. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that dementia knowledge differed statistically significantly between time points $F(1.068, 14.955) = 43.425, p < .005$. Post hoc analysis with a Tukey adjustment revealed that dementia knowledge statistically significantly increased from pretest to posttest (-17.800) (95% CI [-25.655, -9.945]), $p < .005$), from pretest to 3 month follow-up (-19.667) (95% CI [-27.134, -12.199]), $p < .005$), and from posttest to 3 month follow-up (-1.867) (95% CI, [-3.541, -0.192]), $p = .027$). Analysis of effect

size utilizing partial eta square revealed a large effect size (.756). Given these results, the null

hypothesis was rejected and Hypothesis 5 was confirmed.

Table 6

Descriptive Statistics of Dementia Knowledge Scores

	Mean	Standard Deviation	N
Pretest	9.20	7.002	15
Posttest	27.00	8.418	15
3 Month Follow-Up	28.86	7.444	15

Hypothesis VI Analysis

It was hypothesized that participants would develop stronger adherence to the MIND diet

over the 7 week intervention period and maintain that change at the follow-up. Diet adherence

was operationalized using the Lent-Hope Diet Questionnaire and descriptive statistics are shown

in Table 7. Because Mauchly's test of Sphericity was significant, sphericity could not be

assumed and a Greenhouse Geisser correction was performed. A repeated measures ANOVA

with a Greenhouse-Geisser correction determined that MIND diet adherence differed statistically

significantly between time points, $F(1.197, 14.361) = 10.126$, $p = .005$. Post hoc analysis with a

Tukey adjustment revealed that MIND diet adherence statistically significantly increased from

pretest to posttest (-14.846) (95% CI [-27.240, -2.452], $p = 0.018$), and from pretest to 3 month

follow-up (-14.846) (95% CI [-27.587, -2.106], $p = .021$), but not from posttest to 3 month

follow-up (0.00) (95% CI [-4.517, 4.517]), $p = 1.000$). Analysis of effect size utilizing partial eta

square revealed a large effect size (.458). Given these results, the null hypothesis was rejected

and hypothesis 6 was confirmed.

Table 7

Descriptive Statistics of Lent-Hope Diet Questionnaire Scores

	Mean	Standard Deviation	N
Pretest	43.23	9.011	13
Posttest	58.08	12.271	13
3 Month Follow-Up	58.08	13.345	13

Hypothesis VII Analysis

It was hypothesized that exercise would increase over the seven-week intervention period and be maintained at the 3 month follow-up. Exercise was operationalized by the number of daily steps logged into the Step Up mobile application (descriptive statistics shown in Table 8). Because Mauchly's test of Sphericity was significant, sphericity could not be assumed and a Greenhouse Geisser correction was performed. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that anxiety scores did not statistically significantly change between time points, $F(2.346, 28.152) = 0.541$, $p = .616$. As such, the null hypothesis was not rejected.

Table 8

Descriptive Statistics of Average Number of Weekly Steps

	Mean	Standard Deviation	N
Week 1	10189.23	9089.169	13
Week 2	12836.31	12886.068	13
Week 3	11183.54	10994.800	13
Week 4	8498.954	7558.814	13
Week 5	9751.69	6910.040	13
Week 6	9728.54	5785.822	13
Week 7	11063.92	8149.174	13
Posttest	11017.85	7040.193	13
3 Month Follow-Up	10589.23	6172.376	13

Exploratory Analysis

Although not a part of the study hypotheses, additional data was collected participants regarding their medical information (BMI, cholesterol, hypertension, and number of cigarettes). No statistical analyses were run on cholesterol, hypertension, or cigarettes, although qualitatively they are unchanged. BMI, however, did change. Because Mauchly's test of Sphericity was significant, sphericity could not be assumed and a Greenhouse Geisser correction was performed. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that BMI adherence differed statistically significantly between time points $F(1.603, 22.448) = 13.498, p <$ .005. Post hoc analysis with a Tukey adjustment revealed that BMI statistically significantly

decreased from pretest to posttest (0.953) (95% CI [0.454, 1.453], $p < .005$), and from pretest to

3 month follow-up (1.267) (95% CI [0.539, 1.995], $p = .001$), but not from posttest to 3 month

follow-up (0.313) (95% CI [-0.492,1.119], $p = .925$. Analysis of effect size utilizing partial eta

square revealed a large effect size (.802).

Table 9

Descriptive Statistics of BMI Scores

	Mean	Standard Deviation	N
Pretest	28.3	28.3	15
Posttest	26.2	25.6	15
Follow-Up	19.6	19.1	15

In addition to medical data, participants were also asked if they had followed up with any

referrals that were made to them over the course of the intervention period. Of the 15 participants

who completed pretest, posttest, and follow-up, 10 had been referred to a specialist dependent on

their presenting issue (e.g. anxiety, depression, and insomnia); at the 3 month follow-up, all 10

participants who had been referred to a specialist had followed up and sought an appointment. Of

note, multiple participants had more than one referral.

CHAPTER 5: DISCUSSION

Dementia is one of the most feared diseases that appears to be growing more prevalent around the world, with rates of Alzheimer's disease alone expected to surpass 14 million people by 2050 in the U.S. alone. As there is currently no known cure and few effective palliative interventions once the disease is diagnosed, many researchers have directed their efforts to addressing primary prevention of dementia rather than treatment. The purpose of this pilot study was to examine if a brief, manualized intervention to improve behaviors associated with delay or prevention of the most common manifestations of dementia was possible and feasible. This 7 week intervention was conducted completely remotely, in the context of the COVID-19 pandemic, and utilized a hybrid model of MI and CBT to address modifiable risk factors related to dementia.

Interpretations and Implications

The specific interventions in the study were derived from evidence-based CBT and motivational interviewing, which are empirically shown to have salubrious effects on sleep, exercise, diet, stress (i.e. anxiety and depression), weight management, smoking cessation, health-related behavior. The primary outcome measures of this study were health-related behavioral change and change in cognitive functioning, the latter, as evidenced by neuropsychological testing. In summary, this study examined the feasibility of a manualized pilot cognitive behavioral and motivational intervention that we hope will inform more comprehensive and long-term research into health-related behavior modification intended to delay or prevent the onset of Alzheimer's disease.

It was hypothesized that our brief, group MI-CBT intervention would result in significant changes to lifestyle behaviors and psychopathology of the variety that have been empirically related to dementia risk. More specifically, we predicted that there would be adaptive changes at post-test and at three-month follow-up in sleep pathology, depression, anxiety, diet, exercise, and dementia knowledge. It was also hypothesized participants would maintain cognitive functioning at these time points. Although not addressed in the study hypotheses, data was also collected to assess any changes in BMI, hypertension, cholesterol, cigarette smoking, and medical follow-up, due to the relationship of these factors to dementia risk. Results showed statistically significant improvements in insomnia, diet, dementia knowledge, BMI, and medical follow-up. There were no significant differences in cognition, non-insomnia sleep pathology, anxiety, depression, exercise, cholesterol, hypertension, or cigarette smoking at either the post-test or 3-month follow-up. The following is a discussion of these results and implications.

It was first hypothesized that there would be no significant change in cognition, that is, cognitive functioning (operationalized as MoCA scores) post-intervention and at three-month follow-up. It was predicted there would be no change in cognitive functioning because there is limited scientific data to suggest that a brief intervention can improve cognitive functioning in a middle-aged clinical population, especially over such a short period of time as 7 weeks. We also did not expect to see a cognitive decline in this short timeframe (Hultsch et al., 1992). This hypothesis was supported. However, results indicated a trend in cognitive functioning, in the direction of improvement that was remarkably close to statistical significance ($p = .052$). Although possible, it is unlikely that improvement in cognitive functioning could be explained by our intervention. It is also possible, albeit unlikely, that results might have measured practice effects as we employed three different versions of the MoCA for each administration (pre-, post-

test, 3-month follow-up). However, it is possible that improvement could be attributed to familiarity with the format (Cooley et al., 2015). Additionally, mean MoCA scores for the present sample were within normal range at each time-point so that any improvement in cognitive functioning would have been all the more unexpected. These results may have been observed for a number of reasons including increased knowledge of the cognitive domains assessed, due to the intervention; increased self-efficacy, confidence; and even time of day of the testing (Walters & Lesk, 2015). Nonetheless, these results are promising and support the MI-CBT intervention as a means of preserving cognitive functioning.

Our second hypothesis predicted that insomnia-related sleep pathology (operationalized as elevations on items 3-6 on the SDS-CL-25) would improve as a result of the MI-CBT intervention. This hypothesis was supported. Insomnia sleep pathology, showed a statistically significant improvement at posttest and follow-up. However, other sleep domains assessed in the SDS-CL-25 were unchanged. The reasoning for the statistical change in insomnia over other sleep domains could be multi-faceted. First, the sleep intervention for the program primarily focused on sleep hygiene, stimulus control, and cognitive distortions related to sleep. Although these therapeutic modalities have been shown to be highly effective in persons with insomnia (Chung et al., 2018; Perlis et al., 2008), there is limited research as to how it can impact other sleep issues such as sleep apnea, restless syndrome, and narcolepsy. Second, insomnia was overwhelmingly the primary sleep complaint observed in the study group compared to other sleep-related complaints. Additionally, of the small percentage of participants who had elevations on other sleep scores (e.g., sleep apnea), they were already being treated for their sleep complaints with either a sleep specialist or their primary care providers and, as importantly, these other non-insomnia sleep disorders were not addressed in treatment. This suggests that

participants who screened positive for other sleep disorders (e.g. restless leg syndrome, sleep apnea) were already in treatment or had previously been treated prior to the beginning of the study but still endorsed related symptoms. Finally, the SDS-CL-25 allows participants to endorse elevations on multiple domains of sleep pathology. As such, many of the participants (n = 7) screened positive for had more than sleep disorder, which could have impacted their overall sleep outcomes, as research has shown that comorbid sleep disorders can impact overall treatment outcome (Spiegelhalder et al., 2013).

Next it was hypothesized that depression and anxiety would both improve as a result of the intervention (depression was operationalized as scores on the PHQ-9 while anxiety was operationalized as scores on the PSWQ). However, neither of these hypotheses was supported. When examining for potential causes for these results, there could be a number of related factors. First, the intervention for depression and anxiety were grouped into a single session despite being two separate pathologies, often requiring multiple treatment sessions. As such, it may be that the 90 minute intervention was not sufficient for these often complex disorders. This may have impacted the overall efficacy of the intervention as research suggests that, although treating comorbid depression and anxiety is possible and effective, it is difficult to address them simultaneously, let alone in a single session (Cameron, 2007). Additionally, the specific homework/action plan for this domain of treatment primarily focused on thought records and mood monitoring. Although these tools are extremely helpful, participants noted that they focused more on the depression than anxiety and, as such, moving forward participants suggested we have activities related to anxiety specifically. Nonetheless, it was hoped that the anti-depressant aspects of behavioral activation intervention, improvements in sleep, exercise, and social interaction and exposure (to anxiogenic stimuli) in the treatment group setting and in

homework assignments would impact both depression and anxiety. Second, there was a high

degree of variability among participants' knowledge and exposure to mental health treatment, so

it is possible that this heterogeneity of the sample influenced results.

The next hypothesis that the psychoeducational aspects of the MI-CBT program would

increase in knowledge and awareness of dementia and dementia prevention following treatment

and during follow-up was supported. These results indicated that such knowledge increased over

three-fold by the 3 month follow-up and indicated a large effect size. The reasons for these

improvements are likely attributed to the psychoeducational component of the intervention; for

example, in each weekly session, the RI provided education on how the topic of focus directly

related to the brain. Moreover, one of the greatest strengths of the MI-CBT program was

participants actively identified their personal motivation for protecting memory and brain health

continuously throughout the intervention, which likely increased attention and memory for the

relevant material (Parks-Leduc et al., 2015). The impact of increased knowledge of dementia

cannot be understated. It can be plausibly inferred that such a dramatic increase in dementia

knowledge helped contribute to the behavioral change and increased positive self-talk observed

across the other domains assessed in this study. Additionally, research posits that increased

knowledge is reciprocally correlated with increased motivation, which is one of the fundamental

theoretical bases of the current study (Ditta et al., 2020; Barnes et al., 2018). Finally, the

multimedia and interactive nature of the groups meetings likely contributed to increased learning

as research has shown the positive learning effects of visual stimuli (Ulrich et al., 2021). The

videos utilized in the group meetings were curated specifically to aid in the participants'

visualization of the material, specifically the neurological effects of the topic of the week. Such

goals were derived from evidence based theory that shows video-based learning consisting a

relevant and stimulus heavy material is associated with enhanced encoding and retrieval of

course information later (Vasilakes et al., 2018).

It was next hypothesized that participants would report a significant improvement in

adherence to the MIND diet (Morris et al., 2015) following the 7-week group MI-CBT

intervention. Improvement in the MIND Diet was operationalized as improved rating on a self-

report questionnaire regarding the MIND diet. Posttest and follow-up data both indicated a

statistically significant improvement in diet adherence. The reasons for this improvement could

be attributed to a number of reasons. First, the MIND diet had a particularly clear outline as to

which foods to consume and which food to avoid, including specific examples. The concrete

nature of this presentation could have benefitted a number of participants. Coombe and Davidson

(2015) reported that an effective questionnaire is one that covers desired material in the most up-

front way possible and eliminate unnecessary items as it has been found to impact a study's

overall outcome. As such, the direct nature of the Lent-Hope Diet Questionnaire allowed for

direct data collection of necessary material, while eliminating irrelevant diet data found on other

measures. Thus, this method may have had good sensitivity and specificity. Second, when

developing overall goals for the program, 12 out of 15 participants stated that diet was at least

one component of their long-term goals, as such this level of intrinsic value could have impacted

their motivation to adhere to diet over other goals which were more variable. The impact of

intrinsic value on motivation and behavior change cannot be understated. Overwhelming

research suggests that when intrinsic value is placed on certain goals or tasks, the overall success

of that goal or task is significantly higher (Ng, 2018). Higher intrinsic value and motivation on

tasks has been shown to enhance neurocognitive processing and decision making leading to

outward behavioral changes (Maddox & Markman, 2010). As cognition and behavior change,

individuals begin to feel a sense of self-efficacy that contradicts prior core beliefs related to

inadequacy and self-doubt (Holloway & Watson, 2002). These core components are shown to be

a major barrier to behavioral change and, as such, once they are addressed true progress can

occur, as was observed in the current study.

Utilizing intrinsic value to increase motivation can also be seen at a neuronal level.

Research has shown that when intrinsic value is placed on tasks, the central amygdala,

dorsolateral prefrontal cortex, and orbitofrontal cortex are activated on fMRI imaging (Miura et

al., 2017). Third, there was qualitatively more discussion and problem solving related to diet

during the group meetings. For example, during the week of a major holiday, participants spent

about 20 minutes providing support and problem-solving ways of addressing diet related goals in

the meeting. Although this was observed in every group meeting, it was notably more

comprehensive than other meetings.

Of note, although there are a number of concerns related to self-report measures

discussed below, there is some psychological benefit as well which could have impacted our

results related to diet. According to self-perception theory and motivational interviewing

research on psycholinguistics, a positive view of one's own behavior, in such a case diet, can

result in a change in self-concept and commitment language, both of which are associated with

actual healthy behavioral change (Amrhein, 2004). When examining a self-report measure such

as the Lent-Hope Diet Questionnaire, there is a strong possibility that a positive view of their diet

behavior increased their commitment language and outcomes despite concerns related to the self-

report nature of the measure.

Finally, it was hypothesized that participants would report significant increase in

exercise, operationalized as the number of steps walking per day on the Step-Up mobile

application (Synder et al., 2011) and that these results would be maintained during a 3-month

follow-up. Much to the research team's surprise, there was no statistical change in exercise over

time. These findings could be attributed to a number of reasons including weather, medical

conditions, history effect (the height of the COVID-19 pandemic), layout of their

home/community (safety issues for participants living and walking in the city), and

personal/professional barriers.

Weather was the first major theme of obstacles that arose during group meetings; since

the intervention occurred from June through July, the weather was notably hotter, more humid,

and wetter than other times of the year. As such, multiple participants noted that they were

unable to leave their home to walk during these times. This reasoning is also supported in

scientific literature. A 2019 study that examined the relation between exercise behaviors and

weather found that participants were up to 3.49 times more likely to delay exercise during times

that they did not consider the weather to be ideal (e.g., rain, heat, and cold; Wagner et al., 2019).

Next, a number of participants had significant medical conditions that made walking either

painful and/or impractical which likely impacted the number of steps taken. Third, when

discussing ways of problem solving barriers to walking, a number of participants discussed

walking around one's home or another location that protected them from the elements (e.g. heat).

However, other participants noted that either their home was not conducive to walking (e.g.

living in a studio apartment) while three others noted that they lived in a neighborhood that they

either did not feel safe walking alone in or did not have the resources to go somewhere and walk.

Such safety and social justice implications of exercise on low-income and high crime

communities is also supported in the scientific literature. A 2012 comparison study between low-

income individuals and middle to high income individuals found that individuals who lived in

urban areas without sufficient police protection or resources for exercise were less likely to

exercise or have intention to exercise (Murray et al., 2012).

Finally, another common theme of personal barriers to exercise included personal factors

(e.g. children and grandchildren) and professional factors (e.g. employment) that impacted their

exercise. A number of participants noted that their work was intensive and stationary, with little

time/opportunity to walk. These same participants noted that, when they got home from work,

they had prioritized spending time with family or doing other tasks over exercise, likely

impacting our results as well. The above reasons for not exercising are also confirmed in a 2005

focus group study which identified 14 major barriers to exercise which included inertia, fear of

failure, personal safety concerns, time, negative affect, physical limitations, lack of social

support, physical discomfort, weather, age, inconvenience, perceived capability, and verbal

persuasion (e.g., physician directives; Lees et al., 2005).

To address the above concerns, there are three major interventions that have been shown

to be effective at eliciting exercise behavior. First, is to activate values and motivation to make

the intervention as personalized as possible by tailoring to the individuals involved by specifying

their desires, reasons for change, needs, goals, and contextual factors. Second, is to have a broad

reach in your recruitment by targeting those who need services most through community-based

interventions where people actually live and work. Third, involves monitoring for long-term

success by having booster sessions, follow-ups, and using technology (Lachman, et al., 2018).

These three recommendations are consistent with our MI-CBT approach.

Although not addressed in the study hypotheses, data was also collected to assess any

changes in BMI, hypertension, cholesterol, cigarette smoking, and medical adherence, all of

which are empirically-related to dementia risk (Gottesman et al., 2014; Kalmijn et al., 2004; Ott et al., 2004; Ngandu et al., 2018).

Regarding BMI, there was a statistically significant change between the pretest and posttest and 3-month follow-up, with mean BMI decreasing from 30.97 (pretest) to 30.02 (posttest) and 29.71 (follow-up). Such results can be attributed to a number of factors including education about BMI, motivational interventions, changes in diet, and psychoeducation about exercise. As noted above, increased education and knowledge regarding source material is directly correlated with improved outcomes and motivation. As such, the psychoeducational, motivational, and CBT components of the intervention likely impacted motivation and overall outcomes. Additionally, the change in BMI may have been a secondary result of the clinical focus of two other outcomes: diet and exercise. It is widely known that a healthy diet and exercise are two staples of weight loss. Because nearly one third of the intervention focused on factors related to weight loss, it can be posited that the decreased BMI was a secondary gain of the intervention. Although there was no statistically significant change in number of steps outlined in Hypothesis VII, there was a subjective increase (10,189.23 to 11,017.85) in steps among participants overall. This subjective increase, in conjunction with the large effect size observed in the change in diet adherence on the Lent-Hope Diet Questionnaire, may have been enough to change BMI of the group participants overall. However, it is important to acknowledge the role of motivational interviewing has on BMI. The literature demonstrates the efficacy of MI on BMI. In addition, literature suggests that key predictors of successful BMI outcomes include facets of MI covered in the intervention. For example, a 2011 meta-analysis found that goal-setting focused on high-priority items (e.g., values) were associated with better BMI outcomes. As noted earlier, participants cited diet and weight loss as two of the most

commonly endorsed goals in the initial treatment session. The same meta-analysis also posited

that group-based MI for weight loss had successful outcomes due to a number of factors

including accountability, support, and social engagement, all of which were core facets of the

present study (Armstrong et al., 2011).

Another study from 2007 found successful treatment outcomes related to BMI by

utilizing six core components of MI that were also utilized in the current study. These included

understanding the patient's perspective, reflective listening and responses, avoiding unsolicited

advice and other MI-inconsistent behaviors, prioritizing the patient's readiness and willingness to

change, eliciting feedback, and utilizing an action plan/homework between sessions (Martino et

al., 2007). Taken together, the present study adhered to previous research related to MI and BMI,

added CBT techniques and, as such, found similarly positive results.

Finally, group members were screened for elevations for sleep pathology, depression, and

anxiety on a medical adherence questionnaire and subsequently given referrals related to any

elevations that they endorsed on the SDS-CL-25, PHQ-9, or PSWQ. Of the 10 participants who

were referred for medical or psychiatric care, 100 percent, that is all 10, had followed up on their

referral. These findings indicate that the MI-CBT program was an efficacious means of screening

and referring for medical treatment. These results are also consistent with medical adherence

literature related to CBT and MI. A 2014 meta-analysis by Teeter and Kavookjian found that, of

nine MI or CBT based studies aiming at increasing medical adherence, also had a moderate to

large effect in increasing health behaviors. Importantly, related to this study, is that over half of

the studies concluded no difference in the modality that services were delivered: in-person or

telehealth, the latter, further supporting the utility of our virtual intervention, which is designed

to increase accessibility (Teeter & Kavookjian, 2014). Similar findings were observed in another

meta-analysis from 2016. One of the major contributions of this meta-analysis was evidence of

fidelity based evaluation, meaning that extra attention to how participants engaged in the

intervention was a profound indicator of treatment success (Palacio et al., 2016). As such, much

like this study, future interventions should pay particular attention to participants' fidelity to

treatment. One final study that examined core characteristics of patients' success following MI

confirmed that our study utilized key MI-based skills that contributed to our participants' follow-

up. These characteristics included addressing individual motivations to change, addressing

ambivalence, rolling with resistance, and psychoeducation (Salvo & Cannon-Breland, 2015).

Similar findings have been observed on follow-up studies examining the role of CBT on medical

follow up (Prins et al., 2011; LaFrance et al., 2009).

In addition to our study's quantitative findings, there is compelling evidence of the

efficacy of this treatment qualitatively, operationalized as endorsements of those participating in

the study. These qualitative data findings are defined as any patterns, themes, or facets of the

intervention that may have contributed to the study that were not evaluated by a formal outcome

measure. During the final group meeting, members were asked to provide constructive feedback

about their experience in the group. During this group discussion a number of common themes

arose that can provide valuable insight into the clinical utility of this group intervention. The

primary themes that arose in conversation were self-efficacy, goal setting and attainment, visual

learning components, session outline and course material, multidisciplinary collaboration,

convenience and public health, telehealth access, attendance, personal values, thought changes,

and knowledge of dementia.

Group members overall offered significant praise of the group, citing its importance of

the topics addressed and the integrated approach. One of the first themes that arose in the group

conversation related to the collective group change on their behavior. One participant stated that "[their] outlook on their ability dramatically impacted how much [they] accomplished" adding that when their beliefs were challenged by the facilitator and the group members, that she was able to challenge them within herself. Another member added a statement related to the value of CBT interventions, specifically, that learning to identifying and modify thoughts could result in behavioral change was most helpful for her. She realized that doing so consistently helped her to achieve her goals, noting that "being able to see how my thoughts and actions were holding me back in real time allowed me to change it in real time as well."

Another apparent theme that arose quickly in group discussion related to goals and how members worked towards achieving their goals. When asked about their confidence in the beginning of the intervention, reception was mixed; some participants reported that they were confident at their ability to achieve their goals while others immediately felt "overwhelmed" and "self-conscious." However, by the end of the intervention a resounding majority of participants endorsed that their self-confidence in themselves to achieve their goals had increased dramatically. One participant specifically noted how the group discussion of ways to address barriers to success was useful to her in each meeting. She stated that these discussions "helped [her] realize the excuses that [she] was making and motivated [her] to think in the moment of how to fix the issues at hand". Another group member noted that the MI skills related to core values and its connection to behavior was a major turning point for her. She stated that "every session [the group facilitator] would relate how our current behaviors contradict our values. This was a major wake-up call to me and I used this a lot when motivating myself to exercise." Of course, helping participants to increase awareness of the discrepancy between their intrinsic healthy values and goals versus their current unhealthy behavior increases cognitive dissonance

and the motivation to change.

The next theme revolved around the group's delivery of educational material and topics addressed throughout the 7 week intervention period. Participants were very receptive to the video and visually based materials as well. One participant stated that "videos were a good way to break up the material and add a different lens that made it feel less like school." Another group member stated that they are a "visual learner" and benefitted greatly from graphs and other visual materials. The combination of verbal information and imagery to supplement the talking points of each discussion was said to "keep the group on course" and allow the group facilitator to address the material in a linear and cogent fashion.

Participants also noted that many of the topics addressed in the group had opportunity to be explored further in subsequent meetings, offering the recommendation that certain topics gain more attention and are broken up (e.g. depression and anxiety, as noted above). The primary criticism was that certain meetings felt rushed with a need to fit all of the meeting's material into 90 minutes at the expense of meaningful group discussion on a set topic. Many of the group participants suggested that additional follow-up and ongoing support would be beneficial at making gains towards their long-term goals. More specifically they stated that the weekly check-ins were useful but felt that they could have been more frequent. Coinciding with this feedback was the additional notion that live support to problem-solve barriers interfering with their goals would be greatly helpful. They also suggested that expanding the program to younger individuals to help build better lifestyle skills even earlier.

Group members also expressed mild frustration when the group facilitator would review comments that were not relevant to them, personally. A solution that was suggested by one participant was to have a wider range of topics offered in meetings over a longer period of time,

allowing participants to choose which meetings were most relevant to them, taking a modular approach. Of note, this would also allow participants to play a more active role in their goal-setting and increase their own awareness of their personal needs and goals. An approach such as this could also alleviate some of the concerns related to attrition during the study as four of the six participants who withdrew from the program indicated that they did not feel the group content was relevant to them. Of course, the lack of *perceived* relevance may actually present an opportunity. For example, if participants believe that a session on exercise or sleep would not be relevant to them because they are already engaging in healthy activity in these regards; this could be a fortuitous occasion for such participants to serve as role models for other group members, with the opportunity for them to help problem-solve obstacles, and serve as peer support for other group members (Shalaby & Agyapong, 2020). This would have the added advantage of increasing self-efficacy, public and private commitment to healthy behavior, and relapse-prevention for the role models (Miller & Rollnick, 2013) and further increase therapeutic group cohesion (Burlingame et al., 2018).

Another common theme during group discussions was the relative lack of knowledge and awareness of these lifestyle issues and how they affect cognition, brain health, and memory. Participants noted that they were surprised that physicians and other members of the healthcare system were not more proactive at discussing concerns specific to their cognitive health. These remarks point out a salient need which illustrates the growing need for interdisciplinary collaboration among health professions. Studies consistently show that patients treated in multidisciplinary medical programs have better physical and mental health outcomes (Jennings & Astin, 2017); as such by making strides towards proactive collaboration among other health professions, we will be able to better identify and assist persons who may benefit the most from a

program such as this.

Additionally, this study demonstrated a creative and flexible implementation of empirically supported treatment interventions, based in motivational interviewing and CBT, adapted to address a set of public health needs not yet explored in empirical research. This study showcased how a treatment protocol can be delivered to a wide range of individuals using a virtual format, illustrating opportunities for similar interventions to be offered at primary care or medical specialty offices, non-profit organizations, and other community facilities like community centers, libraries, or places of worship. This group intervention demonstrated that an efficacious treatment can be delivered at the least burdensome location for most individuals attending sessions, i.e., in their homes. This is an especially salient point given the public health concerns related to the COVID-19 pandemic, limited financial resources, time, transportation, etc. which will likely continue to impact society in the future. In fact, a number of participants indicated that they would not be comfortable attending live groups in person had they been held specifically citing fears related to their health and COVID-19.

It should be noted that despite easy access to the treatment meetings, there was evidence of irregular attendance, another common theme brought up in the group discussion. Participants reported that this was often caused by practical obstacles. For instance, some individuals reported that they were unable to get home from work in enough time for the meetings to start at 7 PM. Furthermore, the same individuals were unable to find childcare for the time that the group was meeting and could not attend some groups. Similar barriers have also been observed in the scientific literature (Jack et al., 2010). It is important to note that there were time points of the summer that participants reported other commitments that took precedence over the group meetings; examples of such commitments included vacations, birthday parties, and volunteer

events that conflicted with the group's meeting time. Other reasons absences from meetings included illness, bereavement, traffic, and forgetting about the group meeting.

Further related to theme of self-efficacy, the group unanimously agreed that the weight that personal values played could not be overstated. One group participant noted that the Personal Values Card Sorting task during the first group meeting resonated with him and strongly influenced how he developed his goals for the intervention. Values appeared to be a common core component of the group's goal setting process overall. For example, one participant noted family as their primary value whereas they then related to how their value on family motivated them to change in order to spend as much time with their new grandson. Another reported that their sobriety was a major value and related how changing their negative behaviors can have a dramatic influence on their long-term recovery. A third group participant noted that they observed a close family member succumb to Alzheimer's disease and wanted to do everything within her ability to prevent such events from happening to her or her family. There are numerous other examples of how values and lived experiences influenced individuals' goal setting but the theme throughout the group discussion revolved around the influence of using those values to change and maintain adaptive behaviors.

In addition to the role that personal values played on behavioral change, the way that members perceived their behavior (cognitions) also changed dramatically. The three major negative cognitive theme that came up multiple times in conversation related to inadequacy, helplessness, and unworthiness. These cognitions are maladaptive schema posited by Beck (2013) and Burns (1999). As noted above, 12 participants in the group made some form of comment related to their lack of faith in their ability to accomplish their goals in the beginning of the intervention. They cited incidents that they had failed in the past, a lack of time, a lack of

motivation, and poor self-control as primary reasons that they were not confident in their ability. However, during the final group meeting, most group members stated that they were surprised at their progress and their confidence in their ability to achieve their goals. One member stated that "it is like night and day the person that I am" while another noted "I feel like I can actually keep this up," Indicating a cognitive change in the direction of competence and self-efficacy.

The second major maladaptive schema discussed in group related to helplessness. Multiple participants asked "what is the point if this stuff can't be cured?" and "shouldn't you live your best life while you have it then?" However, these same participants reported that the psychoeducational component behind our intervention and the knowledge of prevention changed their outlook on their behavior. During the final group meeting one member noted that they believed "there is actually hope" for dementia prevention while another stated they felt more at ease knowing that there were factors within their control to preserve memory and brain health.

A theme that arose by some group members related to guilt and shame surrounding their behaviors. Two participants in particular stated that they were ashamed of their past unhealthy behaviors while another six members stated that they compared themselves unfavorably to other peers, both which drove down their own feelings of worth. During group discussion these same members stated that group feedback changed the way they viewed themselves. One cited an example from a group discussion that focused on "not being able to change the past but changing the future" which they posited as a major turning point to their progress. During the final moments of the seventh group meeting, this particular cognitive distortion came up and one member in particular ended their talking point with the phrase "we are all worthy of a healthy and happy life." Another volunteered that, "we can now do something to help." This was an unequivocal change from the group discussion in the first week.

The most profound benefit to participants of this project is likely the increased

knowledge of dementia, that it awareness how their health-related behaviors impact their long

term health and the specific behavioral steps they can take to protect their brain and memory. It

seems that this group treatment, designed to provide such education and explore motivations for

change promoted an openness to change, self-efficacy, and an overall willingness to enact

health-related behaviors to reach clearly specified treatment goals. Furthermore, this project also

shows that a short-term, virtual, cognitive behaviorally based treatment to address modifiable

risk factors to dementia is feasible, efficacious, and cost-effective, opening the door to further

research and improvements in implementation.

Limitations

The results of this pilot study had several limitations. One of the most apparent

limitations of this study is the modest sample size ($n = 25$). Additionally, this study did not

utilize control groups, reducing the ability to distinguish causation/treatment effects from some

threats to internal and external validity. Specific limitations include the homogeneity of the

sample, inconsistent group participation, attrition, possible social desirability effect,

operationalization of some dependent variables, and the psychometrics of study measures. These

limitations are elaborated below:

The participants in this study were disproportionately female (81%) and identified as

Caucasian (76%). Many factors contributed to the sample in this study being more homogenous

than that of the general population of the United States, including the method in which

participants were recruited, which preferentially selected for the demographics of those utilizing

social media, an existing behavioral health group, and the research recruitment service:

ReasearchMatch. Therefore, it is possible that these results may not generalize to the general

population (Lieberman et al., 2005). However, it should be noted that there is a significantly

greater risk of females developing dementia (Azad et al., 2007), so that their over-representation

in the study may mirror actual need.

Coinciding with concerns regarding the sample size and homogeneity are additional

limitations in the population in which we were recruiting patients from. First, some participants

were recruited from a pre-existing psychoeducational group for healthy lifestyle and mental

health, and social media postings related to improving health; as such, it is likely that these

patients already had a high level of motivation to improve their health. Second, other participants

were recruited via ResearchMatch, a site with significantly more participants with advanced

degrees (Harris et al., 2012). Such demographic could impact relevant aspects of motivation and

cognition, specifically cognitive reserve. Cognitive reserve theory states that, with sufficient

stimulation (e.g., education, social interaction, high attaining occupation) allows the brain to

compensate for any deficits that develop as a result of degenerative or acquired neurological

occurrences such as injury or disease. Typically, individuals with a higher education have a

greater degree of cognitive reserve and better overall performance on neuropsychological tests

among both healthy and impaired individuals (Meng & D'Arcy, 2012). Given these

considerations, our study sample may not be representative of the general public who may not be

as proactive in behavioral health or as well-educated or have greater cognitive reserve

(Lieberman et al., 2005).

Inconsistent attendance to the group posed another limitation to this study. Overall the

present study's attrition rate was 40% with 25 individuals consenting to participate while 15 had

completed the posttest and 3-month follow-up. Compared to other group treatments, however,

the present study was not dissimilar to a meta-analysis conducted in 2010 which found an

attrition rate among 73 studies to be at 35.26% (Sharf, 2010).

Another limitation to this study is the attrition and inability to acquire posttest and three-month post treatment follow-up data from all of the initial set of group members. Of the 21 group members who participated in the pretest data collection, 15 participated in the posttest and three-month follow-up. This loss of six participants coupled with the study's pre-existing small sample size, limits generalizability. Participants provided two primary reasons for not participating in follow-up data; four participants stated that they did not feel the group material was relevant to them and were not benefitting, One stated that she withdrew because she was diagnosed with a terminal medical condition, and one did not respond to follow-up (Beck, 2013).

Research shows that it is difficult to accurately assess for cognitive change over only a 3 month period. Many of the concepts that are being measured, such as cognition, take a more prolonged period of time to see long-term results (Duff et al., 2017). As such, this study should lay the groundwork for more longitudinal work that investigates the long-term cognitive effects of this combined behavioral change. In addition, it would be beneficial to assess for overall behavioral change over a longer period of time by adding a follow-up assessments over years wither after or during longer term treatment, that is, during the period of expected cognitive decline.

Another limitation of our study is that the MoCA does not fully encompass the complexity of cognitive functioning in comparison to more elaborate neuropsychological evaluations (Coen et al., 2016). Adding more comprehensive assessment, such as a full neuropsychological testing battery assessing for memory, executive functioning, language, processing speed, and motor ability, the same domains affected by Alzheimer's disease would increase monetary costs and time commitment that were beyond the scope of this pilot study.

An additional limitation included the diet measure. The Lent-Hope Diet Questionnaire was developed by a highly-respected weight loss and diet specialist, Dr. Michelle Lent; however, the measure remains invalidated and thus its psychometric properties remain untested.

Like many studies, the study poses some ethical limitations as well. Because the participants in the group might have been compensated for their time via a $50 gift card raffle, the study runs the risk of secondary gain, specifically, monetary motivation to participate and improve (Nylangulu et al., 2019). In addition, there are a number of social justice implications to take into consideration of this study. Because participants were required to use mobile applications to track their exercise and diet, people without these means were unable to participate in our study. Similarly, as we recruited using primarily online means, we had to limit our recruitment base to individuals who have access to a computer, reliable internet, know how to manage technology, and have the accessibility to participate in the intervention groups. Unfortunately, research also suggests that individuals in need of the highest level of support are ones who do not have these resources at their disposal (Wang et al., 2021). Nonetheless, the design allows for recruitment of participants who are in a position to take advantage of a telehealth program.

Recommendations for Future Research

As noted in the literature review, the aging population and related increase in medical comorbidities are strongly associated with dementia risk and the increasing prevalence of this class of disorders. Consequently, the WHO, various national health organizations, and major medical centers are dedicating large amounts of funding for to dementia prevention.

Expanding on the present MI-CBT pilot study with a larger sample size and longer-term treatment could increase the power of the intervention and allow for more personalized

interventions as well as more frequent, supplementary sessions to reinforce adaptive change in motivation, cognition, and behavior. Additionally, longitudinal studies should follow patients over the course of years and use a more comprehensive, multimethod approach to assess for cognitive change over time.

In conjunction with suggesting more longitudinal work to examine long-term cognitive change, future studies would benefit from using a more comprehensive neuropsychological testing battery to measure specific domains of AD and dementia more thoroughly. This can be further specified into studies aimed at assessing how behavioral change can affect certain aspects of cognition over time. For example, researchers can examine how this treatment protocol affects all domains of executive functioning over a period of time absent of assessing for other cognitive domains such as memory, language, or attention. This would help to further distill the effects of interventions on cognitive functioning, given our surprising results of the MoCA, which were remarkably close to statistical significance ($p < 0.52$). This positive trend in cognition was all the more surprising given our small sample size and the truncated nature of the intervention, which was only 7 weeks in duration.

Researchers should also include diverse communities (e.g., rural communities, culturally diverse) in their recruitment to develop a more heterogeneous sample to better represent the U.S. population. Unfortunately, research also suggests that individuals in need of the highest level of support do not have sufficient practical or financial resources at their disposal to participate (Wang et al., 2021). As such, further research studies should incorporate more cost-effective alternatives that can be more applicable to participants off various financial means. Additionally, researchers are advised to explore different venues to facilitate the group. Researchers should also consider recruiting from populations that would benefit most from dementia prevention

services such as primary care offices, neurology offices, sleep centers, endocrinologist offices,

dieticians' practices, long-term care facilities, or other community-based centers.

Participants noted that they were surprised that physicians and other members of the

healthcare system outside of the study were not more proactive at discussing concerns specific to

their cognitive health as they entered middle adulthood. Given these concerns, in conjunction

with overwhelming data to support early intervention of modifiable risk factors for dementia,

healthcare providers are encouraged to talk with their patients about their cognitive health

alongside their physical health, along with referrals for programs to reduce dementia risk.

As noted earlier in the discussion, there was major public health concern surrounding the

COVID-19 pandemic that was a salient point for individuals within the present study; it also

represented a microcosm of the systemic challenge faced by our healthcare system and the

population, in general. Although the COVID-19 pandemic caused immeasurable damage, it also

spurred the evolution of the healthcare system, in that it practitioners adapted quickly by offering

evidence-based virtually delivered services, with limited impact on the quality of patient care

(Zimmerman et al., 2021). As such, our healthcare system made great strides in increasing access

to patients through, which should remain available post-pandemic.

Attrition was one of the major concerns related to the present study with reasons outline

in the limitations section. Given the difficulties expressed by participants, future group

facilitators are encouraged to explore creative ways of not only maintaining group attendance but

also mitigating the effects of missing sessions. One potential solution to alleviate irregular

attendance might be to offer make-up sessions that allow for participants to get access to the

meeting material to allow for active-problem solving and MI skills to be practiced in real-time to

offset any skills lost in their absence. Another solution for irregular attendance would be to

provide video recordings of psychoeducational materials and skills training, which participants

could watch at their convenience. Although these solutions will likely not fully mitigate the

impact of irregular attendance, it does provide the opportunity for members to gain the

knowledge and skills necessary to enact serious behavioral change. In fact, the utilization of

video material to offset deficits in learned material has already been used in MI and found to be

effective (Biddle & Hoover, 2020; Fontaine et al., 2016).

The limitations section also discussed psychometric limitations of the study's diet

measure. As such, adapting pre-existing diet measures specifically to the MIND-diet or

conducting further validation studies on the Lent-Hope Diet Questionnaire would be beneficial.

Second, the self-report nature of the measure could impact the participants' true diet behaviors

due to a number of self-perception factors that should be addressed in future research.

A major area of study that has been evolving in recent years and discussed throughout the

literature review is the concept of cognitive reserve, which develops over the course of years and

decades and not over a 3-month course (Serra et al., 2015). As such, professionals can direct

research on developing cognitive reserve. Moreover, primary prevention campaigns can

publicize the benefits of cognitive stimulation to preserve memory and brain health and

clinicians can motivate patients for change.

Another fruitful area for future research involves other major lifestyle factors that have

been associated with optimal brain health. Factors such as social interaction (Cheng et al., 2014),

drinking more water (Trinies et al., 2016), vitamin D intake (Jing Hu et al., 2018), caffeine

consumption (Zhough & Zhang, 2021), illicit drug use (Schlaerth et al., 2004), and medication

use (Campbell et al., 2019) along with diet, exercise, stress, and sleep (Ngandu et al., 2014) all

have a correlation with cognitive function which likely have an impact, positive or negative, on

the risk of dementia. Conducting research in this regard can provide further insight into how

these different lifestyle factors affect dementia pathology.

A final area of study proposed revolves around medical complexity. There are multiple

complex medical conditions that are associated with increased risk of AD and other forms of

dementia. It would be beneficial to assess for the efficacy of the proposed treatment protocol on

specific medical populations. More specifically patients with a history known risk medical

factors such as of cranial radiation and chemotherapy (Mezencev & Chernoff, 2020), stroke

(Vijayan & Reddy, 2016), hearing and vision loss (Michalowski et al., 2019), head injuries (Li et

al., 2017), Down syndrome (Nixon, 2018), and the long-term effects of COVID-19 (Hariyanto et

al., 2021) should be explored. Research into these and other complex medical conditions, can

unlock valuable information to inform dementia prevention in the field of psychology and

medicine moving forward.

In addition to clinical recommendations, there lies a number of administrative

recommendations for future arms of the present study. Regardless of where the intervention is, or

the modality in which it is offered, it is critical that the group facilitator implement the group

treatment in as effective of a way as possible. The current study utilized the treatment material

proposed by Beck (2013) and Miller (2007), as there is overwhelming evidence related to their

effectiveness among target populations, in changing motivation, mood, and behavior. Planning is

another critical component. In any group, individuals will need to plan multiple facets of their

personal and professional lives (e.g. scheduling shifts, coordinating childcare, etc.); as such it is

imperative to establish a schedule well before the start of treatment and strictly adhere to such

schedule prior to treatment starting. Such considerations that were noted by the present study's

group members included doctor's appointments, illness, childcare, bereavement, and many other

life circumstances.

Group facilitators should establish foundational expectations related to expectations and group responsibility during the first group. Although it is common practice to explain confidentiality and group norms, it is emphasized that extra attention be given to what the group members can expect from the facilitator; namely professionalism, punctuality and reliability. For example, facilitators should emphasize that groups will remain consistent and within the stated expectations regardless of extraneous factors. It is critical that participants know that the group schedule is predictable, reliable, and certain as a number of group members in the present study discussed frustration with other groups in the past that were not reliable. More importantly, such unprofessionalism can undermine the credibility of the facilitator and impact his/her ability to deliver the services they intended to deliver; more broadly this can also impact group members' willingness to participate in groups in the future as members have stated their reluctance to participate given bad prior experiences in groups (Macnair-Semands, 2002). Additionally, coinciding with the psychological principal of modeling and vicarious learning, by communicating explicit high expectations and following through with such commitments, participants are able to observe the benefits of self-imposed discipline and goal setting, likely impacting their treatment success. When such observations are made, participants may be more engaged, diligent at addressing obstacles, and respectful of group norms and expectations. (Yalom & Leszcz, 2005).

A valuable aspect of the current study was the use of weekly's check-in via phone, email, or text message (depending on the participant's preference). This was something that participant's stated was useful to keep them on track with their goals. However, they reported that once per week did not seem like enough at times, particularly during challenging weeks

where it was hard to keep up with their goals. As such, a number of group members recommended that check-in's become more frequent (i.e. 2-3 times per week). Coinciding with this feedback was the additional notion that live support to problem-solve barriers interfering with their goals would be greatly helpful. They also suggested that expanding the program to younger individuals to help build better lifestyle skills even earlier.

Conclusion

The increasing incidence and costs associated with AD and other dementias are sufficient to bankrupt the U.S. medical system by 2050. Fortunately, research continues to provide deeper knowledge of the etiology and epidemiology of these disorders. As such, it is becoming imperative to find an effective, accessible evidence-based approach to working with individuals at the highest risk of neurodegenerative disease. Thankfully, behavioral health interventions show increasing promise. Such interventions should incorporate the empirical research supporting healthy lifestyle behaviors to delay and, hopefully, prevent dementia pathology. Despite a number of limitations in the current study, addressed above, this pilot study provides preliminary empirical support for the efficacy of a brief intervention, based on evidence-based motivational interviewing and CBT designed to help individuals to reduce the maladaptive health-related behaviors that have been shown to be associated with dementia risk factors. These risk factors are all too prevalent in individuals in middle and late-middle age. The findings of post-test data collection also found that the MI-CBT program was also an efficacious means of screening and referring for medical treatment. The MI-CBT program, utilized in this study, attempted to capitalize on the synergistic effect of employing both motivational interviewing and CBT to specifically help participants change motivation, cognition, and behavior (Naar &

Saffren, 2017), so that they could engage in more healthy behaviors, intended to preserve

memory and maintain brain health as they age.

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